ELECTRODIAGNOSIS IN DISEASES OF NERVE AND MUSCLE: PRINCIPLES AND PRACTICE

EDITION 3

JUN KIMURA

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Principles and Practice

Edition 3

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As new scientific information becomes available through basic and clinical research, recommended procedures undergo changes. The author and publisher have done everything possible to make this book accurate, up-to-date, and in accord with accepted standards at the time of publication. Nonetheless, the reader is advised always to check changes and new information regarding the current practice and contraindications before conducting any tests. Caution is especially urged with new or infrequently used equipment.

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To Junko
and
our growing family

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PREFACE AND ACKNOWLEDGMENTS

I know it is unwise to open introductory remarks with excuses because they instantaneously weaken the impact and preempt the thrust of the message. Nonetheless, I wish to offer an explanation for the enormous delay of this publication in spite of my good intention to comply with the warm encouragement for a timely revision.

In 1989, immediately after the completion of the second edition, unforeseen turns of events prompted my unscheduled return to Kyoto to teach at my alma mater. I was able to maintain close ties with the University of Iowa thanks to Dr. Antonio Damasio, Chair of the Department of Neurology, who offered me a joint appointment with a ten-year leave of absence. Despite this liaison, an unplanned relocation at once doomed any hopes of repeating a six year cycle of revisions from the original date of publication in 1983. Besides, continued involvement with the Muscle & Nerve, as well as the International Federation of Clinical Neurophysiology (IFCN) and the World Federation of Neurology (WFN), in essence, precluded any progress toward a timely finish.

Additionally, I found myself in the midst of a re-entry crisis after a 30 year stay abroad which climaxed with a sadly misdirected legal probe into our accounting of research donation from pharmaceutical industry and the fund raising for the 10th International Congress of EMG and Clinical Neurophysiology (X-ICEMGCN Kyoto, 1995). Ironically, the incident provided me with an unexpected opportunity to concentrate on rewriting the manuscripts as prolonged and persistent press surveillance all but forced my unintended seclusion at home. In fact, I found myself in an ideal position to update the text using ample and uninterrupted time with which to analyze bits and pieces of documents assembled over the past several years. The turmoil, which was widely publicized in Japan as one of the biggest scandals of 1997, ended triumphantly (for us) with the resignation of the prosecutor in charge and the disbandment of the special task force, proving yet again that justice may be blindfolded but the truth always sets you free.

During this interim, some new fields have emerged in our discipline requiring their inclusion as additional chapters and other existing areas have gained importance in patient care necessitating expanded coverages. These include magnetic stimulation, human reflexes, late responses, motor unit number estimate, quantitative electromyography, and threshold electrotonus to mention only a few. Advanced technology has brought considerable modifications in theory and practice in many other areas, although the basic premises remain the same in electrophysiologic approaches and in clinical problem solving. Parallel advances in other fields of neuroscience have led to equally exciting progress in the exploration of many disease processes in general, and to the understanding of neuropathies, muscular dystrophies, myasthenic syndrome and movement disorders in particular. I have thus rewritten, in their entirety, the chapters on principles and variation of conduction studies; facts, fallacies and fancies of nerve stimulation technique; other techniques to assess nerve function; the F wave and A wave; somatosensory and motor evoked potentials; electrodiagnosis in the pediatric population; and all the clinical sections included in Part VI and Part VII with the addition of ethical consideration in clinical practice as an appendix. The remaining chapters also underwent substantial changes to reflect current understanding. The addition of some 2500 new papers, which I personally reviewed, attest to the incredible advances in what was once considered to be a static, rather than dynamic, field of clinical electrophysiology. To achieve comprehensive coverage, I retained most of the old articles to document earlier contributions. However, for the sake of brevity, the text emphasizes basic principles, summarizing only pertinent points for day to day practice. The inclusion of ample new references should enable interested readers to consult the original papers for further details.

My decision to take on this venture affected—directly or indirectly—many innocent bystanders who had to shoulder additional workloads while I devoted myself in writing. In particular, I owe special thanks to our staff in Kyoto guided by Dr. Ichiro Akiguchi who, along with Dr. Shinichi Nakamura, Dr. Nobuyuki Oka and Dr. Shun Shimohama, assumed many administrative chores. Dr. Ryuji Kaji, together with Dr. Nobuo Kohara, supervised the Clinical Neurophysiology Laboratory where our post-doctoral fellows contributed many new research insights useful for this revision. I am most grateful to Professor Hiroshi Shibasaki and his staff, which consisted of Dr. Hidenao Fukuyama, Dr. Takashi Nagamine and Dr. Akio Ikeda of the Department of Clinical Brain Pathophysiology for their support. Our secretarial personnel, including Mari Yamane, Kayoko Morii, Kyoko Maekawa, Tomoko Noboru and Kumiko Imai, processed an enormous amount of English literature without having prior exposure to foreign materials. Last, but not least, Machiko Miyamoto typed and retyped the entire volume single-handedly, as she was the only Japanese assistant proficient in English.

It was my good fortune to be able to complete the revision at the Division of Clinical Neurophysiology at the University of Iowa headed by Dr. Thoru Yamada, who directs the EEG section there with the assistance of Drs. Malcom Yeh and Dr. Mark Granner. I enjoyed a most flexible time schedule in the EMG section thanks to Dr. Edward Aul who filled in whenever necessary, along with the help of

Dr. Torage Shivapour and Dr. Jon Tippin. Dr. Eric Dyken, in charge of the Sleep Disorder Laboratory, read the entire book and provided useful suggestions. David Walker, M.S.E.E., rewrote the appendix on electronics, which was previously co-authored by Pete Seaba, M.S.E.E., who also gave helpful advice. I am indebted to Sheila Mennen, Shelli Hahn and Leigha Rios for their indispensable technical and clerical help during my renewed part-time work in Iowa. Ms. Mennen had already assisted with the first and second editions, therefore, I appreciated her sentiment when she inquired as to whether there would ever be a fourth edition!

I would also like to thank Lauren Enck and Susan Hannan at Oxford University Press for inheriting the 3rd edition from F.A. Davis in the midst of production, and for guiding me with patience and encouragement despite the slow progress of the adopted project. I am indebted to the American Association of Electrodiagnostic Medicine (AAEM) and its Nomenclature Committee, who granted me permission to reprint the AAEE Glossary of Terms in Clinical Electromyography (1987) as Appendix 5.

In concluding this acknowledgment, I wish to update a personal note on our household which, in the earlier editions, triggered many kind remarks. We now have an attorney in San Francisco, a resident physician in Madison, and a counselor for handicapped children in our home base in Iowa City. Junko, my wife, often refers to herself as "an international cleaning lady", and periodically visits all five posts including my retreat in Kyoto, which is buried under manuscripts and always ranks bottom in her assessment. Our boys have finally grown old enough to appreciate the magnitude of the work involved in producing a textbook. For my 60th birthday, which in Japan customarily warrants a special celebration in recognition of one's accomplishment (regardless of any achieved), our three sons and a daughter-in-law came to Kyoto to honor my endeavors. I consider it my good fortune to be able to work on this edition in such a warm and conducive environment.

This book is again dedicated to Junko in appreciation for her companionship, and to our growing family to acknowledge their compassionate, albeit spiritual, support. I take great comfort in the thought that, at long last, we may endow the royalty from this book as down payment for their first homes rather than tuition: I am thrilled that, for a change, we can actually witness the rewards of our investment!

Kyoto, Japan J. K.

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PREFACE FOR THE SECOND EDITION

The preparation for the second edition began in 1983 with the original volume still in press, literally before the ink had dried. Kind encouragements and constructive criticisms received from different corners of the world added further incentive for early revision. Most suggestions proved helpful in improving the contents and style. A few requests, however, posed problems because they represented mutually exclusive views: for example, inclusion or exclusion of expanded coverage of evoked potential studies. Here, I had to accept the old maxim that, however much one wishes, one cannot please everybody all the time (or even most people much of the time!). Thus, I followed my own bias as to the relative importance of a topic for the principles and practice of electrodiagnosis.

This revision, though initially conceived as routine and minor, eventually required major changes, in part reflecting the rapid medical and technologic advances in the field during the past five years. The sections rewritten in their entirety include Facts, Fallacies, and Fancies of Nerve Stimulation Techniques (Chapter 7), Single-Fiber and Macro Electromyography (Chapter 15), Somatosensory and Motor Evoked Potentials (Chapter 19), Polyneuropathies (Chapter 22), Myasthenia Gravis and Other Disorders of Neuromuscular Transmission (Chapter 24), Myopathies (Chapter 25), and Fundamentals of Electronics and Electrical Safety (Appendices 2 and 3). Most other sections also underwent substantial changes to update, clarify, and tighten the contents. The book now cites more than 1200 additional references selected from some 2500 recent publications that I personally reviewed, with the hope that the inclusive bibliography helps encourage further research in the area of electrodiagnostic medicine.

The hustle and bustle inherent to the preparation of voluminous manuscripts, by necessity, involve directly or indirectly those who share the work environment with the author. I could not have completed the job without assistance from my colleagues, who endured the fate of "galley" slaves over an extended period of time. Drs. Thoru Yamada and Stokes Dickins ran the busy services of the Division

despite my preoccupation with writing. D. David Walker, M.S.E.E., rewrote the appendix on electronics previously coauthored by Pete Seaba, M.S.E.E., who left the ranks for private enterprise. Sheila Mennen, our Chief Technologist, Deborah Gevock, and Cheri Doggett played major roles in maintaining the daily clinical operation and organizing technical as well as secretarial needs. A number of clinical fellows and residents participated in teaching sessions, shedding new insights into the type of coverage essential in an electrodiagnostic text. A total of 35 research fellows from Japan and elsewhere spent one to two years with us during this interim contributing original data in clinical electrophysiology, much of which found its way into the revised text.

Dr. Maurice Van Allen, who had provided a kind foreword for the first edition, continued to support my literary endeavor until his untimely death in 1986. I lost a teacher and friend, and a new foreword, which he had promised. He had jokingly, but perhaps with good reason, attributed the success of the first edition to his opening remarks, which are retained in his honor. Dr. A. L. Sahs, who initiated me into neurology, rendering help when I needed it most, also passed away later in the same year. It was my good fortune that the Department prospered under the direction of Dr. Antonio Damasio, who, together with Dr. Robert L. Rodnitzky, provided the kind of environment enticing to academic pursuit. I owe my thanks to Mr. Robert H. Craven, Sr., Mr. Robert H. Craven, Jr., Dr. Sylvia Fields, Ms. Linda Weinerman, Ms. Jessie Raymond, and Mr. Herbert Powell of F.A. Davis for their patience and encouragement. I am indebted to the American Association of Electromyography and Electrodiagnosis and its Nomenclature Committee, who granted permission to reprint the AAEE Glossary of Terms in Clinical Electromyography (1987) as Appendix 4.

The work turned into a family project of sorts over the past several years. Our three sons, five years older and perhaps wiser, if not quieter, could now assist in substance by typing the book, cover to cover, into a word processor to facilitate rewriting. I acknowledge the yeomans' service by honoring their request again to dedicate the book to their mother, who, I know, has funded the teenagers' operation from time to time to boost their spirit of devotion. We lost her father and mine during the preparation of the first edition and my mother in this interim. I salute them for their constant support of our venture abroad, with the credit given to whom it is most justifiably due.

J. K.

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, M.D.

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. Mennen, 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

Part I

BASICS OF ELECTRODIAGNOSIS

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Chapter 1

ANATOMIC BASIS FOR LOCALIZATION

1 INTRODUCTION

Electrodiagnosis, as an extension of the neurologic examination, employs the same anatomic principles of localization, searching for evidence of motor and sensory compromise (Fig. 1–1). Neurophysiologic studies supplement the clinical examination by providing additional precision, detail, and objectivity. They delineate a variety of pathological changes that may otherwise escape detection, and they help examine atrophic, deeply situated, or paretic muscles, which tend to defy clinical evaluation. Specialized techniques provide means to test the neuromuscular junction per se, even though it is an integral part of the motor system. Electrical studies also allow quantitative assessment of reflex amplitude and latencies as well as complex motor phenomena.

Individual methods can be used to explore different groups of overlapping neural circuits. Meaningful analysis of electrophysiologic findings, therefore, demands an adequate knowledge of neuroanatomy. In addition, an electromyographer must learn superficial anatomy of skeletal muscles and peripheral nerves as a prerequisite for accurate placement of the recording and stimulating electrodes. The first part of this chapter contains a review of peripheral neuroanatomy important for the performance and interpretation of electrodiagnostic studies. A concise summary of clinically useful information serves as a framework for the rest of the text.

Despite the recognized importance of understanding muscle and nerve anatomy,

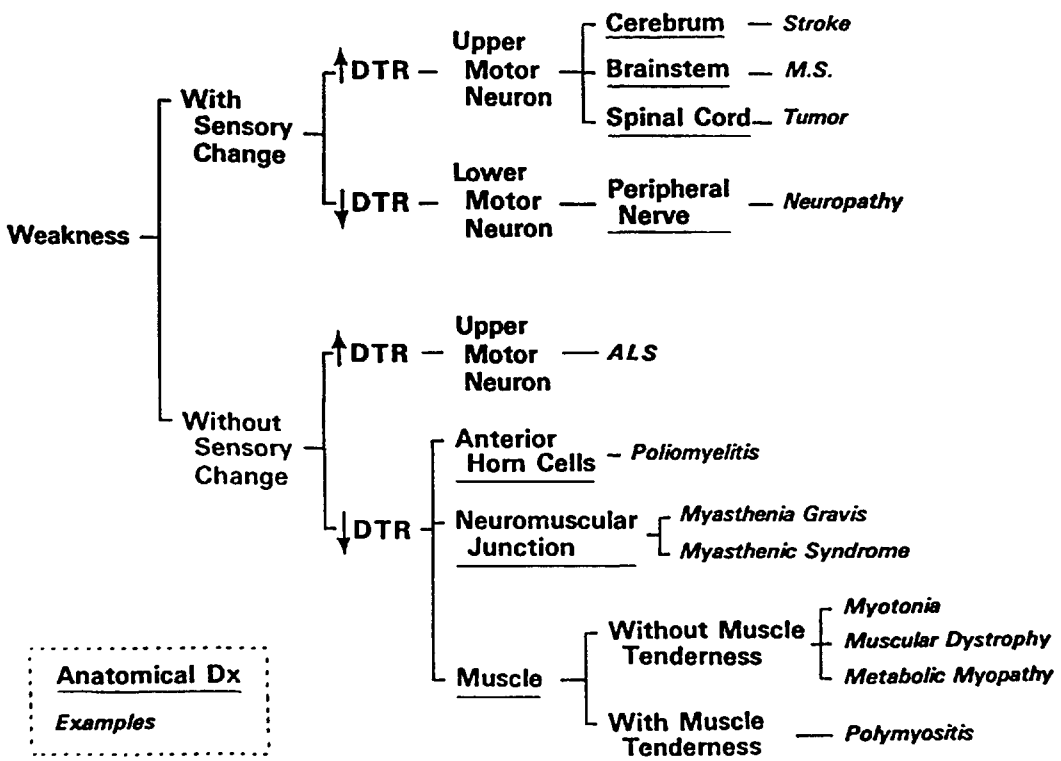


Figure 1–1. Simplified diagram illustrating the differential diagnosis of weakness, with major divisions into those with or without sensory abnormalities. Patients having sensory symptoms must show involvement of the nervous system rather than of muscle or neuromuscular junction. Disease of upper motor neurons characteristically shows increased stretch reflexes, while disease of the lower motor neurons is characterized by decreased stretch reflexes. Patients without sensory disturbances may still have nervous system disease, especially if the weakness is associated with hyperreflexia, as in amyotrophic lateral sclerosis. Most patients, however, exhibit hyporeflexia, as seen in anterior horn cell lesions, diseases of the neuromuscular junction, or primary muscle disorders (see Chapters 23 through 29).

written descriptions render the subject complicated and rather dry. The use of schematic illustrations in this chapter simplifies the discussion to compensate for this inherent problem. Existing texts provide more detailed accounts in regard to the superficial anatomy of skeletal muscles[6,7,10,14] or to the general peripheral neuromuscular anatomy.[1–3,9,13]

2 CRANIAL NERVES

Of the 12 cranial nerves, nine innervate voluntary muscles, as summarized in Table 1–1. The oculomotor, trochlear, and abducens nerves control the movement of the eyes. The trigeminal nerve innervates the muscles of mastication; the facial

Table 1–1 Muscles Innervated by the Cranial Nerves and Cervical Plexus

Nerve	Mesencephalon	Pons	Medulla	C-2	C-3	C-4
Oculomotor	Levator palpebrae Superior rectus Medial rectus Inferior rectus Inferior oblique					
Trochlear	Superior oblique					
Trigeminal	Masseter Temporalis Pterygoid					
Abducens		Lateral rectus				
Facial		Frontalis Orbicularis oculi Orbicularis oris Platysma Digastric & stylohyoid muscles				
Glosso-pharyngeal			Laryngeal muscles			
Vagus			Laryngeal muscles			
Accessory (cranial root)			Laryngeal muscles			
Hypoglossal			Tongue			
Accessory (spinal root)				Sternocleidomastoid	Trapezius Upper Middle	
Cervical plexus					Trapezius Lower	
Phrenic					Diaphragm	

nerve, the muscles of facial expression. The laryngeal muscles receive innervation from the glossopharyngeal and vagal nerves and the cranial root of the accessory nerve. The hypoglossal nerve supplies 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 an electromyographic laboratory include the facial, trigeminal, and accessory nerves.

Facial Nerve

The course of the facial nerve, from the nucleus to the distal trunk, consists of four arbitrarily subdivided segments (Fig. 1–2). The central component, referred to as the intrapontine portion, initially courses posteriorly to loop around the sixth nerve nucleus. Its elongated course 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. Acoustic neuromas or other cerebellopontine angle masses may compress the nerve in this area. After traversing the subarachnoid space, the facial nerve enters the internal auditory meatus. Here it begins the longest and most complex intraosseous course of any nerve in the body. Within this segment lies the presumed site of lesion in Bell's palsy. Upon exiting from the skull through the stylomastoid foramen, the facial nerve penetrates the superficial and deep lobes of the parotid gland. It then branches with some variation into five distal segments (Fig. 1–3).

Trigeminal Nerve

The trigeminal nerve subserves all superficial sensation to the face and buccal and

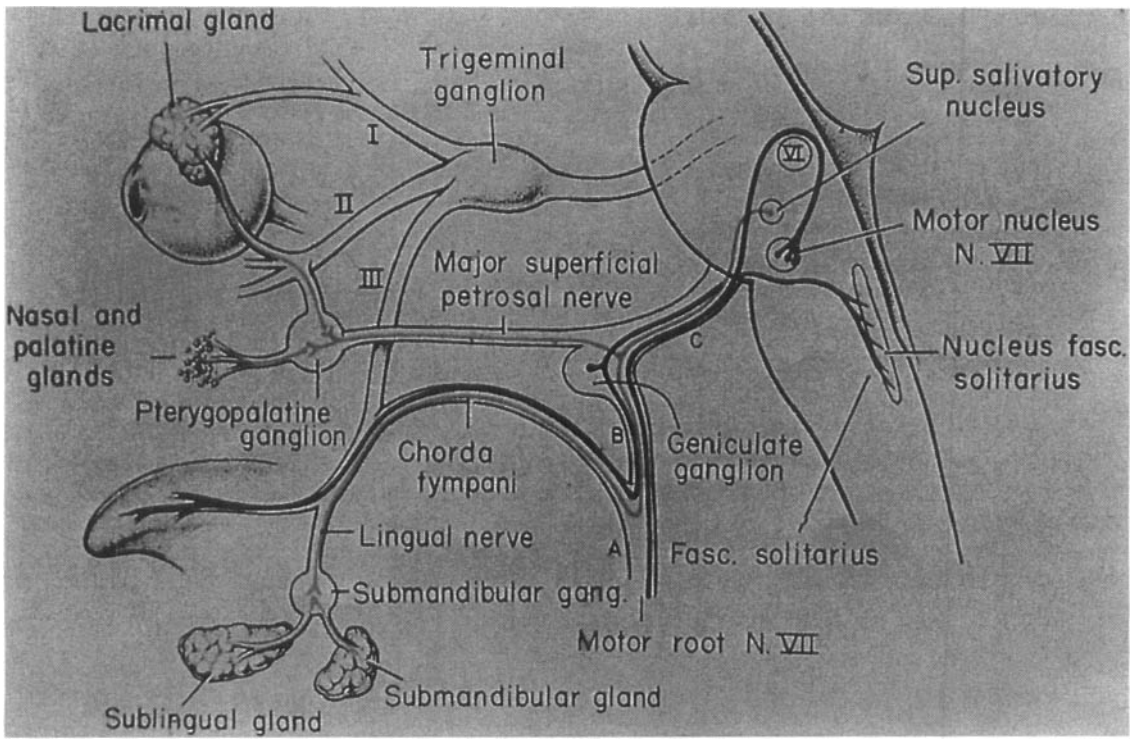


Figure 1–2. Functional components of the facial nerve and the three major divisions of the trigeminal nerve. The facial nerve (N, VII), consists of the portion at the stylomastoid foramen (*A*), middle segment distal to the geniculate ganglion (*B*), and a more proximal segment that includes extrapontine and intrapontine pathways (*C*). [From Carpenter,[3] with permission.]

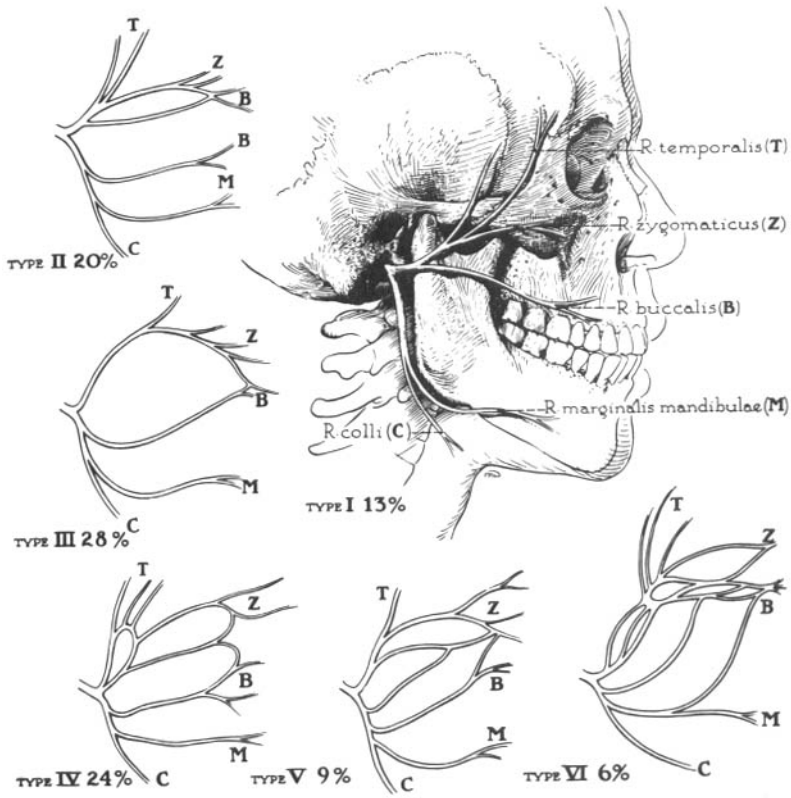


Figure 1–3. Major types of facial nerve branching and intercommunication with percentage occurrence of each pattern in 350 recordings. [From Anson,[1] with permission.]

nasal mucosa. It also supplies the muscles of mastication, which consist of the masseters, temporalis, and pterygoids. The ophthalmic and maxillary divisions of the trigeminal nerve supply sensation to the upper and middle parts of the face, whereas the mandibular division carries the sensory fibers to the lower portion of the face as well as the motor fibers (see 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 subserving 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 afferent fibers, subserving proprioception from the muscles of mastication, have their cell bodies in the mesencephalic nucleus. They make monosynaptic connection with the motor nucleus of the trigeminal nerve located in the midpons, medial to the main sensory nucleus. This pathway provides the anatomic substrate for the masseter reflex. The first component of the blink reflex probably follows a disynaptic connection from the main sensory nucleus to the ipsilateral facial nucleus. The pathway for the second component, relayed through polysynaptic connections, include the ipsilateral spinal nucleus and the facial nuclei on both sides (see Fig. 17–1).

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

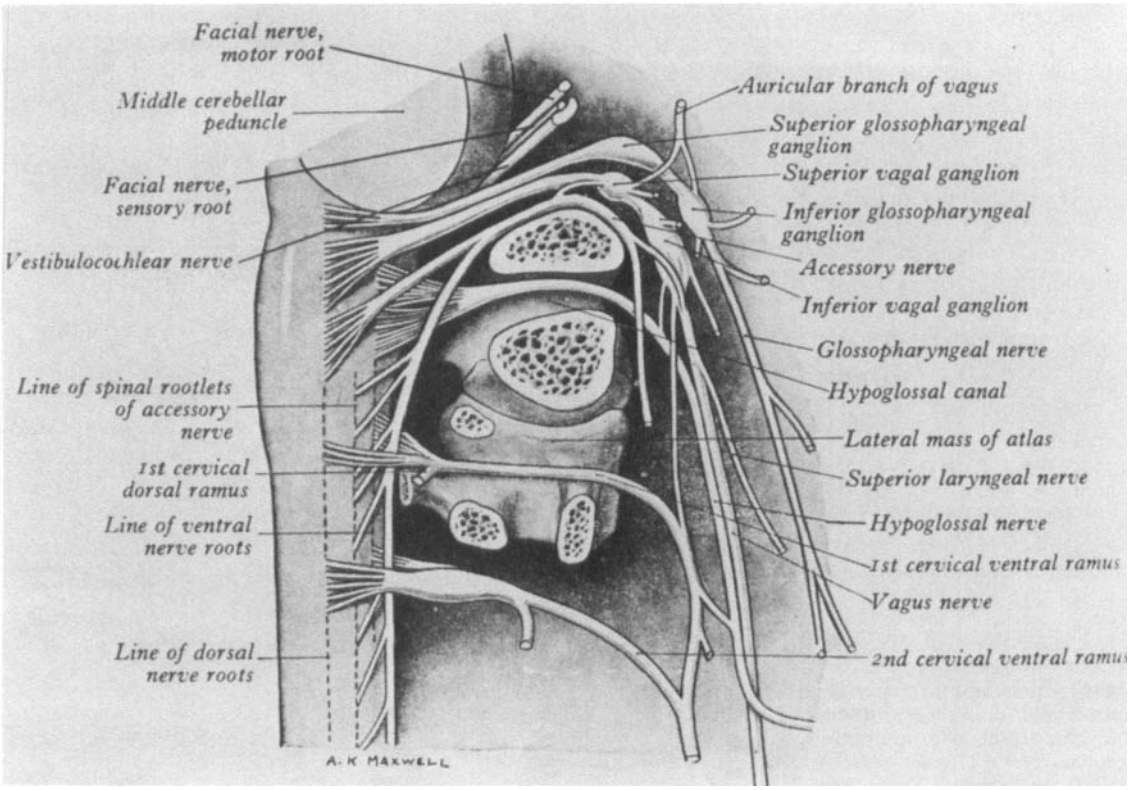


Figure 1–4. Communication between the last four cranial nerves on the right side viewed from the dorsolateral aspect. Note the division of the accessory nerve into the cranial accessory nerve, which joins the vagal nerve, and the spinal accessory nerve, which supplies the trapezius and sternocleidomastoid muscles. [From Williams and Warwick,[15] with permission.]

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 leave by 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 although their motor contribution is minimal.[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 affect it only in part, causing partial paralysis of the muscle groups innervated by this nerve. This central dissociation could mimic a peripheral lesion affecting individual branches.

3 ANTERIOR AND POSTERIOR RAMI

The anterior and posterior roots, each composed of several rootlets, emerge from the spinal cord carrying motor and sensory fibers, respectively (Fig. 1–7). They join to form the spinal nerve that exits from the spinal canal through the respective intervertebral foramina. A small ganglion, containing the cell bodies of sensory fibers, lies on each posterior root in the intervertebral foramina just proximal to its union with the anterior root but distal to the cessation of the dural sleeve. There are 31 spinal nerves on each side: 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.

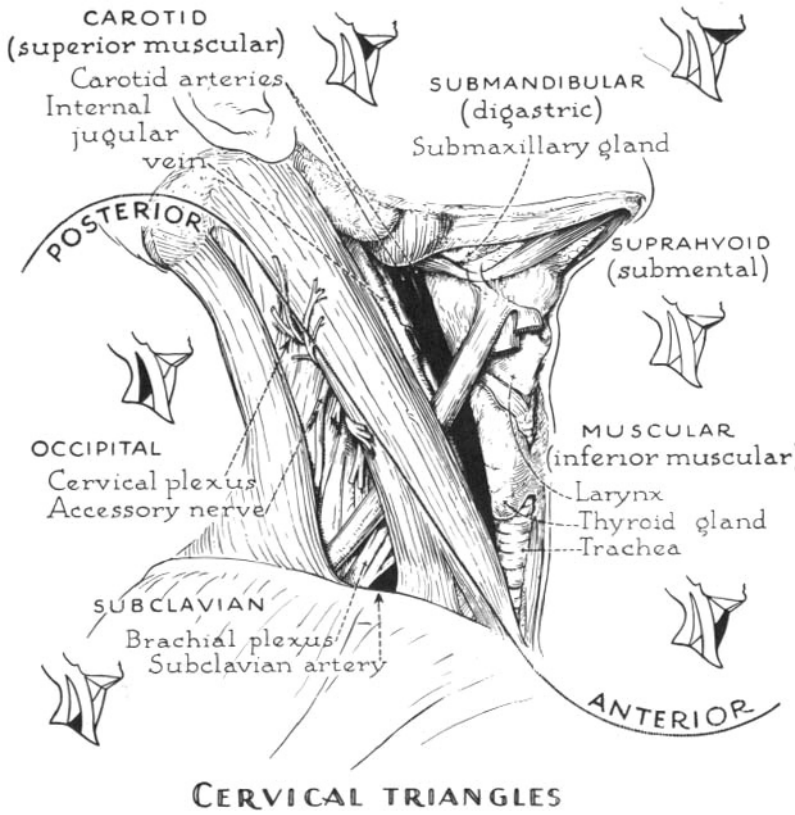


Figure 1–5. The sternocleidomastoid divides the field bounded by the trapezius, mandible, midline of neck, and clavicle into anterior and posterior triangles. The obliquely coursing omohyoid further subdivides the posterior triangle into occipital and subclavian triangles. The contents of the occipital 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 percutaneous stimulation. [From Anson,[1] with permission.]

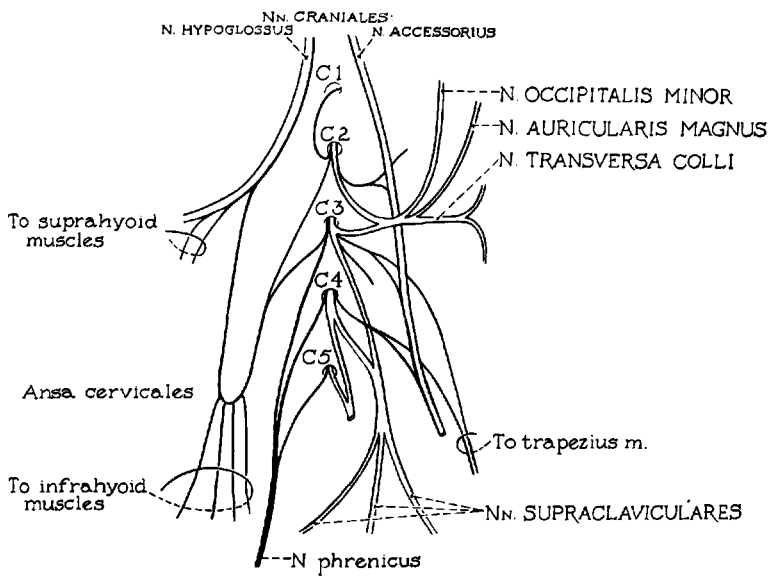


Figure 1–6. Anterior rami of the cervical spinal nerves, forming the cervical plexus. Note the phrenic nerve supplying the diaphragm, and the branches from C2, C3, and C4 roots and the accessory nerve, both innervating the trapezius. [From Anson,[1] with permission.]

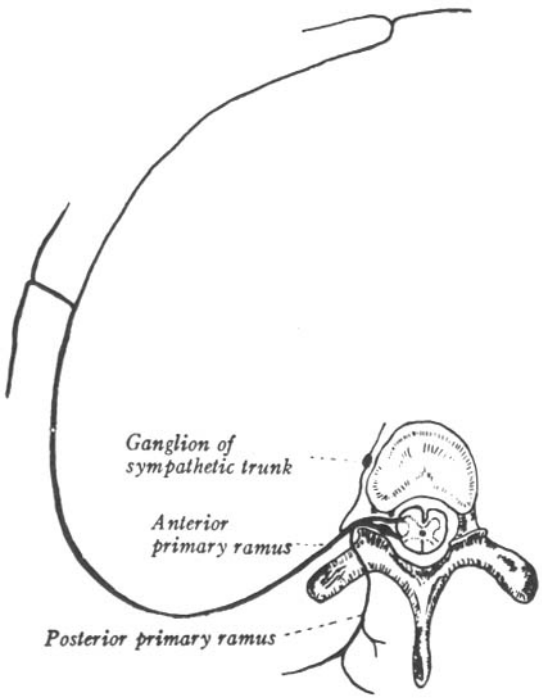


Figure 1–7. Ventral and dorsal roots forming the spinal nerve, which divides into the anterior and posterior rami. The sensory ganglion of the dorsal root lies within the respective intervertebral foramen. [From Ranson and Clark,[12] with permission.]

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, respectively. 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 supply 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 peripheral nerve. 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. Futhermore, spontaneous discharges appear in the denervated muscles only two to three weeks after nerve injury. 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 (Fig. 1–6). 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. 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 root, trunk, cord, and peripheral nerve (Fig. 1–8). Two nerves originate directly from the roots 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 roots then combine to give rise to three trunks. The union of C5 and

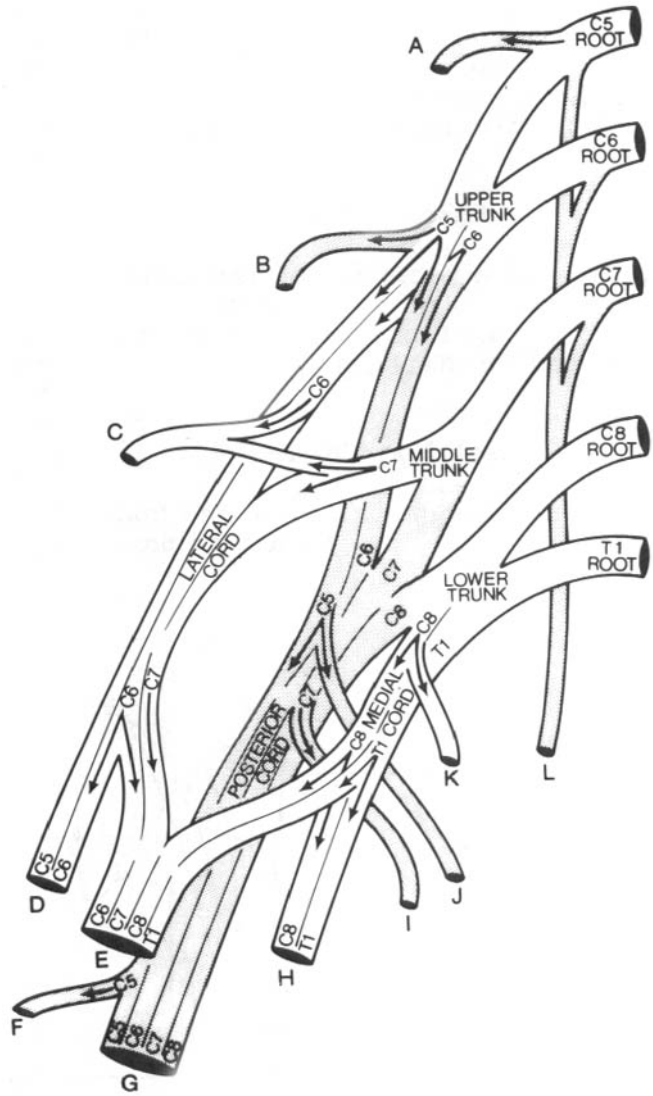


Figure 1–8. Anatomy of the brachial plexus with eventual destination of all root components. The brachial plexus gives rise to (*A*) dorsal scapular, (*B*) suprascapular, (*C*) lateral pectoral, (*D*) musculocutaneous and its sensory branch, (*E*) lateral antebrachial cutaneous, (*F*) median, (*G*) axillary, (*H*) radial, (*I*) ulnar, (*J*) medial antebrachial cutaneous, (*K*) thoracoorsal, (*L*) subscapular, (*M*) medial pectoral, and (*N*) long thoracic nerves. In addition, the radial nerve gives off the posterior antebrachial cutaneous nerve (not shown) at the level of the spiral groove. [Modified from Patten,[9] with permission.]

C6 forms the upper trunk, and that of C8 and T1, the lower trunk, whereas the C7 root alone continues as the middle trunk. Each of the three trunks gives off anterior and posterior divisions. The posterior cord, formed by 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 form the lateral cord, which gives rise to the musculocutaneous nerve and its sensory branch, lateral antebrachial cutaneous nerve, and the outer branch of the median nerve. The anterior division of the lower trunk, forming the medial cord, 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; those below, the cords. A more distal lesion involves 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 and C4 roots and innervates the ipsilateral hemidiaphragm (Table 1–1).

Dorsal Scapular Nerve

The dorsal scapular nerve, derived from C4 and C5 roots 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 a single root (C5) in contrast to the other shoulder girdle muscles supplied by multiple roots.

Suprascapular Nerve

The suprascapular nerve arises from C5 and C6 roots 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).

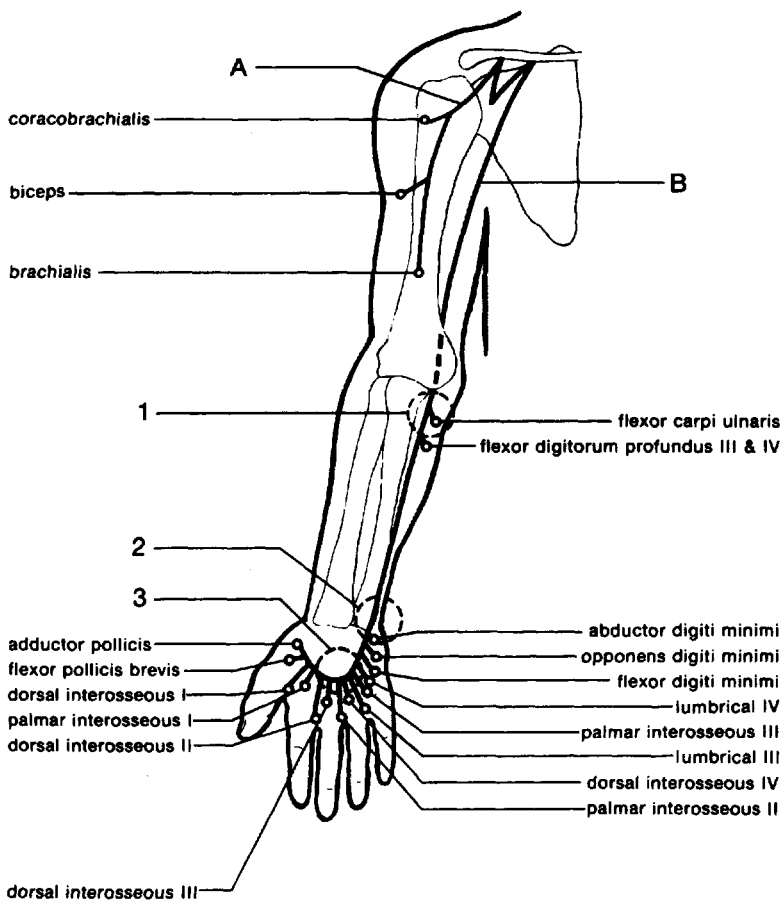


Figure 1–9. Musculocutaneous nerve (*A*) and ulnar nerve (*B*), and the muscles they supply. The common sites of lesion include ulnar groove and cubital tunnel (*1*), Guyon's canal (*2*), and midpalm (*3*). [Modified from The Guarantors of Brain: Aids to the Examination of the Peripheral Nervous System.[7]]

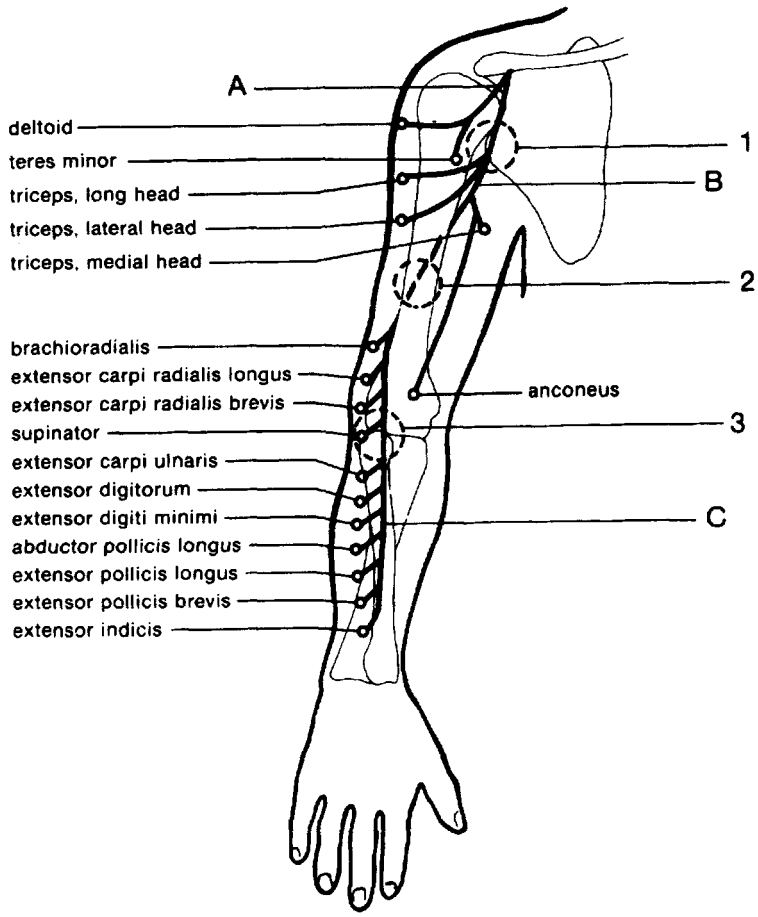


Figure 1–10. Axillary nerve (*A*) and radial nerve (*B*) with its main terminal branch, the posterior interosseous nerve (*C*), and the muscles they supply. The nerve injury may occur at the axilla (*1*), spiral groove (*2*), or elbow (*3*), as in the posterior interosseous nerve syndrome. [Modified from The Guarantors of Brain: Aids to the Examination of the Peripheral Nervous System.[7]]

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 roots, 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, supplies the skin over the lateral aspect of the forearm.

Axillary Nerve

The axillary nerve, originating from C5 and C6 roots, arises from the posterior cord as the last branch of the brachial plexus. It supplies the deltoid and teres minor, and a small area of the skin over the lateral aspect of the arm (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) giving 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 interosseous nerve, and a sensory branch, which surfaces in the distal third of the forearm. The muscle branch innervates the supinator, the abductor pollicis longus, and all the extensor muscles in the forearm: extensor carpi radialis longus and brevis, extensor carpi ulnaris, extensor digitorum communis, extensor digiti minimi, extensor pollicis longus and brevis, and extensor indicis. The sensory fibers, originating from the C6 and C7 roots, pass through the upper and middle trunks and the posterior cord, branching off the main truck about 10 cm above the wrist as the superficial radial nerve, which supplies the skin over the lateral aspect of the dorsum of the hand.

Median Nerve

The median nerve arises from the lateral and medial cords of the brachial plexus as a mixed nerve derived from the C6 and T1 roots (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, the index and middle fingers, and half of the ring finger. The sensory fibers of the index and middle fingers enter the C7 root through the lateral cord and middle trunk, whereas the skin of the thumb receives fibers mainly from C6, with some contribution from the C7 root, through the lateral cord and upper or mid-

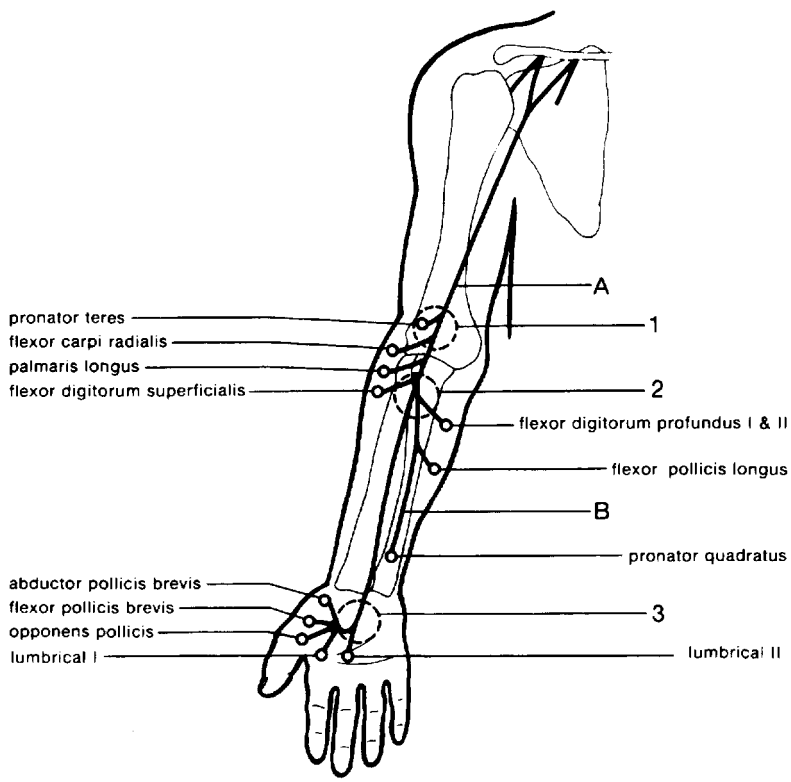


Figure 1–11. Median nerve (*A*) with its branch, the anterior interosseous nerve (*B*), and the muscles they supply. The nerve may undergo compression at the elbow between the two heads of pronator teres (*1*), or slightly distally (*2*), as in the anterior interosseous syndrome, or at the palm (*3*),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

dle 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 interosseous 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 innervate 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 the C8 and T1 roots (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, and 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 (see Chapter 26–6). The superficial branch supplies the palmaris brevis and the skin distally from the wrist over the medial aspect of the hand, including the hypothenar eminence, the fifth digit, and half of the fourth digit. The deep muscle branch first innervates the hypothenar muscles, that is, 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 three volar and four dorsal interossei, and lumbricals III and IV.

General Rules and Anomalies

Table 1–2 summarizes the pattern of nerve supply in the upper limbs. One cannot memorize the exact innervation for all the individual muscles, but learning certain rules helps broadly categorize muscles. The radial nerve innervates the brachioradialis, triceps, and with its main terminal branch, the posterior interosseous 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 the neutral or half-pronated position. The nerve subserves all the extensors of the upper limb except for the four lumbricals, which, supplied by median and ulnar nerves, extend the digits at the interpharangeal joints. The median nerve supplies most flexors in the forearm, 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. With the exception of the flexor carpi ulnaris and the flexor digitorum profundus III and IV, the ulnar nerve supplies only intrinsic hand muscles, including all the interossei.

The most common anomaly of innervation in the upper limb results from the presence of a communicating branch from the median to the ulnar nerve in the forearm. The fibers involved in this crossover, called the Martin-Gruber anastomosis, usually supply 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 median nerve and then reunites with

Table 1–2 Innervation of Shoulder Girdle and Upper Limb Muscles

Nerve	C-4	C-5	C-6	C-7	C-8	T-1
Dorsal scapular	Levator scapulae	Rhomboideus major & minor				
Supra-scapular		Supraspinatus Infraspinatus				
Axillary		Teres minor Deltoid Anterior Middle Posterior				
Subscapular		Teres major				
Musculo-cutaneous		Brachialis Biceps brachii		Coraco-brachialis		
Long thoracic		Serratus anterior				
Anterior thoracic		Pectoralis major (clavicular part)	Pectoralis major (sternocostal part) Pectoralis minor			
Thoracodorsal			Latissimus dorsi			
Radial nerve		Brachioradialis Extensor carpi radialis longus & brevis		Triceps—long, lateral & medial heads Anconeus		
Posterior interosseous nerve			Supinator	Extensor carpi ulnaris Extensor digitorum Extensor digiti minimi Abductor pollicis longus Extensor pollicis longus Extensor pollicis brevis Extensor indicis		

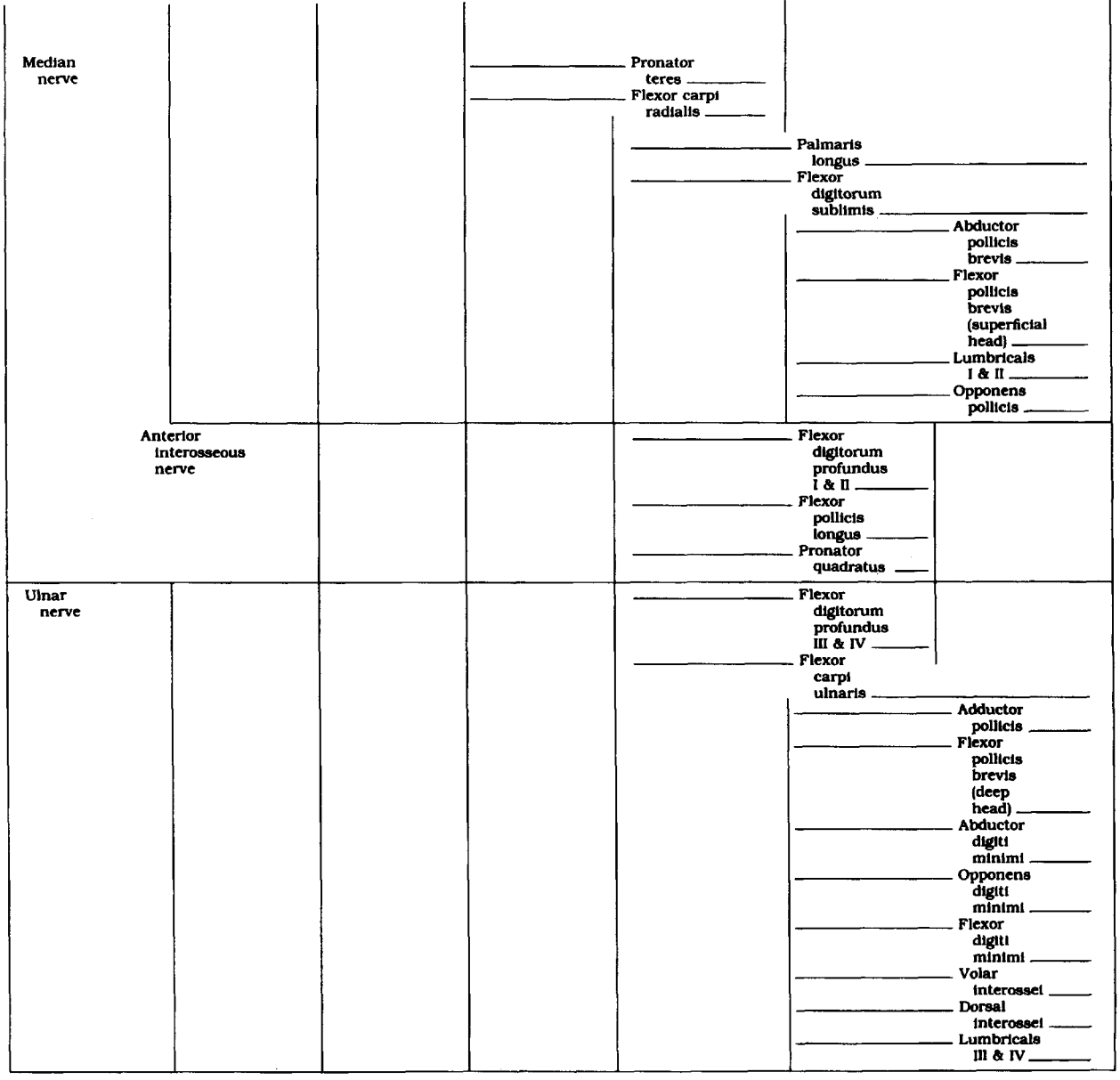
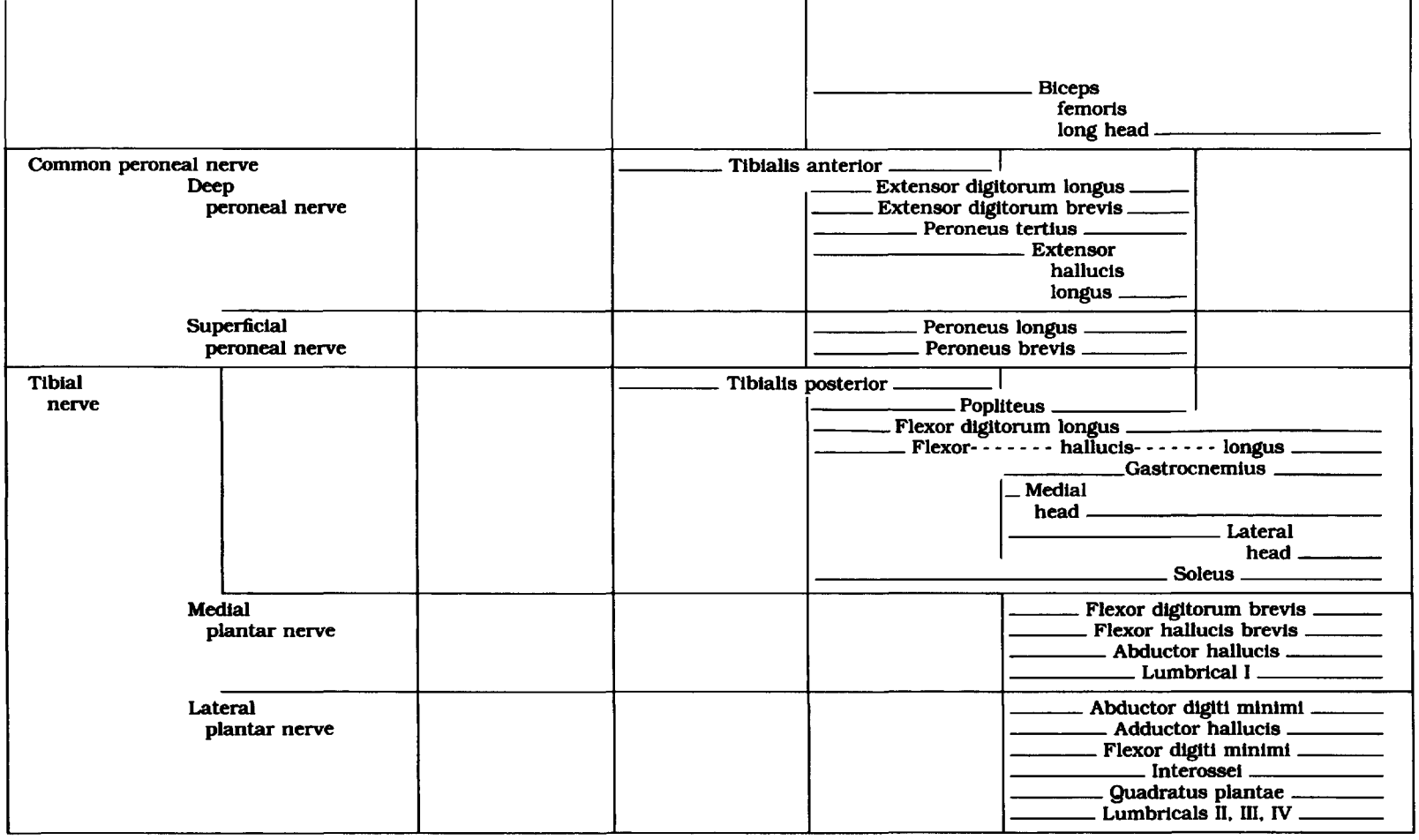

Median nerve
Pronator teres
Flexor carpi radialis
Palmaris longus
Flexor digitorum sublimis
Abductor pollicis brevis
Flexor pollicis brevis (superficial head)
Lumbricals I & II
Opponens pollicis
Anterior interosseous nerve
Flexor digitorum profundus I & II
Flexor pollicis longus
Pronator quadratus
Ulnar nerve
Flexor digitorum profundus III & IV
Flexor carpi ulnaris
Adductor pollicis
Flexor pollicis brevis (deep head)
Abductor digiti minimi
Opponens digiti minimi
Flexor digiti minimi
Volar interossei
Dorsal interossei
Lumbricals III & IV

Table 1–3 Innervation of Pelvic Girdle and Lower Limb Muscles

Nerve	L-2	L-3	L-4	L-5	S-1	S-2
Femoral nerve	Iliopsoas Pectineus Sartorius Vastus Rectus femoris Vastus lateralis Vastus medialis		Sartorius intermedius			
Obturator nerve	Gracilis Adductor longus & brevis Adductor magnus Obturator externus					
Superior gluteal nerve			Gluteus medius Gluteus minimus Tensor fasciae latae			
Inferior gluteal nerve				Gluteus maximus		
Sacral plexus			Obturator internus Superior & inferior gemelli Quadratus femoris		Piriformis	
Sciatic nerve trunk — Peroneal division				Biceps femoris short head		
Sciatic nerve trunk — Tibial division				Semitendinosus Semimembranosus		


Biceps femoris long head
Common peroneal nerve
Deep peroneal nerve
Tibialis anterior
Extensor digitorum longus
Extensor digitorum brevis
Peroneus tertius
Extensor hallucis longus
Superficial peroneal nerve
Peroneus longus
Peroneus brevis
Tibial nerve
Tibialis posterior
Popliteus
Flexor digitorum longus
Flexor hallucis longus
Gastrocnemius
Medial head
Lateral head
Soleus
Medial plantar nerve
Flexor digitorum brevis
Flexor hallucis brevis
Abductor hallucis
Lumbrical I
Lateral plantar nerve
Abductor digiti minimi
Adductor hallucis
Flexor digiti minimi
Interossei
Quadratus plantae
Lumbricals II, III, IV

the ulnar nerve proper in the distal forearm. Other anomalies reported in the literature include 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. These extremely rare patterns stand in contrast to the high incidence of the median-to-ulnar anastomosis. Failure to recognize an anomaly leads to misinterpretation in clinical electrophysiology as a common source of error (see Chapter 7–4).

6 LUMBAR PLEXUS AND ITS PRINCIPAL NERVES

The spinal cord ends at the level of the L1 to L2 intervertebral space as the preconus, which consists of the L5 and S1 cord segments, and the conus medullaris, which contains the S2 through S5 levels. 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. 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 roots, unite to form the lumbar plexus within the psoas major muscle (Figs. 1–12 through 1–14). The iliohypogastric and ilioinguinal nerves arise from the L1 root and supply the skin of the hypogastric region and medial thigh, respectively. The genitofemoral nerve, derived from the L1 and L2 roots, innervates the cremasteric muscle and the skin of the scrotum or labia major. The lateral femoral cutaneous nerve originates from the L2 and L3 roots. It leaves the psoas muscle laterally to supply the lateral and anterior thigh. The anterior divisions of the L2 through L4 anterior rami join to form the obturator nerve, which exits the psoas muscle medially to innervate the adductor muscles of the thigh. The posterior divisions of the same rami give rise to the femoral

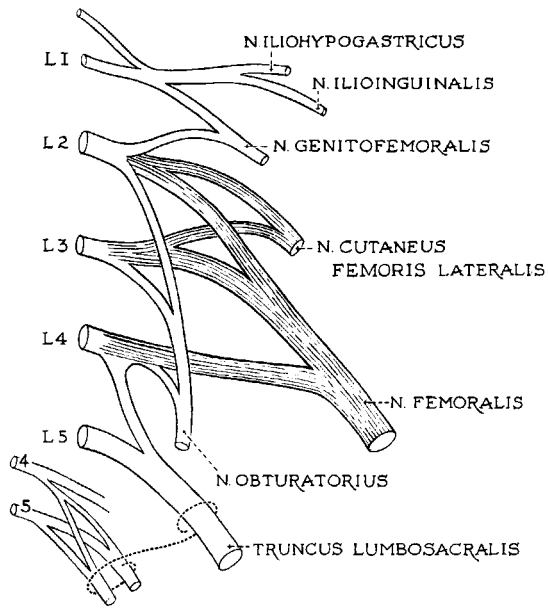


Figure 1–12. Anterior rami of the lumbar spinal nerve forming the lumbar plexus, with the major nerves derived from this plexus. The *shaded portion* indicates the dorsal divisions. [From Anson,[1] with permission.]

nerve, which leaves the psoas muscle laterally. It then descends under the iliacus fascia to reach the femoral triangle beneath the inguinal ligament. Though primarily a muscle nerve, it also gives off sensory branches—the intermediate and medial cutaneous nerves, and the saphenous nerve.

Iliohypogastric Nerve

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

Ilioinguinal Nerve

The ilioinguinal nerve, arising from the L1 and L2 roots, supplies the skin over the upper and medial part of the thigh, the root of the penis, and the 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

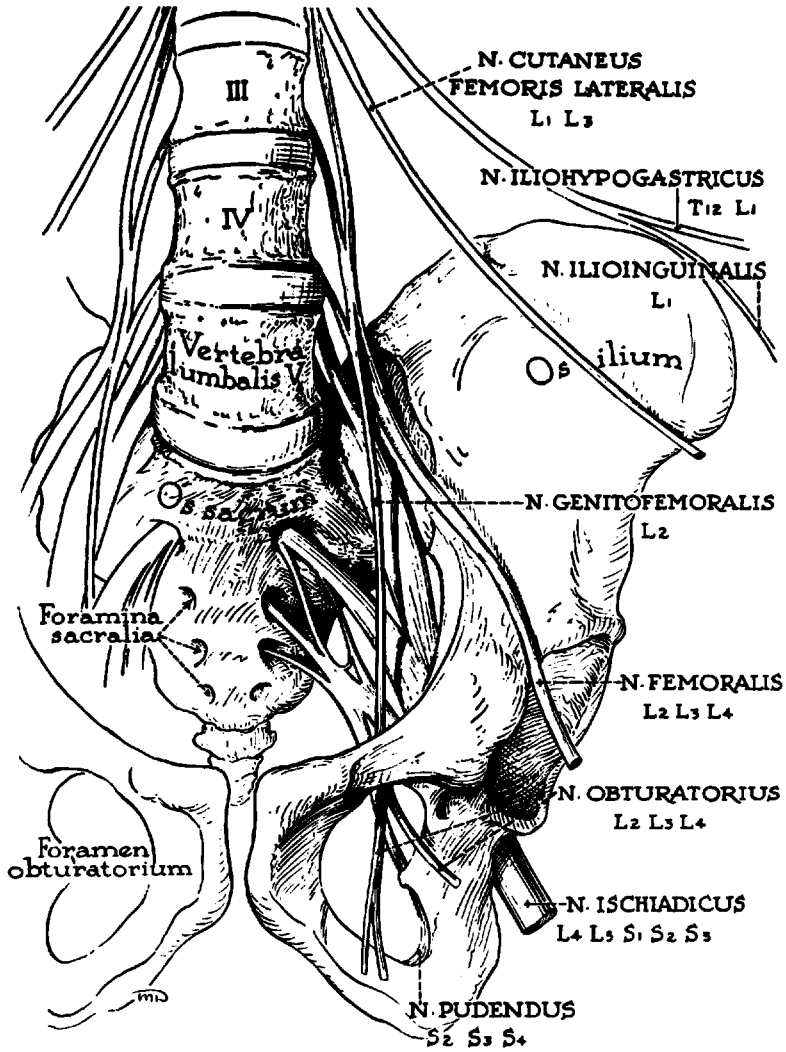


Figure 1–13. Lumbosacral plexus and the courses of the femoral, obturator, and sciatic nerves. [From Anson,[1] with permission.]

the inner side of the trunk to the medial anterior iliac spine.

Genitofemoral Nerve

The genitofemoral nerve, arising from the L1 and L2 roots, 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 the skin of the inner aspect of the upper thigh, scrotum, or labium.

Lateral Femoral Cutaneous Nerve

The lateral femoral cutaneous nerve, the first sensory branch of the lumbar plexus, receives fibers from the L2 and L3 roots. 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 tun-

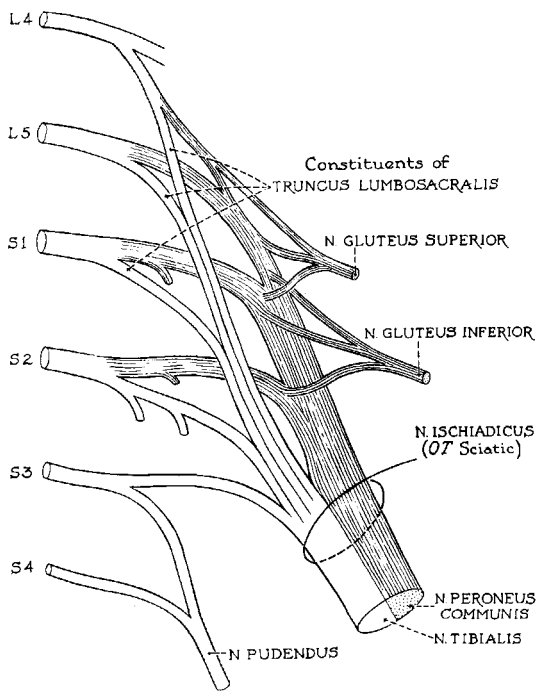


Figure 1–14. Anterior rami of the lumbosacral spinal nerve forming the sacral plexus with the major nerves derived from this plexus. The *shaded portion* indicates the dorsal divisions. [From Anson,[1] with permission.]

nel, 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 anterior rami of the L2 through L4 roots (Fig. 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. Of the muscles innervated by this nerve, the iliopsoas flexes the hip at the thigh, 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 maximum innervation through the L3 and L4 roots[11] 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. The nerve gives off the infrapatellar branch at the lower thigh, which 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.

Obturator Nerve

The obturator nerve arises from the anterior divisions of the L2 through L4 roots (Fig. 1–15). Formed within the psoas muscle, it enters the pelvis immediately anterior to the sacroiliac joint. As it passes through the obturator canal, the obturator nerve gives off an anterior branch, which supplies the adductor longus and brevis and the gracilis, and a posterior branch, which 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 the L5, S1, and S2 roots in front of the sacroiliac joint (Figs. 1–13 and 1–14). Designation as the

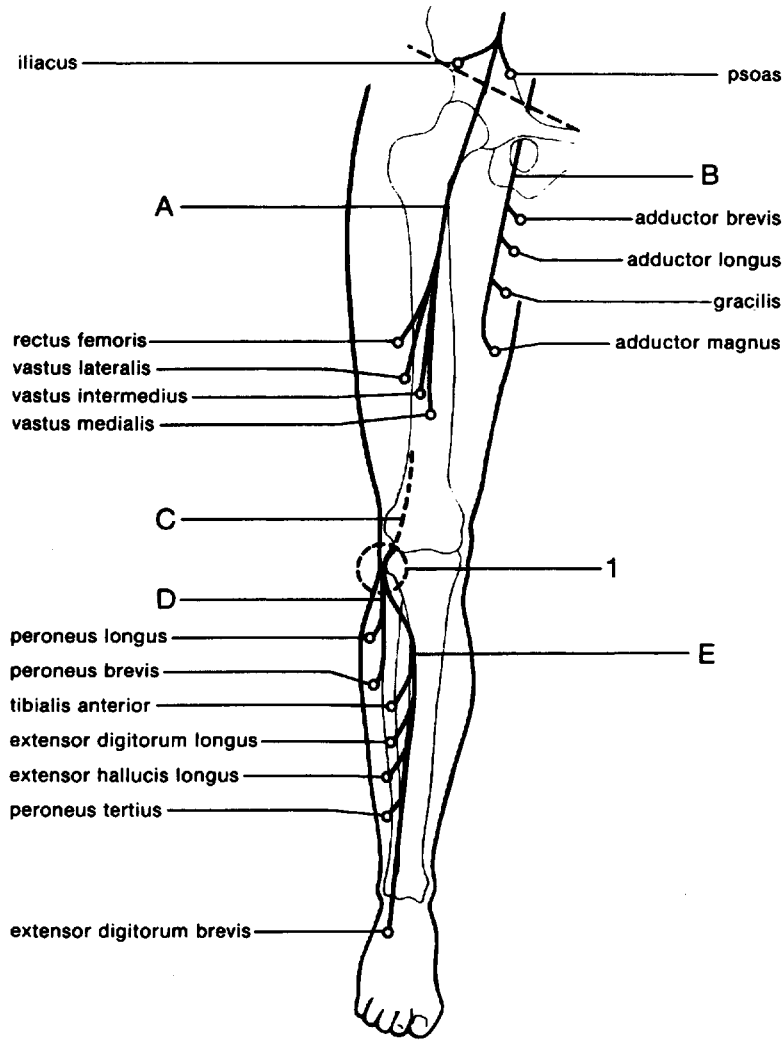


Figure 1–15. Femoral nerve (*A*), obturator nerve (*B*), and common peroneal nerve (*C*) branching into superficial (*D*) and deep peroneal nerve (*E*) and the muscles they supply. The compression of the peroneal nerve commonly occurs at the fibular head (*1*). [Modified from The Guarantors of Brain: Aids to the Examination of the Peripheral Nervous System.[7]]

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

Superior and Inferior Gluteal Nerves

The superior gluteal nerve, derived from the L4 through S1 roots, innervates the gluteus medius and minimus, and the tensor fascia lata, which together abduct and rotate the thigh internally. The inferior gluteal nerve, arising from the L5 through S2 roots, innervates the gluteus maximus, which extends, abducts, and externally rotates the thigh.

Sciatic Nerve

The union of all of the L4 to S2 roots gives rise to the sciatic nerve, which leaves the pelvis through the greater sciatic foramen (Fig. 1–16). The nerve consists of a peroneal portion derived from the posterior division of the anterior rami, and a tibial portion composed of the anterior divisions. The peroneal and tibial components eventually separate 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, which consist of the long head of the biceps femoris, semitendinosus, and semimembranosus. The peroneal component supplies the short head of the biceps femoris, which, if affected in patients with foot drop, implies a lesion above the knee. The adductor magnus, primarily supplied by the obturator nerve, also receives partial innervation from the sciatic trunk.

Tibial Nerve

The tibial nerve arises as an extension of the medial popliteal nerve that bifurcates 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. This bi-

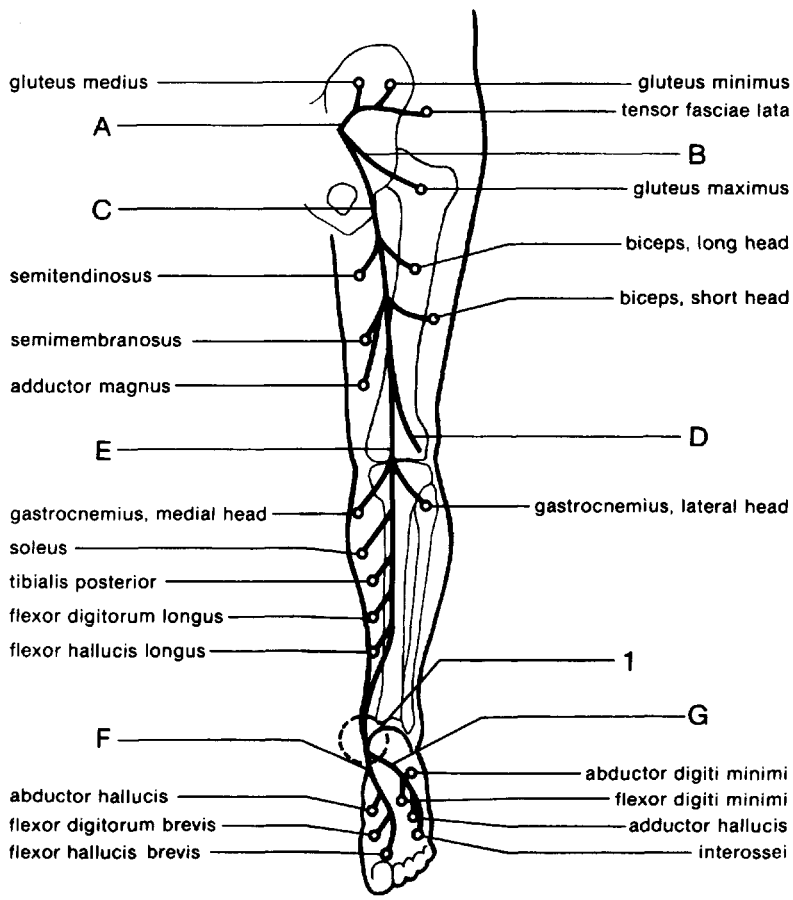


Figure 1–16. Superior gluteal nerve (*A*), inferior gluteal nerve (*B*), and sciatic nerve trunk (*C*), and the muscles they supply. The sciatic nerve bifurcates to form the common peroneal nerve (*D*) and the tibial nerve (*E*). The tibial nerve in turn gives rise to the medial (*F*) and lateral plantar nerve (*G*). The 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]]

furcation occurs within one centimeter of the malleolar-calcaneal axis in 90 percent of feet.[4]

The medial plantar artery, which accompanies the medial plantar nerve, serves as the landmark to locate the nerve just below the medial malleolus. The muscle branches innervate the abductor hallucis, flexor digitorum brevis, and flexor hallucis brevis. The sensory fibers of the medial plantar nerve supply the medial anterior two thirds of the sole and the plantar skin of the first three toes and part of the fourth toe. The lateral plantar nerve winds around the heel to the lateral side of the sole to innervate the abductor digiti minimi, flexor digiti minimi, abductor hallucis, and interossei. It supplies the skin over the fifth toe, the lateral half of the fourth toe, and the lateral aspect of the sole.

Common Peroneal Nerve

The common peroneal nerve arises as an extension of the lateral popliteal nerve, which branches off laterally from the sciatic trunk in the politeal fossa (Fig. 1–15). It consists of fibers derived from the L4, L5, and S1 roots. 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 dorsum of the foot and toes.

The deep peroneal nerve innervates the muscles that dorsiflex and evert the foot. These muscles include the tibialis anterior, extensor digitorum longus, extensor hallucis longus, peroneus tertius, and extensor digitorum brevis. 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 (see Chapter 7–4). The deep peroneal nerve also supplies the skin over a small, wedge-shaped area between the first and second toes.

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 fifth toe. It receives maximum innervation from the S1 root, with the remainder coming from the L5 or S2 root,[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 changes. A fascicular biopsy of the sural nerve allows in vitro recording of nerve action potentials (see Chapter 4–4). Therefore, in vivo studies of the sural nerve before such a procedure provide an interesting opportunity to correlate the data directly with in vitro conduction characteristics and the histologic findings of the biopsy speciman.[5]

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Chapter 2

ELECTRICAL PROPERTIES OF NERVE AND MUSCLE

1 INTRODUCTION

The nervous system conveys information by means of action potentials, which, under physiological 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. Electromyography permits analysis of electrical properties in the skeletal muscle at rest and during voluntary contraction. Thus, proper interpretations of electrodiagnostic data in the clinical domain requires an understanding of the electrical properties of nerve and muscle.

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. In contrast to intracellular recording in animal experiments, clinical electrodiagnostic procedures analyze extracellular 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 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, intended merely as a background for forthcoming discussion, covers only the fundamental principles relevant to clinical electrophysiology. Subsequent sections, such as Chapters 7, 8, and 20 further elaborate on these points. Interested readers can find a more detailed account of basic cell physiology in established texts.[4,7,26,27,29,33,34,44,47,62,63]

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,[52] 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 (K^+) and lower concentration of sodium (Na^+) and chloride (Cl^-) ions relative to the extracellular fluid (Table 2–1).

Table 2–1 Compositions of Extracellular and Intracellular Fluids of Mammalian Muscle

	Extracellular (mmol/l)	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	

From Patton,[48] with permission.

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, provides 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 potassium from inside to outside the cell, reflecting the higher concentration inside. This force per mole of potassium, or its chemical work (W_c), increases in proportion to the logarithm of the ratio between internal and external concentration of the cation, $(K^+)_i$ and $(K^+)_o$, according to the equation

$$W_c = RT \log(e) (K^+)_i/(K^+)_o$$

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 (E_k) pulling the positively charged potassium from outside to inside the cell. This force per mole of potassium, or the electrical work (W_e), increases in proportion to the transmembrane voltage E_k, according to the equation

$$We = Z_k \, F \, E_k$$

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

In the steady state, the sum of these two energies, W_c and W_e, must equal zero, as

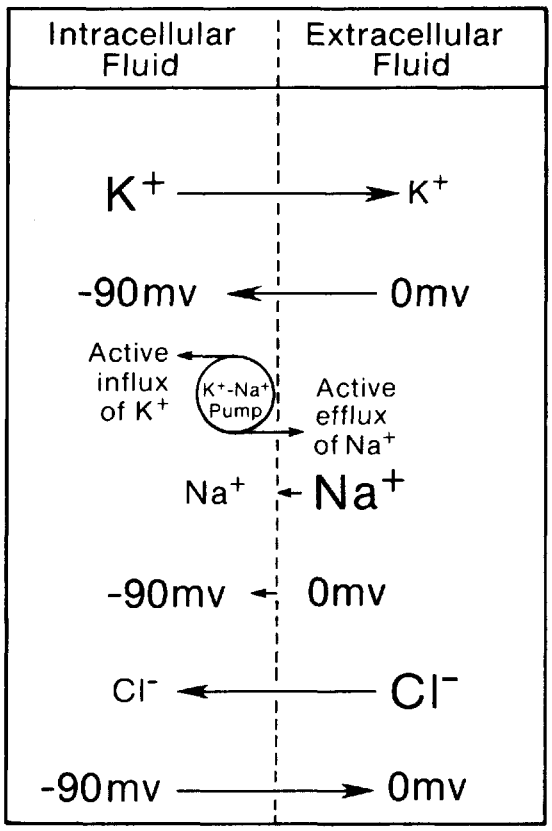

Figure 2–1. Simplified scheme of active and passive fluxes of potassium (K^+), sodium (Na^+), and chloride (Cl^-) in the steady state with driving force on each ion shown by vectors. For potassium, the efflux along the concentration gradient equals the influx caused by the electrical force plus the active influx by the sodium-potassium pump. For sodium, the electrical and chemical gradient produces only a small influx because of membrane resistence. The sum of the two 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, although this diagram illustrates a neutral pump with a ratio of 1:1.

they represent forces with opposite vectors. Therefore,

$$Z_k\ F\ E_k + RT\ \log(e)\ (K^+)_i/(K^+)_o = 0$$

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

$$E_k = -(RT/Z_kF)\ \log(e)\ (K^+)_i/(K^+)_o$$

The same equation applies to calculate the sodium and chloride equilibrium potentials, E_{na} and E_{cl}, as follows:

$$E_{Na} = -(RT/Z_{Na}F)\ \log_e\ (Na^+)_i/(Na^+)_o$$

and

$$E_{Cl} = -(RT/Z_{Cl}F)\ \log_e\ (Cl^-)_o/(Cl^-)_i$$

Table 2–1 shows the values of E_k (−97 mV), E_{na} (+66 mV), and E_{cl} (−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

In the case of potassium, an additional factor, the active transport of potassium by an energy-dependent pump, explains the small discrepancy between E_k(−97 mV) and E_m(−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. Active transport of sodium from inside to outside counters the small amount of sodium that does leak inwards.

This energy-dependent process, known as the potassium-sodium 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 ex-

change averages 3 to 2 in most tissues.[47] Such an imbalanced arrangement, called an electrogenic potassium-sodium pump, directly contributes to the membrane potential, but only minimally compared with changes in membrane permeability.

Goldman-Hodgkin-Katz Equation

The Nernst equation closely predicts membrane potential for highly diffusible chloride and potassium ions. It does not fit well with much less permeable sodium ions, because it ignores 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.

$$E_m = (RT/F) \log_e \frac{P_{Na}(Na^+_o) + P_K(K^+_o) \text{ ----- } + P_{Cl}(Cl^-_i)}{P_{Na}(Na^+_i) + P_K(K^+_i) \text{ ----- } + P_{Cl}(Cl^-_o)}$$

where P_{Na}, P_K, and P_{Cl} represent permeabilities of the respective ions.

According to this equation, the concentration gradient of the most permeable ions dictates the transmembrane potentials. In the resting membrane with very high P_K relative to negligible P_{Na}, the Goldman-Hodgkin-Katz equation would approximate the Nernst equation using the potassium concentration gradients. 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 negligible P_K relative to high P_{Na}. In this situation, 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 below.

3 GENERATION OF 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. If, on the other hand, the membrane potential reaches a critical level with about 15–25 mV of depolarization, from −90 mV to −65 to −75 mV in the case of human muscle cell,[52] the action potential develops in an all-or-none fashion; that is, the same maximal response occurs through a complex energy-dependent process regardless of the kind or magnitude of the stimulus, as described below (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 controls 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 potential, whereas sodium ions remain static. Depolarization to a critical level opens the sodium channels, giving rise to a 500-fold increase in sodium permeability. An externally applied current for nerve stimulation, for example, will depolarize the nerve under the cathode, or negative pole, inducing negativity outside the axon and thus making the inside relatively more positive. When this positivity, or depolarization, reaches a critical level, voltage-dependent sodium channels open, initiating the sequence of events leading to nerve excitation. In short, nerve stimulation accomplishes its objective by opening 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

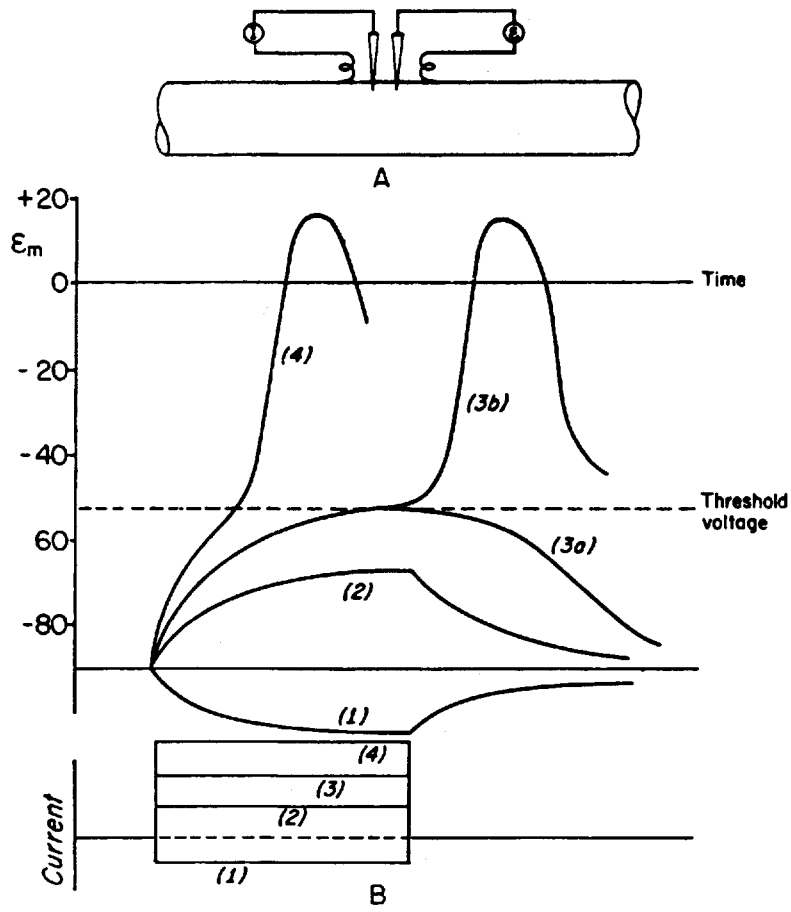

Figure 2–2. Schematic diagram of graded responses after subthreshold stimuli and generation of action potentials after suprathreshold stimuli. The experimental arrangement shows intracellular stimulation (*I*) and recording electrodes (*E*) on *top* (**A**) and polarity, strength, and duration of a constant current on *bottom* (**B**): Hyperpolarizing (*1*) and subthreshold depolarizing current (*2*) induces a 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,[62] with permission.]

of this regenerative sequence, an action potential develops explosively to its full size. The dramatic change in sodium permeability during the course of the action potential 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 generation of an action potential. This shift of intracellularly recorded membrane potential from negative to positive gives rise to negative spike when recorded extracellularly according to the convention in clinical electrophysiology.

In the depolarized membrane, permeability to potassium ions also increases as a result of a molecular change, but only after a delay of about one 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, giving rise to the refractory period (see Chapter 8–2). 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, a transient increase in potassium conductance 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 alters the concentration gradients of these two ions very little.

Although repolarization primarily results from a delayed increase in potassium conductance in squid giant axon,[28] this may not apply to mammalian peripheral or central myelinated axons.[61] Voltage clamp ex-

periments indicate that sodium channels abound at the nodes of Ranvier, where potassium conductance may be minimal or absent in the intact mammalian peripheral myelinated axons[8,9,49] or mammalian dorsal column axons.[40,50] In contrast, potassium channels are distributed 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, allows an increased rate of firing (see Chapter 8–2).

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.[10] In other words, a current enters the cell at the site of depolarization (sink) and passes out to adjacent regions of the polarized membrane (source) (see Fig. 4–3). 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 Chapter 4–3).

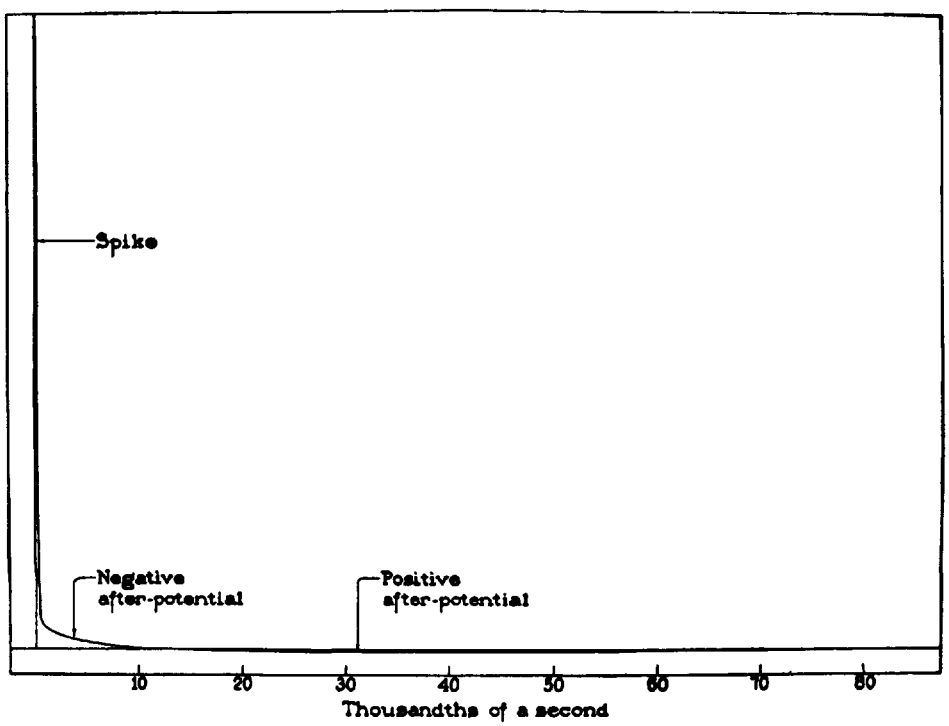

Figure 2–3. Diagrammatic representation of an action potential in A fibers of the cat, with the spike and negative and positive afterpotentials drawn in their correct relative size and true relationships. [From Gasser,[21] with permission.]

Afterpotentials

In an extracellular recording, an action potential consists of an initial negative spike of about one millisecond duration representing the intracellular positive spike of depolarization, and two subsequent afterpotentials, negative, or depolarizing, and positive, or hyperpolarizing (Fig. 2–3). The negative afterpotential, an externally negative deflection grafted onto the declining phase of the negative spike, corresponds to a super-normal period of excitability. This phase results from sustained internodal positivity and the extracellular accumulation of potassium ions associated with the generation of an action potential. The subsequent positive afterpotential, a prolonged externally positive deflection signals a subnormal period of excitability. This phase reflects the elevated potassium conductance at the end of the action potential and an increased rate of the potassium-sodium pump to counter the internal sodium concentration (see Chapter 8–2).

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 register no difference of potential between them. If, in the tissue activated at one end, the propagating action potential reaches the nearest electrode (G_1), then G_1 becomes negative relative to the distant electrode (G_2). This results in an upward deflection of the tracing according to the convention of clinical electrophysiology (although one could also set the oscilloscope to display negativity of G_1 as a downward deflection as some investigators do against the general trend.) With further passage of the action potential, the trace returns to the baseline at the point where the depolarized zone affects G_1 and G_2 equally. When the action potential moves further away from G_1 and toward G_2, G_2 becomes negative relative to G_1, or G_1 becomes positive relative to G_2. Therefore, the trace now shows a downward deflection. 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 as shown in Figure 2–4.[51]

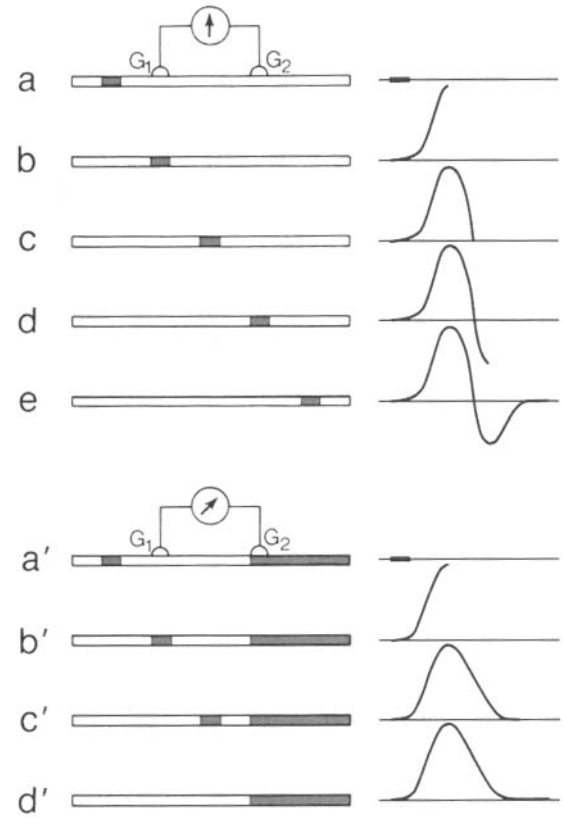

Figure 2–4. Diphasic (*top*) and monophasic recording (*bottom*) of an action potential represented by the *shaded area*. As the impulse propagates from left to right in the top series, the two electrodes see no potential difference in *a*, *c*, and *e*. Relative to the reference electrode (G_2), the active electrode (G_1) becomes negative in *b*, and positive in *d*, resulting in a diphasic potential. In the *bottom tracing*, the darkened area on the right indicates a killed end with permanent depolarization, making G_1 positive relative to G_2 in a', c', and d'. In b', G_1 and G_2 have no potential difference, causing upward deflection from the positive baseline to 0 potential.

Effect of Volume Conduction

The above discussion dealt with a directly recorded action potential in animal ex-

periments with no external conduction medium intervening between the pick-up electrodes and the nerve or muscle. During a clinical study, however, connective tissue and interstitial fluid act as volume conductors surrounding the generator sources.[10,16,22] Here, an electrical field spreads from a source represented as a dipole; that is, a pair of positive and negative charges.[3] 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 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.[12]

The theory of solid angle approximation pertains to analyzing of 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.[5,27] 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 as schematically shown in Figure 2–5. The propagating action potential, visualized as a positively charged wave front, or

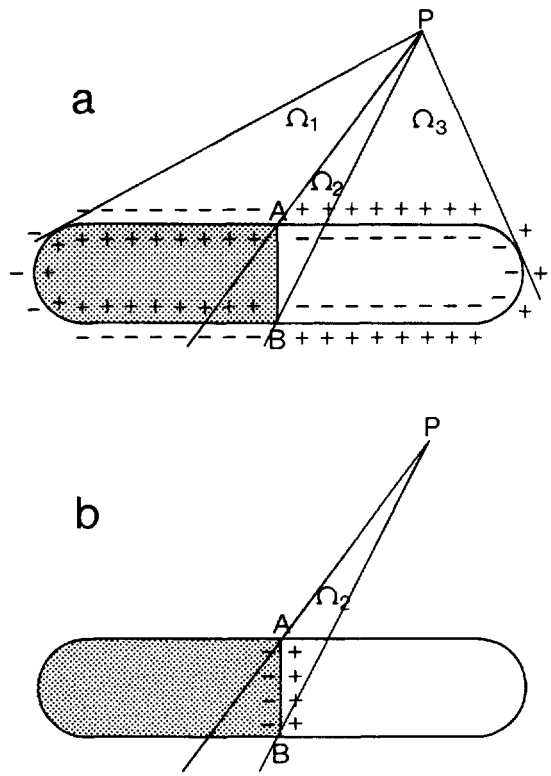

Figure 2–5. Potential recorded at *P* from a cell with active (*dark area*) and inactive regions. In **a**, total solid angle consists of Ω_1, Ω_2, and Ω_3. Potential at *P* subtending solid angles Ω_1 and Ω_3 equals zero as, in each, the nearer and farther membranes form a set of dipoles of equal magnitude 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 are placed 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. [Adapted from Patton.[48]]

leading dipole, represents depolarization at the cross-section of the nerve at which the transmembrane potential reverses.[46] A negatively charged wave front, or trailing dipole, follows, signaling repolarization of the activated zone.

Analysis of Triphasic Waveform

Analyzing waveforms plays an important role in the assessment of nerve or muscle action potentials. A sequence of potential

changes arise as two sufficiently close wave fronts travel in the volume conductor from left to right (Fig. 2–6). 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, therefore, appears as a negative-positive diphasic waveform when recorded with the active electrode near the end-plate region where the volley 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.

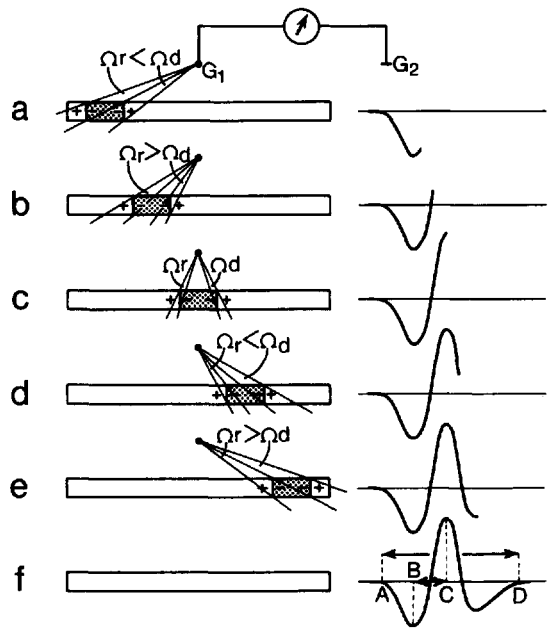

Figure 2–6. Triphasic potential characterized by amplitude, duration (*A–D*), and rise time (*B–C*). A pair of wave fronts of opposite polarity represent depolarization and repolarization. The action potential travels from left to right in a volume conductor with the recording electrode (G_1) near the active region and the reference electrode (G_2) on a remote inactive point. **A.** G_1 initially registers the positivity of the first dipole, which subtends a greater solid angle (Ω_d) than the second dipole of negative front (Ω_r). **B.** The relationship shown in **A** reverses, with gradual diminution of Ω_d, compared with Ω_r, as the active region approaches G_1. **C.** The maximal negativity signals the arrival of the impulse directly under G_1, which now registers only negative ends of the dipoles. **D.** The negativity declines as G_1 begins to register the positive end of the second dipole. **E.** The polarity reverses again as Ω_r exceeds Ω_d. **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.

The number of triphasic potentials generated by individual muscle fibers summate to give rise to a motor unit potential recorded in electromyography (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.[6,19,23,57,59] 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 results in an obvious reduction in amplitude. Additionally, the duration of the positive-to-negative rising phase, or rise time, becomes greater. The rise time gives an important clue in determining proximity to the generator source. Amplitude may not serve for this purpose, because it may decrease with smaller muscle fibers or lower fiber density.

According to the volume conductor theory, the location of the needle dictates the waveform of recorded potentials. Thus, the same single fiber discharge may be registered as initially positive triphasic fibrillation potential, initially negative biphasic endplate spike, or initially positive biphasic positive sharp wave (see Chapter 14–4). Despite this prevailing unifying concept,[14,15] an accurate description of the observed potential often provides clinically useful information.[41,42] For example, 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 blocks a propagating impulse, the recorded potential appears as a positive sharp wave signaling only the approach of the positive front of depolarization.

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.[11,13,37,38,45,56] The near- and far-field potentials distinguish two different manifestations of the volume-conducted field.[30,31,53] 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 a voltage step long before the signal arrives at the recording site, usually by a pair of widely separated electrodes located far from the traveling volleys. A referential montage preferentially records far-field potentials unless one of the electrodes lies near the passage of the traveling volley.

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[30,31,53] suggested that synaptically activated neurons in the brainstem gave rise to stationary peaks. Subsequent animal studies[60] emphasized the role of a synchronized volley of action potentials within afferent fiber tracts as their source. Further work with the human peripheral nerve has documented that stationary peaks can result solely from the propagating impulse in the absence of synaptic discharge.[20,35,37–39,43] Hence, stationary activities registered in far-field recording may represent a fixed neural source such as synaptic discharges or, alternatively, a nonpropagating peak from an advancing front of axonal depolarization.

As for the second of the two possibilities discussed above, short sequential segments of the brainstem pathways may each summate in far-field recording, resulting in successive peaks of the recorded potentials.[1,2,60] 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. In short-latency somatosensory evoked potentials (SEP) of the median[24,25,58] or tibial nerve[54] a voltage step develops between the two compartments when the moving volley encounters a sudden geometric change at the border of the conducting medium.[38] The same principles apply in the analysis of motor unit action potential and spontaneous single-fiber discharge.[17,18,23]

Here, 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.[11,32,36,55] Consequently, the potential difference remains nearly, though not exactly, the same regardless of the distance between G_1 and G_2, thus allowing detection of the voltage step in far-field recording. The designation, junctional or intercompartmental potential, differentiates this type of stationary peaks from fixed neural generators and helps specify the mechanism of the voltage step generated by the travelling impulse at a specific location (see Chapter 20–3).

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Chapter 3

ELECTRONIC SYSTEMS AND DATA ANALYSIS

1. INTRODUCTION
2. ELECTRODES
    - Preparation of Needle Electrodes
    - Types of Available Electrodes
3. ELECTRODE AMPLIFIERS
    - Differential Amplifiers
    - Common Mode Rejection Ratio
    - Means of Reducing Interference
    - Input Impedance
    - Frequency Response
4. VISUAL DISPLAYS
    - Cathode-Ray Tube
    - Delay Line
    - Multiple Channel Recording
    - Storage Oscilloscope
5. OTHER RECORDING APPARATUS
    - Loudspeaker
    - Magnetic Tape Recorder
6. ARTIFACTS
    - Electrode Noise
    - Amplifier Noise
    - Defective Apparatus
    - Movement Artifact
    - Electrostatic and Electromagnetic Interference
    - Radio and Mobile Phone Interference
7. STIMULATORS
    - Electrical Stimulation Requirements
    - Stimulus Isolation
    - Constant-Voltage versus Constant-Current
    - Magnetic Coil Stimulation
8. NORMATIVE DATA AND STATISTICS
    - Control Values
    - Statistical Analysis
    - False-Positive versus False-Negative Results
9. EXPERT SYSTEMS AND QUALITY DEVELOPMENT
    - KANDID
    - ESTEEM
    - MUNIN
    - Interlaboratory Communication

1 INTRODUCTION

The apparatus used in the performance of routine electrodiagnosis includes electrodes, amplifiers, displays, loudspeakers, and data storage devices. Muscle or nerve action potentials can be recorded by either a surface electrode placed on the skin over the target or a needle electrode inserted closer to the source. Surface electrodes register a summated electrical activity from many muscle or nerve fibers, whereas needle electrodes discriminate individual motor unit potentials discharging within a narrow radius from the recording tip. The electrical and physical characteristics of recording electrodes dictate the amplitude and other aspects of the potentials under study.[43,44]

Electromyographers analyze both the amplified waveform of action potentials on a visual display 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. Devices for permanent recordings include photographs with Polaroid films, a fiber-optic system with sensitive papers, a magnetic tape recorder, and digital storage. Amplitude and time calibrations verify the accuracy of the stored signals. This chapter deals with practical aspects of instrumentation,[12,39,40,60] without a detailed discussion of electronics (see Appendix 2).

2 ELECTRODES

The signals recorded during voluntary muscle contraction depend to a great extent on the type of recording electrode used.[15,38] Surface electrodes placed over the muscle record summated activities from many motor units. The use of a needle electrode allows recording of individual motor unit potentials during mild muscle contraction. With increased effort, synchronous activity in many adjacent motor units precludes the identification of single motor units. For routine purposes, clinical electromyographers use standard concentric, bipolar concentric,[2] or monopolar needles.[50] Single-fiber electrodes have a leading edge small enough to allow recording of potentials derived from single muscle fibers in isolation.[30,72] Less commonly used "special purpose" electrodes include the multielectrode, the flexible wire electrode, and the microelectrode placed intracellularly.[14] Electrode lead wires should have protected pins to prevent inadvertent connection to a power source, causing shocks, burns and electrocutions.[3]

Preparation of Needle Electrodes

Sterilization of needle electrodes in boiling water for at least 20 minutes prior to use 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 nonautoclavable connectors and lead wires before the sterilization procedure. Gas sterilization also suffices, although the chemicals used may damage the plastic, causing defects in insulation. Thorough outgassing of electrodes reduces the amount of the agent retained in the plastic material. Electrode manufacturers provide instructions for optimal sterilization methods.

With the advent of less costly disposables, it has now become a common practice in many laboratories to discard needle electrodes after use in each patient. The American Association of Electromyography and Electrodiagnosis[42] recommends this practice to circumvent any concerns of possible transmission of diseases, especially after studying a patient with AIDS, hepatitis, or any other contagious disorder. Jakob-Creutzfeldt disease poses special problems because the transmissible agent responsible for the disease may resist conventional sterilization procedures.[37,58] Further precaution before disposal, therefore, calls for incinerating used needles and blood-contaminated materials, or autoclaving them for one hour at 120° C and 15 PSI.[8]

Electrical properties of commercial needle electrodes vary considerably. Electrolytic treatment of reusable needles temporarily improves their performance.[23] Periodic examination of needle electrodes ensures their structural integrity. The inner concentric shaft may become corroded. The Teflon coating of monopolar needles may peel off, exposing the insulated portion of the conductor. An increase in recording surface tends to reduce the amplitude and area of the recorded motor unit potentials with relatively little effect on its duration.[21] The use of a dissecting microscope with a magnifying factor of ten helps detect a slight bend in the shaft or a crack in the tip. To test needle insulation, one terminal of a battery can be connected to the lead of a needle and the other terminal to an ammeter with a small exploring metal hook or moist cotton. A current should flow only if the exploring hook touches the exposed tip of the needle. 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 leads of standard or bipolar concentric needles unless there is a short circuit at the needle tip. A current will flow normally with immersion of the needle tip in water.

Types of Available Electrodes

Figure 3–1 illustrates common electrodes used in electromyography.

SURFACE ELECTRODES

Surface electrodes, square or round metal plates made of platinum or silver, come in different sizes with an average dimension of 1 × 1 cm. An adhesive tape suffices for applying them to the skin, although the use of collodion improves stability in long-term monitoring. Cleansing the skin with alcohol, scraping the calloused surface, and applying electrolyte cream under the electrode reduces impedance. Too much paste, however, can form a bridge between the two recording electrodes, cancelling the voltage difference. A short circuit between the stimulator and pick-up electrodes or ground introduces a large stimulus artifact. Perspiration can act in a similar manner. Time-efficient application of adhesive electrodes, including those marketed for electrocardiography, provides the same results as those obtained by the usual disc electrodes applied with adhesive tapes.[11]

Steady electrode offset voltage at the interface, not recorded by the amplifier, can

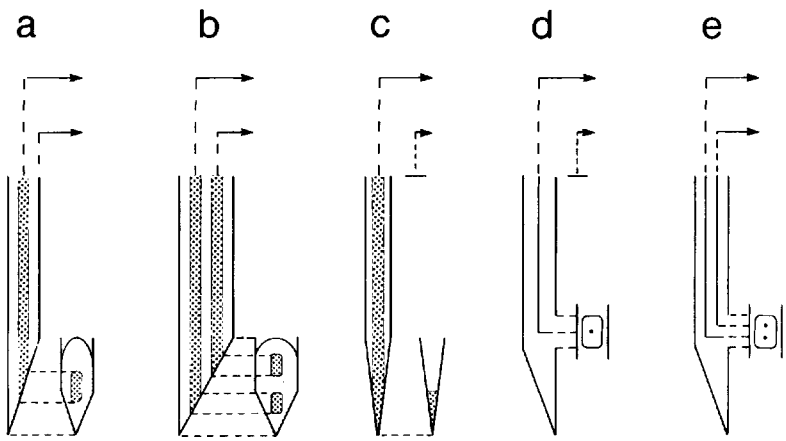

Figure 3–1. Schematic illustration of (*a*) standard or coaxial bipolar, (*b*) concentric bipolar, (*c*) monopolar, and (*d,e*) single-fiber needles. Dimensions vary, but the diameters of the outside cannulas shown resemble 26-gauge hypodermic needles (460 μm) for *a*, *d*, and *e*, a 23-gauge needle (640 μm) for b, and a 28-gauge needle 360 μm for c. The exposed tip areas measure 150 × 600 μm for *a*, 150 × 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.[72]]

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 surface electrode is best suited for monitoring voluntary muscle contraction during kinesiologic studies and recording evoked compound nerve or muscle action potentials. It registers electrical activities nonselectively from a wider region, covering the recording radius of some 20 mm compared to selective pickup from a 500 μm radius by a needle electrode.[10] The amplitude of compound muscle action potentials decreases with increasing electrode size.[79] The surface electrode also serves well as a stimulating probe, a reference, or a ground lead in conjunction with the monopolar needle, but not as an active electrode to study motor unit potentials, because it fails to reproduce high-frequency components adequately.

STANDARD OR COAXIAL CONCENTRIC NEEDLE

This electrode, introduced by Adrian and Bronk[2] in 1929, has a stainless-steel cannula similar to hypodermic needles, with a wire in the center of the shaft. The wire, usually made of nichrome, silver, or platinum, measures 0.1 mm or slightly larger as compared to the external rim of the shaft, 0.3 mm in diameter. The pointed tip of the needle has an oval shape with an exposed area of about 150 μm $\times$ 600 μm, and an impedance of around 50 kilohms. The wire and shaft, bare at the tip, form a spheric rather than hemispheric recording territory as might be anticipated by the direction.[28] The needle, when near a source of electrical activity, registers the potential difference between the wire and the shaft, showing a restricted recording area. In fact, in the recording of a single motor unit discharge that extends at least 1 cm in diameter, 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.[27] 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. A separate surface electrode, taped or applied with a suction cup, serves as the ground.[26] 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.[62]

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 for the same size wires embedded. 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 electrical activity.[55] This restricted recording range provides selectivity, but at the risk of disregarding the overall activity of motor units. Concentric electrodes tend to detect more spontaneous potentials than monopolar needles probably because of increased tissue injury.[71]

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. Its sharp tip causes less pain during insertion, but it is less stable electrically, hence noisier than the concentric electrode.[52,74] The average impedance ranges from 1.4 megohms at 10 Hz to 6.6 kilohms at 10 KHz.[80] Presoaking the elec-

trodes 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,[54] differ considerably from one type of needle to another. In general, a monopolar needle registers a potential that is twice as large and more complex,[29,61,65], from the same source, than a concentric needle, although duration and firing rate remain the same.[49]

SINGLE-FIBER NEEDLE

Single-fiber electromyography 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 muscle fiber potentials.[31] 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.[72] 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.[53,72]

MULTIELECTRODES

Multielectrodes contain three or more insulated wires, usually 1 × 1 mm in size, exposed through the side of the cannula.[16] One of the wires serves as the indifferent electrode; the outside cannula of the electrode, 1 mm in diameter, is connected to 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 1.0 mm for neuropathy. The single-fiber needle may also contain multiple wires exposed along the shaft. Similar multi-lead electrodes may usefully serve for intraoperative nerve recording.[6]

FLEXIBLE WIRE

A flexible wire, usually 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.[13] Although this type of electrode comes in different sizes, the most commonly used type has insulated platinum wires 50–100 μm in diameter with the tip bare. A small hole made in the insulation of the wire may provide smaller lead-off surfaces on the order of 10–20 μm.[45] These electrodes, however, lack the rigid standardization required for quantitative studies of action potentials.[72]

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 requires amplifiers of exceedingly high input impedance.[14]

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 2–2000. 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 a high input impedance, a low noise level, and a large dynamic range.

Differential Amplifiers

During electromyographic 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 of the signal, therefore, requires its selective amplification without, at the same time, magnifying the noise. This would be impossible if the apparatus amplifies any voltage appearing between an input terminal and the ground terminal. Differential amplifiers used in most electromyography, therefore, amplify only the voltage difference between the two input terminals connected to the recording electrodes. 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.

Common Mode Rejection Ratio

Inherent imbalance in the electrical system of an amplifier renders rejection of the common mode voltage less than perfect. The common mode 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; that is, 100,000 times more amplification of the signals than unwanted potentials appearing as a common mode voltage. A very high rejection ratio, however, will not guarantee the complete elimination of external interference caused by undesired distant potentials, for two reasons. First, electromagnetic interference affects the two recording electrodes almost, but not quite, equally depending on their relative positions. Second, the contact impedances inevitably differ between the two recording electrodes, leading to unequal distribution of the same common mode voltage. A common mode voltage too large to be perfectly balanced overloads the amplifier.

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. To be effective it should enclose the examining room as one continuous conductor and be grounded at one point. The 50 or 60 Hz filter available in most instruments reduces power line interference at the expense of distorting electromyographic signals. Thus, only special situations, such as portable recording in an intensive care unit, may warrant their application 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. For recording muscle or nerve action potentials, the tissue and electrode wires add only negligible impedances compared with those at the needle tip and at the input terminal of the amplifier. In this circuit, the needle

tip and the input terminal act as a voltage divider with voltage changes occurring in proportion to the respective impedance. 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 to a level much higher than that of the electrode tip would minimize the loss. The input impedances of most amplifiers range from 100 kilohms to hundreds of megohms. An amplifier with a high input impedance also improves the common mode rejection ratio because the higher the input impedance, the smaller the effect of electrical asymmetry of the recording electrodes. Higher electrode impedances increase amplifier noise and external interference, although electrode impedances as high as 50 times usual values apparently cause no major waveform distortion.[1]

Frequency Response

Most commercially available apparatuses have variable high- and low-bandpass filters to adjust frequency response according to the type of potentials under study.[39,40] Fourier analysis of complex waveforms encountered in electromyography 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 10 KHz. For clinical electromyography, the frequency band of the amplifier ideally should cover this range.[19,20] In the presence of interfering high-pitched noise or DC drift, however, a bandpass extending from 20 Hz to 5 KHz suffices. Filter settings must remain constant in serial studies. Their modification within the routine range results in statistically significant alteration of waveform.[66]

A high frequency filter (low pass), if set too low, reduces 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 filter (high pass), if set too high, distorts the slowly changing potential. 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 latency of peaks. The use of digital filtering, which introduces zero phase shift, circumvents this problem in clinical assessments.[41,56,57]

A square wave pulse of known amplitude and duration usually serves as a calibration signal to accurately determinine 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. A2–18 and A2–20). Other calibration signals include sine waves from the power line or discontinuous waveforms of known frequency and amplitude.

4 VISUAL DISPLAYS

Appropriate amplification ensures an optimal display of the waveform for visual analysis. The cathode-ray tube (CRT), with no mechanical limitations in dynamic high-frequency response, provides an excellent means to trace rapidly changing amplitude against time.

Cathode-Ray Tube

An electron gun discharges an electron beam internally toward the glass screen of a CRT. When struck by a beam of electrons, the phosphor coating on the inside surface of the screen emits light. The adjustable voltage between a pair of vertically placed plates (called horizontal deflection plates) determines the horizontal position of this bright spot. Applying a linearly increasing voltage to the plates makes the spot sweep at a constant speed.

A pair of horizontally placed plates (called vertical deflection plates), connected to the signal voltage from the amplifier, control the vertical position of the electron beam. The waveform displayed on the face of the screen, therefore, represents changing amplitude of the signal voltage in time. The vertical axis represents response amplitude, whereas the horizontal axis shows units of time. Electromyographic examination usually uses a free-running mode: when the spot reaches the end of the screen, it returns rapidly to the beginning to repeat. Most manufacturers now provide digital circuitry to process and store the potentials before displaying them on a monitor.

Delay Line

Instead of being free running, the horizontal sweep may initate on command. In this mode of operation, a motor unit potential itself can trigger the sweep. Thus, a given motor unit potential recurs successively at the beginning of each sweep for detailed analysis, although, by design, the portion of the waveform preceding the trigger point fails to appear on the screen. In an analog machine, an electronic delay circumvents this difficulty by storing the recorded motor unit potential 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.[63] 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 electromyographic instruments have multiple channels to allow simultaneous recording from two or more sets of electrodes. Typically, two or more channels share a beam from a single gun by switching the point vertically between the baselines of different traces as the beam sweeps horizontally across the screen. This electrical switching takes place so fast that each trace appears to be continuous despite the interruption from one trace to the next.

Storage Oscilloscope

Storage oscilloscopes have a different cathode ray tube 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 have made such storage oscilloscopes obsolete.

5 OTHER RECORDING APPARATUS

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 needle examination. 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 13–5). In fact, an experienced examiner can detect the difference between near and distant units by sound better than by oscilloscope display. The acoustic cues often guide in properly repositioning the needle close to the source of the discharge.

Magnetic Tape Recorder

Magnetic tape provides one means to store electrical potentials for later analysis. Am-

plitude modulation (AM) impresses the signal itself on the tape, whereas frequency modulation (FM) records the signal after converting it to a varying frequency of constant amplitude. The AM recording registers high frequency potentials well but not low-frequency responses below 10 to 15 Hz. In contrast, the FM method has a better low-frequency response, although it requires a very high tape speed to achieve the high-frequency response required for electromyography. The FM method reproduces the amplitude of potentials more accurately than the AM method.

6 ARTIFACTS

Not all electrical potentials registered during an electromyographic examination originate in muscle or nerve. Any voltage not attributable to the biologic potential sought represents an artifact, which usually causes a unique discharge pattern on the oscilloscope and distinct sounds through the loudspeaker.[40] 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 exogenous activities may result from peculiarity of the patient, like those induced by a cardiac pacemaker (Fig. 3–2) or transcutaneous stimulator (Fig. 3–3). More commonly, they result from 60 Hz interference caused by the electrostatic or electromagnetic fields of electrical appliances. 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

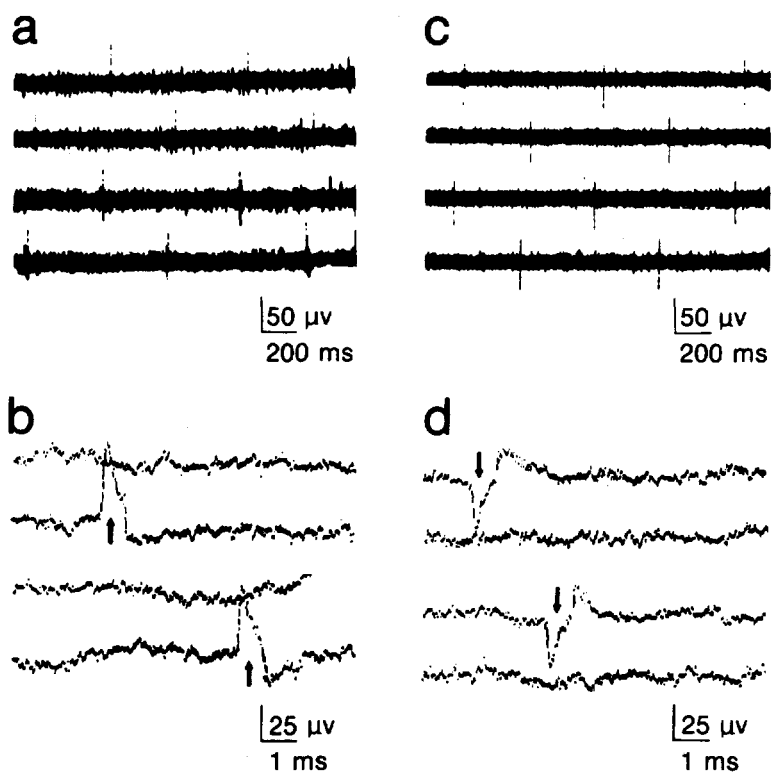

Figure 3–2. Artifacts induced by a cardiac pacemaker recorded by a monopolar needle electrode from (*a*, *b*) gluteus medius and (*c*, *d*) paraspinal muscle. Note opposite polarity of the sharp discharge at the two recording sites. The interval between the successive impulses of 800 ms corresponds to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

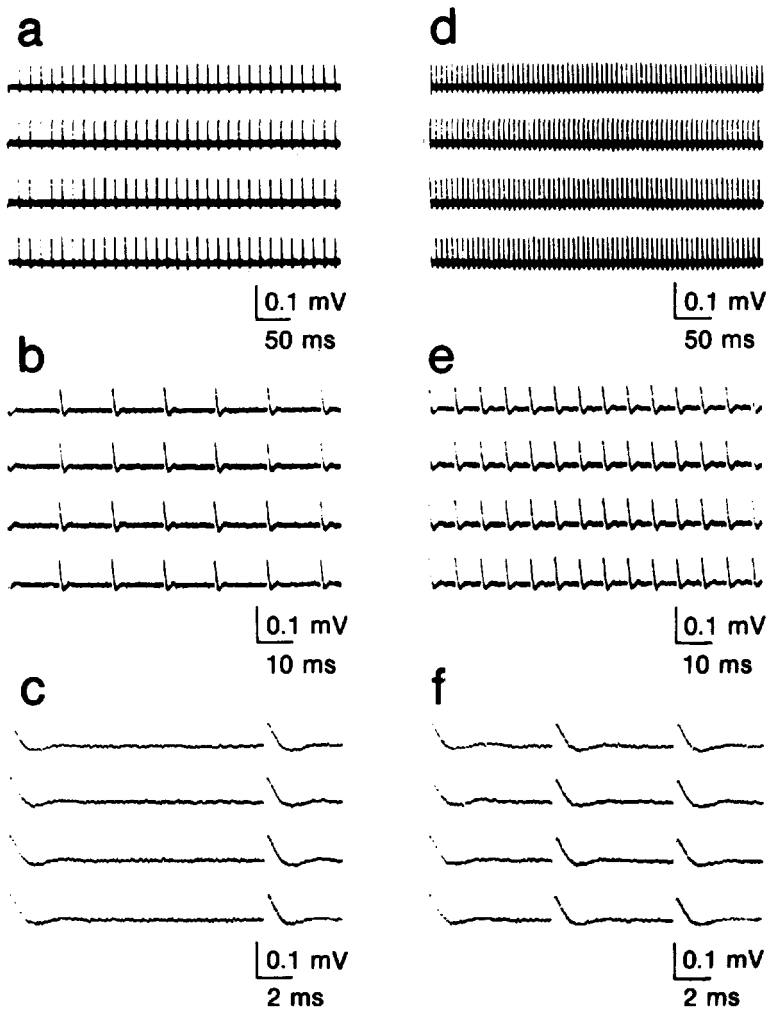

Figure 3–3. Artifact induced by a transcutaneous stimulator. The 14 ms interval between the successive impulses (*a, b, c*) corresponds to an approximate discharge rate of 70 impulses per second; the 7 ms interval (*d, e, f*), a faster rate of 140 impulses per second.

the muscle action potential. Impedance variability within the muscle tissue may also cause electrical activity, depending on the location of the needle tip. Genuine biologic potentials generated in the muscle include end-plate noises and end-plate spikes (see Chapter 13–4). These artifacts may mimic the intended signals sought during electromyographic examination (see Figs. 13–3 and 13–4).

Electrode Noise

Potentials may arise from two active metals or the metal-fluid junction at the needle electrode located intramuscularly. 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. Thus, the smaller the electrode surface, the greater the interference from its polarization or electrode noise. Therefore, the type of metal alters the recording characteristics of the needle electrode much more than those of the surface electrode. In fact, an electrode potential from active metals too small to affect surface recording could undermine the function of intramuscular studies. The use of relatively inert metals for needle electrodes, such as stainless steel or platinum, minimizes such adverse effects.

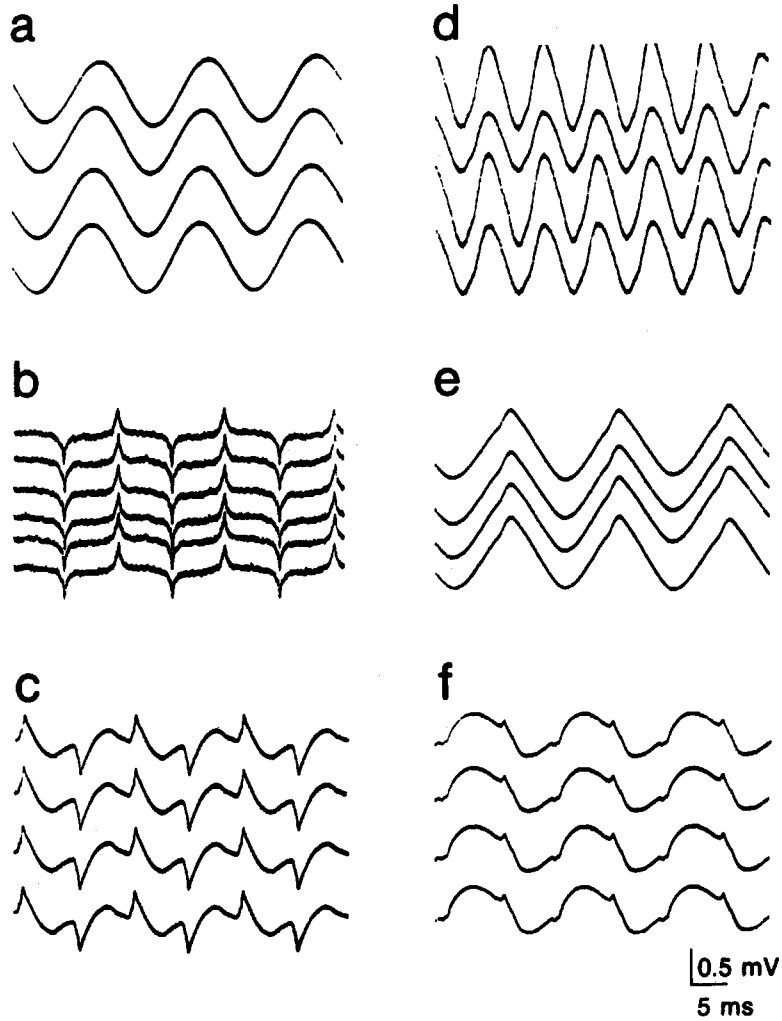

Figure 3–4. Various types of 60 Hz interference induced by nearby electrical appliances. They include (*a*) common pattern, (*b*) spikes from high impedance of the recording electrode, (*c*) fluorescent light, 120 Hz interference from (*d*) diathermy unit and (*e* and *f*) heat lamp.

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 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.

Defective Apparatus

By far the most likely cause of recording problems relates to a defect in one of the three recording electrodes or its application. A broken wire induces bizarre and unsuspected artifacts even if the insulat-

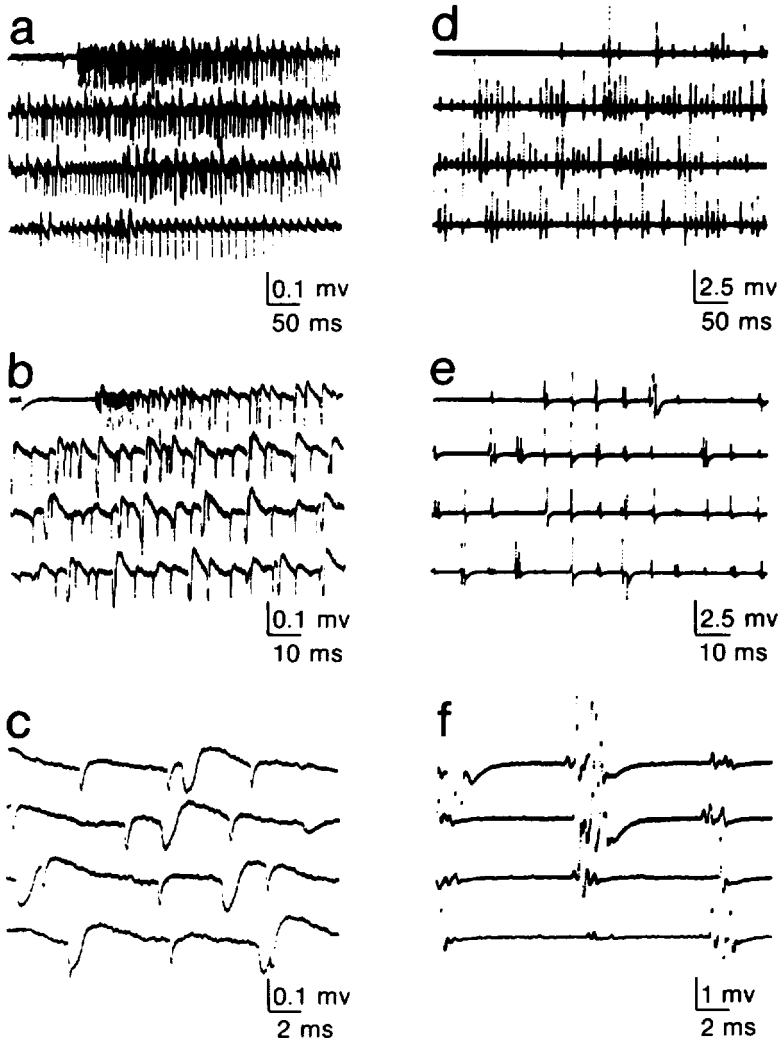

Figure 3–5. Effect of (*a, b, c*) a hammer drill operated nearby, and (*d, e, f*) oscillation of the amplifier circuits probably induced by an excessively high impedance of the electrode tip. Both superficially resemble the complex repetitive discharge, but the recordings with a fast sweep speed (*c*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

ing 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.

A 2-year study on durability revealed the feasibility of reusing monopolar electrodes on the average in 20–63 patients.[59] Failure occurred, in order of frequency, as the result of Teflon retraction, a dull or burred tip, a break in a wire or pin, electrical artifacts, or a bend in the needle shaft. Inadvertent insulation of the electrode tip by blood protein "baked on" in the process of autoclaving can also distort the potential. Careful cleaning of the needle tip prior to autoclaving will alleviate this problem. If necessary, application of an ultrasonic vibrator loosens dried material from the needle. The use of disposable needles precludes problems inherent to sterilization, but unused electrodes may manifest similar artifacts, caused by mechanical defects induced during the manufacturing process.

Movement Artifact

When a patient contracts a muscle, the surface electrode may slide over the skin.

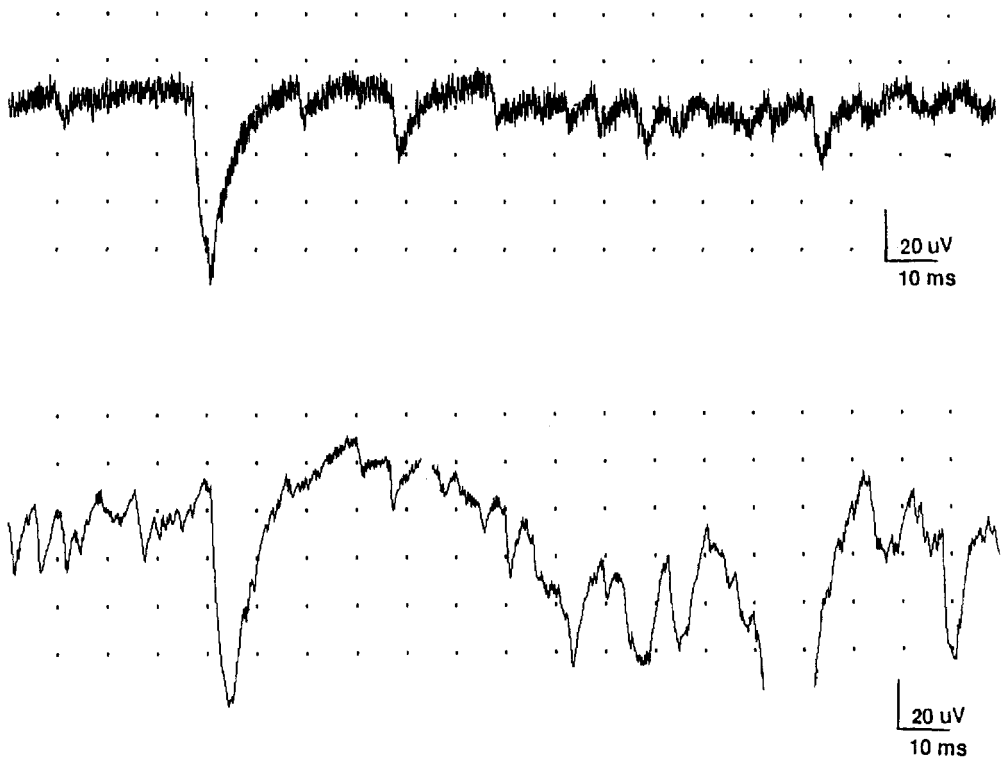

Figure 3–6. Amplifier noise superficially resembling positive sharp waves. Both traces were recorded with a disposable monopolar needle placed in the edematous subcutaneous tissue. The baseline thickness changed abruptly with slight relocation of the needle tip, probably altering the impedance, which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

This causes a movement artifact primarily because of the change in 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.[73] 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, cathode-ray tube screens, electric motors, light dimmers, and even unused power cords plugged into wall outlets. The use of an ungrounded wheelchair or metal examining table enhances this type of artifact. Appliances sharing the same circuit with the electromyographic instrument cause especially noticeable interference. Radio frequency electromagnetic waves can also "carry" alternating current. A strong field from a nearby diathermy apparatus produces a characteristc wave pattern. Federal regulations now restrict the amount of interference that such a unit can render to other equipment. Intermittent powerline load causes power-line voltage transient changes, which in turn give rise to artifact. In an examining room located near a driveway, auto ignition causes a popping sound. The examiner, if not properly grounded, acts as an antenna by touching the needle.

Simple but effective measures to reduce electromagnetic interference include bundling or weaving the lead wires from the pickup and ground electrodes to minimize the area susceptible to the field of interference, relocating them relative to the patient or recording apparatus, and repositioning the patient and recording apparatus within the room. With power cords near the patient, turning off power to the offending appliance does not necessarily eliminate the artifacts. To avoid interference pickup from a cathode-ray tube screen or monitor, the patient and operater should not come too close to the source. If these simple precautions fail, adequate control may require removing all electrical appliances from a room and shielding the examining area.

Radio and Mobile Phone Interference

High-frequency interference or audio interference may appear on the screen of the oscilloscope from radio broadcasts, television, or radio paging systems. This type of artifact may escape detection because of its transient nature unless the sounds heard through the loudspeaker alert the examiner. Their elimination may require relocation or screening of the electromyographic instrument. An examining room located on the side of the building farthest from transmitting antennas has least interference. Screening the noise caused by power wiring may require the use of power-line radio frequency filters to remove the effect. A mobile phone in use near the electromyographic laboratory also can give rise to substantial artifacts, which may mimic high-frequency complex repetitive discharges.[75]

7 STIMULATORS

Electrical Stimulation Requirements

Electrical stimulation of the nerve provides a clearly defined, reproducible response for nerve conduction studies. A potential applied to electrodes, usually on the skin surface but sometimes inserted subcutaneously, induces a current of short duration, 50–1000 μs, in the fluid surrounding a nerve bundle. The stimulating current, directed primarily along the course, depolarizes the nerve under the cathode and hyperpolarizes it under the anode. Increasing the current to obtain a repeatable and maximal recorded response assures that essentially every nerve fiber in the bundle discharges. Surface electrode stimulation requires 50–500 V to drive currents of 5–50 mA, depending on skin impedance. Higher shock intensities can usually, though not always, compensate for decreased nerve excitability seen in some neuropathic conditions (see Chapter 7–5, Chapter 25–3). Stimulation with subcutaneus needle electrodes, already in good fluid contact and closer to the nerve, uses much less intensity for adequate activation. Just a few volts may elicit a response in this case, requiring much tighter electrical control over stimulus values for consistent and safe practice than in the case of surface delivery. Effective depolarization displays an inverse relationship between stimulus intensity and duration. Thus, a lower intensity suffices if applied for a longer duration, but within limits. Generally, patients tolerate stimulus durations exceeding 1000 μs poorly. With durations of less than 50 μs, tissue capacitances limit the rate of rise, preventing the stimulus from reaching a full effective amplitude.

The equipment must also provide control and timing of the stimuli for different types of measurements. In performing the paired-shock technique, the first shock with reduced intensity may subliminally excite the motor neuron pool, which then fires 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 latencies, delivered to the same or to different sets of electrodes. Train stimulus techniques deliver 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 are "isolated" from the recording amplifiers and other equipment circuits, for safety and artifact reduction. Thus, the stimulation circuits have no conductive path to other circuits except through the patient's body when stimulating and recording electrodes have been applied. 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 distributed in the body can divide into additional paths, causing a large stimulus artifact, amplifier overload, or even spurious stimulation at unintended sites. Furthermore, under conditions of component failure, these additional paths might 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

"Constant-voltage" stimulators deliver an adjustable voltage across the stimulating electrodes, essentially independent of stimulus current. Adjusting the voltage varies the current through the stimulating electrodes to achieve a desired level of stimulation. At a fixed output voltage, changes in stimulating electrode impedance alter the stimulus current level. "Constant-current" stimulators deliver 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. Constant-current stimulators provide more consistent stimulus control, especially for techniques that require a train of stimuli or response averaging.

Magnetic Coil Stimulation

Magnetic coil stimulation serves as an alternative means of nerve activation, more widely used for excitation of the central rather than peripheral nervous system.[9,22,46–48] A rapidly changing magnetic field of high intensity can induce sufficiently localized current in the body fluid to cause nerve excitation (see Chapter 21–3). The apparatus consists of a hand-held, doughnut- or figure 8–shaped coil and a capacitive-discharge power unit, triggered from conventional electromyography equipment. The advantages of magnetic stimulation include the capability of exciting the brain non-invasively, a lower level of pain associated with the stimulus, and the elimination of stimulus electrode application. It might seem that magnetically inducing the stimulus would provide a high degree of isolation and thus reduce stimulus artifact, but in fact, the huge coil currents and high voltages couple substantial artifact into low-level recording circuits. The major disadvantages of magnetic stimulation include a greater uncertainty and variability as to the point of stimulation, and the greater expense of the stimulating equipment. Ordinary magnetic pulse generators require a few seconds for recharge between stimuli, eliminating the possibility of closely paired or train stimuli. Despite the advent of specially constructed devices for these purposes, safety considerations preclude routine application of train stimuli to the cortex. At this time, the U.S. Food and Drug Administration (FDA) has approved magnetic stimulation for human use only in studies of the peripheral nerve. The national review board has granted permission for some limited research applications conducted in the central nervous system.

8 NORMATIVE DATA AND STATISTICS

Most neurophysiological evaluation in the clinical setting makes comparison between a patient finding and some set of normative data. Thus, the quality of such database plays an essential role for diagnostic accuracy and yields.[25] Established control values should accompany a description of a new technique for clinical

use, even though testing large numbers of healthy subjects is tedious.[18] The compilation of normative data must conform to established principles.[7,17,67–70]

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 normal on the basis of test results for inclusion into a normative database represents a circular argument that defies 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. Further, the population with illness may well contain a higher proportion than normal of preexisting conditions which, even if subclinical, may affect the test outcome.

Statistical Analysis

In as much as population variables conform to a bell-shaped Gaussian distribution, statistical analysis shows an identical value for mean, median, and mode. Gaussian distribution, though generally symmetrical, tends asymmetrically to the baseline at both ends, reflecting a small proportion of extreme high and low values or outlyers. These values dictate "the range," which, unlike other methods for deriving normative data, critically depends on 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 sometimes be usefully transformed for statistical manipulations. For example, the natural or base 10 logarithm, or square root will render positively skewed distributions more Gaussian. The mean and standard deviations of the transformed data may then be converted back to original units to set up normative limits for clinical application.

Normative limits of the Gaussian distribution are customarily set at ±2 standard deviations about the mean, which include 95.44 percent of the entire population. About 5 percent 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.[33,76] The overall chance equals the sum of the probabilities in each of the individual tests.[67,69] If each measurement allows a 2.5 percent rate of false-positivity using 2 standard deviations as the criterion, then an examination that consists of 10 independent electrophysiological measurements has a probability of more than 1 in 5 (20%) in turning up one or more abnormal values on the basis of chance alone.

False-Positive versus False-Negative Results

False-positive outcomes present a major problem for clinical application.[32] In general, therefore, we prefer to err on the side of false-negativity—that is, calling more borderline abnormalities normal than the reverse. The incidence of false-positivity will decrease with the use of a broader limits, for example, mean ±2.5 standard deviations. In this case the false-positive rate falls to about 1 percent in aggregate, at the cost of a correspondingly higher false-negativity rate.[24] 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 two, powerful statistical tests may show a significant difference comparing, as a group, the values in normal subjects and diseased individuals. Such scientific con-

clusions, though valid, provide only limited practical applications. In the clinical context, a single patient value must fall outside the established normative limits to declare its abnormality with reasonable confidence. Common sense must prevail in questioning an isolated borderline abnormality just outside the normal limit, a surprise result unrelated to the patient signs and symptoms, or a pattern of abnormalities inconsistent with each other and 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 electrophysiological data (or both) in an effort to resolve discrepancy.

9 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 automated 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 eventually 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 also helps 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.[34]

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 decide when to stop the electrodiagnostic examination.

A prospective European multicenter field trial tested the validity of KANDID at seven independent laboratories.[36] The agreement level among nine clinical neurophysiologists who participated in 159 electrodiagnostic examinations averaged 81percent for pathophysiological conclusions and 61 percent for diagnostic categories. The pronounced inter-examiner 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 European Standardized Telematic Tool to Evaluate EMG Knowledge Based Systems and Methods, or ESTEEM. This project used a multicenter database of neuromuscular cases to obtain diagnostic consensus by expert electromyographers and establish standards and guidelines of electrodiagnostic practice to develop an acceptable expert system. ESTEEM also served as a prototype for an electrophysiology platform that integrated different tools within the laboratory and for telematically communicated pertinent data at various posts within one hospital and also among different institutions

Studies in 81 patients from the ESTEEM database 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.[77] The selected experts then interpreted the data in each case with respect to pathophysiological 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.

MUNIN

Another EMG expert system, MUNIN, uses a causal probabilistic network in contrast to the rule-based KANDID.[4,64] The microhuman prototype[4] 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 of muscle and nerve, as well as commonly used measures of electromyography and nerve conduction studies. For diagnostic purpose, a probabilistic inference engine "reasons" from test results to different aspects of pathophysiology to neuromuscular disorders. It can also provide causal reasoning in the opposite direction, from disorders to pathophysiology to expected test results. At the end of a 5-year project sponsored by the 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 thought that MUNIN performed at a level similar to an experienced neurophysiologist.[5]

Compared to KANDID, MUNIN does not explicitly help in the planning of an examination. If such an interaction were available, the probabilities provided by the system would help direct the physician toward a proper course of action. Compared to 39 percent 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. MUNIN utilizes very few clinical findings. Thus, the system does not accept the cases with limited EMG examination performed only to confirm a clinical diagnosis. Methodological 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 muscle examination and near-nerve technique for nerve conduction studies, whereas others use qualitative muscle examination and surface electrodes. To improve the quality of studies, expert systems must consider these widely variable patterns of practices,[35] and standardize terminology for pathophysiological interpretations and diagnoses. To facilitate interaction among different laboratories via the Internet, the ESTEEM project developed an electromyography communication protocol.[51] It consists of general data, examination techniques, reference values, pathophysiological 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.[78]

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Part II

NERVE CONDUCTION STUDIES

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Chapter 4

ANATOMY AND PHYSIOLOGY OF THE PERIPHERAL NERVE

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 peripheral nerve disorders.[32] In particular, in vitro recordings of compound nerve action potentials from the sural nerve have 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.[45] 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 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, and discuss types of conduction abnormalities. A number of excellent texts provide a more detailed review of the subject for interested readers.[56,183,199] Chapters 23 through 26 will present the clinical aspects of peripheral nerve disorders.

2 ANATOMY OF PERIPHERAL NERVES

Gross Anatomy

Nerves have a structure of considerable complexity and features of special relevance to nerve injury and regeneration.[201] 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.[209] Fascicular groups destined for the same endpoint remain localized within the nerve for long distances.[218] The epineurium, composed of collagen tissue, elastic fibers, and fatty tissue, tightly binds individual fascicles together providing a protective cushion against compression.[201] This outermost layer of supporting structure for the peripheral nerve merges in the dura mater of the spinal roots.[83] Paucity of endoneurial collagen at the roots as compared with the nerve trunk may explain why some disease processes selectively involve the root. The vasa nervorum, located in the epineurium, branch into arterioles that 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.

Myelinated and Unmyelinated Fibers

The nerve trunks contain myelinated and unmyelinated fibers. Certain inherent properties of the axon apparently determine whether or not myelination will eventually occur. 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 myelin thickness.[189] 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.[74]

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 myelinated early achieve larger diameters and wider spacing between the nodes of Ranvier. In other words, 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. In unmyelinated nerves,

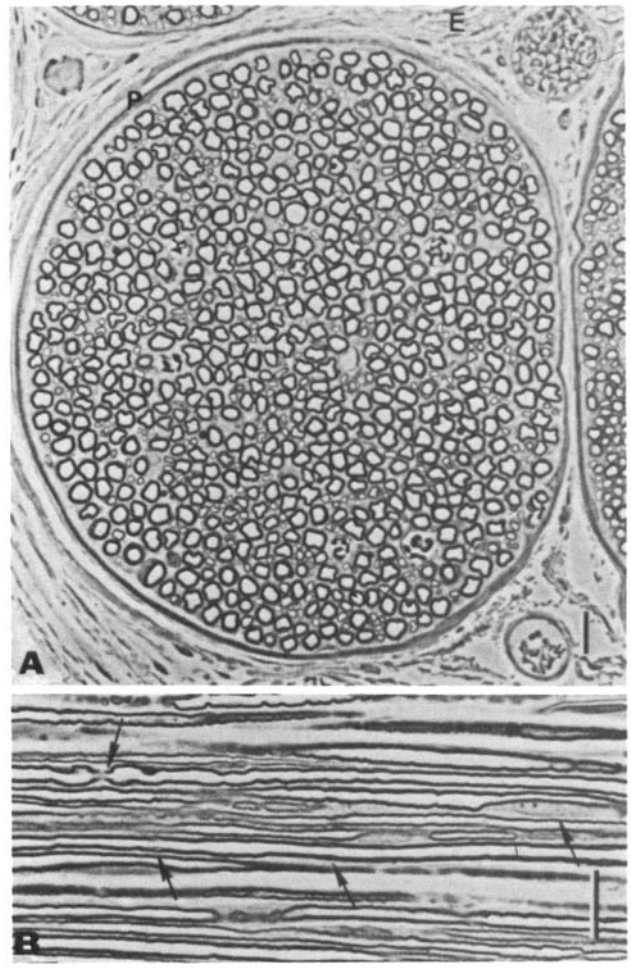

Figure 4–1. Transverse (**A**) and longitudinal (**B**) sections of the sciatic nerve shown at low magnification. Vertical scales at *lower right* represent 20 μm. In **A**, the epineurium (*E*) contains vessels, fibro-blasts, and collagen. The perineurium (*P*) surrounds fascicles of nerve fibers, which are separated by endoneurial connective tissue. 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,[225] with permission].

conduction velocity varies in proportion to the square root of the fiber diameter. The largest and fastest conducting fibers include the sensory fibers transmitting proprioceptive, positional, and touch sensations and the alpha motor neurons. Small myelinated or unmyelinated fibers subserve pain and temperature sense and autonomic functions (see this chapter, part 4). Those found in the human epidermis apparently originate from nerve trunks in the dermis, subserving some sensory function.[109]

Axonal Transport

In the peripheral nervous system, a small cell body with a diameter of 50–100 μm regulates axons up to 1 m in length. A complicated system of axonal transport provides the metabolic needs of the terminal axon segments. Hence, the axons not only conduct propagating electrical potential 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 flows centrifugally, though some particles seem to move centripetally.

Axonal transport plays a complex role in maintaining the metabolic integrity of the peripheral nerve. Axonal flow of trophic substances, at least in part, dictates the histochemical and electrophysiologic properties of the muscle fibers. No particles other than acetylcholine (ACh), however, seem to transfer across the neuromuscular junction. Therefore, acetylcholine mol-

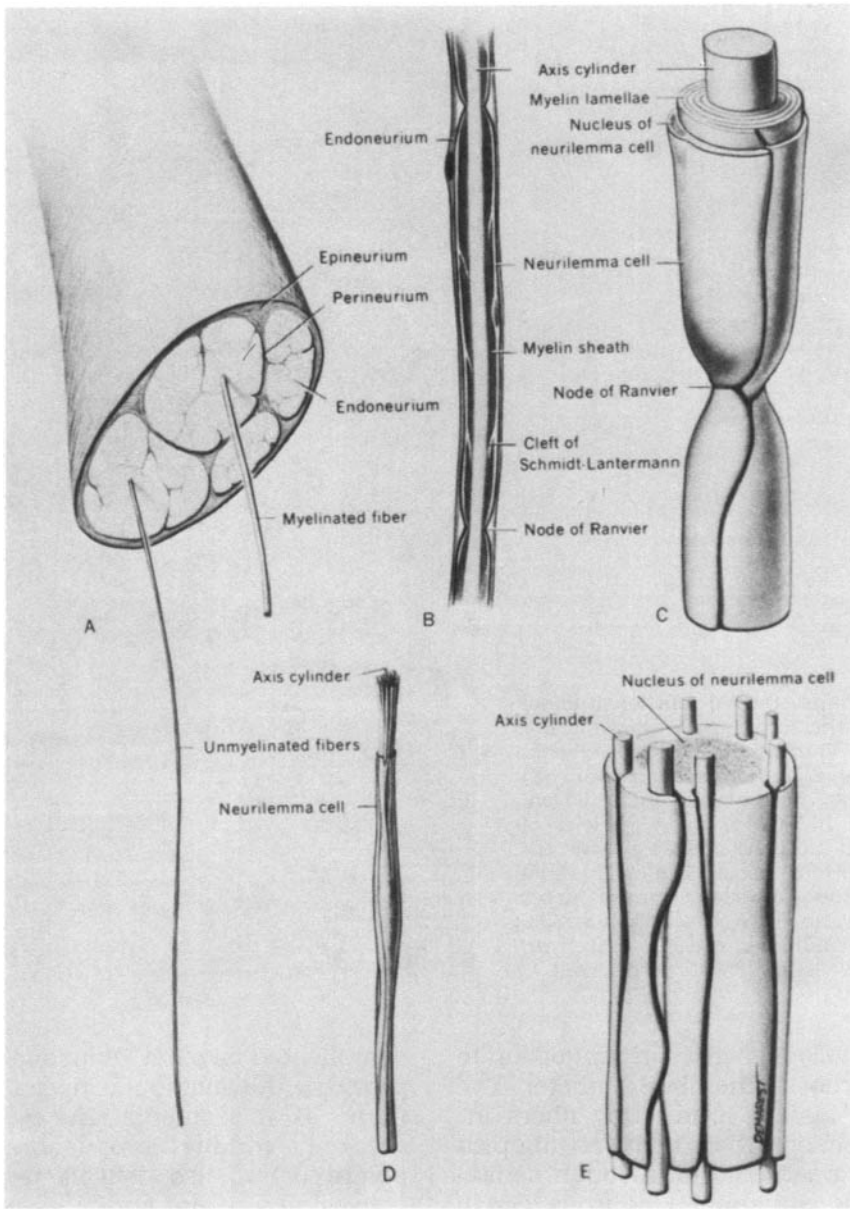

Figure 4–2. Fine structures of the peripheral nerve as visualized with the light microscope (*A, B, D*) and as reconstructed from electron micrographs (*C, E*). **A.** The epineurium covers the entire nerve, whereas the perineurium surrounds individual fascicles and endoneurium nerve fibers. **B.** The myelinated fiber consists of axis cylinder, myelin sheath, and Schwann (neurilemma) cells. The myelin sheath is absent 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,[145] with permission.]

ecules 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.[35,136] Neuromuscular transmission fails, and the nerve terminals degenerate faster with distal than with proximal axonotmesis. Similarly, membrane changes in denervated muscle appear more rapidly after nerve injury close to the muscle.[86]

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 as the result of increased sodium conductance. A local subliminal change in the transmembrane potential rapidly diminishes with distance. In contrast, threshold 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 (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 (anodal hyperpolarization). The cell plasma resistance and membrane conductance and capacitance limit the subliminal local changes of depolarization or hyperpolarization only within a few millimeters of the point of origin. After about 10–30 mV of depolarization, the membrane potential reaches the critical level for opening the voltage dependent sodium (Na^+) 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 period of a few milliseconds, supernormality lasting 30 ms or so, and subnormality extending up to 100–200 ms (see Chapter 8–2).

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.[85] 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 or 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 pathological 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.[165] In isolated nerve-muscle and leg preparations, electric ac-

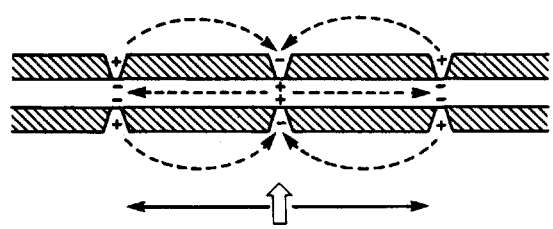

Figure 4–3. Saltatory conduction along the myelinated fiber. The myelin sheath effectively insulates the internodal segment with the bare axon at the node of Ranvier, where the current flows between intracellular and extracellular fluid. A local current (*broken arrows*) produced by an action potential 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.

tivity of frog muscle can show ephaptic influence on contiguous nerves under various conditions.[14]

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 5 percent per 1 °C from 29° to 38 °C.[89] Thus, the change ranges 2–3 m/s per °C in a normal nerve conducting at 40–60 m/s. Other elements of clinical importance (see Chapter 5–6) include internodal length,[31] variation among different nerves and segments, effect of age, and metabolic factors such as hyperglycemia.[187]

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 (Fig. 4–3) instead of the continuous propagation observed in unmyelinated fibers. An increase in internodal distance allows a longer jump of the action potential, but at the same time causes greater loss of current through the internodal membrane. Typically, it takes approximately 20 μs for the local current to excite the next node. The conduction velocity would then be 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 by 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.[220] 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. More local current is lost 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.[166] Thus, demyelinated axons characteristically exhibit conduction failure, decreased velocity, and temporal dispersion.[219] After segmental demyelination, smaller diameter fibers may show continuous rather than saltatory conduction if the demyelinated region has a sufficient number of sodium channels.[21] Reduction in length of the adjacent internodes tends to facilitate conduction past focally demyelinated zones.[221]

Conduction abnormalities do not necessarily imply demyelination. They can result from toxins or anesthetic agents.[30] 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 (see Chapter 8–3).

4 TYPES OF NERVE FIBERS AND IN VITRO RECORDING

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[61] 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 with 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[124]; for example, referring to the initial peak as either A-alpha[75] or A-beta,[60] and the subsequent peak, now considered an artifact of recording, as A-gamma.[75] Current practice designates the two peaks in the A potential of cutaneous nerves as A-alpha and A-delta.

The three types of nerve fibers, A, B, and C, have histologically and electrophysiologically distinctive characteristics (Table 4–1). The A fibers are myelinated somatic axons, either afferent or efferent. The B fibers are myelinated efferent axons that constitute the preganglionic axons of the autonomic nerves. The unmyelinated C fibers consist of the efferent postganglionic axons of autonomic nerves and the small afferent axons of the dorsal root and peripheral nerves. Despite histologic resemblance, physiologic characteristics can differentiate B fibers from small A fibers. For instance, the B fibers lack negative afterpotentials 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 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, allow 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.[29] As documented in the human median nerve, both myelinated and unmyelinated fibers show intrafascicular segregation by modality rather than random distribution.[84] Despite specificity, two types of afferent input—for example, A-delta and C fibers—may interact at primary afferent level.[229]

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-alpha and A-delta fibers. The muscle nerves comprise efferent and afferent A fibers. The efferent fibers consist of the axons of alpha and gamma motor neurons. 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, represent-

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

ing small pain fibers. In this designation, the A-alpha fibers of cutaneous nerve correspond in size to groups I and II, the A-delta fibers to group III, and the C-fibers to group IV.

Modality Dependency of Nerve Conduction Velocity

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. This relationship also holds in humans, although differences tend to be smaller. For example, direct recording from human nerves can differentiate A-alpha and A-delta peaks as shown in the intracranially recorded potentials from the sensory root of the trigeminal nerve.[169]

In Vitro Recording and Fiber Diameter Histogram of the Sural Nerve

An in vitro study of the sural nerve action potential complements the quantitative morphometric assessment of the excised nerve.[54] The technique allows comparison between the fiber diameter spectrum and the range of conduction velocities for different components of the sensory nerve action potential. Some authors caution, however, that the sural nerve may occasionally contain some 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.[148] The distal half serves as the specimen for histologic studies and the proximal half for in vitro electrophysiologic evaluation. The segment used for conduction studies is immediately placed in cool Tyrode's solution and transferred to a sealed chamber filled with 5 percent carbon dioxide in oxygen and saturated with water vapor. Immersing the chamber in a warm water bath helps maintain a constant temperature at 37 °C.

A series of silver electrodes support the nerve under slight tension by the pull of a 0.5–0.9 gm weight attached to each end. Stimulation at the distal end of the nerve allows recording of the compound nerve action potential with a pair of wire electrodes placed 20–30 mm proximally. A monophasic waveform results with the nerve crushed between the recording electrodes following application of 0.1 percent procaine at the distal electrode (see Fig. 2–4). The compound nerve action potential recorded in vitro consists of three distinct peaks: A-alpha, A-delta, and C components with an average conduction velocity of 60 m/s, 20 m/s, and 1–2 m/s (Fig. 4–4). Each component requires different supramaximal intensity for full activation. The gradual onset of A-delta and C peaks precludes accurate calculation of the maximal conduction velocity.

Figure 4–5 shows a fiber diameter histogram for the A-alpha and A-delta components. Here, the fiber diameter increases from left to right on the abscissa, thus, the first peak on the left corresponds

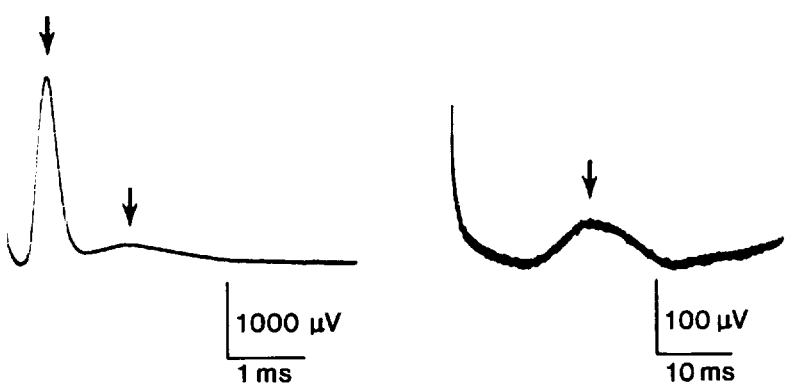

Figure 4–4. Compound nerve action potential of a normal sural nerve recorded in vitro from an 11-year-old boy who had an above-knee amputation for osteogenic sarcoma. The *arrows*, from left to right, indicate A-alpha, A-delta, and C components, measuring 2.6 mV, 0.22 mV, and 70 μV in amplitude and 42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

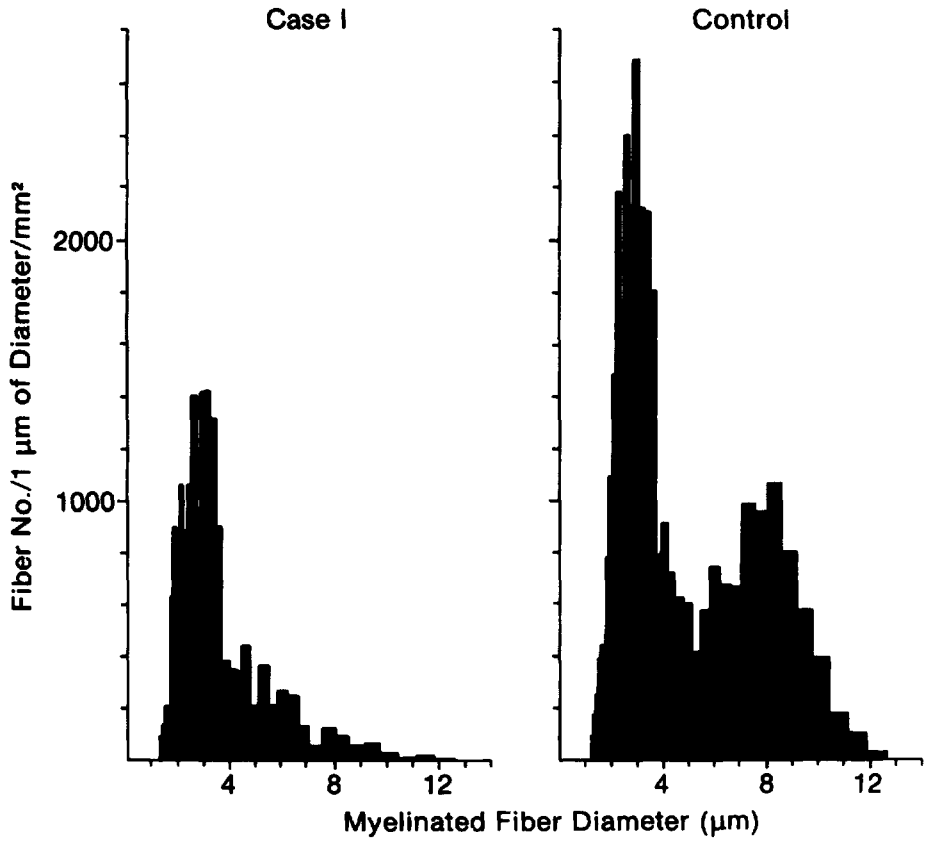

Figure 4–5. Myelinated fiber size-frequency histogram plotting the number of fibers with increasing diameter from left to right. The first large peak on the *left* corresponds to A-delta and the second smaller peak to A-alpha. Note a bimodal distribution of myelinated fiber diameter in a normal subject (*control*). A patient (*Case I*) with familial pressure-sensitive neuropathy had an abnormal unimodal pattern with preferential loss of the larger myelinated fibers. [Courtesy of E. Peter Bosch, M.D., Mayo Clinic, Scottsdale, AZ.]

to A-delta and the second smaller peak to A-alpha fibers. In the opposite arrangement with decreasing diameter plotted 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-alpha and A-delta peaks reflects a high concentration of fibers within the continuous spectrum.[15] The largest fibers, with a diameter close to 12 μm, conduct at an approximate rate of 60 m/s, indicating a 5:1 ratio between the two measurements.

Morphological evaluation of the peripheral nerve must take into account the maturational and age related changes.[106,204] In one study of 51 normal sural nerve biopsies,[179] 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. With age, total transverse fascicular area increased in the face of a stable number of nerve fibers, thus decreasing fiber density. Determining the internodal length spectra in teased fiber preparation also provides quantitative data in elucidating distribution of histologic abnormalities (Fig. 4–6).[94] Statistical analyses show significant correlations between teased fiber changes and conduction abnormalities affecting both motor

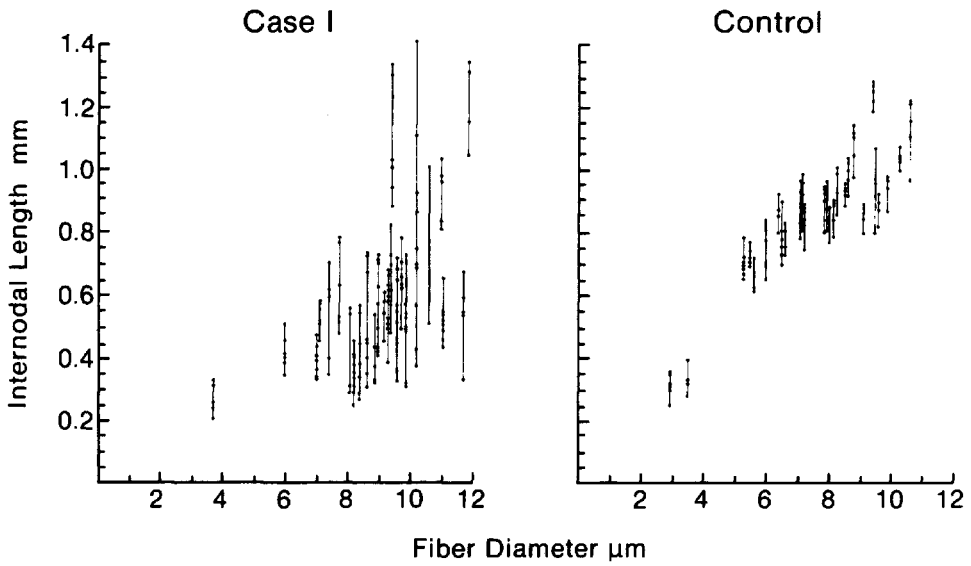

Figure 4–6. Internodal length spectra of the same nerves shown in Figure 4–5. Each vertical line indicates internodal lengths measured on a given myelinated fiber. The marked variability of internodal length in the patient reflects the effects of chronic demyelination and remyelination. [Courtesy of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

and sensory nerves in patients with sensory motor polyneuropathies.[18]

Analysis of Compound 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 is 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, have 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.[124]

More current flows as the nerve fibers increase in number whereas the resistance falls in proportion to the square diameter of the nerve. Thus, fiber density or the number of fibers per unit 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 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 7–5).

5 CLASSIFICATION OF NERVE INJURIES

Seddon[183] 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 because of associated demyelination, re-

turns 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 1–3 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 compression neuropathies such as carpal tunnel syndrome or tardy ulnar palsy.

Neurapraxia

The mildest form of nerve block results from local injection of procaine or the transient loss of circulation—for example, with leg crossing. These insults are immediately reversible and cause no structural changes of the axon. Tetrodotoxin has similar but more widespread reversible effects on myelinated nerve fibers throughout the entire length of the axon. It acts by lowering the conductance of sodium currents at the nodes of Ranvier.[154]

During transient paralysis experimentally induced in humans by an inflated cuff around the arm, conduction velocity may fall by as much as 30 percent. 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 rat sciatic nerve, transcient conduction block developed within 10 minutes after femoral artery occlusion, reached a nadir at 45–60 minutes, and then improved to normal within 24 hours.[158] The fall in amplitude with less than 15 percent slowing of conduction velocity implied relative sensitivity of slower conducting myelinated fibers to the effect of acute ischemia. These short-term changes in nerve conduction probably result from anoxia secondary to ischemia.[105] Intraneural microelectrode recordings show spontaneous activity in 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.[153]

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.[17] In experimental animals, partial infarction resulted in degeneration of fibers in the center of the nerve with no evidence of selective fiber vulnerability.[157] Hypothermia, by reducing metabolic demands, rescues the nerve from ischemic fiber degeneration.[110] Chronic nerve ischemia may also play a role in the pathogenesis of some neuropathies such as multifocal motor conduction.[149]

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.[135] A neurapraxia causing incomplete and reversible paralysis 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.[150] Conduction may return immediately after decompression or at times even under the prolonged compression, albeit markedly slowed.[9] Complete recovery will ensue with remyelination. The degree of compression determines the severity of the initial conduction block, but not the subsequent recovery rate of conduction.[91]

Although demyelination in these cases can result from anoxia secondary to ischemia, studies of experimental acute pressure neuropathy have stressed the importance of mechanical factors[76,156,173] 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.[19,172]

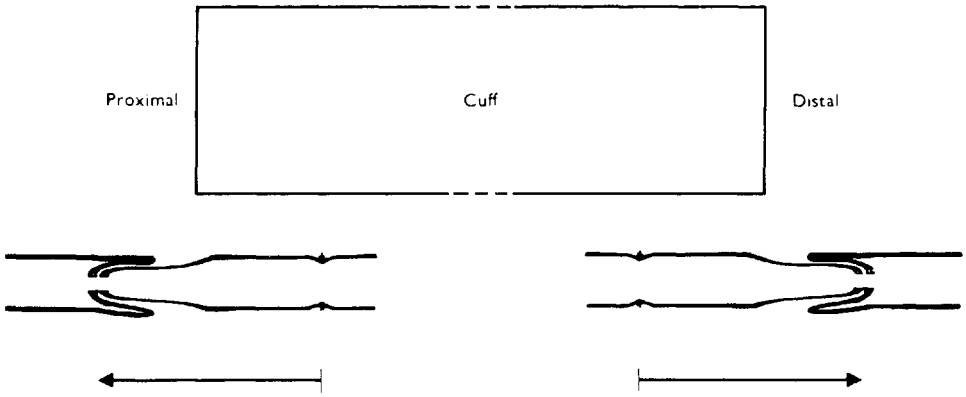

Figure 4–7. Diagram showing the direction of displacement of the nodes of Ranvier in relation to the cuff placed to induce a localized mechanical compression in experimental acute neuropathy. Proximal and distal paranodes are invaginated by the adjacent one. [From Ochoa, Fowler, and Gilliatt,[151] with permission.]

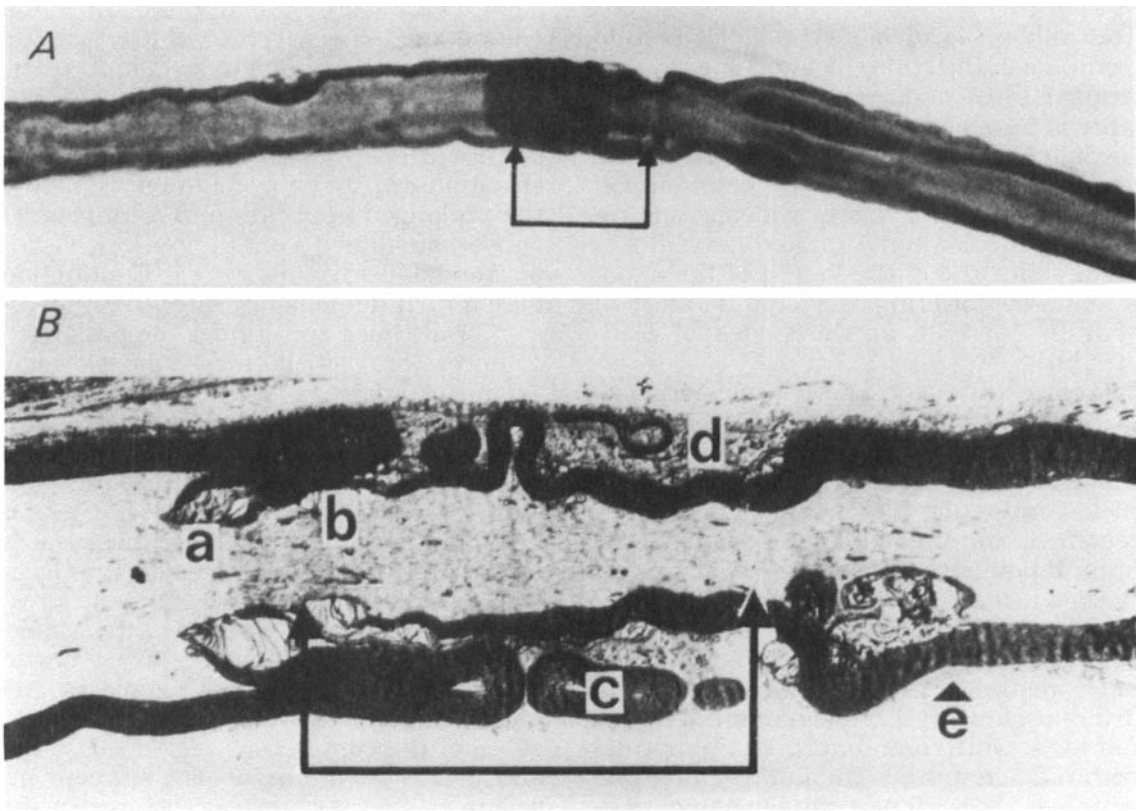

Figure 4–8. A. Part of a single teased fiber showing an abnormal node. **B.** Electron micrograph of nodal region shown in **A.** *a*, terminal myelin loops of ensheathing paranode; *b*, terminal myelin loops of ensheathed paranode; *c*, myelin fold of ensheathing paranode cut tangentially; *d*, Schwann cell cytoplasm; *e*, microvilli indicating site of Schwann cell junction. *Large arrows* show length of ensheathed paranode (~20 μm). [From Ochoa, Danta, Fowler et al,[150] with permission].

Chronic entrapment states such as carpal tunnel syndrome or tardy ulnar palsy also show focal demyelination.[112,152,227] Like acute compression, local demyelination in chronic entrapment results from mechanical forces rather than ischemia, although microscopic findings of single fibers suggest different pathophysiology in the two types. Unexpected abnormalities of nerve conduction studies in asymptomatic subjects suggest a high incidence of subclinical entrapment neuropathy. Routine autopsies in patients without known disease of the peripheral nerve have also documented unpredicted focal anatomic abnormalites.[144]

Patients with demyelinating neuropathy develop paralysis primarily because of conduction block rather than slowed conduction velocity. The paralyzed muscles may show fibrillation potentials and positive sharp waves followng a prolonged lack of neural influence, despite the structural integrity of the axons. In one study,[210] 25 percent of 31 patients had spontaneous discharges solely on the basis of a conduction block lasting more than 14 days. In the remaining 75 percent, spontaneous discharges accompanied an axonal change.

Axonotmesis

In this condition, axonal damage results in loss of continuity and wallerian degeneration of the distal segment followed by denervation-induced muscle atrophy (Fig. 4–9).[129] Conduction ceases immediately across the site of nerve injury followed by irreversible loss of excitability, first at the neuromuscular junction, then the distal nerve segment.[35,136] The time course of such degeneration varies among different species but generally not until four or five days following acute interruption.[80] The proximal stump also undergoes relatively mild retrograde changes. Structurally, sodium (Na^+) channel reorganization follows peripheral target disconnection involving not only the cutaneous afferent cell bodies but also their axons.[175]

In an experimental axotomy in cats, sensory fibers degenerated more quickly than did motor fibers of similar diameter, and velocities of the fast-conducting fibers

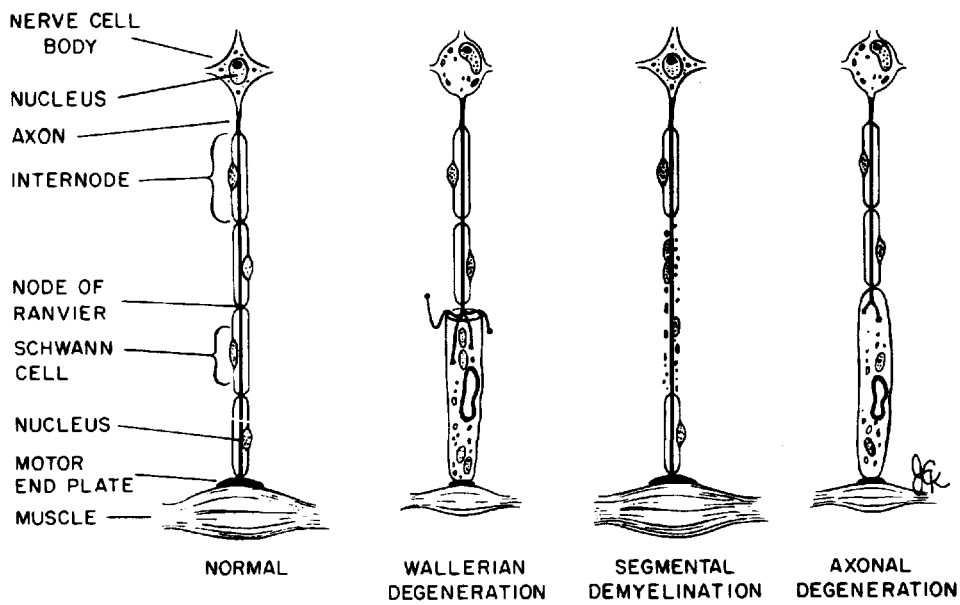

Figure 4–9. Schematic representation of nerve axon and myelin sheath. From left to right: normal structures, wallerian degeneration following transection of the fiber, segmental demyelination, and axonal degeneration secondary to disorders of the nerve cell. [From Asbury and Johnson,[8] with permission.]

decreased at the most rapid rate.[138] 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 and remyelination.[53] In the baboon, the muscle response to nerve stimulation disappears four or five days after nerve section, but an ascending nerve action potential may persist in the segment distal to the section for two or three more days.[78] 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. The central stump of a transected nerve fiber, though excitable, may show reduction in nerve action potentials and conduction velocity, possibly from retraction of the myelin sheath.[99,207] Transverse section at this level reveals a marked reduction in the number of myelinated fibers.[6]

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.[116–118] 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.[184] 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.[118]

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 1–3 mm per day, eventually restoring nearly the normal number and size of fibers.

Available data lack detailed information to precisely characterize conduction abnormalities during wallerian degeneration in humans. In one series, muscle amplitudes fell 50 percent in 3–5 days, and abated completely by the ninth day after injury. Sensory amplitudes declined 50 percent in 7 days and disappeared by the eleventh day. Shorter distal stumps showed an earlier loss of amplitude.[35] 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.[161] During the first few days after nerve injury, studies of distal nerve excitability fail to distinguish axonotmesis from neuropraxia. Finger amputation[177] 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.[37,39,40] Other types of axonotmesis include nerve injuries caused by injections or tourniquets,[228] sustained high intensity electric stimulation,[2] and extreme cooling.[1,95]

Severe compressive neuropathy may at times provide the opportunity to study a single motor axon showing a discrete abnormality.[142] 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 de-

gree 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. Injured axons undergo wallerian degeneration after the first few days of injury. With the loss of distal excitability, the compound action potential elicited by distal stimulation declines steeply. Electromyography shows positive sharp waves one to two weeks and fibrillation potentials two to three weeks after axonotmesis. Rarely, distal nerve inexcitability may result from a proximal nerve lesion without frank axonal degeneration based on the time course of quick recovery.[130] In these cases, changes in the number or property of sodium (Na^+) channels[58] and impaired axoplasmic transport below the lesion may cause the initial inexcitability of the distal axons.

Neurotmesis

Sunderland[199] has proposed three subdivisions of Seddon's neurotmesis. In the first type, the injury damages the axon and surrounding connective tissue, preserving the perineurium and architecture of the nerve sheath. Unlike the central nervous system pathways,[71,107] 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.[115,202] In the second type, which involves the perineurium 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.[125] Surgical intervention includes sensory-motor differentiated nerve repair.[47] The last 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.[63,134,143] If the storage of nerve grafts becomes feasible, the use of peripheral nerve allografts may provide an attractive alternative to conventional nerve autografts.[62] Sometimes, nerve anastomosis, for example, from spinal accessory nerve to facial nerve may achieve a better cosmetic and functional outcome.[57]

Despite the advent of microsurgical techniques, functional recovery following peripheral nerve lesion remains poor.[137] The poor restoration of motor function primarily reflects the limited capacity of injured axons to regenerate across the lesion site and select the appropriate target to reinnervate.[181,200] The complex factors that guide regenerating axons toward appropriate terminations involve such mechanisms as neurotrophic and neurite promoting factors, chemotactic influences, and properties of the extra cellular matrix.[164,181,208] The average axon diameter in the proximal segment of a transected and reconstructed peripheral nerve will decrease shortly after the transection and increase again when the regenerating axons make contact with their targets. As some axons reach their target organs and start to mature, a number of the axons which have not reached a proper target organ will lose their conduction. This loss of signal cancels out the expected maturational increase in compound nerve action potential.[121]

Misdirected regeneration is the rule, not the exception, with motor axons entering any muscles in an almost random fashion, sometimes even from the homologous contralateral motor nucleus.[67] Thus, after nerve repair, especially with proximal injury, aberrant reinnervation abounds, accounting for a poor quality of functional restoration.[16,196] Misdirection of motor axons after proximal section of the nerve probably accounts for the absence of orderly recruitment of motor units.[205] Proprioceptors and other sensory axons may also reinnervate inappropriate end organs, sometimes giving rise to abnormal connections between sensory and motor fibers.[119] Misdirected axon regrowth without central adaptation leads faulty tactile digit localization.[55]

Regeneration may progress poorly, with frequent formation of neuroma.[128] Spontaneous discharges of nerve impulses re-

sult from changes in membrane properties as the source of pain associated with neuromas.[217,223] The accumulation of sodium channels at injured axonal tips may account for ectopic axonal hyperexcitability and the resulting pain and paresthesias.[58] Chronic axonal injury may also lead to intraneuronal heterogeneity of the populations of sodium channels in cutaneous afferents, one population activating the other, leading to membrane instability and possibly to ectopic impulse generation.[170,224] Following re-anastomosis of the nerve, regenerating nerve fibers increase in number and in size gradually over many years, although they regain neither the original number nor diameter.[141,155] The conduction velocity increases slowly, reaching 60 percent of the normal value within 4 years[90] and a mean value of 85 percent after 16 years.[194] Persistent prolongation of the distal latencies suggests the presence of limited number of fibers distally. Metabolic recoveries of the crush denervated muscle follow a similar time course as the sequentially tested conduction characteristics of the damaged nerve.[123] The force produced by the reinnervated muscle depends on the length of time the muscle remained denervated.[68]

In detailed sequential studies of the median nerve after complete section and suture,[27] the regeneration took place at an average rate of 1.5–2.0 mm per day in three patients. The sensory potential, when first recorded 3–4 months after the injury, propagated very slowly at a velocity between 10 percent and 25 percent of normal. The conduction velocity increased 3 percent per month during the first 2 years, and 10 times slower thereafter. The tactile sensibility had returned to normal by 40 months, when the sensory potential showed a normal amplitude but increased duration five times greater than normal. Conduction velocity reached 65–75 percent of normal in the adults. In children, the same degree of recovery occurred 13 to 19 months after anastomosis. The sensory potential returned five times faster after a compressive nerve lesion than after section and repair.

Few studies have dealt with the neurophysiologic recovery of human peripheral nerves after repair with an autogenous nerve graft.[10,119,146] In one series,[203] motor and sensory nerve conduction velocities 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 percent of the normal values obtained in the contralateral limb. Sensory nerve action potentials returned in 44 percent of the nerves after 18 months, though greatly reduced in amplitude and conduction velocity. In another study,[48] based on experience with 67 injured nerves, voluntary motor unit activity returned 7 months after repair and 12 months after grafting. Nerve stimulation elicited a compound muscle action potential by 10 months after suture and 14 months after graft. Motor unit potentials 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 patterns of nerve regeneration as it pertains to the donor and recipient nerves. In one series, the transplanted toe achieved 70–90 percent recovery for temperature, pinprick, light touch, and vibration, but to a lesser extent for two-point discrimination.[41] In fact, the transplanted toe behaved more like a normal toe than a normal finger with regard to current perception threshold.[38] Conduction studies also showed incomplete recovery in toe-to-digit transplantation as compared with digit-to-digit replantation, which resulted in almost complete repair.[41] 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, function in motor endplate was restored in about half a year with the completion of the myelination of the grafted nerve.[213] Long-term alterations may persist or develop after regenerated axons have established connections with their targets.[24] 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.[49,162]

6 INVOLVEMENT OF AXON VERSUS MYELIN IN NEUROPATHIC DISORDERS

The preceding section has dealt with types of conduction abnormalities associated with nerve injuries. These form the basis for assessing electrophysiologic features found in other disease processes, either localized as in entrapment syndromes, or more diffuse as in polyneuropathies. Histologic[96] 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) axonal degeneration with centripetal or dying back degeneration from metabolic derangement of the neuron; and (3) segmental demyelination with slowed nerve conduction.[8,100,131,133] Of these, wallerian and axonal degeneration cause denervation and reduce the amplitude of compound action potential, whereas demyelination slows the nerve conduction with or without conduction block.

Axonal Degeneration

Axons may degenerate in neuropathies after mechanical compression of the nerve, exposure to vibration,[44,127] application of toxic substances, or death of the cell body. Nerve ischemia also causes axonal degeneration, affecting large myelinated fibers first, followed by smaller myelinated fibers and unmyelinated axons.[70] The extent of abnormality varies with location of occlusion.[122] Electromyography reveals normal motor unit potentials that recruit poorly during the acute stage of partial axonal degeneration. Long-duration, high amplitude polyphasic potentials appear in the chronic phase. Fibrillation potentials and positive sharp waves develop in two to three weeks after the onset of illness.

Axonal degeneration, if mild, affects nerve conduction only minimally, especially if the disease primarily involves the small fibers.[215] More commonly, selective loss of the large, fast-conducting fibers results in reduced amplitude and slowing of conduction below the normal range especially when recorded from distal as opposed to proximal muscles.[167] In these cases, the reduction in size of the compound muscle or sensory action potential shows a correlation to the degree of slowing in nerve conduction. In milder cases with the amplitude of the recorded response greater than 80 percent of the expected value, conduction velocity should remain above 80 percent of the lower limits (80% rule).[7,11,26,43] A greater loss of fast conducting fibers would result in further conduction slowing but not beyond 70 percent of the lower limits of the normal value. Thus, physiologic criteria rarely misclassifies a neuropathy with predominant axon loss on biopsy as demyelinating.[126] 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 motor neuron disease have slightly reduced motor conduction velocities. Slower conduction in patients with more severe atrophy, however, may in part reflect lowered temperature of the wasted extremities (see Chapter 5–4).

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 25). Most axonal neuropathies affect both sensory and motor fibers, as exemplified by uremic neuropathies and amyloidosis. Acute intermittent porphyria and hereditory motor sensory neuropathy Type II or neuronal type of Charcot-Marie-Tooth disease (CMT2),[50] however, show prominent motor abnormalities. In contrast, sensory changes predominate in the majority of toxic or metabolic polyneuropathies, Friedreich's ataxia, and some cases of carcinomatous neuropathies. Histological studies in diabetic rats revealed paranodal axonal swellings

and nodal bulgings of the axon during the early metabolic phase of the distal symmetrical polyneuropathy.[185] These alterations correlate with intra-axonal sodium accumulation and decreased sodium equilibrium potentials that account for the early nerve conduction defect. Nerve growth factors not visualized in normal adult nerves become readily demonstrable in nerves undergoing active axonal degeneration.[191]

In neuropathies secondary to chronic alcoholism, carcinoma, and 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.[167] 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,[46] tri-orthorcresyl phosphate neuropathy,[33] acute intermittent porphyria,[34] and experimental acrylamide neuropathies.[73,163,197] In these conditions, impaired axoplasmic flow initially affects the segment of the nerve that is 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.[192]

Single-unit recording in dying back axons has confirmed the earliest failure of impulse generation in the nerve terminal when impulse still propagates normally throughout the remainder of the axon.[195] In acrylamide dying back neuropathy in rats, a sequential morphometric study of the end-plate region showed the initial enlargement of the nerve terminal area distended by neurofilaments.[212] The postsynaptic regions eventually became denuded as more than half of all nerve terminals subsequently disappeared. Unlike the experimental acrylamide neuropathy with clear dying back phenomenon,[93,178] not all the peripheral neuropathies with a distal predominance may 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.[25] 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.[222] In some neuropathies, studies fail to reveal the exact site of the primary damage responsible for axonal degeneration.

Segmental Demyelination in Animal Models

In the second group, disturbance of the Schwann cells causes segmental demyelination associated with unequivocal reduction of nerve conduction velocity, commonly, though not always, substantially below the normal range.[28] 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.

Experimental allergic neuritis serves as one of the most useful animal models for pathogenetic studies of demyelinative neuropathies.[87,193,198] In animal experiments, demyelination blocks the transmission of nerve impulses through the affected zone in some fibers as well as dorsal root ganglion for sensory conduction.[193] 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. Focal segmental demyelination gives rise to slowed conduction locally across the demyelinated segment but not below the lesion.[88] In addition to various toxins,[59] injection of proteinase K to the nerve[226] or removal of a small piece of perineurium in amphibian nerve[160] causes a lesion consistent with demyelination. Experimental conduction block may also results from serum containing anti-myelin-associated glycoprotein (MAG), IgM M protein[211] or anti-GM_1 antibodies.[176] These antibodies could affect sodium channels[64,216] at the nodes of Ranvier where GM_1 abounds.[42]

In an experimental study on demyelination induced by diphtheria toxin, conduction velocity began to decline one week

after inoculation, reached a plateau during the sixth to eighth weeks, and recovered to the original level between the 18th and 20th weeks.[97,98] The dose of toxin administered determined the degree of slowing and the severity of paralysis. The amplitude of the compound muscle action potential predicted the loss of strength more accurately than the conduction velocity. 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.[198] 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 16 days. Morphologic studies revealed evidence of remyelination with two to eight myelin lamellae around each axon coincident with the onset of clinical and electrophysiologic recovery. Conduction velocities returned to pre-injection values by the 37th day, when the myelin layer of remyelinating fibers averaged only about one third that of control nerves. Serial studies of an experimentally produced demyelinating lesion in cat spinal cord[188] revealed the onset of conduction block during the initial phase. Remyelination commenced in the latter part of the second week concomitant with restoration of conduction through the lesion in the affected fibers. Within three months the initially prolonged refractory period returned to normal, even though the newly formed internodes remained abnormally thin. In the adult rat spinal cord, transplantation of cultured myelin-forming cells from the peripheral nervous system resulted in the functional repair of demyelinated axons.[92,214]

Pathophysiology of Demyelination

Myelin normally provides high impedance and low capacitance, preventing leakage current through the internodal membrane to sustain saltatory conduction. Action current through sodium channels at the activated node of Ranvier produces "inward ionic current," which subsequently causes "outward capacitative current" at the next node to be excited. This in turn depolarizes the nodal membrane to threshold, thus opening the sodium channels and initiating another cycle of "inward ionic current." The safety factor of transmission, defined as a ratio of action current available at a node to threshold current, must exceed unity for successful conduction through a node.

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. Reorganization of sodium channels also plays an important role in the pathophysiology of demyelination.[132,147,180] 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. With advanced demyelination, the safety factor eventually falls below unity, and the conduction fails because the current no longer depolarizes the next node of Ranvier beyond threshold. Raising the body temperature reduces the amplitude of action potentials, further lowering the safety factor. Thus, demyelinated nerves suffer from temperature-induced inpulse blocking more than healthy nerves.[36,69]

It is possible to raise the safety factor above unity by prolonging the action current using an inhibitor of the voltage-dependent potassium (K^+) channel such as scorpion toxin.[23] Similarly, 4-aminopyridine partially reverses symptoms in patients with multiple sclerosis,[22] but not in those with inflammatory demyelinating neuropathies.[13] Ion channel blockers may also exert immunomodulatory effects, which may have implications for their therapeutic application in neuropathic disorders.[139]

Normal nerves can transmit impulses at high rates over several hours[104,171] exceeding the maximal motor unit firing frequency of 50–70 Hz under physiologic conditions. By contrast, demyelinated nerve fibers, though capable of transmitting lower-frequency impulses faithfully, may block higher-frequency discharges.[120] Rate-dependent failure also characterizes other neuropathies. For example, in rats

with acute streptozotocin-induced diabetes, insulin therapy preserves normal nerve conduction velocity and amplitude but not under the stress produced by high-frequency stimulation.[5] This type of block should impair information coded in frequencies up to 250 Hz or more in the central nervous system and peripheral sensory nerves. The severity of the physiologic defect dictates the critical frequency for block at the site of the lesion. Important factors include fiber geometry, sodium (Na^+)-potassium (K^+) pump activation and ion channel density in the demyelinated segment. After an action potential, sodium accumulates in axoplasm, more so after transmission of high-frequency impulses. This increase in sodium concentration surpasses the physiologic range in a demyelinated axon, which, to compensate for the current dissipation, must sustain more action current than in normal axons. High sodium concentration in turn activates the electrogenic sodium-potassium pump, which removes sodium in exchange for potassium at a 3 to 2 ratio, thus raising the threshold of the nodal membrane by hyperpolarization.[20] A raised threshold may lower the safety factor below unity, leading to rate-dependent conduction block.

One new therapeutic strategy exploits digitalis, which specifically inhibits the sodium-potassium pump,[102,103] thus circumventing rate-dependent conduction block by pump activation. In animal models with demyelination, digitalis not only reversed rate-dependent block but also normalized complete conduction block. The inhibition of the pump, lowering the resting membrane potential or the threshold of activation, also explains this additional action. Another experimental study[81] confirmed the beneficial action of digitalis. In this study, the combined use of 4-aminopyridine and digitalis provided a more than additive action to reverse conduction block. These experimental data provided a rationale for the use of intravenous digitalis in selected patients with multiple sclerosis.[101] Despite transient improvement of the symptoms clinically and as tested by physiologic means, the use of digitalis could not serve as a general therapeutic approach because of its very modest action and possible cardiac side effects. Perhaps a digitalis derivative with better penetrance through the blood-brain barrier would render a better therapeutic effect.

Clinical Consequences of Demyelination

The pathophysiology of demyelination and its clinical consequences[77,104,114,190] include (1) elevated thresholds and conduction block resulting in clinical weakness and sensory loss; (2) increased desynchronization of volleys causing 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 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 major loss of strength. In contrast, slowing of conduction by itself leads to few, if any, clinical symptoms, as long as all the impulses arrive at the target organ. Further, a prolonged refractory period for transmission, though helpful as a diagnostic indicator,[79] causes no symptoms because the time intervals between voluntarily induced repetitive discharges in motor axons substantially exceed the refractory periods under physiologic conditions. Nonetheless, the identification of demyelination by these means offers potentially important clues to conditions that may reverse by pharmacologic, immunologic, or surgical measures. Slow nerve conduction resembling demyelination, however, can result from physiological sodium channel blockage by toxins.[82] Nitric oxide also reversibly blocks axonal conduction.[168] Other possibilities include excitability changes of the axons during hyperventilation and ischemia.[140]

Common demyelinating diseases of the

peripheral nerve include the Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy, myelomatous polyneuropathy, hereditary motor sensory neuropathy type I or the hypertrophic type of Charcot-Marie-Tooth disease, hereditary neuropathy with susceptibility to pressure palsies, metachromatic leukodystrophy,[72] and Krabbe's leukodystrophy (see Chapter 25–3 and 25–5). Some cases of diabetic and carcinomatous neuropathies also belong to this category, although most paraneoplastic syndromes show axonal degeneration rather than demyelination. Diphtheritic polyneuritis no longer affects humans very often. Alterations in nerve conduction in this condition resemble those seen in animal experiments, with marked reduction in conduction velocity diffusely or, in the case of focal demyelination, over a relatively resticted region. Despite the well-established concept of segmental demyelination in experimentally induced chronic lead intoxication, nerve conduction studies in human cases show either normal[186] or only mildly slowed values.[66]

In some hereditary neuropathies, the demyelinative process uniformly affects the nerve throughout its length, delaying saltatory conduction more or less at all the nodes of Ranvier. By contrast, segmental conduction block in certain parts of the nerve characterizes acquired demyelinating neuropathies with non-uniform involvement. Slowing of nerve conduction then accompanies a reduction of amplitude, indicating localized neurapraxia.[65] Conduction block may also occur as an early sign of reversible injury in ischemic neuropathy.[105] Thus, electrophysiologic evidence of conduction block does not always imply the presence of focal demyelination.[159,182] Conversely, conventional nerve conduction studies, basically designed for assessment of the distal segments, may fail to elucidate a focal proximal demyelinating lesion in the proximal segment.[111] Increased range of conduction velocity results if the disease affects smaller fibers exclusively or out of proportion to its effect on larger fibers. The evoked action potential broadens, indicating a pathologically increased 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. Unless damage of the myelin sheath results in secondary axonal degeneration, electromyography reveals little or no evidence of denervation. The motor unit potentials, though normal in amplitude and waveform, recruit poorly, indicating a conduction block in severely demyelinated fibers.

Types of Abnormalities in the Clinical Domain

In the arbitrary division into axonal and demyelinating neuropathies, few cases fall precisely into one group or the other. A neuropathy with extensive demyelination often accompanies slight axonal degeneration.[52,206] In a study of antiserum-mediated demyelination, the inflammatory reaction could account for the axonal degeneration seen in 5–15 percent of myelinated fibers.[174] Conversely, axonal atrophy proximal to a neuroma or distal to constriction may cause secondary paranodal demyelination in the presence of healthy Schwann cells.

Other conditions that may belong to this mixed category include neuropathies associated with diabetes, uremia, myeloma, and Friedreich's ataxia. Axonal enlargemet can also cause axon-triggered demyelination as in giant axonal neuropathy or hexacarbone intoxication (see Chapter 25–4). 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 nerve conduction studies.[12]

Despite the possibility of mixed abnormalities, the electrophysiologic finding of any true axonal or demyelinating component provides an important and major contribution in the differential diagnosis. Certain conduction abnormalities support the diagnosis of a predominantly demyelinating component even when superimposed upon moderate axonal degeneration as demostrated on needle electromyography.[7,11,26,43,126] These include reduction of conduction velocity below 70–80 percent of the lower limit, prologation of dis-

tal motor or sensory latency and F wave latency above 120 percent of the upper limit, and the presence of unequivocal conduction block.[3,108] In contrast, the absence of these criteria does not necessarily preclude an early demyelinating process. In fact, a substantial number of patients with the Guillain-Barré syndrome have no major slowing of conduction along the nerve trunk initially. Beyond such a broad classification, electrical studies have limited value in distinguishing one variety of neuropathy from another.[51] In particular, conduction studies and electromyography rarely elucidate a specific etiology. Further, clinical electrodiagnosis assists only indirectly in the differential diagnosis of neuropathic pain caused primarily by diseases of small-caliber nerve fibers, which routine methods fail to assess adequately, and in the exclusion of a large number of patients with chronic pain syndrome who probably suffer from disorders other than neuropathy. These limitations notwithstanding, conduction studies can provide diagnostically pertinent information if used judiciously in appropriate clinical contexts.[113]

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Chapter 5

PRINCIPLES AND VARIATIONS OF NERVE CONDUCTION STUDIES

1. INTRODUCTION
2. ELECTRICAL STIMULATION OF THE NERVE
   - Cathode and Anode
   - Types of Stimulators
   - Stimulus Intensity and Duration
   - Stimulus Artifact
3. RECORDING OF MUSCLE AND NERVE POTENTIALS
   - Surface and Needle Electrodes
   - Optimal Recording of Intended Signals
   - Averaging Technique
   - Display and Storage of Recorded Signals
4. MOTOR NERVE CONDUCTION
   - Stimulation and Recording
   - Calculation of Conduction Velocity
   - Possible Sources of Error
   - Types of Abnormalities
5. SENSORY NERVE CONDUCTION
   - Stimulation and Recording
   - Waveform, Amplitude, and Duration
   - Latency and Conduction Velocity
6. NERVE CONDUCTION IN THE CLINICAL DOMAIN
   - Physiologic Variation Among Different Nerve Segments
   - Effects of Temperature
   - Maturation and Aging
   - Height and Other Factors
   - Clinical Values and Limitations
7. STUDIES OF THE AUTONOMIC NERVOUS SYSTEM
   - Heart-Rate Variation with Breathing
   - Valsalva Ratio
   - Response to Change in Posture
   - Sympathetic Skin Response
8. OTHER EVALUATION OF NERVE FUNCTION
   - Microneurography
   - Thermal, Pain, Vibratory, and Tactile Sensation
   - Thermography

1 INTRODUCTION

Helmholtz (1850)[133] originally recorded the mechanical response of a muscle to measure conduction velocity of motor fibers (see Appendix 1). Piper (1909)[251] used the muscle action potential for this purpose. Subsequent animal experiments[21] and human studies[138] popularized the technique as a clinical test. Eichler (1937)[84] recorded nerve potentials percutaneously in man. Dawson and Scott (1949)[58] introduced photographic superimposition and later electrical averaging for better resolution, making it possible to record sensory nerve action potentials through surface electrodes after stimulation of the digital nerves.[60]

With steady improvement of recording apparatus, nerve conduction studies have become a simple and reliable test of peripheral nerve function. With adequate standardization, the method now provides a means of not only objectively indentifying the lesion but also precisely localizing the site of maximal involvement.[162] Electrical stimulation of the nerve initiates an impulse that travels along the 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 the motor fibers and from the nerve itself, in the case of the sensory fibers. The same principles apply in all circumstances, although the anatomic course and pattern of innervation dictates the exact technique used for testing a given nerve.[201] In addition to electrical shocks, used in most clinical studies, tactile stimulation can also elicit nerve action potentials.[15,35,222] Assessment of mechanical characteristics helps delineate contractile properties of the isometric twitch induced by stimulation of the nerve.[219]

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 0.5–1.0 cm in diameter. Stimulating electrodes consist of a cathode (negative pole) and an anode (positive pole), so called because they attract cations and anions. As the current flows between them, negative charges that accumulate under the cathode depolarize the nerve. Conversely, positive charges under the anode hyperpolarize the nerve, although probably not to the extent of blocking the conduction during routine studies.[74] 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. Clearly labeling the stimulating electrodes avoids inadvertent surface measurement from the cathode at one stimulus site to the anode at another, which would lead to an erroneous results.

Types of Stimulators

Most commercially available stimulators provide a probe that mounts the cathode and the anode at a fixed distance, usually 2–3 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. Some electromyographers prefer a monopolar stimulation with a small cathode placed on the nerve trunk over the volar surface and a large anode over the dorsal surface in the same limb. The conduction velocities obtained in this fashion differ slightly, but randomly, from those determined by bipolar arrangements. The use of a needle inserted subcutaneously as the cathode reduces the current necessary to excite the nerve compared to surface stimulation. The maximum current during such stimulation causes neither electric nor heat damage to the tissue.[248] Either a surface electrode located on the skin nearby or a

second needle electrode inserted in the vicinity of the cathode may serve as the anode.

Electromyographers use two basically different kinds of electric stimulators in nerve conduction studies (see Chapter 3–7). Of these, constant-voltage stimulators regulate the output in voltage so that the actual current varies inversely with the impedance of the electrode, skin, and subcutaneous tissues. In constant-current units, the voltage changes according to the impedance, so that a specified amount of current 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 provides a better means of serially assessing the level of shock intensity as a measure of nerve excitability.

Stimulus Intensity and Duration

The output impulse provides a square wave of variable duration, ranging from 0.05 to 2.0 ms. Surface stimulation of 0.1 ms duration and 100–300 V or 10–30 mA intensity usually activates a healthy nerve fully. A study of diseased nerves with decreased excitability may require a maximal output of 400–500 V or 40–50 mA. Electrical stimulation within the above intensity range causes no particular risk unless the patient is electrically sensitive. Any current, if delivered near the implantation site, for example, could inhibit a cardiac pacemaker.[27] Special care to safeguard such patients includes proper grounding and placement of the nerve stimulator at sufficient distance from the pacemaker.[1,179]

Similarly, in patients with indwelling cardiac catheters or central venous pressure lines inserted directly into the heart, all the current may directly reach the cardiac tissue. This possibility makes routine nerve conduction studies contraindicated in such patients. Implanted cardioverters and defibrillators also pose safety hazards that usually preclude electric stimulation near the implantation site. Consultation with a cardiologist with special expertise in this area should address feasibility of a nerve conduction study in any patient using such a medical device, and the need to turn the system off or on during the procedure. Placing the stimulator at least 6 inches away may minimize the chance of externally triggering the device.[233] Electromyographers should always keep in mind these and other problems related to general electrical safety (see Appendix 3).

It is common to qualify electrical stimuli on the basis of the magnitude of the evoked potential. A threshold stimulus barely elicits a response in some, but not all, of the axons contained in the nerve. Increasing the duration of stimulation decreases the threshold intensity, thereby prolonging the latency of nerve volleys whether tested in single motor axons, compound nerve potentials or H reflexes.[227,228,243] A maximal stimulus activates the entire group of axons, so that further increase in shock intensity causes neither additional increase in the amplitude nor shortening in latency of the evoked potential. Unlike a threshold stimulus, a maximal shock activates the axon at or close to its rising edge, independent of its duration. 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 supramaximal stimulus has an intensity greater than the maximal stimulus. Increasing the intensity of an already supramaximal stimulus continue to shorten the latency of nerve volleys because the spread of current tends to activate the nerve segment away from the cathodal point.

If fibers with large diameters have the lowest threshold in humans, as in experimental animals,[89,300] 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,[269] the exact order of excitation also depends on the spatial relationship of various fibers and the stimulating electrode.[109,252] Further, in motor conduction studies, the length of the axon terminals, which partially determines the latency of the muscle response, varies

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.[151] 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 and a train of stimuli of different rates and duration. Ideally, each of the paired stimuli should have independent controls of both duration and intensity. A trigger output for the oscilloscope sweep should precede each stimulus by a variable delay, to allow a clear marking of the exact stimulus point on the display.[285]

Stimulus 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.[48] Not only does this eliminate amplifier overloading, but it also protects the patient from unexpected current leakage. 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 circumvents the problem of stimulus artifacts.[324] Even then, optimal recording of short-latency responses calls for adequate reduction of surface spread of stimulus current, as stated below.

Shock artifacts increase with less separation between stimulus and recording sites and greater distance between the active (G_1) and reference (G_2) electrodes. The stimulator leads, which have no shield, can also cause a large artifact if placed near the recording electrodes. With excessive surface spread, a square pulse of 0.1 ms duration can affect the active electrode for several milliseconds at the signal level of recording with high sensitivity. Thus, reduction in surface spread of stimulus current ensures an optimal recording of short-latency responses. Wiping with alcohol helps dry the moist skin surface before the application of the stimulus. 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 electrode 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, in general, are better suited than needle electrodes for recording a compound muscle action potential in assessing contributions from all discharging units. Its onset latency indicates the conduction time of the fastest fibers, and its amplitude serves as a measure of the number of available axons. Averaging technique, though not usually required, may help in evaluating markedly atrophic muscles.[14] A needle electrode registers only a small portion of the muscle action potential, showing a more abrupt onset and less interference from neighboring discharges. Thus, its use may help in evaluating small atrophic muscles when surface recording fails. It also improves seg-

regation of an action potential from a target muscle after proximal stimulation, which tends to excite many muscles simultaneously.

Surface electrodes suffice for recording sensory and mixed nerve action potentials. Some electromyographers, however, prefer needle electrodes placed perpendicular to the nerve to improve the resolution. With this technique, the amplitude of the recorded potential increases by a factor of 2–3 times.[269] 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. Many laboratories now use ring electrodes placed over the proximal and distal interphalangeal joints to record the antidromic sensory potentials from the digital nerves. Studies of the commonly tested nerves usually require no averaging because individual stimuli give rise to sensory potentials of sufficient amplitude. Unnecessary averaging is often a poor excuse for a bad technique.

Optimal Recording of Intended Signals

The principles of amplification and display used in electromyography also apply to nerve conduction studies (see Chapter 3–3). Instead of continuous runs, a prepulse intermittently triggers the sweep, followed, after a short delay, by the stimulus. This arrangement allows 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 amplitude and the latency. Overamplification results in truncation of the recorded response, whereas underamplification precludes accurate measurements of its take-off from the baseline.

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,[32] as does placing the first stage of the amplifier near the electrode site with a remote preamplifier box.[324] The use of digital averaging represents a major improvement over the photographic superimposition[58] and early averager[59] with its motor-driven switch and multiple storage capacitors. The electronic devices now in use are triggered by repetitive stimulation to sum consecutive samples of waveforms that are stored digitally after each sweep.

The voltage from noise that randomly changes its 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 from the background noise within certain limits. In 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.[235] 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 every time the number of trials is doubled.

Display and Storage of Recorded Signals

The use of an oscilloscope with digital storage capacity can display a series of responses with a stepwise vertical shift of the baseline, to facilitate the comparison of successively elicited potentials in waveform and latency. An automatic device digitally displays the latency based on mathematically defined take-off from the baseline. When necessary, manual positioning of the marker to the desired spot of the waveform improves accuracy. Conversely, minor adjustments inconsistent with the overriding definition may induce measurement errors. 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 channels, however, have a distinct advantage in simultaneous recording of related events. Oscilloscopes with four or more channels allow multichannel analysis.

A magnetic tape recorder can store the original potentials using either frequency modulation (FM) or amplitude modulation (AM). The FM mode has a limited high-frequency response, but can adequately record the frequency range of the compound action potential, including DC changes. Further, in the analysis of evoked muscle or nerve potentials, the FM method preserves the amplitude of the recorded potential very accurately. In contrast, the AM modulation responds well to high-frequency bands but distorts the amplitude of the recorded response. The AM method preserves the high-frequency components better for recording motor unit potentials with needle electrodes (see Chapter 3–5).

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 muscle action potentials (Fig. 5–1) with a pair of surface electrodes: an active lead (G_1) placed on the belly of the muscle and an indifferent lead (G_2) placed on the tendon.[168,330] Depolarization under the cathode results in the generation of a nerve action potential, whereas hyperpolarization under the anode tends to block the propagation of the nerve impulse (see Chapter 4–3). Although this

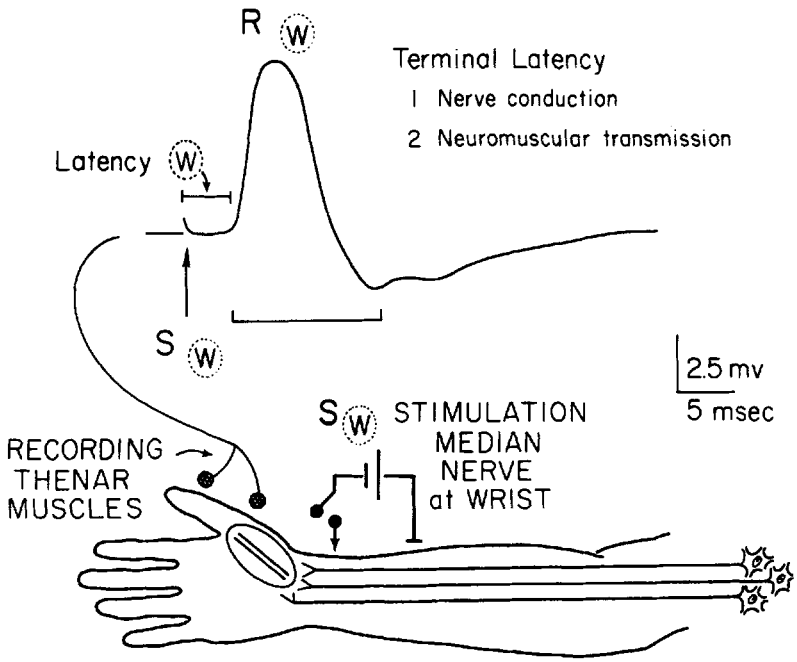


Figure 5–1. Compound muscle action potential recorded from the thenar eminence following stimulation of the median nerve at the wrist. The distal or terminal latency includes (*1*) nerve conduction from the stimulus point to the axon terminal and (*2*) neuromuscular transmission, including the time required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

poses theoretical rather than practical concern in the usual clinical setup, placing the anode 2–3 cm proximal to the cathode precludes the possibility of blocking the propagation of the nerve impulse. Pulses of moderate intensity help adjust the position of the cathode until further relocation causes no change in the size of the muscle action potential. With the cathode at the best stimulating site, increasing the intensity elicits a progressively larger response until it reaches a maximal potential. Increasing the stimulus further should result in no change in the size of the muscle potential. The use of a 20–30 percent supramaximal intensity guarantees the activation of all the nerve axons innervating the recorded muscle.

With belly-tendon recording, the propagating muscle action potential, originating under G_1, located near the motor point, gives rise to a simple biphasic waveform with the initial negativity (see Chapter 2–4). A small positive potential may precede the negative peak with inappropriate positioning of the recording electrodes.[77] If G_1 placed outside the motor point records a positivity from one part of muscle and a negativity from another, canceling effect makes the initial segment isoelectric with apparent delay of onset.[298] This "false" motor point may also result from inadvertent recording from nearby muscles.[63] The location of G_2 substantially influences the waveform of recorded response.[27]

The compound muscle action potential 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.[16] A single shock applied to the nerve activates a group of motor units slightly asynchronously, reflecting the difference in conduction velocity and in terminal length of individual nerve axons (see Chapter 7–5). 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 pick up electrodes determines the spatial orientation to the constituent motor units and consequently the pattern of their contribution.[30,161,168,184,221,318,319] The use of large electrodes tends to reduce site-induced variability of recorded potentials.[305,317]

The usual measurements include amplitude from the baseline to the negative peak or between negative and positive peaks; duration from the onset to the negative or positive peak or to the final return to the baseline; and latency, from the stimulus artifact to the onset of the negative response. Electronic integration can provide the area under the waveform, which shows a linear correlation to the product of the amplitude and duration measured by conventional means.[108] 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 end plate, including the time required for generation of muscle action potential. Onset latency in general provides a measure of 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, and neuromuscular transmission including 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

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

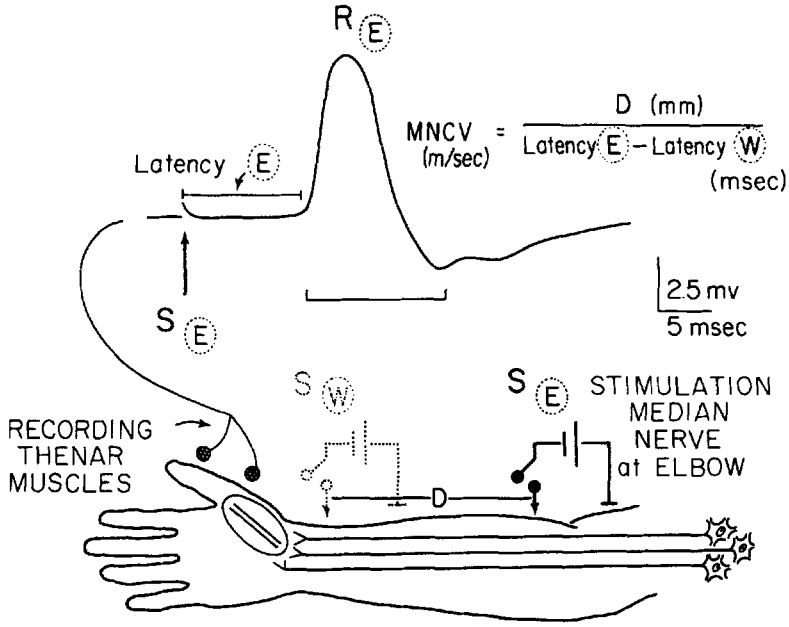


Figure 5–2. Compound muscle action potential recorded from the thenar eminence following the stimulation of the median nerve at the elbow. The nerve conduction time from the elbow to the wrist equals the latency difference between the two responses elicited by the distal and proximal stimulations. The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

where D is the distance between the two stimulus points in millimeters, and L_p and L_d, 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 centimeters, and preferably more than 10, 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 6–2, 7–6).

The latency from the most distal stimulus point to the muscle includes not only the nerve activation and conduction time but also neuromuscular transmission time. The inclusion of the additional factors precludes calculation of conduction velocity over the most distal segment. Here, meaningful comparison requires the use of either premeasured fixed distance or anatomic landmarks for electrode placement.[223] Both approaches equally improve the accuracy of latency determination.[226] 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.[153,172] 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 6–2).[280] For example, a patient with a measured distal latency (L_d) of 4.0 ms for the terminal distance 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/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).

Possible Sources of Error

In normal subjects, shocks of supramaximal intensity elicit almost, but not exactly, identical compound muscle action potentials, 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 7–5). 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. 7–11). The evoked potentials of dissimilar shapes preclude accurate calculation of conduction velocity, because the two onset latencies may represent motor fibers of different conduction characteristics.

Distorted waveforms result from the use of an inappropriately low stimulus intensity, which activates only part of the nerve fibers. Conversely, an excessive stimulus intensity can cause an erroneously short latency because the spread of stimulus current depolarizes the nerve a few millimeters away from the cathode.[250] 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.[334]

When recorded with a high sensitivity, a small negative peak sometimes precedes the main negative component of the muscle action potential.[33,117,285] This small potential, disregarded in latency determination, probably originates from small nerve fibers near the motor point.[76] A small nerve action potential recorded from the digital nerve by the G_2 electrode has a longer latency and opposite polarity.[118] In addition, G_2 electrodes placed distal to the metacarpophalangeal junctions usually register a positive far-field potential (see Chapter 20–3),[166] which may constitute the premotor potential recorded by G_1 as a small negativity preceding the main muscle response.[64,78,244] Awareness of these possibilities helps one avoid miscalculation, especially if the nerve potential not seen with stimulation at one point appears at a second point with the use of a higher sensitivity for improved resolution. The use of the same amplifier sensitivity minimizes this type of error for comparison of successively elicited potentials with stimulation along the course of the nerve.

Types of Abnormalities

In general, axonal damage or dysfunction results in loss of amplitude, whereas demyelination leads to prolongation of conduction time (see Chapter 4–5 and 4–6). 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, three basic types of abnormalities characterize motor nerve conduction studies when stimulating the nerve proximal to the presumed lesion (Fig. 5–3): (1) reduced amplitude with normal or slightly increased latency, (2) increased latency with relatively normal amplitude, and (3) absent response. In the first variety, a shock below the lesion may elicit a normal compound muscle action potential, even though proximal stimulation above the lesion evokes reduced amplitude (Fig. 5–4). This finding, if seen during the first few days of injury, fails to differentiate a partial nerve lesion causing neurapraxia or early axonotmesis before the onset of distal degeneration. Distinction between the two becomes possible by stimulating the nerve below the lesion several days after the injury, when degenerating axons will have lost their excitability. In partial neurapraxia, the distally evoked muscle response still exceeds the proximally elicited potential in amplitude. In contrast, stimulation above or below the lesion elicits an equally reduced amplitude in axonotmesis. Because the amplitude of the muscle response varies considerably from one normal subject to another, minor diminution in the recorded potential seen diffusely often escapes detection.

In the second variety, slowed conduction accompanies relatively normal amplitude in stimulation above the lesion (Fig. 5–5). These changes generally imply segmental demyelination without conduction block affecting a majority of the nerve fibers. As shown in rabbits, incomplete proximal compressive lesions may also give rise to slowed conduction with a reduction in external fiber diameter distal to the site of constriction.[12] The time course of recovery suggests that in these cases, conduction slowing along the dis-

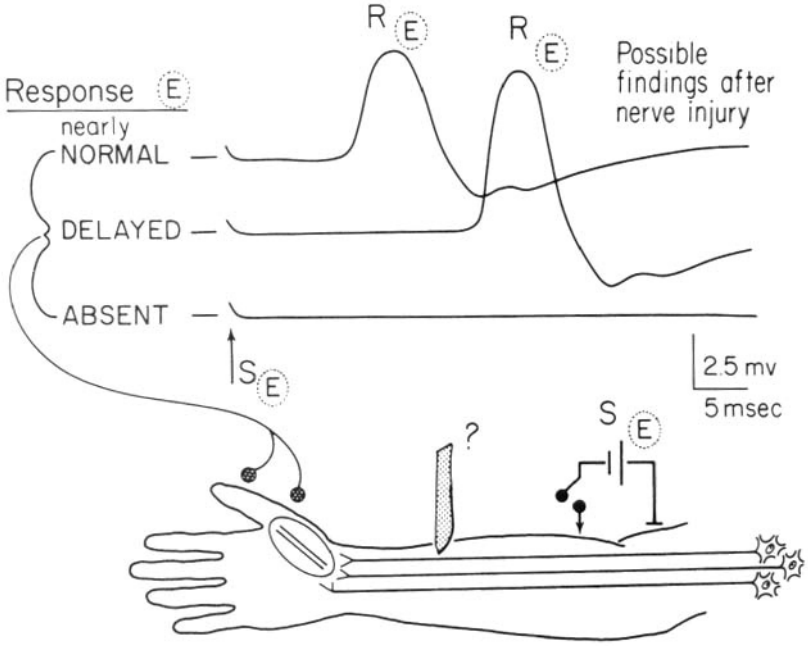


Figure 5–3. Three basic types of alteration in the compound muscle action potential occur after a presumed nerve injury distal to the site of stimulation; mildly reduced amplitude with nearly normal latency (*top*), normal amplitude with substantially increased latency (*middle*), or absent response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

tal nerve segment results from distal paranodal demyelination.[13] With neurapraxia, proximal stimulation above the lesion gives rise to a smaller compound muscle action potential than does a distal stimulation below the lesion (Figs. 5–6 and 5–7). A reduction in size of the compound muscle action potential may also result from phase cancellation between peaks of opposite polarity based on pathologically increased temporal dispersion in the absence of a conduction block.[165] Such an excessive temporal dispersion commonly develops in acquired demyelinative neuropathies (Fig. 5–8). If the distal and proximal responses assume dissimilar wave-

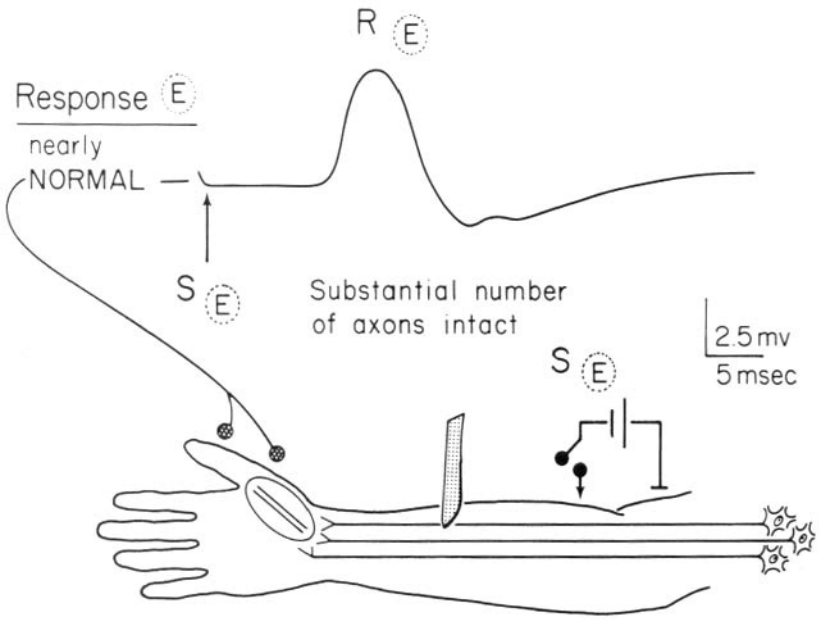


Figure 5–4. Mild reduction in amplitude of the compound muscle action potential with a nearly normal latency. This type of abnormality indicates that a substantial number of axons remain functional. The affected axons, constituting only a small portion of the total population, have either neurapraxia 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 major abnormality.

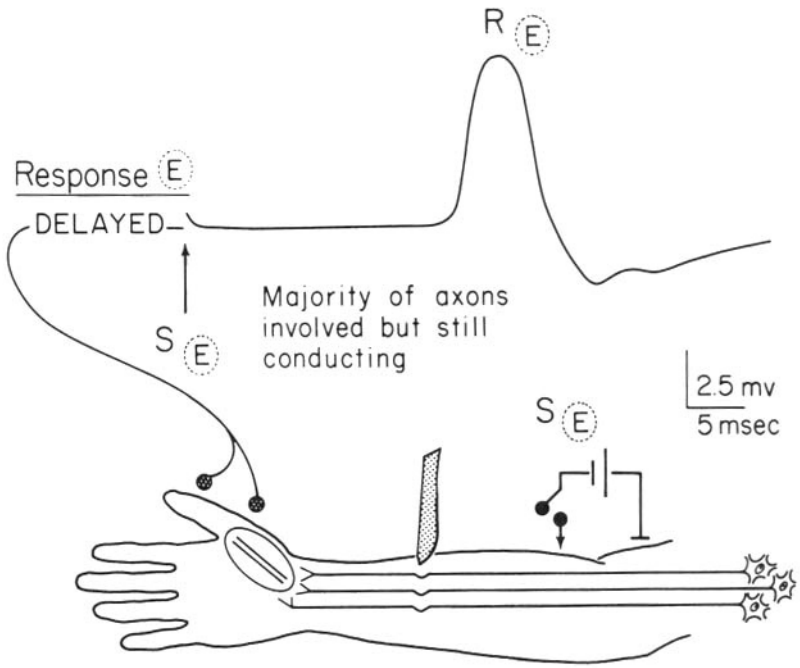


Figure 5–5. Increased latency of the compound muscle action potential with normal amplitude. This type of abnormality indicates demyelination affecting the majority of nerve fibers, as in a compression neuropathy. Conduction block, if present during acute stages, will also diminish the amplitude of the recorded response.

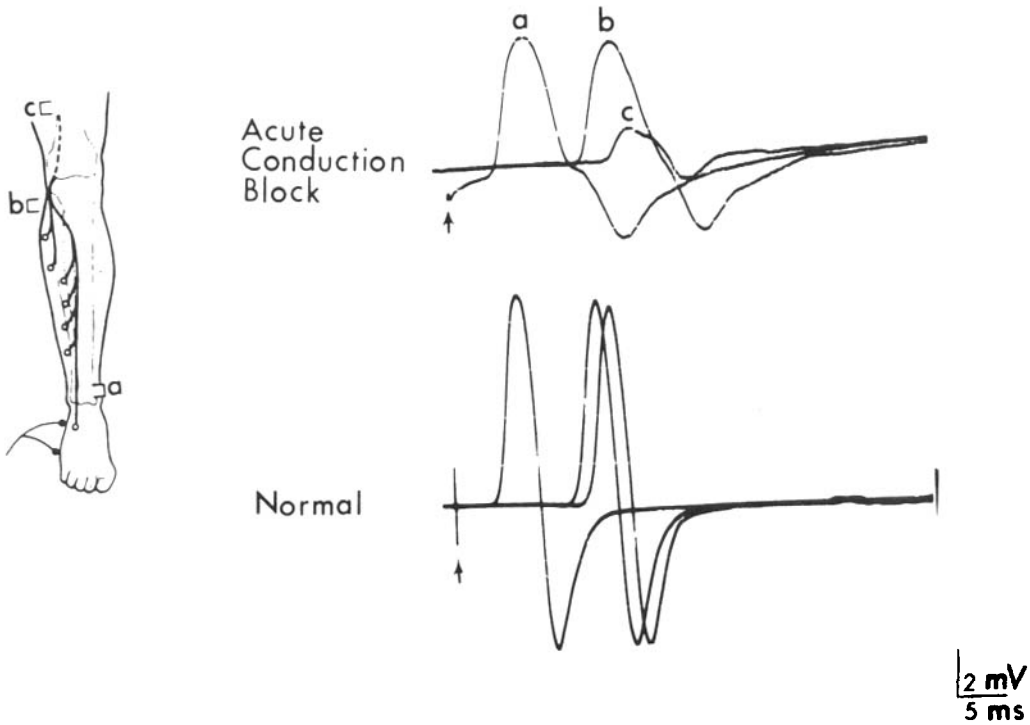


Figure 5–6. A 67-year-old man with an acute onset of footdrop after chemotherapy and radiation treatment of prostate cancer. Although epidural metastasis was suspected clinically because of backache, nerve conduction studies showed evidence of a conduction block at the knee, indicating a compression neuropathy. [From Kimura,[163] with permission.]

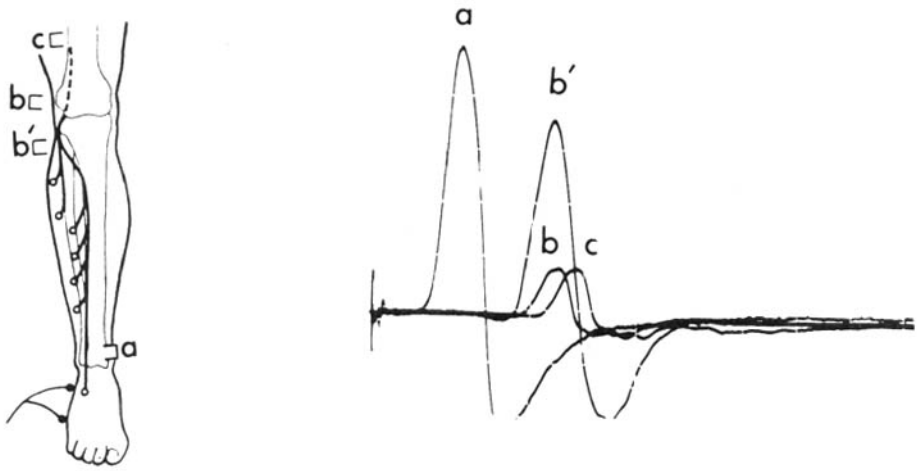


Figure 5–7. A 34-year-old man with selective weakness of foot dorsiflexors and low back pain radiating to the opposite leg. Nerve conduction studies revealed a major conduction block between the two stimulation sites, *b* and *b′*, at the knee. The weakness abated promptly when the patient refrained from habitual leg crossing. [From Kimura,[163] with permission.]

forms, their onset latencies may represent two groups of motor fibers with different conduction characteristics, precluding accurate calculation of velocity.

A prolonged latency or slowing of the conduction velocity may also result from axonal neuropathy with loss of the fast-conducting fibers.[95] A major reduction in amplitude to less than 40–50 percent of the mean of the normal value usually accompanies this type of slowing. In fact, if the amplitude remains more than 80 percent of the control value, a reduction of the conduction velocity to less than 80 percent of lower limits of normal suggests the presence of demyelination. With a further diminution of amplitude to less than half the mean normal value, the conduction velocity may fall to 70 percent of the lower limit without demyelination. For the same reason, slowed motor conduction also results from loss of large anterior horn cells in myelopathies. Here, the motor conduction velocity can decrease to 70 percent of the mean normal value with diminution of amplitude to less than 10 percent of normal.[180] Regardless of the amplitude, however, a conduction velocity reduced to less than 60 percent of the mean normal value suggests peripheral nerve disease, not myelopathy.[181]

Absent or very small proximal responses indicate that most of the nerve fibers fail to conduct across the site of the presumed lesion (Fig. 5–9). One must then differentiate a neurapraxic lesion from nerve transection. In either case, nerve stimulation distal to the lesion elicits an entirely normal muscle action potential for the first 4–7 days. During the second week, however, the normal distal excitability distinguishes neurapraxic changes from axonal abnormalities. With neurotmesis, stimulation below the point of the lesion produces no muscle action potentials, because of the initial failure at the neuromuscular junction (Fig. 5–10). The loss of nerve excitability follows during subsequent wallerian degeneration. Serial electrophysiologic studies help delineate progressive recovery from severe axonopathy on the basis of the amplitude of the evoked potential (Fig. 5–11).

Single stimulation may also evoke various types of delayed responses usually representing focal reexcitation of hyperexcitable axons or abnormalities of the neuromuscular junction (see Chapter 18–3).[316] Stimulation applied at different lev-

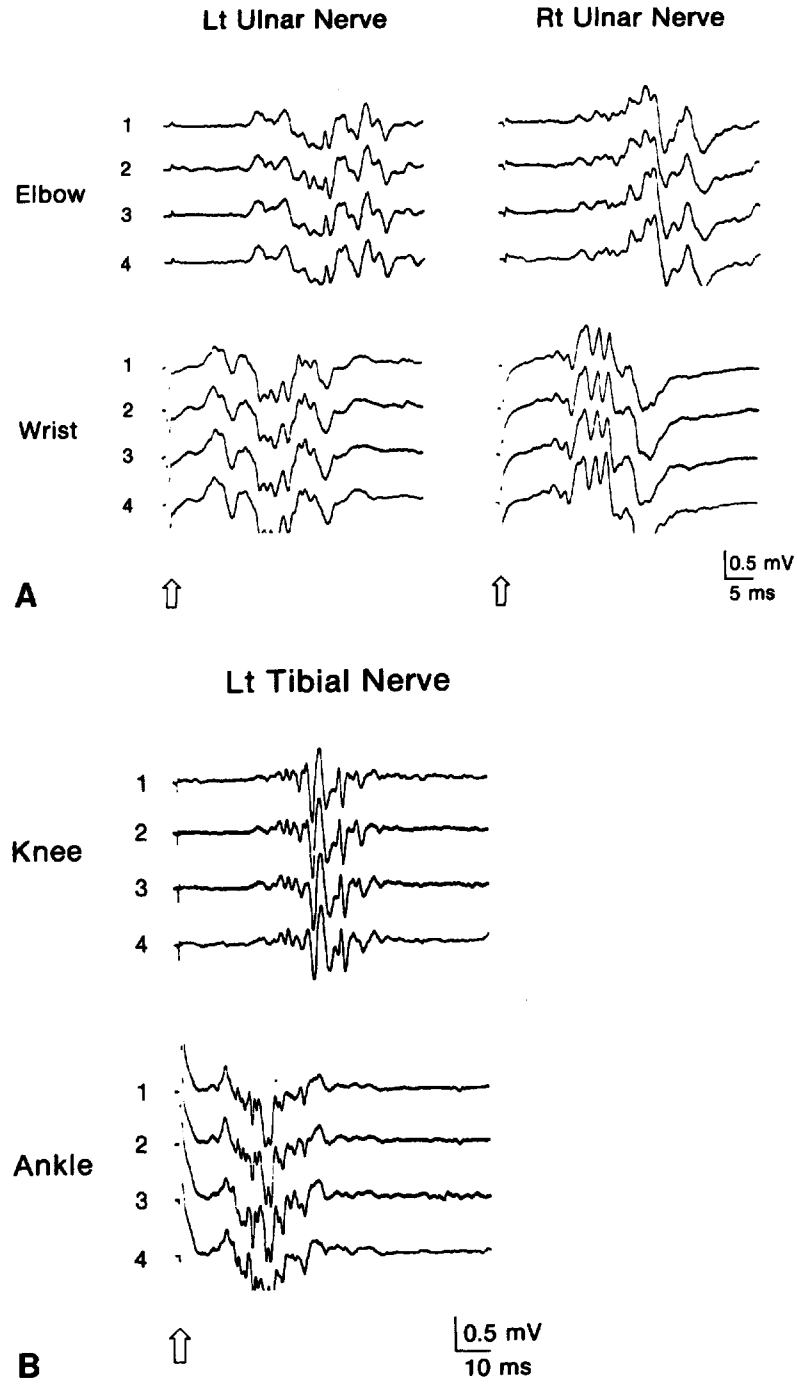


Figure 5–8. A. A 31-year-old man with the Guillain-Barré syndrome. Stimulation of the ulnar nerves at the elbow or wrist elicited delayed, temporally dispersed compound muscle action potentials of the abductor digiti minimi bilaterally. Four consecutive trials at each stimulus site confirmed the consistency of the evoked potentials. **B.** Compound muscle action potential in the same patient as shown in **A.** Stimulation of the tibial nerve at the knee or ankle elicited delayed and very irregular compound muscle action potentials of the abductor hallucis.

els combined with the collision method helps clarify the origin of stimulus-induced high frequency discharges,[246,271,288] Other causes of repetitive muscle action potentials[316] include intramuscular nerve reexcitation,[270] excess acetylcholine or acetylcholinesterase inhibition[88] at the neuromuscular junction (see Chapter 27–4) and neuromyotonia[185] and related disorders (see Chapter 29–4).

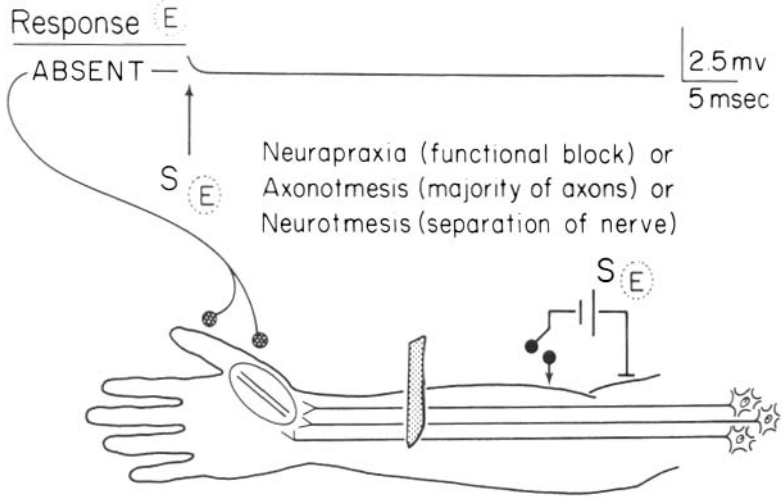


Figure 5–9. No evoked potential with supramaximal stimulation of the nerve proximally. This type of abnormality indicates the loss of conduction in the majority of axons but fails to distinguish neurapraxia from axonotmesis or neurotmesis.

5 SENSORY NERVE CONDUCTION

Stimulation and Recording

For sensory conduction studies in the upper limbs, stimulation of the digital nerves elicits an orthodromic sensory potential at a more proximal site. Alternatively, stimulation of the nerve trunk proximally evokes the antidromic digital potential distally and mixed nerve potential proximally. For example, shocks applied to the ulnar or median nerve at the wrist give rise to an action potential along the nerve trunk at the elbow. Sensory fibers with large diameters have lower thresholds and conduct faster than motor fibers by about 5–10 percent.[60] Thus, mixed nerve potentials allow determination of the fastest sensory nerve conduction velocity in healthy subjects and in

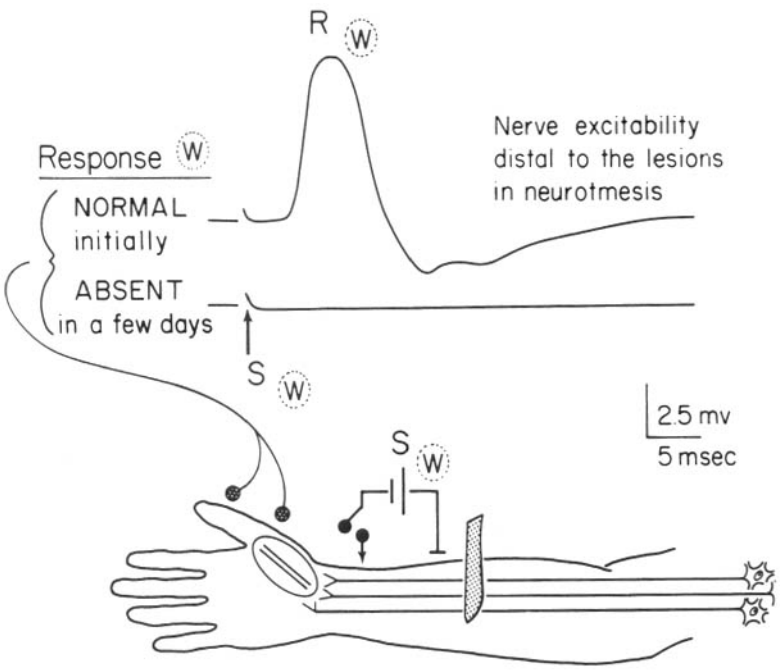
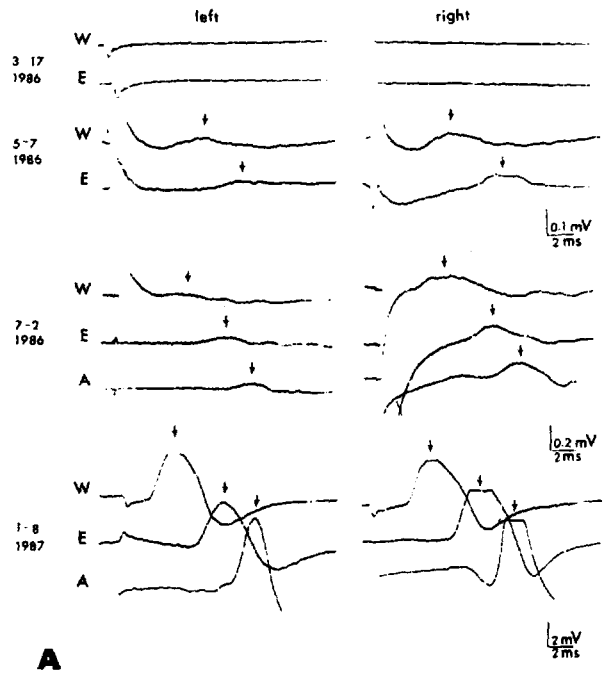


Figure 5–10. Nerve excitability distal to the lesion in neurotmesis or substantial axonotmesis. Distal stimulation elicits a normal compound muscle action potential during the first few days after injury, even with a complete separation of the nerve. Unlike neurapraxia, wallerian degeneration subsequent to transection will render the distal nerve segment inexcitable in 3 or 4 days.



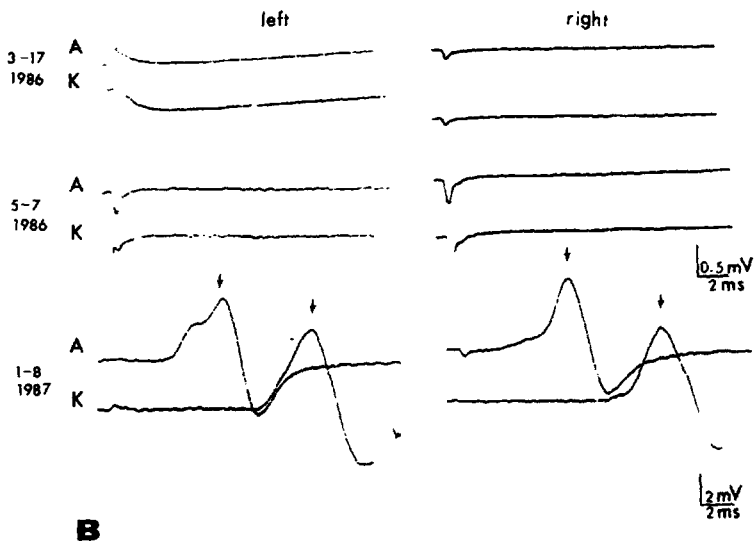


Figure 5–11. A 2½-year old boy with hypothermia-induced axonal polyneuropathy after prolonged exposure to severe freezing weather on a frigid winter night in Iowa. **A.** Compound muscle action potentials recorded over the thenar eminence after stimulation of the median nerve at the wrist (*W*), elbow (*E*), or axilla (*A*). The initial study on March 17, 1986, revealed no response on either side, followed by progressive return in amplitude and latency, with full recovery by January 8, 1987. **B.** 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, 1986, revealed no response on either side, with full recovery by January 8, 1987.

patients with neuropathies affecting motor fibers more than the sensory axons.[207] This relationship, however, may not always hold in disease states that affect sensory fibers selectively. Such circumstances would preclude differentiation between the sensory and motor components of mixed nerve potentials.

For routine clinical recordings, surface electrodes provide adequate and reproducible information noninvasively.[6,96] Some electromyographers prefer needle recording to improve the signal-to-noise ratio, especially in assessing temporal dispersion.[141,142,173,176,242,269,311] Here, a signal averager provides a sensitive mea-

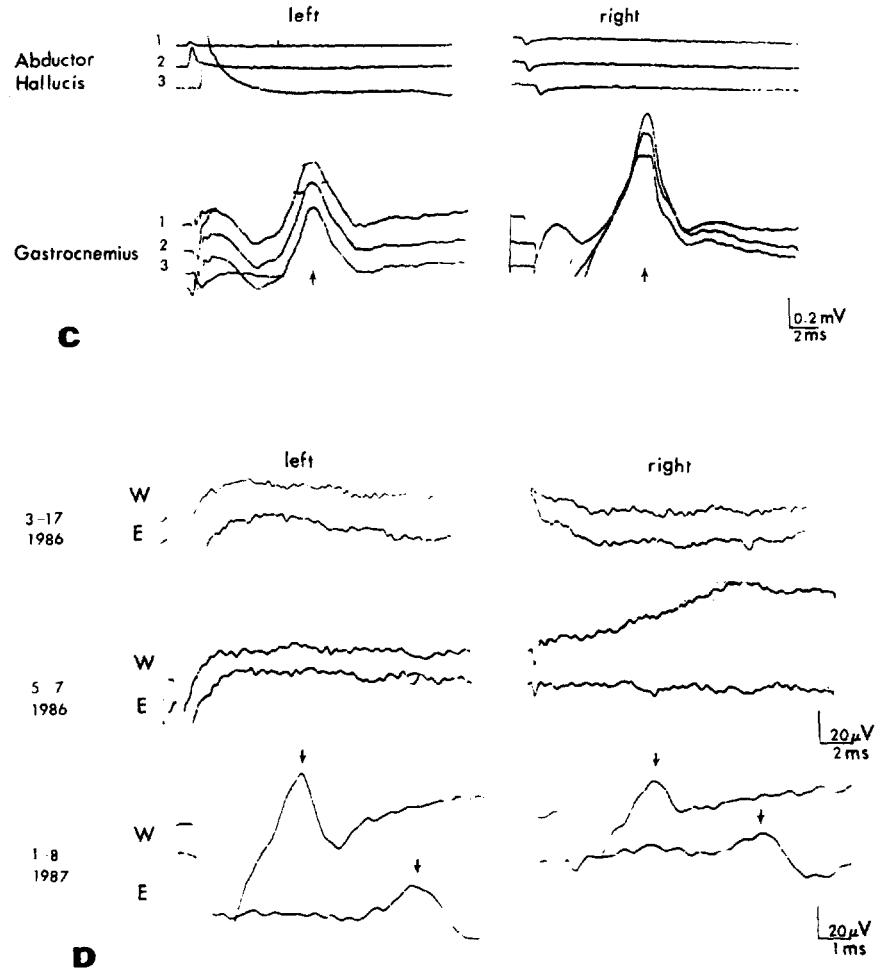


Figure 5–11 (*Cont.*). C. Motor conduction studies of the tibial nerve on May 17, 1986. Stimulation at the knee elicited no response in the intrinsic foot muscle on either side (*top three tracings*), but a small compound action potential in the gastrocnemius bilaterally (*bottom*) as the result of early reinnervation. **D.** Antidromic sensory nerve action potential recorded from the second digit after stimulation of the median nerve at the wrist (*W*) or elbow (*E*). The studies on March 17 and May 7, 1986, showed no response on either side, with full recovery by January 8, 1987. [From Afifi et al.[4] with permission.]

sure of early nerve damage by defining small late components that originate from demyelinated, remyelinated, or regenerated fibers.[34,114,269] Minimum conduction velocity calculated from these late components normally, averages 15 m/s corresponding to the fibers of about 4 μm in diameter.[281] A reduction in minimum conduction velocity seves as a sensitive measure of neuropathy, often showing otherwise undetectable abnormalities.[140]

The technique of near nerve recording also provides unique opportunity to establish physiologic characteristics of various skin and muscle afferents in humans.[44,45,47,173,175,284] For example, this method allows selective recording from nerve fibers with similar functional characteristics excited by a mechanical stimulus that mostly activates Meissner's corpuscles[46] or by vibration, which presumably drives pacinian corpuscles.[126] In contrast, the conventionally recorded orthodromic compound sensory action potentials result from activation of all the large-diameter fibers excited by supramaximal electrical shocks that bypass the receptors and terminals axons.

Waveform, Amplitude, and Duration

With the use of surface electrodes, the antidromic potentials from digits generally have a greater amplitude than the orthodromic response from the nerve trunk, because the digital nerves lie nearer to the surface.[33] The relationship reverses with the use of needle electrodes placed near the nerve. Some motor axons have thresholds similar to those of large myelinated sensory axons.[112] In studying the mixed nerve, therefore, superimposition of action potentials from distal muscles may obscure antidromically recorded sensory potentials. Stimulation distal to the termination of the motor fibers selectively activates sensory fibers of mixed nerves (see Chapter 6–2). Moving more proximally, overlapping muscle action potentials, if any, become apparent by an abrupt change in waveform.[160]

The position of the recording electrodes alters the waveform of a sensory nerve action potential.[8,256,263,335] An initially positive triphasic waveform characterizes the orthodromic potential recorded with an active electrode (G_1) on the nerve and a reference electrode (G_2) at a remote site. A separate late phase may appear in the temporally dispersed response recorded at a more proximal site. Placing G_2 near the nerve at a distance of more than 3 cm from G_1 makes the recorded potential tetraphasic, with addition of the final negativity.[33] Bipolar recording register a signal as the potential difference between G_1 and G_2 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 G_1 site before being picked up at the G_2 location. Thus, the waveform distortions are least with the 4 cm interelectrode separation.[83,116,187] Theoretical consideration notwithstanding, some favour the use of a 3 cm over a 4 cm separation for two practical reasons; less noise and easier application when recording from short digits.[323] We prefer a 2 cm separation, as do many others, to be consistent with our normative values established using commercially available recording bars mounting the electrodes at this fixed distance. The antidromic digital potential recorded with a pair of ring electrodes has no initial positive phase, clearly seen in the orthodromic potential. The lack of potential difference between G_1 and G_2 implies the stationary character of the positive phase along the digit, as predicted by the far-field theory (see Chapter 20–3).

The amplitude of the sensory potential, measured either from the baseline to the negative peak or between the negative and positive peaks, varies substantially among subjects and to a lesser extent between the two sides in the same individual. The same degree of variability occurs in recording with surface or needle electrodes.[33] In addition to the density of sensory innervation, body mass index, as a measure of the depth of the nerve from the skin surface, determines the amplitude of the nerve action potentials.[36] Women tend to have greater sensory nerve action potentials than men for a yet undetermined reason,[24,142,189] but possibly because the nerves lie more superficially. Left-handers often have greater median sensory potentials at the wrist on the right side, and vice versa.[214] Most electromyographers measure the duration of the negative-positive diphasic antidromic potential from the initial deflection to the intersection between the descending phase and the baseline. Some use the negative or positive peak as the point of reference, and still others resort to the less definable point where the tracing finally returns to baseline.

The types of abnormalities described for motor conduction apply in principle to sensory conduction as well. Substantial slowing in conduction velocity implies demyelination of the sensory fibers, whereas axonotmesis results in reduced amplitude of the compound nerve action potentials with stimulation either distally or proximally to the site of the lesion. Sural nerve potential serves as a sensitive measure for length-dependent distal axonal polyneuropathy.[5] In patients with neuropathy, sural to radial nerve sensory potential ratio often falls below 0.40, compared to the mean of 0.71.[272] The sensory fibers degenerate only with a lesion distal to the sensory ganglion (Fig. 5–11D). Thus, the presence of distal sensory potential serves

as a criterion for differentiating preganglionic root avulsion from plexopathy.[113] Intra-spinal canal lesions such as radiculopathy, however, could involve the ganglion or postganglionic portion of the root affecting the digital nerve potential.[157,192] Distinction from plexopathy then depends on the distribution of sensory involvement. Plexopathy tends to affect multiple digits, whereas radiculopathy will show selective change of the first digit by C6, the second and third digits by C7, and the fourth and fifth digits by C8 root lesions.[97] This type of assessment must take into account the relative amplitude values of the sensory action potential for each digit.[55,56,231]

Latency and Conduction Velocity

Unlike motor latency, which includes neuromuscular transmission, sensory latency consists only of the nerve activation and conduction time from the stimulus point to the recording electrode. Therefore, stimulation of the nerve at a single site suffices for calculation of conduction velocity. The latency of activation, or a fixed delay of about 0.15 ms at the stimulus site[174] makes the calculated conduction velocity slightly slower with the use of measured latency from a stimulus to a recording site compared to the latency difference between two recording sites flanking the same nerve segment. In measuring the latency of the orthodromic sensory potentials, some electromyographers use the initial positive peak and others the subsequent negative peak, as the point of reference.[149] Sensory potentials elicited by stimulation at different sites vary in waveform because of temporal dispersion between fast and slow fibers. The interval between the positive and negative peaks also increases in proportion to the nerve length tested. Therefore, the conduction velocity calculated with the latency to the negative peak does not necessarily relate to the fastest conducting sensory fibers.

The measurement to the negative peak circumvents the technical problems of identifying the preceding smaller positive peak, especially in diseased nerves.[110] In this practice, the conduction distance determined to the midpoint of G_1 and G_2, rather than to G_1 itself, compensates for the discrepancy between the arrival of the impulse and the appearance of the negative peak.[73] The use of modern amplifiers with high resolution now makes it feasible in most cases to measure the sensory latency to the initial positive peak. Determining the conduction distance from the stimulus point to G_1 then allows accurate calculation of conduction velocity of the fastest fibers.[33]

With the biphasic digital potential recorded antidromically, the onset latency measured to the initial take-off of the negative peak corresponds to the conduction time of the fastest fibers from the cathode to G_1. The use of the peak latency has some justification as a quick estimate of abnormal temporal dispersion, which increases the duration of the evoked potential. Mesuring both the onset latency and duration, however, provides more complete data especially with easily detectable antidromic digital potentials, which considerably exceed orthodromic potentials in amplitude. In one study, antidromic conduction times, despite identical mean values, showed slightly higher standard deviations than orthodromic measurements.[33] In another study, the orthodromic recording revealed a shorter distal latency than the antidromic method in both median and ulnar nerves.[51] For the same segment of the sensory nerve, however, the orthodromic and antidromic potentials recorded using the same interelectrode distance have the identical latencies.[53]

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 take-off of the evoked response, inappropriate stimulus strength, and inaccurate calibration. Errors in es-

timating 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 of the nerve length 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 5–10 m/s because of the limitations inherent in the technique (see Chapter 7–6).[171] Changes in limb temperature in part account for this variability.[23] 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 study. Unlike conduction velocity, latency comparison calls for a constant distance between the stimulating and recording electrodes. A number of factors, listed below, can modify the results of motor and sensory conduction studies. A combined index improves diagnostic classification over use of single test results.[264] Analyzing multiple measurements, however, poses statistical problems, necessitating a technique for data reduction (see Chapter 3–8).[265] The common assumption that conduction values follow a normal, bell-shaped Gaussian distribution appears unwarranted.[41] If so, calculation of reference values as the mean ± 2 (or 3) standard deviations, for example, must use the optionally transformed data to remove the effect of skew and unacceptable rate of misclassification (see Chapter 3–8).[267]

Physiologic 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.[167,304] Longer nerves generally conduct more slowly than shorter nerves, as suggested by an inverse relationship between height and nerve conduction velocity.[40,196,336,340] 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.[290] These findings might suggest, without histologic proof, abrupt distal axonal tapering in the lower limbs. The other factors possibly responsible for the velocity gradient include progressive reduction in axonal diameter, shorter internodal distances, and lower distal temperatures. Statistical analyses of conduction velocities show no difference between median and ulnar nerves or between tibial and peroneal nerves. These measures also show a high degree of symmetry with only small side-to-side differences (see Chapter 6).[29]

The nerve impulse propagates faster in the proximal than in the distal nerve segments.[111,134] For example, the most proximal motor nerve conduction velocity determined by F-wave latency clearly exceeds the conventionally derived most distal conduction velocity.[54,85,158,164,169] Statistical analyses show no significant difference between cord-to-axilla and axilla-to-elbow segments.[158] The F ratio (see Chapter 18–5) compares the proximal and distal motor nerve conduction time from the stimulus site at the elbow or the knee.[159] In healthy subjects, faster proximal conduction compensates for the difference in length between the cord-to-elbow and elbow-to-muscle segments or between the cord-to-knee and knee-to-muscle segments.[164] Hence, approximately equal conduction time along the proximal and distal segments from the site of stimulation makes this ratio close to unity.

Effects of Temperature

Lower temperatures slow down impulse propagation while at the same time augmenting the amplitude of nerve and muscle potential, as demonstrated in the squid axon,[139] and in human studies.[68,182,186,249] For example, distal latencies increase by 0.3 ms per degree for both median and ulnar nerves upon cooling the hand.[42] These principles apply for both normal and demyelinated fibers as a straightforward

consequence of the temperature coefficients governing voltage-sensitive sodium (Na^+) and potassium (K^+) conductance. In particular, cold-induced slowing of sodium channel opening and a delay of its inactivation probably account for the slowing of conduction and the increase in amplitude. A parallel temperature-dependent change also affects the refractory period.[202]

In contrast, nerve impulses conduct faster at a higher body temperature,[61] as is seen, for example, after physical activity.[125] The conduction velocity increases almost linearly, by 2.4 m/s, or approximately 5 percent per degree, as the temperature measured near the nerve increases from 29° to 38 °C.[135,148] Conduction velocity changes nonlinearly with increase in skin temperature, showing more pronounced effect in the lower temperature range.[306] Very high temperatures, however, induce a pronounced effect, decreasing motor and sensory potentials by 27 percent and 50 percent in amplitude, and 19 percent and 26 percent in duration with warming of the limb from 32 °C to 42 °C.[273] In demyelinated nerve fibers, conduction velocity increases as temperature rises until propagation ceases at a vulnerable site. The nerve conducts faster, reflecting quick activation of Na^+ channels over a length of a fiber that is normal except for a short segment of demyelination. Conduction fails at a particular site with a low safety factor when the rising temperature reduces the action potential below the critical level.[102,326] Thus, the latency and amplitude measure two completely separate effects of change in temperature.

Studies conducted in a warm room with ambient temperature maintained between 21° and 23 °C reduce this type of variability. Although impractical and unnecessary in clinical practice, a warmer room at 26°–28 °C or even 30 °C minimizes the temperature gradient along the course of a nerve.[154] To check the intramuscular temperature, the insertion of a thermometer through the skin requires an additional puncture for each muscle tested. In prac-

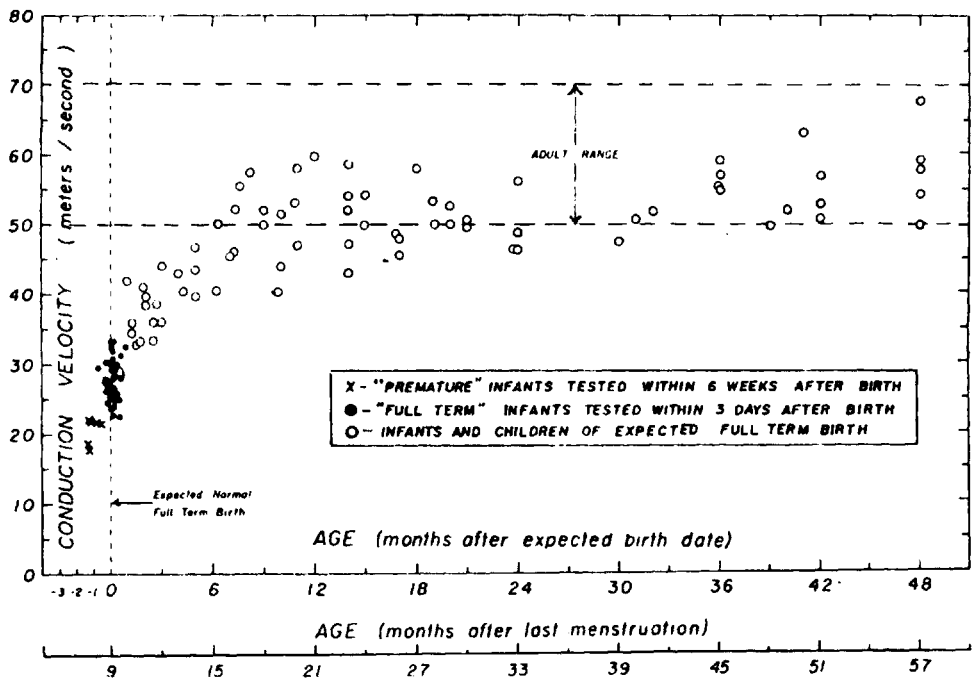


Figure 5–12. Relation of age to conduction velocity of motor fibers in the ulnar nerve between elbow and wrist. Velocities in normal young adults range from 47 to 73 m/s, with most values between 50 and 70 m/s. Ages plotted indicate the month after the expected birth date based on calculation from the first day of last menstruation. [From Thomas and Lambert,[302] with permission.]

Table 5–1 Normal Motor Nerve Conduction Velocities (M/S) in Different Age Groups

Age	Ulnar	Median	Peroneal
0–1 week	32 (21–39)	29 (21–38)	29 (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)

Source: From Gamstorp,[107] with permission.

tice, the skin temperature measured with a plate thermistor correlates linearly with the subcutaneous and intramuscular temperatures.[123,124] A skin temperature of 34 °C or above indicates a muscle temperature close to 37 °C.[69] A measured value falling below 32 °C calls for warming of the limb with an infrared heat lamp or by its immersion in warm water for a sufficient time in the order of 30 minutes.[101] Alternatively, one may add 5 percent of the calculated conduction velocity for each degree below 32 °C to normalize the result. Such conversion factors, based on an average of many healthy subjects, however, may provide misleading interpretations in diseases of the peripheral nerve.[11,19,40,71,237]

Maturation and Aging

Nerve conduction velocities increase rapidly as the process of myelination advances from roughly half the adult value in full-term infants[302] to the adult range at age 3–5 years (Fig. 5–12). Conduction velocity of slower fibers also show a similar time course of maturation.[122] Table 5–1 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.[107] Premature infants have even slower conduction velocities, ranging from 17 to 25 m/s in the ulnar nerve and from 14 to 28 m/s in the peroneal nerve.[49] The

Table 5–2 Normal Sensory and Motor Nerve Conduction Velocities (M/S) in Different Age Groups

	Age 10–35 Years (30 Cases)		Age 36–50 Years (16 Cases)		Age 51–80 Years (18 Cases)	
Nerve	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.
Values are means ± 1 standard deviation.
Source: From Mayer[220] with permission.

Table 5–3 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

MMCV, motor nerve conduction velocity in the distal segment; FWCV, F-wave conduction velocity in the proximal segment; F number, number of responses out of 16 trials.

*Amplitude was significantly reduced in the older group for all the nerves tested, whereas measures of conduction showed no changes except for peroneal MNCV and tibial H latency.

Source: From Kumura,[163] with permission.

values at 23–24 weeks of fetal life average roughly one third those of newborns of normal gestational age.[57,225,286] In premature infants, motor and proprioceptive conduction show a different time course of maturation when studied on the expected date of birth.[26] Fetal nutrition may alter peripheral nerve function by influencing myelin formation.[268]

In 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.[183] Conduction velocities begin to decline after 30–40 years of age, but the values normally change by less than 10 m/s by the sixtieth year[301,322] or even the eightieth year.[236] The most distal branches, such as the interdigital nerves, may degenerate earlier.[188] Table 5–2 summarizes the results of one study[220] showing a reduction in the mean conduction rate of about 10 percent at 60 years of age. Aging also causes a diminution in amplitude and changes in the shape of the evoked potential (Table 5–3),[94] especially when recorded across the common sites of compression.[55,56] The latencies of the F wave and somatosensory evoked potentials also gradually increase with advancing age,[72] probably reflecting preferential loss of the largest and fastest conducting motor units.[327]

Height and Other Factors

In addition to temperature and age, other factors that influence nerve conduction measures include anthropometric characteristics.[274,292] For example, height shows negative association with sensory amplitude and positive association with distal latencies. Sural, peroneal and tibial nerve conduction velocities all have inverse correlation with height in normals[261] and in patients with diabetic neuropathy.[106] Women have faster conduction velocity and greater amplitude for both motor and

sensory studies than men.[266] Most gender differences resolve when adjusted by height, whereas amplitude differences persist despite such correction. In one study[312] dealing with sural nerve conduction velocity, the changes attributable to height fell within the experimental error of 2.3 percent expected from the method.

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.[277] These changes affect the median nerve more rapidly in patients with carpal tunnel syndrome than in normal control subjects.[105] Conversely, patients with diabetes or uremia or elderly subjects have a greater resistance to ischemia with regard to peripheral nerve function.[43] Threshold tracking provides confirmatory evidence for the ischemic resistance in motor axons of diabetic subjects (see Chapter 8–3).[331] In chronic hypoxemia and diabetes, reduction in amplitude of nerve potential during ischemia shows a time course correlated with the blood oxygen saturation. Thus, hypoxic exposures may induce resistance to ischemic conduction failure.[127] Animal studies in rats suggest that both glucose and insulin also play an important role.[245]

Clinical Values and Limitations

Over the years, nerve conduction studies have made major contributions to the understanding of peripheral nerve function in health and disease states.[115] Such evaluations can precisely delineate the extent and distribution of the lesion, providing an overall distinction between axonal and demyelinating involvement.[303] 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 delineated close relationships between histologic and physiologic findings.[20]

In addition to such a broad classification, the pattern of nerve conduction abnormalities can often characterize the general nature of the clinical disorder. For example, hereditary demyelinating neuropathies commonly show diffuse abnormalities, with little difference from one nerve to another in the same patient and among different members in the same family.[195] Approximately equal involvement of different nerve fibers limits the degree of temporal dispersion despite a considerably increased latency. In contrast, acquired demyelination tends to affect certain segments of the nerve disproportionately,[159,169] giving rise to more asymmetric abnormalities and substantial increases in temporal dispersion. Pattern of distribution in sensory nerve conduction abnormalities also helps differentiate demyelinating and axonal polyneuropathies. For example, a reduced median amplitude compared with the sural amplitude supports the diagnosis of a primary demyelination.[28] In contrast, a reduced sural amplitude compared with the radial amplitude implies axonal polyneuropathy.[272]

Optimal application of the nerve conduction study depends on an understanding of the principles and a recognition of the pitfalls of the technique. The conventional methods deal primarily with distal nerve segments in the four limbs. Special techniques enable assessment of nerve segments in less accessible anatomic regions for better evaluation of a focal lesion, and improved detection of subclinical abnormalities. Despite certain limitations, these methods can provide diagnostically pertinent information if used judiciously in appropriate clinical contexts.

7 STUDIES OF THE AUTONOMIC NERVOUS SYSTEM

Electrophysiologic evaluations of the sympathetic and parasympathetic pathways help confirm a clinical diagnosis of autonomic neuropathy.[3,254] 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.[75,98,203]

Noninvasive studies for cardiovascular function include heart-rate (R-R intervals) variation with breathing, spectral analysis of heart rate,[104] Valsalva ratio, blood pressure, and heart-rate response to change in posture and to eyeball pressure for vagal overreactivity.[99] Studies of sudomotor function consist of sympathetic skin response (SSR), thermoregulatory sweat test, quantitative sudomotor axon reflex test,[293] and sweat imprint method.[155,204] Studies routinely used in a clinical neurophysiology laboratory comprise R-R intervals and SSR.[278,279] Some investigators advocate power spectral analysis.[198,199]

Heart-Rate Variation with Breathing

The heart rate increases physiologically during inspiration and decreases during expiration. The R-R intervals recorded using an electrocardiogram (ECG) test the degree of this change during deep breathing. After a resting period of 5 minutes, the patient breathes deeply, in a recumbent position, at the rate of 6 breaths per minute for 1 minute. A standard electromyographic instrument suffices to display the ECG with a surface electrode placed at the midpoint of the left clavicle and the other electrode over the sternum.[131,291]

The difference between the shortest and longest R-R intervals during 1 minute serves as the most reliable method, showing little intraindividual variation, whether tested manually or using automatic methods of analysis.[291,332] With deep breathing, heart rates should normally change more than 15 beats per minute. Values of less than 10 beats usually indicate an abnormality, although the result depends on the age of the subject.[144,205,232,291] 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.[297] Subjects younger than 40 should have an E/I ratio above 1.2, which then decreases with age.[144] Transfer function analysis may also provide an easy measure of respiratory-induced heart rate variability.[103]

The heart rates, determined mainly by vagal activity, reveal parasympathetic function. Atropine but not propranolol blocks its increase during inspiration.[150,333] Heart rate variation during breathing decreases with age, and in diabetes and other disorders affecting autonomic pathways.[144,199,255,278]

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 s, 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.[191] The highest ratio from three successive attempts, each separated by 2 minutes,[206] normally exceeds 1.4 in subjects younger than 40. The Valsalva ratio reflects both parasympathetic and sympathetic function. In addition, patients with heart and lung disease may have low values for reasons unrelated to the autonomic system.

Response to Change in Posture

When a person stands from the supine position, the heart rate increases usually from 10 to 20 beats per minute. After reaching a maximum at about the fifteenth heart beat, it declines to a relatively stable rate at about the thirtieth 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.[90] Young adults should have a ratio of more than 1.04. Atropine blocks the effect, suggesting its dependency on vagal innervation of the

heart.[90] 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.[144]

Sympathetic Skin Response

In the conventional nerve conduction studies, unmyelinated fibers do not contribute to the surface recorded responses. Recording SSR using a non-invasive technique provides a means to test these axons.[119,279] A surface electrode placed on the palm of the hand (Fig. 5–13) or sole of the foot (Fig. 5–14) serves best as the active electrode, G_1, with the reference electrode, G_2, on the dorsal surface of the same limb. In contrast, G_1, 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. 5–15) with low frequency components requires a very slow sweep (0.5–1 s per division), a high gain (100 μV per division), and a wide band-pass (0.16 or DC to 2–3 kHz). Effective stimuli comprise a surprise element such as a loud noise delivered unexpectedly. To trigger the osciloscope sweep for latency measurement, we apply an electrical shock 0.1 ms in duration, and 10–20 mA in intensity to the ipsilateral or contralateral wrist, ankle, or any digit.[279] The temperature of the limbs is maintained at 32°–34° C.

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,[152] 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. In one study of 30 healthy subjects,[170] normal values (mean ± SD) for palmar and plantar responses consisted of the onset latency of 1.52 ± 0.135 s and 2.07 ± 0.165 s and amplitude of 479 ± 105 μV and 101 ± 40 μV. In another study,[86] measurements of the normal

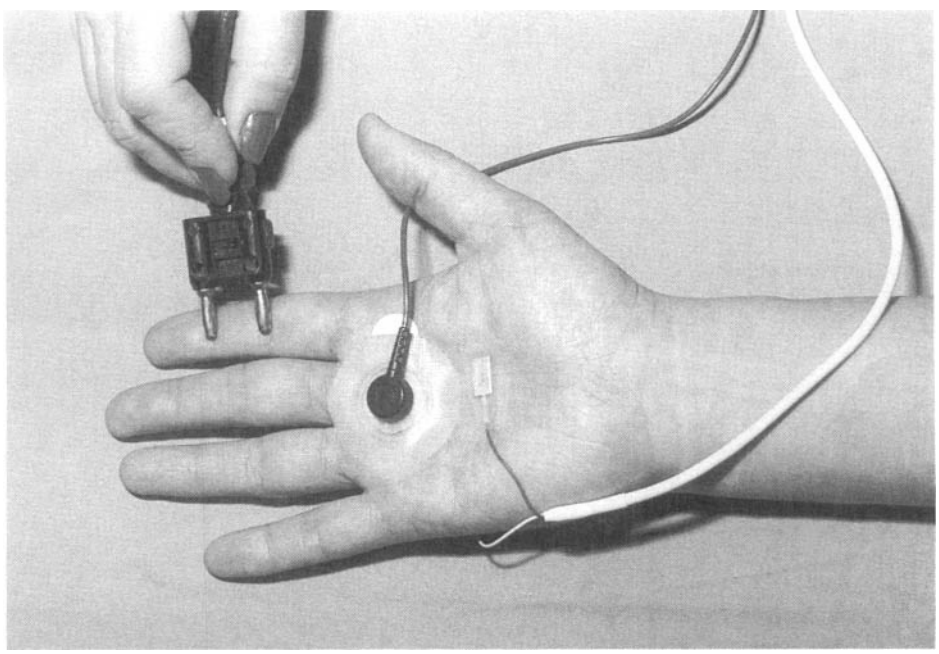


Figure 5–13. Electrical stimulation of the index finger and recording of sympathetic skin response over the palm (G_1) and the dorsal surface (G_2) of the same hand.

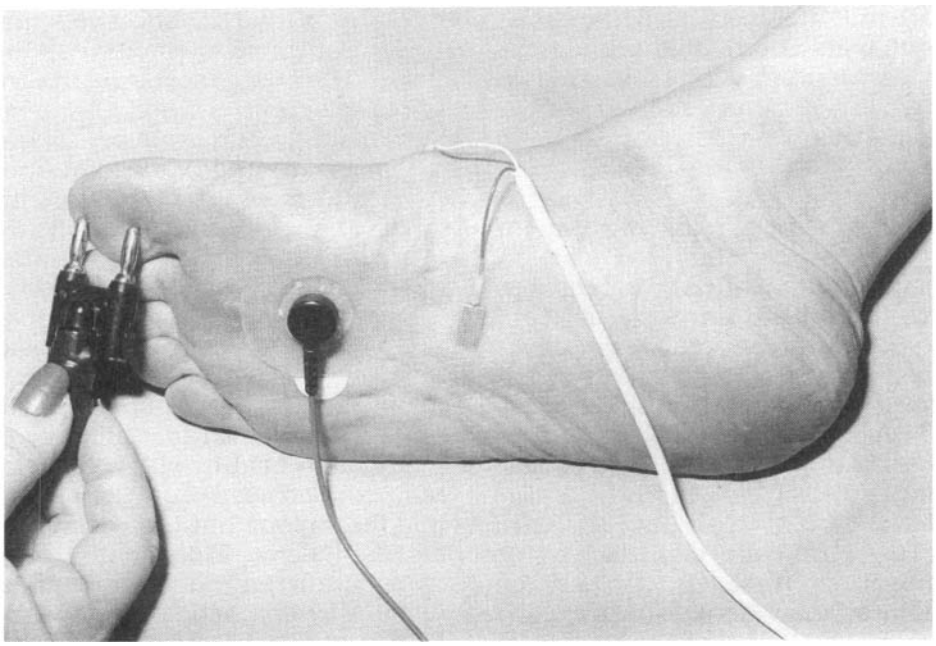


Figure 5–14. Electrical stimulation of the big toe and recording of sympathetic skin responses over the sole (G_1) and the dorsal surface (G_2) of the same foot.

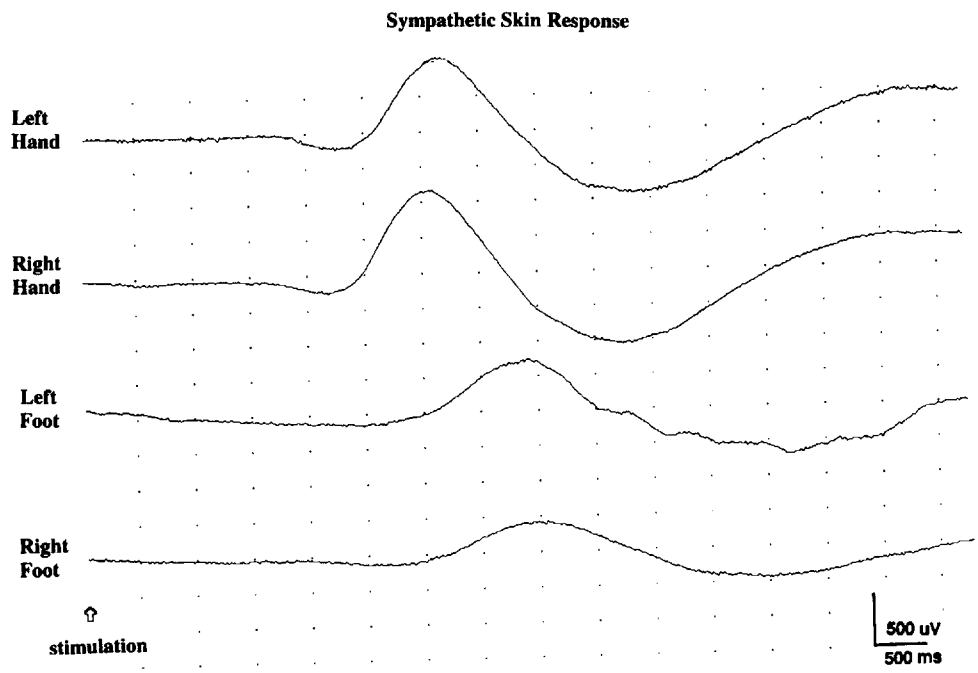


Figure 5–15. Sympathetic skin responses recorded simultaneously in four limbs of a normal subject after electrical stimulation of the left wrist. A greater latency for the foot responses than the hand responses reflects the different lengths of the descending pathways. Oscilloscope settings consisted of very slow sweep (500 ms/division), high gain (500 μV/division), and a wideband pass (0.16–3 kHz).

mean onset latency and amplitude were 1.50 ± 0.08 s and 3.1 ± 1.8 mV for the hands, and 2.05 ± 0.10 s and 1.4 ± 0.8 mV for the feet. Neither the site[314] nor the type of stimulation[275] alters the onset latency with any consistency, which reflects not only the peripheral C fiber function but also conduction in a long multineuronal pathway. In contrast, the density of spontaneously activatable sweat glands dictates the amplitude as a measure of peripheral sympathetic activity. Lower temperatures reduce the amplitude and prolong the latency. In one study,[62] cooling the 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,[194] a change in temperature over 32°–34 °C range increased the amplitude by 8.5 percent and decreased the latency by 2.5 percent per degree.

Although SSR can occur in the absence of normal sweat gland function,[18] its abnormalities in general correlate reasonably well with other sweat tests[215] and certain other measures of autonomic function.[215,278,289] Its variability and rapid habituation combined with a nonquantitative nature tend to limit clinical application. Some consider only its absence or major reduction in amplitude as a definite abnormality,[309,310] whereas others regard a prolonged latency as a sign of neuropathy.[66] Magnetic stimulation applied to the neck evokes easily recordable, highly reproducible sympathetic skin responses, refrecting strong afferent sensory in-puts proximally. The potentials thus recorded revealed an orderly latency gradient from proximal to distral sites of all limbs.[200,217,218,315] Reported onset latencies include 1.0 ± 0.1 s (mean ± SD) for the arm, 1.2 ± 0.1 s for the forearm, 1.1 ± 0.1 s for thigh, 1.5 ± 0.1 s for the calf, and 1.7 ± 0.2 s for the sole.[313]

Iontophoresis of atropine into the skin under the recording site abolishes the response. Patients with diabetes,[194,289,339] scleroderma,[253] familial amyloid polyneuropathy,[283] or sympathectomy[190] have absent or reduced response on the affected limbs. This contrasts to normal autonomic function in Friedreich's ataxia, which primarily involves large myelinated fibers, sparing smaller fibers.[143] Ischemic conduction block of the arm abolishes the previously obtainable response.[314] Disorders associated with delayed or absent responses include lepromatous leprosy,[31] hereditary motor sensory neuropathy,[67] chronic uremia,[329] and palmar hyperhidrosis.[197]

The SSR also reflects preganglionic sympathetic activity, providing information different from the somatic pathway in evaluating myelopathy[338] and other heterogeneous systemic diseases such as multiple sclerosis,[87,199,338] amyotrophic lateral sclerosis,[70] Parkinson's disease,[328] and rheumatoid arthritis.[299] Patients show no detectable assymetry in the foot as the result of L5 or S1 radiculopathies[7] or after sural nerve biopsy.[247]

8 OTHER EVALUATION OF NERVE FUNCTION

Microneurography

Conventional nerve conduction studies provide accurate measurement of the fastest conduction velocities, as well as an approximate number of volleys and the pattern of their distribution, 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 assess the involvement of small fibers only indirectly by localizing focal abnormalities of large axons, which may have little to do with the patient 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.[121] Recording of this type in an alert human subject provides a great deal of physiologic information about various types of fiber populations.[37,120] Most human studies have centered on post-ganglionic sympathetic fibers innervating autonomic effector organs.[22,91-93,211,282,296,325] Other areas of possible interest include cutaneous afferents from mechano-, thermo- and nociceptors,[239,280] and muscle afferents from spindles and Golgi tendon organs. Surface stimulation of the receptive field gives rise to evoked sensory action potentials with late components, representing either the high-threshold small-diameter fibers seen in normal subjects, or the abnormally low-threshold regenerating or demyelinating fibers seen in patients with neuropathy.[177]

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.[145,209,241] The findings suggest that the abnormal sensation results from ectopic discharges of hyperexcitable cutaneous afferent. Combined with intraneural microstimulation,[241] 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 give rise to distinctive perception correlated with the type of cutaneous receptor in question.[210,241] Microstimulation of individual muscle afferents fails to evoke a coherent sensation, but stimulation of joint afferents evokes sensation of pressure or movement in 50 percent of cases.[37]

In addition to physiologic studies conducted in healthy subjects, this technique can explore the pathophysiologic mechanisms underlying various abnormalities of the somatosensory, motor, and autonomic systems.[178] 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.[38,39,234,238] High-frequency discharges also originate at the site of nerve damage, spontaneously or during and after ischemia.[9,25,156] 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 2–5 spikes occurring at a frequency of 7–10 Hz with peak instantaneous frequencies usually exceeding 300 Hz.[208]

In the clinical context, microneurographic techniques allow recording of neural activity in single C fibers[240,307,308] or autonomic fibers.[211,212,294] Despite theoretical interest in correlating cutaneous pain with neural discharges and vasoconstriction with sympathetic activity, however, the technique has limited value for electrodiagnostic purposes, primarily because the nature of recording requires the expertise not generally available in an ordinary electromyography laboratory.

Thermal, Pain, Vibratory, and Tactile Sensation

The cutaneous sensory tests usually include warm and cold thermal perception, vibration, touch-presure sensation and current threshold study.[10,79,337] These quantitative measures have found a limited but useful role in the characterization and quantitation of cutaneous sensory function.[80-82,213] As a noninvasive, nonaversive method, the test yields reliable results even in children as young as 4 years old.[137] Like those of any psychophysiological tests, however, the findings vary among different control groups—for example, between paid volunteers and laboratory personnel familiar with the procedure.[259] Automated tactile testers measure threshold values for light touch, high-frequency vibration, pinprick, warming, and two-point discrimination.[129] Weighted needle pinprick using in-

expensive apparatus may give information on small-fiber dysfunction that compares with thermal threshold determination.[50] These tests may allow documentation of abnormalities in a higher percentage of patients than do more traditional clinical evaluations.

Thermal thresholds tests use either the method of limits or a forced-choice technique.[17] A large-scale survey in patients with diabetes[193] indicates that either approach serves as a simple, noninvasive tool to evaluate small-fiber neuropathy. Quantitative assessment of thermal sensitivity may detect early small-fiber dysfunction, even if conventional electrophysiologic studies reveal no abnormalities.[146] Thus, some advocate that vibratory and thermal testing should constitute the primary screening test for diabetic neuropathy.[321] Nerve conduction studies, however, provide better diagnostic value than quantitative sensory testing.[257,258]

As expected, thermal and vibratory threshold increases in proportion to the severity of neuropathy.[147] 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.[128,320] In one study on diabetes,[230] 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. In one experiment measuring reaction times to stimuli at two sites on the lower limb,[100] 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 the sensation of warming via the unmyelinated peripheral nerve fibers and that of cooling via small myelinated peripheral nerve fibers. Compared to thermal discrimination thresholds, vibratory perception tests in general show a better reproducibility.[65] Such quantitative measurements also help detect minor sensory signs of central origin in patients with multiple sclerosis.[132]

Current perception threshold testing uses constant current sine wave stimulator usually at three different frequencies of 5, 250, and 2,000 Hz, which may selectively activate three subsets of nerve fibers.[260] Some studies have shown good correlation of high-frequency stimulation with large-fiber function, and low-frequency stimulation with small-fiber function,[216] but its clinical usefulness remains uncertain.[2,262] Measurement of alternating current perception thresholds may improve the quantitative assessment, as shown in grading the severity of diabetic sensory neuropathy,[260] and the degree of sensory function recovery after nerve transplant.[52] Determination of the thresholds for heat pain in the foot may help evaluate disturbances of C-fiber–mediated sensibility in lumbosacral disc disease.[295] The test may also provide a quantitative means to confirm elevated heat pain thresholds, or heat hypoalgesia, which indicates advanced stages of small fiber neuropathy.[229] For this test, thermal stimulation must exceed 43 °C, bearing some risk of burn injury in patients with sensory loss.[136]

Thermography

Despite the initial enthusiasm and favorable reports concerning thermography in the carpal tunnel syndrome and many other neurological disorders, more recent studies conclude that the technique offers only limited value as a test of neural function in the clinical context. For example, a well-controlled study[224] documented thermographic alterations in 0 of 9 hands with mild nerve conduction abnormalities and 7 of 14 hands with marked nerve conduction changes. Similarly, thermography provides nonspecific findings of uncertain diagnostic or prognostic relevance in the evaluation of lumbosacral radiculopathy.[130,287]

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Chapter 6

ASSESSMENT OF INDIVIDUAL NERVES

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 all studies, although the anatomic peculiarities dictate specific approaches to each of the commonly tested individual nerves. This section will describe the usual points of stimulation and recording sites together with the normal values as reported in the literature or established in our institution. To minimize the bias induced by different techniques, each laboratory should develop its own normal ranges, using a standardized method.

Most electromyographers assess the latency and conduction velocity against the upper and lower limits of normal defined as a mean plus or minus two standard deviations in a healthy population. The same criterion does not apply to amplitude, which distributes in a non-Gaussian manner. In our experience, most individual measures of amplitude in healthy subjects exceed one half the mean of the control value, 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 express the normal range in terms of plus or minus two standard deviation confidence intervals (see Chapter 3–8).

The conduction studies commonly involve the readily available motor and sensory fibers of the median, ulnar, and radial nerves; the motor fibers of the accessory, peroneal, and tibial nerves; and the sensory fibers of the sural and superficial peroneal nerves. Less easily accessible structures include the phrenic nerve, brachial plexus, musculocutaneous, and other nerves of the shoulder girdle; lateral, medial, and posterior antebrachial cutaneous nerves; the dorsal sensory branch of the ulnar nerve; the lumbo-sacral plexus, femoral and sciatic nerves, lateral femoral cutaneous nerve, saphenous nerve, and lateral and medial plantar nerves.

The ordinary nerve conduction studies provide limited information regarding the central or most proximal nerve segment such as the radicular portion. Supplemental methods help evaluate the motor and sensory conduction in this region by measuring the F wave, H reflex, or somatosensory evoked potentials (see Chapters 18, 19, and 20). Studies of the facial nerve and blink reflex constitute an integral part of cranial nerve testing (see Chapters 7–3 and 17–2).

2 COMMONLY TESTED NERVES IN THE UPPER LIMB

Median Nerve—Motor Fibers

The median nerve runs relatively superficially in its entire course from the axilla to the palm (Fig. 6–1A and B). The conventional sites of stimulation include Erb's point, axilla, elbow, and wrist. Stimulation at Erb's point or at the axilla tends to coactivate other nerves in close proximity.[63] The use of the collision technique circumvents that problem (see Chapter 7–3). In our laboratory, we place the cathode over the brachial pulse near the volar crease at the elbow, and 3 cm proximal to the distal crease at the wrist. The anode is located 2 cm proximal to the cathode, with the ground electrode around the forearm between the stimulating and recording electrodes, if necessary to contain a stimulus artifact (Fig. 6–2A). Additionally, the nerve is accessible to percutaneous stimulation in the palm.[92,137,149] Tables 6–1 and 6–2 summarize normal values in our laboratory.

With stimulation at the wrist, elbow, or axilla, the convention calls for placing the cathode distally to the anode. This arrangement does not work in the palm, where the proximally placed anode could activate the thenar nerve if the distally located cathode has already passed the target point (see Chapter 7–3), thus concealing the actual site of nerve activation. With the reversal of electrode polarity (i.e., the anode located distally), the cathode placed mid-palm elicits no muscle response because neither electrode lies on the nerve. Moving 1–2 cm proximally, the cathode activates the palmar branch of the ulnar

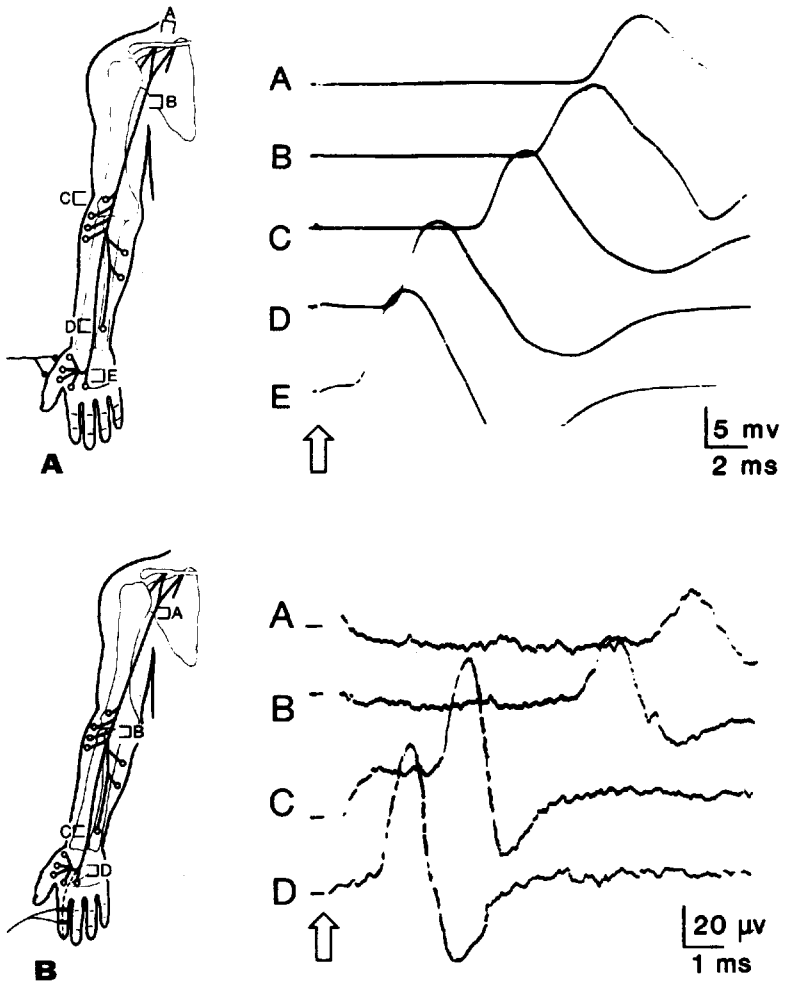


Figure 6–1. A. Motor nerve conduction study of the median nerve. The sites of stimulation include Erb's point (*A*), axilla (*B*), elbow (*C*), wrist (*D*), and palm (*E*). Compound muscle action potentials are recorded with surface electrodes placed on the thenar eminence. **B.** Sensory nerve conduction study of the median nerve. The sites of stimulation include axilla (*A*), elbow (*B*), wrist (*C*), and palm (*D*). Antidromic sensory potentials are recorded with a pair of ring electrodes placed around the second digit.

nerve, adducting the thumb, and 1 cm further proximally, it activates the origin of the thenar nerve, abducting the thumb (Fig. 6–3). Unlike the sensory nerve, the motor axons take a recurrent course along the thenar nerve off the median nerve trunk. Thus, unless dealing with the exposed nerve for intraoperative monitoring,[12] palmar stimulation may inadvertently activate the distal segment of the thenar nerve rather than the intended branching point (see Chapter 7–3). Specifically, surface stimulation aimed at the origin of the thenar nerve in the palm commonly depolarizes the distal branch near the motor point, resulting in an erroneously short latency. An unreasonably large latency increase between the wrist and palm then presents a false impression of carpal tunnel sydrome. Careful selection of the most distal point of palmar stimulation avoids this error, guided by an appropriate thumb twitch, indicating contraction of the abductor pollicis brevis. To further compound the problem, in rare instances the recurrent branch may take an anomalous course.[182]

Recording leads consist of an active electrode (G_1) over the belly of the abductor pollicis brevis and an indifferent electrode (G_2) just distal to the metacarpophalangeal joint (Fig. 6–2A). Depending on the electrode positioning, the potentials from other intrinsic hand muscles innervated by the median nerve contribute to the evoked response. Comparison between the muscle action potentials from the second lumbrical innervated by

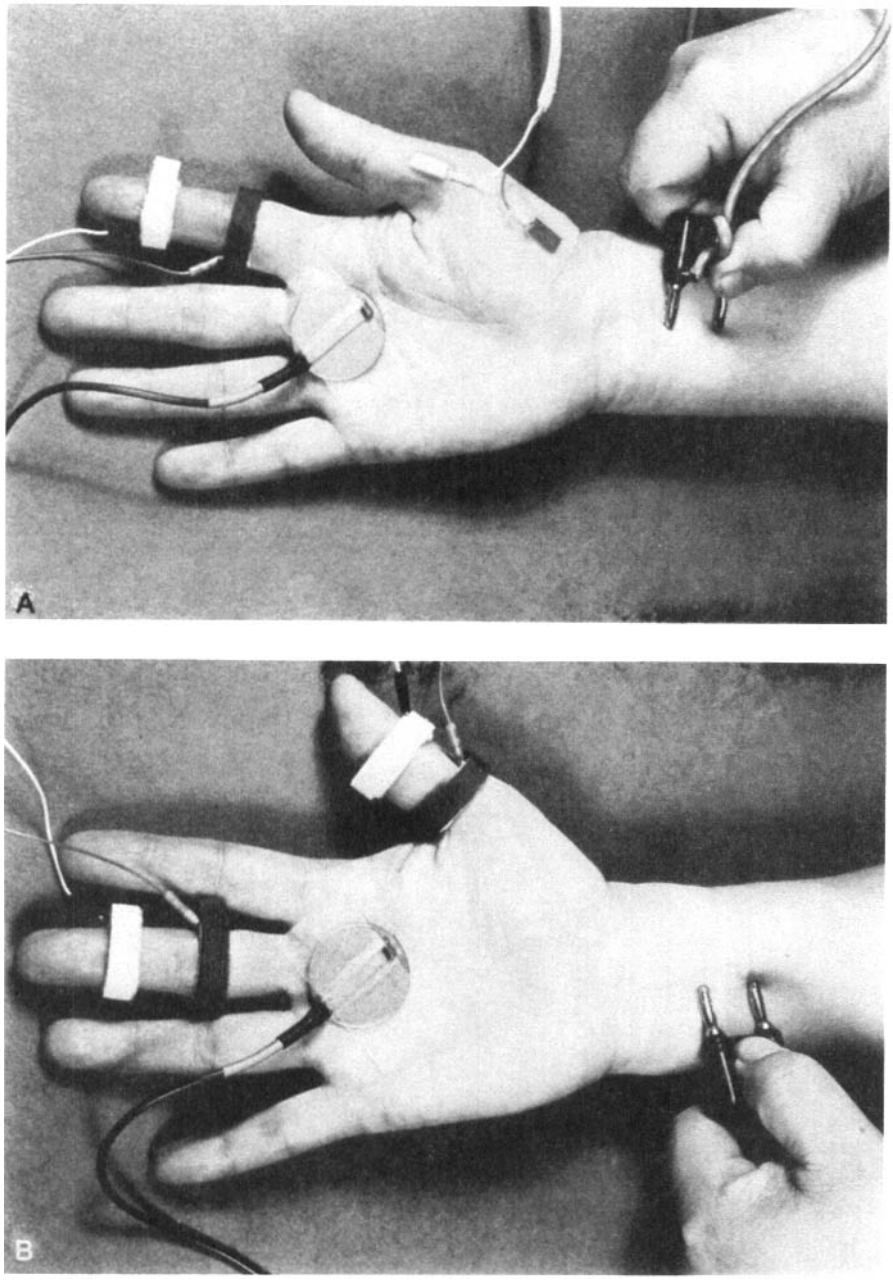


Figure 6–2. A. Motor and sensory conduction studies of the median nerve. The photo shows stimulation at the wrist, 3 cm proximal to the distal crease, and recording over the belly (G_1) and tendon (G_2) of the abductor pollicis brevis for motor conduction, and around the proximal (G_1) and distal (G_2) interphalangeal joints of the second digit for antidromic sensory conduction. The ground electrode is located in the palm. **B.** Alternative recording sites for a sensory conduction study of the median nerve, with the ring electrodes placed around the proximal (G_1) and distal (G_2) interphalangeal joints of the third digit or the base (G_1) and the interphalangeal joint (G_2) of the first digit.

the median nerve and the volar interosseous innervated by the ulnar nerve provides an additional technique to evaluate the distal segment.[35,57,143,159,173,187] A latency difference greater than 0.4–0.5 ms suggests an abnormal delay in conduction across the distal segment. Recording from the pronator quadratus

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)¶		
				1.65 ± 0.25 (2.2)¶	48.8 ± 5.3 (38)**
Wrist	7.0 ± 3.0 (3.5)	3.49 ± 0.34 (4.2)	0.24 ± 0.22 (0.7)		
				3.92 ± 0.49 (4.9)	57.7 ± 4.9 (48)
Elbow	7.0 ± 2.7 (3.5)	7.39 ± 0.69 (8.8)	0.31 ± 0.24 (0.8)		
				2.42 ± 0.39 (3.2)	63.5 ± 6.2 (51)
Axilla	7.2 ± 2.9 (3.5)	9.81 ± 0.89 (11.6)	0.42 ± 0.33 (1.1)		
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 patients, 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, with the cathode at the origin of the thenar in the 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.

Table 6–2 Latency Comparison Between Two Nerves in the Same Limb*

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 patients, 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.

helps evaluate the lesion involving the anterior interosseous nerve.[127,147] In the presence of an anomalous crossover from the median to ulnar nerve in the forearm, distal and proximal stimulation elicits compound muscle potentials of dissonant wave forms. The latencies of these responses represent two different nerves, precluding their comparison for calculation of the nerve conduction velocity (see Chapter 7–4).

The terminal latency index serves as a measure of the terminal latency adjusted to the terminal distance and expressed as a percentage of the proximal conduction velocity. Thus, it equals terminal distance divided by the product of terminal latency and conduction velocity.[49,158,163,164] A value of 0.34 or less suggests disproportionate distal slowing as in the carpal tunnel syndrome and distally prominent polyneuropathy (see Chapter 5–4).

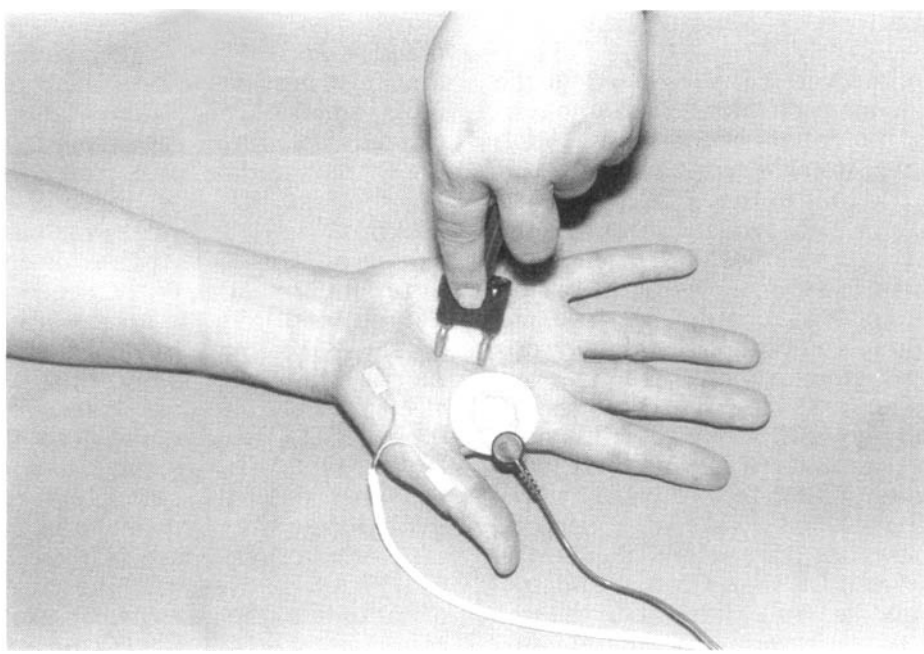


Figure 6–3. Stimulation of the median nerve with the cathode placed at the origin of the recurrent thenar nerve and the anode placed 2 cm distally, and recording of the muscle response over the belly (G_1) and tendon (G_2) of the abductor pollicis brevis, with the ground electrode placed between the stimulating and recording electrodes.

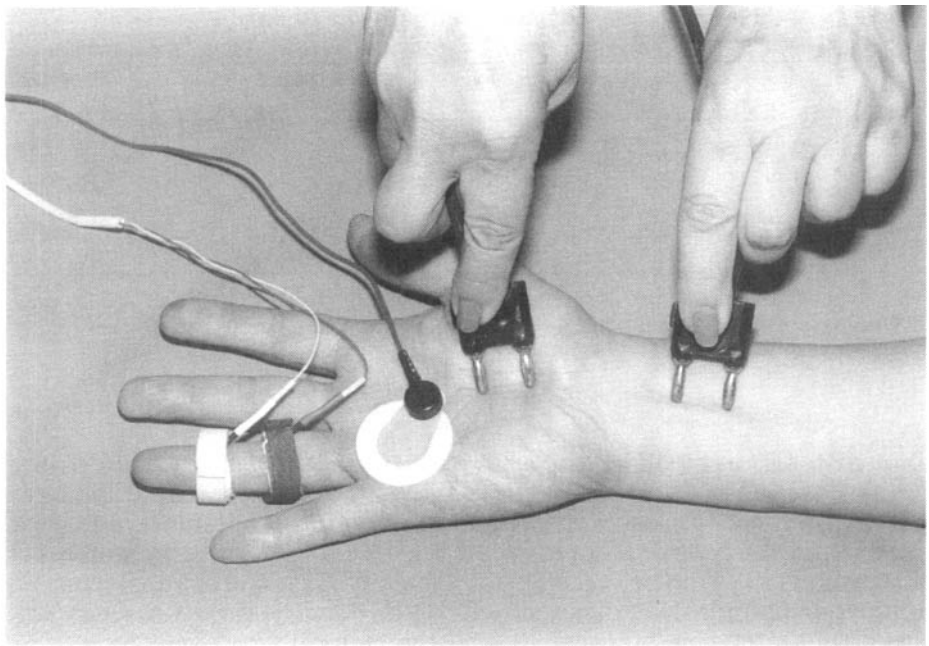


Figure 6–4. Stimulation of the median nerve at the wrist and palm with the cathode placed 3 cm proximal, and 5 cm distal, to the wrist crease, and the anode placed 2 cm proximally, and recording of the antidromic digital potential with the ring electrodes placed 2 cm apart around the proximal (G_1) and distal (G_2) interphalangeal joints of the ring finger (cf. Figure 6–11).

Median Nerve—Sensory Fibers

Stimulation delivered at sites listed for the motor fibers also activates antidromic sensory action potentials of the first through fourth digits. Motor axons have a threshold similar to that of the large myelinated sensory axons. Thus, when one studies the mixed nerve, superimposition of action potentials from distal muscles may obscure the antidromically recorded sensory potential. Palmar stimulation distal to the origin of the recurrent 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.[93] Sensory fibers innervating the second digit originate more from C7 than C6 root and traverse the middle trunk rather than the upper trunk before entering the lateral cord. Thus, the second digit provides far less reliable results than the first digit in detecting upper trunk lesions.[56] The sensory potentials recorded from the first or third digit (Fig. 6–2B), or the lateral half of the fourth digit (Fig. 6–4) often reveal abnormalities not otherwise detectable.[178] The first digit provides asssessment of the C6 root, upper trunk, and lateral cord, whereas the third digit serves to evaluate the C7 root, middle trunk, and lateral cord. 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.

Table 6–1 summarizes normal values for the digital potentials recorded with ring electrodes placed 2 cm apart around the proximal (G_1) and distal (G_2) interphalangeal joints of the second digit (Fig. 6–2A). For wrist and palm stimulation, we place the cathode 3 cm proximal and 5 cm distal to the distal crease of the wrist (Fig. 6–4).[93] Alternative techniques use a fixed distance from the recording electrode, most commonly 12–14 cm.[39] Because of mixed sensory innervation, stimulating the radial nerve also elicits a sensory nerve potential over the first digit; stimulating the ulnar nerve, over the fourth digit. Thus, inadvertent spread of stimulating current to the

other nerves may confuse the issue. Some investigators take advantage of this spread to gain an instantaneous comparison of the median nerve to the ulnar nerve[79,178] or the radial nerve.[136]

Separate stimulation of the median and ulnar nerves at the wrist evokes a corresponding sensory potential of the fourth digit at nealy the identical latency for the same conduction distance (Fig. 6–5). Additional palmar stimulation at a fixed distance from the wrist, usually 8 cm, allows segmental latency calculation as one of the most sensitive, practical measures of comparison between the two nerves (Fig. 6–6). Unnecessarily strong shocks applied to the palm tend to coactivate the median and ulnar sensory fibers innervating the fourth digits. Selective stimulation of one or the other branch results from careful application of electrodes along the line connecting the medial or lateral aspect of the fourth digit and the ulnar or median nerve at the wrist. Slight twich of ulnar or median innervated muscle usually signals proper placement of the stimulator. In our series (Table 6–3), normal values consisted of 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 was 0.01 ± 0.17 ms with an upper limit of normal of 0.4 ms defined as the mean +2 SD.

Unlike the compound muscle action potentials that maintain nearly the same amplitude irrespective of stimulus site, the antidromically activated digital potentials diminish substantially with increasing nerve length under study. Indeed, stimulation at Erb's point or the axilla may fail to elicit unequivocal digital potentials without the use of an averaging technique. Here, temporal dispersion between fast- and slow-conducting fibers results in duration-dependent phase cancellation (see Chapter 7–5).[13,96] In addition, naturally recurring orthodromic sensory impulses may partially extinguish the antidromic impulse by collision. These tendencies favor a proximal stimulation over a more distal stimulation in proportion to the distance between the stimulating and recording electrodes.

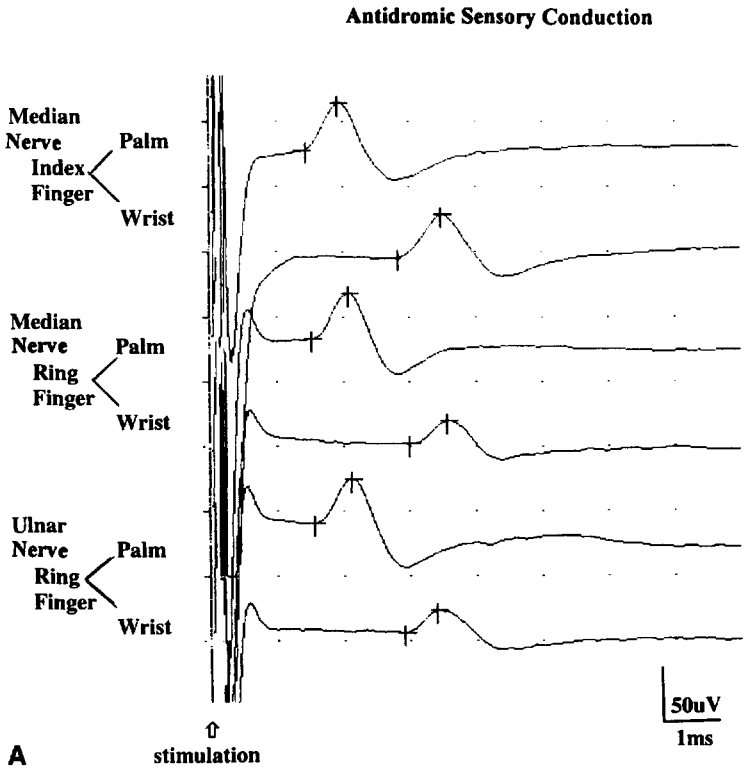
Recording of the antidromic sensory potentials suffices for routine clinical purposes. Alternatively, digital[14,32] or palmar stimulation[31,45]allows recording of the orthodromic sensory potential at the palm, wrist, or elbow with either surface electrodes or needle electrodes. This method demands a higher resolution to compensate for a smaller size of the orthodromic potential. The averaging technique offers a distinct advantage in detecting such small nerve potentials, especially in a diseased nerve. Women tend to have greater orthodromic median sensory nerve action potential at the wrist than men, possibly reflecting smaller wrist size.[110]

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. Antidromic stimulation of the median nerve elicits sensory potentials over the midthenar 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.[111] This technique may help differentiate the carpal tunnel syndrome that spares the palmar cutaneous branch from a more proximal injury.

Multiple Stimulation Across the Carpal Ligament

The use of palmar stimulation provides a simple means of identifying conduction abnormalities of sensory or motor fibers under the transverse carpal ligament or along its most terminal segment.[108,168] This distinction differentiates the carpal tunnel syndrome from a distal neuropathy seen, for example, in digital nerves of diabetics.[22,66] Stimulation of the median nerve at multiple sites across the wrist (Fig. 6–7) further localizes the point of maximal conduction delay within the distal segment of the median nerve.[92,93,128,148] Short segmental stimulation of the motor fibers poses a less technical challenge when recording from the lumbricals than from abductor pollicis brevis (see Chapter 7–3). Incremental stimulation provides the only way to precisely localize a motor lesion, which may deviate from the usual site of compression (see Chapter 26–5).

The sensory axons normally show a pre-



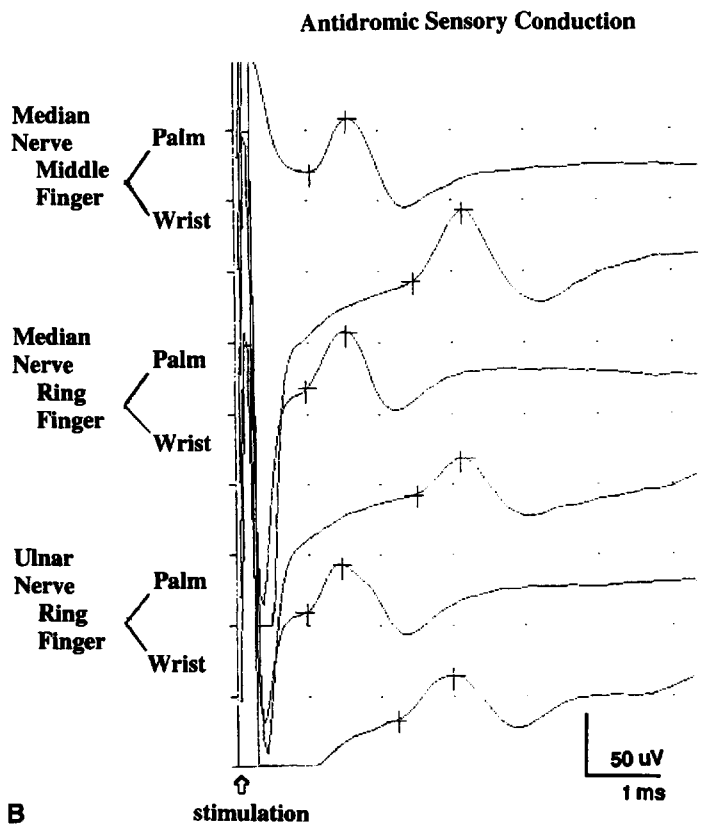


Figure 6–5. A. Antidromic sensory potentials in a healthy subject recorded from the index (*top*) and ring finger (*center*) after stimulation of the median nerve at the palm and wrist, and from the ring finger (*bottom*) after stimulation of the ulnar nerve at the comparable sites (see Figures 6–4 and 6–11). 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 use of the middle finger (*top*) instead of the index finger for one of the median responses in another healthy subject.

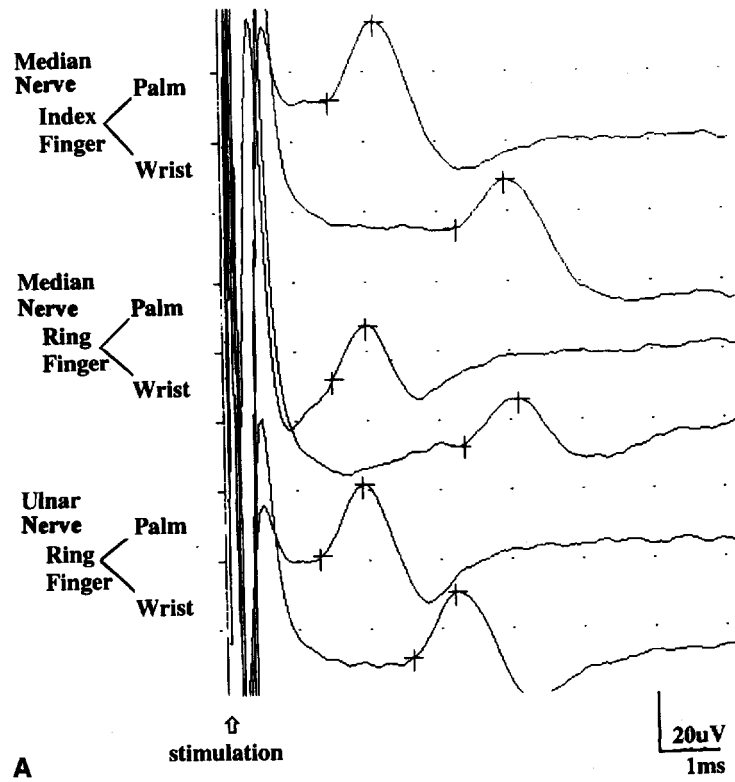


Figure 6–6. A. The same arrangement as in Figure 6–5 in a patient with a mild carpal tunnel syndrome. Despite normal latency from the wrist to the index finger (3.2 ms) and to the ring finger (3.2 ms), the latency difference between median and ulnar nerve (0.7 ms) clearly exceeded the upper limit of 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 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 amplitude of median nerve response recorded from the ring finger. A normal median response elicited by palm stimulation suggests focal demyelination across the carpal ligament with no evidence of distal axonal degeneration.

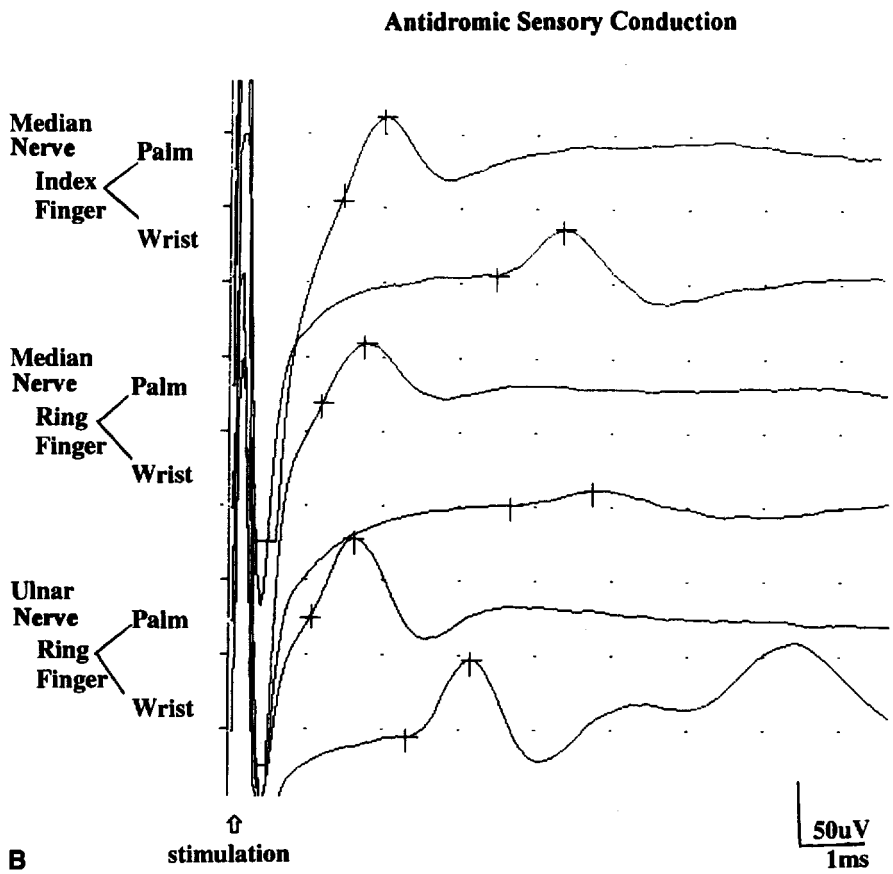


Table 6–3 Distal Sensory Conduction Study Comparing Median and Ulnar Nerves*

Recording	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 2nd Digit	Palm	49.8 ± 21.5 (25)§	1.43 ± 0.16 (1.7)¶	1.44 ± 0.20 (1.9)¶	57.1 ± 8.3 (40)**
	Wrist	38.4 ± 15.6 (19)	2.87 ± 0.31 (3.5)		
Median Nerve 4th Digit	Palm	37.6 ± 17.2 (19)	1.45 ± 0.20 (1.9)	1.43 ± 0.22 (1.9)	57.4 ± 8.9 (40)
	Wrist	22.3 ± 8.2 (11)	2.88 ± 0.35 (3.6)		
Ulnar Nerve 4th Digit	Palm	46.1 ± 24.3 (23)	1.48 ± 0.26 (2.0)	1.38 ± 0.30 (1.8)	59.1 ± 8.3 (43)
	Wrist	29.0 ± 14.8 (25)	2.86 ± 0.37 (3.6)		
Median & Ulnar Difference	Palm	8.5 ± 20.7	0.02 ± 0.17 (0.3)	0.04 ± 0.20 (0.4)	
	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.

dictable latency change of 0.16–0.20 ms/cm with series of stimulation from mid-palm to distal forearm in 1 cm increments (Fig. 6–7B). A sharply localized latency increase across a 1 cm segment indicates focal abnormalities of the median nerve (Fig. 6–7, C, D, E). A nonlinear jump in latency usually accompanies an abrupt change in waveform showing abnormal temporal dispersion. A paradoxical increase in size of responses proximal to this point indicates the loss of physiologic phase cancellation because excessive desynchronization no longer superimposes fast and slow signals (see Chapter 7–5). Stimulation of the median nerve at the digit[95] or at the elbow[70] evokes orthodromic and mixed nerve potentials simultaneously recordable at several sites across the carpal tunnel with multi-channel-recording electrodes. This technique provides instantaneous comparison of latencies but not amplitudes, which vary so much depending on the depth of the nerve at the site of recording.[95,156]

Ulnar Nerve

Like the median nerve, the ulnar nerve takes a relatively superficial course along its entire length. Routine motor conduction studies consist of stimulating the nerve at multiple sites and recording the muscle potential from the hypothenar muscles with

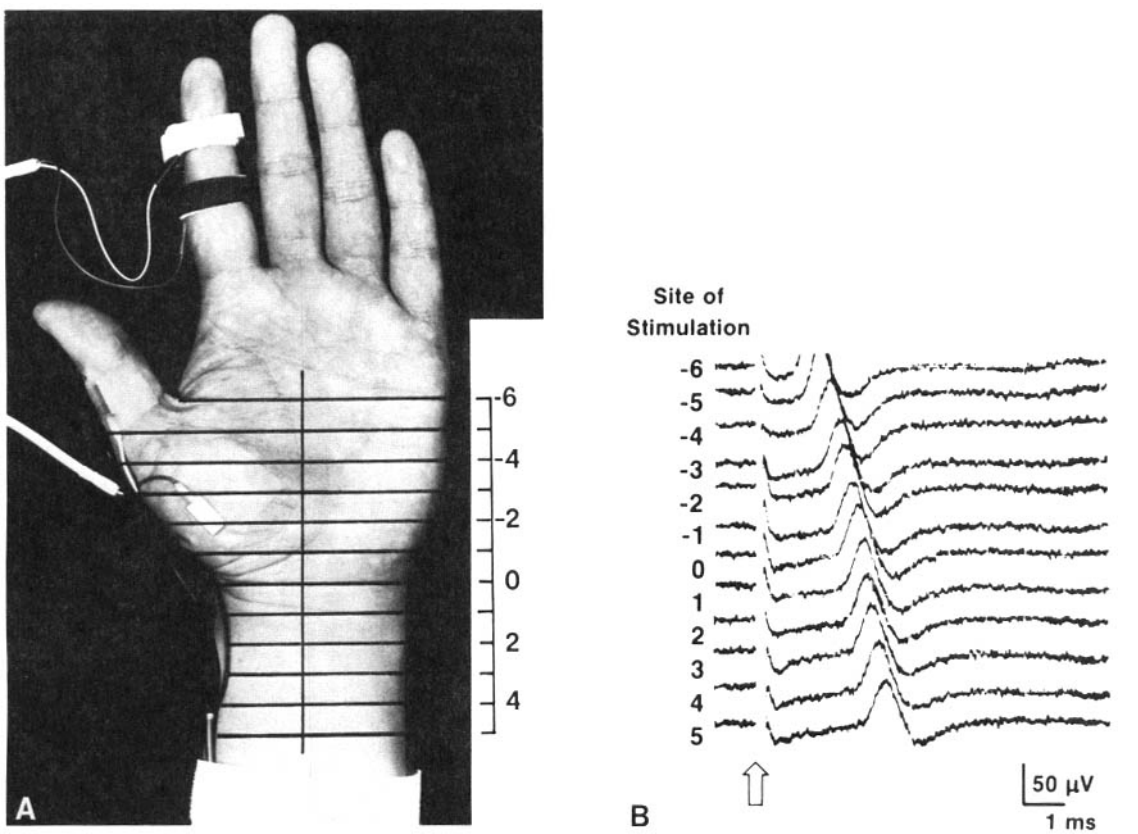
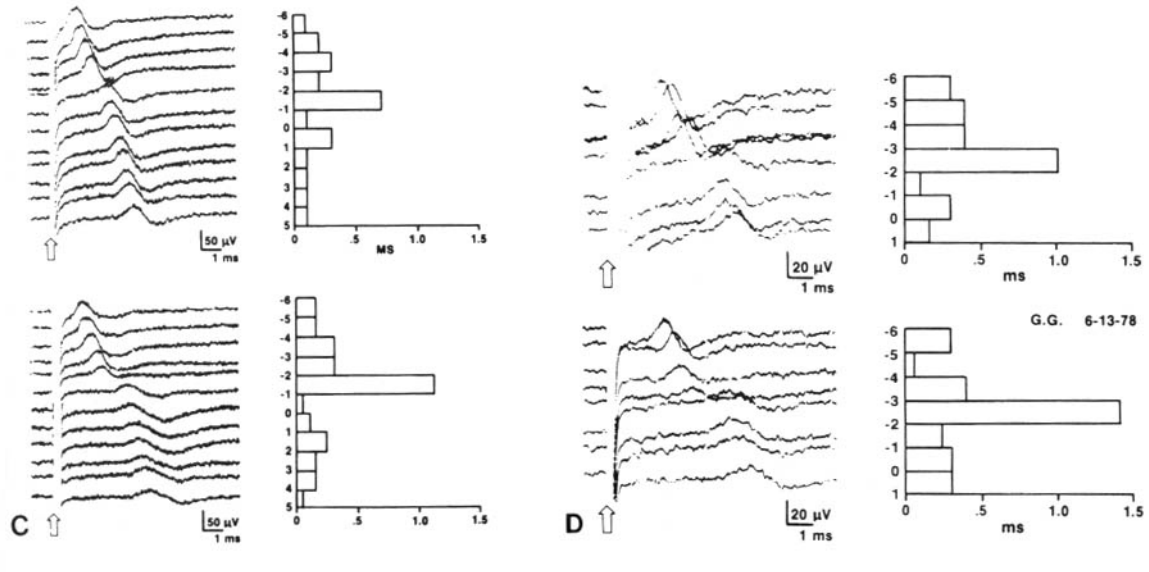


Figure 6–7. A. Twelve sites of stimulation in 1 cm increments along the length of the median nerve. The "0" level at the distal crease of the wrist corresponds to the origin of the transverse carpal ligament. The photo shows a recording arrangement for sensory nerve potentials from the second digit and muscle action potentials from the abductor pollicis brevis. [From Kimura, 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 (compare with **A**). The latency increased linearly with stepwise shifts of stimulus site proximally in 1 cm increments. [From Kimura,[93] with permission.]



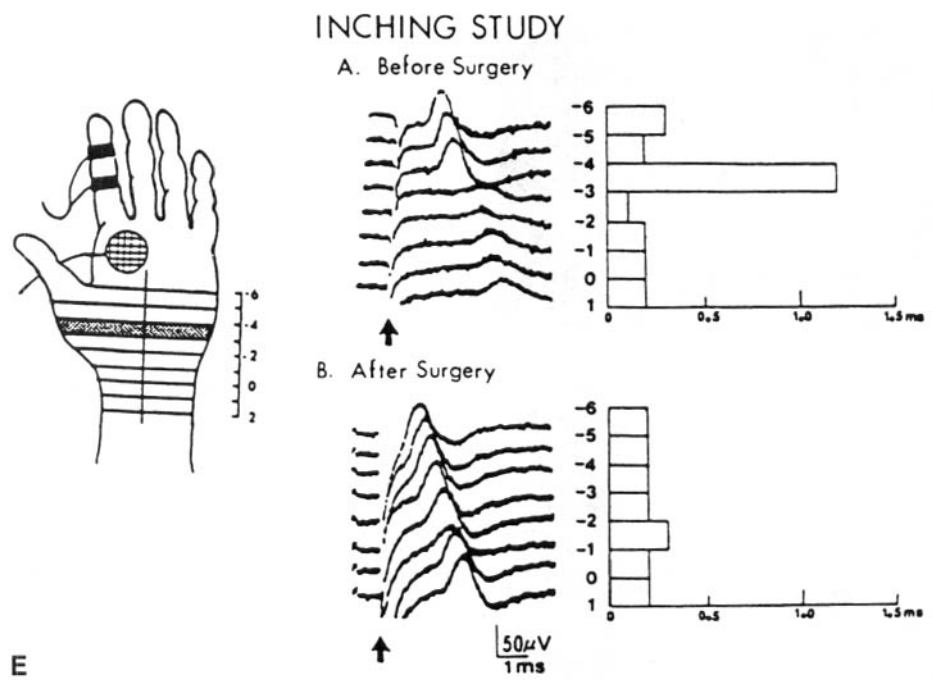


Figure 6–7. C. Sensory nerve potentials in a patient with the carpal tunnel syndrome. Both hands showed a sharply localized slowing from −2 to −1 with the calculated segmental conduction velocity of 14 m/s on the left (*top*) and 9 m/s on the right (*bottom*). Note a distinct change in waveform of the sensory potential at the point of localized conduction delay. Double-humped appearance at −2 on the left suggests sparing of some sensory axons at this level. Temporarily dispersed responses on the right at −1 and beyond had greater negative and positive peaks in area compared to normal, more distal responses, presumably because of loss of physiologic phase cancellation (see Chapter 7–5). [From Kimura,[93] with permission.] **D.** Sensory nerve potential in a patient with the 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. [From Kimura,[93] with permission.] **E.** Sensory nerve potential in a patient with the carpal tunnel syndrome before (*A*) and after (*B*) surgery. Preoperative study showed a localized slowing from −4 to −3 with a calculated segmental conduction velocity of 8 m/s, which normalized in a repeat study conducted six months postoperatively.

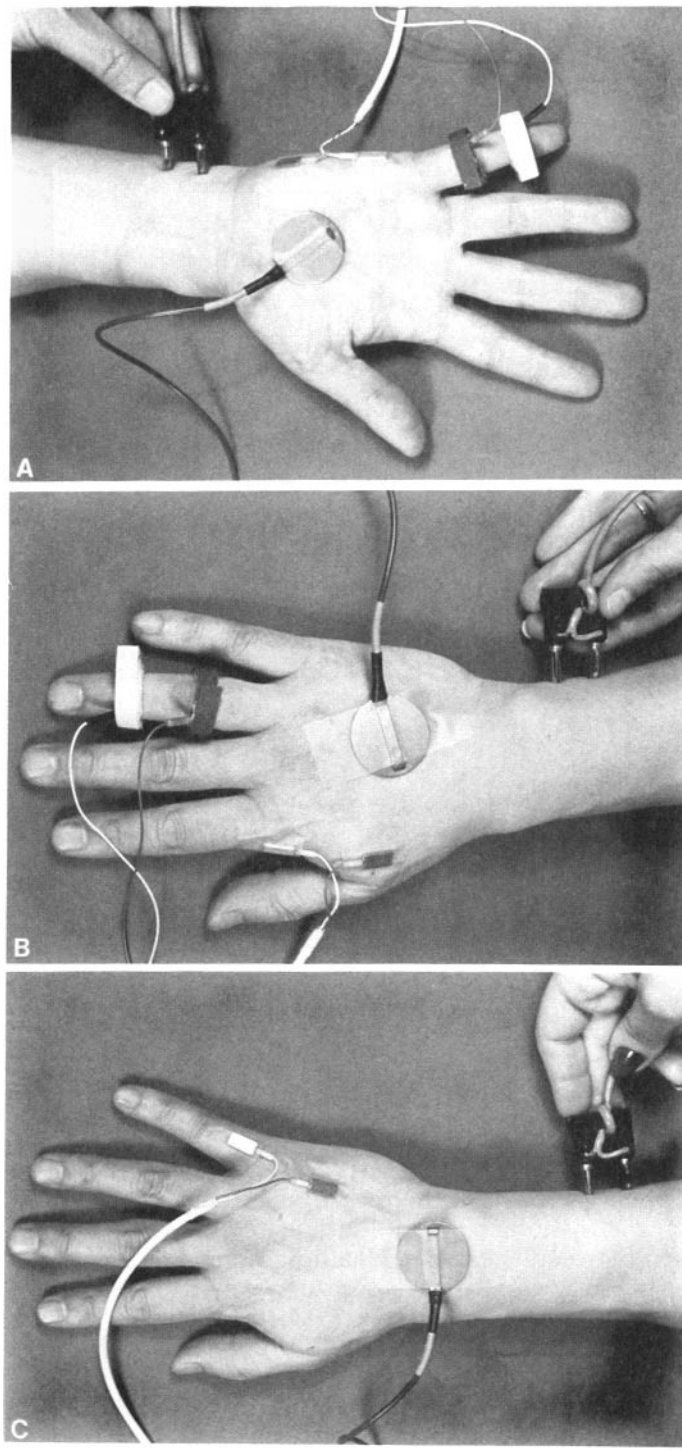


Figure 6–8. A. Motor and sensory conduction study of the ulnar nerve. The photo shows stimulation at the wrist, 3 cm proximal to the distal crease, and recording over the belly (G_1) and tendon (G_2) of the abductor digiti minimi for motor conduction, and around the proximal (G_1) and distal (G_2) interphalangeal joints of the fifth digit for antidromic sensory conduction. **B.** Alternative recording sites for motor and sensory conduction studies of the ulnar nerve with the surface electrodes over the belly (G_1) and tendon (G_2) of the first dorsal interosseous muscle for motor conduction and around the proximal (G_1) and distal (G_2) interphalangeal joints of the fourth digit 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 (G_1) and the base of the fifth digit (G_2).

surface electrodes placed over the belly of the abductor digiti minimi (G_1) and its tendon (G_2) 3 cm distally (Fig. 6–8A).[1] Alternative recording sites include forearm muscles such as flexor carpi ulnaris[177] or flexor digitorum profundus.[53] Common sites of stimulation include palm, wrist, axilla, and Erb's point (Fig. 6–9A,B). The use

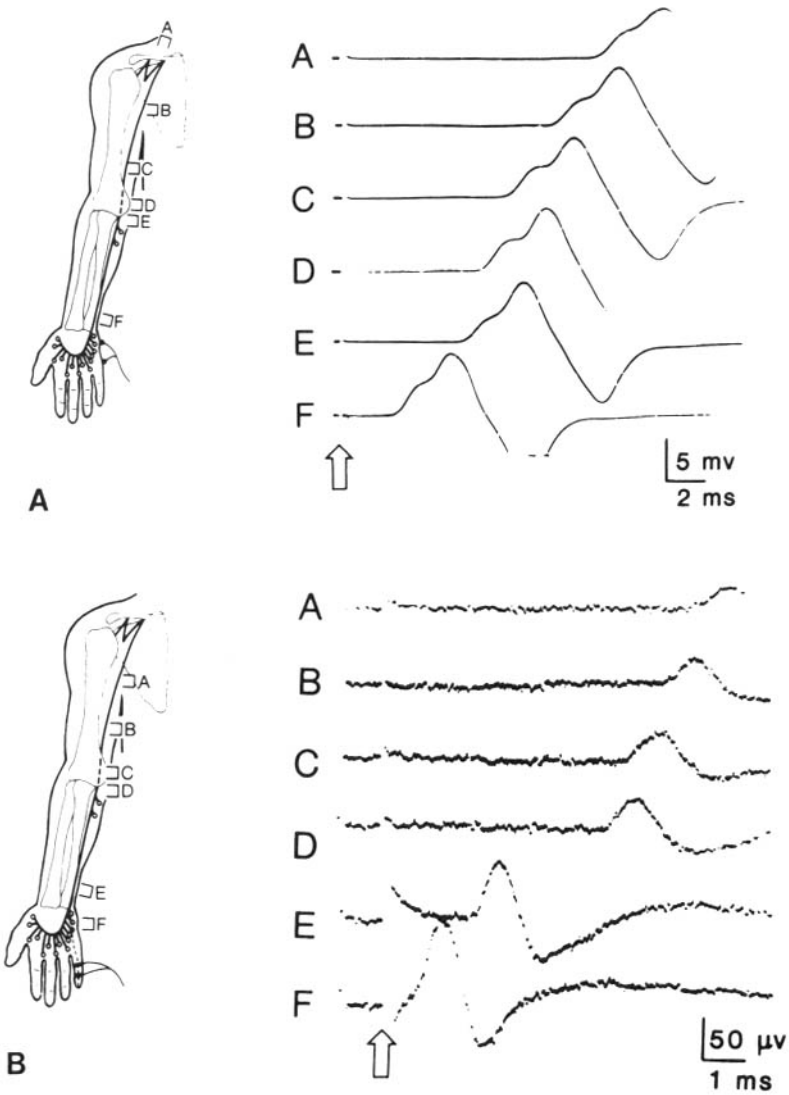


Figure 6–9. A. Motor nerve conduction study of the ulnar nerve. The sites of stimulation include Erb's point (*A*), axilla (*B*), above the elbow (*C*), elbow (*D*), below the elbow (*E*), and wrist (*F*). Compound muscle action potentials are recorded with surface electrodes placed on the hypothenar eminence. **B.** Sensory nerve conduction study of the ulnar nerve. The sites of stimulation include axilla (*A*), above the elbow (*B*), elbow (*C*), below the elbow (*D*), wrist (*E*), and palm (*F*). The tracings show antidromic sensory potentials recorded with the ring electrodes placed around the fifth digit.

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 problems in studying the ulnar nerve, as compared with the median nerve, because the hypothenar eminence contains only ulnar-innervated muscles. Nonetheless, coactivation of the median nerve gives rise to volume-conducted potentials from the thenar eminence, unless eliminated by the collision technique.[91] Tables 6–2 and 6–4 show the normal values in our laboratory.

Stimulation of the motor fibers above and below the elbow helps document a tardy ulnar palsy and a cubital tunnel syndrome. For accurate determination of conduction velocity, the distance between the proximal and distal sites of stimulation should exceed 10 cm to minimize measurement error. The conventional studies often fail to uncover the abnormalities early because a focal slowing induces an insignificant delay when calculated over a longer segment. Segmental stimulation across the elbow in 1–2 cm

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)¶		
				3.51 ± 0.51 (4.5)¶	58.7 ± 5.1 (49)**
Below elbow	5.5 ± 2.0 (2.7)	6.10 ± 0.69 (7.5)	0.29 ± 0.27 (0.8)		
				1.94 ± 0.37 (2.7)	61.0 ± 5.5 (50)
Above elbow	5.5 ± 1.9 (2.7)	8.04 ± 0.76 (9.6)	0.34 ± 0.28 (0.9)		
				1.88 ± 0.35 (2.6)	66.5 ± 6.3 (54)
Axilla	5.6 ± 2.1 (2.7)	9.90 ± 0.91 (11.7)	0.45 ± 0.39 (1.2)		
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 patients, 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.

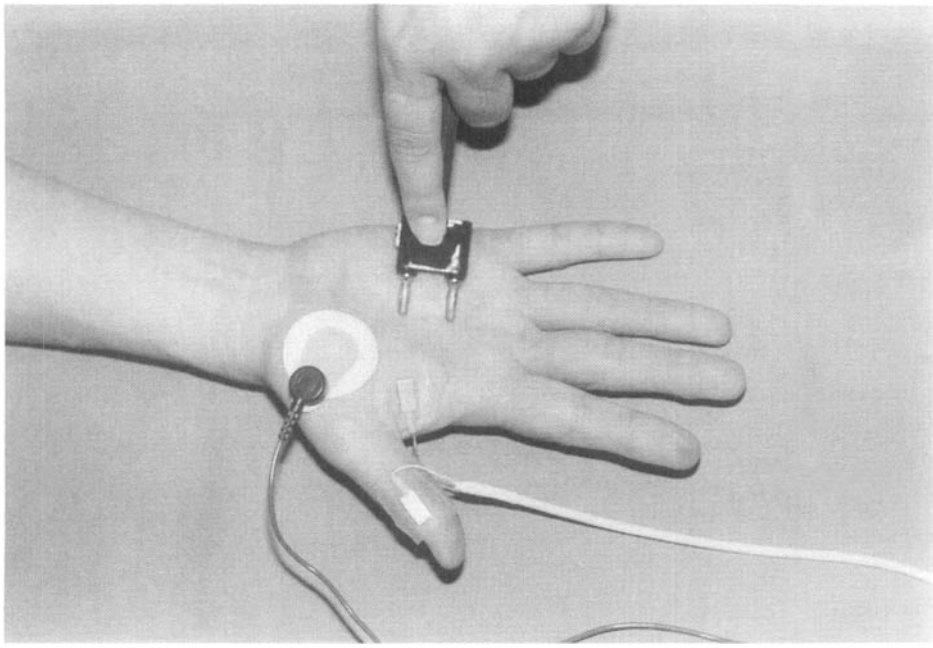


Figure 6–10. Stimulation of the ulnar nerve in the palm with the cathode placed over the palmar branch and the anode 2 cm distally, and recording of the muscle response over the belly of the adductor pollicis brevis (G_1) referenced to the thumb (G_2). Appropriate thumb twitch confirms activation of the deep palmar branch of the ulnar nerve as opposed to the recurrent thenar nerve, which usually lies 1 cm more proximally (cf. Figure 6–3).

increments detects an abrupt change in latency and waveform of the compound action potential at the site of localized compression.[18,83,94] The ulnar nerve slides back and forth in the cubital tunnel with flexion and extension of the elbow joint.[67] Thus, normal values vary depending on the position of the elbow[8] and, to a lesser degree, of the wrist.[151] Holding the arm either at 135° or 90° flexion during stimulation and measurement minimizes the error.[98,100]

The study of the deep palmar motor branch depends on recording the muscle potential from the first dorsal interosseous or adductor pollicis after stimulation of the ulnar nerve at the wrist (Fig. 6–8B). The latency difference between the hypothenar and thenar responses provides a measure of conduction along the deep branch. In one series, the upper limit of the normal range based on 373 studies included 4.5 ms for the distal latency to the first dorsal interosseous, 2.0 ms for the latency difference between this muscle and adductor digiti minimi and 1.3 ms for the latency difference between the two sides.[132] In the assessment of the deep palmar branch, the size of muscle response elicited by stimulation in the palm distal to the site of the lesion provides a good measure of the number of remaining motor axons (Fig. 6–10). Lumbrical-interosseous comparison described for median nerve study (see above) also serves in assessing a distal ulnar nerve lesion, which typically causes a latency difference greater than 0.2 ms in the reverse direction.[101,160]

Stimulation of the ulnar nerve trunk elicits an antidromic sensory potential of the fourth and fifth digits (Fig. 6–8A,B). The common sites of cathodal points include above and below the elbow,[54] 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. 6–11). These stimulus sites make the studies comparable to those of the median nerve (see Fig. 6–4). The fourth and fifth digits provide assessment of C8 and T1

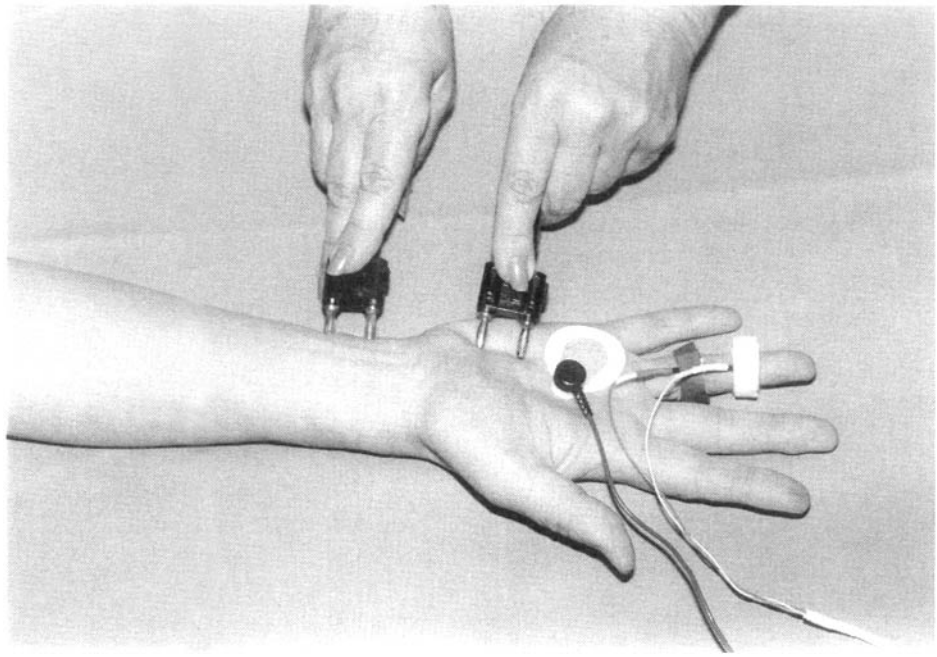


Figure 6–11. Stimulation of the ulnar nerve at the wrist and palm with cathode placed 3 cm proximal, and 5 cm distal to the wrist crease and the anode placed 2 cm proximally, and recording of the antidromic digital potential with the ring electrodes placed 2 cm apart around the proximal (G_1) and distal (G_2) interphalangeal joints of the ring finger. This arrangement yields results directly comparable to the analogous study of the median nerve (cf. Figs. 6–4, 6–5, and 6–6).

roots, lower trunk, and medial cord. Stimulation of the digital nerve with ring electrodes placed around the interphalangeal joints of the fifth digit, cathode proximally, elicits orthodromic sensory potential 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 (Fig. 6–12). These studies help differentiate lesions of C8 and T1 roots from those of the lower trunk, medial cord of the brachial plexus, or ulnar nerve. Preganglionic C8 and T1 root avulsion should spare sensory potentials despite clinical sensory loss.

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.[77,89] It becomes superficial between the tendon of the flexor carpi ulnaris and the ulna.[10] Surface stimulation here selectively evokes antidromic sensory potentials over the dorsum of the hand, although anatomic variations may alter cutaneous innervation.[138] Placing the active electrode (G_1) between the fourth and fifth metacarpals optimizes the recording with the reference electrode (G_2) at the base of the fifth digit (Fig. 6–8C). 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–T1 roots, the lower trunk and the medial cord, but it escapes compression at Guyon's canal.

The normal values of the sensory potential established in one study[77] include amplitude of 20 ± 6 μV with distal stimulation, distal latency of 2.0 ± 0.3 ms (mean ± SD) when recorded 8 cm from the point of stimulation and conduction velocity of 60 ± 4.0 m/s between elbow and forearm. This technique complements the conventional study of the ulnar nerve after a severe lesion at the wrist that has precluded the recording from the hypothenar muscles or digits. It also helps localize a lesion within

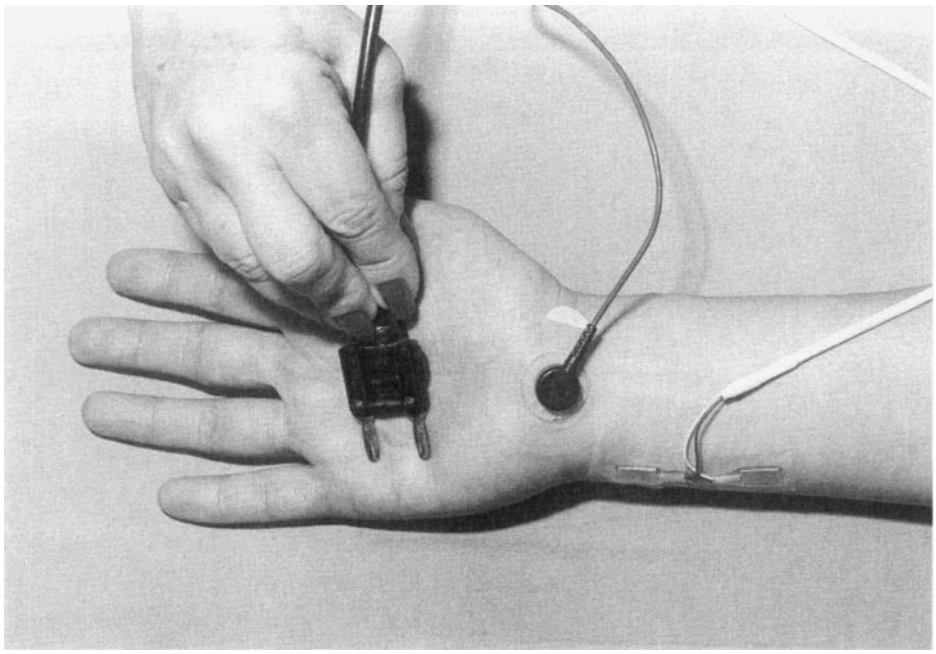


Figure 6–12. Stimulation of the ulnar nerve in the palm with the cathode placed 2 cm proximal to the anode, and recording of mixed nerve potential with the active electrode (G_1) over the ulnar nerve trunk 8 cm proximal to the cathode and the reference electrode (G_2) 2 cm further proximally.

the forearm in the segment proximal or distal to the take-off of this branch with its origin an average distance of 6.4 cm above the wrist.[10] Its abnormality implies axonal degeneration with localization of the lesion to a more proximal site. Conversely, the presence of a normal response combined with abnormal digital ulnar sensory potential usually,[68,89] though not always,[179] localizes an ulnar neuropathy to the wrist.

Radial Nerve

The radial nerve becomes relatively superficial at supraclavicular fossa, in the axilla near the spinal groove, above the elbow, and in the forearm (Fig. 6–13A,B). The optimal sites of electrical stimulation of the motor fibers therefore include (1) Erb's point, (2) between the coracobrachialis and medial edge of the triceps about 18 cm proximal to the medial epicondyle, (3) between the brachioradialis and the tendon of the biceps 6 cm proximal to the lateral epicondyle, and (4) between the extensor carpi ulnaris and extensor digiti minimi on the dorsal aspect of the ulna, 8 to 10 cm proximal to the styloid process. Either a needle electrode or surface electrodes suffice (Fig. 6–14A) when recording muscle action potentials from the extensor digitorum communis[188] or the extensor indicis.

In motor conduction studies, commonly encountered errors result from such technical problems as submaximal stimulation in an obese or muscular limb, coactivation of a number of extensors, and distortion of the waveform by volume-conducted potentials from distant muscles. Further, 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.[50] Needle electrodes also enable relatively selective recording from more proximal muscles such as the anconeus, brachioradialis, and triceps. In assessing the axilla to elbow segment, anterior surface tape measurement compares most favorably with the actual anatomic length.[80]

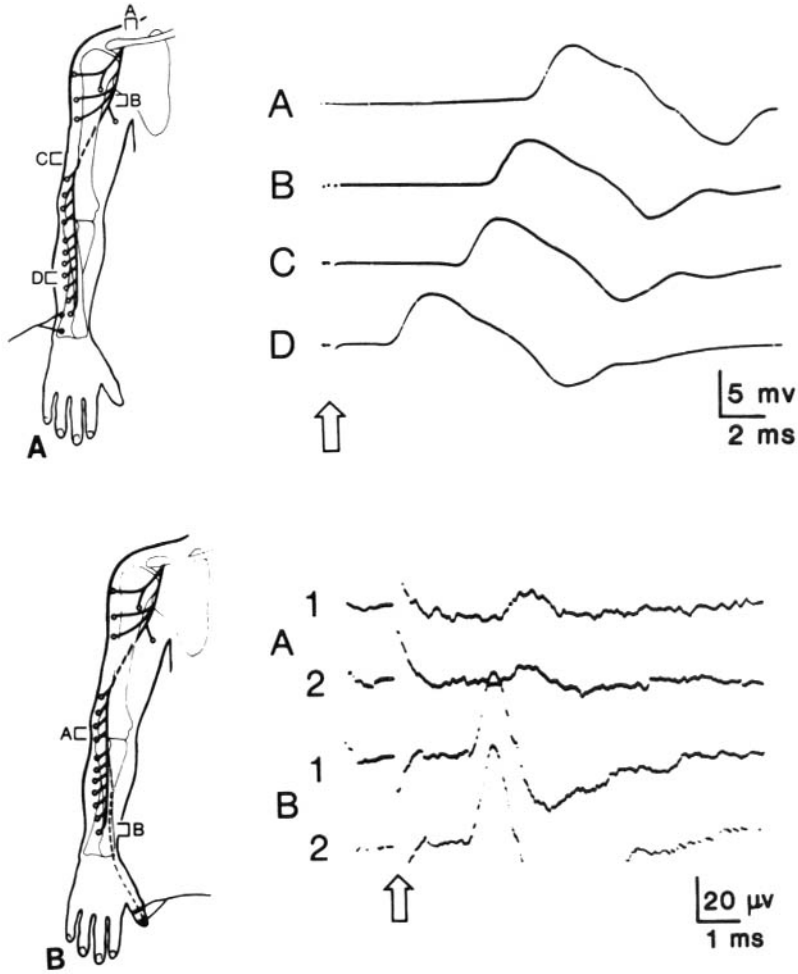


Figure 6–13. A. Motor nerve conduction study of the radial nerve. The sites of stimulation include Erb's point (*A*), axilla (*B*), above the elbow (*C*), and mid-forearm (*D*). Compound muscle action potentials are recorded from the extensor indicis with a pair of surface electrodes. **B.** Sensory nerve conduction study of the radial nerve. The sites of stimulation include elbow (*A*) and distal forearm (*B*). Antidromic sensory potentials are recorded using the ring electrodes placed around the first digit.

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.[23] It then becomes more superficial about 10 cm above the lateral styloid process. The sensory fibers cross the extensor pollicis longus at the base of the thumb[41,42] and are palpable at this point. Percutaneous stimulation at the lateral edge of the radius in the distal forearm 10–14 cm proximal to the base of the thumb elicits an antidromic sensory potential recordable by a pair of ring electrodes placed around the thumb (Fig. 6–14B). Alternative arrangements combine the disc electrode (G_1) over the first web space or slightly more proximally in the snuffbox, with the reference electrode (G_2) near the first dorsal interosseous[113,116] or between the second and third metacarpals.[167] An additional stimulation at the elbow under the brachioradialis muscle lateral to the biceps tendon (see Fig. 6–13B) allows determination of conduction velocities in the segments between elbow and wrist and wrist and thumb.[24,52,157,162] Sensory fibers innervating the thumb originate from C6 and C7 roots and traverse upper and middle trunk before entering the posterior cord. Preganglionic avulsion of the C6 and C7 roots results in a clinical sensory loss associated with no abnormalities of the sensory potentials.

Stimulation of the radial nerve at the thumb or the wrist elicits orthodromic sensory potentials at the elbow or axilla. Spread of current to the median nerve, which partially supplies the thumb, accounts for 25 percent of the sensory po-

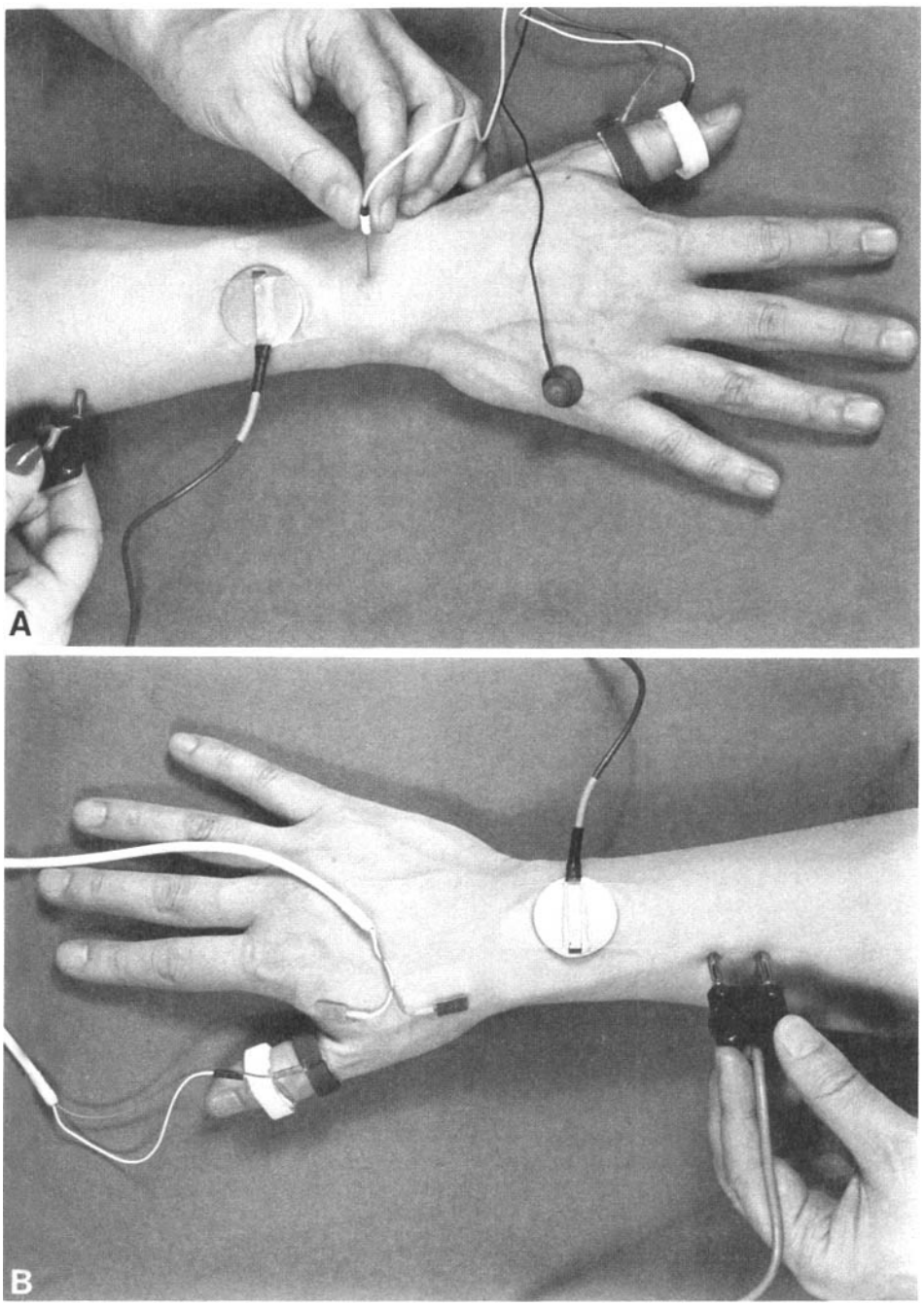


Figure 6–14. A. Motor and sensory conduction studies of the radial nerve. The photo shows stimulation in the forearm with the cathode at the lateral edge of the extensor carpi ulnaris muscle, 8 to 10 cm proximal to the styloid process. The monopolar needle electrode (G_1) is inserted in the extensor indicis with a reference electrode (G_2) over the dorsum of the hand laterally for motor conduction studies. The recording electrodes are placed around the base (G_1) and interphalangeal joint (G_2) of the first digit 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 placed 2 cm proximally. The recording electrodes are placed either around the base (G_1) and interphalangeal joint (G_2) of the first digit or over the palpable nerve between the first and second metacarpals (G_1) and 2–3 cm distally (G_2).

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

Source: From Trojaborg and Sinrup,[175] with permission.

tential recorded over the radial nerve at the wrist or elbow, and 50 percent of that recorded at the axilla.[175] Stimulation at the wrist, especially with needle electrodes placed along the nerve, accomplishes more selective activation of the radial nerve. Table 6–5 summarizes the results in one series.[175] Orthodromic potentials may be recorded from the snuffbox after stimulation of the third digit,[81] indicating inconsistent anomalous innervation of this finger by the radial nerve.[181]

3 OTHER NERVES DERIVED FROM THE CERVICAL OR THORACIC NERVE ROOTS

Phrenic Nerve

Conduction studies of the phrenic nerve, though described early,[33,130] have not gained popularity in part because surface stimulation in the cervical area requires shocks of a relatively high intensity. Moreover, some patients tolerate the esophageal electrode used for recording the diaphragmatic potentials poorly.

As an alternative method, some investigators[118] use a standard monopolar needle electrode inserted medially from the lateral aspect of the neck at the level of the cricoid cartilage (Fig. 6–15). 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. With an optimally placed needle, shocks of very low intensity suffice for selective stimulation of the phrenic nerve, contracting the diaphragm as evidenced by hiccup or interruption of voluntarily sustained vocalization. Supramaximal stimulation may coactivate the brachial plexus located posteriorly behind the anterior scalene muscle. The diaphragmatic action potential gives rise to a strong positivity at the

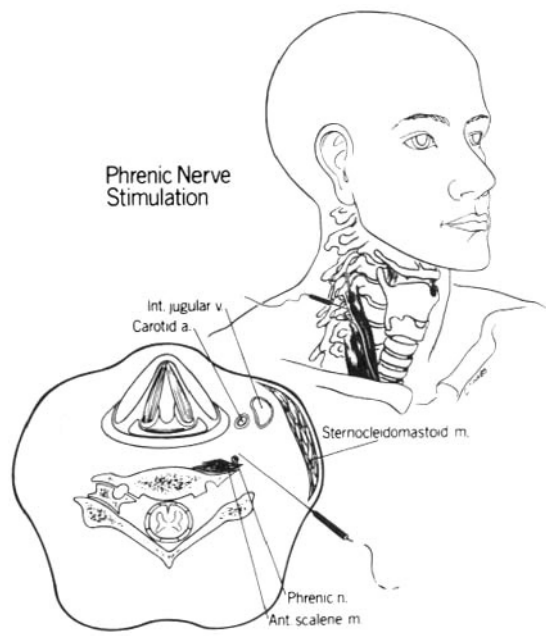


Figure 6–15. Motor conduction study of the phrenic nerve. The diagram shows stimulation with a needle inserted medially through the posterior margin of the sternocleidomastoid at the level of the cricoid cartilage. The recording electrodes are placed on the xiphoid process (G_1) and at the eighth intercostal space near the costochondral junction (G_2). [From MacLean and Mattioni,[118] with permission.]

Table 6–6 Phrenic Nerve

Authors	Stimulation Point	Recording Site	No.	Amplitude (μV)	Duration (ms)	Onset Latency (ms)	Difference Between Sides (ms)
Newsom Davis (1967)[78]			18			7.7 ± 0.80	
Delhez (1965)[16]			30 on right			7.5 ± 0.53	
			30 on left			8.2 ± 0.71	
MacLean and Mattioni (1981)[68]	Needle electrode placed posterior to sternocleido-mastoid	Xiphoid process	30	8.5 ± 40.5	48.1 ± 12.2	7.4 ± 0.59	0.08 ± 0.42

7th or 8th intercostal space near the costochondral junction and a mild negativity at the xiphoid process.[120] Paired surface electrodes placed over these recording sites, therefore, register the largest amplitude with summation of out-of-phase activities. Normal ranges established using needle stimulation in 30 healthy subjects[118] very closely approximate the earlier results obtained by surface stimulation (Table 6–6).[130]

Phrenic nerve conduction studies complement needle electromyography of the diaphragm by identifying the nature and site of disorder of the respiratory system.[9] Diaphragmatic compound muscle action potentials show good intraindividual side-to-side agreement for latency but not for amplitude.[171] Nonetheless, amplitude value serves as a better measure than the latency in predicting respiratory dysfunction.[21] In one study of 50 phrenic nerves in 25 healthy subjects,[25] 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.

Greater Auricular Nerve

The greater auricular nerve, derived mainly from the C2 and C3 roots, winds around the posterior border of the sternomastoid and ascends cephalad on the surface of that muscle from the neck to the ear. Stimulation with a pair of surface electrodes firmly placed against the lateral border of the sternocleidomastoid muscle elicits an orthodromic sensory potential easily 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,[133] and latency of 1.9 ± 0.2 ms, and amplitude of 22.4 ± 8.9 μV in 32 normal control subjects.[97]

Cervical Spinal Nerve and Brachial Plexus

The brachial plexus comprises the anterior rami of the spinal nerves derived from the C5 through C8, and T1 roots. Surface stimulation at Erb's point (see Fig. 1–8) activates the proximal muscles of the shoulder girdle.[60] 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. A collision technique circumvents this difficulty by blocking the unwanted impulse with a second stimulus applied distally to the nerve not under consideration (see Chapter 7–3). The use of needle electrodes accomplishes more selective stimulation but carries the risk of inducing pneumothorax.[135]

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 horizontaly directed endplates mostly in the mid-

dle of the fibers.[121–123,125] 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. Recording from the serratus anterior[85] permits conduction studies of the long thoracic nerve.[139,140]

The needle electrodes register from a more limited area, providing a reliable measure of latencies, even with simultaneous activation of many nerves.[102] Intramuscular recordings, however, fail to reveal the true waveform of the compound muscle action potential because of restricted recording area. When testing a unilateral involvement of the brachial plexus, comparison between the affected and normal sides offers the most sensitive indicator (Table 6–7). 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, and particularly that of the triceps for the reasons stated previously.

A localized stimulus applied through a needle electrode can directly activate the spinal nerve at the junction of the respective ventral and dorsal roots.[7,86,118,119,126] 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. 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. 6–16A). 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. 6–16B). 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 serves as the anode. Alternatively, placing the anode over the T2 spinous process allows activation of the C8 and T1 with the stimulating cathode inserted at the C5–C6 level, minimizing the risk of pneumothorax.[135,153]

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. Table 6–8 summarizes the conduction time across the brachial plexus calculated by subtracting the distal latency of the ulnar nerve.[17] The side-to-side difference exceeding 0.6 ms indicates unilateral lesions, making it a more sensitive index than the absolute latency.

Musculocutaneous and Lateral Antebrachial Cutaneous Nerves

Optimal sites of stimulation for motor conduction[129,172] include the posterior cervical triangle 3 to 6 cm above the clavicle just behind the sternocleidomastoid

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

Source: Modified from Gassel,[60] with permission.

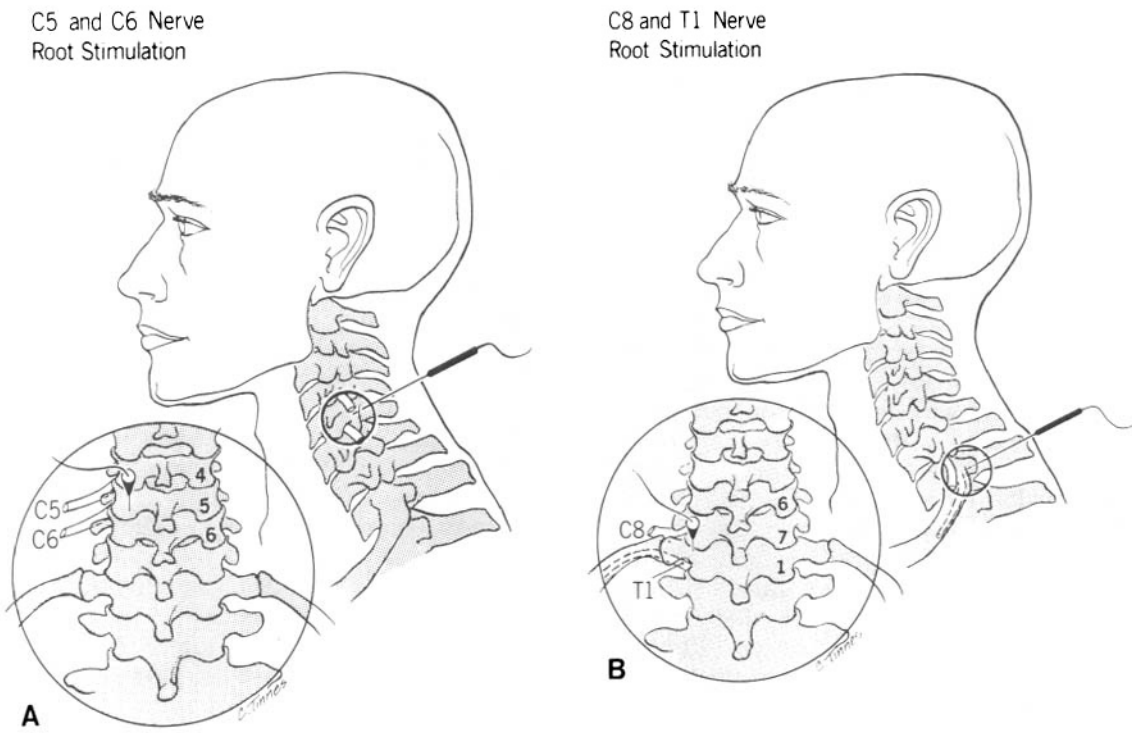


Figure 6–16. A. C5 and C6 root stimulation. The diagram shows the needle inserted perpendicular to the skin, 1–2 cm lateral to the C5 spinous process. **B.** C8 and T11 root stimulation. The diagram shows the needle inserted slightly caudal to the C7 spinous process. [From MacLean,[117] with permission.]

muscle (see Fig. 1–9)[61,102] and the axilla between the axillary artery medially and the coracobrachialis muscle laterally.[145] 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).

The sensory branch runs superficially at the level of the elbow, just lateral to the tendon of the biceps. Stimulation of the nerve between the tendon of the biceps medially and the brachioradialis laterally elicits orthodromic sensory potentials recordable at the posterior cervical triangle and axilla by the same electrodes positioned to stimulate motor fibers. The same stimulus also elicits antidromic sensory potential of the distal branch, the lateral antebrachial cutaneous nerve of the forearm (Fig. 6–17). The recording electrode is placed 12 cm distally over the course of the nerve in the forearm, along the straight line from the stimulus point to the radial artery at the wrist. Table 6–10 summarizes normal values reported in two series.[74,166] Study of the musculocutaneous nerve provides evaluation of the

Table 6–8 Brachial Plexus Latency with Nerve Root Stimulation

Plexus	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 T1 Ulnar nerve	Abductor digiti quinti	3.7–5.5	4.7	0.5

Source: From MacLean,[117] with permission.

Table 6–9 Musculocutaneous Nerve

	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		
			Range of Amplitude (μV)							
Age	n	Range of Conduction Velocity (m/s)	Axilla	Erb's Point	n	Range of Conduction Velocity (m/s)	Range of Amplitude (μV)	n	Range of Conduction Velocity (m/s)	Range of Amplitude (μV)
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

Source: From Trojaborg,[172] with permission.

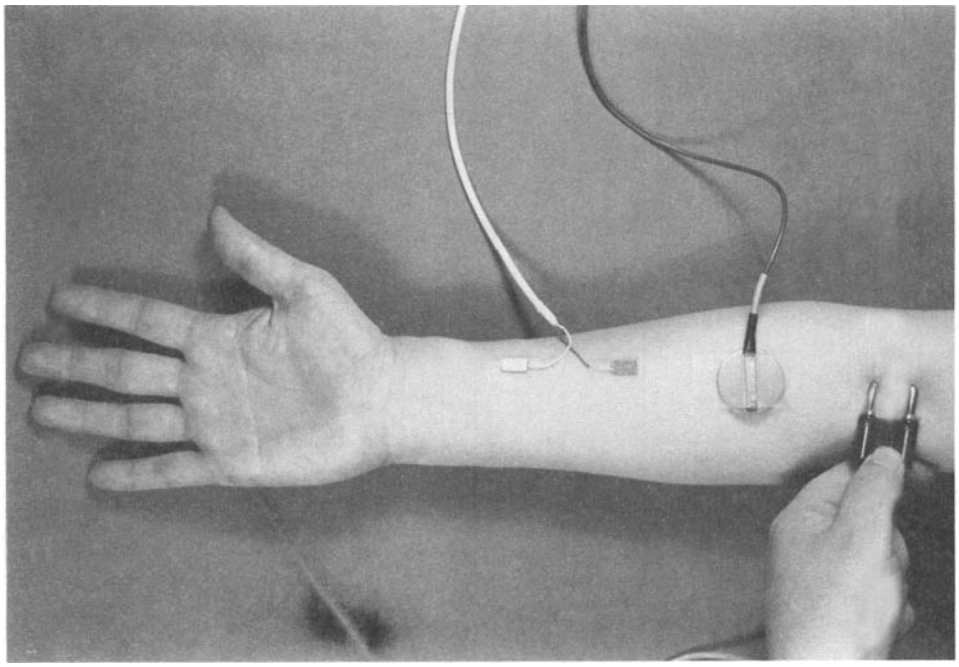


Figure 6–17. Sensory conduction study of the lateral cutaneous nerve of the forearm. The photo shows stimulation just lateral to the tendon of the biceps and recording from the nerve with the electrodes placed 12 cm distal to the cathode along the straight line to the radial artery (G_1) and 2–3 cm further distally (G_2).

C6 root, upper trunk, and lateral cord better than the median sensory potentials recorded from the second digit, which, more often than not, represent the C7 root and middle trunk.[56]

Medial and Posterior Antebrachial Cutaneous Nerves

The medial antebrachial cutaneous nerve, like the ulnar nerve, originates from the C8 and T1 roots via the lower trunk and medial cord.[99] 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 sensory potentials best recorded over the course of its volar branch on the same line extended distally 8 cm from the elbow (Fig. 6–18). Table 6–10 shows the results of two studies.[74,144]

The posterior antebrachial cutaneous nerve, derived from the C5 through C8 roots 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, separating into proximal and distal branches. Surface stimulation above the lateral epicondyle, between the biceps and triceps brachii, elicits antidromic sensory potentials recordable 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. 6–19).

Intercostal Nerves

Surface stimulation of this nerve elicits intercostal muscle action potentials with inconsistent latency. Recording from the rectus abdominis muscle improves reproducibilites of the waveform and allows calculation of conduction velocity after stimulating the nerve at two points.[142]

Table 6–10 Lateral and Medial Cutaneous Nerve (Mean ± SD)

Authors	Nerve	Number of Patients Seen	Age (mean)	Distance (cm)	Latency Onset (ms)	Latency Peak (ms)	Conduction Velocity (m/s)	Amplitude (μV)
Spindler and Felsenthal[166]	Lateral cutaneous nerve	30	20–84 (35)	12	1.8 ± 0.1	2.3 ± 0.1	65 ± 4	24.0 ± 7.2
Izzo et al.[74]	Lateral cutaneous nerve	154	17–80 (45)	14		2.8 ± 0.2	62 ± 4	18.9 ± 9.9
	Medial cutaneous nerve	155	17–80 (45)	14		2.7 ± 0.2	63 ± 5	11.4 ± 5.2
Reddy[144]	Medial cutaneous nerve	30	23–60 (38)	18	2.7 ± 0.2	3.3 ± 0.2	66 ± 4	15.4 ± 4.1

4 COMMONLY TESTED NERVES IN THE LOWER LIMB

Tibial Nerve

Motor conduction studies record the muscle response from one of the intrinsic foot muscles after stimulation of the tibial nerve at the popliteal fossa and at the ankle posterior to the medial malleolus. The nerve bifurcates into two branches within 1 cm of the malleolar-calcaneal axis in 90 percent of feet.[34] The usual choices for recording sites include the abductor hallucis and flexor pollicis brevis, innervated by the me-

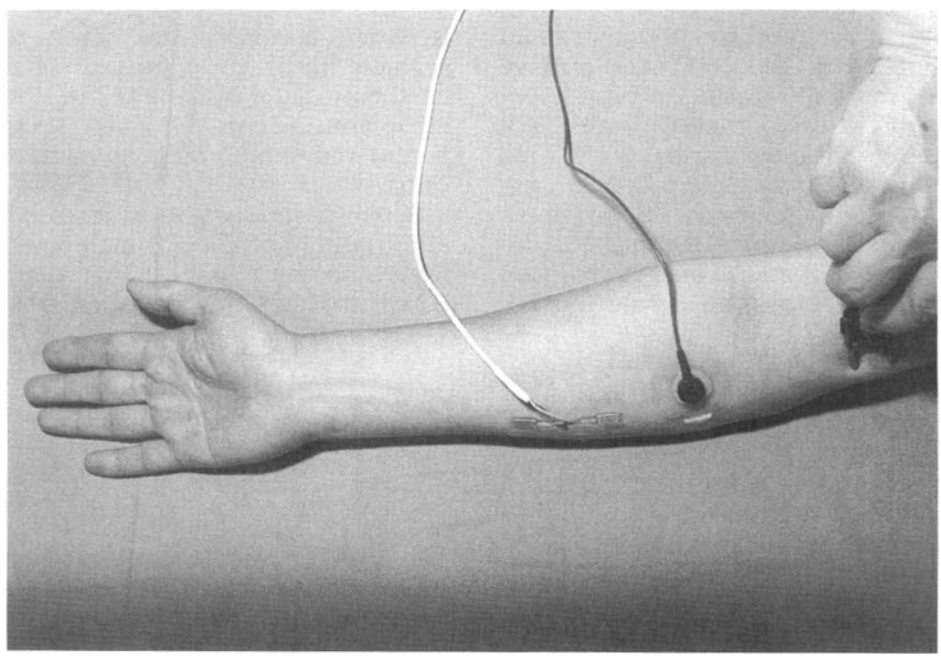


Figure 6–18. Stimulation of the medial antebrachial cutaneous nerve of the forearm with the cathode placed medial to the brachial artery 4 cm above the elbow crease on a line drawn from the ulnar styloid process to a point halfway between the medial epicondyle and biceps brachii tendon, and recording of the antidromic sensory potential with the active electrode (G_1) 8 cm distal to the elbow crease and the reference electrode (G_2), 3–4 cm further distally along the same line. This arrangement yields results directly comparable to the analogous study of the lateral antebrachial cutaneous nerve (cf. Fig. 6–17).

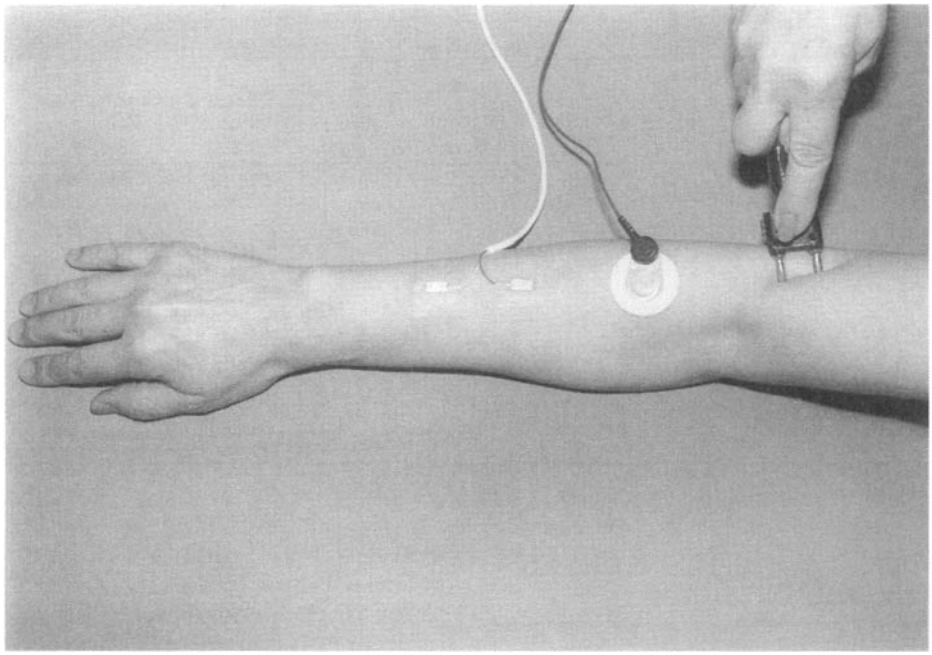


Figure 6–19. Stimulation of the posterior antebrachial cutaneous nerve with the cathode placed just above the lateral epicondyle between the biceps brachii and triceps brachii, and recording of the antidromic sensory potentials with the active electrode (G_1) 12 cm distally and the reference electrode (G_2), 3–4 cm further distally along a line extended from the stimulus point to the mid-dorsum of the wrist, midway between the ulnar and radial styloid processes.

dial plantar nerve, and the abductor digiti quinti, supplied by the lateral plantar nerve (Figs. 6–20 and 6–21A,B). 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.[72] Stimulation of the tibial nerve above and below the medial malleolus determines the conduction characteristics of the motor fibers across the tarsal tunnel.[55] Reported normal values across a 10 cm segment (mean ± SD) include 3.8 ± 0.5 ms for the medial and 3.9 ± 0.5 ms for the lateral plantar nerves.[58] Tables 6–11 and 6–12 summarize the normal values in our laboratory.

Sensory conduction studies consist of stimulating the medial or lateral plantar nerves on the sole 11–13 cm distal to the G_1 electrode[184] and recording orthodromic

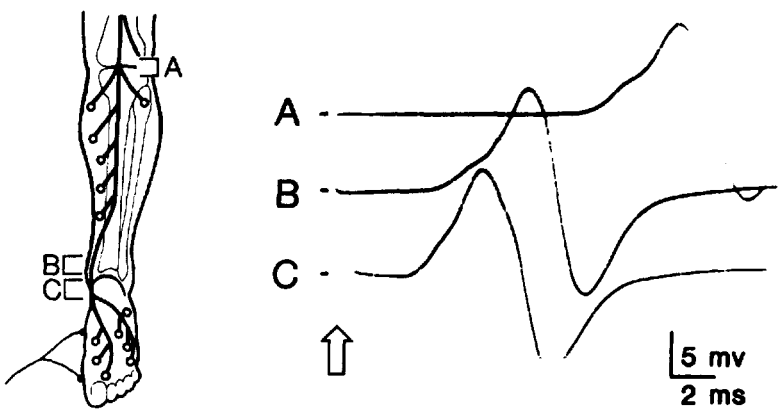


Figure 6–20. Motor conduction study of the tibial nerve. The sites of stimulation include the knee (*A*), above the medial malleolus (*B*) and below the medial malleolus (*C*). Compound muscle action potentials are recorded with surface electrodes placed over the abductor hallucis.

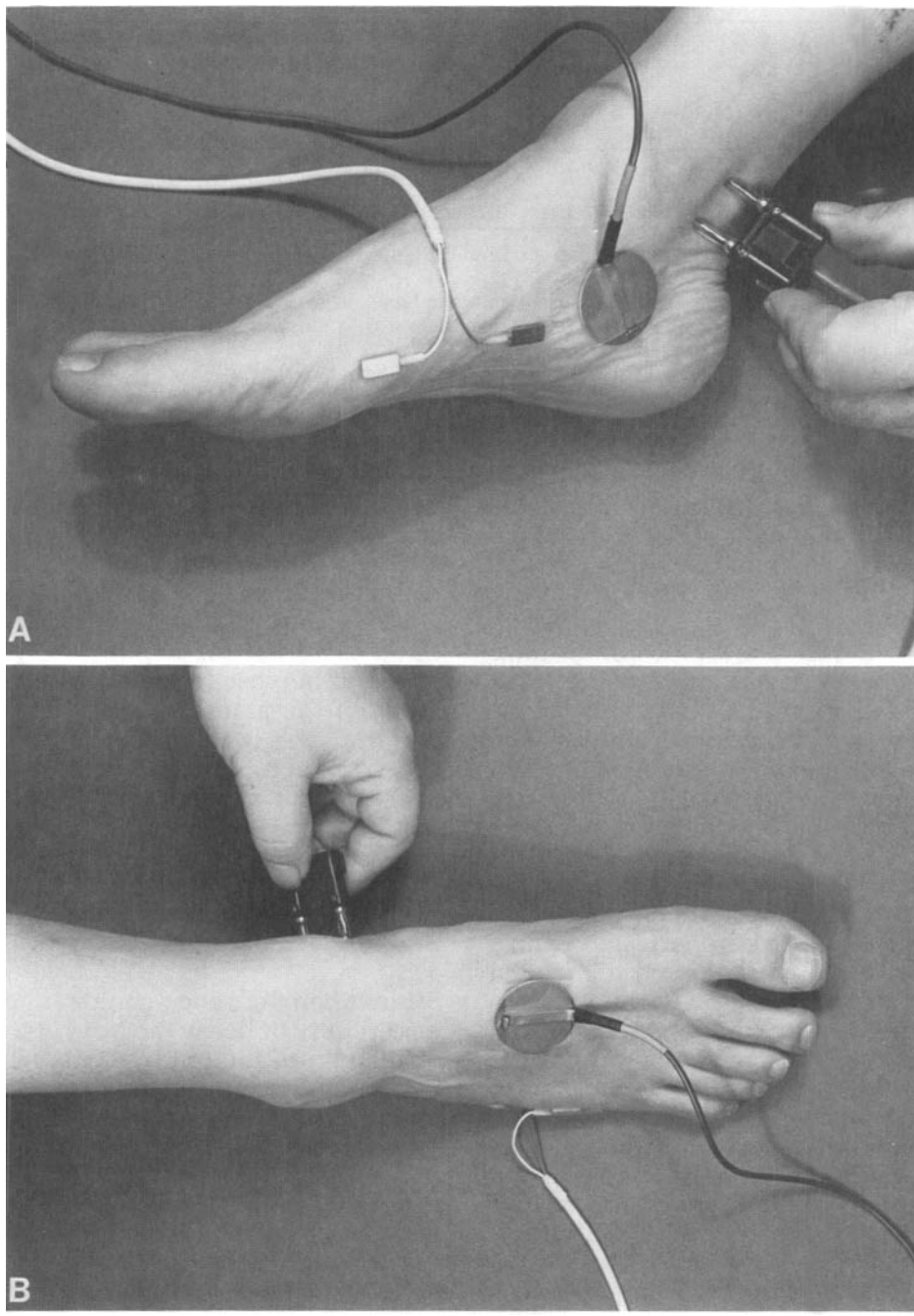


Figure 6–21. A. Motor conduction study of the medial plantar nerve. The photo shows stimulation of the tibial nerve posterior to the medial malleolus, 10 cm from the recording electrodes placed over the belly (G_1) and tendon (G_2) of the abductor hallucis. **B.** Motor conduction study of the lateral plantar nerve. The photo shows stimulation posterior to the medial malleolus and recording with surface electrodes placed on the belly (G_1) and tendon (G_2) of the abductor digiti quinti.

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 patients, 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.

sensory potentials with surface or needle electrodes placed just below the medial malleolus (Fig. 6–22 and 6–23).[6,141,152] Alternative sites of stimulation include the first and fifth toes with a pair of ring electrodes. The medial plantar potentials have average 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, respectively. The lateral plantar latencies average 3.2 ± 0.3 ms and 4.0 ± 0.3 ms for 14 and 18 cm segments. As a modification of this method, selective stimulation of the interdigital nerve also gives rise to an orthodromic sensory potential for assessment of interdigital neuropathy or Joplin's neuroma.[51,131] Stimulation on the medial aspect of the hallux selectively activates the terminal sensory branch of the medial plantar nerve, or medial plantar proper digital nerve, another uncommon site of Joplin's neuroma.[28]

The responses recorded at the knee after stimulation of the tibial nerve at the ankle comprise orthodromic sensory and antidromic motor potentials.[124] 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[73,90] and of the medial calcaneal nerve at the heel.[134] 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 the L4 and L5 roots, for example, in patients with footdrop.[65]

Common and Deep Peroneal Nerve

Stimulation of the common peroneal nerve above or below the head of the fibula or just above the ankle elicits muscle action potentials in the extensor digitorum brevis (Figs. 6–24 and 6–25). This muscle, primarily supplied by the deep peroneal nerve, may also receive an anomalous innervation from the superficial peroneal nerve. The communicating branch, called the accessory deep peroneal nerve, passes behind the lateral malleolus to reach the

Table 6–12 Latency Comparison Between Two Nerves in the Same Limb*

Site of Stimulation	Peroneal Nerve	Tibial Nerve	Difference
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 patients, 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.

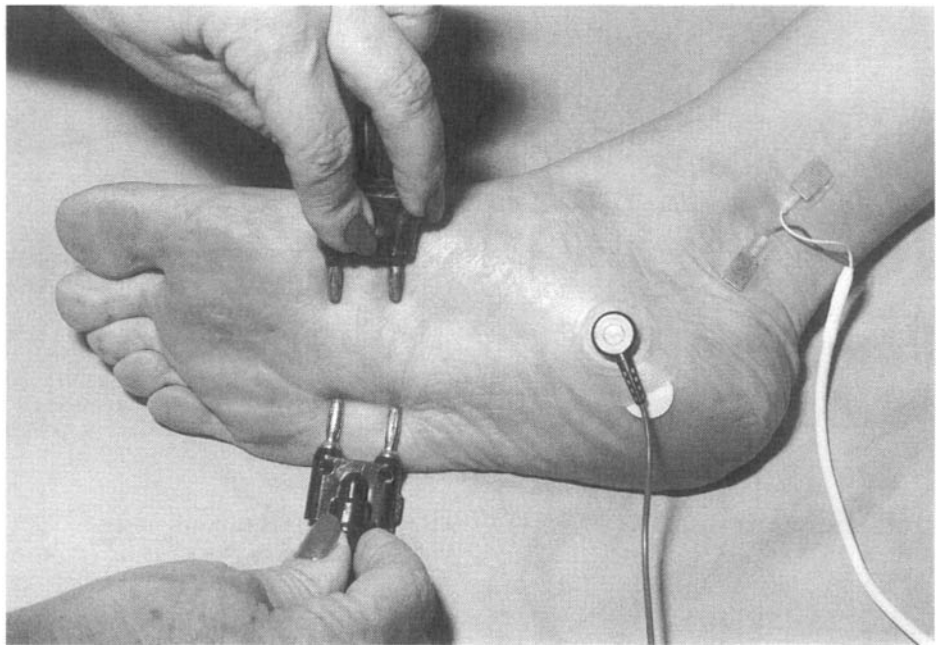


Figure 6–22. Stimulation of the sensory branch of the medial and lateral plantar nerves with the cathode placed over the medial and lateral aspects in the mid-portion of the sole and the anode placed 2 cm further distally, and recording of the orthodromic sensory nerve potential with the active electrode (G_1) placed immediately posterior to the medial malleolus 11–13 cm from the cathode, and reference electrode (G_2) 3–4 cm further proximally.

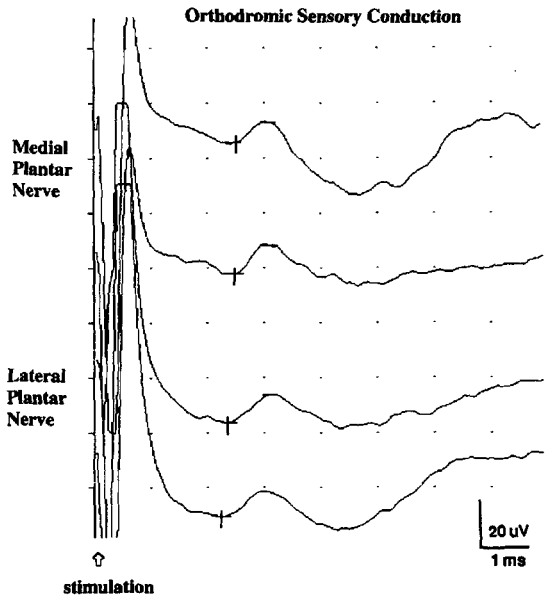


Figure 6–23. Orthodromic sensory nerve potentials of the medial (*two top tracings*) and lateral plantar nerves (*two bottom tracings*) recorded from the tibial nerve at the ankle following stimulation of each nerve on the sole in a 48-year-old healthy man (cf. Fig. 6–22).

lateral portion of the muscle. In the presence of this anomaly, stimulation of the deep peroneal nerve at the ankle evokes a much smaller compound muscle action potential than the shocks applied at the knee (see Chapter 7–4).

For accurate determination of conduction velocity across the knee, the distance between the proximal and distal sites of stimulation should exceed 10 cm. A series of shocks applied in short increments, however, is better suited for delineating a focal conduction abnormality.[82,94] In an advanced neuropathy, recording from the extensor digitorum longus[30] or tibialis anterior[36] instead of from the atrophic extensor digitorum brevis may facilitate the assessment. Stimulation of the peroneal nerve at the ankle elicits mixed nerve potentials at the fibula head.[62] The use of needle electrode and averaging technique improves resolution in recording small potentials of the deep peroneal sensory nerve[105] from the web between the first and second toes. Tables 6–12 and 6–13 summarize the normal values in our laboratory.

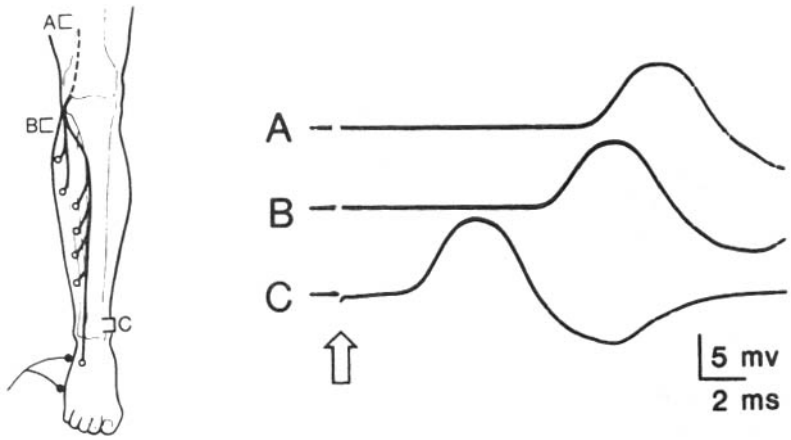


Figure 6–24. Motor conduction study of the common peroneal nerve. The sites of stimulation include above the knee (*A*), below the knee (*B*), and at the ankle (*C*). Compound muscle action potentials are recorded with surface electrodes over the extensor digitorum brevis.

Superficial Peroneal Nerve

This mixed nerve, derived from the L5 root, originates below the fibular head as a branch of the common peroneal nerve. It 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.[19,37] 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. The averaging technique helps identify the potential with amplitude approximately half that of the sural nerve, especially in recording from a diseased nerve.

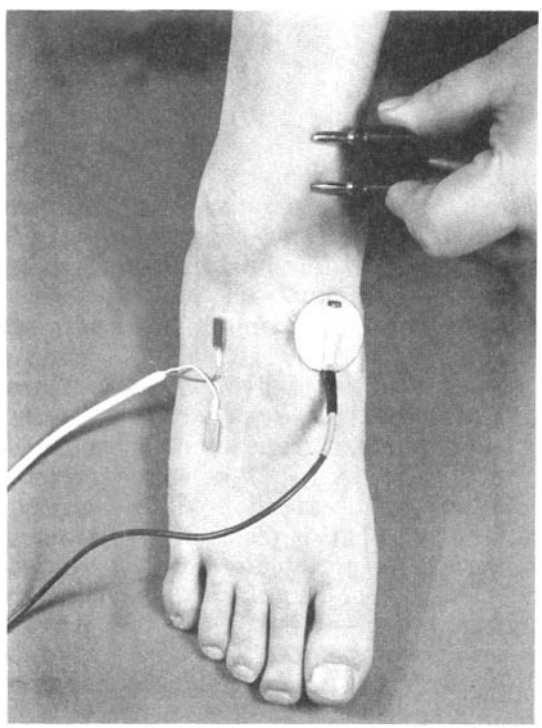


Figure 6–25. Motor conduction study of the common peroneal nerve. The photo shows stimulation over the dorsum of the foot near the ankle, 7 cm from the recording electrodes over the belly (G_1) and tendon (G_2) of the extensor digitorum brevis.

In another method,[75,78] stimulation of the intermediate dorsal cutaneous branch with the cathode placed against the anterior edge of the fibula elicits the antidromic sensory potential at the ankles just medial to the lateral malleolus (Fig. 6–26). 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 an L-5 radiculopathy from more distal lesions.[78] The near nerve needle recording with signal averaging makes it possible to assess small sensory action potential from interdigital nerves.[134] Table 6–14 summarizes the normal values.

Sural Nerve

This sensory nerve, primarily derived from the S1 root, originates in the popliteal

Table 6–13 Common and Deep Peroneal Nerves*

Site of Stimulation	Latency‡ to Amplitude† (mV)	Difference Between Recording Site (ms)	Conduction Time Right and Left (ms)	Conduction Between Two Points (ms)	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 patients, 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.

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. 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 percent of individuals.[3]

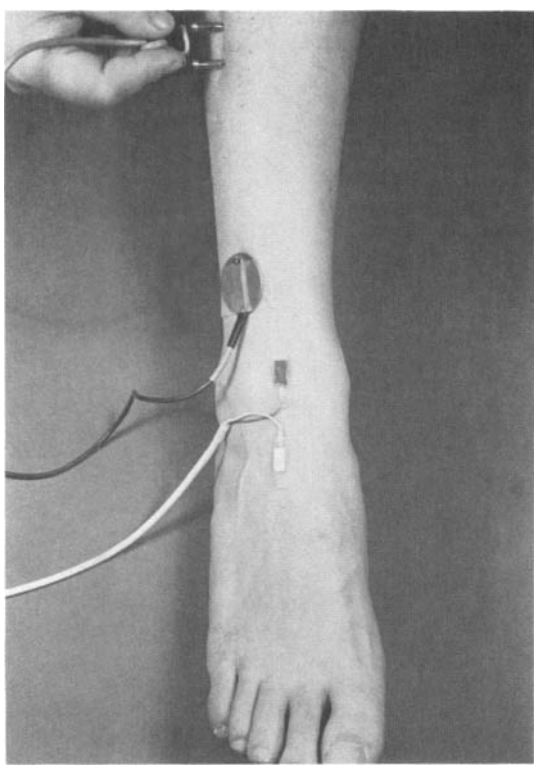


Figure 6–26. Sensory conduction study of the superficial peroneal nerve. The photo shows stimulation against the anterior edge of the fibula, 12 cm from the active electrode (G_1) located just medial to the lateral malleolus at the ankle with the reference electrode (G_2) placed 2–3 cm distally.

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. 6–27 and 6–28), but at times more distally for the study of the lateral dorsal cutaneous branch.[106] Sural potentials need no averaging for recording except perhaps in older population or patients with diseased nerve.[15,17,38] Segmental studies dividing the nerve into three contiguous portions of 7 cm each have revealed a smaller mean velocity in the most distal segment than in the middle or proximal segment.[176]

Averaging technique facilitates the study of orthodromic potentials after stimulation of the nerve over the lateral aspect of the foot.[4,5,69,87,161] Segmental studies depend on recording at the popliteal fossa and high at the ankle, 10–15 cm proximal to the lateral malleolus (Table 6–15). Near-nerve technique revealed a greater latency when measured from the stimulus to the recording sites than the true conduction time calculated as latency difference over the same

Table 6–14 Superficial Peroneal Nerve

Stimulation Point	Recording Site	n	Age	Amplitude (μV)	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)

Source: Data from Di Benedetto,[37] Jabre,[78] and Izzo et al.[75]

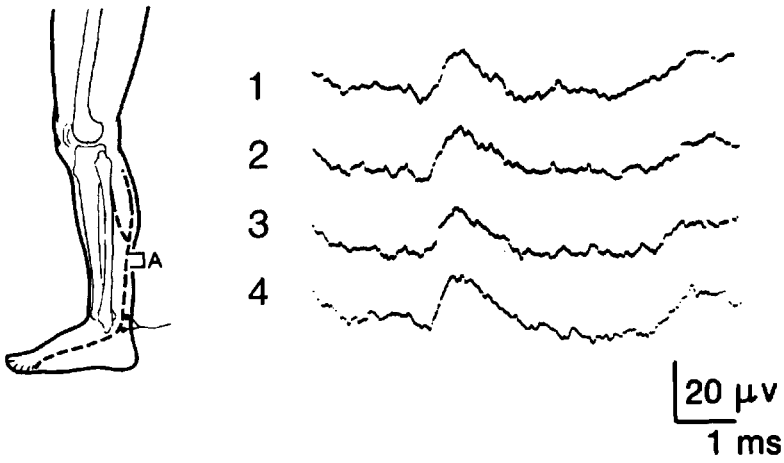


Figure 6-27. Antidromic sensory nerve conduction study of the sural nerve. The diagram shows stimulation on the calf slightly lateral to the midline in the lower third of the leg, and recording with surface electrodes placed behind the lateral malleolus.

segment. This discrepancy results from the latency of activation at the stimulus site, or utilization time of about 0.15 ms, depending on the type of stimuli.[103] The near-nerve potential recorded at midcalf showed a 32 percent higher amplitude in women than in men, probably reflecting different volume conductor properties.[69]

Sural nerve study conducted with care[174] offers one of the most sensitive means of detecting electrophysiologic abnormalities in various types of neuropathies. In addition to absolute amplitude, sural to radial amplitude ratio may serve as a sensitive measure. In one study,[150] a ratio less than 0.40, as compared to the normal mean of

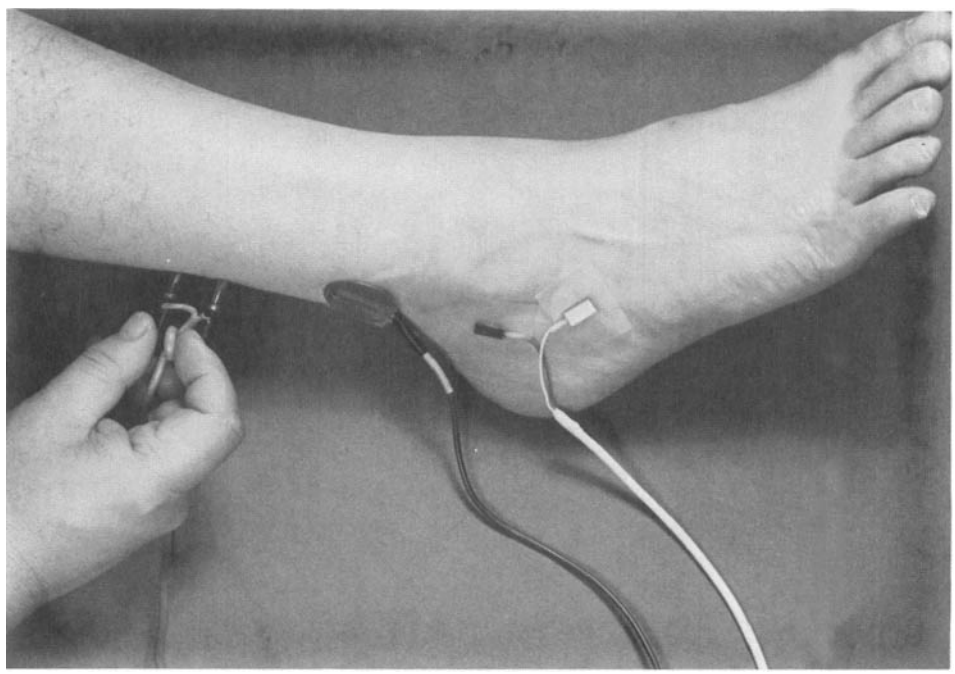


Figure 6-28. Sensory conduction study of the sural nerve. The photo shows stimulation along the posterior surface of the leg, slightly lateral to the midline and 7–10 cm from the ankle. The active electrode (G_1) is placed above or immediately below and behind the lateral malleolus with the reference electrode 2–3 cm distally along the lateral dorsum of the foot (G_2).

Table 6–15 Sural Nerve

Authors	Stimulation Point	Recording Site	n	Age	Amplitude (μV)	Latency (ms)	Conduction Velocity (m/s)
Shiozawa and Mavor[161]	Foot	High ankle	40	13–41	6.3 (1.9–17)		44.0 ± 4.7
DiBenedetto[37]	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[4]	15 cm above lateral malleolus	Dorsal aspect of foot	71	15–30			51.2 ± 4.5
				40–65			48.3 ± 5.3
Wainapel et al.[180]	Lower third of leg	Lateral malleolus	80	20–79	18.9 ± 6.7	3.7 ± 0.3 (Peak)	41.0 ± 2.5
Truong et al.[176]	Distal 10 cm	Lateral malleolus	102				33.9 ± 3.25
	Middle 10 cm		102				51.0 ± 3.8
	Proximal 10 cm		102				51.6 ± 3.8
Kimura (Unpublished)	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

0.71, predicted axonal neuropathy. Sural nerve study also provides a unique opportunity for direct comparison between physiologic and histologic findings of the biopsied specimen (see Chapter 4–4).[44] Preganglionic pathology consistently spares the sensory action potential despite the clinical symptoms. Thus, studies of the sural nerve help distinguish peripheral lesions from S1 or S2 radiculopathy or cauda equina involvement.

5 OTHER NERVES DERIVED FROM THE LUMBOSACRAL NERVE ROOTS

Lumbosacral Plexus

The lumbosacral plexus consists of the lumbar plexus with fibers derived from the L2, L3, and L4 roots and the sacral plexus, which arises from the L5, S1, and S2 roots. Conventional conduction studies fall short of adequately evaluating their integrity because of their inaccessibiity to percutaneous electrical stimulation. The use of the F wave and H reflex provides an indirect measure of impulses propagating across this region (see Chapters 18 and 19). An alternative method involves needle stimulation[47,48,117,126] or percutaneous high voltage electrical stimulation[71] of L4, L5, or S1 spinal nerve just proximal to the plexus and stimulation of the peripheral nerve just distal to the plexus. Conduction time through the plexus then equals the difference between the distal and proximal 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. 6–29A,B). With

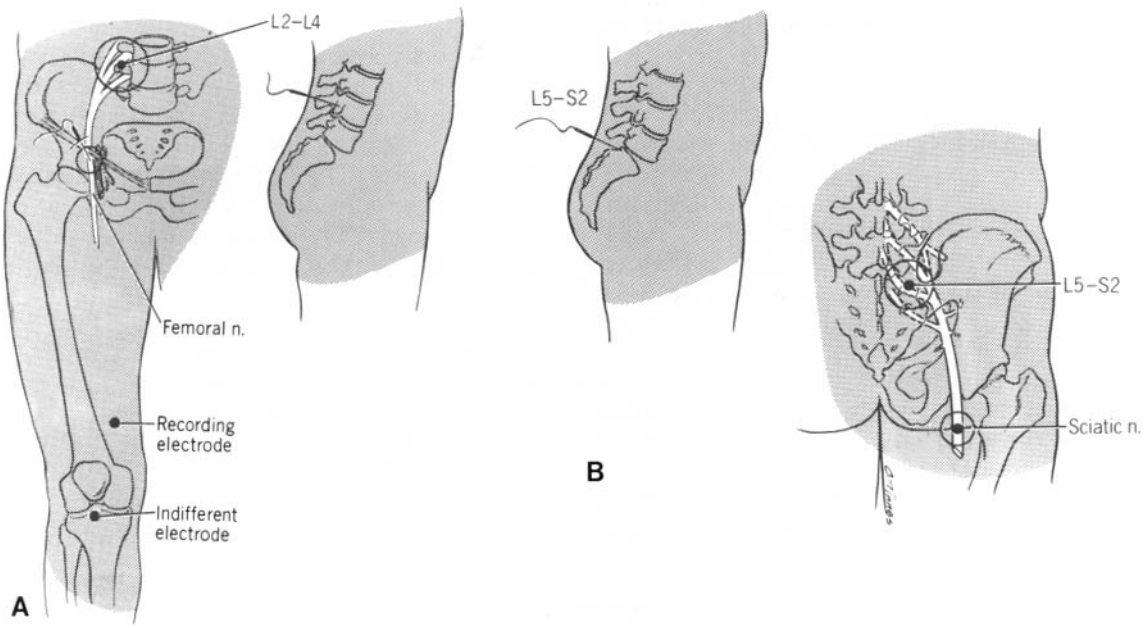


Figure 6–29. A. Motor conduction study of the lumbar plexus. The diagram shows stimulation of the L4 root, with the needle inserted perpendicular to the skin just below the level of the iliac crest, and of femoral nerve distal to the inguinal ligament immediately lateral to the femoral artery. Muscle potentials are recorded with surface electrodes over the vastus medialis (G_1) and patella (G_2). **B.** Motor nerve conduction study of the sacral plexus. The diagram shows stimulation of the S1 root with the needle inserted at the level of the posterior iliac spine, of the L5 root halfway in between the L4 and S1 roots and of the sciatic nerve at the level of the gluteal skinfold midpoint between the ischial tuberosity and the greater trochanter of the femur. The recording electrodes (not shown) are placed on the belly (G_1) and tendon (G_2) of the tibialis anterior for L5 and of the abductor hallucis for S1 root studies. [From MacLean,[112] with permission].

an optimal needle position, a shock of very low intensity elicits the maximal compound muscle action potential of the vastus medialis. Stimulation of the femoral nerve just distal to the inguinal ligament, with either a surface or a needle electrode, provides the distal latency (Fig. 6–29A). The nerve lies immediately lateral to the readily palpable femoral artery, as discussed later in this section.

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. At the level of the gluteal skin fold, the sciatic nerve bisects a line drawn between the ischial tuberosity and the greater trochanter of the femur. Needle stimulation here provides the distal latency required for calculation of conduction time across the sacral plexus (Fig. 6–29B). With careful adjustment of the needle position, shocks of very low intensity elicit a maximal compound muscle action potential of the tibialis anterior for the L-5 and of the abductor hallucis for the S1 spinal nerve. Inadvertent activation of the neighboring spinal nerves induces volume-conducted potentials from distant muscles. Without proper care to avoid such spread of stimulus, the recording electrodes placed over the tibialis anterior, for example, would regularly register a simultaneously activated action potential of the triceps surae. Table 6–16 summarizes the normal value in one series.[117]

The commercially available magnetic coils fail to optimally stimulate lumbosacral roots as diagnostic aids.[47,48,115] Specially constructed large-diameter coils, placed flat on the skin surface, however, adequately excite the cauda equina lying deep below the surface.[114] Over proximal cauda equina, cranially directed induced current via vertically oriented coil junction preferentially activates root entry zone of the conus medullaris. Over distal cauda equina, horizontally oriented junction excites the lumbar roots—and vertically oriented junction, sacral roots—at or near the intervertebral foramina. The latency difference between proximal and distal stimulation typically yields the onset latency of 1.9 ms for vastus medialis, 2.3 ms for tibialis anterior, and 3.5 ms for abductor hallucis (see Chapter 21–5). High-voltage electrical stimulation given percutaneously can also activate the sciatic nerve for proximal and segmental nerve conduction measurements.[71] This type of stimulation simultaneously excites the peroneal and tibial division of the sciatic nerve, requiring the collision technique to eliminate the unintended impulse.[91]

Femoral Nerve

Shocks delivered to the femoral nerve above or below the inguinal ligament elicits the response recordable in the rectus femoris muscle at various distances from the point of stimulation. The latency of the response increases progressively with the distance reflecting vertical orientation of the endplate region.[59] 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 (Table 6–17). This calculation, however, does not hold unless all branches supplying proximal and distal parts of the muscle have similar and directly comparable electrophysiologic characteristics.

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 S1 Sciatic nerve	Abductor hallucis	2.5–4.9	3.9	0.7

From MacLean,[117] with permission.

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	

Source: Modified from Gassel,[59] with permission.

Saphenous Nerve

This largest and longest sensory branch of the femoral nerve lies deep along the medial border of the tibialis anterior tendon (Fig. 6–30). The nerve stimulation uses the surface electrodes pressed firmly between the medial gastrocnemius muscle and tibia, usually 12–14 cm above the ankle. Signal averaging improves the resolution of small antidromic sensory potentials recorded just anterior to the highest prominence of the medial malleolus (Table 6–18). Orthodromic studies[46,155,169] 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. 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 sensory nerve potentials despite clinical deficits.

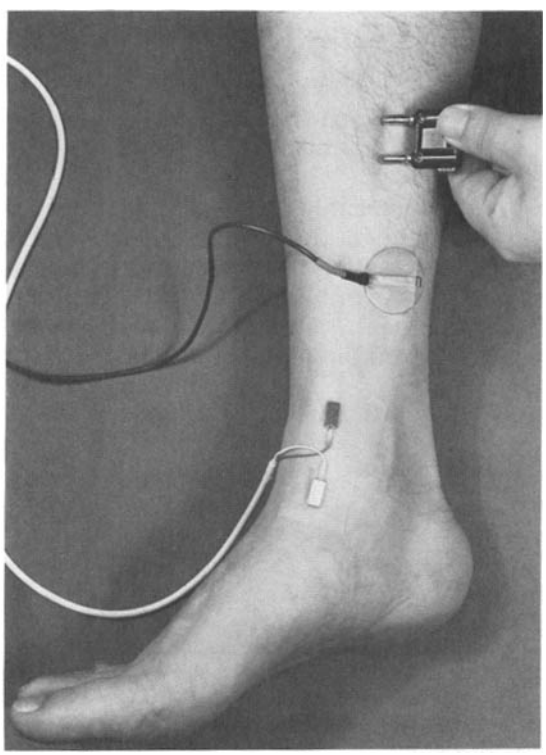


Figure 6–30. Sensory conduction study of the saphenous nerve. The photo shows stimulation 14 cm above the active electrode (G_1) along the medial surface of the leg between the tibia and the gastrocnemius and recording at the ankle 2–3 cm above (G_1) and just anterior to the medial malleolus (G_2).

Lateral Femoral Cutaneous Nerve

The nerve becomes superficial about 10–12 cm below the anterior superior ilac spine, where it divides into large anterior and small lateral branches. Surface stimulation at this point elicits the orthodromic sensory potential recordable with a needle electrode inserted 1 cm medial to the lateral end of the inguinal ligament.[112] Alternative technique consists of stimulation at the inguinal ligament with a needle electrode and recording antidromic sensory potentials from the thigh (Fig. 6–31). In one study[16] using a pair of specially constructed 1.2 × 1.9 cm lead strips fastened 4 cm apart, the normal

Table 6–18 Saphenous Nerve

			Inguinal Ligament—Knee			Knee—Medial Malleolus		
Authors	Method	Age	Number	Amplitude (μV)	Conduction Velocity	Number	Amplitude (μV)	Conduction Velocity (m/s)
Ertekin[46]	Orthodromic	17–38	33	4.2 ± 2.3	59.6 ± 2.3	10	4.8 ± 2.4	52.3 ± 2.3
Stöhr et al.[169]	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 et al.[180]	Antidromic	20–79			Peak latency of 3.6 ± 1.4 for 14 cm	80	9.0 ± 3.4	41.7 ± 3.4
Senden et al.[155]	Orthodromic	18–56	71					54.8 ± 1.9

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 velocity of 47.9 ± 3.7 m/s. In another study,[165] 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 onset conduction velocity of 62.3 ± 5.5 m/s (mean ± SD) and amplitude of 2.00 ± 1.0 μV.

Posterior Femoral Cutaneous Nerve

This sensory nerve originates from the anterior and posterior divisions of the S1, S2, and S3 roots, 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 midpopliteal fossa register an antidromic sensory potential after stimulating the nerve 12 cm further proximally on a line drawn to the ischial tuberosity. Normal values (mean ± SD) obtained in 40 subjects[43] 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.

Medial Femoral Cutaneous Nerve

Sensory abnormalities occasionally involve anterior medial thigh innervated by this nerve. Conduction studies[107] may help distinguish this condition from radiculopathy involving the L2 and L3 roots with overlapping dermatomal distribution.[104]

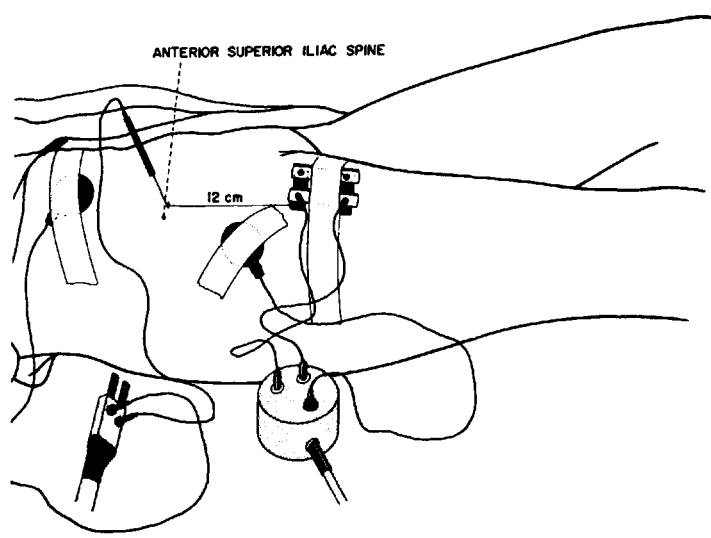


Figure 6–31. Sensory nerve conduction of the lateral femoral cutaneous nerve. The diagram shows stimulation above the inguinal ligament and recording over the thigh 12 cm below the anterior-superior iliac spine (G_1) and 2–3 cm distally (G_2). [From Butler, Johnson and Kaye,[16] with permission.]

Pudendal Nerve

The technique consists of stimulating the pudendal nerve and recording compound muscle action potential from the external anal sphincter.[170] A specially constructed disposable electrode, when properly mounted onto the gloved right hand, has the stimulating cathode at the tip of index finger. Locating the ischial spine and lateral margin of the sacrum with the fingertip 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. Latency values exceeding 2.2 ms suggest pudendal neuropathy.[26,88,183]

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 antidromic sensory nerve potential recordable at the distal shaft along the dorsal midline with G_1 placed 2 cm proximal to G_2.[11,29] 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.[186] A specially constructed urinary catheter electrode placed in the urethra also registers sensory potential following stimulation of the dorsal nerve of the penis.[185]

6 CRANIAL NERVES

The most commonly tested cranial nerves in the electromyographic laboratory include the facial and trigeminal nerves (see Chapters 7–3 and 17–2).

Mylohyoid, Deep Temporal, and Lingual Nerves

The mandibular nerve comprises motor axons originating in the trigeminal motor nucleus in the mid pons,[2] proprioceptive afferents having their cell bodies in the mesencephalic nucleus of the midbrain,[84] and sensory fibers arising from the gasserian ganglion.[20] The jaw jerk reflex, elicited by tapping on the chin, evaluates jaw closure (see Chapter 19–3) whereas the blink reflex assesses the afferent trigeminal fibers and the efferent facial nerve (see Chapter 17–2). Less commonly used techniques include motor studies of the mylohyoid and deep temporal nerves[40] and sensory conduction of the lingual nerve.[109]

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 the active recording electrode. In one study of 42 healthy subjects,[40] who all had the response bilaterally, the reported value included latency of 1.9 ± 0.2 ms (mean $\pm$ SD) and amplitude of 4.9 ± 1.8 mV.

For stimulation of the deep temporal nerve, the cathode, placed in the pterigomandibular fossa faces posteriorly near the upper rear molar. The patient activates the temporalis muscle by clenching the jaw for placement of the active recording leads. Only 60 percent of healthy subjects had bilateral responses, showing an average latency of 2.1 ± 0.3 ms and amplitude of 4.3 ± 2.0 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.[109] 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.[76,154]

Accessory Nerve

The accessory nerve runs superficially along the posterior border of the stern-

ocleidomastoid muscle. Surface stimulation at this point elicits a compound muscle action potential of the trapezius, usually recorded from the upper portion by an active electrode (G_1) placed at the angle of the neck and shoulder and a reference electrode (G_2) over the tendon near the acromion process. Some electromyographers prefer needle electrodes to stimulate the nerve.[139,140] 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.[27] In another study of 21 nerves, the onset latency (mean ± SD) averaged 3.0 ± 0.2 ms to the middle trapezius and 4.6 ± 0.3 ms to the lower trapezius.[64] Changes in amplitude also provide reliable information, with reduction to one half that of the response on the healthy side suggesting distal degeneration.

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.[146]

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Chapter 7

FACTS, FALLACIES, AND FANCIES OF NERVE STIMULATION TECHNIQUES

1 INTRODUCTION

Nerve conduction studies 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,[42,89] such studies have become a reliable means of testing not only for precise localization of a lesion but also for accurate characterization of peripheral nerve function.[25,73] This chapter reviews the fundamental principles and changing concepts of nerve stimulation

techniques and their proper application in the differential diagnosis of peripheral nerve disorders.

Despite simple basic principles that dictate the method in theory, pitfalls abound in practice.[74,77,78,104] Commonly encountered sources of error that are often overlooked 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 may result from a moving source not only in a referential but also a bipolar derivation, usually selected for recording near-field potentials (see Chapter 20–3). Lack of awareness of these possibilities can cause confusion in the interpretation of the results. All these factors limit the reproducibility of conduction studies, making it imperative to maintain good quality control.[87,168]

Conventional studies deal primarily 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 help in evaluating other aspects, such as conduction velocity of the slower fibers and the time course of the absolute and relative refractory periods. The phenomenon of collision provides a useful means of assessing these features of nerve conduction.[53,56,70,71,82] Here, a second stimulus delivered distally to the nerve blocks the unwanted impulses not under study. Other areas of interest include studies of threshold electrotonus and motor unit number estimates, described in Chapter 8. Although these methods supplement the conventional technique in theory, their clinical application in practice awaits further clarification.

2 COMMON TECHNICAL ERRORS

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 expected manifestations of the disease under consideration. Commonly unidentified yet easily correctable problems include malfunction of the stimulating electrodes or the recording system.

Stimulating System

Absent or unusually small responses result from inappropriately low shock intensity or from a stimulus that is misdirected despite adequate current strength. The amplitude should improve with relocation of the stimulating electrode, pressing it firmly closer to the nerve, and, if necessary, increasing shock intensity or duration. The use of monopolar or concentric needles may help, especially in obese patients. Profuse perspiration or an excessive amount of cream over the skin surface may shunt the cathode and anode, rendering the otherwise sufficient stimulating current ineffective. Inadvertent reversal of the anode and cathode would, in theory, block the propagating impulse; however, in the usual clinical setup with a 2–3 cm separation, anodal hyperpolarization abates too quickly to render any detectable effects. More important, misidentifying the cathodal and anodal positions would invalidate the relationship between the measured distance and latency. Regardless of the responsible technical fault, submaximal activation of the nerve proximally may erroneously suggest a conduction block, especially if a distal stimulus elicits a full response. In some neuropathic states with an abnormally elevated threshold, an ordinarily sufficient intensity may fail to excite the nerve at the site of pathology, necessitating more proximal stimulation to confirm propagation of impulses across the lesion (see this chapter, part 5).

Recording System

Even optimal stimulation elicits a small response if a faulty connection hampers recording. Common problems include inappropriate placement of the pick-up electrodes; breaks in the electrode wires; use of a disconnected preamplifier; loss of power supply; and incorrect oscilloscope settings for sensitivity, sweep, or filters. A

broken recording electrode may escape detection because it shows no change in appearance if the insulating sheath remains intact. With partial damage to the wire, stimulus-induced muscle twitches cause movement-related potentials, which can mimic a compound muscle action potential. A quick check of the recording system should be the first step: 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 prevent a normal display of muscle action potentials on the oscilloscope.

An initial positivity preceding the major negative peak of the compound muscle action potential usually results from incorrect positioning of the active electrode away from the end-plate region. Alternatively, it may represent a volume-conducted potential from distant muscles, activated by anomalous innervation or by spread of stimulation to other nerves. The compound muscle action potential reverses its polarity with an inadvertent switch of the active (G_1) and reference (G_2) electrodes. Similarly, any deviation from the standard belly (G_1) and tendon (G_2) placement of recording electrodes distorts the waveform.

3 SPREAD OF STIMULATION CURRENT

With an inappropriately high shock intensity, stimulating current can spread to a nerve or muscle not being tested. Failure to recognize this possibility may result in false determination of latencies to the onset of a volume-conducted potential from unintended muscles. Under these circumstances, visual inspection of the contracting muscle, rather than the waveform on the oscilloscope, will identify the generator source. In some such cases, the collision technique (see this chapter, part 5) can, in effect, activate the intended nerve selectively by blocking the unwanted nerve.[70] The use of needle pick-up also restricts the recording to limited target areas for such special purposes as studying innervation of individual motor branches, patterns of anomaly, and function of atrophic muscles that may escape surface detection. This type of recording, by design, fails to provide the most important information on the total size of muscle response.

Stimulation of the Facial Nerve

The facial nerve becomes accessible to surface or needle stimulation as it exits from the stylomastoid foramen (see Chapter 17–2) (see Figs. 17–2 and 17–3). The distal segment, tested by stimulating the nerve here and recording compound muscle action potentials from various facial muscles, remains normal for a few days 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 also activate the motor point of the masseter muscle. A volume-conducted potential then erroneously suggests a favorable prognosis, when in fact the facial nerve has already degenerated (Fig. 7–1). As stated before, visual inspection would verify that the contraction involved the masseter, not the facial, muscle. Surface stimulation of the facial nerve may also activate cutaneous fibers of the trigeminal nerve, causing reflexive contraction of the orbicularis oculi (see Chapter 17–2). The reflex response may mimic a late component of the compound muscle action potential or recurrent response from antidromic activation of motor neurons.

Axillary Stimulation and Collision Technique

With the use of ordinary shock intensity, stimulation of the median or ulnar nerve activates only the nerve in question at the wrist or elbow, but not at the axilla, where the two nerves lie in close proximity.[70] If the current intended for the median nerve spreads to the ulnar nerve, the electrodes placed on the thenar eminence register not only median but also ulnar innervated muscle potential. The measured latency will then indicate normal ulnar conduction if the median nerve conducts more slowly, as in carpal tunnel syndrome (Fig. 7–2). In

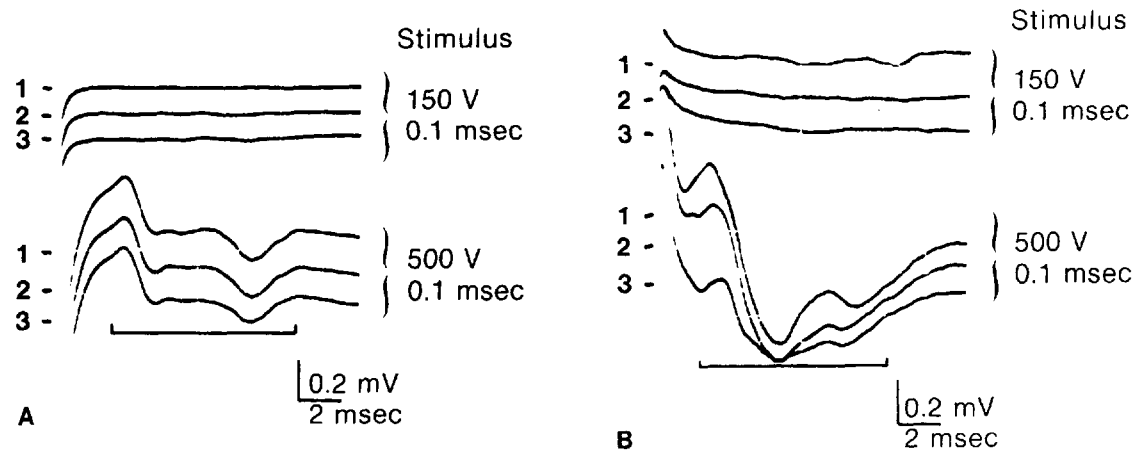


Figure 7-1. Compound muscle action potential from the orbicularis oculi after stimulation of the facial nerve in a patient with traumatic facial diplegia. **A.** Left side. **B.** Right side. Shocks of ordinary intensity (*top three tracings*) elicited no response but with a much higher intensity, a definite muscle response appeared (*bottom three tracings*). Close observation of the face revealed contraction of the masseter rather than the orbicularis oculi.

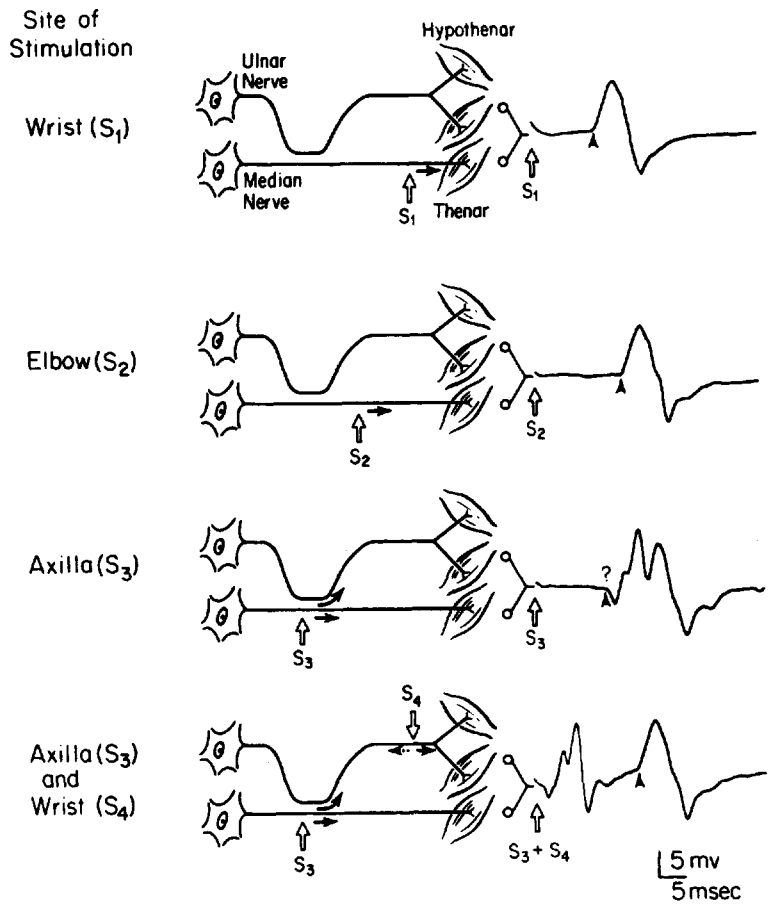


Figure 7-2. A 39-year-old man with carpal tunnel syndrome. The stimulation of the median nerve at the wrist (S_1) or elbow (S_2) elicited a muscle action potential with increased latency in the thenar eminence. Spread of axillary stimulation (S_3) to the ulnar nerve (*third tracing from top*) activated ulnar-innervated thenar muscles with shorter latency. Another stimulus (S_4) applied to the ulnar nerve at the wrist (*bottom tracing*) blocked the proximal impulses by collision. The muscle action potential elicited by S_4 occurred much earlier. The diagram on the left shows collision between the orthodromic (*solid arrows*) and antidromic (*open arrows*) impulses. [From Kimura,[70] with permission.]

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 can occur in a study 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 thenar muscles or lumbricals as a small positive potential of 1–5 mV in amplitude and 10–20 ms in duration. This positivity, though usually buried in a much larger ulnar response occurring simultaneously, becomes obvious if the ulnar nerve conducts slower than the median nerve as in tardy ulnar palsy (Fig. 7–3). The earlier median component from thenar muscles then obscures the onset of the ulnar response originating from hypothenar muscles. The short latency measured to the onset of the median component fails to correctly reflect a delayed ulnar response. A stimulus at the elbow in the same case activates only the ulnar nerve with a prolonged latency, leading to misculculation of an erroneously fast conduction velocity from axilla to elbow.

A physiologic nerve block with collision allows selective recording of the median or ulnar component despite coactivation of both nerves proximally.[70] In studies of 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. 7–2). The ulnar response induced by

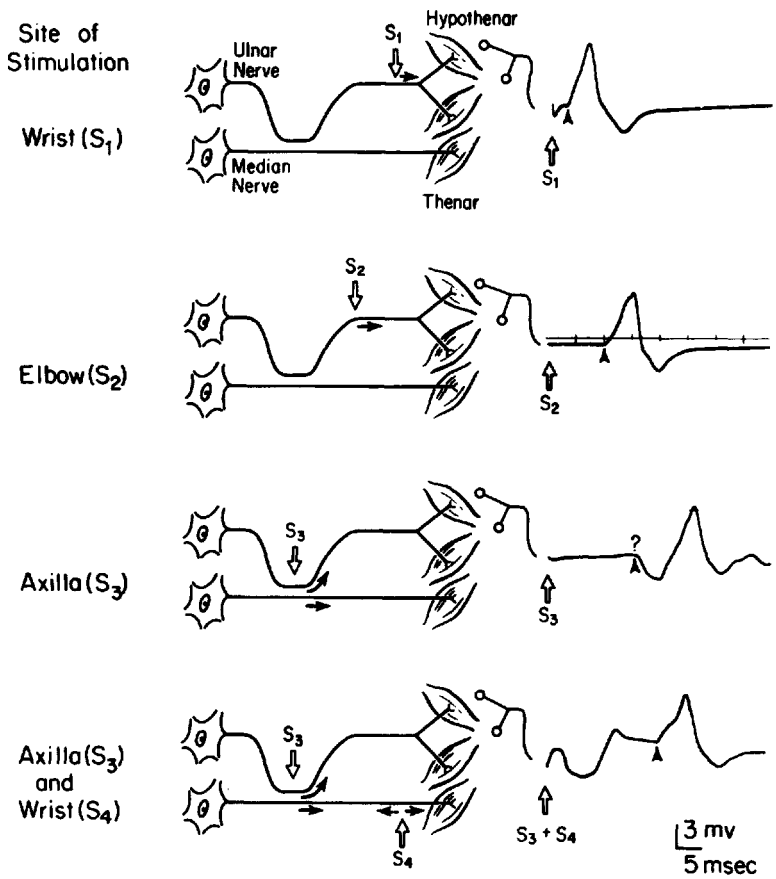


Figure 7–3. A 29-year-old man with tardy ulnar palsy. Stimulation at the wrist (S_1) or elbow (S_2) selectively activated the ulnar nerve giving rise to an abnormally delayed muscle action potential over the hypothenar eminence. Spread of axillary stimulation (S_3) to the median nerve (*third tracing from top*) elicited an additional short latency median response with initial positivity. This potential, registered through volume conduction, obscurred the onset (*arrowhead*) of the muscle response under study. Another stimulus (S_4) applied to the median nerve at the wrist (*bottom tracing*) blocked the proximal impulses by collision. The positive median potential elicited by S_4 clearly preceded the ulnar component under study. [From Kimura,[70] with permission.]

the distal stimulus precedes the median response under study, usually without obscuring it. If necessary, delivering the distal stimulus a few milliseconds before the proximal stimulation accomplishes a greater separation. This time interval should not exceed the conduction time between the distal and proximal points of stimulation, lest the antidromic impulse from the wrist pass 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. 7–3).

The collision technique can clarify otherwise confusing results of motor nerve conduction studies in patients with carpal tunnel syndrome or tardy ulnar palsy. In each of the illustrated cases (see Figs. 7–2 and 7–3), spread of the 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 the procaine nerve block previously employed to identify the origin of the recorded muscle potentials. Optimal studies of motor nerve conduction depend on either selective activation of the nerve in question or isolated recording from the target muscle. The collison method improves latency and waveform determination even under circumstances that preclude selective stimulation of the nerve at a proximal point. As an alternative method, the use of needle electrodes renders reliable latencies even after coactivation of more than one nerve, but its restricted recording area precludes assessment of the size of the compound muscle action potential.

Palmar Stimulation of the Median and Ulnar Nerves

Palmar stimulation provides a unique contribution in evaluating the distal segment of the median nerve, although studies of the motor conduction in this region pose some technical problems.[10,24,72,126,165] With serial stimulation in 1 cm increments from palm to wrist, the sensory latency increases linearly (see Fig. 6–7B). The motor study, when recorded from the thenar eminence, sometimes shows unexpected latency changes reflecting the recurrent course of the motor fibers. For example, a stimulus directed to the branching point of the thenar nerve in the palm could accidentally activate a terminal portion near the motor point. If another stimulus, delivered 1 cm proximally, excites only the median nerve trunk, the latency difference between the two stimulus points becomes unreasonably large, erroneously suggesting a focal slowing (Fig. 7–4A). Thus, a disproportionate latency change indicates a localized pathology only if serial stimulation shows a linear latency increase in the segment proximal and distal to the presumed site of lesion (Fig. 7–4B).

Placing the pick-up leads over the second lumbrical, in lieu of the abductor pollicis brevis, circumvents this problem because tracking the terminal branch innervating this muscle poses no technical difficulty (Fig. 7–5 A and B). As an additional advantage, the same pair of electrodes may also be used to register muscle action potentials from the first volar interosseous muscle for inching study of the ulnar nerve along the course of the palmar branch and across the wrist (Fig. 7–5 C and D). The pattern of muscle twitch, rather than recorded waveforms, should be used to confirm selective activation of the intended nerve; for example, thumb abduction 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.

The same sort of error occurs in the calculation of motor latency over the wrist-to-palm segment unless palmar stimulation activates the median nerve precisely at the origin of the thenar nerve as intended. Incremental stimulation from the wrist toward the digit with the cathode placed distally to the anode can activate the thenar nerve at the anodal point (acting as a floating cathode), even when the actual cathode lies clearly distal to the origin of the nerve.

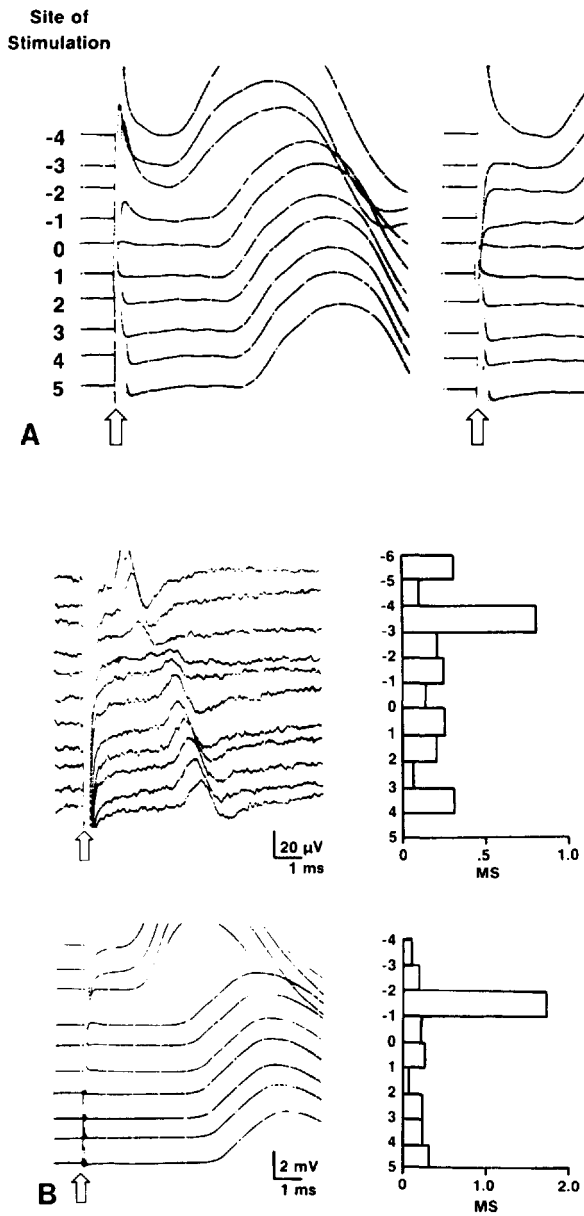
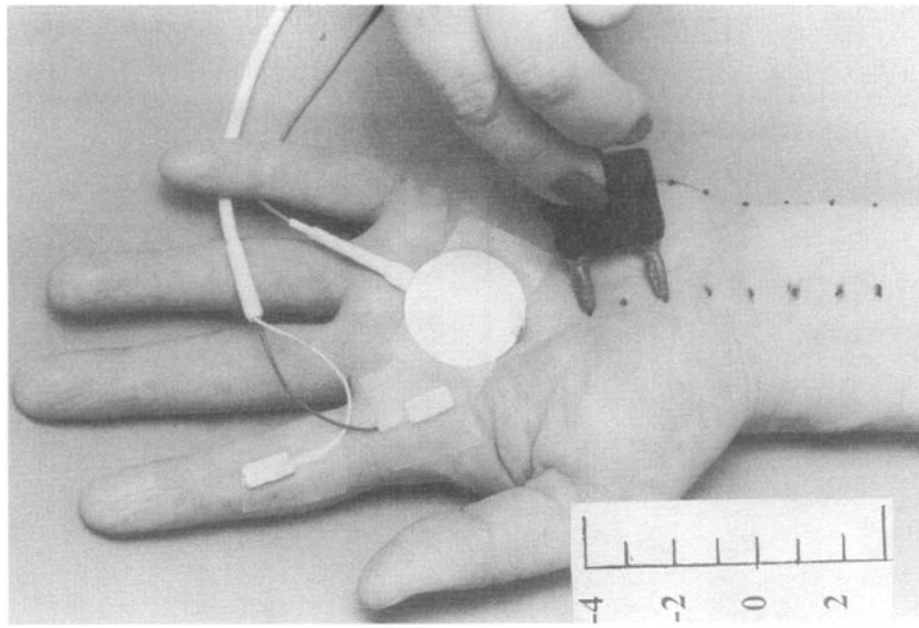
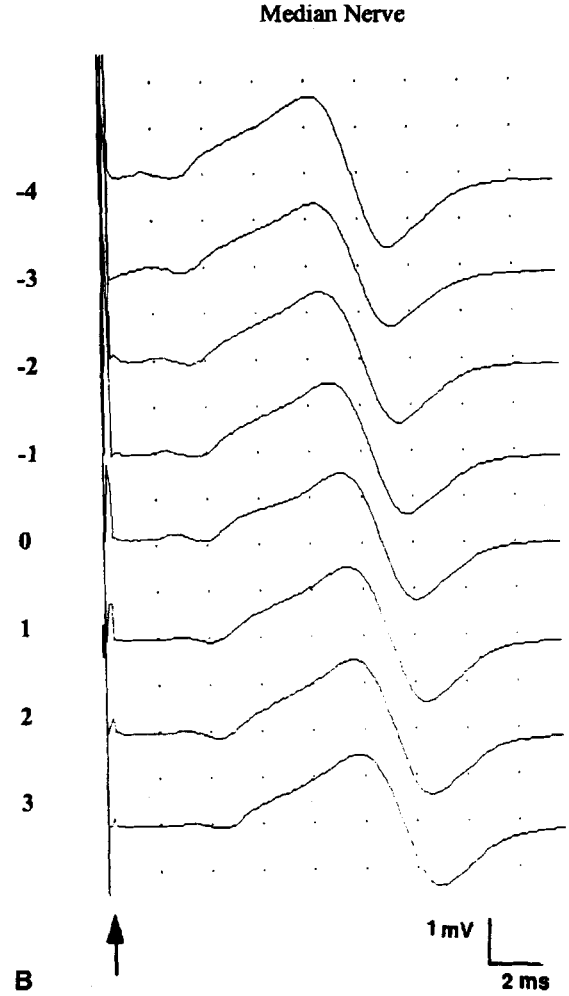


Figure 7–4. A. Compound muscle action potentials in a normal subject recorded after stimulation of the median nerve at multiple points across the wrist. On the initial trial (*left*), the latency decreased with the cathode inching proximally from −4 to −2, indicating inadvertent spread of stimulating 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 zero level at the distal crease of the wrist corresponds to the origin of the transverse ligament (cf. Figure 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. Figure 6–7). [From Kimura,[72] with permission.]

A surface distance measured to the cathodal point would then overestimate the nerve length, thereby making the calculated conduction velocity erroneously fast. Proceeding from the distal palm toward the wrist with reversal of the electrode position, that is, cathode proximally to the anode, circumvents this problem. In this approach, palmar stimulation initially fails to produce a twitch, then causes thumb adduction, activating the deep branch of the ulnar nerve and, about one cm more proximally, thumb abduction, signaling the arrival of the cathode just over the origin of the thenar nerve. In most subjects, this point lies 3 to 4 cm from the distal crease of the wrist, near the edge of the transverse carpal ligament.[64] The use of needle stimulation renders more precise increments with less shock intensity, facilitating the process, especially when testing the palm, with its thick skin surface.

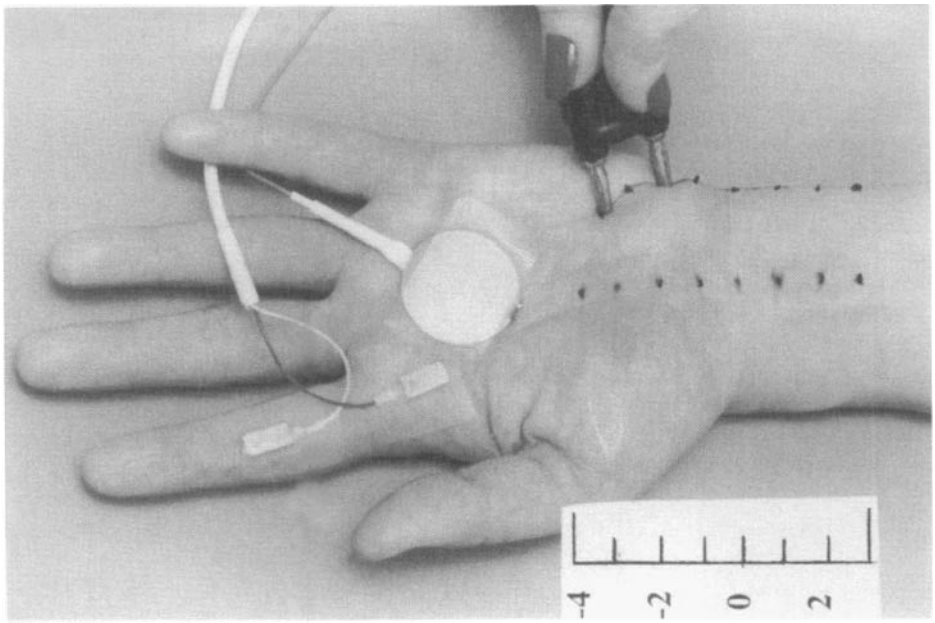


A

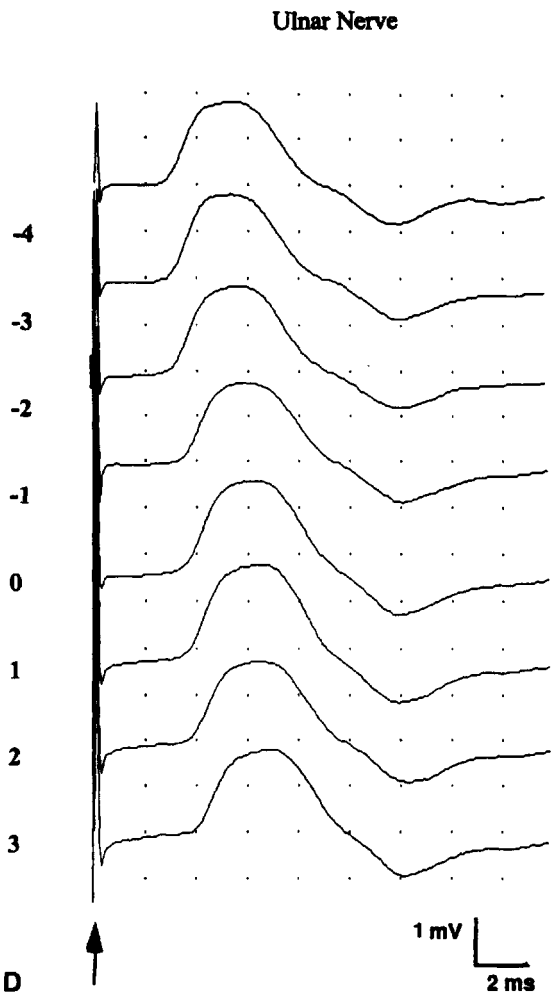


B

Figure 7–5. An inching study of median (**A** and **B**) and ulnar nerve (**C** and **D**, overleaf) 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 photographs show a recording arrangement for muscle action potentials from the second lumbrical 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**).



C



D

Figure 7–5—Continued. An inching study of the ulnar nerve (**C** and **D**) across the wrist in 1 cm increments at eight sites of stimulation.

4 ANOMALIES AS SOURCES OF ERROR

Martin-Gruber Anastomosis

The anatomic studies of Martin[103] and Gruber[45] 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.[157] This anastomosis, often originating from the anterior interosseous nerve, predominantly consists of motor axons with rare sensory contribution, which may follow a different distribution.[19,160] The communicating branch usually, though not always,[93] supplies ordinarily ulnar-innervated intrinsic hand muscles, most notably the first dorsal interosseous, adductor pollicis, and abductor digiti minimi.[100,143,166] The number of axons taking the anomalous course varies widely.[2] 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. 7–6).[82] 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 15–32 percent of subjects in an unselected population.[2,82] The higher incidence of this anomaly reported among congenitally abnormal fetuses in general and those with trisomy 21 in particular indicates its phylogenetic origin.[143] The communicating fibers rarely cross from the ulnar to the median nerve in the forearm,[44,113] occasionally involving only the sensory axons.[55] Other anomalies associated with Martin-Gruber anastomosis include innervation of the ulnar aspect of the dorsum of the hand by the superficial radial sensory nerve.[105]

Careful analysis of the compound muscle action potentials readily reveals the presence of a Martin-Gruber anomaly during routine nerve conduction studies. This anastomosis, in effect, represents a

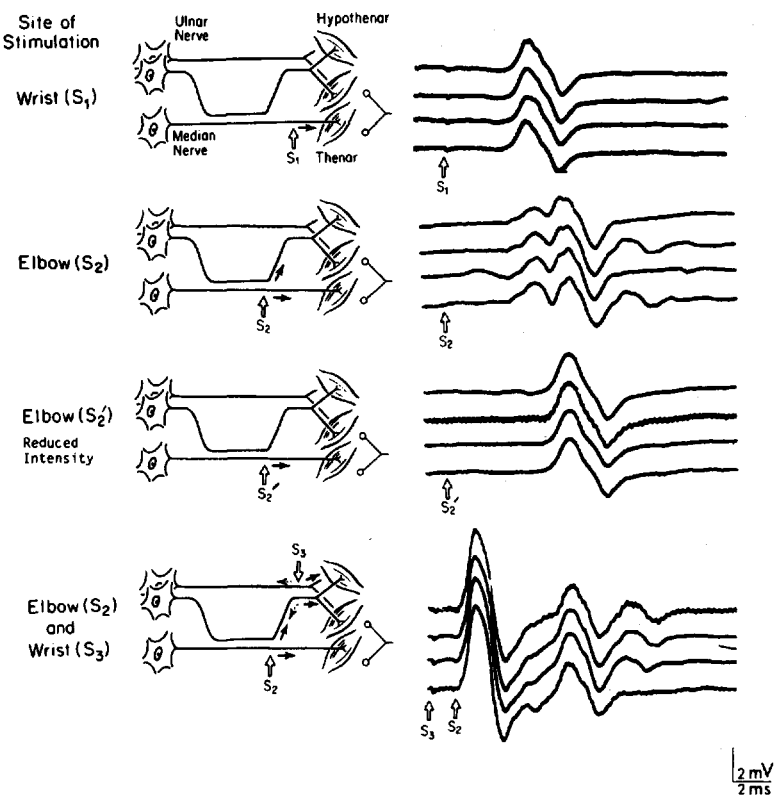


Figure 7–6. A 46 year old woman with the carpal tunnel syndrome and the Martin-Gruber anomaly. Stimulation at the elbow (S_2) activated not only the median nerve but also communicating fibers, giving rise to a complex compound muscle action potential. With proper adjustment of electrode position and shock intensity, another stimulus at the elbow (S_2) excited the median nerve selectively without activating the anastomosis. Another stimulus (S_3) applied to the ulnar nerve at the wrist (*bottom tracing*) achieved the same effect by blocking the unwanted impulse transmitted through the communicating fibers. [From Kimura,[76] with permission.]

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 excites the small bundle of the ulnar nerve, activating not only the median-innervated thenar muscle but also the anomalously innervated thenar and hypothenar muscles. In contrast, stimulation of the median nerve at the wrist elicits a smaller response lacking the ulnar component. If proximal stimulation elicits a larger response as compared to distal stimulation, it always implies the presence of an anomalous communication or technical problem. The reverse discrepancy may pose difficulty, mimicking a conduction block. For example, in the presence of Martin-Gruber anastomosis, studies of the ulnar nerve show a smaller amplitude of thenar or hypothenar compound muscle action potentials elicited by proximal rather than distal stimulation.[86] Here stimulation at the wrist activates the additional anomalous fibers, giving rise to a full response, whereas stimulation at the elbow spares the communicating branch still attached to the median nerve, sometimes mimicking ulnar neuropathy at the elbow.[102]

When recording from the first dorsal interosseous, adductor pollicis, or hypothenar muscles after stimulation of the median nerve at the elbow, volume-conducted potentials from distant median-innervated muscles may mimic an anomalously activated response. Under this circumstance, a careful comparison between distal and proximal stimulation usually clarifies the ambiguity.[11,39,70,89,140] In difficult cases, recording with a needle electrode may localize the origin of the recorded response, although distant activities, if present, may still confuse the issue. The collision technique[70,132] provides selective blocking of unwanted impulses transmitted via the communicating fibers (Fig. 7–7). Normally, antidromically directed impulses from the distal stimulation will completely block the orthodromic impulses from the proximal stimulation in the same nerve.[53,152] The orthodromic impulses traveling through an anastomotic branch to the ulnar nerve, however, would bypass the antidromic impulses and escape collision.[70]

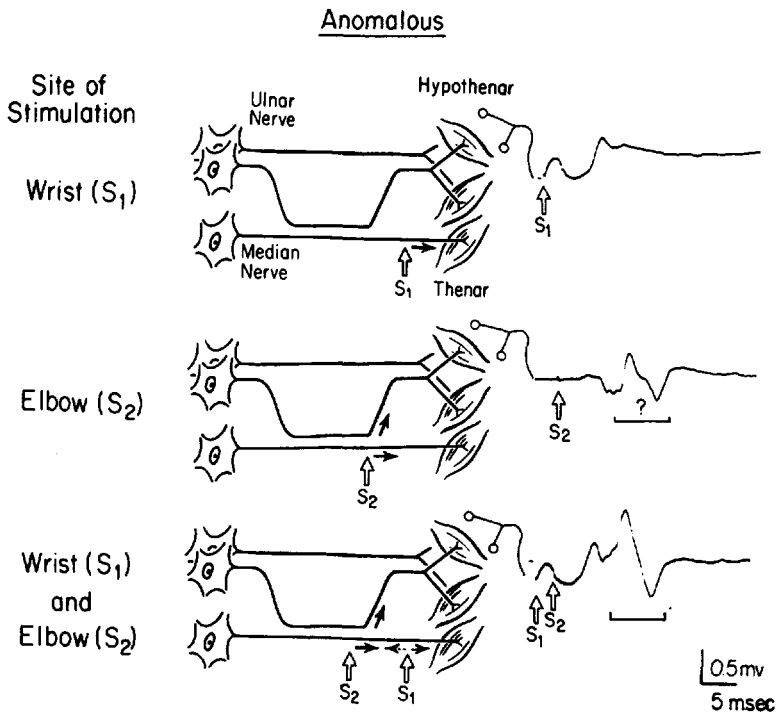


Figure 7–7. Muscle action potentials recorded from the hypothenar eminence after stimulation of the median nerve at the wrist (S_1) or elbow (S_2). The *top tracing* shows a volume conducted potential from thenar muscles (U-shaped wave of positive polarity). The *middle tracing* reveals a small negative potential superimposed upon the thenar component. In the *bottom tracing*, collision technique clearly separated the anomalous response (*bracket*), with S_1 preceding S_2 by 4 ms. [From Kimura,[76] with permission.]

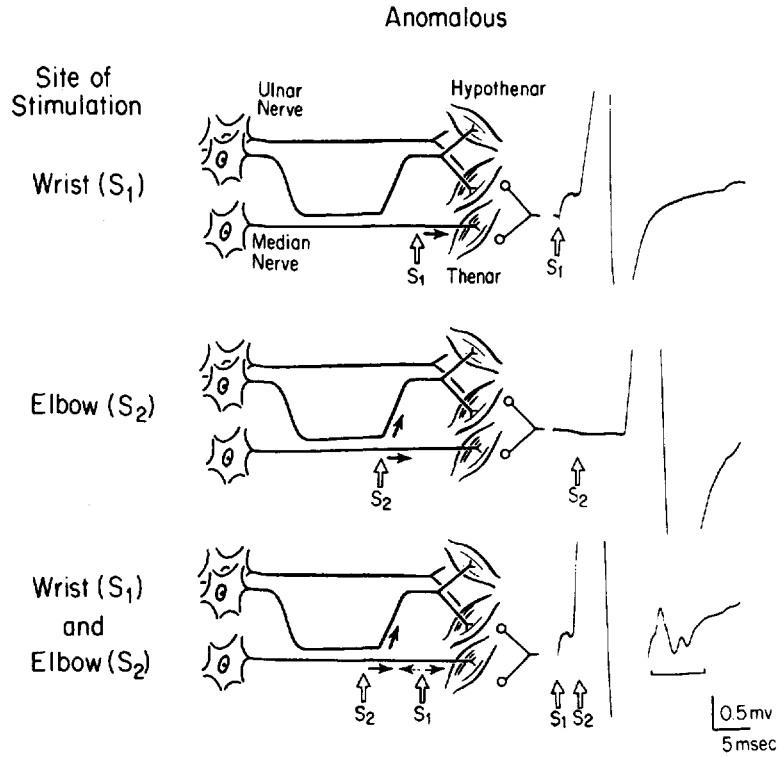


Figure 7–8. Muscle action potentials recorded from the thenar eminence after stimulation of the median nerve at the wrist (S_1) or elbow (S_2) as in Figure 7–7. In the *middle tracing*, a large compound action potential buried a small anomalous response mediated by the anastomosis. In the *bottom tracing*, a collision technique separated the anomalous response (*bracket*) with S_1 preceding S_2 by 4 ms. [From Kimura,[76] with permission.]

The technique helps 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 distally (Fig. 7–8). Delay of the proximal stimulation by a few milliseconds usually achieves its satisfactory separation from the distally elicited response. The time interval must not exceed the latency difference between the two stimulus sites, lest the orthodromic impulse escape antidromic collision in the absence of an anomalous route of transmission.

If this anastomosis accompanies the carpal tunnel syndrome, stimulation of the median nerve at the elbow evokes two temporally dispersed potentials, a normal ulnar component and a delayed median component. The latency of the initial ulnar response erroneously suggests the presence of normal-conducting median fibers. In contrast, stimulation of the median nerve at the wrist evokes a delayed response without an ulnar component.[62,70,89] The discrepancy between proximal and distal stimulation would lead to an unreasonably fast conduction velocity from the elbow to the wrist.[11,70,89] 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.[47] As mentioned earlier, a collision technique can block impulses in the anomalous fibers without affecting those transmitted along the median nerve proper (Fig. 7–9).

Severence or substantial injury of the ulnar nerve at the elbow ordinarily results in wallerian degeneration and inexcitability of the distal 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 extreme cases, separation of the ulnar nerve at the elbow may not appreciably affect the intrinsic hand muscles because all or nearly all ulnar fibers attached to the median nerve escape injury. In this rare condition, called all-median hand, the intrinsic hand muscles ordinarily sup-

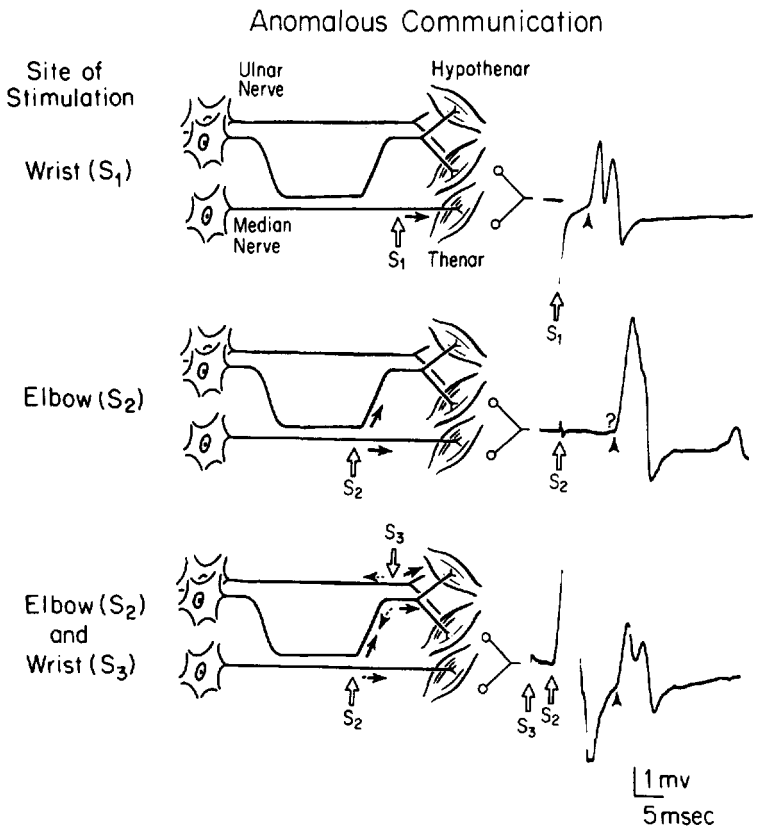


Figure 7–9. A 55-year-old man with the carpal tunnel syndrome and the Martin Gruber anastomosis. Stimulation at the elbow (S_2) spread to the ulnar nerve through the anomalous communication (*middle tracing*). Another stimulus (S_3) applied to the ulnar nerve at the wrist (*bottom tracing*) blocked the impulses transmitted through the communicating fibers. In the *bottom tracing*, S_3 preceded S_2 by 4 ms to avoid the overlap of the muscle responses. [From Kimura,[76] with permission.]

plied by the ulnar nerve receive innervation via the communicating fibers.[101] Electromyography may reveal normal motor unit potentials in the ulnar-innervated muscles, despite severe damage to the ulnar nerve 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.[48,161]

Anomalies of the Hand

Common anomalies of the peripheral nerves include variations in innervation of the intrinsic hand muscles.[136] Although not as widely recognized as the median-to-ulnar communication, they too constitute sources of error in the evaluation of nerve conduction velocity and electromyography. Electrophysiologic techniques often hint at the presence of such anastomoses, although precise characterization and delineation of the extent of the anomaly call for anatomic studies.[147] Various communications may link the recurrent branch of the median and the deep branch of the ulnar nerve in the lateral portion of the hand.[14,32,98,122,128] Any of the intrinsic hand muscles, the flexor pollicis brevis in particular, may receive median, ulnar, or dual innervation.[135] In a small percentage of cases, thenar muscles, including the adductor pollicis, may derive their supply exclusively from the median or ulnar nerve.[38,130] In addition to neural anastomoses, skeletal anomalies of the upper limb may confuse the clinical picture. The congenital absence of thenar muscles, for example, may suggest a false diagnosis of carpal tunnel syndrome.[15] The posterior interosseous nerve may innervate accessory hand muscles consistent with extensor digitorum brevis manus.[107] The deep branch of the ulnar nerve may form a motor neural loop, caus-

ing an atypical clinical presentation after penetrating injuries or compression neuropathy at the wrist.[123]

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 20–28 percent of an unselected population, the superficial peroneal nerve also contributes via a communicating fiber. This branch, called the accessory deep peroneal nerve (Fig. 7–10), descends on 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.[58,90,162] Occasionally, the extensor digitorum brevis

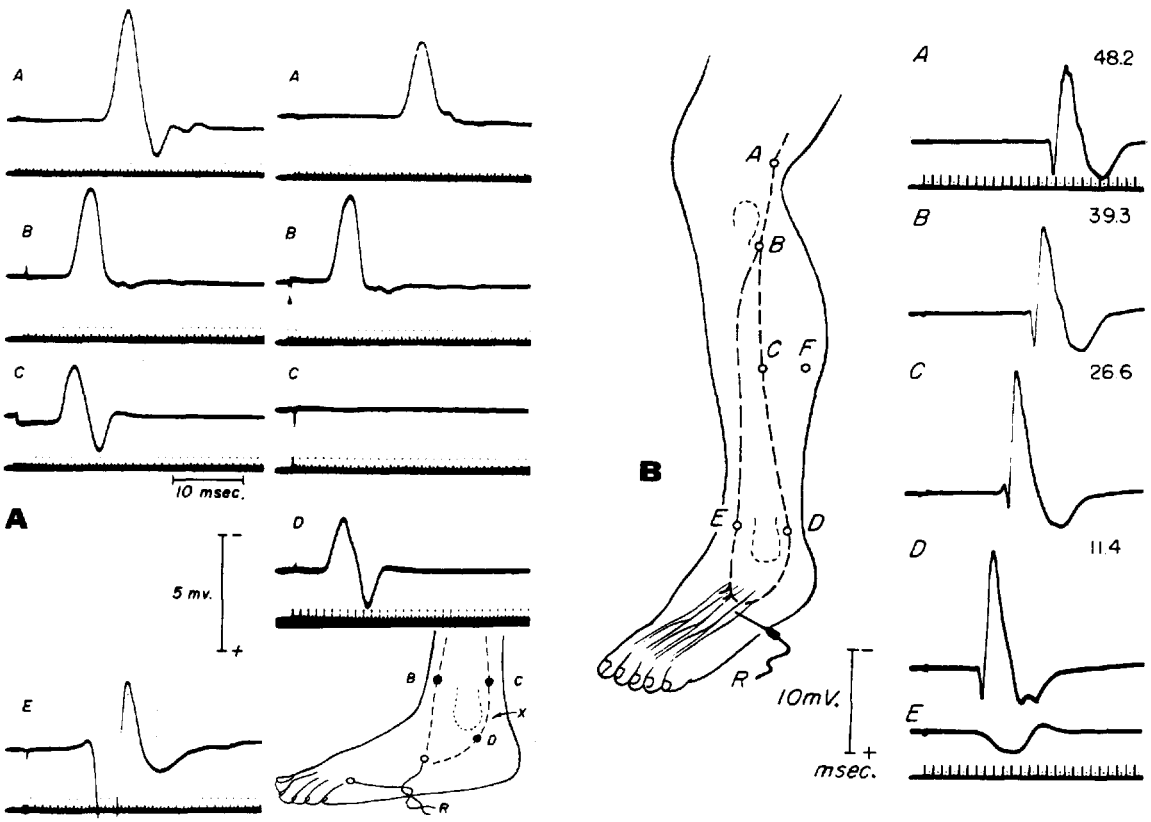


Figure 7–10. A. Compound muscle action potentials recorded from surface electrodes over the extensor digitorum brevis after a maximal stimulus to the common peroneal nerve at the knee (*A*), deep peroneal nerve on the dorsum of the ankle (*B*), accessory deep peroneal nerve posterior to the lateral malleolus (C and *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 percent 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 potential from the medial bellies of the extensor digitorum brevis (*E*) reduces amplitude of action potential of the lateral belly with simultaneous stimulation of the common peroneal nerve at *A* or *B*. [From Lambert,[90] with permission.]

may receive exclusive supply from this communication.[111] The anomaly, when inherited, shows a dominant trait.[21]

In patients with the anastomosis, stimulation of the deep peroneal nerve at the ankle elicits a smaller compound muscle action potential 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. Overlooking this possibility would, therefore, lead to an erroneous interpretation.[28,46] The collision technique[70] may help identify isolated abnormalities of the accessory deep peroneal nerve.[133]

Anomalous Communication Between Peroneal and Tibial Nerve

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.[119] Although the nerve usually consists purely of sensory fibers, its anomalous motor branch may innervate the abductor digiti quinti of the foot.[96] Rare motor anastomosis between the peroneal and tibial nerves, if undetected, may give rise to an erroneous conclusion by showing patterns of waveform change similar to those seen in Martin-Gruber anomaly.[142] In rare anomalies, the tibial nerve may supply all the intrinsic foot muscles.[97] In documenting the innervation pattern of this and other rare anastomoses, volume-conducted responses often confuse the issue.[3,99] 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 selectively recording from individual intrinsic foot muscles. In questionable cases, a collision technique[70] or a nerve block usually provides conclusive evidence.

5 PRINCIPLES AND PITFALLS OF WAVEFORM ANALYSIS

Physiologic and Pathologic Temporal Dispersion

In nerve conduction studies, latency measure of the fastest fibers allows calculation of the maximal motor or sensory velocities. In addition, waveform analyses of compound muscle and sensory nerve action potentials help estimate the range of the functional units.[25,74,118] This aspect of the study provides an equally, if not more, important assessment, especially in the study of peripheral neuropathies with segmental block, in which surviving axons may conduct normally.[41,51,95,109,145,151] In clinical tests of motor and sensory conduction, the size of the recorded response approximately parallels the number of excitable fibers. Any discrepancy between responses to proximal and distal shocks, however, does not necessarily imply an abnormality.

The impulses of slow-conducting fibers lag increasingly behind those of fast-conducting fibers over a long conduction path.[9,22,89] 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, the size of the recorded response depends to a great extent on the site of stimulation. In fact, stimulation proximally in the axilla or Erb's point may normally give rise to a small or undetectable digital potential, despite a large response elicited by stimulation at the wrist or palm.[73,117,164] For the same number of conducting fibers activated by the stimulus, the size of sensory potentials changes linearly with the length of the nerve segment.[79,85] A physiologic reduction both in amplitude and in the area under the waveform may erroneously suggest a conduction abnormality between the proximal and the distal sites of stimulation.

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. 7–11 and 7–12A). According to computer simulation,[83,121] this phenomenon alone can reduce the normal sensory nerve action potential to below 50 percent in area as well as in amplitude, a conservative figure based on computation of a limited number of nerve fibers for analysis. Thus, a major reduction in the size of the compound sensory action potential can result solely from physiologic phase cancellation. In contrast, the same temporal dispersion has less effect on compound muscle action potential[35,116] because motor unit potentials of longer duration superimpose nearly in phase rather than out of phase, despite the same latency shift, resulting in less cancellation compared to sensory potentials (Fig. 7–12B). In support of this view, the duration change of the sensory potential, expressed as a percentage of the respective baseline values, far exceeds that of the muscle response.[79] As expected from the term, duration-dependent phase cancellation,[79] a physiological temporal dispersion, also reduces substantially the amplitudes of short-duration muscle action potentials such as those recorded from intrinsic foot muscles.

The degree of overlap between peaks of opposite polarity depends on the separation between G_1 and G_2, which dictates the duration and waveform of unit discharges.[9] A maximal cancellation results when a waveform contains negative and positive phases of comparable size. In a triphasic orthodromic sensory potential, as compared with biphasic antidromic digital potentials, the initial positivity provides an additional probability for phase cancellation. 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.[129] The equations for the best fit lines between nerve length and other measurements in one study may not necessarily apply to another unless the recording technique conforms to the particular specifications.

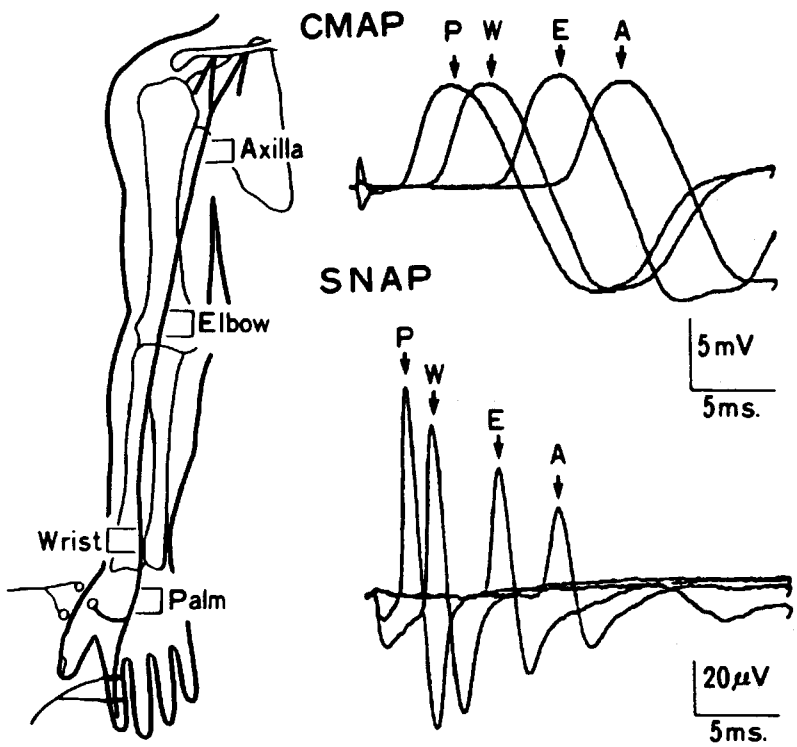


Figure 7–11. Simultaneous recordings of compound muscle action potentials (*CMAP*) from the thenar eminence and sensory nerve action potentials (*SNAP*) from index and middle fingers after stimulation of the median nerve at palm, wrist, elbow and axilla. With progressively more proximal series of stimuli elicited nearly the same CMAP but progressively smaller SNAP from the wrist to the axilla. [From Kimura et al.,[79] with permission.]

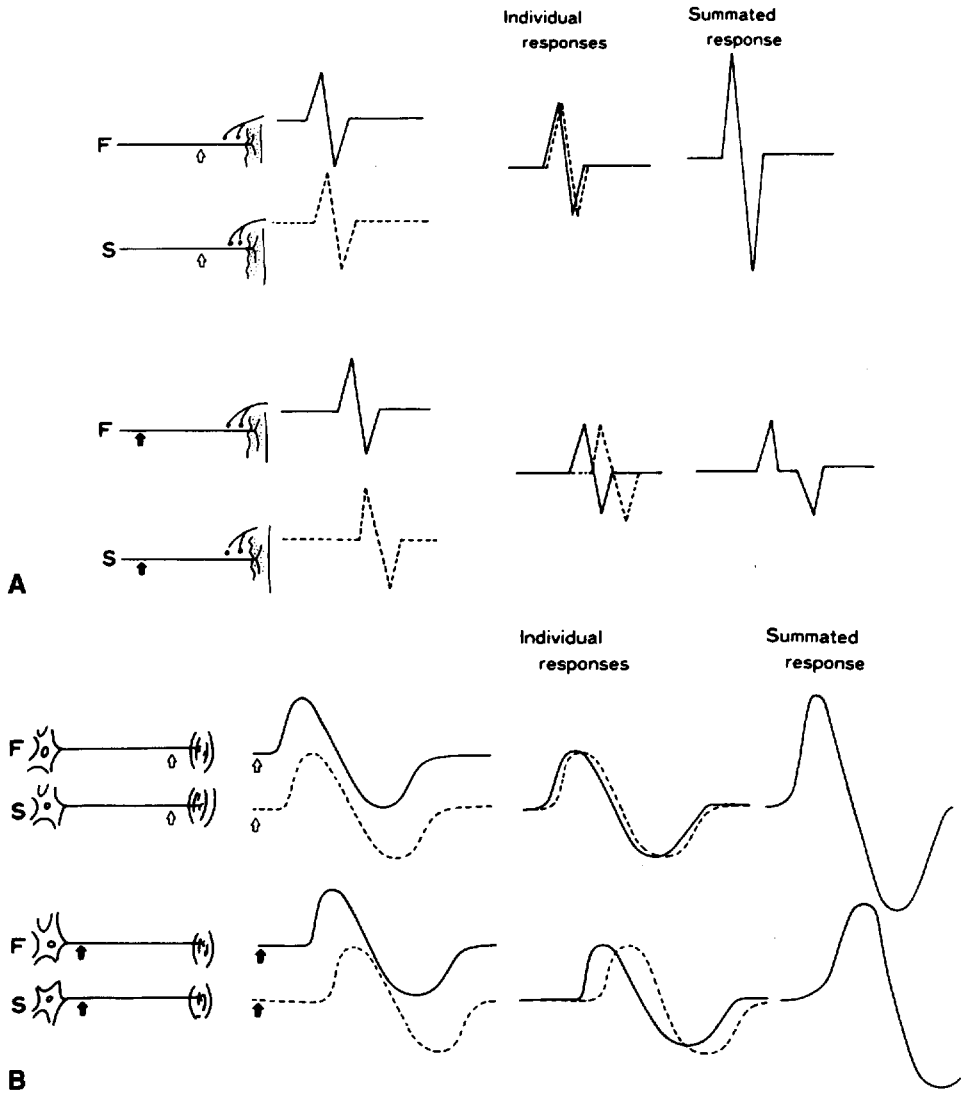


Figure 7–12. A. Sensory action potentials. A model for phase cancellation between fast (*F*) and slow (*S*) conducting sensory fibers. With distal stimulation two unit discharges summate in phase to produce a sensory action potential twice as large. With proximal stimulation, a delay of the slow fiber causes phase cancellation between the negative peak of the fast fiber and the positive peak of the slow fiber, resulting in a 50% reduction in size of the summated response. [From Kimura et al.,[79] with permission.] **B.** Compound muscle action potentials. Same arrangements as in A to show the relationship between fast (*F*) and slow (*S*) conducting motor fibers. With distal stimulation, two unit discharges representing motor unit potentials summate to produce a muscle action potential twice as large. With proximal stimulation, long duration motor unit potentials still superimpose nearly in phase despite the same latency shift of the slow motor fiber as the sensory fiber shown in A. Thus, a physiologic temporal dispersion alters the size of the muscle action potential only minimally, if at all. [From Kimura et al.,[79] with permission.]

If the latency difference between fast- and slow-conducting motor fibers increases substantially, as might be expected in demyelinating neuropathy, muscle responses also diminish dramatically based solely on phase cancellation as predicted by our model[83] and computer simulation with a broader spectrum of motor nerve conduction velocities.[92] This type of phase cancellation reduces the amplitude of muscle response well beyond the usual physiologic limits in the absence of conduction block.

Thus, in pathologic temporal dispersion associated with segmental demyelination, focal phase cancellation of the muscle action potential could give rise to a false impression of motor conduction block. This phenomenon explains an occasionally encountered discrepancy between severe reduction in amplitude of the compound muscle action potential, on the one hand, and relatively normal recruitment of the motor units and preserved strength, on the other. Thus, sustained reduction in size of compound muscle action potential may result from a pathological temporal disper-sion rather than a prolonged neurapraxia.[83,109,121]

A simple model provides an excellent means to test the effects of desynchronized inputs.[83] A shock applied to the median (S_1) or ulnar (S_2) nerve at the wrist evokes a sensory potential of the fourth digit and a muscle potential over the thenar eminence. Hence, a concomitant application of S_1 and S_2 with varying interstimulus intervals simulates the effect of desynchronized inputs (Fig. 7–13). In 10 hands, an interstimulus interval on the order of 1 ms between S_1 and S_2 caused a major reduction in sensory potential by as much as 50 percent but little change in muscle action potential. With further separation of S_1 and S_2, the muscle response began to decrease in amplitude and area, reaching a minimal size at interstimulus intervals of 5–6 ms. The duration also increased in proportion to the latency shift, although a gradual return of the response to the baseline obscured the magnitude of 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 dif-

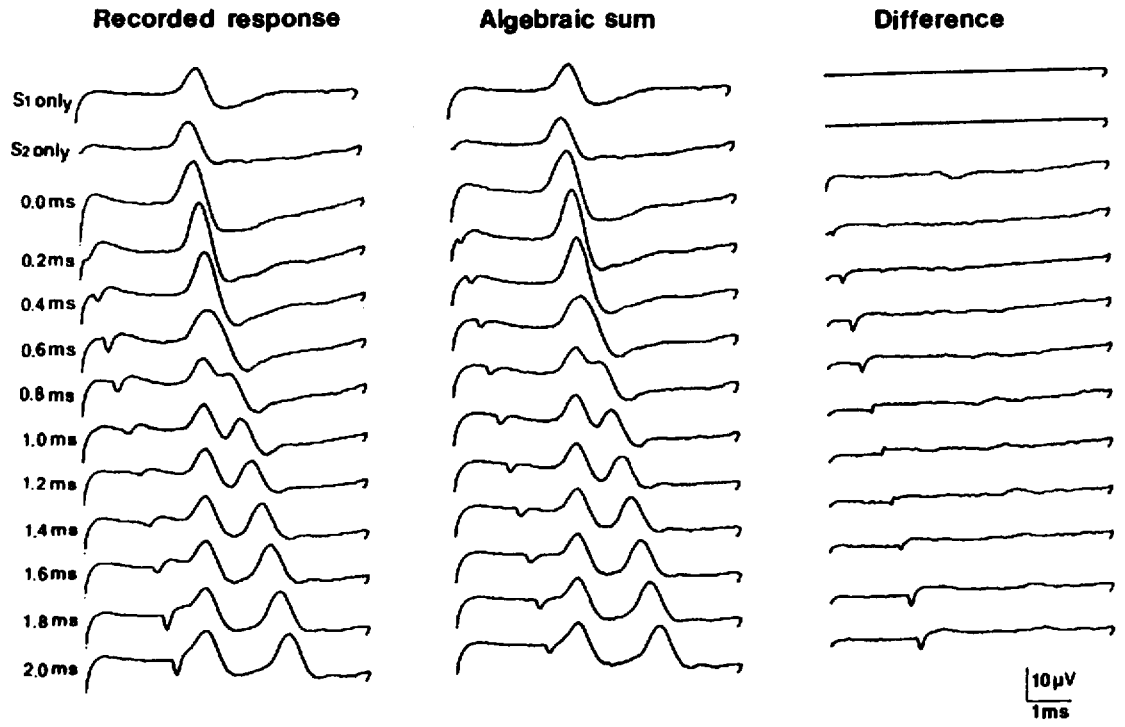


Figure 7–13. A. Antidromic sensory potentials of the fourth digit elicited by stimulation of the median (S_1) or ulnar (S_2) nerve (*top two tracings*), or by both S_1 and S_2 at interstimulus intervals ranging from 0 to 2.0 ms (*left*). Algebraic sums of the two top tracings (*middle*) closely matched 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. [From Kimura et al.,[83] with permission.]

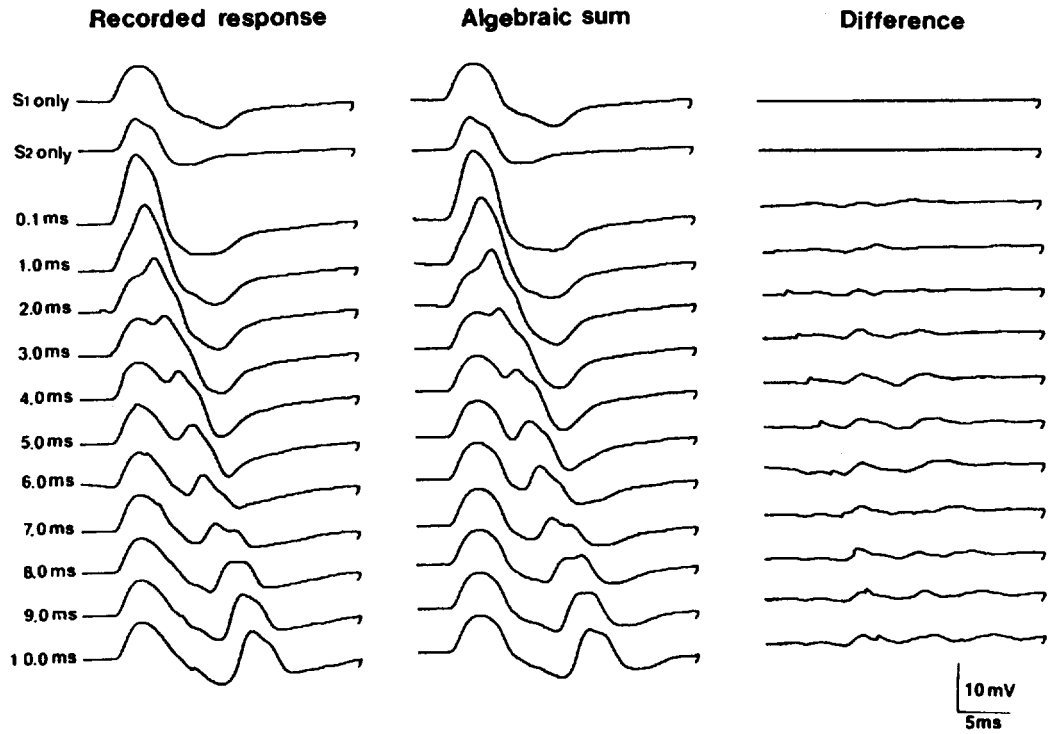


Figure 7–13. B. Compound muscle action potentials from the thenar eminence elicited by stimulation of the median (S_1) and ulnar (S_2) nerve (*top two tracings*), or by both S_1 and S_2 at interstimulus intervals ranging from 0 to 10 ms (*left*). Algebraic sums of the top two tracings almost, but not 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. [From Kimura et al.,[83] with permission.]

ference results in complete separation of the two potentials, precluding phase cancellation. As an inference, pathological temporal dispersion may decrease the size of the compound sensory or muscle action potentials or conversely counter physiologic phase cancellation, causing paradoxical increase of the responses (see Figure 6–7).

Comparison between distally and proximally elicited responses often fails to differentiate physiologic, as opposed to pathologic, temporal dispersion, not to mention conduction block. Many variables, such as electrode position and distance, make the commonly held criteria based on percentage reduction nearly untenable except in entirely standardized studies.[91] A simpler, more practical approach relies on a linear relationship seen in physiological phase cancellation between the latency and the size of the recorded responses[78] (see Fig. 7–11). Although this calls for segmental stimulation at more than two sites to test the linearity of observed changes, it enjoys the distinct advantage of having a built-in internal control for all recording variables such as inter-electrode spacing. A nonlinear reduction in amplitude or area, often associated with waveform changes, indicates either a pathological temporal dispersion or conduction block. The distinction between the two possibilities must in part depend on clinical cue as stated below (Fig. 7–14 and 7–15).

In summary, physiologic as well as pathologic temporal dispersion can effectively reduce the area of diphasic or triphasic evoked potentials recorded in bipolar derivation. The loss of area under the waveform seen in the absence of conduction block implies a duration-dependent phase cancellation of unit discharges

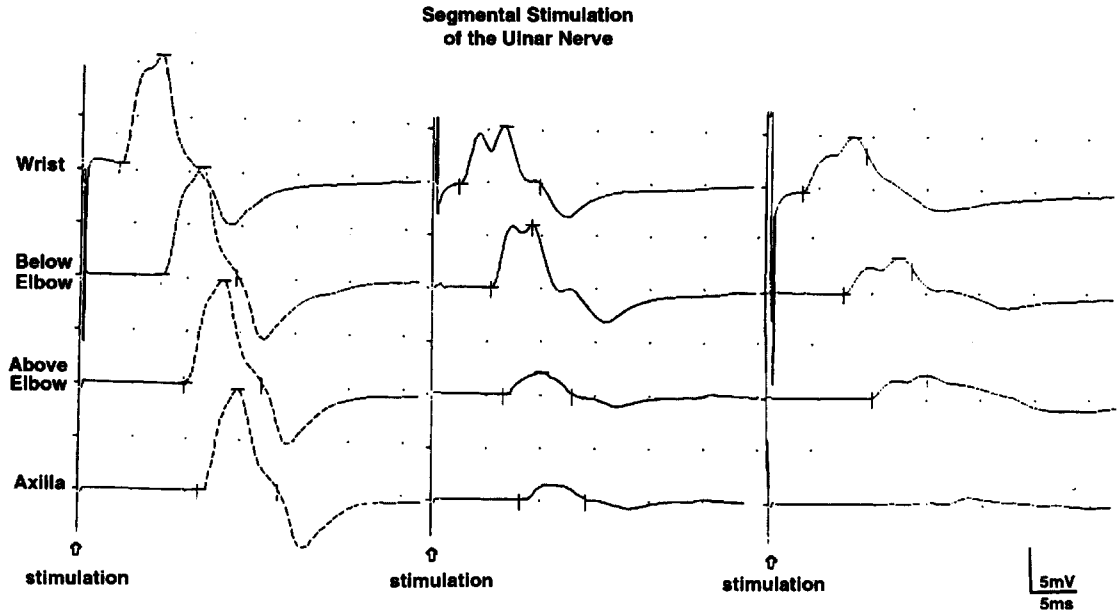


Figure 7–14. Ulnar nerve conduction study with segmental stimulation at the wrist, below elbow, above elbow, and at the axilla. Traces show a complete conduction block in a 42-year-old patient (*right*), a partial conduction block in a 40-year-old patient (*center*), and a normal study (*left*) for comparison.

within the compound action potential. Segmental studies provide the best means of detecting pathologic nonlinear changes as opposed to physiologic linear regression in amplitude and area of compound action potential. An awareness of this possibility helps analyze dispersed action potentials in identifying various patterns of

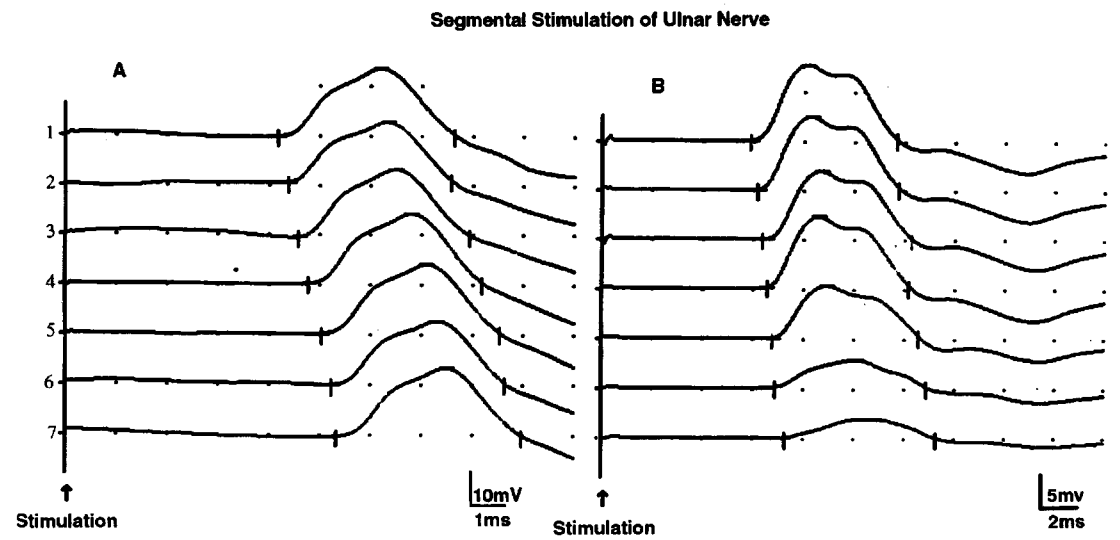


Figure 7–15. Segmental study of the ulnar nerve in 1 cm increments from below elbow (*1*) to above elbow (*7*). **A.** A 41-year-old man with distal ulnar neuropathy had prolonged terminal latency (3.7 ms) with normal conduction across the elbow. **B.** A 52-year-old woman with a tardy ulnar palsy showed 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.

neuropathic processes.[74] Area difference between negative and positive peaks in each unit discharge provides a unique measure, which sums without phase cancellation irrespective of desynchronization among different units. A composite of this calculated value should also remain the same between proximal and distal sites of stimulation. Thus, in analyzing compound muscle or nerve action potentials, subtraction of the positive peak from the negative peak should theoretically yield an identical value regardless of the site of stimulation along the course of the nerve. This approach, therefore, can circumvent the ambiguity of waveform changes caused by temporal dispersion and phase cancellation. 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, making its precise determination difficult. Also, a baseline shift or other electrical interference poses a major technical problem for reliable measure of area for this purpose.

Referential derivation of a monophasic waveform in a "killed-end" arrangement also conserves the area irrespective of stimulus sites showing no phase cancellation. This type of recording, however, may register a stationary far-field potential generated by the propagating impulse crossing the partition of the volume conductor.[80,81] Such a steady potential could, in turn, distort the waveform of the near-field activity (see Chapter 20–3).

Detection of Conduction Block

In a demyelinating polyneuropathy, slowing of nerve conduction often accompanies a reduction of amplitude associated with a partial conduction block.[8,34,63,155] Conversely the evidence of conduction block usually implies the presence of focal demyelination,[134] although other conditions such as ischemic neuropathy can cause similar reversible changes.[41,54] Increased ranges of conduction velocities result in pathological temporal dispersion broadening the evoked action potential. Desynchronization of the nerve volley may also result from repetitive discharges at the site of axonal injury after the passage of a single impulse. Unless secondary axonal degeneration is induced by damage of the myelin sheath, electromyography reveals little or no evidence of denervation. The motor unit potentials, though normal in amplitude and waveform, show poor recruitment because some fibers fail to transmit the impulse.

The usual criteria for conduction block in motor fibers revolve around the comparison of compound muscle action potentials elicited by proximal versus distal stimulation, expressed in the ratio of their amplitudes or areas.[1,114,146,158] This ratio remains normal in axonal neuronopathy, which reduces distal and proximal responses equally. Generally accepted diagnostic clues used for motor conduction block comprises a reduction in amplitude ratio greater than 20–50 percent, with less than 15 percent increase in duration of the compound muscle action potential elicited by proximal stimulation. These criteria, however, do not neccessarily apply in all studies because the effects of temporal dispersion vary depending on the electrode placement. A triple stimulation method with double collisions allows identification of motor conduction block in the face of desynchronization.[127] The technique, however, fails if the lesion is too proximal or if it compromises nerve excitability at stimulus sites as the consequence of demyelination or degeneration.

In documenting motor conduction block, the combination of clinical and electrophysiologic finding usually circumvents the ambiguity of the criteria based purely on waveform analysis.[77] In the presence of conduction block, a shock applied distally to the nerve lesion in question elicits a vigorous twitch and a large distal amplitude despite disproportionately severe clinical weakness[75] associated with paucity of voluntarily activated motor unit potentials.[20] As an exception, the same finding also characterizes any weakness attributable to upper motor neuron involvement or hysteria or during the first few days of axonal lesion before the distal stum loses its excitability.[106] In equivocal cases, inability to distinguish focal pathological temporal dispersion

from conduction block poses no major practical problem because either finding usually suggests demyelination, leading to an appropriate treatment. The absence of F waves complements conventional nerve conduction studies to document conduction block in the proximal segment.[36,69]

Several other factors play an important role in the clinical assessment of conduction block. The use of insufficient stimulus intensities at the proximal site erroneously reduces the proximal amplitude. Likewise, increased threshold for excitation in regenerated or chronically demyelinated nerves may account for a reduced proximal response.[108] In some cases of multifocal motor neuropathy, failure to maximally excite the involved segment 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 (Figs. 7–16). During the course of wallerian degeneration, the distal stump of the nerve remains viable for several days at a time when its proximal part fails to transmit the signal across the injury site. In this situation, conduction studies performed soon after nerve severance show a decreased proximal-distal amplitude ratio. Unexpected excitation of anomalous branches such as Martin-Gruber anastomosis may lead to a confusing discrepancy in amplitude, as does inadvertant current spread to a neighboring nerve.[70] In addition, lesions selectively affecting smaller myelinated fibers may not result in major loss of the proximal-to-distal ratio. In antiserum-mediated experimental demyelination,[88] smaller fibers underwent conduction block first. If this holds in the acute phase of demyelinating neuropathies such as Guillain-Barré syndrome, normal conduction studies do not necessarily rule out such selective involvement that might account for weakness. More slowly conducting fibers, however, belong to motor units generating relatively small twitches, whose contributions, if lost through conduction block, may cause only limited weakness.

Contrary to motor studies, which rely heavily on clinical assessment of weakness to define conduction block, sensory studies usually depend solely on waveform analysis of antidromic response elicited by short incremental stimulation (see this chapter, part 6). Surface stimulation applied at multiple sites may not necessarily indicate the exact point of nerve activation. An alternate method consists of stimulating the digital nerve and recording the orthodromic sensory potential at multiple points with a series of electrodes mounted 1 cm apart on a specially constructed flexible strap.[57,74] Though applicable to any other superficially located sensory or mixed nerve, the method suffers from a major limitation. Using surface recording, the depth of the nerve from the skin surface greatly influences the amplitude of the evoked potential. Thus, a small potential derived from a deeply located nerve segment under the area in question may erroneously suggest a conduction block.

In contrast to peripheral study, segmental recording registers comparable spinal somatosensory evoked potentials in intraoperative spinal cord monitoring. All recording electrodes are nearly equidistant to the spinal cord[115,139,148,150,156] if placed in the subdural or epidural space, the ligamentum flavum, or the intervertebral disc. Figure 7–17 show 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 of waveform changes, indicating a complete focal conduction block. Paradoxically enhanced negative peak 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

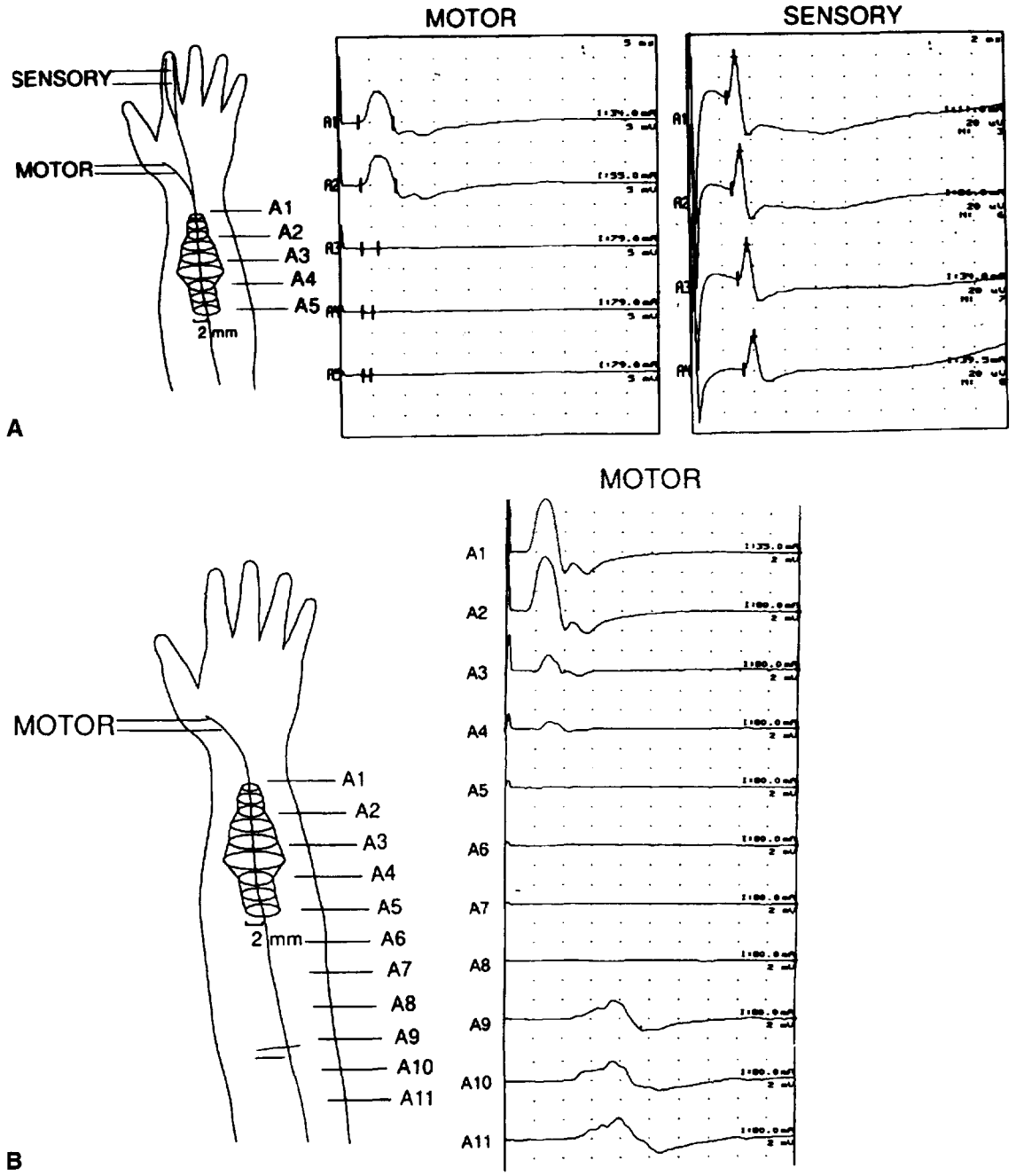


Figure 7-16. A. Motor and sensory conduction studies of the left median nerve in a patient with multifocal motor neuropathy. The *left diagram* illustrates the consecutive slices of MR images in relation to the sites of stimulation at the wrist crease (*A1*) and at 2 cm increments more proximally. One horizontal division equals 5 ms (motor) or 2 ms (sensory), and one vertical division corresponds to the gain indicated at the end of each trace, together with stimulus intensity. Note the complete and selective motor conduction block across the segment between A2 and A3, corresponding to the site of maximal nerve enlargement. [From Kaji et al,[66] 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 responses associated with thumb abduction, indicating recovery of conduction. [From Kimura,[77] with permission.]

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.[78,149]

Distribution of Conduction Velocities

In contrast to the onset latency of the action potential, which relates only to the fastest conducting fibers, its waveform reveals the functional status of the remaining slower conducting fibers. With the loss of nerve fibers, a smaller range of conduction velocity reduces the duration of the compound action potential. Conversely, disproportionate slowing of slower conducting fibers will result in increased temporal dispersion. The greater the range between the fastest and slowest nerve fibers, the longer the duration of the evoked potential. Temporal dispersion also increases with more proximal stimulation in proportion to the distance to the recording site.[35,71,80] Near-nerve recordings uncover the late components of sensory action potentials not detectable by surface electrodes. The minimum conduction velocity thus determined for the slower fibers may serve as a sensitive measure of both axonal and demyelinating peripheral nerve pathology.[138] The use of needle electrodes improves the selectivity of recording in measuring conduction velocity of different motor units within a given muscle. A wide range of mo-

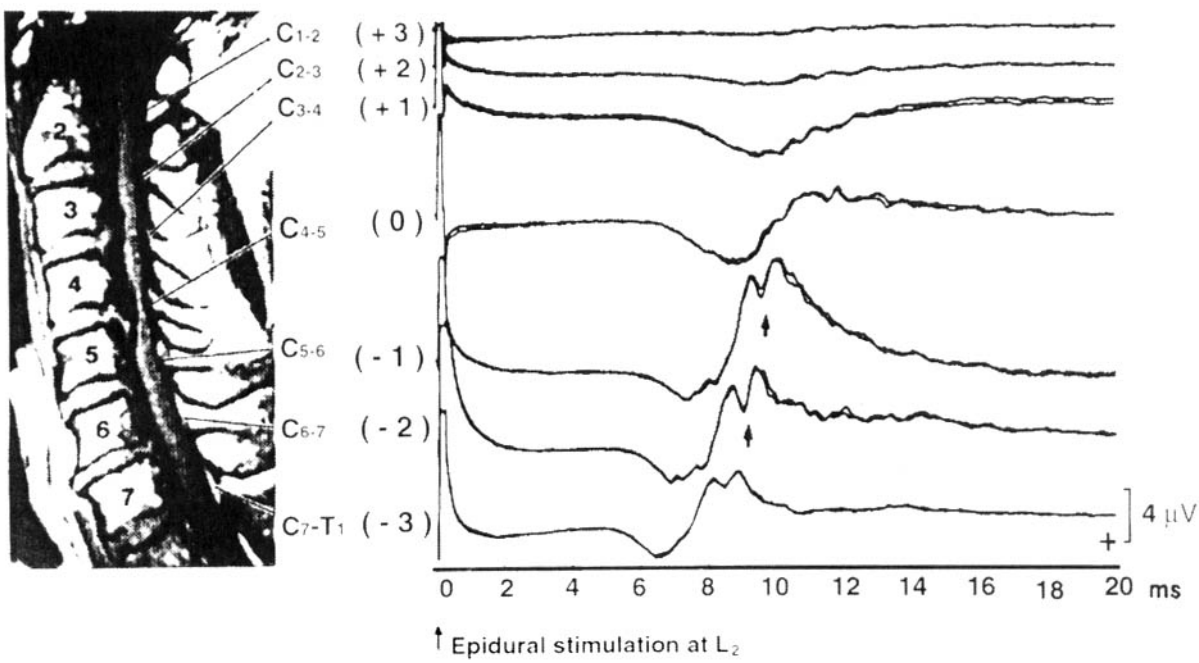


Figure 7-17. A. A T_1-weighted MR image (TR 400 ms; TE 13 ms) (*left*) and a recording of spinal somatosensory evoked potentials (*right*) obtained from a 65-year-old patient with cervical myelopathy. Epidural stimulation at L2 elicited a series of potentials recorded unipolarly from the ligamentum flavum of C7 to T1 through C12. Note the progressive increase in size of the negative component (*arrows pointing up*) from C7 to T1 (−3) through C5 to C6 (−1) with the abrupt reduction at C4 to C5 (0) followed by a monophasic positive wave at C3 to 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 MR image. [From Tani, Ushida, Yamamoto, et al,[149] with permission.]

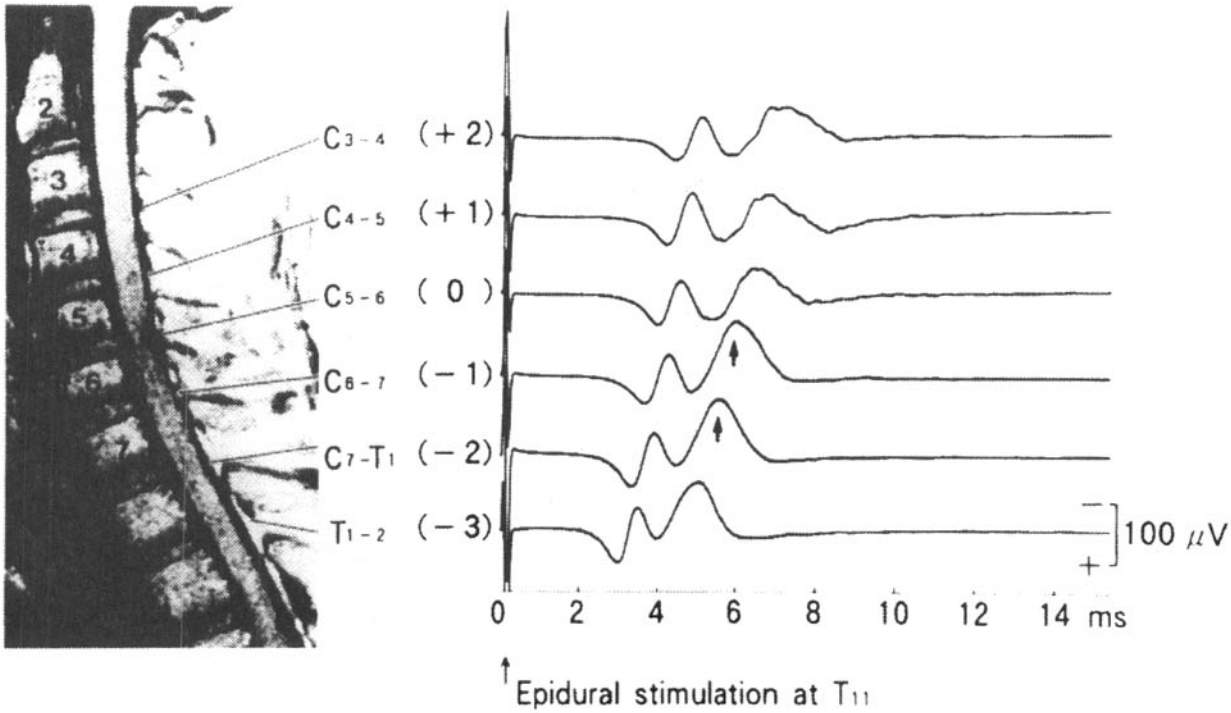


Figure 7-17. B. A T_1-weighted MR image (TR 600 ms; TE 90 ms) (*left*) and a recording of spinal somatosensory evoked potentials (*right*) obtained from a 36-year-old patient with cervical spondylotic myelopathy. Epidural stimulation at T11 elicited a series of potentials recorded unipolarly from the ligamentum flavum of T1 to C2 through C3 to C4 after epidural stimulation at T11. Note the progressive increase in size of the second negative component (*arrows pointing up*) from T1 to T2 (−3) through C6 to C7 (−1) with the abrupt reduction at C5 to C6 (0). The zero corresponded to the level of the spinal cord, showing a moderate compression on the MR image. [From Tani, Ushida, Yamamoto, et al,[149] with permission.]

tor fibers with different conduction characteristics sampled by this means show a close correlation to the twitch tension and recruitment threshold.[27] The technique has limited clinical application because patients tolerate poorly the multiple needle insertions required for isolation of the slowest-conducting fibers.

A number of publications have dealt with mathematical models for studying the waveform.[23,94,110,144,163] The method allows estimation of conduction velocity distribution in a nerve bundle based on a detailed model of the compound action potential as a weighted sum of asynchronous single-fiber action potentials.[31] The technique has provided some interesting, though unconfirmed, results. Distribution of conduction velocity may reflect the pathologic changes as reported in the study of the sural nerve affected by *n*-hexane neuropathy.[169] Nerve conduction velocity of the large myelinated axons, which contribute to the surface recorded response, may vary 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.[30] This observation, although not universally accepted,[29] would in part explain the different effect of temporal dispersion on sensory and motor fibers for a given length of nerve segment.[117]

Decomposition techniques in general suffer from the inherent limitation of identifying individual elements no longer retained within the compound action potential because of phase cancellation. Any sophistication in technology cannot retrieve the information, if already lost. Besides, some of the assumptions derived from normal distributions may not necessarily apply in various types of neuropathy.[26,153] In the analysis of compound muscle action potential, the length of

axon, rather than the conduction characteristics, may dictate the order of line-up of motor unit potentials. Thus, in motor conduction, unlike in sensory conduction, short latencies do not necessarily imply fast-conducting elements. This explains why the use of peak latencies does not necessarily yield a slower conduction velocity compared to the conventional calculations based on the onset latencies.

Careful attention to the waveform of each evoked potential improves the accuracy of interpretation in any electrophysiologic study. If the responses have dissimilar shapes when elicited by distal and proximal stimuli, the onset latencies probably represent fibers of different conduction characteristics. This discrepancy results, for example, from the use of a submaximal stimulus at one point and a supramaximal stimulus at a second site. In diseased nerves, the impulse from a proximal site of stimulation may fail to propagate in some fibers because of conduction block even with an adequate shock intensity. In addition, apparently supramaximal stimuli may not activate a bundle of regenerating or severely demyelinated axons if local structural changes or nerve pathology per se effectively prevent the excitation of the nerve segment. The impulses, once generated voluntarily or reflexively at a proximal site, however, may propagate along these fibers, giving rise to a confusing set of electrophysiologic findings. Any of these circumstances preclude the calculation of conduction velocity with the conventional formula.

Collision Technique to Block Fast- or Slow-Conducting 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.[152] 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, does not always hold, because the order of activation with threshold stimulation depends in part on the position of the stimulating electrode in relation to the different fascicles.[65]

An alternative method utilizes a series of paired shocks of supramaximal intensity.[43,49,50,53,59,60,112,125,129] 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 muscle action potential provides an indirect assessment of the slowest conduction (Table 7–1).

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 delivery of two stimuli, $S(A_1)$ and $S(A_2)$, through the proximal electrodes and another shock, S(W), through the distal electrodes. The antidromic impulse of S(W) blocks the orthodromic impulse of $S(A_1)$, provided the distal shock precedes the arrival of the proximal im-

Table 7–1 Range of Conduction Velocity in Motor Fibers of the Ulnar Nerve

Authors	Fastest Fibers	Slowest Fibers	Range
Thomas et al.[152]			30–40%
Poloni and Sala[120]			35–39%
Hopf[53]	60.0 ± 3.2		4–7 m/s
Skorpil[141]	61.1 ± 4.5	37.7 ± 7.1	22.4 m/s

pulse. With an appropriate adjustment of the interstimulus interval between S(A_1) 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(A_2), collides with the antidromic activity only in the fast fibers. In this way, the muscle action potential elicited by S(A_2) corresponds to the remaining slow conducting fibers that selectively transmit the orthodromic impulses (Fig. 7–18).

This technique allows direct determination of the amplitude and latency of the slowest-conducting fibers. The muscle action potential elicited by S(A_2) 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(A_1) and S(W), presumably because the impulses in the slowest conducting fibers do not necessarily arrive at the motor end-plate last. The conduction time must depend not only on the speed of the propagated impulse but also, and perhaps more importantly, on the length of fine terminal branches that characteristically lack myelin sheath. Even though the branches vary in length only on the order of a few millimeters, this degree of difference can still give rise to a

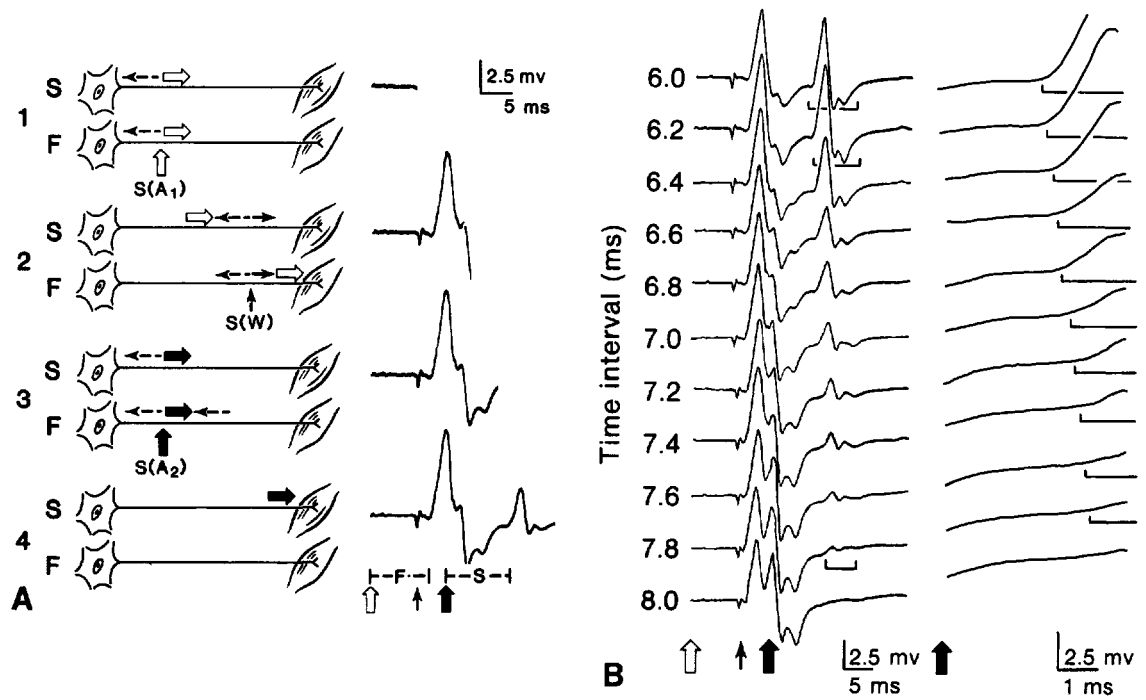


Figure 7–18. A. Compound muscle action potential recorded by surface electrode placed over the abductor digiti minimi after stimulation of the ulnar nerve. The *diagrams on the left* show orthodromic (*solid line*) and antidromic (*dotted line*) impulses generated by three stimuli, S(A_1), S(W), and S(A_2) delivered at the axilla, wrist, and axilla, respectively. Note the collision between the orthodromic impulse from S(A_1) and antidromic impulse of S(W) in slow conduction fibers (S), and between the orthodromic impulse of S(A_2) and antidromic impulse of S(W) in the fast conducting fibers (*F*). The orthodromic impulse of S(A_2) 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 (cf. bottom tracing in A). The first axillary stimulation, S(A_1) 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(A_2), to recur always 6.0 ms after S(W) automatically determined interstimulus interval between S(A_1) and S(A_2). The *figures on the left* shows the entire tracing with a slow sweep triggered by S(A_1) for amplitude measurement. The *figures on the right* illustrate latency determination with a fast sweep triggered by S(A_2) 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.

6 STUDIES OVER SHORT AND LONG DISTANCES

Segmental Stimulation in Short Increments

Ordinary conduction studies suffice to approximate the site of involvement in entrapment neuropathies.[25] More precise localization requires inching the stimulus in short increments along the course of the nerve in order to isolate the affected segment.[72] In the evaluation of a focal lesion such as compressive neuropathy, inclusion of the unaffected segments in calculation dilutes the effect of slowing at the site of lesion and lowers the sensitivity of the test. Therefore, incremental stimulation across the shorter segment helps isolate a localized abnormality that may otherwise escape detection (see Chapter 6–2). Thus, the study of short segments provides better resolution of restricted lesions. For example, assume a nerve impulse conducting at a rate of 0.2 ms/cm (50 m/s) except for a 1 cm segment where demyelination has doubled the conduction time to 0.4 mc/cm. In a 10 cm segment, normally covered in 2.0 ms, a 0.2 ms increase would constitute a 10 percent change, or approximately one standard deviation, well within the normal range of variability. The same 0.2 ms increase, however, would represent a 100 percent 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.[12,40]

This technique is best suited for assessing a possible compressive lesion, such as in carpal tunnel syndrome,[57,72,124,137] ulnar neuropathy at the elbow,[13,68] or peroneal nerve entrapment at the knee.[67] With stimulation of a normal median nerve in 1 cm increments across the wrist, the latency changes approximately 0.16–0.21 ms/cm from mid-palm to distal forearm. A sharply localized nonlinear latency increase across a 1 cm segment indicates a focal abnormality. An abrupt change in waveform nearly always accompanies a latency increase across the site of compression.[72] In fact, waveform analysis often localizes a focal lesion, unequivocally confirming the validity of excessive latency change that might have resulted from inaccurate advances of the stimulating electrodes or inadvertent spread of stimulus current, activating a less affected and consequently more excitable neighboring segments. If technical difficulties preclude a complete study across the presumed site of the lesion, incremental stimulation of the more proximal and distal segments suffices to delineate the abnormality. In these cases, the waveform analysis shows abrupt changes together with nonlinear shift of the onset (or peak) latencies of successive responses above and below the affected zone, forming two parallel lines rather than one. These findings confirm a focal lesion within the short interval in question encompassed by normal segments proximally and distally.

Late Responses for Evaluation of Long Pathways

Nerve stimulation studies commonly used in an electromyographic laboratory apply mainly to the distal, relatively short segments of the peripheral nerves. In assessing a more diffuse or multi-segmental process as might be seen in polyneuropathies, the longer the segment under study, the more evident the conduction delay. In other words, this approach has an advantage in 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), for example, a 20 percent delay for a 10 cm segment is only 0.4 ms, whereas the same change for a 100 cm segment amounts to 4.0 msec, an obvious increase that is easily detectable. In addition, evaluating a longer as compared to shorter segment improves the accuracy of latency and distance measurement be-

cause the same absolute error constitutes a smaller percentage. Measuring the surface distance (carelessly) in a 10 cm segment, the actual value may vary between 9.5 and 10.5 cm. A 1 cm difference constitutes a 10 percent error. Thus, the calculated conduction velocity based on this measurement could vary between 50 m/s and 55 m/s. The same 1 cm error in a 100 cm segment represents only 1 percent error, resulting in the range of calculated conduction velocity between 50 m/s and 50.5 m/s. The same argument applies in determining the effect of possible error in latency measurement.

Consequently, the study of a longer path offers a better sensitivity and accuracy and, as stated later, improved reproducibility in serial studies. A number of neurophysiological methods supplement the conventional techniques for the assessment of longer pathways.[37] 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 18–6 and 19–2).

Reproducibility of Various Measures

In the assessment of polyneuropathy, nerve conduction studies serve as a measure of abnormality to document serial changes during the clinical course.[84] Although the method provides a sensitive and objective indicator, its accuracy primarily depends on the adherence to technical details.[17] Any deviations from the standards result in inconsistencies of the results. The awareness of this possibility plays an important role in designing a multicenter clinical trial, which involves many investigators of different backgrounds and training. Nonetheless, few studies have emphasized technical factors influencing the reproducibility of nerve conduction measurements in the evaluation of polyneuropathy.[159]

Several investigators[5–17,52,131] reported on the reliability of nerve conduction velocity in normal subjects and patients with diabetic polyneuropathy.[18,33,159] A study of median and peroneal nerves in patients with diabetic polyneuropathy[18,33] revealed good reproducibility in nerve conduction velocity but not in amplitude. A few studies[4,33,159] of diabetic polyneuropathy yielded excellent reproducibility of the median and peroneal F-wave latencies. In contrast, amplitude varied considerably for both the motor and sensory nerves although the use of large electrodes improved reproducibility of compound muscle action potentials.[154] Of a few reported studies of F waves, all but one[159] dealt with the experience at a single laboratory, showing variations of up to 10 m/s in conduction velocity.[6,52]

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.[77,87] All measurements, repeated twice at a time interval of 1–4 weeks, followed a standardized method. In all, 32 centers participated in the study of 132 healthy subjects (63 men) and 65 centers in the evaluation of 172 patients with diabetic polyneuropathy (99 men). Motor nerve conduction studies consisted of stimulating the left median and tibial nerves and measuring amplitude, terminal latency, and minimal F-wave latency and calculating motor conduction velocity and F-wave conduction velocity. Sensory nerve conduction studies comprised antidromic recording of latency and amplitude after distal stimulation of the left median and sural nerves and calculation of sensory conduction velocities over the distal segment.

In both the control group 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 only 10 percent for the study of the median nerve and 11 percent for the tibial nerve in normal subjects and 12 percent and 14 percent, respectively, in patients with diabetic polyneuropathy. These results support the contention that minimal F-wave latency serves as the most stable and consequently reliable measure for a sequen-

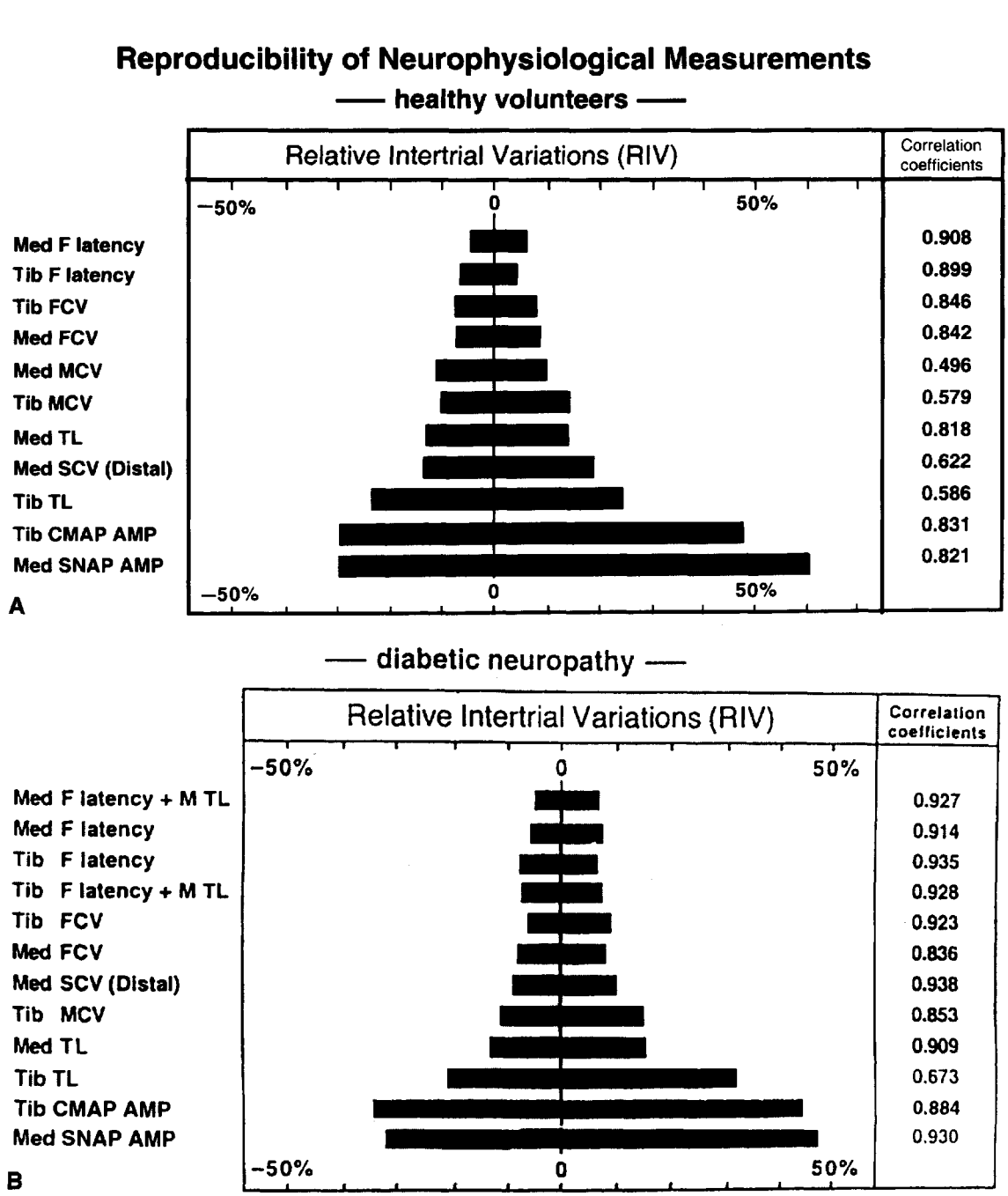


Figure 7–19. Reproducibility of various measures in (**A**) healthy volunteers and (**B**) patients with diabetic neuropathy. All studies were repeated twice at a time interval of 1–4 weeks to calculate relative intertrial variations as an index of comparison. [From Kimura,[77] courtesy of Nobuo Kohara, M.D. et al, data from a multicenter reliability study sponsored by Fujisawa Pharmaceutical Co., Ltd.]

tial nerve conduction study of individual subjects. 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, some prefer the use of a nomogram, plotting the latency against the height as a simple, albeit indirect, measure of limb length.

In the assessment of reproducibility, we use two independent indices, relative intertrial variation (RIV) and intertrial correllation coefficiency (ICC). Of the two, RIV directly represents a variation of measurements expressed as the percentages of the difference between V_1 and V_2 over the mean value of the two. Thus,

$$RIV(\%) = 100*(V_2 - V_1)/0.5(V_1 + V_2)$$

where V_1 and V_2 represent the values of the first and the second measurements of the pair. The ranges of RIV within ±10 percent usually indicate a higher precision.

Measures having larger interindividual differences are expected to show a greater intra-individual 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,

$$ICC = \sigma s^2/(\sigma s^2 + \sigma \epsilon^2)$$

where σs^2 and $\sigma \epsilon^2$ represent among-subject variance and experimental error. The value exceeding 0.9 indicates a reliable measure although, as seen from the formula, this may indicate a large among-subject variance rather than a small experimental error.

Figure 7–19 shows the 5th to 95th percentiles of RIVs and ICC in both groups; Figure 7–20 illustrates some examples of the individual data from the patients. The measures showing the range of RIV within ±10 percent included F-wave latency and F-wave conduction velocity of both median and tibial nerves, 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 sensory nerve potential and median and tibial compound muscle action potentials had a large range of RIV despite a high ICC. In

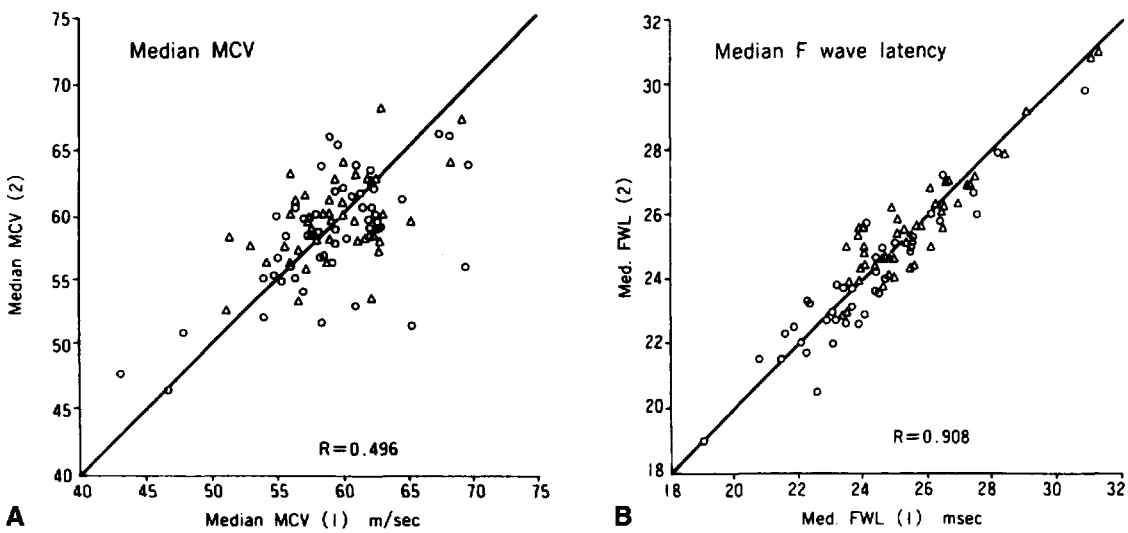


Figure 7–20. Comparison between the first and the second measures of (**A**) median nerve motor conduction velocity and (**B**) F-wave latency. Individual values plotting the first study on the abscissa and the second study on the ordinate show a greater reproducibility of the F-wave latency compared to the motor nerve conduction velocity (cf. Fig. 7–19). [From Kimura,[77] courtesy of Noboru Kohara, M.D. et al, data from a multicenter reliability study sponsored by Fujisawa Pharmaceutical Co., Ltd.]

these amplitude measurements, a large among-subject variance of the amplitudes made σs^2 much greater than $\sigma \epsilon^2$, leading to a high ICC despite a considerable intertrial variability.

Although a high ICC indicates a statistical correlation between two measurements,[33,167] 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 1 ICC (>0.9) with a small RIV (±10 percent).

Clinical Considerations

The main factors contributing to 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.[6,16,17] Amplitudes vary most probably because of a shift in the recording site.

A question often posed in regard to the accuracy and sensitivity of latency or velocity 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.

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Chapter 8

OTHER TECHNIQUES TO ASSESS NERVE FUNCTION

1 MOTOR UNIT NUMBER ESTIMATES

In neuromuscular disorders characterized by a loss of lower motor neurons, a patient's strength depends primarily on the number of remaining motor units in a group of muscles. A variety of techniques provide the means for calculating motor unit number estimates (MUNE).[31,104,132] Each method relies on dividing an average size of a single motor unit potential into a maximal compound muscle action potential that represents the sum of all motor units. All the methods have certain assumptions relating to the adequacy of sampling in estimating average size. Technical limitation in achieving unbiased selection constitutes a major source of error.

Compound Muscle Action Potential

The amplitude of a maximal compound muscle response directly relates to the total number and size of muscle fibers, providing a rough estimate,[73] although phase cancellation may distort the pattern of summation.[4,54] Supramaximal stimulation of a peripheral nerve activates all the

muscles innervated by that nerve, eliciting a muscle response as a sum of activity from multiple sources rather than from a single source. For example, a thenar response elicited by stimulation of the median nerve represents the activity of all the intrinsic hand muscles innervated by this nerve. In a strict sense, therefore, the motor unit number estimate relates to a group of muscles that contribute to the measure 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 units number.

Although the maximal amplitude is usually proportional to the number of axons, abnormally large motor unit potentials after reinnervation partially restore the size, thus concealing the loss of axons. In fact, despite the loss of over one half of its motor innervation, a muscle may maintain its normal amplitude. Therefore, a reliable motor unit number estimate requires the knowledge about the average size of individual motor unit potentials in addition to a measure of the total response. 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[55] and, to a much greater extent, in patients with neuromuscular diseases.

Sampling of Single Motor Unit Potential

A severe neurogenic process may reduce the number of axons to a level that allows identification of all the existing motor units individually. In general, direct counts provide a reliable, reproducible result up to a maximum of 10 units. With a greater number of units, an overlap precludes a complete count of all the units, necessitating the selection of a subset for calculation of an average size of single motor unit potentials. 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, sampling a greater population leads to more reproducible results.[128] In chronic neurogenic processes, the ease of measuring the reduced number of larger potentials compensates for the inaccuracy resulting from an increased size variation of individual units. The same motor unit potential may vary in size from one stimulus to the next, with defects of neuromuscular transmission requiring special interpretation. These include myasthenia gravis, amyotrophic lateral sclerosis, and neurogenic processes with ongoing reinnervation. With a decrement of compound muscle action potentials on slow repetitive stimulation, for example, the calculated value falls short of the actual number of motor units.

Methods for Quantitative Assessments

The methods described for obtaining single motor unit action potential values include (*1*) all-or-none increments of compound muscle action potential, (*2*) F-wave measurements, (*3*) spike-triggered averaging, 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.[52,104,133] Different methods place varying technical emphasis on meeting the underlying assumptions mentioned above, although basic principles remain the same. All these techniques, when properly executed, yield the same order of estimates.[32]

The original incremental method[103,104] provides the easiest and most direct approach to counting of single motor unit potentials. Based on the all-or-none characteristic of the activation of motor axons, application of finely controlled current in very small steps allows measurement of successively recruited individual motor units. The maximal muscle action poten-

tial derived 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 could result in an overestimation of the size of individual elements and consequently underestimation of motor unit numbers. This technique may also fail to identify the increments by very small motor unit potentials, such as nascent units or those seen in severe myopathies. Several modifications introduced to minimize these errors tend to favor the low-threshold units, with a selection bias against the high-threshold units.[9,49,51,60,61] As a variation, stimulating the nerve at several points with very low intensity yields only the first recorded single motor unit potentials.[51,52,56,78,144] The average sizes of the units obtained with stimulation along the nerve divided into the maximal compound muscle action potential yields the number of motor units.

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. In the presence of two units, for example, three distinct potentials would be recognized, one each or both together, giving the count of three rather than two. 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[127] 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.[90,131] Alternation can occur as described above. The mistaken inclusion of F waves activated by multiple instead of single motor units inflates the average size of individual elements, lowering the estimated number.[43] Automated use of submaximal stimulation and template matching reduce the risk and improve the accuracy.

Spike-triggered averaging uses a two-channel recorder to isolate voluntarily activated motor units as a measure of single motor unit potentials.[33,44] 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 muscle potential recorded from the same surface electrode yields the number of motor units. As a variant, motor units recruited at three levels of effort and recorded at two locations on the surface provide a broader sampling.[125] The sources of error unique to this method include recording with a spurious and erroneous trigger[29] and missing some motor units at the surface, unless studying the muscle located superficially.[10] Further, voluntary activation preferentially recruits smaller motor units, without recruiting larger units. Despite these concerns, the method provides values comparable to those expected from histologic studies and those obtained with other methods of recording. Microstimulation of nerve terminals in the endplate region may activate the full range of motor units, thus reducing the selection bias characteristic of voluntary activation.[107]

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 compound muscle action potential.[45,127] 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 are 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. In the interest of brevity, an initial scan of the compound muscle response identifies large steps with a series of 30 stimuli increasing in equal increments. The scan thereby defines appropriate stimulus intensity levels to recognize the representative single units for the particular nerve under study. In neurogenic disorders, for example, the axons with large motor unit potentials may have a higher threshold than the axons of smaller potentials, necessitating stimulation at higher 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 high-amplitude compound muscle action potentials. 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 are assigned a motor unit size estimate made at any stimulus strength. Thus, this stimulus strength influences the final result excessively.[126] Defective neuromuscular transmission also causes inaccuracies in this measurement, from varying sizes of motor unit potentials. A shift from Poisson to normal distributions can produce errors of up to 10 percent, necessitating a display of the histogram of the individual responses.

Normal Values and Clinical Application

Normal values, though they vary among authors using different techniques,[45,52] range from 200 to 350 for the thenar muscles tested with stimulation of the median nerve and from 150 to 220 for the extensor digitorum brevis tested with stimulation of the peroneal nerve. According to histological estimation, the flexor digit minimi has about 130 motor units.[111] This result is in agreement with 411 motor units estimated for the four hypothenar muscles by an automated incremental method.[61] 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.[30,60] Table 8–1 summarizes normal MUNE values obtained by the statistical method for distal muscles innervated by median, ulnar, and tibial nerves tested at different stimulus intensities.[45]

Earlier clinical studies used near-threshold methods,[9,52,103] which are best suited to test a muscle with a reduced number of motor units, allowing individual recognition of each unit with successive increments of stimulus current. In addition, reproducibility improves in absolute values with a smaller number of motor units in the muscle. In contrast, the method tends to underestimate the number of motor units in myopathies, which render some of the increments too small to identify. A 20 percent accuracy gives estimates in the range of 16–24 for 20 motor units and 160–240 for 200. Thus, a larger number of units makes a small loss harder to detect. Stim-

Table 8–1 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. The mean and lower limit (XX/YY) is shown for each stimulus level for each nerve. Multipoint recordings measured MUNE at 5–10 percent, and at 15–20 percent at two distal sites 1 cm apart along the nerve.
Source: From Daube,[45] with permission.

ulus currents above 15 percent of threshold also yield unreliable results, even in normal subjects. The technique supplements conventional studies in documenting the loss of motor units in patients with a normal compound muscle action potential amplitude. These include congenital brachial palsy,[123] tetraplegia[64] and amyotrophic lateral sclerosis.[92] It also serves to quantitate the number of motor units for follow-up studies, documenting the rate of loss in patients with motor neuron disease and other neurogenic processes,[5,6,29,46,57,58,144,147] although it sheds no light on the functional status of the surviving motor units.[41]

2 ASSESSMENT OF NERVE EXCITABILITY

This section reviews the modulation of axonal excitability following a single action potential.[38,138] The behavior of a single axon in this regard remains poorly understood. The altered excitability of many fibers collectively determines the size of a compound potential that will yield even more complex, yet important biophysical information. Axonal excitability also undergoes profound change after subthreshold stimulation, as discussed in subsequent sections.

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 its prestimulus excitability within the ensuing few milliseconds during the relative refractory period. Direct measurement of the nerve action potentials in experimental animals[13,67,142] substantiates the results in human studies, mostly tested in the sensory nerves or mixed nerves.[15,35,63,71,139] When measured by muscle response, the refractory period depends not only on the excitability of the nerve but also the excitability of the neuromuscular junction, as implied by the term refractory period of transmission.[62,105] Modified paired-shock techniques, however, make the study of the refractory characteristics possible as they pertain to the motor fibers per se.[70,87,91,121] Although a considerable amount of data has accumulated, its clinical value and limitations await clarification.[86]

The physiologic mechanism underlying the refractory period centers on inactivation of sodium (Na^+) 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, 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 is prolonged with low temperature,[35,40,113,114] advanced age,[50] slow conduction velocity,[113,114] and after experimental demyelination.[48,96,129,130]

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 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,[16,142] the paired-shock technique has found its way to the study of human sensory potentials[35,137,140] and mixed-nerve potentials.[63,99]

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.[15,91] The size of the test response measured, however, still depends on the excitability change of not only the motor axons but also the neuromuscular junction and muscle fibers.[34] 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.[70]

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.[84] 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. 8–1). Its magnitude and speed depends 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 it is eliminated 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 fibers by demonstrating the serial recovery of the test response amplitude (Fig. 8–2A). In contrast, the latency of the test response elucidates the duration of the relative refractory period of the most excitable fibers (Fig. 8–2B). Table 8–2 summarizes the results in 20 ulnar nerves from 10 healthy subjects studied in our laboratory.[87]

Changes in Amplitude versus Latency

The amplitude changes of the test response obtained with shocks of maximal

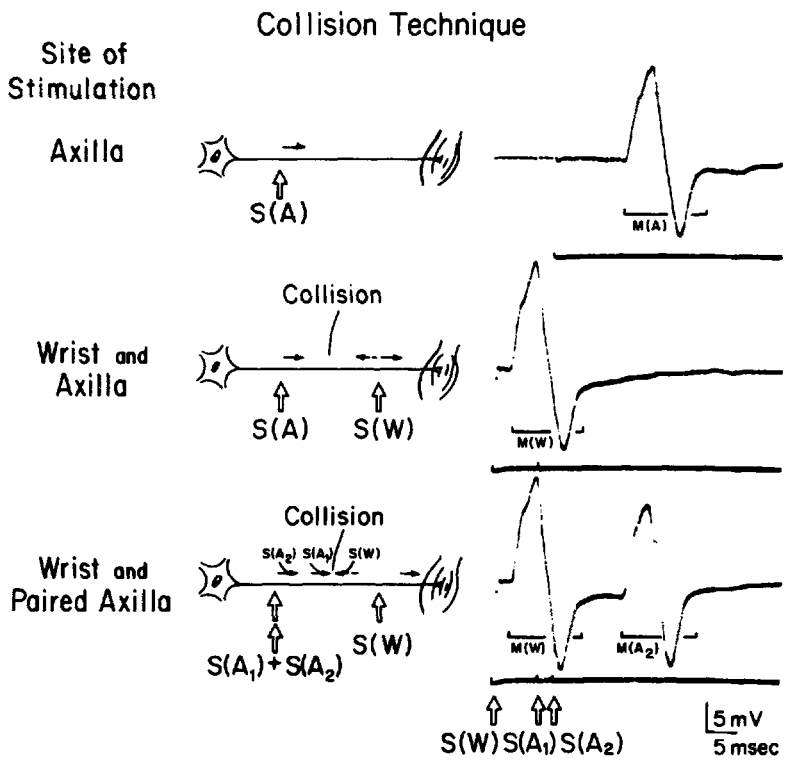

Figure 8–1. Compound muscle action potentials recorded by surface electrodes placed over the abductor digiti minimi after stimulation of the ulnar nerve. The diagrams on the *left* show the collision between orthodromic (*solid arrows*) and antidromic (*dotted arrows*) impulses. Axillary stimulation, 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*), $M(A_2)$ appeared because the first axillary stimulus, $S(A_1)$, cleared the path for the second stimulus, $S(A_2)$. [From Kimura, Yamada, and Rodnitzky,[87] with permission.]

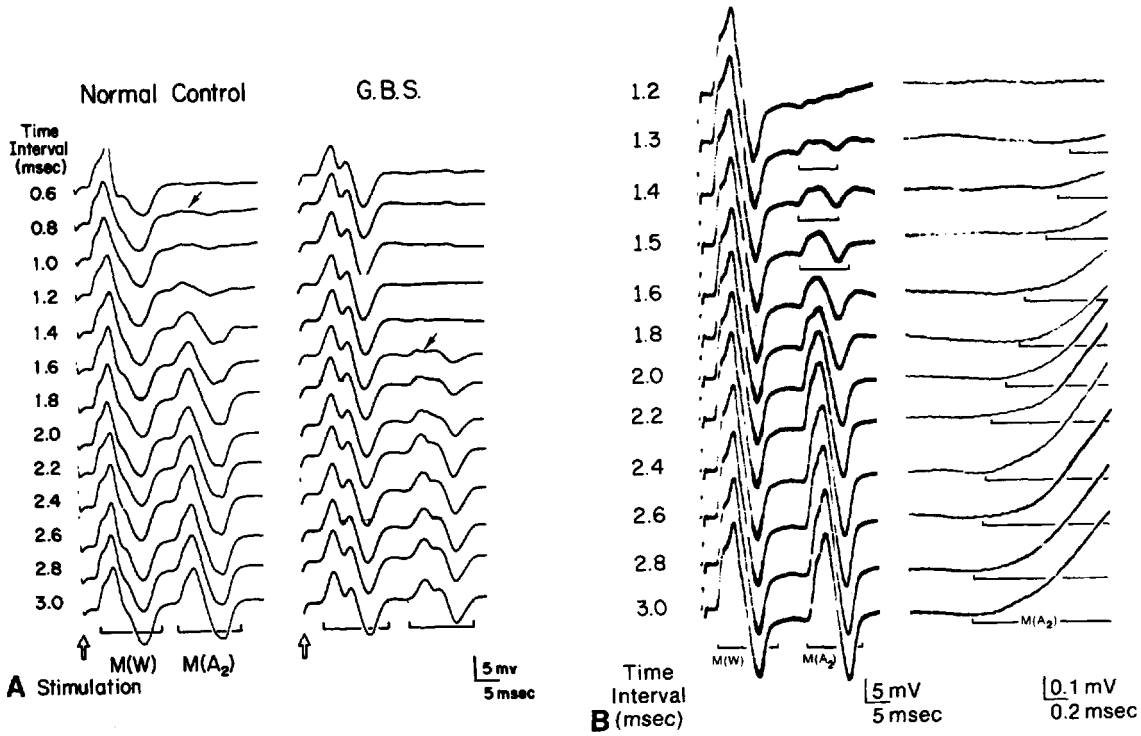

Figure 8–2. A. Paired axillary shocks, $S(A_1)$ and $S(A_2)$, of just maximal intensity combined with a single shock at the wrist, S(W). Interstimulus intervals between $S(A_1)$ and $S(A_2)$ ranged from 0.6 to 3.0 ms. $S(A_2)$ always occurred 5.0 ms after S(W), which triggered sweeps on the oscilloscope. In the normal subject, $M(A_2)$ first appeared (*small arrows*) at an interstimulus interval of 0.8 ms and recovered completely by 3.0 ms. The patient with the Guillain-Barré syndrome showed delayed and incomplete recovery. [From Kimura,[85] with permission.] **B.** Paired axillary shocks, $S(A_1)$ and $S(A_2)$, of just maximal intensity combined with a single shock at the wrist, S(W) (cf. bottom tracing in A). Delivering $S(A_1)$ 6.0 ms after S(W) allowed collision to occur 1.5 ms after $S(A_1)$. The interstimulus intervals between $S(A_1)$ and $S(A_2)$ 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 $S(A_2)$ and displayed after a predetermined delay of 11.0 ms. [From Kimura,[87] with permission.]

Table 8–2 Interstimulus Intervals of the Paired Shocks and Conduction Velocity of the Test Response (Mean ± SD)

	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%)
Length of Refractory Segment	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

Source: From Kimura et al.[87] with permission.

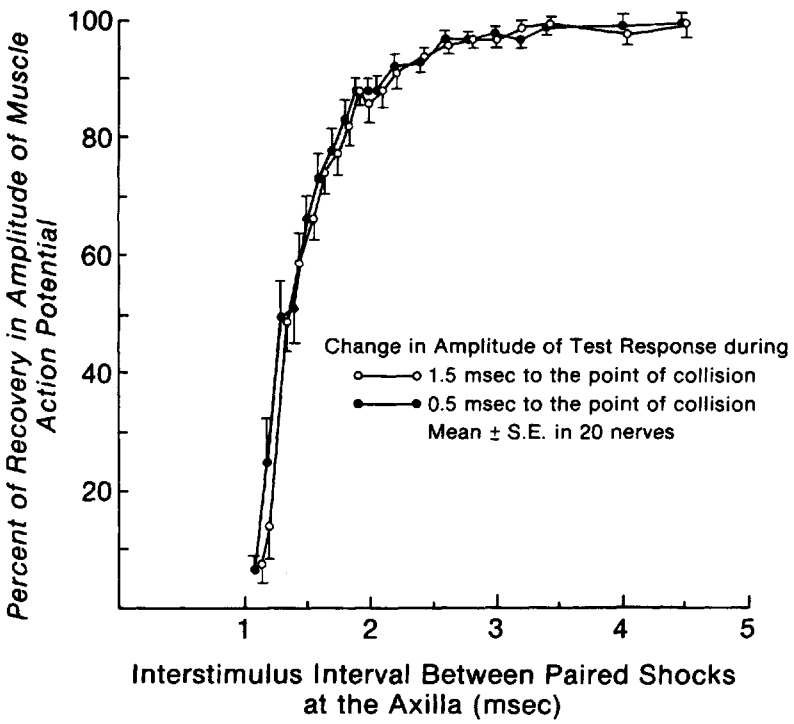

Figure 8–3. The pattern of recovery in amplitude of $M(A_2)$ during the refractory period in 10 healthy subjects. The return of $M(A_2)$ followed the identical time course with the passage of impulse along the shorter (0.5 ms) or longer refractory segment (1.5 ms). The gradual increase of $M(A_2)$ indicates the range of the absolute refractory periods of different motor fibers. [From Kimura, Yamada, and Rodnitzky,[87] with permission.]

intensity follow a nearly identical course irrespective of the length of the refractory segment (Fig. 8–3). 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. 8–4). 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 unit length decreases for a longer conduction distance. Therefore, the average conduction velocity improves as the refractory segment increases (Fig. 8–5).

These findings confirm the results of an animal study[142] that indicate (*1*) that 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*) that 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.[85] Electrophysiologic studies of human sensory fibers,[35] as well as computer simulation, have shown the same relationship between the refractory period and the length of the nerve segment.[145]

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 analysis helps improve numeric quantification of the

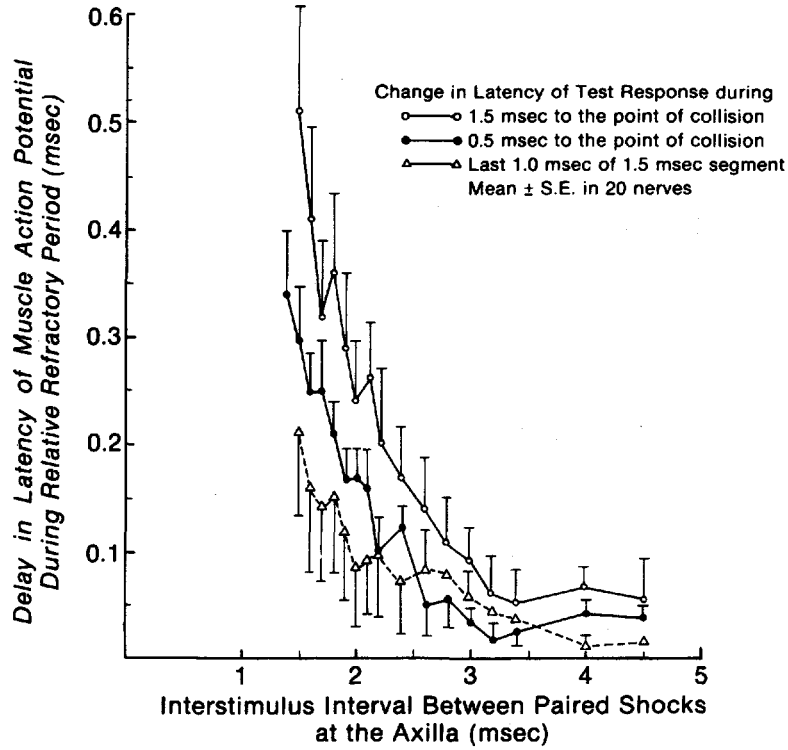

Figure 8–4. The pattern of recovery in latency of $M(A_2)$ in the same subjects as shown in Figure 8–3. The curve shows the latency difference between the response to a single axillary shock M(A), and the response to the second axillary shock $M(A_2)$ of the pair. The passage of impulse across the longer 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. [From Kimura, Yamada, and Rodnitzky,[87] with permission.]

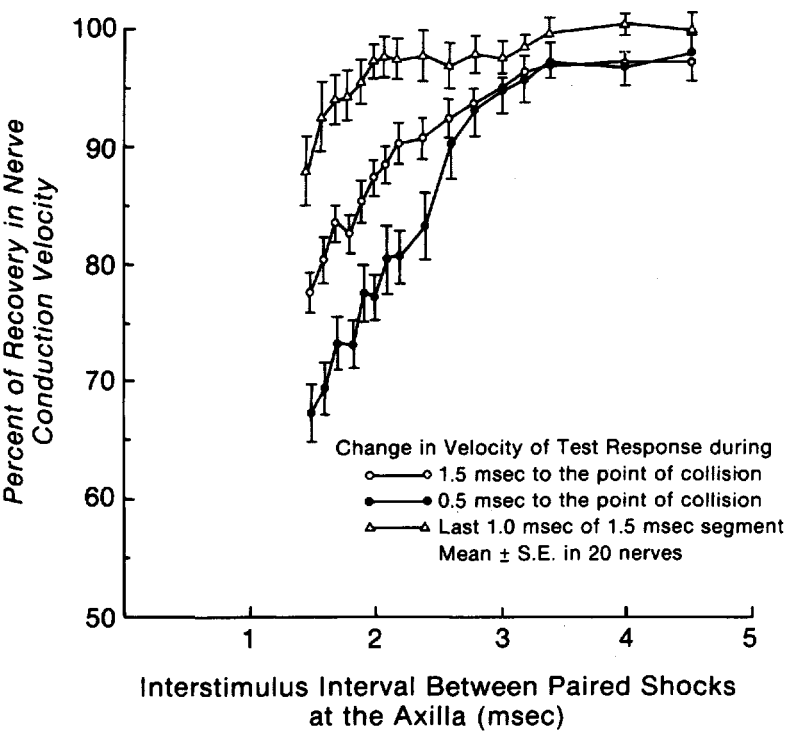

Figure 8–5. The time course of recovery in conduction velocity of $M(A_2)$ in the same subjects shown in Figures 8–3 and 8–4. The conduction velocities were calculated assuming that the delay of $M(A_2)$ occurred primarily in the segment proximal to the point of collision. In contrast to the pattern of recovery in latency (compare Figure 8–4), 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 $M(A_2)$ over the last 1.0 ms of the 1.5 ms segment. [From Kimura, Yamada, and Rodnitzky,[87] with permission.]

compound muscle potential in shape and latency.[53] 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.[3,74,75]

A number of studies have shown prolongation of the refractory period of sensory and mixed nerve fibers in diseases of the peripheral nerve.[98,99,140] Patients with alcoholic neuropathy had an increased refractory period of the median sensory fibers.[2] In patients with chronic renal failure, the initially abnormal relative refractory period reverted to normal after hemodialysis.[97] 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.[68] Conversely, hypokalemia of various origins shortened the relative refractory period.[102]

Most previous studies in humans have dealt with the sensory or mixed-nerve fibers, but similar alterations probably occur in the refractory characteristics of motor fibers. In fact, the absolute and relative refractory periods affect motor fibers,[87] sensory fibers, and mixed fibers[63] alike. For example, full recovery in the amplitude of the test response precedes full recovery of the conduction velocity, regardless of the type of nerve fiber tested.[35,63,69,87]

Determining the refractory period of individual motor fibers requires recording of single motor unit potentials after delivery of paired stimuli to the nerve.[17] 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. These uncertainties make the measurement of the refractory period less useful than might be expected on theoretical grounds as a clinical test in diagnosing diseases of the motor fibers and in elucidating their pathophysiology.

Excitability Changes after Passage of an Impulse

Studies of the myelinated axons reveal superexcitable and late subexcitable phases of excitability changes (see Chapter 4–3) after absolute and relative refractory periods.[12,63,138] Superexcitability reflects negative, or depolarizing, afterpotential from long-lasting depolarization of the internodal axon.[11] Activation of fast potassium channels terminates this phase by regulating the conductance of the internodal axon membrane. Thus, blocking these channels by 4-aminopyridine breaks down the normal relationship between superexcitability and membrane potential.[8] The late subexcitability results from a positive, or hyperpolarizing, afterpotential that reflects two very different mechanisms: opening of slow potassium channels[8,11,138] and activation of an electrogenic sodium pump triggered by intracellular sodium accumulation.[12,24,82,83]

These 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.[13] These paradoxical hyperexcitability and spontaneous discharges may account for neuropathic sensory disturbance and neuromyotonia.[14] Threshold tracking study of a single motor axon during posttetanic hyperexcitability[24] revealed a build-up of extracellular potassium (K^+) ions. Rat axons show similar phenomena after injection of potassium ions into or under a myelin sheath.[47,80] In either case, a reversal of the electrochemical gradient causes the influx of potassium ions across the internodal axolemma into the axon, resulting in depolarization and further opening of potassium channels, accelerating inward potassium current.

3 THRESHOLD TRACKING

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. 8–6 A and 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. To formulate numerical indices of excitability, *rheobase* is defined as the minimal current strength below which no response occurs even if the current lasts infinitely or at least 300 ms. *Chronaxie* is the minimal duration of a current required to excite the cell at twice the rheobase strength. The same prinicple applies to the study of sensory fibers as a measure of sensory deficit in peripheral neuropathy. Although of historical interest, neither rheobase nor chronaxie has proven satisfactory as a test in clinical practice.[94] 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.

Threshold tracking techniques test nerve excitability to assess the membrane potential, properties of ion channels, and electrogenic ion pumps.[26] 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 tests refractoriness and superexcitability that follow the passage of an action potential (Fig. 8–7). 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 neuropathy, than focal abnormalities, as in demyelinating neuropathies. Although these methods provide important insights into the physiology and pathophysiology of neuronal properties, their clinical utility awaits confirmation.

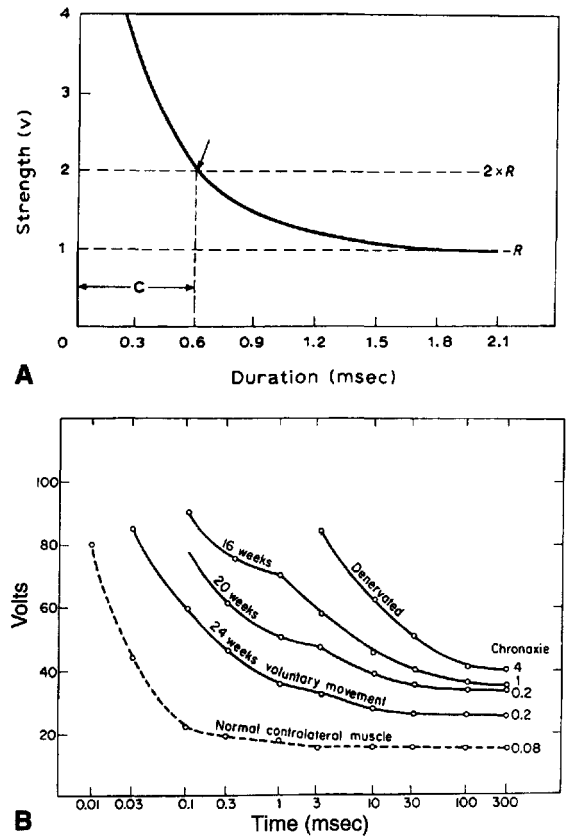

Figure 8–6. A. The strength-duration curve showing the stimulus intensity (*ordinate*) required for each duration of stimulus (*abscissa*). In this example, the stimulus intensity required remains the same after the stimulus duration reaches 1.8 ms. This strength is the rheobase (*R*). Chronaxie (*C*) is determined (*arrow*) as that duration along the strength-duration curve at a strength twice the rheobase ($2 \times R$). [From Ochs,[112] with permission.] **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. [From Ochs,[112] with permission.]

Threshold Measurement of Strength-Duration Time Constant

In the simplest type of threshold tracking, only test stimuli delivered alone determine

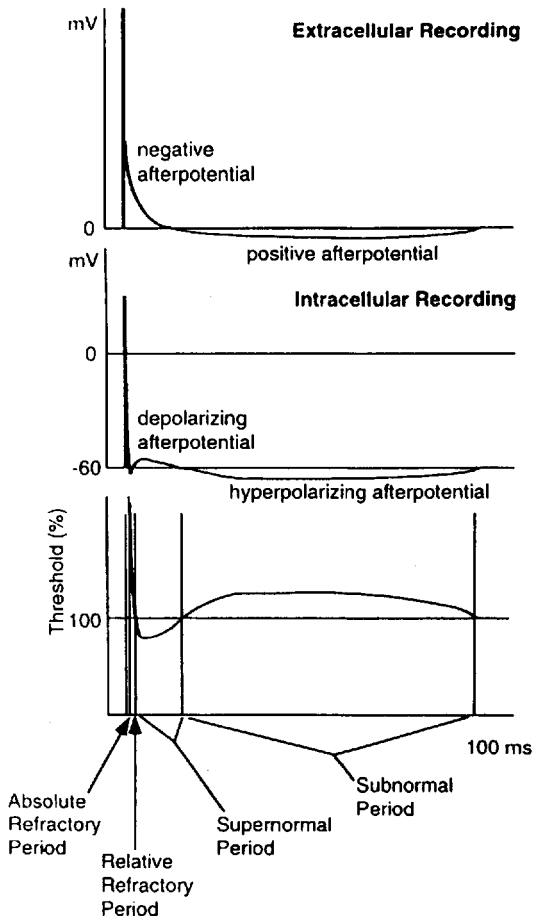

Figure 8–7. Nerve excitability changes following action potential. [From Ochs,[112] with permission.]

the nerve excitability change brought about by ischemia, hyperventilation, anesthetic agents, or other drugs.[59,146] 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 percent 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 multi-fiber preparations.

As shown in the strength-duration curve, increased duration reduces the current strength needed to excite the same fraction of a compound action potential. Threshold tracking tests this relationship in human peripheral nerve.[108] The old term, *chronaxie*, corresponds to the strength-duration time constant defined from the thresholds for just two pulses of different duration.[108] The sensory fibers with more prominent, persistent sodium conductance[27] have longer strength-duration time constants than the motor fibers.[108,115] Abnormalities may result from changes in resting membrane potential, sodium conductance, or myelination. An increase by depolarization and a decrease by hyperpolarization[24,27] will reflect the voltage-dependent behavior of sodium (Na^+) conductance.

For example, patients with acquired neuromyotonia, a condition of peripheral nerve hyperexcitability, have an increased strength-duration time constant of motor but not sensory axons.[101] This finding suggests relative axonal depolarization, greater persistent sodium conductance or enlarged nodal area as a result of paranodal demyelination.

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. For example, studies may remain normal in carpal tunnel syndrome, despite abnormally high rheobase.[109] This limitation applies to all threshold-tracking techniques, making them unsuitable for studying focal neuropathies, especially if a pathologic segment shows hypoexcitability instead of hyperexcitability.

Latent Addition and Accommodation

Very brief subthreshold conditioning pulses produce a membrane potential called *local response*, which is 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*.[141] 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 mem-

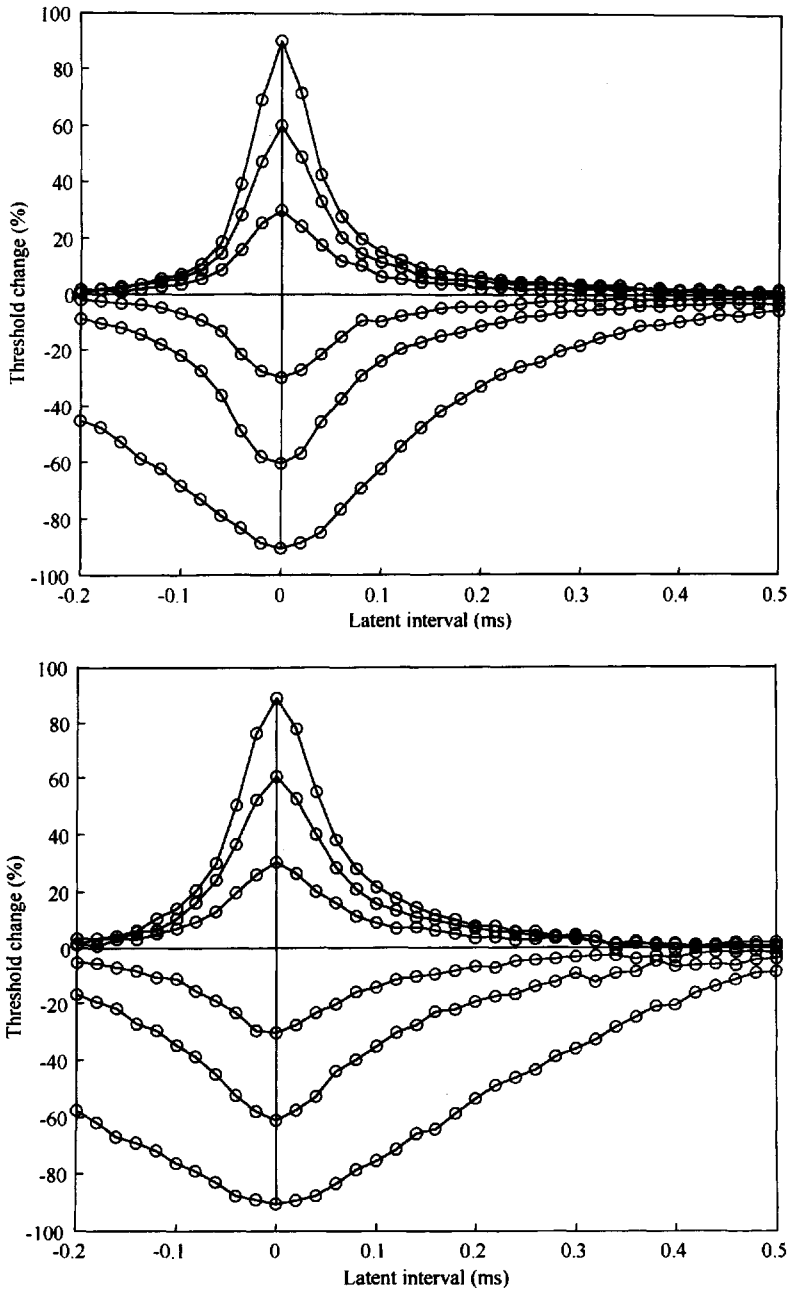

Figure 8–8. A. Latent addition for the motor axons of a human ulnar nerve, plotting percentage threshold changes (*ordinate*) against time delay (*abscissa*). From *top to bottom*, the traces show time course of recovery after three sets each of hyperpolarizing and depolarizing conditioning stimuli of 60 μs duration. The intensities used equal −90, −60, and −30 percent (*top half*) and 30, 60, and 90 percent (*bottom half*) of the control stimulus established by threshold tracking to maintain a 30 percent 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, M.D., Department of Neurology, Cheng-Kung University Hospital, Tainan, Taiwan.] **B.** Latent addition for the sensory axons of a human ulnar nerve, using the same arrangements as for the motor axons in **A**, except for the use of the target threshold to maintain 30 percent 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, M.D., Department of Neurology, Cheng-Kun University Hospital, Tainan, Taiwan.]

brane. Activation of a variety of nodal and internodal ion channels regulates this type of change of membrane potential, termed *electrotonus*. The threshold also changes in association with electrotonus, as implied by the term *threshold electrotonus*.[8,19,21]

A brief subthreshold depolarizing current increases nerve excitability (or decreases its threshold) because it brings 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. Brief hyperpolarizing currents show the opposite effect on membrane excitability, elevating its threshold to the test stimulus (Fig.

8–8). One study of latent addition estimated the sensory fibers to have about three times larger average time constants of a local response than motor fibers with depolarizing conditioning stimuli.[116] This difference dropped to about one and a half with hyperpolarizing conditioning stimuli.[116] Another study,[27] 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.[27,37] Latent addition allows in vivo study of persistent sodium conductance, which may explain the mechanism underlying some forms of axonal hyperexcitability.

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 actions of voltage-dependent ion channels tend to modify the effect induced by hyperpolarizing current. 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.[7,21,22,23,100]

Capacitative and resistive membrane properties[11] determine the internodal potential changes in the axons induced either by a nerve impulse or by externally applied currents.[18,95] 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 contributions of gK_s, gK_f, and gIR were inferred from the effects of the channel blockers tetraethyl ammonium (TEA), 4-amino pyridine (4-AP), and Cs^+, respectively.[8]

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.[26] Multiunit recording enables direct comparisons between the changes in threshold determined by this method and the changes in membrane potential measured by extracellular recordings.[7] According to these studies, the change in threshold normally follows the electrotonic changes in membrane potential caused by the subthreshold polarizing currents.[21] The channel blockers seem to affect these two measures in the same way, confirming the close causal correspondence between electrotonic and threshold changes.[21]

The threshold measurements usually parallel electrotonic potentials; thus, the term *threshold electrotonus*[8] 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, can be used to study 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.*[7,21]

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 has been shown in isolated toad fibers.[143] Mammalian fibers rapidly accommodate only when they are depolarized by 15–20 mV.[26] The insensitivity to potassium channel blockers of this fast accommodation supports the hypothesis that sodium channel inactivation plays a role.[7]

Techniques to Measure Threshold Electrotonus

Threshold electrotonus[21] 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 K_s currents inducing accommodation. Hyperpolarizing current pulses, usually 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; that value is chosen to be long compared with the time constant of the nodes of Ranvier but short compared with 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 1Hz, determine the "threshold" current that is just sufficient to maintain a constant response in amplitude of a predetermined size. The value usually chosen equals 40 percent 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 percent and ± 40 percent 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 interval between the start of the test and conditioning shocks is slowly advanced from +2 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 percent threshold reduction (Fig. 8–9).

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,[19] with a partial repolarization of the nodal membrane, caused mainly by the activation of slow potassium channels[21] present in the nodal and internodal axon membrane.[8] Hyperpolarization gives rise to only two phases of response, the fast 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,[21] a phenomenon more prominent in the sensory than the motor fibers.[25]

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 channel and three types of potassium channels.[26] For example, increased activation of potassium channels would decrease the axonal membrane resistance, resulting in "fanning-in" or flattening of

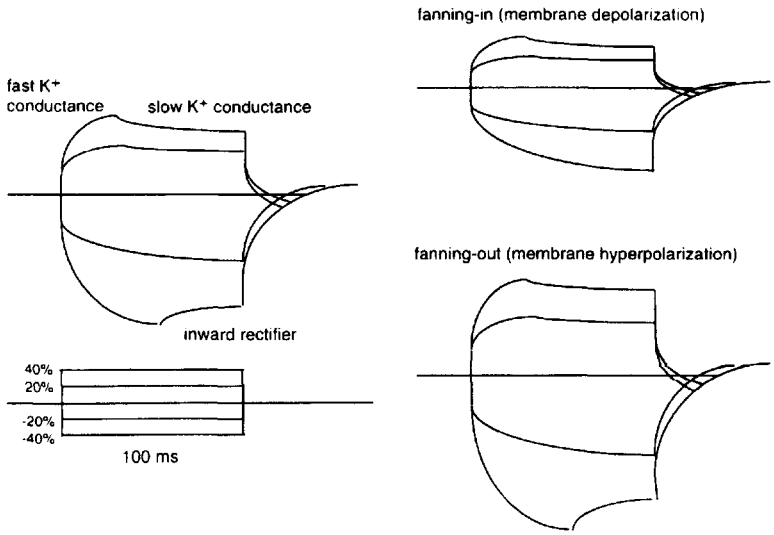

Figure 8–9. Membrane potential and threshold electrotonus showing increased excitability followed by accommodation to depolarizing subthreshold currents (*top half*) and decreased excitability followed by negative accommodation to hyperpolarizing currents (*bottom half*). Prior membrane depolarization or hyperpolarization shifted the response curves toward the baseline (fanning-in) or away from the baseline (fanning-out). [From Kaji et al,[79] with permission.]

the excitability curve. The opposite abnormalities would result in 'fanning out' of the threshold electrotonus.

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,[27] the axonal responses to brief current pulses depend for the mostpart 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, as described above.

The classical theory based on nodal currents suffices to analyze the normal waveform of an action potential. Modern approaches emphasize internodal mechanisms to account for pathologic nerve activity, as seen in Barrett and Barrett's equivalent circuit[11] derived from the electrical interaction between nodes and internodes.[122] This model can explain many conditions in which threshold electrotonus closely parallels electrotonus:[23,25,134,135] for example, pathophysiology of postischemic ectopic discharges[23] and mechanisms underlying the difference in inward rectification between motor and sensory nerve fibers.[25] The model must be modified in reproducing abnormal features when threshold electrotonus deviates from electrotonus in such conditions as amyotrophic lateral sclerosis[28] or prolonged depolarized state.[7]

Motor and sensory axons show very similar depolarizing responses but different hyperpolarizing responses. Hyperpolarization deactivates potassium channels in the internodal axon and later 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 helps to explain the characteristic behaviors of the motor and sensory axons on release of experimentally induced ischemia[25,36] and on the cessation of prolonged tetanization.[81,83]

Applying a pneumatic tourniquet to a limb induces substantial ischemia, which inhibits the electrogenic sodium (Na^+)-potassium (K^+) pump, causing membrane depolarization. The extracellular accumulation of potassium ions also reduces membrane potential.[12] On release of the cuff, hyperactivity of the electrogenic sodium pump rapidly hyperpolarizes the axons. In tests of these changes, threshold tracking of a constant fraction of the compound muscle action potential shows

results similar to those obtained from tracking of a single fiber.[12,22,59] Ischemia, like depolarization, 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. This close relationship breaks down, however, if the axons become so depolarized that sodium channel inactivation becomes a major determinant of excitability.[7] This occurs during prolonged ischemia, and in a few patients with amyotrophic lateral sclerosis.

During ischemia, motor latency increases despite depolarization, reflecting inactivation of sodium channels.[109] Postischemia, latency stays prolonged, reflecting the hyperpolarization of axons with a threshold increase exceeding 200 percent. Studies of sensory fibers have shown similar observations.[25,106] Threshold tracking studies have also elucidated the mechanism of postischemic ectopic discharges in motor axonsm[22,23] as well as postischemic paresthesias originating from cutaneous afferents.[25] Patients with diabetic neuropathy show resistance to ischemia,[136] as indicated by a deviation of threshold changes from the normal pattern within 5 minutes of arterial occlusion[146] and an even greater dissociation during postischemic hyperpolarization.[136] A similar study in patients with amyotrophic lateral sclerosis, however, failed to confirm previous reports of ischemic resistance.[110]

Clinical Assessments

The first clinical studies of amyotrophic lateral sclerosis showed two kinds of findings during depolarization:[28,88] type 1, abnormally reduced threshold or loss of physiologic accommodation, probably reflecting an imbalance between sodium and potassium currents, and type 2, sharply increased threshold, indicating sodium channel inactivation. In another series[72] many responses fell within the normal range, but the average showed significant fanning-out, resembling the effects of hyperpolarization. The results of these studies suggest deactivation of potassium channels and, consequently, reduced potassium conductances. Later series had more equivocal results, with the mean responses not significantly different from those of the controls, although the depolarizing responses showed distinctive changes in some patients. When divided into subgroups, the "definite amyo-trophic lateral sclerosis" and "progressive muscular atrophy" groups—not the "bulbar" and "primary lateral sclerosis" groups—exhibited these abnormalities. Threshold electrotonus cannot test the abnormal membrane properties related to fasciculations[20,79] if the change primarily involves the motor nerve terminals.[93] In addition to motor fibers, cutaneous sensory axons may show excitability change in patients with amyotrophic lateral sclerosis.[39]

In one study of diabetic polyneuropathy in which the motor and sensory axons were tested at the wrist, only a minority of responses lay outside the normal range.[72] The group means, however, showed a highly significant difference when compared to those of normal control subjects or patients with amyotrophic lateral sclerosis. The abnormalities, seen only in response to hyperpolarization, implied a deficit in inward rectification involving both motor and sensory nerves.[118] The inward rectification depends on the level of intracellular cyclic adenosine monophosphate,[1,76] a substance reportedly lacking in diabetic nerves.[77] Interestingly, threshold electrotonus applied to biopsied human sural nerve in vitro has shown the most prominent inward rectification in C fibers,[65] often most severely affected in diabetic neuropathy. This method has also demonstrated the reversal of the pathologic resistance to ischemia after therapy in patients with diabetes.[120]

Threshold electrotonus showed a marked symmetrical fanning-in of the responses[66,124] in rapidly developing, predominantly large-fiber sensory neuropathy induced by combination chemotherapy of Taxol and cisplatin.[42] These

findings, seen before any clinical or neurological signs of neuropathy,[124] indicate disturbances in membrane excitability caused by depolarization or increased conductance of the internodal axon membrane. Taxol also depolarized human sural nerves in vitro.[119] Patients with carpal tunnel syndrome show no abnormalities, probably because stimulation at the point of involved sites preferentially excites adjacent, normal nodes, or other more normal fibers.[109] The other conditions tested by threshold electrotonus include multifocal motor neuropathy with conduction block, showing abnormalities restricted to the site of the lesion,[79] and monomeric amyotrophy with spinal hemiatrophy.[89]

Threshold tracking is a powerful tool for investigating excitable membranes. A single stimulus or a train of suprathreshold stimuli causes refractoriness and superexcitability. Brief and prolonged subthreshold currents induce excitability changes that latent addition and threshold electrotonus can delineate. In particular, threshold electrotonus can serve as an index of membrane potentials, which under most circumstances closely correspond to the changes in membrane excitability. It provides a more sensitive indicator of changes in membrane potential than simple threshold tracking. This approach, though in theory well suited for studying human peripheral nerves in vivo, has so far found little use in practice because of its inherent limitations in the clinical context. The method tests the excitability of only a small population of axons with thresholds close to the level chosen for tracking, omitting the remaining, more or less excitable, fibers. 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 because stimuli tend to activate the more excitable neighboring segments. In contrast, these measures provide important insights into membrane properties in normal and diffuse neuropathies that affect the axons uniformly. Their usefulness as a diagnostic test awaits clarification.

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Part III

Assessment of Neuromuscular Transmission

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Chapter 9

ANATOMY AND PHYSIOLOGY OF THE NEUROMUSCULAR JUNCTION

1 INTRODUCTION

The neuromuscular junction is a synaptic structure consisting of the motor nerve terminal, junctional cleft, and muscle end plate. Its chemical mode of transmission has properties that are fundamentally different from the electrical propagation of impulses along the nerve and muscle. For example, the release of acetylcholine (ACh) ensures unidirectional conduction

from the axon terminal to the muscle end plate. The same principle applies to synaptic transmission in a sequence of neurons. In contrast, the nerve axons conduct an impulse bidirectionally from the point of stimulus unless the impulse originates at the cell body or axon terminal, as expected for any physiologic activation. The muscle fibers also show bidirectional propagation of impulses initiated at the motor point. Other characteristics common to the nerve synapse and neuromuscular junction include synaptic delay of a fraction of a millisecond and the nonpropagating nature of end-plate potentials (EPPs). These local potentials cause no refractoriness, unlike the all-or-none response of the nerve or muscle action potential. 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 the complex physiology in preparation for a subsequent more detailed clinical discussion (see Chapter 27). 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. At the muscle end plate, they produce small depolarizations of the postsynaptic membrane. These miniature EPPs (MEPPs) do not attain the critical level for generation of a muscle action potential. Depolarization of the presynaptic ending at the axon terminal triggers an influx of calcium (Ca^{2+}), 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 (Na^+) channels leads to the generation of an action potential. Propagation of the muscle potential activates the contractile elements through excitation–contraction coupling.

2 ANATOMY OF THE NEUROMUSCULAR JUNCTION

End Plate

Nerve and muscle become dependent on each other during the course of embryogenesis. The formation of the neuromuscular junction follows differentiation of presynaptic nerve terminals, innervation of postsynaptic components, and elimination of the remaining multiple axons.[112] The name *motor end plate* 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 end plate, and each branch of a motor axon innervates one end plate. The motor nerve fiber loses the myelin sheath at the nerve terminals. Distal to the myelin sheath, therefore, only the Schwann cells separate the nerve terminals from the surrounding tissue. Thus, the neuromuscular junction consists of the motor nerve ending, Schwann cell, and muscle end plate (Fig. 9–1). At the junctional region the nerve ending also loses the Schwann cells, forming a flattened plate lying within a surface depression of the end plate. 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.

Electron-microscopic studies have delineated the ultrastructural features of the end plates in human external intercostal muscles.[45] The presynaptic nerve terminal contains clear, round synaptic vesicles, lying mostly clustered in the regions called *active zones*, where acetylcholine (ACh) release into the synaptic cleft takes place. On average, a nerve terminal that

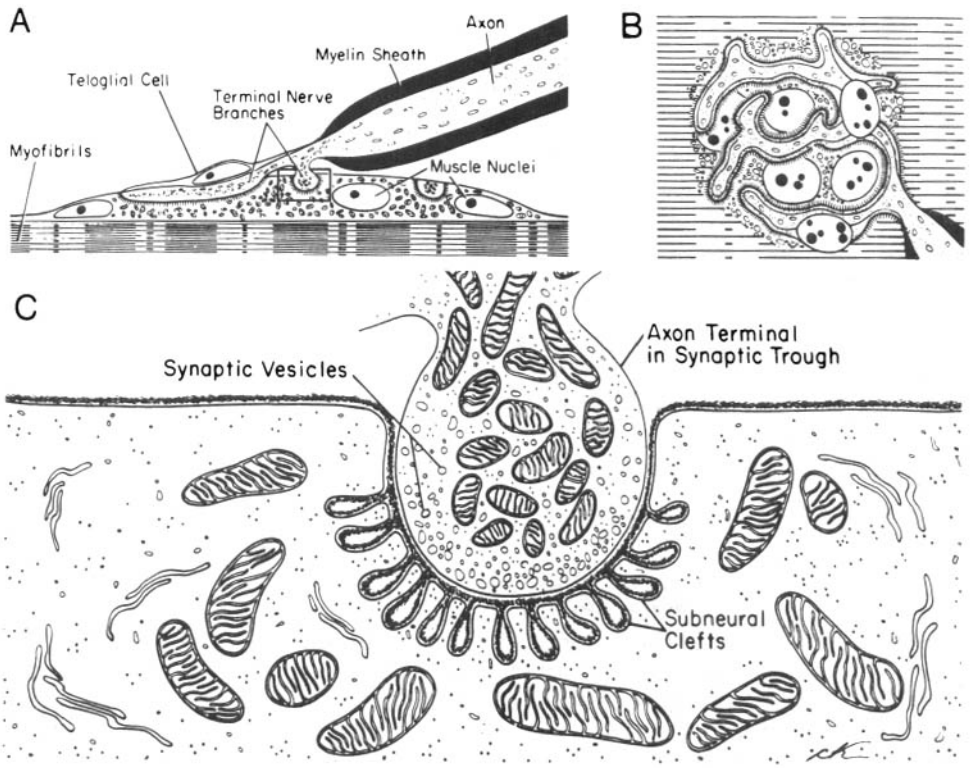

Figure 9–1. Motor end plate as seen in histologic sections in the long axis of the muscle fiber (**A**) and in surface view (**B**) under the light microscope, and a section through the motor end plate (*area in the rectangle in* **A**) under the electron microscope (**C**). The myelin sheath ends at the junction at which the axon terminal fits into the synaptic cleft. The Schwann (teloglial) cells cover the remaining portion without extending into the primary cleft. The plasma membrane of axon (axolemma) forms the presynaptic membrane and that of muscle fiber (sarcolemma), the postsynaptic membrane of the end plate. Interdigitation of the sarcolemma gives rise to the subneural or secondary clefts. The axon terminal contains synaptic vesicles and mitochondria. [From Bloom and Fawcett,[15] with permission.]

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 the muscle cell has a special composition containing, among other molecules, acetylcholinesterase.[91] The postsynaptic membrane, 10 times longer than the presynaptic membrane, forms elaborate invaginations known as *junctional folds*, containing a concentration of ACh receptors.[109] The postsynaptic folds cover an area about two and a half times that of the terminal itself. Diseases of neuromuscular transmission alter the end-plate profile (Fig. 9–2). In myasthenia gravis, the terminal occupies less area, and postsynaptic folds appear simplified. In contrast, in the myasthenic syndrome or Lambert-Eaton syndrome[30,78] the terminal, though normal in area, contains an elongated and sometimes markedly hypertrophic postsynaptic membrane. Neither disease is characterized by significant alteration in the mean synaptic vesicle diameter or the mean synaptic vesicle count per unit nerve terminal area. Clinically unaffected limb muscles may show the ultrastructural changes of the motor end plate in patients with ocular myasthenia gravis.[117]

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

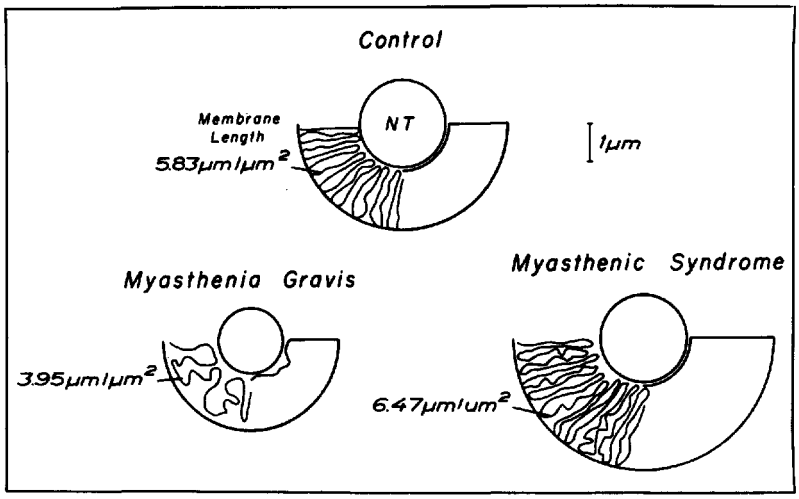

Figure 9–2. Schematic representation of the motor end-plates in control, myasthenia gravis, and myasthenic syndrome drawn to the scale of the mean figure. The diagram shows an oversimplification of the postsynaptic membrane in myasthenia gravis and marked hypertrophy in myasthenic syndrome. [From Engel and Santa,[44] with permission.]

acetyltransferase, which synthesizes ACh, and acetylcholinesterase, which hydrolyzes ACh. The proximal portions of neurons also possess the neurotransmitter and the two enzymes, although to a much lesser extent. This finding suggests that enzymatic synthesis takes place in the cell body before transport to the nerve terminals.[86] Each vesicle contains 5000–10,000 molecules of ACh or a quantum.[64] Some quanta (about 1000) located adjacent to the cell membrane are immediately available 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) forms the main store as a reserve supply for the mobilization store.

Acetylcholine Receptors

The nicotinic acetylcholine receptor, a transmembrane glycoprotein, comprises five subunits, $\alpha\times2$, β, γ, and δ in the fetus and $\alpha\times2$, β, ϵ, and δ 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.[88] Patch-clamp studies have shown bursts of ACh channel activation alternating open intervals and brief closures.[20] Synaptic maturation with switching from the γ to the ϵ subunit results in change of channel open time, and consequently, conductance. Studies of the kinetic properties of the normal ACh receptor[94] help elucidate pathologic alterations seen in some congenital myasthenic syndromes.[47]

3 ELECTRICAL ACTIVITY AT THE END PLATE

Miniature End-Plate Potential

Many resting muscle fibers show a spontaneous subliminal electrical activity, miniature end-plate potential (MEPP). It represents a small depolarization of the postsynaptic membrane induced by sustained but random release of a single quantum of acetylcholine (ACh) from the nerve terminal.[49] An ordinary needle electrode placed near the end plate of the muscle fibers can record the MEPP (see Chapter 13–4). A microelectrode inserted directly into the end-plate 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 frequency of the MEPP varies over a wide range. It increases with elevated temperatures and upon depolarization of the motor nerve terminals. It decreases with de-

ficiency of calcium (Ca^{2+}), the ion known to enhance quantal release by increasing fusion of the ACh vesicles with the membrane of the nerve terminal.

The factors that dictate the amplitude of the MEPP or quantum size include the number of ACh molecules in a vesicle, diffusion properties of the liberated molecules, structural characteristics of the end plate, and sensitivity of the ACh receptors. In normal human intercostal muscles, an MEPP recurs roughly every 5 seconds, measuring approximately 1 mV in amplitude when recorded intracellularly.[32] Hence, the MEPP falls far short of the excitability threshold of the muscle fiber, averaging about 2–4 percent of the normal end-plate potential (EPP) generated by a volley of nerve impulses. A small dose of curare greatly reduces the amplitude of the MEPP, whereas an equivalent dose of neostigmine (Prostigmin) increases it.[73] The MEPP ceases after denervation or nerve anesthesia. In myasthenia gravis, receptor insensitivity results in reduced amplitude of the MEPP, despite normal discharge frequency. Conversely, defective release of ACh reduces the rate of firing in the myasthenic syndrome and in botulism, although the MEPP remains normal in amplitude (see Chapter 27–2 and 3).

Events Related to Nerve Action Potential

In the resting state, the interior of the muscle fibers is negative relative to the exterior by about 90 mV. This transmembrane potential primarily results from an unequal distribution of inorganic ions across the membrane, with a high concentration of potassium (K^+) intracellularly and of sodium (Na^+) and chloride (Cl^-) 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 compensates for a slight inward movement of sodium and outward movement of potassium at steady state to maintain the electrochemical potential equilibrium (see Fig. 2–1).

As mentioned earlier, spontaneous release of a single quantum of ACh induces a 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 many MEPPs, giving rise to a localized EPP. Thus, the number of immediately available ACh quanta and the voltage-dependent 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 25–50, based on the amplitude ratio, EPP/MEPP.

End-Plate Potential

Like MEPPs, EPPs result from depolarization of the motor end plate by ACh. The opening of ACh receptors by the synaptic transmitter increases the conductance of various diffusible ions, principally those of sodium and potassium. Therefore, these ions move freely down their electrochemical gradients, resulting in depolarization of the motor end plate. The rise time, amplitude, and duration characterize this nonpropagated local response, which declines rapidly with distance from the end plate. 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, rather than all-or-none, response, increases in proportion to the number of ACh quanta liberated from the nerve terminal. The sensitivity of the end plate to the depolarizing action of ACh also affects the degree of depolarization. Like the excitatory post-synaptic potential (EPSP), two or more subthreshold EPPs generated in near synchrony can summate to cause a depolarization exceeding the critical level for generation of an action potential.

4 EXCITATION–CONTRACTION COUPLING

Generation of Muscle Action Potential

An end-plate potential (EPP) exceeding the threshold or the critical level of depolarization to open the sodium channel 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 in 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. In contrast to the all-or-none characteristic of the amplitude dictated by sodium channel kinetics, the latency of the action potential changes depending on the speed of initial 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 end plate. For example, even healthy muscle shows reversible changes of neuromuscular transmission after a period of disuse.[56] Once generated at the end plate, the action potential propagates bidirectionally to the remaining parts of the fiber. The impulse conducts only in the range of 3–5 m/s along the muscle membrane, compared with 60 m/s over the nerve (see Chapter 12–2). A neuromuscular block results when the EPP fails to reach the critical level. A subliminal EPP may imply insufficient liberation of acetylcholine from the axon terminal or reduced sensitivity of the muscle end plate. In contrast to the all-or-none generation of a muscle action potential in each muscle fiber, the compound muscle action potential 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 end plate to the transverse tubules initiates muscle contraction. This process, called excitation-contraction coupling, links electrical and mechanical activity.[77,102] Electrical activity of a muscle fiber consists of two temporally separate components attributable to different structures within the fiber.[22] The first portion originates at the motor end plate 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). These tridimensional tubules, though structurally internal to the cell, contain extracellular fluid. Consequently, the inside of the tubule is 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. 9–3). These tubules have a 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 to the sarcoplasmic reticulum gives rise to a small electrical potential referred to as *intramembranous charge movement.*[19] The action potential crossing the terminal cistern initiates the release of calcium (Ca^{2+}) from the longitudinal tubules into the sarcoplasm that surrounds the myofilaments. The presence of calcium there triggers a chemical interaction that leads to the formation of bridges between thin and thick filaments.

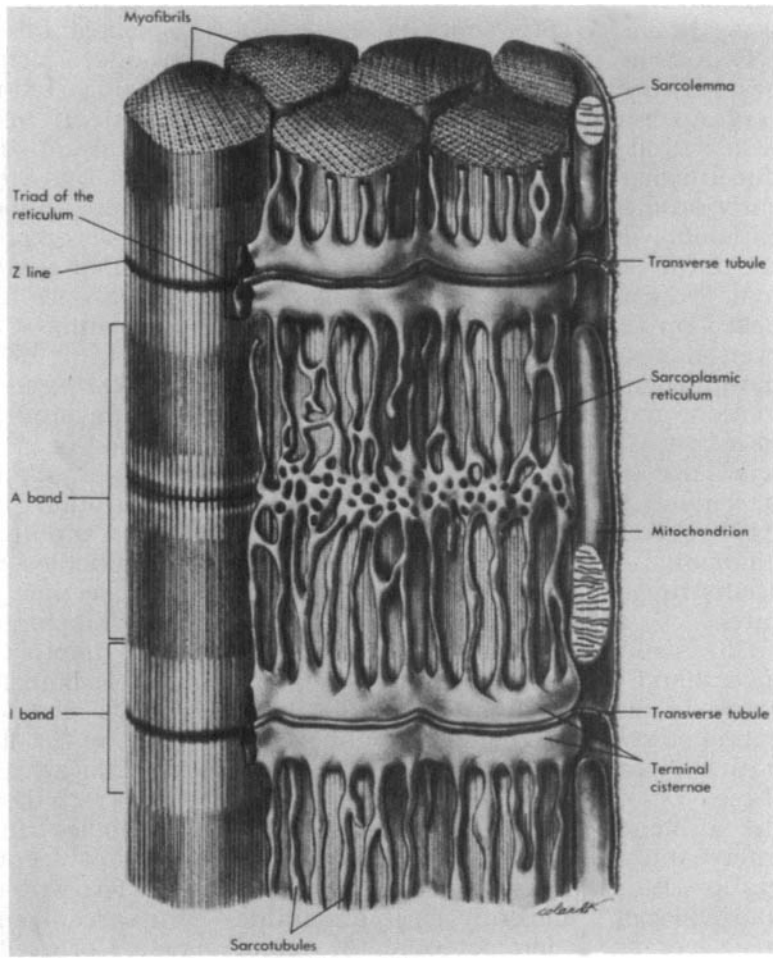

Figure 9–3. Anatomic relationship between the perpendicularly oriented longitudinal and transverse tubules. Propagating muscle action potentials initiate electromechanical coupling at the triad of the reticulum, which consists of two terminal cisterns of the longitudinal tubules and one transverse tubule between them. [From Bloom and Fawcett,[15] with permission.]

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 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 myasthenia gravis (see Chapter 27–2) intracellular recordings from the intercostal muscles have revealed reduced amplitude of miniature end-plate potential (MEPP) or small quantum size but normal or nearly normal discharge frequency.[32] Consequently, the end-plate potential (EPP) elicited by a nerve impulse also shows a reduced amplitude, despite a normal number of acetylcholine (ACh) quanta liberated by a single volley or normal EPP 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 amplitude of compound muscle action potential. Neuromuscular transmission fails first in small motor units, perhaps

because they have a lower margin of safety than the large motor units.[69,70]

Reduction in amplitude of MEPP suggests (*1*) decreased numbers of ACh molecules per quantum, (*2*) diffusional loss of ACh within the synaptic cleft, or (*3*) reduced sensitivity of the ACh receptor. In early studies, postsynaptic sensitivity to carbachol and decamethonium added to the bath solution appeared to be normal.[33] 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 end-plate region has since disclosed impaired postsynaptic sensitivity to ACh.[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 end-plate profile, indicating postsynaptic membrane abnormalities.[45] Another experiment has revealed three types of neuromuscular junctions in the surface fibers of internal and external intercostal muscles of myasthenics.[1] One group with mild morphologic alterations had EPPs 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 frequency of the MEPP and in amplitude of the EPP. The last group had totally degenerated endplates showing neither MEPPs nor EPPs.

Not every myasthenic end plate shows morphologic alterations, despite diminished MEPP amplitude demonstrated uniformly. Therefore, changes in end-plate geometry per se may not totally explain the physiologic defect. Myasthenic muscles have decreased functional receptor sites detected by radioactively labeled alpha-bungarotoxin, a snake venom that binds to the ACh receptor.[31,48,57] Further, the number of functional ACh receptors, when counted by this technique, shows positive correlation with the mean amplitude of the MEPP.[66] These findings indicate the presence of an ACh receptor abnormality in myasthenia gravis. Partial blocking of the ACh receptors with curare produces a similar physiologic defect.

Studies using plasma exchange have revealed an inverse relationship between clinical muscle strength and antibody titers. This finding supports the view that the auto antibody against nicotinic acetylcholine receptor plays the most important role in impairing neuromuscular transmission in myasthenia gravis and experimental autoimmune myasthenia gravis.[4,28,55,96,97,126] Cytokines produced by $CD4^+$ and $CD8^+$ T helper cells mediate the production of anti-ACh receptor antibodies,[125] sometimes induced by an external stimulus.[7] ACh receptor subunits found in the thymus alone, however, do not produce myasthenia gravis.[71]

Antibodies mediate obstruction of the ACh receptor, presumably by binding with complement to the receptor zone of the postsynaptic membrane.[40] Intercostal muscle biopsies show reduced numbers of ACh receptors and binding of antibodies to many of the remaining receptors in patients with myasthenia gravis.[84] Patients with thymoma often have striational antibodies in addition to anti-acetylcholine receptor antibodies.[67] This may interfere with calcium (Ca^{2+}) release from the sarcoplasmic reticulum, resulting in a defect of excitation–contraction coupling and contractility reported in myasthenic muscle.[100,101] Autoantibody also appears to mediate seronegative myasthenia gravis, a heterogeneous disorder that can be passively transferred to mice.[17]

Experimental Models in Animals

Experimental autoimmune myasthenia gravis shares the morphologic and physiologic abnormalities of the disease in humans.[28,29,46,51,61,83,105,107] Studies in rats showed reduced receptor content and increased receptor-bound antibody. Thus, defective neuromuscular transmission seems to result from a reduced number of fully active receptors.[84] Typical histologic and electrophysiologic myasthenic features develop in mice after passive transfer of human serum fractions obtained from patients with myasthenia gravis.[116]

Decamethonium causes paralysis by persistent depolarization of the end-plate region in normal muscle.[93] Reduction of postsynaptic sensitivity to depolarization renders myasthenic muscles resistant to this type of neuromuscular blocking. Antibodies to the ACh receptor do not impair the ionophore, an ion-conductance modulator protein thought to control the permeability change following a reaction of ACh with ACh receptor. Experimental autoimmune myasthenia gravis improves by administration of dantrolene sodium, which induces accumulation of free calcium in the subcellular store.[115]

Intracellular recordings from muscle end plates of immunized rabbits show reduced amplitude of MEPPs but a normal number of ACh quanta released per nerve impulse.[35] Rats with chronic experimental myasthenia have reduced amplitude of MEPPs despite normal ACh output at rest and during stimulation.[74] After passive transfer of human myasthenia gravis to rats, reduction of MEPP amplitude does not develop immediately, but occurs after the first 24 hours, reaching minimum levels by 6 days.[63] The delayed development of reduced MEPP amplitude suggests a more complex mechanism by IgG antibodies[63] than a simple block of ACh receptors like that caused by curare. Similarly, despite a precipitous drop of antibody titers, electrophysiologic findings usually improve with a delay of at least 7 days from the start of plasmapharesis in men.[18]

Presynaptic Defect in Lambert-Eaton Myasthenic Syndrome

In the Lambert-Eaton myasthenic syndrome (see Chapter 27–3), myasthenia of skeletal muscles and autonomic symptoms result from an autoimmune mechanism against the voltage-gated calcium channel located in the motor nerve terminal[79,82,98,103,111] and parasympathetic nerve.[62,121,122] In contrast to the receptor insensitivity of myasthenia gravis, defective release of ACh quanta characterizes the myasthenic syndrome.[30] Microelectrode recordings from excised intercostal muscles reveal no abnormality in amplitude of the MEPPs, and consequently in quantum size, or the sensitivity of the muscle end plate to ACh. The discharge frequency of the MEPP, however, does not increase as expected in response to depolarization of the motor nerve terminal.[78] Thus, a single nerve impulse releases a smaller number of ACh quanta than normal or decreased quantum content. The EPP then fails to trigger an action potential in some muscle fibers, which leads to a reduced amplitude of the compound muscle action potential.[80]

The defect improves immediately with various maneuvers to prime the nerve terminals.[34] For example, the EPP augments progressively with repetitive stimulation of the nerve. Postexercise augmentation lasts longer after cooling, which reduces the rate of removal of calcium (Ca^{2+}) from the nerve terminal.[87] 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.[45]

Heterogeneous Pathophysiology of Congenital Myasthenic Syndromes

Congenital myasthenic syndromes result from different types of pre- or postsynaptic mechanisms[39] caused by one or more specific genetic abnormalities (see Chapter 27–4).[8,37,43,53,54,72,108] They comprise a number of myasthenic disorders not associated with detectable anti-ACh receptor antibodies. These entities, presenting at birth or in early life, share many common clinical features, despite distinct etiologies identified by physiologic, ultrastructural, and cytochemical studies. Typical patients have such features as deficient muscle acetylcholinesterase, decreased frequency but normal amplitude of the MEPP, 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 reflects a reduced store of ACh vesicles, rather than a low probability of release, as in the case of the classic myasthenic syndrome. A congenital defect in the molecular assembly of acetylcholinesterase or its attachment to the postsynaptic membrane also represents a basic abnormality. A familial congenital myasthenic syndrome shows deficient synthesis of ACh.[60]

The syndromes adequately characterized to date include acetylcholinosterase deficiency,[36,65] defective resynthesis or vesicular packaging of ACh,[38,95] ACh receptor deficiency such as congenital paucity of secondary synaptic clefts,[81,110,124] kinetic dysfunction of ACh receptor, such as slow channel syndrome,[52,99] high-conductance, fast channel syndrome[42,47] and other abnormalities of interaction with ACh,[118] and familial limb-girdle myasthenia with tubular aggregates.[50,92]

Effect of Toxins and Chemicals

Abnormalities in calcium (Ca^{2+})-dependent ACh release also reduce the amplitude of the EPP in a number of other conditions, including a neuromuscular block by botulinum toxin[89,106] (see Chapter 27–5 and 6). The neuromuscular insufficiency in botulism 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 by cleaving synaptic protein 25 (see Chapter 27–5). Thus, the reduced frequency of the MEPP, not affected by the addition of calcium, recovers after the administration of a spider venom known to neutralize the toxin.

High concentrations of magnesium (Mg^{2+}) block neuromuscular transmission.[16,114] Lowering the temperature increases transmitter release and reactivates previously paralyzed muscle in botulinum paralysis, but not in normal muscle blocked by high magnesium concentration.[85] Experimental evidence indicates an inhibitory effect of manganese (Mn^{2+}) on transmitter release at the neuromuscular junction.[5] The long-term use of various nondepolarizing neuromuscular blocking agents can also cause prolonged muscle weakness.[6]

Aminoglycoside antibiotics such as neomycin and kanamycin not only interfere with ACh release directly[3,75] but also inhibit the transmission by postsynaptic block.[24] A number of other drugs induce dysfunction of the neuromuscular junction.[3] These include the HIV protease inhibitor ritonavir,[104] D-penicillamine, used to treat rheumatoid arthritis[27] and Wilson's disease,[2] and cocaine.[9,23] In addition, β-blockers[21,68] and calcium channel blockers[113,119,123] may aggravate myasthenia gravis or induce a myasthenic syndrome.

6 TIME COURSE OF NEUROMUSCULAR TRANSMISSION

Enhanced Excitability Causing Repetitive Discharges

The amount of acetylcholine (ACh) in the immediately available store and the concentration of calcium (Ca^{2+}) at the nerve terminal, together, 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 congenital myasthenia with acetylcholinesterase deficiency[39] (see Chapter 27–4 and 6). Excess amounts of ACh may result from the use of anticholinesterase as therapy for myasthenia gravis[37] or after organophosphate poisoning.[10–13] Reactivation of muscle response results, despite the normal amounts of ACh molecules, in the slow channel syndrome with prolonged depolarization.[41,99] In this entity, as in organophosphate poisoning, repetitive stimulation of the nerve show a rate-dependent decrement of all muscle potentials, although secondary responses diminish first.[58,59,120]

Effects of Paired or Repetitive Stimulation

Repetitive stimulation affects the release of ACh and the end-plate potential (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.[26]

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 100–200 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, because the negligible electrosecretory facilitation at such stimulus intervals can no longer compensate for the loss of ACh stores. 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 will lead to reduced release of the transmitter. The partially depleted ACh store recovers exponentially in 5–10 seconds through the slow reloading of ACh ejection sites.

Neuromuscular Depression and Facilitation

Reduction in the number of ACh quanta released by the second nerve impulse results in a smaller EPP, which no longer reaches the threshold in some muscle fibers. The amplitude of the second compound muscle action potential decreases, or shows a decrement, compared with the first response. Conversely, an increase in the number of quanta released by the second nerve impulse gives rise to a larger EPP. Such true facilitation is based on the neurosecretory potentiation rather than on summation of two EPPs elicited by paired shocks with a very short interstimulus interval.[26]

Both facilitation and summation result in larger compound muscle action potentials through recruitment, provided that the initial stimulus failed to activate all the muscle fibers. The greater amplitude and area under the waveform in recruitment imply the discharge of additional muscle fibers. An increased amplitude may also result from better synchronization of different muscle fibers without recruitment. In this 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 (Na^+)–potassium (K^+) pump triggered by preceding shocks also potentiates the amplitude of the subsequent single action potentials as the result of hyperpolarization.[90]

Normal Recovery Cycle

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 delivered a few milliseconds after the first falls in the refractory periods of the muscle and nerve (Fig. 9–4). For intervals of 10–15 ms, an overlap between the first and second muscle responses precludes accurate measurement of the individual potentials. Thereafter, the second compound muscle potential recovers to the size of the first in the normal muscle. This finding, however, does not necessarily imply that the first and second stimuli elicit the same EPPs.

At interstimulus intervals of 100–200 ms, the second shock may normally evoke 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 no additional fibers. A slow rate of stimulation depresses the number of ACh quanta released successively, 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,

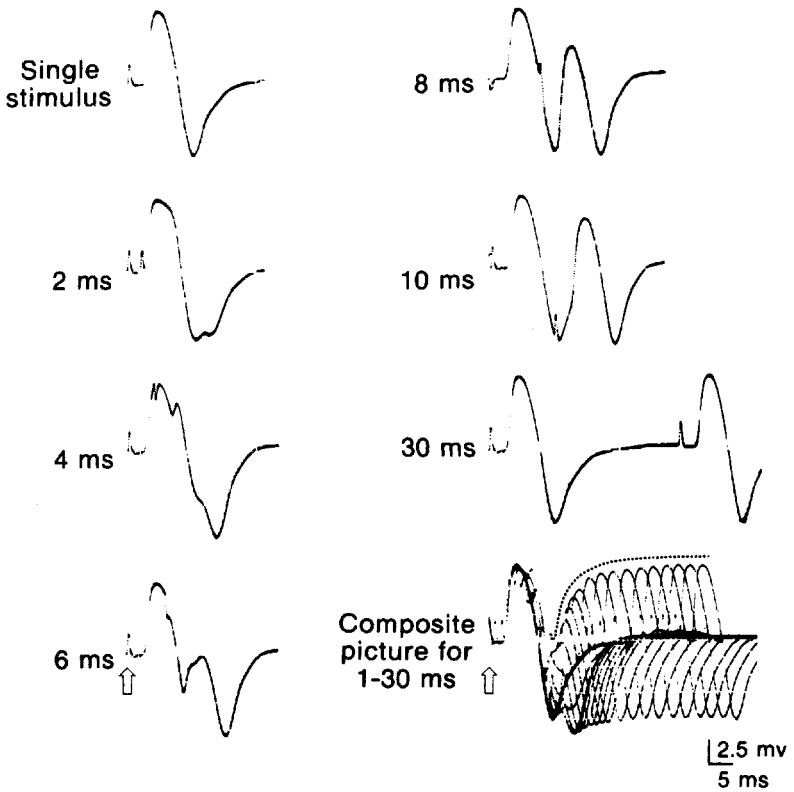

Figure 9–4. Compound action potentials from the thenar muscles elicited by paired shocks delivered to the median nerve at the wrist. Time intervals ranged from 2 to 30 ms between conditioning (*arrow*) and test stimuli. The *top tracing on the left* shows a response to a single stimulus. The *bottom tracing on the right* is a composite picture superimposing 20 paired responses. The conditioning response of each pair appeared in the same spot, 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. [From Kimura,[76] with permission.]

changes in the amount of ACh do not alter the size of compound muscle action potential 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.[25] With paired stimuli, the second muscle response equals or exceeds the first for the interstimulus intervals of 100–200 ms that accompany calcium-dependent neurosecretory facilitation.[14,25] With longer intervals, the second response falls below the first, because depleted stores of available ACh quanta can no longer overcome the receptor insensitivity. The maximal depression at interstimulus intervals ranging from 300 to 600 ms is followed by a slow recovery. Full return to the control value in about 10 s implies restoration of releasable ACh through replenishment of the stores. In myasthenia gravis, a reduced amount of ACh also fails

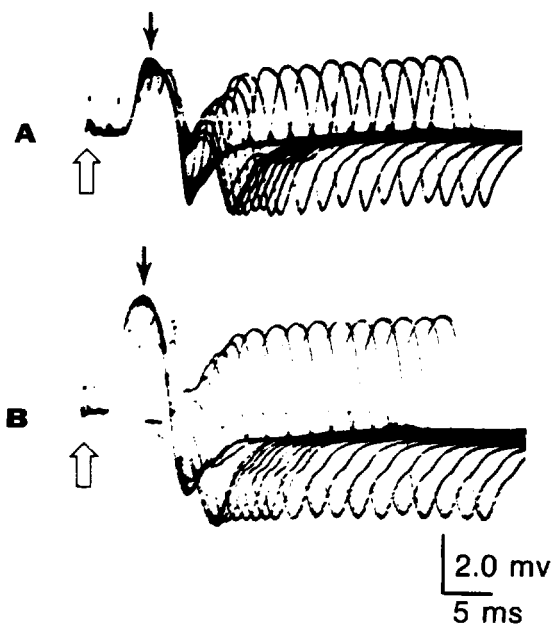

Figure 9–5. Composite pictures superimposing 20 paired responses from the thenar muscles (compare bottom tracing on right in Figure 9–4.) A patient with myasthenia gravis (**A**) and a normal control (**B**) showed the same recovery course for the interstimulus intervals ranging from 1 to 30 ms.

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 (Figs. 9–5 through 9–8). In either case, the maximal depression results from repetitive stimulation at 2–3 Hz, the rate fast enough for the depletion of ACh but slow enough for the diffusion of calcium out of the axon.

In the myasthenic syndrome, 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 a few milliseconds, the summated EPPs will recruit additional muscle fibers. With stimuli delivered at a longer interval of 100–200 ms, EPPs no longer summate, but the electrosecretory facilitation partially overcomes the defective release of ACh (Fig. 9–8). Increased EPPs will in turn recruit some of the muscle fibers not activated by the first stimulus, which will lead to an increase in amplitude of the second compound muscle action potential.[26] This finding, though characteristic, reveals only a nonspecific abnormality seen whenever the first stimulus evokes less than the maximal response, including some cases of

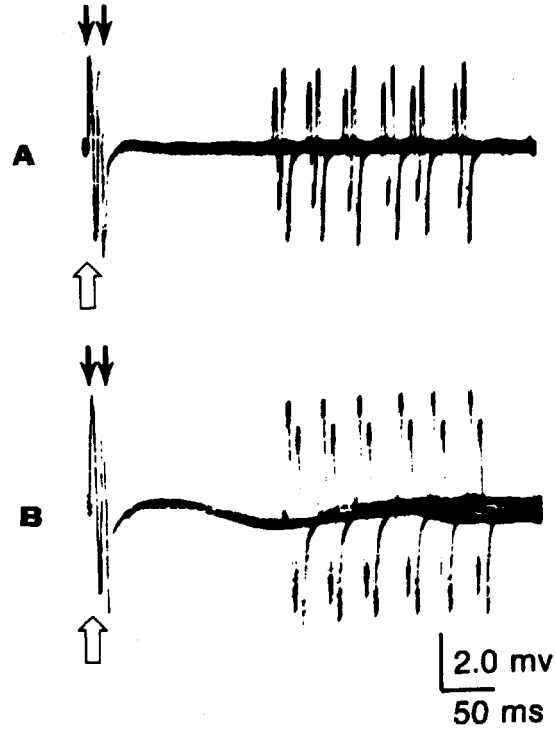

Figure 9–7. Composite pictures similar to those shown in Figures 9–5 and 9–6. Unlike the previous tracings, both conditioning and test stimuli consist of paired shocks with interstimulus intervals of 10 ms. The paired test stimuli followed the paired conditioning stimuli (*open arrow*) by the interval of 200–400 ms. The double-peaked conditioning responses appeared in the same spot of each tracing (*paired arrows*). The second peak of the pair, though displaced downward, had the same amplitude as the first. 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 each test response of the normal muscle, the maximal size of the first peak precluded any amplitude increase of the second peak.

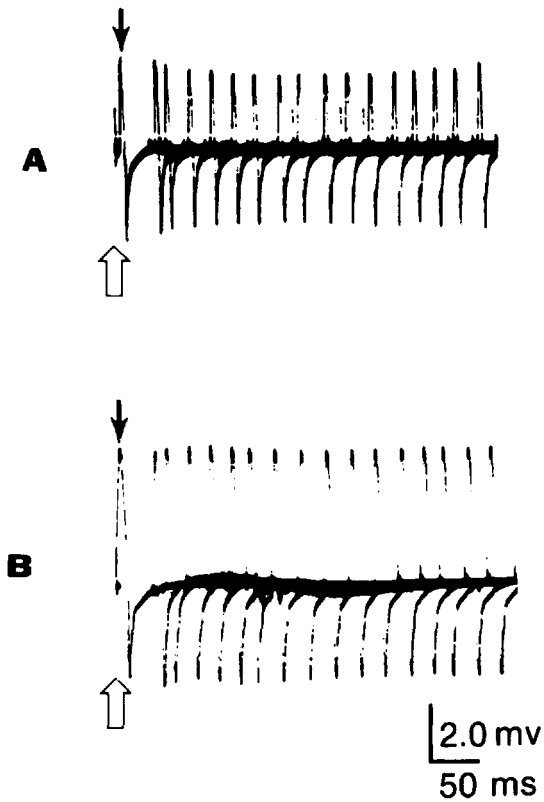

Figure 9–6. Composite pictures of 16 paired responses from the thenar muscles arranged in the same manner as in Figure 9–5. The interstimulus intervals of paired shocks ranged from 30 to 400 ms. The conditioning response of each pair appeared in the same spot of each tracing (*arrows pointing down*), 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**).

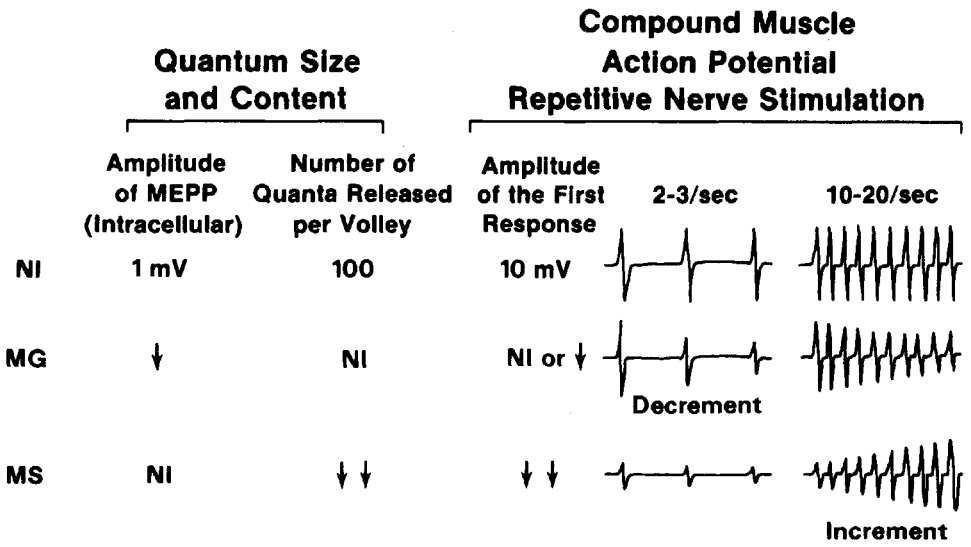

Figure 9–8. Typical changes in quantum size and quantum content as determined by intracellular recordings in myasthenia gravis (*MG*) and myasthenic syndrome (*MS*). The compound muscle action potential show a decrement to repetitive nerve stimulation with dropout of individual muscle fibers and an increment with recruitment of additional fibers.

myasthenia gravis (Fig. 9–7). At a slower rate separated by more than 200 ms, the second EPP diminishes because calcium no longer accumulates to compensate for depletion of available ACh stores. Limited release of ACh by the first stimulus, however, may preclude major decremental muscle responses in most patients.

Defective release of ACh also underlines the electrophysiologic abnormality in botulism. With paired stimuli, summation of the EPPs 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 100–200 ms. As expected, paired shocks of longer intervals usually cause depression of the second response, though not as consistently as in myasthenia gravis.

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.[25]

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Chapter 10

TECHNIQUES OF REPETITIVE STIMULATION

1 INTRODUCTION

Nerve stimulation techniques as tests for neuromuscular transmission began with Jolly (1895),[43] who applied faradic current repeatedly at short intervals. 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 during the faradization. Faradic current 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. His equipment consisted of a double-coil stimulator capable of eliciting only submaximal responses and a mechanical, rather than electrical, recorder.

The use of supermaximal 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[37] noted that in myasthenia a single muscle response induced a prolonged depression, during which a second maximal motor nerve stimulus excited a reduced number of muscle fibers, and that a train of impulses resulted in a progressive decline in amplitude of compound muscle potential. Later studies have established optimal frequency of stimulation, proper control of temperature, appropriate selection of muscles, and various activation procedures to enhance an equivocal neuromuscular block.[25]

Microelectrode studies provide direct recording of end-plate 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, or repetitive stimulation at fast and slow rates.[22,51,85,96] Transmission defects affect a variety of disease states, such as myasthenia gravis, myasthenic syndromes, botulism, amyotrophic lateral sclerosis, poliomyelitis, and multiple sclerosis. This chapter deals with the physiologic techniques for elucidating decremental or incremental responses in the differential diagnosis of clinical disorders (see also Chapter 27).

2 METHODS AND TECHNICAL FACTORS

Belly-Tendon Recording

Belly-tendon recording consists of stimulating the nerve with supramaximal intensity and recording the muscle action potential with the active electrode (G_1) placed over the motor point and the reference electrode (G_2) 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 muscle fibers activated. The magnitude of the unit discharge from individual muscle fibers also alters the size of the compound muscle potential, especially in myogenic disorders. In clinical studies, measurement of the amplitude suffices in a train of responses that shows the same duration and waveform.

Movement-Induced Artifacts

Movement-related artifacts abound during repetitive stimulation of the nerve. The recording electrode may continuously slide away from the muscle belly, or the stimulating electrodes may gradually slip from the nerve, causing subthreshold activation. In either case, a progressively smaller amplitude of a train mimics a decremental response. Changes in limb position alter the shape of the volume conductor and the spatial relationship of muscle and recording electrodes, leading to a misleading alteration in amplitude of the recorded response (Fig. 10–1). Firm immobilization of the limb together with visual inspection of the contracting muscle under study minimizes the movement-induced variability.

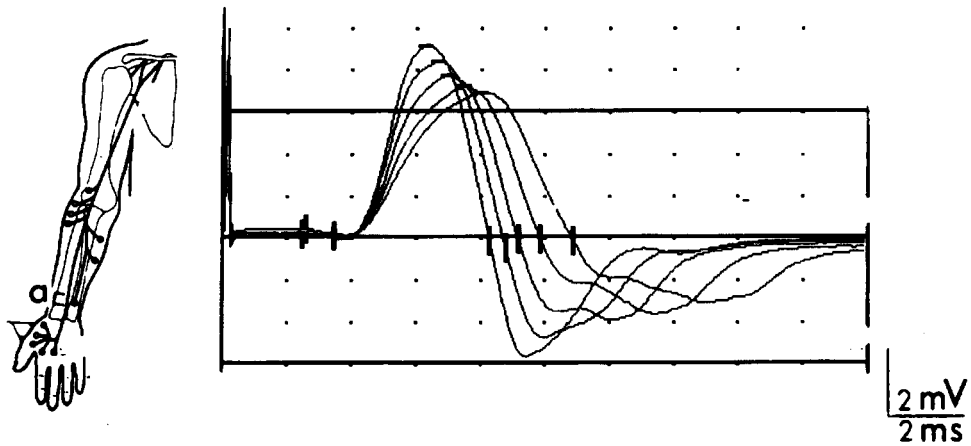

Figure 10–1. A train of responses recorded from the thenar muscle with stimuli delivered one per second to the median nerve at the wrist in a healthy subject. Intentional stepwise alteration in thumb position from abduction to adduction after each shock gave rise to a smooth reduction in amplitude with concomitant increase in duration of successive potentials. The area under the waveform showed relatively little change from the first to the fifth response.

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 closely 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 shape of the volume conductor. In our experience, even gradually changing waveforms represent artifacts if repetitive stimulation induces excessive movement. Repeated trials help establish the reproducibility of the finding, increasing the reliability of the results. Intertrial intervals should exceed 30 s to avoid the effect of subnormality of neuromuscular transmission that 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 myasthenic patients.[8,90] Similarly, electrophysiologic abnormalities of weak muscles may appear only after local warming. Physiologic mechanisms that account for the improved neuromuscular transmission with cooling include (*1*) facilitated transmitter replacement in the presynaptic terminal,[38,39] (*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,[23] (*3*) decreased hydrolysis of acetylcholine (ACh) by acetylcholinesterase, allowing sustained action of the transmitter already released from the axon terminal,[32,79,80] (*4*) increased postsynaptic receptor sensitivity to ACh,[36] and (*5*) reduced rate of removal of calcium ions (Ca^{2+}) from the nerve terminal after stimulation.[60]

Elevated body temperature up to 42° C causes no abnormality in healthy subjects,[80] but enhances the decrement on repetitive nerve stimulation in patients with myasthenia gravis.[81] Lowering the intramuscular temperature from 35° to 28° C increases the amplitude of the compound muscle action potential and enhances the force of the isometric twitch and tetanic contraction.[9] Patients with the myasthenic syndrome also experience distinct improvement after cooling,[72,99] as do those with amyotrophic lateral sclerosis,[24] botulism,[100] or tick paralysis.[19] Cooling reduces the decrement to repetitive nerve stimulation (Fig. 10–2). Paradoxically, brief stimulation at high rates may produce a decremental response in normal muscles cooled below 32° C.[52] Prior immersion of the limb in warm water or the

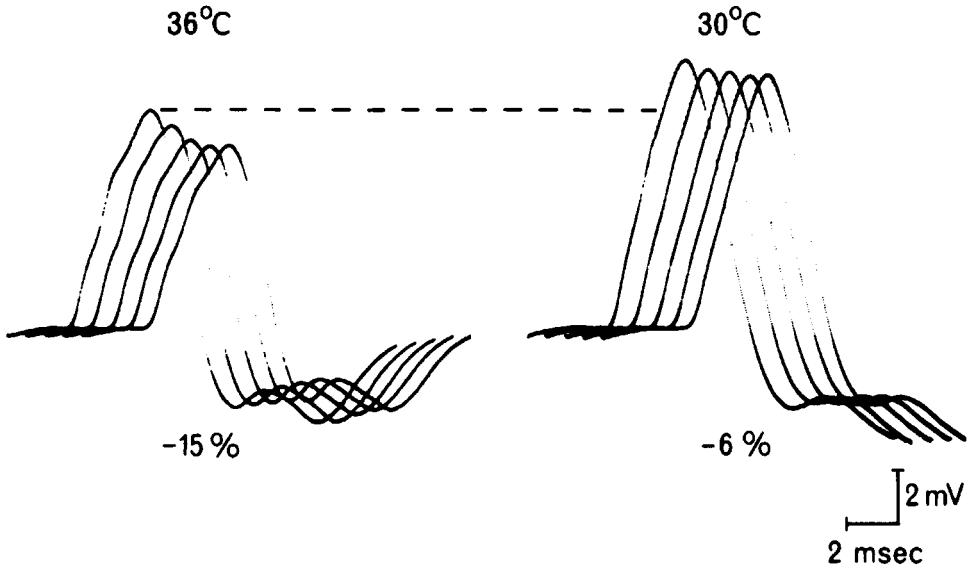

Figure 10–2. Decremental response of the hypothenar muscle with stimulation of the ulnar nerve at two per second in a patient with myasthenia gravis. On the *left*, stimulation at 36 °C and on the *right*, after cooling of the hand to 30 °C. Note the reduction in the decrement from 15 percent to 6 percent, and the increase in amplitude after cooling of the hand. [From Denys,[23] with permission.]

use of an infrared heat lamp helps maintain the recommended skin temperature over the tested muscle, above 34° C in most laboratories for diagnostic application. The effect of cholinesterase inhibitors also influences the results of repetitive stimulation. Administration of anticholinesterase 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 anticholinesterase drugs, a single nerve impulse may cause a repetitive muscle response, and repetitive stimuli at a high rate give rise to a decremental response (see Chapter 9–6).

3 COMMONLY USED NERVES AND MUSCLES

Distal Versus Proximal Muscle

Patients with myasthenia gravis rarely have a decremental response in clinically unaffected muscle. Thus, isolated bulbar or respiratory muscle weakness may pose a diagnostic challenge.[61] Weak proximal or facial muscles show a higher incidence of electrical abnormality than stronger distal muscles.[92] In a series of experiments, electrical and mechanical responses to repetitive stimuli revealed substantially greater decrement and posttetanic potentiation in the platysma than in the adductor pollicis.[48,49] Also, the trapezius has proven more sensitive than the distal hypothenar muscles in detecting abnormalities of neuromuscular transmission in amyotrophic lateral sclerosis.[45] Similarly, electrophysiologic findings in botulism may involve only weak muscles of the clinically affected limbs. In contrast, patients with the myasthenic syndrome usually have prominent abnormalities not only in the proximal muscles but also in distal muscles, albeit less severely.[13]

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, studies of the distal musculature provide technically more reliable results than those of more proximal muscles in the limb or facial muscles.

Stimulation of the ulnar nerve at the elbow allows simultaneous recordings from one proximal muscle and three distal muscles: the flexor carpi ulnaris, abductor digiti quinti, first dorsal interosseous, and adductor pollicis.[26] A negative result with distal muscles should prompt examination of the proximal muscles, such as the deltoid, biceps, and upper trapezius. Stimulation of the brachial plexus at the supraclavicular fossa tends to activate many muscles simultaneously. In contrast, stimulation of the accessory nerve selectively excites the trapezius without contamination from other muscles.[59,87] Studies of the lower limb pose greater technical difficulty, yielding a wider normal range compared to the upper limb.[67] Wise choice of the nerve and muscle based on distribution of weakness increases test sensitivity.

Upper Limb and Shoulder Girdle

HYPOTHENAR MUSCLES

The ulnar nerve is stimulated at the wrist with G_1 placed over the belly of abductor digiti quinti and G_2 on the tendon. Binding the four fingers together with a bandage or Velcro strap prevents interference from movement. The use of a restraining metal bar also helps hold the hand flat, palm down, on the examining table. The patient exercises by abducting the fifth digit against the restraint.

THENAR MUSCLES

The median nerve is stimulated at the wrist with G_1 placed on the belly of the abductor pollicis brevis and G_2 placed 2 cm distally. The hand, held palm up by the restraining metal bar, lies flat on the board with the thumb in the adducted position. The patient exercises the muscle by abducting the thumb against the bar.

ANCONEUS

The distal branch of the radial nerve is stimulated 4 cm above the elbow on the line bisecting the line connecting the olecranon and lateral epicondyle, with G_1 placed 4 cm below the elbow on the same line. The patient upright in a chair holds on to the handle with the arm flexed approximately 130 degrees and exercises the muscle by extending the elbow.

BICEPS

The musculocutaneous nerve is stimulated at the axilla with G_1 on the belly of the biceps and G_2 over 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

The brachial plexus is stimulated at Erb's point with G_1 on the belly of the muscle and G_2 on 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 for self-restraint by the opposite hand, and exercises by abducting the arm against his own resistance. Weak or uncooperative patients do better with a Velcro strap applied firmly against the trunk holding the arm adducted at the side.

TRAPEZIUS

The spinal accessory nerve is stimulated along the posterior border of the sternocleidomastoid muscle, with G_1 on the upper trapezius muscle at the angle of neck and shoulder and G_2 over 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, shrugging the shoulders against his own resistance.

Lower Limb

ANTERIOR TIBIAL

The peroneal nerve is stimulated at the fibular head, with G_1 on the belly of the

muscle and G_2 a few centimeters distally. The patient sits in a chair with the thigh restrained firmly by Velcro straps and exercises by dorsiflexing the foot held on a restraining foot board.

QUADRICEPS

The femoral nerve is stimulated at the groin, just lateral to the femoral artery, with G_1 placed on the rectus femoris and G_2 on 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 by a Velcro strap and exercise by lifting the foot off the bed.

Face

ORBICULARIS OCULI, ORBICULARIS ORIS, AND NASALIS

A branch of the facial nerve is stimulated in front of the ear as distally as technically feasible. This usually allows nearly selective recording from the target muscle with G_1 placed on its belly and G_2 on the opposite side or on the bridge of the nose (see Figs. 1–3 and 17–2). The patient, lying supine, exercises by contracting the muscle as vigorously as possible without the benefit of a restraining device to immobilize facial muscles.

4 RECOVERY CURVES BY PAIRED STIMULATION

Short Interstimulus Intervals

Paired stimuli applied at various intervals reveal the time course of recovery of neuromuscular transmission (see Chapter 9–6). 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. 9–4). The second potential then progressively recovers, with some overlap of the two responses at intervals of less than 15 ms.

In typical cases of myasthenia gravis, the first stimulus elicits a maximal or near-maximal muscle response. The recovery curve also follows a normal pattern for short interstimulus intervals up to 15 ms. The curve deviates from normal in the Lambert-Eaton myasthenic syndrome, where the first stimulus elicits a submaximal response; a 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 represents recruitment, based on summation of two end-plate potentials (EPPs), of those fibers activated only subliminally by the first stimulus. Most patients with botulism (Fig. 10–3)[17] and, occasionally patients

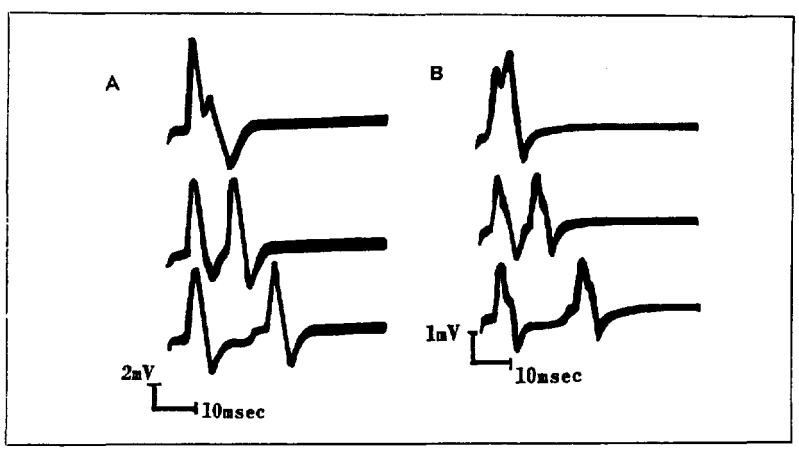

Figure 10–3. The effect of paired shocks given at interstimulus intervals of 2.5 ms (*top*), 15 ms (*middle*), and 25 ms (*bottom*). On the *top tracings*, the reduced test response in a healthy subject (**A**) indicates the effect of the refractory period, whereas the increased test response in a patient with botulism (**B**) suggests summation of two closely elicited end-plate potentials. [From Cherington,[15] with permission.]

with myasthenia gravis who have less than maximal initial responses also show the same phenomenon.

Long Interstimulus Intervals

Two EPPs no longer summate at interstimulus intervals exceeding 15 ms. Potentiation of the second response here represents true facilitation, resulting from an increased number of quanta liberated by the second stimulus. Despite the release of a greater amount of acetylcholine (ACh), the second muscle potential normally shows no increment from the already maximal first response. Most patients with myasthenia gravis or botulism also have minimal change at this interstimulus range. In contrast, patients with myasthenic syndrome show an increment at interstimulus intervals ranging from 15 to 100 ms as one of the most characteristic electrophysiologic features.

The decremental response in myasthenia gravis 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. 9–6). At shorter intervals, concomitant facilitation attributable to the electrosecretory mechanism obscures the depression. The response slowly returns to the baseline in about 10 s. The results of paired stimuli predict that a train of stimuli produces the maximal decrement at the rate of 2–3 Hz.[25]

5 DECREMENTAL RESPONSE AT SLOW RATES OF STIMULATION

Normal Muscles

Repetitive stimulation at a rate of 1–5 Hz depletes the immediately available acetylcholine (ACh) store, without superimposed facilitation from neurosecretory mechanisms (see Fig. 9–8). At slow rates of stimulation, movement-related artifacts are minimal 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 geometry of the volume conductor, which in turn affects the waveform of the successive responses.

Random or irregular variations in amplitude or waveform suggest artifacts. Occasionally, inadvertent movement may cause smooth, reproducible changes erroneously suggesting abnormality of neuromuscular transmission. Even when the amplitude measures show a deceptive change, careful evaluation of the waveform and close visual inspection of the contracting muscle usually disclose the source of artifacts. Most modern equipment automatically calculates the percentage reduction for the smallest of the initial five to seven responses, compared with the first in the same train. Accepting the computed results without verification of the waveform may lead to an erroneous conclusion. In normal muscles, decrement at stimulation of 2–3 Hz, if present, does not exceed 5–8 percent.[91] 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 myasthenia gravis, 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. 10–4). 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 percent, especially after several seconds of repetitive stimulation. More characteristically, continued stimulation induces a long, slow decline after a transient increment.[42] To avoid a false-positive result, most electromyographers use a conservative criterion of abnormality: A reprducible decrement of 10 percent or more between the first response and the smallest of the next four to six responses.[40] In

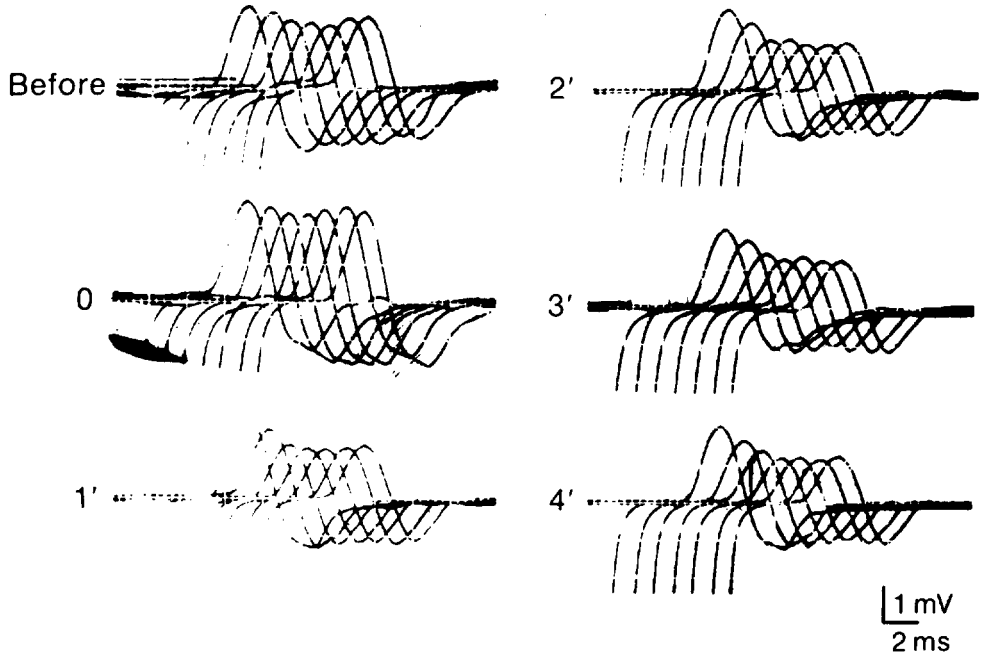

Figure 10–4. Thenar muscle potentials elicited by a train of stimuli of three per second to the median nerve before and after 1 minute of exercise in a patient with generalized myasthenia gravis. Amplitude comparison between the first and fifth responses revealed a decrement of 25 percent at rest, 12 percent immediately after exercise, and 50 percent 4 minutes later.

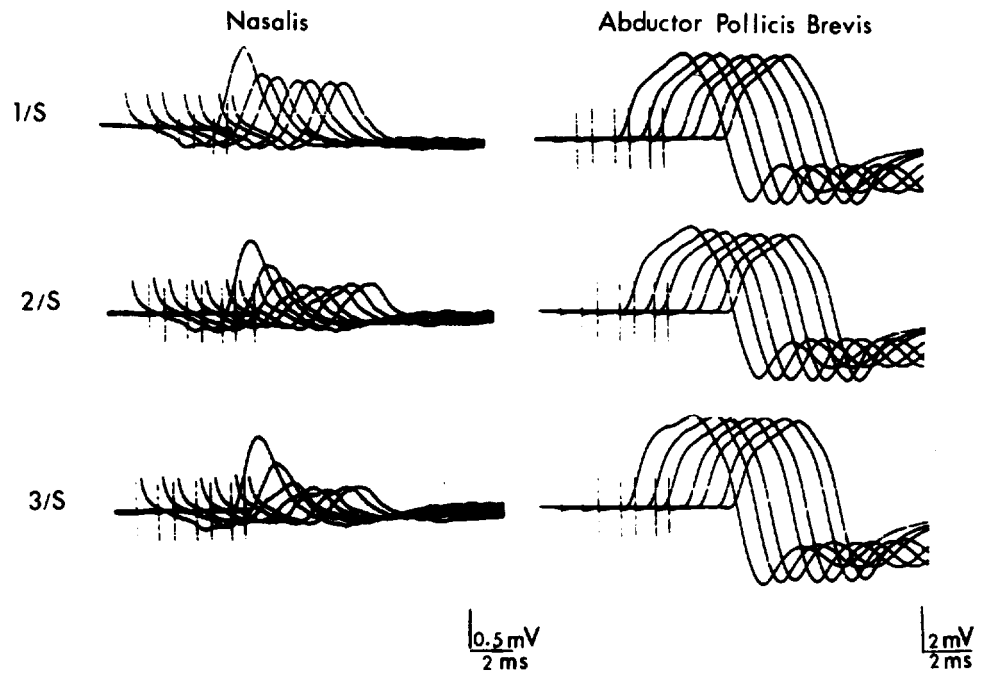

Figure 10–5. A 25-year-old woman with double vision of $1^1/_2$ months duration. A train of shocks of one, two, and three per second to the median nerve revealed no detectable abnormalities in the abductor pollicis brevis. Stimulation of the facial nerve elicited decrementing responses in the nasalis. Note greater change within the train as the rate of stimulation increased from one to three per second. [From Kimura,[46] with permission.]

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 myasthenic weakness. In particular, a negative result in the distal limb muscles by no means precludes electrical abnormalities detectable in the proximal or facial musculature (Fig. 10–5).

The administration of edrophonium (Tensilon) or neostigmine (Prostigmin) helps further delineate the characteristics of defective neuromuscular transmission. These agents potentiate the action of ACh by blocking acetylcholinesterase (AChE) in patients with postjunctional abnormalities. Therefore, a partial or complete reversal of the decrement by anticholinesterase agents tends to confirm the diagnosis of myasthenia gravis.

Other Neuromuscular Disorders

A train of stimuli at a slow rate causes decrementing responses not only in myasthenia gravis but also in a number of other conditions with reduced margins of safety. These include the Lambert-Eaton myasthenic syndrome (Figs. 10–6 and 10–7), congenital myasthenic syndromes, botulism, multiple sclerosis,[4,30,45,66] motor neuron disease, and regenerating nerve.[33] A partially curarized muscle will develop a similar decrement to a train of stimuli. In the patient with the myasthenic syndrome 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.

In depolarizing block seen in slow-channel congenital myasthenic syndrome or end-plate AChE deficiency syndrome, as in organophosphate poisoning,[5,7] markedly prolonged end-plate potential remains excitatory beyond the refractory period of neuromuscular junction. Thus, single stimuli of the motor nerve typically elicit more than one compound muscle action potential, an initial main response followed by one or more smaller recurrent responses, which appear at 3–7 ms inter-

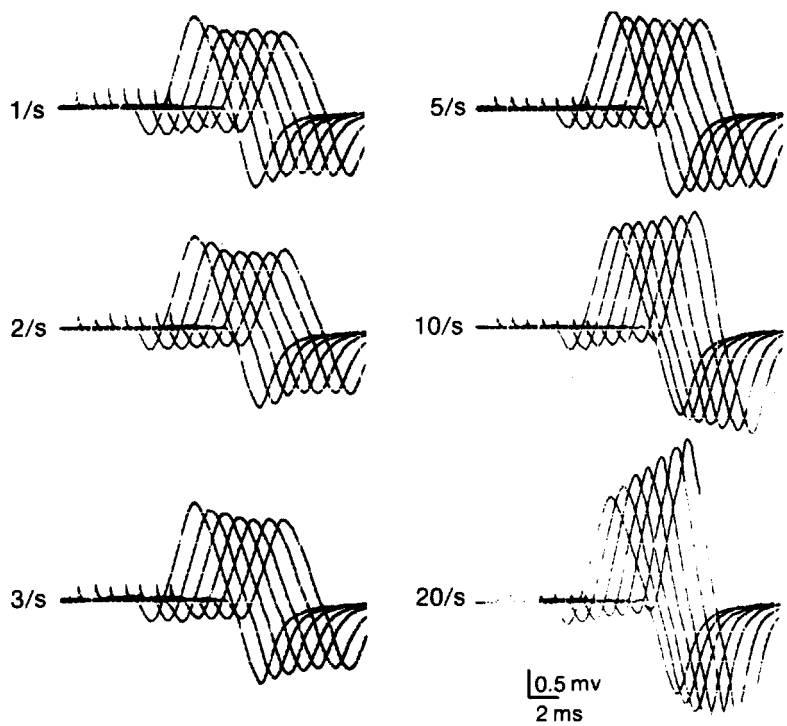

Figure 10–6. Thenar muscle potential elicited by a train of stimuli 1 through 20 per second to the median nerve in a patient with myasthenic syndrome. Note decremental responses to slow rates of stimulation up to five per second and incremental responses to faster rates of stimulation at 10 per second and to a much greater degree at 20 per second.

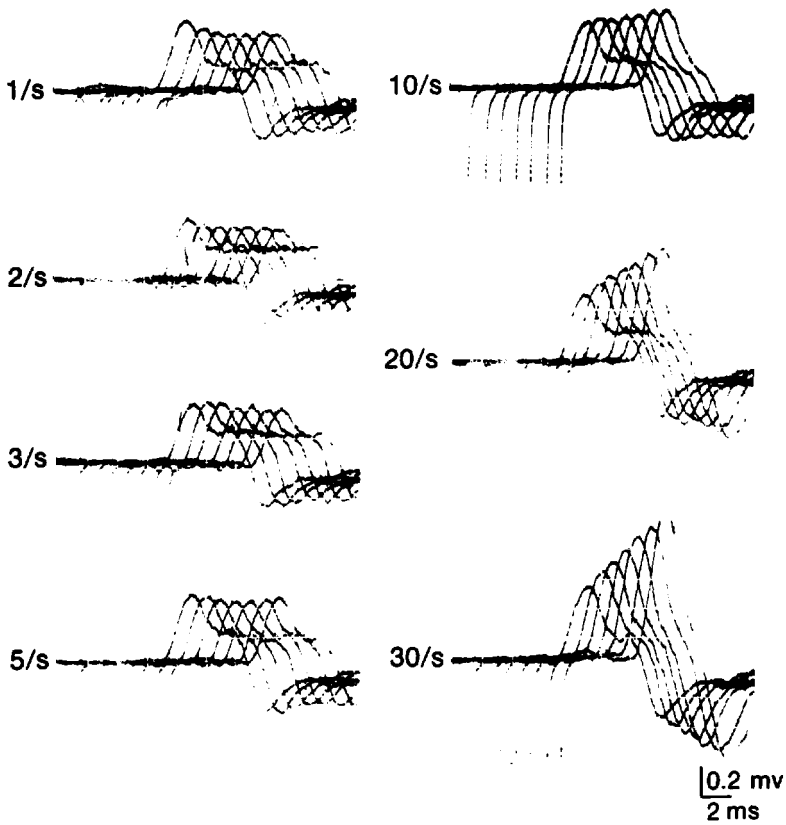

Figure 10–7. A repeat study in the same patient as in Figure 10–6 using the same recording arrangements. Note further diminution in amplitude of the compound muscle action potentials compared with the earlier study, slight decrement at slow rates of stimulation up to five per second, and progressively more prominent increment at faster rates of 10–30 per second.

vals.[34,98] With repetitive stimulation both responses show a rate-dependent decrement, although the recurrent potentials diminish more rapidly and disappear after brief exercise (Fig. 10–8). Quinidine sulfate therapy reverses this abnormality concomitant with clinical improvement.[35] A low dose of pancuronium, an ACh receptor antagonist, repairs the decrement seen in organophosphate intoxication, countering prolonged depolarization at the end-plate (Fig. 10–9).[6]

6 INCREMENTAL RESPONSE AT FAST RATES OF STIMULATION

Normal Muscles

Supramaximal stimulation normally activates all muscle fibers innervated by the nerve. This precludes any increment in response to greater amounts of acetylcholine (ACh) released by subsequent stimuli. The recruitment of muscle fibers not activated by the first stimulus underlines the incremental tendency seen in the myasthenic syndrome, botulism, and, occasionally, myasthenia gravis. Muscles stimulated repetitively at a high rate tend to discharge with increased synchrony without recruitment of additional muscle fibers. The compound muscle action potential may then increase in amplitude, but not in area under the waveform, as implied by the term *pseudofacilitation.*

In normal adults, muscle action potentials remain stable during repetitive stimulation at a rate of up to 20–30 Hz.[70] 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. At such a fast rate, however, inherent movement artifacts render the measurement unreliable.

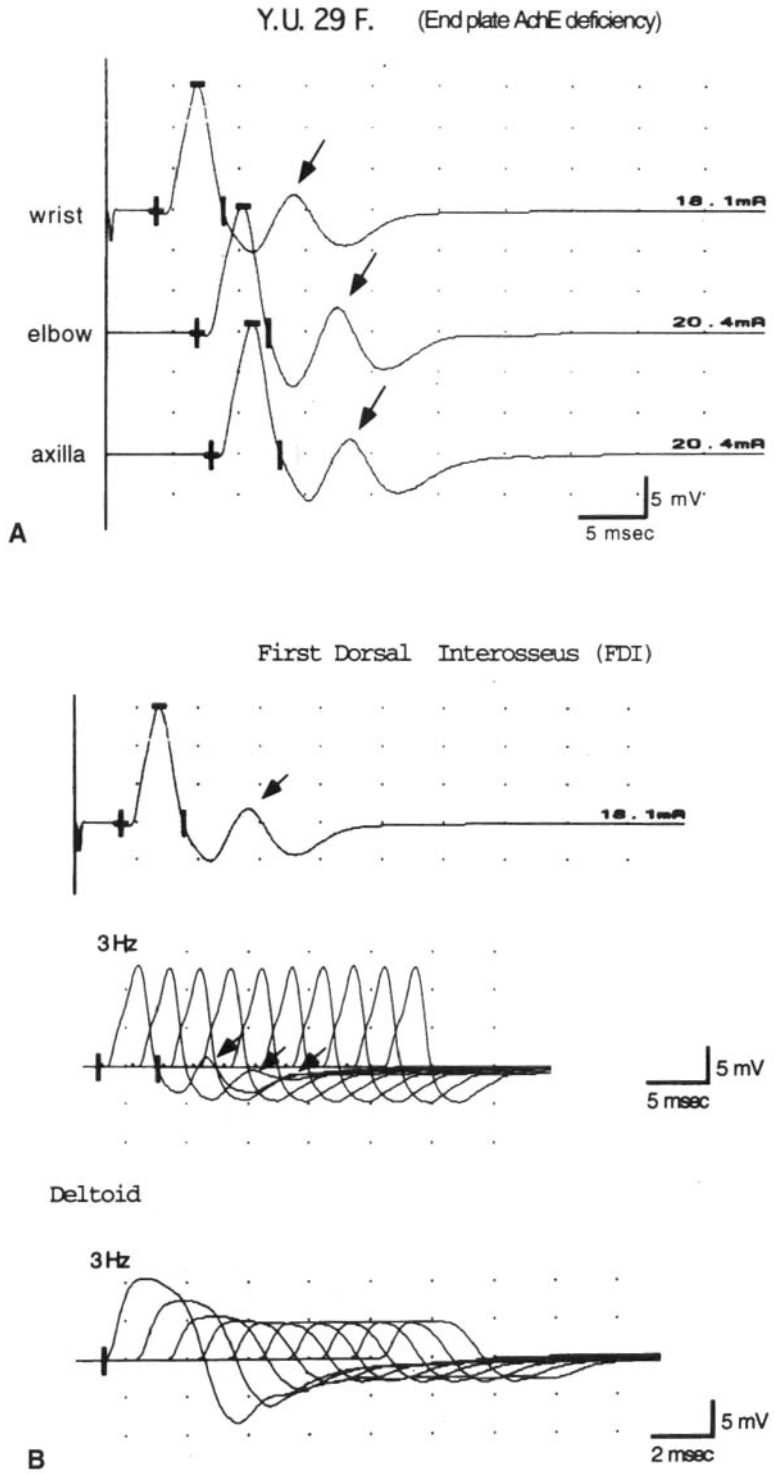

Figure 10–8. A 29-year-old woman with congenital myasthenic syndrome from acetylcholinesterase deficiency. Generalized weakness began in her childhood, peaking at the age of 15–16 years with increasing fatigability of truncal and proximal limb muscles and development of scoliosis on standing. Administration 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, M.D., Department of Neurology, Kyoto University School of Medicine.]

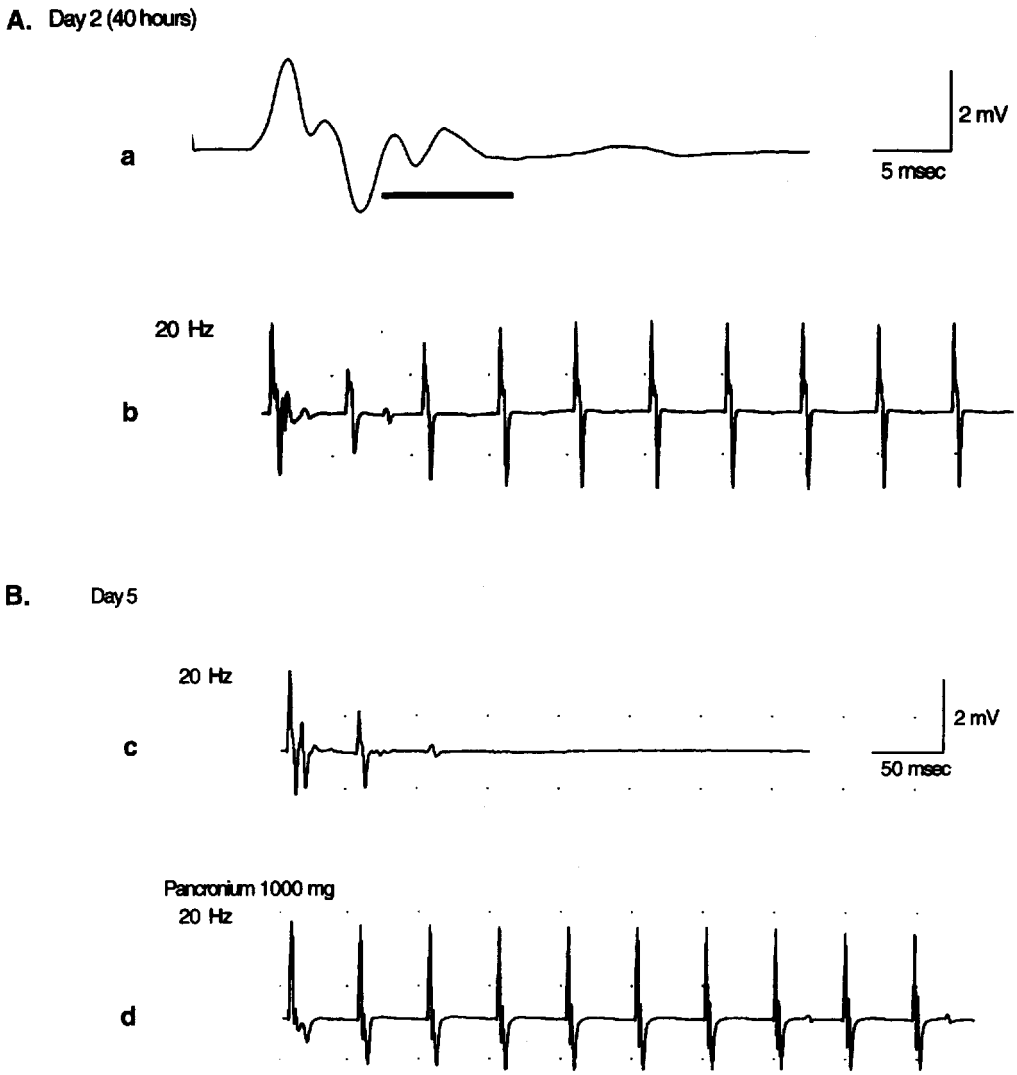

Figure 10–9. A 25-year-old woman with organophosphate intoxication after attempting suicide by ingestion of phenitrothion. Severe cholinergic crisis resulted in a respiratory failure necessitating mechanical ventilation for 70 hours. The patient remained comatose for a week, followed by gradual improvement; she returned 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, M.D., Department of Neurology, Kyoto University School of Medicine.]

Lambert-Eaton Myasthenic Syndrome and Botulism

In the myasthenic syndrome[29] single stimuli typically elicit a strikingly small compound muscle action potential (Fig. 10–10). The amplitude varies over a wide range among different subjects. Thus, a decrease by as much as 50 percent of the maximal response in some individuals may still remain above the lower limit of a population norm. 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.[56]

A train of stimulation at high rates, despite its theoretical interest,[69] has seen only limited clinical application. Because of the discomfort it causes, most patients tolerate the procedure poorly. Besides, voluntary contraction usually induces greater potentiation.[96] Repetitive stimulation given at 20–50 Hz induces a remarkable increment of successive muscle action potentials to a normal or near normal level (see Figs. 10–6 and 10–7). 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.[54] The electrophysiologic abnormalities often improve in parallel to the clinical course after the administration of guanidine or 3,4-diaminopyridine.[68,86]

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. 10–11). Incrementing responses, though smaller in

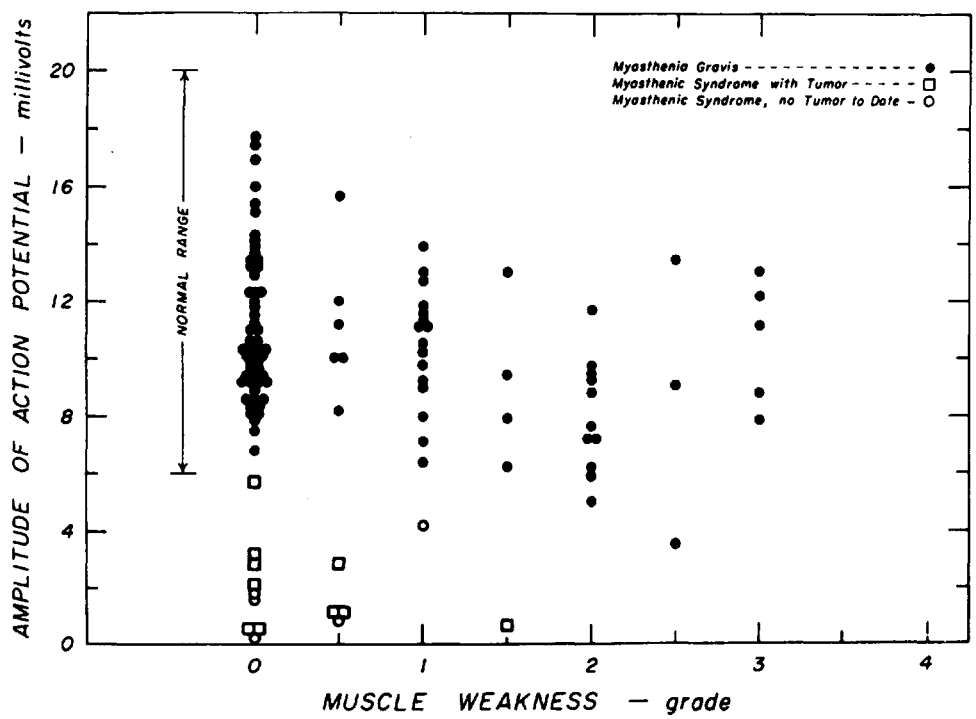

Figure 10–10. Relationship between clinical estimate of weakness and the amplitude of muscle action potential in patients with myasthenia gravis and myasthenic syndrome. The histogram plots the amplitude of the hypothenar muscle potential elicited by single maximal stimuli to the ulnar nerve. The scale on the abscissa denotes normal strength (0), 75 percent (1), 50 percent (2), 25 percent (3), and complete paralysis (4). [From Lambert, Rooke and Eaton,[55] with permission.]

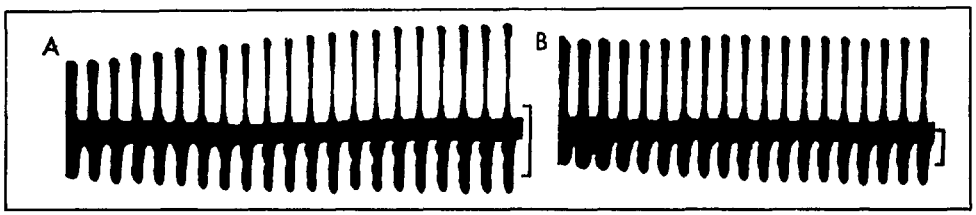

Figure 10–11. Muscle action potentials to a train of stimulation applied to the motor nerve at 50 per second in a patient with botulism. Note incremental responses when the patient received a 7 mg/kg daily dose of guanidine (**A**) and electrophysiologic recovery after the dosage was increased to 35 mg/kg (**B**). Vertical calibration is 2 mV. [From Cherington,[15] with permission.]

range, resemble those found in the myasthenic syndrome.[62,89] Tetanic and posttetanic facilitation, the most characteristic abnormality of infantile botulism, persists for a number of minutes.[20,31,84]

Other Neuromuscular Disorders

An incremental response, though characteristic of the myasthenic syndrome and botulism, by no means excludes other disorders of the neuromuscular junction (see Chapter 27–6). Patients with myasthenia gravis not infrequently show such a pattern, either during a progressive phase of the disease or during steroid therapy.[21,63,88] In contrast to the marked potentiation in the myasthenic syndrome, however, changes rarely exceed the initial value by more than 40 percent at the end of 1 minute. Other disorders associated with depressed neuromuscular transmission and incremental tendency by a train of stimuli include antibiotic toxicity,[71] hypocalcemia, hypermagnesemiam,[11,94] and snake venom poisoning.[44] Again, a limited degree of potentiation seen in these conditions stands in sharp contrast to the multifold increase characteristic of the myasthenic syndrome.

7 EFFECT OF TETANIC CONTRACTION

Use of Prolonged Stimulation

A short train of several shocks at a slow rate suffices for routine evaluation of neuromuscular transmission. 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. 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 myasthenia gravis. This phenomenon, called a *positive staircase*, has no diagnostic specificity as a clinical test.[27,91] Whatever the purpose, clinicians must resort to a train of rapid stimulation judiciously to avoid inflicting unnecessary discomfort.

Tetany develops after electrical stimulation of a 20–30 s train 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 after voluntary or involuntary tetanic contraction consists of two phases: Posttetanic potentiation,[42] lasting for about 2 minutes, and posttetanic exhaustion,[25] lasting up to 15 minutes.

Posttetanic Potentiation

Tetanic contraction not only causes calcium (Ca^{2+}) to accumulate inside the axon but also mobilizes acetylcholine (ACh) vescicles from the main store. Subsequent nerve stimulation gives rise to a larger

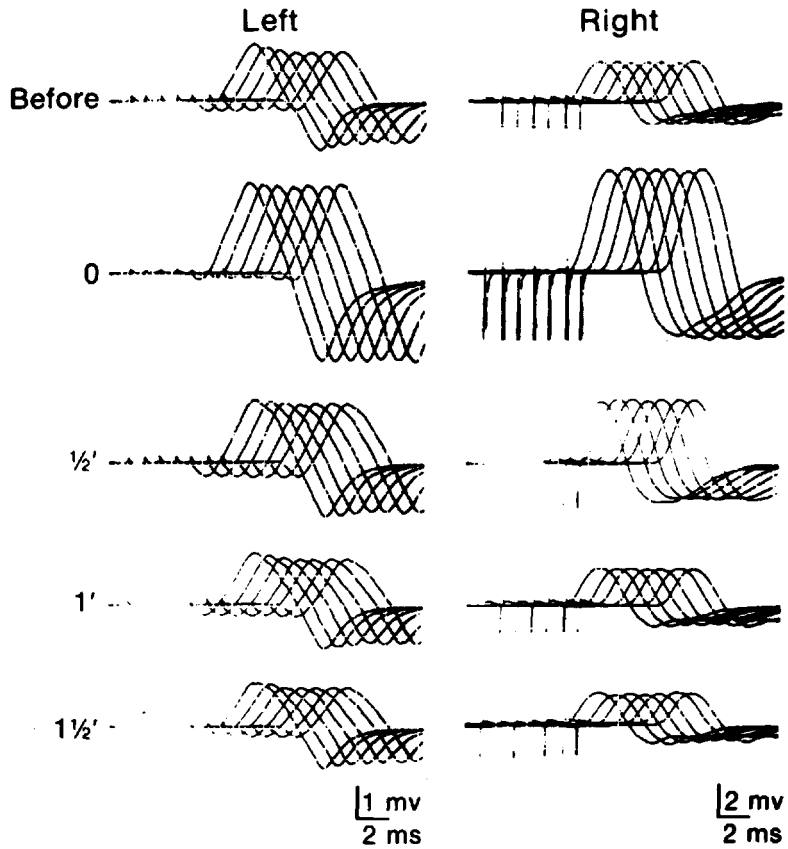

Figure 10–12. Thenar muscle potential elicited by a train of stimuli three per second to the median nerve before and after 10 s of exercise in a patient with the myasthenic syndrome. Note a posttetanic potentiation of 70 percent on the left and 160 percent on the right immediately after the exercise and a posttetanic exhaustion, $1^1/_2$ minutes later.

EPP, thus recruiting additional muscle fibers not previously activated in the Lambert-Eaton myasthenic syndrome or related disorders with defective release of ACh (Figs. 10–12 and 10–13). In physiologic experiments of single 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.[60]

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 exercise. A striking increase in amplitude, usually reaching a level more than twice the baseline value, indicates a presynaptic defect of neuromuscular transmission.[55] Posttetanic augmentation lasts about 20 s, showing less decay after cooling, reflecting slower removal of calcium ions from the nerve terminal.[60] Duration of exercise should not exceed 15 s, to minimize depletion of ACh during voluntary contraction. In general, a posttetanic potentiation greater than twice the preactivation response suggests the diagnosis of Lambert-Eaton syndrome. The magnitude of potentiation, however, varies considerably from one subject to another and during the course of the illness within the same patient (Fig. 10–14). A lesser degree of facilitation also implies a presynaptic disturbance seen not only in myasthenic syndrome but also in congenital myasthenic syndromes, botulism, and occasional cases of myasthenia gravis.

The use of a train of stimuli at 3 Hz instead of a single shock allows simultaneous evaluation of the decremental trends. The procedure consists of repeating the same train before and immediately after the exercise and then every 30 s thereafter for a few minutes. In this arrangement, posttetanic potentiation partially compensates for depletion of ACh during

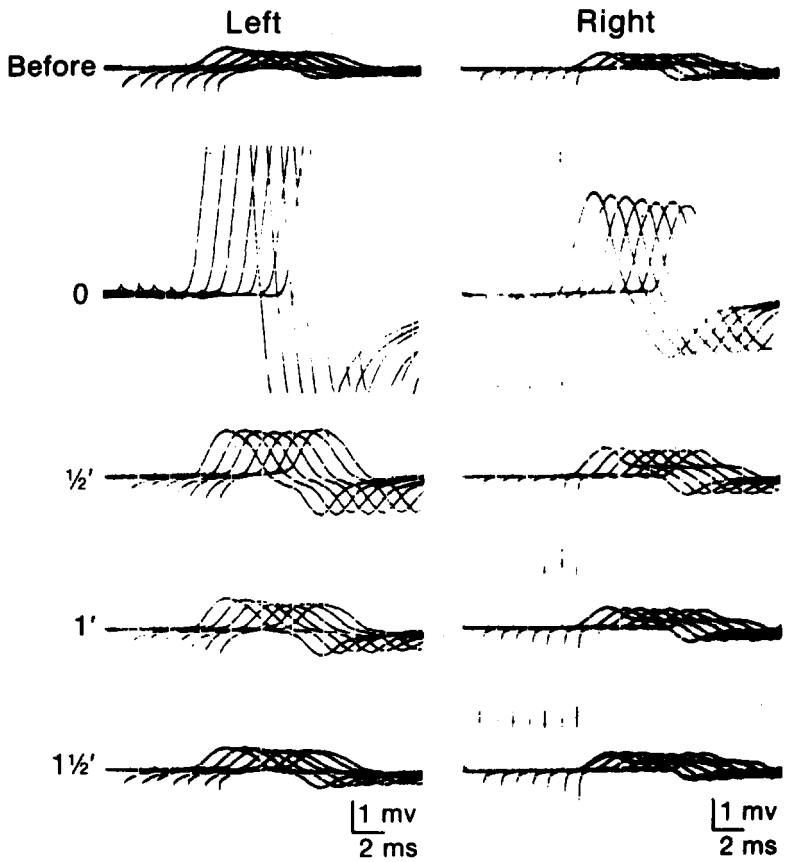

Figure 10–13. A repeat study in the same patient as in Figure 10–12 using the same recording arrangements. Compared with the earlier study, the patient had further diminution in amplitude of the compound muscle action potentials and a greater posttetanic potentiation on both sides.

each train, repairing the deficit caused by the slow rate of stimulation (see Fig. 10–4). Thus, the characteristic decrement seen within a train in myasthenia gravis tends to normalize immediately after the tetanic stimulation.

Posttetanic Exhaustion

Decreased excitability of the neuromuscular junction follows a transient potentiation in 2–4 minutes after exercise. 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 normal subjects 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,[47] however, the amplitude of the compound muscle action potential progressively declines at high rates of stimulation.

In myasthenia gravis, 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 (see Fig. 10–4). In the myasthenic syndrome, a reduced EPP after exercise results in further diminution of the originally small compound muscle action potential (see Figs. 10–12 and 10–13). Thus, the use of exercise increases the sensitivity of the nerve-stimulation technique as a test of neuromuscular transmission. In the evaluation of posttetanic exhaustion, a 1 minute period of voluntary contraction results in optimal depletion of the ACh store. In contrast, a shorter exercise, for a period ranging from 10 to 15 seconds, suffices for assessment of the posttetanic

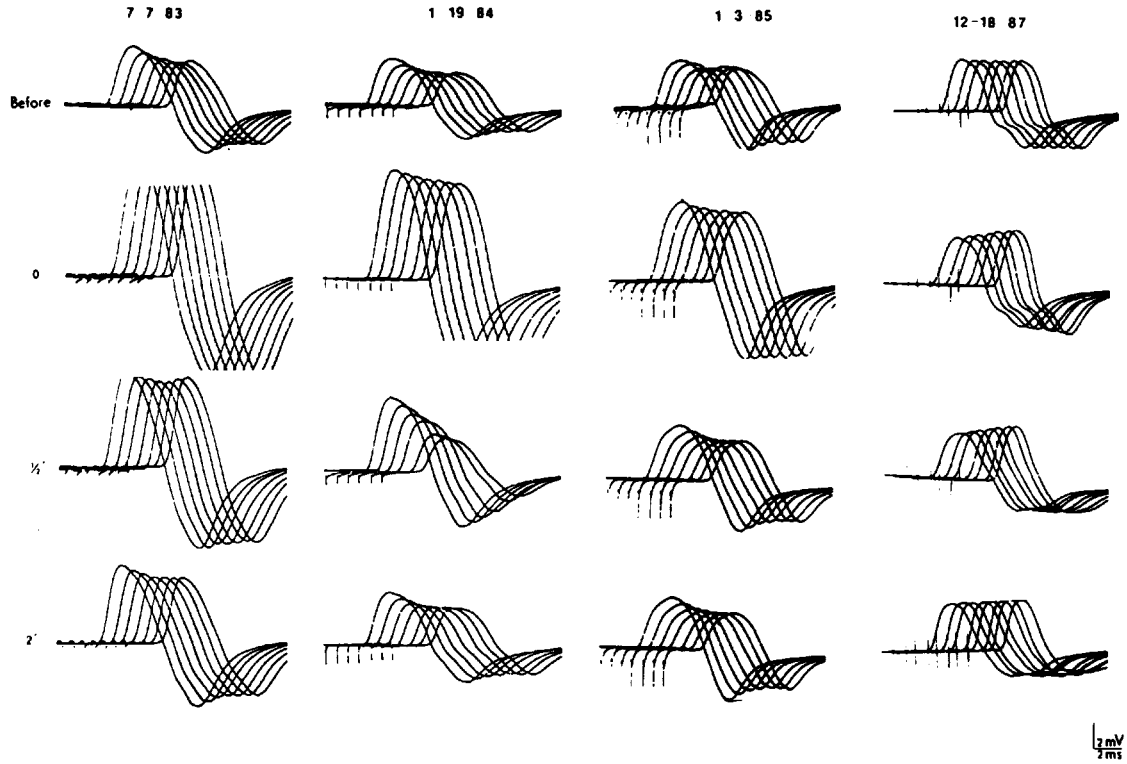

Figure 10–14. A 63-year-old woman with proximal weakness of all four extremities since October 1982. Thenar muscle potentials were elicited by stimuli applied to the median nerve at the wrist at three per second before and after 15 s of exercise. Notice the gradual reduction in the magnitude of posttetantic 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. [From Kimura,[46] with permission.]

potentiation to avoid excessive depletion of ACh, which would mask the expected change.

8 CHANGES IN MYOGENIC DISORDERS

A train of stimuli causes an apparent decrement of the compound muscle action potentials in a number of myogenic disorders, such as McArdle's disease, myotonia, paramyotonia congenita, and periodic paralysis, but not in proximal myotonic myopathy (see Chapter 27–6).[93]

Muscle Glycogenosis

In McArdle's disease and other disorders of muscle glycogenesis, painful, electrically silent muscle contracture develops after exercise (see Fig. 12–3). With rapid repetitive stimulation of a motor nerve, the amplitude of the compound muscle action potential progressively declines, eventually leading to the development of contracture.[10,75] Low-rate nerve stimulation during regional ischemia also gives rise to abnormal reduction of muscle response in patients with muscle glycogenoses as compared with control subjects.[57]

Myotonia

In myotonic muscles, repetitive nerve stimulation produces commonly but not invariably decrementing responses.[2,12,28,53,58] Unlike the responses in myasthenia gravis, a train fails to show a repair, or leveling off, after the fourth or fifth stimulus. In-

stead, 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 and the shorter the latent periods. The presence of clinical weakness also favors the possibility of finding prominent electrical decrement. The change occurs at a lower stimulation frequency in myotonia congenita than in myotonia dystrophica.

The decremental changes in myotonia may result from prolonged afterdepolarization, induced by accumulation of potassium (K^+) in the transverse tubules.[1] Direct stimulation of the muscle evokes decreasing response, suggesting an excitability change of the muscle, rather than the neuromuscular junction.[12] Direct stimulation of single muscle fibers at 10–20 Hz gives rise to a progressive decline of single muscle fiber action potential associated with either increasing or decreasing propagation velocity.[50,65,97] Intracellular recording of a myotonic discharge also shows a progressive decline in amplitude.[77] Myotonic bursts may render some of the muscle fibers refractory to subsequent stimuli. In contrast to muscles in myasthenia gravis, myotonic muscles show neither posttetanic potentiation nor exhaustion. Indeed, the amplitude of the muscle response is less than the baseline value immediately after exercise. The decremental tendency also worsens after exercise, gradually restoring the resting value in about two to three minutes.

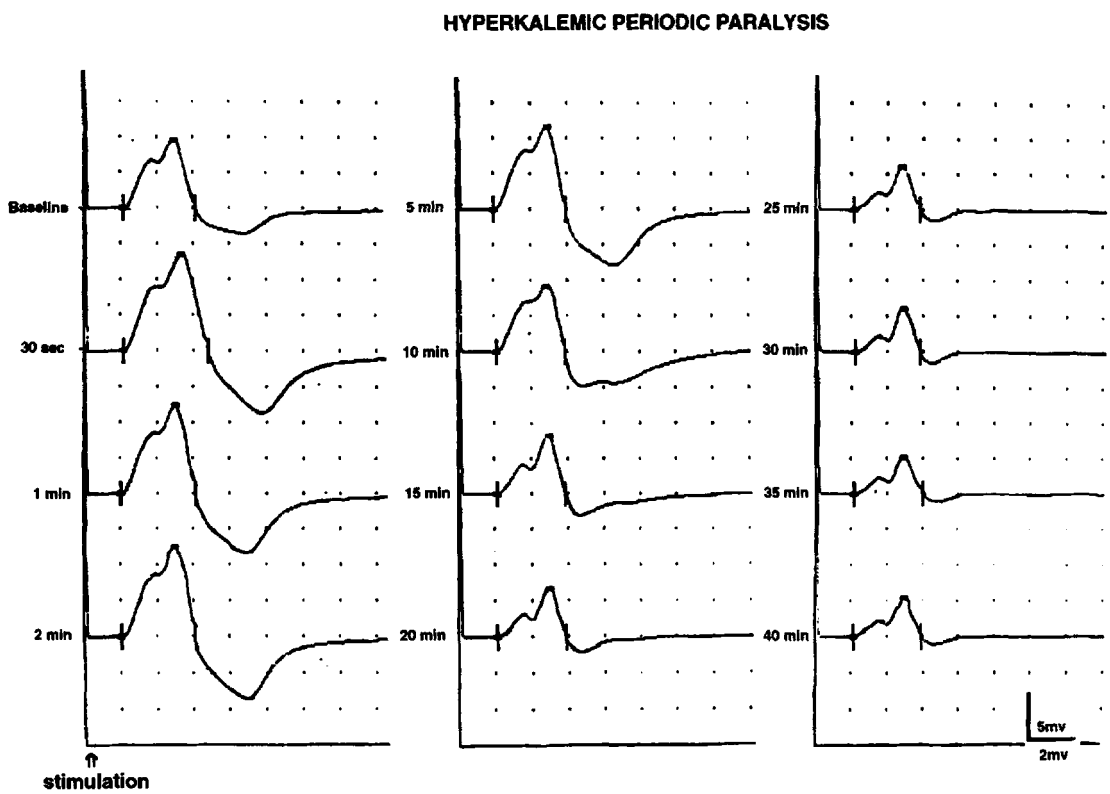

Figure 10–15. A 27-year-old woman with a 10-year history of hyperkalemic periodic paralysis occurring two or three times a year. Stimulation of the ulnar nerve at the wrist elicited a normal compound muscle action potential (CMAP) of the abductor digiti minimi (9.7 mV). After a 5 minute exercise alternating 20 s maximal contraction and 3 s rest, CMAP initially increased in amplitude, peaking at 30 s 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 CMAP amplitude of the target muscle. [Courtesy of Mark Ross, M.D., Department of Neurology, University of Kentucky.]

Paramyotonia Congenita and Periodic Paralysis

In paramyotonia congenita, 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.[41]

In vitro study has shown decreased excitability of the muscle membrane in hypokalemic periodic paralysis.[78] This abnormality probably underlies the decline of the compound muscle action potential amplitude elicited after prolonged exercise[3,64] and decrementing response on repetitive stimulation, associated with increasing muscle membrane refractoriness.[76] During a paralytic episode, a single stimulus elicits a small compound muscle action potential, 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, a compound muscle action potential 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. 10–15).

Proximal Myotonic Myopathy

In proximal myotonic myopathy, which clinically resembles myotonic dystrophy,[73,74,82,95] exercise tests of the distal muscle resulted in no diminution of response in one small series.[83] This finding stands in sharp contrast to the post-exercise depression seen in myotonic dystrophy (see Chapter 29–2).

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Chapter 11

ACTIVATION PROCEDURES AND OTHER METHODS

1 INTRODUCTION

Not all muscles show electrophysiologic abnormalities in diseases of the neuromuscular junction. Thus, conventional nerve stimulation techniques may fail to substantiate the clinical diagnosis. Imposing metabolic stress with regional ischemia or application of curare reduces the safety factor of the system, thus increasing the yields of detection of neuromuscular transmission abnormalities. Obviously, such activation maneuvers used to improve the diagnostic yields must avoid false-positive results.

A number of other electrodiagnostic methods supplement the technique of paired or repetitive electrical stimuli. Measuring the fatigability of a few accessible muscles serves to document a decremental tendency. Electromyographic analyses of motor unit potentials can also elucidate the stability of neuromuscular transmission. In particular, assessment of the extraocular muscles provides useful information in patients with ocular myasthenia. Single-fiber electromyography has added the calculation of jitter as a very sensitive and most useful measure of neuromuscular transmission. The in vitro analysis of miniature end-plate potentials (MEPPs) of intercostal muscles allows a direct quantitative measure of neuromuscular transmission.[6] This technique, however, is not feasible as a routine clinical test.

Other laboratory methods of diagnostic value include tonography and infrared optokinetic nystagmography for ocular myasthenia,[26] and stapedius reflex for facial weakness.[1] Electrophysiologic methods also help in quantitating edrophonium (Tensilon) and neostigmine (Prostigmin) tests. Measurement of serum antibodies against the muscle end plate detects immunologic abnormalities in most patients

with myasthenia gravis.[13,14] As a part of the clinical evaluation, pulmonary function tests provide useful objective criteria in documenting neuromuscular fatigue.[9]

2 PROVOCATIVE TECHNIQUES

Ischemic Test

A double-step test may increase the diagnostic sensitivity of nerve stimulation techniques in some patients with mild, generalized, or ocular myasthenia gravis.[3,5] The first step consists of continuous supramaximal stimulation of the ulnar nerve at 3 Hz for 4 minutes and recording the compound muscle action potential from the ulnar-innervated intrinsic hand muscles or the flexor carpi ulnaris in the forearm. Thereafter, a train of 3 Hz stimulation for several shocks at 30 s intervals determines the amount of decrement within each three-per-second trial. In cases of a negative or equivocal result, the second step consists of the same procedure under ischemia induced by a cuff inflated above arterial pressure proximal to the stimulation site.

The double-step test has helped elucidate different degrees of myasthenic involvement in the same patient. How much additional help this procedure provides in the early diagnosis of myasthenia gravis remains unclear.[19]

Regional Curare Test

The amount of acetylcholine (ACh) released with each nerve impulse normally produces an end-plate potential (EPP) that substantially exceeds the critical level for excitation of all the muscle fibers. This margin of safety protects the neuromuscular transmission with a latent deficit, rendering clinical and electrophysiologic evaluation difficult. Curare causes a nondepolarizing block by competing with ACh for the end-plate receptors. Its administration, therefore, reduces or eliminates the functional reserve and elucidates the defect of neuromuscular transmission that otherwise escapes detection.[7,8] In one series of 600 patients, the repetitive stimulation at the wrist and shoulder verified the diagnosis in 320 (53 percent).[11] In the remaining 280 patients, the regional curare test revealed abnormality in 72 (26 percent), including 52 (74 percent) of 70 patients with definite generalized myasthenia gravis, 13 (10 percent) of 136 patients with possible generalized myasthenia gravis, and 7 (14 percent) of 49 with ocular myasthenia.

The concentration of curare that reaches the muscle depends on diffusion through the volume of tissue, which probably varies from one case to the next. Thus, titrated dosages of curare do not always differentiate normal and pathologic responses.[10] Studies have revealed undue sensitivity to curare not only in myasthenia gravis[23] but also in amyotrophic lateral sclerosis[18] and muscular weakness after administration of antibiotics.[21] Therefore, an abnormal regional curare test indicates a defect in neuromuscular transmission but not necessarily myasthenia gravis. These uncertainties notwithstanding, the regional curare test, as a measure of last resort, supplements conventional nerve stimulation techniques in difficult cases. Patients with established myasthenia gravis should not undergo the procedure, to avoid the possible risk.

3 ELECTROMYOGRAPHY

In normal muscles, a motor unit firing repetitively under voluntary control gives rise to identical potentials in waveform and amplitude every time it discharges, as long as the needle electrode remains in the same location relative to the generator source. This does not hold in myasthenic muscles, because nerve impulses may not always depolarize all the individual muscle fibers to the critical level, as the result of a reduced margin of safety. Intermittent failure of some muscle fibers innervated by the same axon in response to successive nerve impulse causes amplitude variability of the recurring motor unit potentials. Blocking at the neuromuscular junction also explains diminished mean amplitude and duration of

motor unit potentials in myasthenic muscles.

Varying Motor Unit Potentials

Electromyography can assess the stability of isolated motor unit potentials by slowly advancing or retracting the needle for optimal display of the repetitive discharges. During minimal contraction of the muscle, the amplitude variability of an isolated potential, heard over the loudspeaker, alerts the examiner to search for unstable motor unit discharges. This method does not necessarily provide accurate quantitative assessment of neuromuscular transmission. The needle examination, applicable to any muscles, including those not tested by the stimulation technique, has the added advantage of not requiring muscle immobilization. For example, electromyography helps establish the diagnosis of ocular myasthenia (see Chapter 15–3).

The administration of anticholinesterase reverses the abnormalities of motor unit potentials in patients with myasthenia gravis. Thus, the injection of edrophonium (Tensilon) increases motor unit potentials recorded in the extensor digitorum communis by 30–130 percent in amplitude and 10–25 percent in duration.[20] In patients with ocular myasthenia gravis, a progressive decrease in amplitude and frequency during a prolonged period of voluntary contraction partially reverses after intravenous administration of edrophonium.[24]

Jitter and Blocking

The single-fiber recording has proven useful in early detection of neuromuscular disturbances as an important adjunct technique in the evaluation of myasthenia gravis.[27,28] As described in detail later (see Chapter 16–5) the method consists of recording a pair of single-fiber potentials simultaneously and measuring fluctuation of the neuromuscular transmission by the stability of the interpeak intervals. Either blocking or increased jitter characterizes neuromuscular disturbances.

The end plate potential (EPP) generated by voluntary contraction normally reaches the threshold in all muscle fibers. If the EPP falls short of this critical level at some neuromuscular junction, those muscle fibers fail to discharge. This blocking affecting only some fibers of a motor unit reduces the size of the motor unit potential on standard needle recordings. If an EPP barely reaches the necessary level, its rate of rise falls below the normal range, delaying, rather than blocking, the action potential. This abnormality escapes detection in conventional electromyography because, unlike blocking, delayed discharge of muscle fibers alters the motor unit potential very little.

On single-fiber recording of a pair of potentials, an intermittent delay of the action potential in either fiber increases the jitter or the variability of interpotential interval. This finding, as the first sign of neuromuscular instability, precedes blocking of transmission. Thus, increased jitter heralds variation of motor unit potentials or decrementing response to repetitive stimulation of the nerve. The practice of single-fiber electromyography has added a new dimension to the assessment of neuromuscular transmission, although it requires additional training. Most commercially available instruments have the capability of computerizing the method, which surpasses the manual calculation of the recorded responses.

4 OTHER TECHNIQUES

Minature End-Plate Potentials

Microelectrode recordings from single intercostal muscles provide the only means of measuring the size of minature endplate potentials (MEPP) and the number of the acetylcholine (ACh) quanta released per volley of nerve impulses. These determinations in turn can precisely characterize the abnormality of neuromuscular transmission. The method helps elucidate the specific pathophysiology underlying the deficits in production or mobilization of ACh. It also measures the sensitivity of the motor end plate by quantitative as-

sessment. This method, which depends on intercostal muscle biopsy, lies beyond the scope of routine clinical tests. In selected cases that pose a diagnostic challenge, however, it helps differentiate myasthenia gravis, the myasthenic syndrome, and other disorders involving the neuromuscular junction. A spectral analysis of endplate noise recorded by a conventional monopolar needle may help evaluate ACh receptor ion channel kinetics, but its clinical value waits further clarification.[15]

Tonography

Other techniques not ordinarily used in an electromyographic laboratory include edrophonium (Tensilon) tonography. The intraocular pressure results in part from contraction of the extraocular muscles. Thus, measurements of the pressure with an electronic tonometer reveal the effect of anticholinesterase on ocular motility. Some investigators advocate simultaneous recording of muscle action potentials with needle electrodes placed in the extraocular muscles.

In normal subjects, intraocular pressure may fall, on average, 1.6–1.8 mm Hg over a 1 minute period after an intravenous injection of edrophonium up to 10 mg.[4] Patients with decreased extraocular tone, as in ocular myasthenia, have low intraocular pressures. The administration of edrophonium produces changes in tonography coincident with a moderate increase in electrical activity in the extraocular muscles. A sudden increase in extraocular muscle tone alters intraocular pressure by a mean of 1.6 mm Hg within 35 s of injection. This phenomenon does not necessarily imply ocular myasthenia, being also seen, for example, in ocular myositis without other features of myasthenia gravis.[30] Intraocular pressure may also rise with the Valsalva maneuver. In this case, a control injection of saline can identify a false-positive result.

Stapedius Reflex

The stapedius muscles contract bilaterally in response to unilateral sound stimulation. This contraction in turn dampens the acoustic sensitivity of the middle ear and prevents hyperacusis. Thus, impedance audiometry can measure the function of the stapedius muscle. In normal subjects, a sound stimulus 70–100 dB above the hearing threshold elicits the stapedius reflex. It shows no decay during sustained contraction for up to 1 minute with stimulus frequencies of 250–1000 Hz.

In patients with myasthenia gravis, weakened stapedius muscles enhance transmission of sound in the 1–4 kHz range, resulting in hyperacusis. Here, only high-intensity sound can induce the acoustic reflex.[17] In addition, reflex contraction of the stapedius muscle shows a rapid decrement, analogous to the similar response of the limb muscles to repetitive electrical stimulation of the nerve.[1] The administration of edrophonium enhances the acoustic reflex, diminishes hyperacusis, and improves the decay of the stapedius reflex in response to repetitive sound stimulation. In some patients with myasthenia gravis, testing the stapedius reflex may reveal the only electrophysiologic abnormality.[29] In one study, stapedial reflex showed clear abnormalities in 84 percent of the patients with myasthenia gravis as compared with 56 percent by repetitive stimulation and 91 percent by single-fiber electromyography.[12]

Tests for Oculomotor Function

Electronystagmography provides quantitative measurements of amplitude, velocity, and frequency of optokinetic nystagmus to document fatigue of extraocular muscles. In patients with ocular myasthenia, edrophonium induces an increase in previously reduced oculomotor function.[2] In one series, electrooculography revealed neuromuscular fatigue in 50 percent of myasthenic patients.[4] The infrared reflection technique improves the sensitivity of the test with the use of numeric criteria in grading neuropharmacologic effects on oculomotor fatigue.[25] For example, velocity of saccade measured by this means increases after administration of edrophonium.[16] The Lancaster red-green

test also detects oculomotor fatigue, which improves after rest or with administration of edrophonium in patients with myasthenia gravis.[22]

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Part IV

ELECTROMYOGRAPHY

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Chapter 12

ANATOMY AND PHYSIOLOGY OF THE SKELETAL MUSCLE

1 INTRODUCTION

The skeletal muscles comprise the extrafusal and intrafusal fibers, which show distinct anatomic and physiologic features. The alpha motor neurons innervate the extrafusal fibers that occupy the bulk of muscle mass as contractile elements. The skeletal muscles usually have innervation zones with abundant motor end plates in the middle length of the muscle, though the detailed configurations vary among different subjects.[110] Many muscles in the limbs have multiple motor points[169] that in part dictate their contraction characteristics.[101] Mammalian skeletal muscles may consist of two or more separate subdivisions known as neuromuscular compartments, with unique anatomic and functional characteristics.[44,98,100,152] The gamma motor neurons subserve the stretch-sensitive in-

trafusal 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 motor neuron and all the muscle fibers innervated by its axon.

A nerve impulse initiates muscle contraction in two distinct steps: neuromuscular transmission and electromechanical coupling (see Chapter 9–3 and 9–4). Acetylcholine (ACh), released at the neuromuscular junction, depolarizes the end-plate 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 (Ca^{2+}) 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 present a description of the anatomy of the contractile elements, the mechanism underlying the shortening of the muscle fibers, and the anatomy and physiology of motor units.

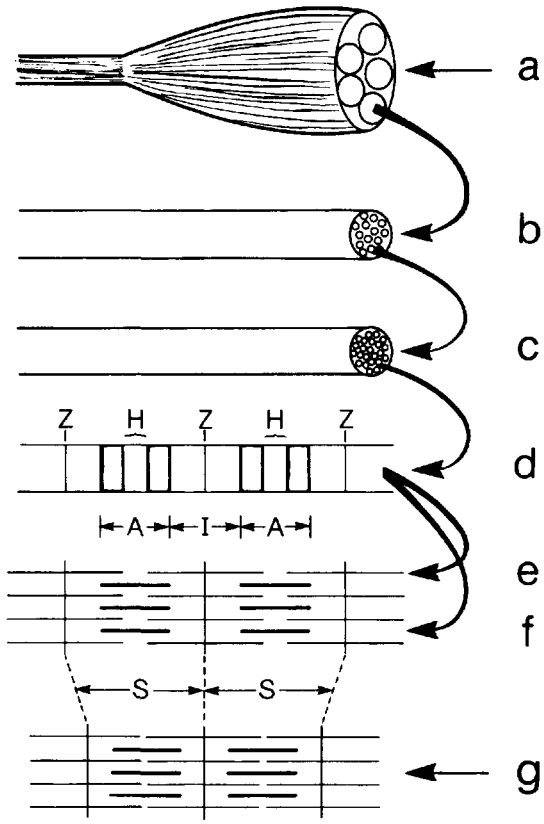

Figure 12–1. Anatomic composition of the skeletal muscle. The epimysium surrounds the entire muscle (*a*), which consists of many fascicles bound by perimysium (*b*). Individual muscle fibers (*c*) in the fascicle are covered by endomysium. Each muscle fiber contains many bundles of myofibrils (*d*), which in turn consist of thin (*e*) and thick (*f*) myofilaments. Thin actin filaments slide past thick myosin filaments during muscle contraction (*g*).

2 FUNCTIONAL ANATOMY

Gross Anatomy of Muscle

A connective tissue called epimysium covers the surface of each muscle. Inside this sheath are many fascicles bound by the coarse sleeves of the connective tissue perimysium (Fig. 12–1). Individual fascicles contain many muscle fibers, each surrounded by a delicate network of fine connective tissue, called endomysium. A muscle fiber, the smallest anatomic unit capable of contraction, averages in diameter 10 μm in a newborn and 50 μm in an adult.[22] 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.

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.[109] An ordinary electromyography instrument suf-

fices to measure muscle fiber conduction velocity using needle recording. With surface studies, computerized data analyses of frequency and time domain give rise to an average estimate from many motor units at different contraction levels.[89,196] 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.[132] The measurements with electric stimulation of single or a bundle of fibers, in general, yield lower values than those obtained during voluntary contraction.[4,58,201] When measuring electrically elicited contraction of single motor units, the higher the stimulation rate, the greater the velocity within certain ranges.[133]

During submaximal contractions, two opposing factors influence the average values of muscle fiber conduction velocity: Increase with recruitment of fresh motor units, and decrease with fatigue of already active motor units.[5] On average, the conduction velocity increases with the level of contraction force either measured with surface electrodes or needle electrode.[128,150] Muscle fiber conduction velocity also changes with length.[19,91] In one study using single fiber electromyography,[180] propagation velocity increased by 33 percent on shortening and decreased by 22 percent 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.

Compared to the nerve axons, muscle fibers conduct considerably more slowly, with an estimated rate of 3 to 5 m/s.[22,53,78,107,108,134,153,161,179,195] The propagation velocities increase with age, body height, and muscle diameter in the growing normal child.[106] Surface and needle recording reveal a reduced muscle fiber conduction velocity in myopathies,[201] although a needle study may show the change more clearly.[184] Peripheral vascular diseases[138] and high-dose methylprednisolone therapy[183] also alter surface myoelectric signals. Despite some encouraging results, muscle fiber conduction studies have found only limited clinical value as a diagnostic measure.

Myofibrils and Myofilaments

The semi-fluid 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. The structural subunit, called the sarcomere, extends between two adjacent Z lines. The center of the sarcomere contains the longitudinally oriented thick myosin myofilaments. 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 of only 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 are attached to each end of the elongated tropomyosin molecule, which, in turn, is intimately bound 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.[25]

Mechanism of Contraction

The mechanism of the sliding begins with the formation of calcium (Ca^{2+})-dependent bridges that link the actin and myosin filaments. At rest, tropomyosin physically blocks the formation of bridges between myosin and actin. The propagation of the action potential into the sarcoplasmic reticulum via the transverse tubules releases calcium from the terminal cistern of the longitudinal tubules. 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,

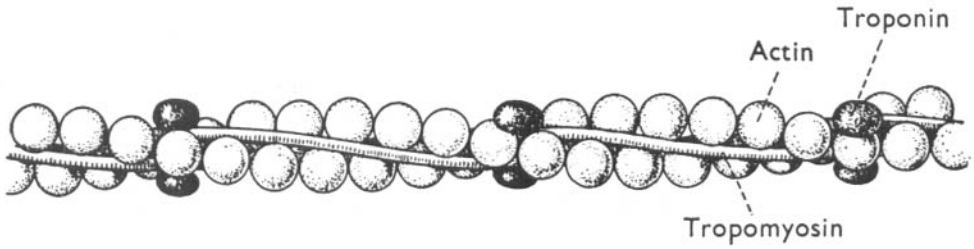

Figure 12–2. Fine structure of the thin actin filament with actin molecules attached to globe-shaped troponin and rod-shaped tropomyosin in an orderly arrangement. [From Ebashi, Endo, and Ohtsuki,[52] with permission.]

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. 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.

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. Muscle contractility depends in part on extracellular calcium concentration.[103,104] In McArdle disease, characterized by deficiency of muscle phosphorylase, this initial step of muscle relaxation does not occur, presumably because of an insufficient amount of ATP. 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.[156]

Although the degree of muscle contraction determines strength and endurance, the amount of force generated serves only partially as an index of motor skill. Functional alteration, for example, occurs with sarcopenia or loss of lean tissue with aging, and its metabolic and physiologic consequences.[51,154]

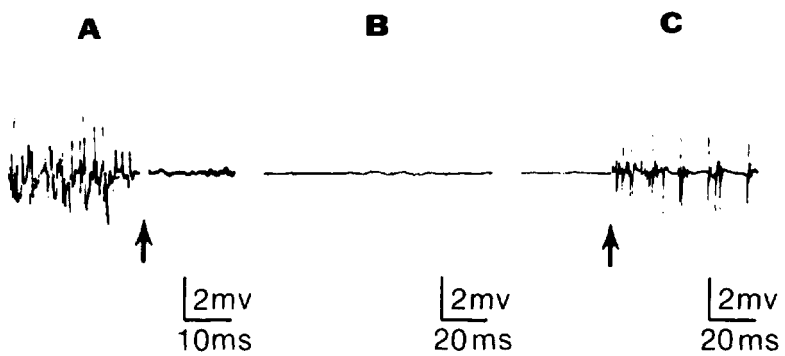

Figure 12–3. Contracture during ischemic exercise in a 66-year-old man with McArdle disease. With an inflated pressure tourniquet placed around the arm and a concentric needle electrode inserted into the flexor digitorum profundus, the patient exercised the forearm flexors. Contracture began 45 seconds 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, M.D., Mayo Clinic, Scottsdale.]

3 TYPES OF MUSCLE FIBERS

The subdivision of muscle fibers depends on their histologic and physiologic profiles. Important determining factors 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.[160] Table 12–1 summarizes the commonly used classification of muscle fibers into type I and type II according to histochemical reactions;[18,50,56] slow (S), fast resistant (FR), and fast fatiguing (FF), based on twitch and fatigue characteristics;[35] or slow oxidative (SO), fast oxidative glycolytic (FOG), and fast glycolytic (FG), by twitch and enzymatic properties.[141]

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 show the reverse reactivity.[50] Three subtypes of type II fibers, IIA, IIB, and IIC, emerge according to their ATPase reactions (Table 12–1) after preincubation at different pH values.[17,18,56] Type IIC fibers constitute fetal precursor cells, rarely seen in adult muscles.

The myosine ATPase content dictates the speed of contraction,[6] which forms the basis for the physiologic subdivision of muscle fibers. Thus, in general, physiologic data correlate the slow twitch fibers to histochemical type I, and fast twitch fibers to type II,[36,94] though exceptions abound. For example, histochemically mixed extensor digitorum longus of the rat contains only fast fibers;[41] slow soleus muscle of eels shows greater myosin ATPase activity than fast gastrocnemius muscle. Therefore, the intensity of histochemical ATPase reaction cannot serve as the sole criterion in distinguishing fast and slow twitch fibers.[37]

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.[137] Accompanying functional development includes a change of the fiber population with an increase of type 2 fibers from about 35 percent at the age of 5, to 50 percent at the age of 20, most likely by a transformation of type 1 to type 2 fibers.[95] Aging atrophy or sarcopenia begins around age 25 and then accelerates,[51,96,154] mainly reflecting a loss of

Table 12–1 Types of Muscle Fibers

Commonly used designations			
Fiber types[18]	Type I	Type II A	Type II B
Twitch and fatigue characteristics[35]	Slow (S)	Fast resistant (FR)	Fast fatigue (FF)
Twitch and enzymatic properties[141]	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 end-plate potentials	Low	High	High

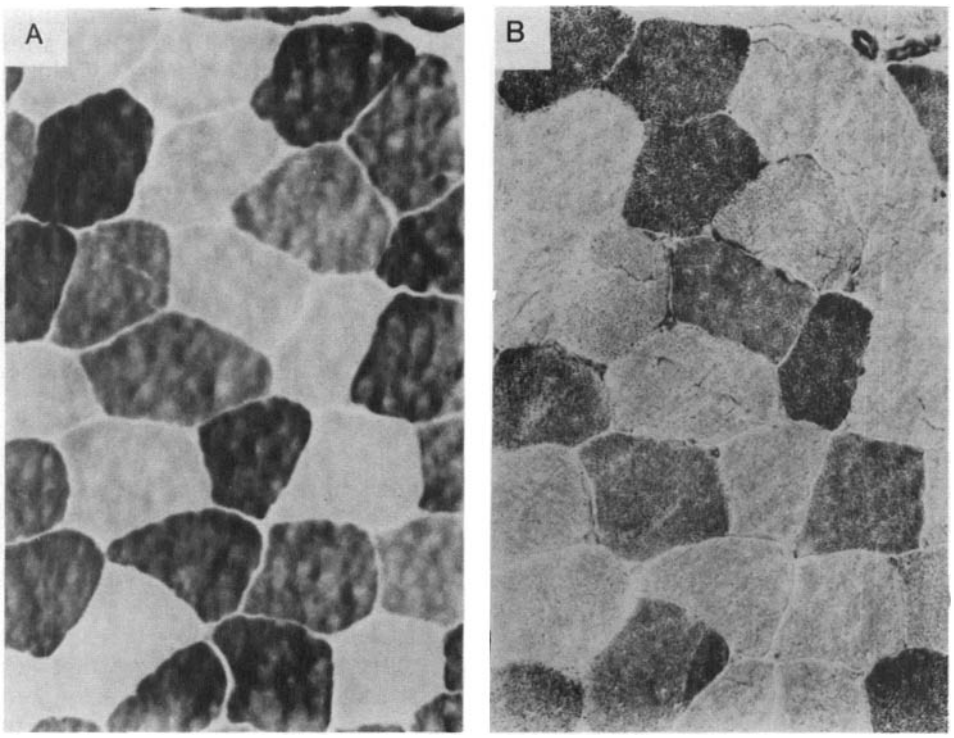

Figure 12–4. Cross-section of a normal skeletal muscle stained with adenosine triphosphatase (ATPase) at pH 9.4 in **A**, and with nicotinamide adenine dinucleotide dehydrogenase (NADH) in **B**. The darker fibers represent type II in **A** and type I in **B**. [Courtesy of Linda Ansbacher, M.D., and Michael N. Hart, M.D., Department of Pathology, University of Iowa Hospitals and Clinics.]

fibers of all types, and to a lesser extent, reduction in fiber size mostly of type 2 fibers.

Fast and Slow Twitch Fibers

Muscle fibers differ in their contraction time, force-velocity curves, and rates of decay.[141] 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.[35] These findings suggest that glycolytic capacity generally relates to twitch characteristics, and oxidative capability dictates fatigability. Intracellular recordings have shown that 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.[188] The slow twitch fibers have higher antioxidative capacity than the fast twitch fibers.[83] 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.[93]

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 humans because most human limb muscles consist of slow and fast twitch motor units in various combinations.[30] 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.[27] Slow oxidative fibers occupy 38 and 44 percent of superficial and deep areas in the vastus lateralis and 47 and 61 percent in the vastus medialis.[84] Further, fibers of the same types do not necessarily share the same contractile speed in different muscles.[147]

Effect of Muscle 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[9,159] without affecting the major gene expression in the uninjured parts of the fiber.[200] Transient loss of functional innervation has a permanent effect on the myosin composition.[81] After denervation, the pattern of phosphorylation in fast muscle changes to resemble that of slow muscle, a finding consistent with denervation-induced changes observed using other phenotypic markers.[118,131,184] Denervation usually causes irreversible muscle atrophy unless denervated muscles receive reinnervation promptly.[80] In one study, muscles grafted with nerve implants had a higher mass and generated twice the force compared with denervated muscle receiving only nerve implants without muscle graft.[8] Functional recovery also depends critically on the duration of denervation before nerve repair.[90]

The rate of stimulation dictates the contractile characteristics of muscle fibers in animals,[82,102,142,143,144,145,151,170,187] as well as in humans.[39] Brachial plexus palsy at birth alters isometric contraction time and half relaxation time of the affected muscles.[167] The finding suggests that denervation during infancy impairs normal development of muscle contractile properties. In patients with chronic neuromuscular diseases, normal muscle fiber histochemistry persists as long as motor neuron differentiation remains. In patients with long-term spastic hemiplegia, some motor units show greater fatigability and longer twitch contraction times than normal. Thus, the dynamic properties of the muscle seem to change even in upper motor neuron lesions.[198]

Alterations in histochemical properties may reflect the firing pattern and axonal conduction velocity of the motor neurons.[12] Athletes engaged in endurance training have a greater number of slow fibers,[63] whereas weight lifters have more fast fibers.[176] Exercise training alone, however, induces little change in basic muscle contractility in humans.[3,63,176] Hence, motor neuron 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[66] include effects of neurons on muscle in tissue cultures[199] and the inverse relationship of nerve length on the time interval before the development of muscle membrane changes after nerve section.[38] 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.[67,185] Reactive hypertrophy of the masticatory muscle, induced by increased workload, also accompanies progressive type I fiber predominance and type II fiber atrophy.[73]

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.[31,85,146,197] Such a relationship between the type of innervation and muscle activity also determines the mechanical characteristics of contraction in some fibers,[28] but not others.[190] For example, motor neurons innervating fast twitch muscles have shorter afterhyperpolarization than those supplying slow twitch muscles.[54] A study of the effect of cross-innervation in patients with muscle transfer for

facial palsies have shown considerably less plasticity than in animal models in the conversion of slow to fast twitch fibers.[74] Also, the minimal changes in the spatial distribution of fiber types following self-reinnervation in adults suggests a limited degree of conversion of muscle fibers to myosin heavy chain phenotype matching the motor neuron characteristics.[182]

Studies using inactivity with and without cross-reinnervation have shown that electrically silent motor neurons can influence type-related skeletal muscle properties.[148] Further, activity-dependent fiber-type modulation differs substantially among fibers in a relatively homogeneous muscle.[171] Thus, the driving forces for this regulation, though not yet elucidated, probably include not only the discharge pattern of the motor neuron but also the axoplasmic transplantation of trophic substances from the nerve to the muscle. Many other factors influence the twitch and other characteristics of muscle fibers. In one study,[20] capsaicin treatment, which selectively eliminated fibers belonging to the group III and IV muscle afferents,[43,192] 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.[65]

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.[57,86] 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

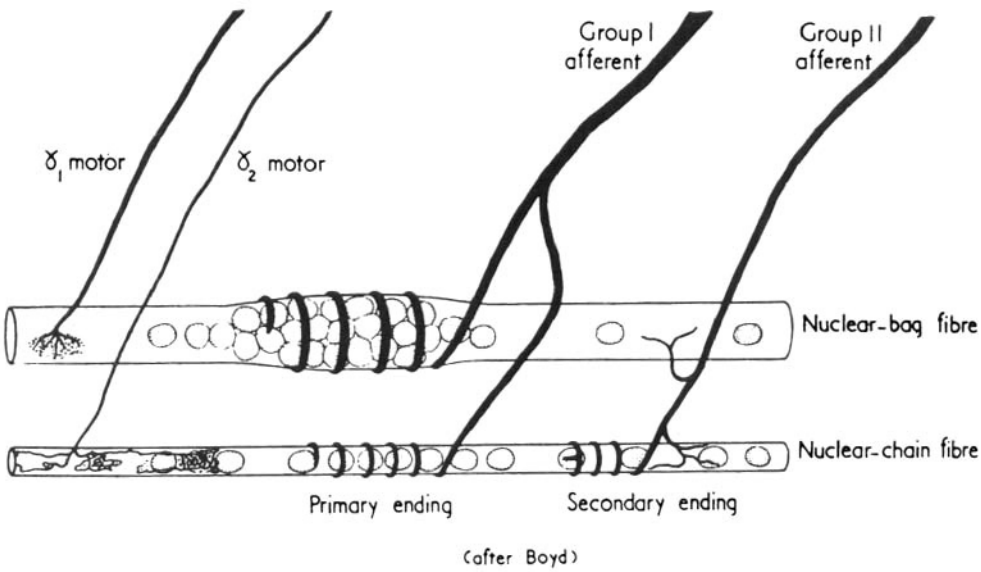

Figure 12–5. Simplified diagram of the central region (about 1 mm) of the nuclear bag fiber (*top*) and nuclear chain fiber (*bottom*) showing two types of motor endings, two types of afferent fibers, and two types of gamma motor neurons. [From Matthews,[111] with permission.]

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 (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. Although both kinds of motor endings can innervate either type of intrafusal fibers, the plate endings tend to supply preferentially the nuclear bag; the trail endings, 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.[29,111] The trail endings mediate static changes, whereas the plate endings primarily con-

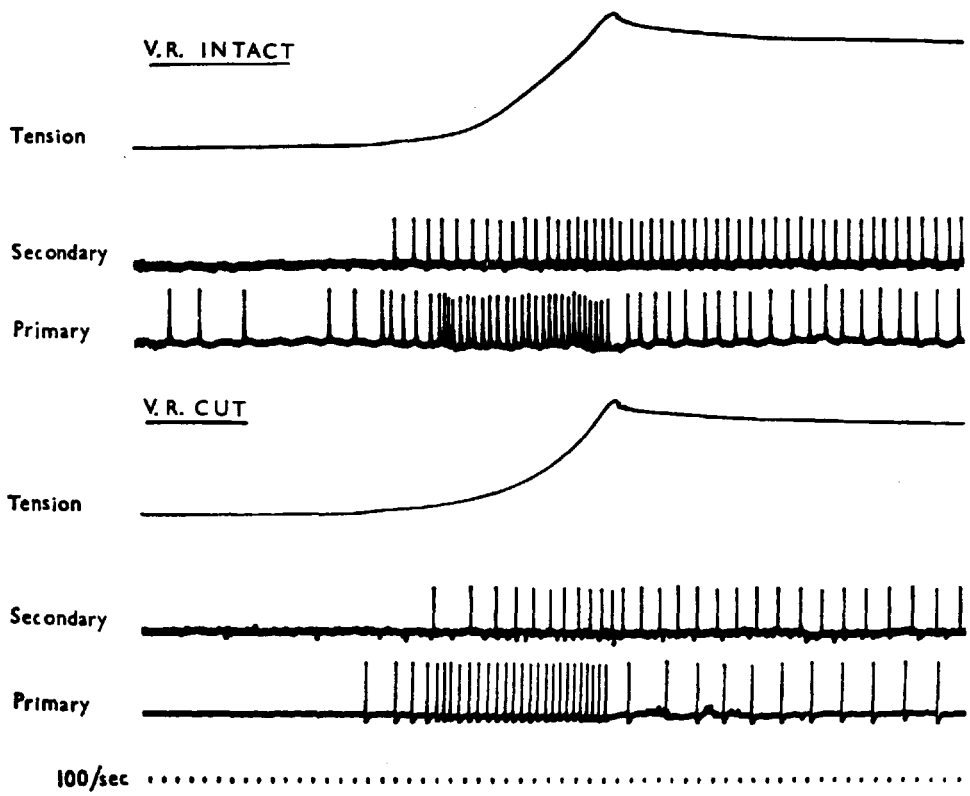

Figure 12–6. Responses of primary and secondary endings to a rapidly applied stretch before (*top*) and after (*bottom*) cutting the ventral root. Spontaneous fusimotor discharge maintained a steady intrafusal contraction in the decerebrate cat. The primary endings show a greater sensitivity to stretch than the secondary endings, but both types respond equally to changes in muscle length. [From Matthews,[112] with permission.]

trol dynamic changes.[113] The bag fibers receive a sufficiently distinctive motor innervation to subserve preferentially dynamic fusimotor effects, and the chain fibers, static fusimotor effect.[13,14] Muscle spindles, using the contraction-dependent discharge pattern, monitor activity of motor units in the vicinity.[32,116] Receptor feedback, however, has a negligible effect on the motor neuron pool, compared with the excitatory drive during voluntary contraction.[117] During prolonged, sustained contractions, afferent spindle discharges decline, whereas motor unit discharges of the parent muscles increase. This may give the impression of an α–γ dissociation, although the decline in spindle discharge may result from a progressive failure in the peripheral mechanisms by which the fusimotor system normally excites the spindle endings.[68,69,70,105]

Table 12–2 shows a simplified summary of sensory endings found in muscle spindles. The basic structural elements comprise two types of 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, as evidenced by sensory effects of pulling or vibrating exposed tendons in humans,[114] although cutaneous afferents may also provide a dominant input.[129]

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 motor neurons that innervate the stretched muscle. According to the traditional view, this inhibitory mechanism provides a safety function to prevent excessive muscle tension when motor neuron firing reaches a certain level. The threshold tension, much less than previously believed, however, excites the tendon organ, especially during active stretch.[79] 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,[97] the motor unit consists of a motor neuron and the few hundred muscle fibers that it supplies. A single discharge of a motor neuron 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.[158]

Innervation Ratio

The innervation ratio relates to the average size of a motor unit expressed as a ratio between the total number of extrafusal

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

Table 12–3 Summary of Innervation Study

Material	Muscle	Number of Large Nerve Fibers	Number of Muscle Fibers	Calculated Number of Motor Units	Mean Number 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		>129,200315	>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		164	10,500	98	107	21	0.037
♂40	Anterior tibial	742	250,200	445	562		
♂22			292,500		657	57	1.7
♂28	Gastrocnemius medial head	965	1,120,000	579	1,934		
♂22			946,000		1,634	54	3.4

Source: From Feinstein et al.[59] with permission.

fibers and the number of innervating motor axons. 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.[173] Table 12–3 summarizes the results of one study.[59] Table 12–4 shows the territory of motor units estimated histologically[42] or electrically.[21]

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.[84] Single-fiber electromyography[164,165,166] and electrophysiologic cross-section analysis[163] 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. In general, motor unit fibers may be arranged in clusters or subgroups of varying size, rather than distributed widely throughout the territory of the unit.[10] One study even refutes a random arrangement of mammalian muscle fibers but argues for a more orderly dis-

Table 12–4 Mean Values of Motor Unit Territory and Maximum Voltage in Normal Muscles

Muscle	Number of Muscles	Number of Motor Units	Spike Level (μV)	Territory at Spike Level (mm)	Standard Deviation (mm)	Maximum Voltage (μV)	Standard Deviation (μV)
Biceps brachii	24	129	100	5.1 ± 0.2	2.4	370 ± 17	190
Deltoid	7	52	100	6.7 ± 0.4	3.0	450 ± 27	190
Extensor digitorum communis	11	43	100	5.5 ± 0.3	2.1	800 ± 59	390
Opponens pollicis	10	34	150	7.4 ± 0.4	2.6	1,000 ± 83	500
Rectus femoris	9	65	100	10.0 ± 0.6	4.6	550 ± 38	300
Biceps femoris	5	35	150	8.8 ± 0.7	4.1	900 ± 67	400
Tibialis anterior	8	47	100	7.0 ± 0.4	3.0	620 ± 43	300
Extensor digitorum brevis	5	25	200	11.3 ± 0.8	4.1	3,000 ± 300	1,500

Source: From Buchthal et al.[21] with permission.

position at certain stages of development to minimize adjacencies of individual muscle fibers of the same motor unit.[193] Such specification may have the functional advantage of maximizing muscle action potential dispersal for smooth muscle contraction and in compensating for lost motor units.

Another mapping technique has also substantiated motor unit overlap.[10,16,49,55] 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 the territory of a motor unit and the number of fibers in the motor unit.[149] As the density of unit fibers remain unchanged, the same factor must regulate the number of fibers innervated by a motor neuron and its territory. Many muscles have divisions that may function independently, showing motor unit territories often confined to a compartment bounded by anatomic structures.[178] 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.[181] Under these arrangements, a motor unit acts in concert with other units, transmitting forces generated to the tendon via adjoining muscle fibers.[62,149]

Histologic findings in partially denervated muscle once prompted some investigators[23,24] 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 results from completely synchronized firing of all fibers belonging to a subunit. Electrophysiologic studies of rat phrenic-hemidiaphragm preparation[92] and of rat peroneus longus muscle,[136] however, failed to substantiate this concept. Histochemical studies showed no groupings of fibers within the motor unit in rat or cat muscle.[15,49,55] Human studies with the single fiber needle revealed no evidence of muscle fiber grouping within a motor unit in normal extensor digitorum communis or biceps brachii muscles.[162] 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 the subunit in normal human muscle.[26]

6 PHYSIOLOGY OF THE MOTOR UNIT

Table 12–1 summarizes types of muscle fibers, as described earlier in this chapter. The same criteria apply to the classification of motor units, because all the muscle fibers of a given motor unit have identical histologic and physiologic properties. The animal and human data briefly reviewed below pertain to the understanding of motor unit potentials in clinical electromyography.

Animal Experiments

Series of animal experiments have clearly established the close relationship between the fundamental physiologic properties of motor units and the size of the motor neuron (see Table 12–1). The large motor neurons have fast conducting axons of large diameter[87,119] and a higher innervation ratio; that is, a greater number of muscle fibers supplied by one axon.[75,121,194] Larger motor units have, in turn, greater twitch tensions, faster twitch contractions, and a greater tendency to fatigue.[34,76,77] According to the size principle of Henneman, the motor neurons recruit not at random but in an orderly manner determined by the fixed central

drive that preferentially activates small motor neurons first.[75,87,88]

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 motor neurons, innervating smaller motor units, discharge initially with minimal effort, before a greater effort of contraction activates larger motor neurons.

Recruitment

Most findings in animal studies also apply to humans (see Table 12–1). 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.[33,125] Factors correlated with motor neuron excitability include axon diameter[61] conduction velocity,[11,60,72] and motor unit size.[125] High and low threshold motor units also differ histochemically.[191] Earlier studies hinted at a distinction between tonic and phasic motor units on the basis of their firing pattern and the order of recruitment.[177] Later studies, however, have shown a relatively continuous rather than bimodal pattern of recruitment.[60,71,126,139]

Despite certain exceptions documented under some experimental circumstances,[7,64] the size principle generally applies to any voluntary activation of motor units, including rapid ramp or ballistic contractions.[47,140] The same rule governs the order of presynaptic inhibition after activation of group IA afferent fibers by tonic vibration.[46] Neuropathy or motor neuron disease does not alter the size principle, but a previously transected peripheral nerve may show a random pattern of recruitment.[124] Misdirection of motor axons accounts for the absence of orderly recruitment after complete ulnar or above-elbow median nerve sections. 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 after complete median nerve section at the wrist.[175]

Twitch Characteristics

Different human muscles contain either fast or slow units whose twitch contraction approximates the contraction time of the whole muscle.[157] 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.[125,130,168,174] 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.[99] Thus, in some muscles such as the human masseter, this method may prove inappropriate for determining highly task dependent single motor unit force.[120] Successive averages from the same data using different interval scales revealed progressively greater fusion of twitches as the instantaneous firing rate increases.[135]

In humans, as in animals, the twitch tension generated by a motor unit increases in proportion to its action potential amplitude measured by macroelectromyography[186] and the voluntary force required for its activation. 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.[168] Partially denervated muscles generally have a prolonged contraction time and reduced twitch tension.[122] In contrast, the twitch tension of individual motor units may become larger[115] or smaller[124] after denervation. In one study,[2] reinnervation after nerve section normalized the distribution of motor unit force in adult rats but not in neonatal animals. 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 motor neurons sprout to reinnervate denervated fibers. Daily locomotor activity can enhance the tension-generating capacity of chronically enlarged motor units.[155]

Rate Coding

The muscle force increases either by recruitment of previously inactive motor neurons or through more rapid firing of already active units. In early studies, discharge frequency appeared to stabilize over a wide range of forces, although the firing rate ranged from several Hz to 30 Hz during early phases of voluntary contraction.[40,172] These findings suggested to some that rate coding mostly regulated fine control at the beginning of contraction and during maximal effort. Work in humans,[127,130] 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.[45,60,127] After the activation of most units, additional increases in force must result from faster firing of individual motor units. In strong or ballistic contractions, instantaneous firing may reach 60 to 120 Hz at the onset.[45] To maintain the same twitch tensions, muscle fibers tend to fire at a higher rate in myopathy and at a lower rate in neuropathy, compared with controls[48] although only extremely weak muscles show a significant difference.[123]

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Chapter 13

TECHNIQUES TO ASSESS MUSCLE FUNCTION

1 INTRODUCTION

Electromyography tests the integrity of the entire motor system, which consists of upper and lower motor neurons, the neuromuscular junction, and muscle. Further subdivision in each category reveals seven possible sites of involvement that may cause muscle weakness (Fig. 13–1). Electromyographers must first learn physiologic mechanisms of normal muscle contraction to understand the various abnormalities that characterize disorders of the motor system.[55] Multiple factors affect the outcome of recordings. These include the age of patients and the particular properties of the muscle under study in addition to the electrical specifications of the needle electrodes and recording apparatus, as discussed earlier (see Chapter 3–2)

A trained physician must conduct electromyography as an extension of the physical examination, rather than a laboratory procedure.[54,233] The clinical symptoms and signs guide the optimal selection of specific muscle groups.[101,191] An adequate study consists of multiple sampling at rest and during different degrees of voluntary contraction. The findings in the initially tested muscles dictate the course of subsequent exploration. Thus, no rigid protocol suffices for a routine electromyographic examination. Certain basic principles apply, 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 pain,[140] predictors of the patients' experience of pain during the procedure included their assessment of their own low-back pain, their trait-anxiety levels, and

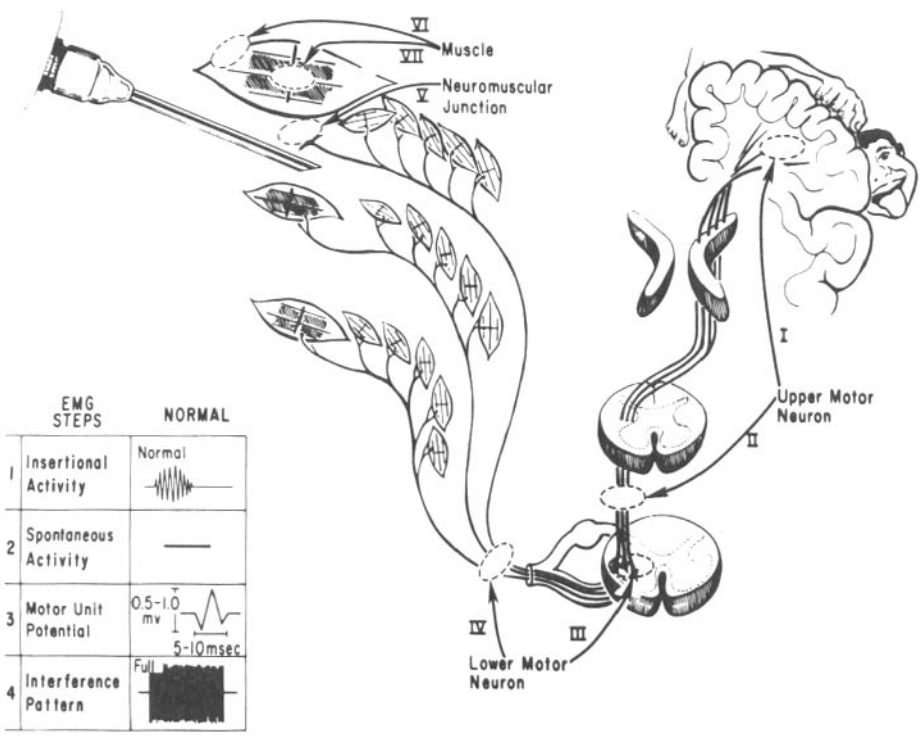

Figure 13–1. Schematic view of the motor system with seven anatomic levels. They include (1) upper motor neuron from the cortex (*I*) to the spinal cord (*II*); (2) lower motor neuron with the anterior horn cell (*III*) and nerve axon (*IV*); (3) neuromuscular junction (*V*); and (4) muscle membrane (*VI*) and contractile elements (*VII*). The insert illustrates diagrammatically four steps of electromyographic examination and normal findings. The cortical representation is adapted from Netter.[185]

female gender. In another survey in a pediatric population,[116] children's behavioral distress during the study showed a positive correlation with younger age, uncooperative attitude with previous painful procedures, negative experiences with medical or dental care and their mothers' fear and anxiety about the electrical studies. Children 2–6 years of age[117] showed extreme behavioral distress in 35 percent of examinations usually conducted without major pain medication (see Chapter 22–1).

2 PRINCIPLES OF ELECTROMYOGRAPHY

Recording of Muscle Action Potential

The electrical properties of the cells (see Chapter 2–2) form the basis of clinical electromyography. Extracellular recording of the muscle action potential through the volume conductor reveals an initially positive triphasic waveform 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 low-amplitude, slow negativity follows a large initial positivity.

The size of an action potential detected in the external field varies, 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 percent at a distance of 1 mm from the generator source. Normally, neural impulses give rise to synchronous discharges of all muscle fibers of a motor unit, producing a motor unit potential. In an unstable denervated muscle, individual 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 electromyography. Surface recording may suffice for a special purpose such as noninvasive estimation of motor unit size[243] or longitudinal tracking of the same single motor unit[103] but not for routine electromyographic studies.

Contraindications and Precautions

Two possibilities deserve special mention in screening patients for electromyographic examination: bleeding tendencies and unusual susceptibility to recurrent systemic infections. Specific inquiry in this regard often reveals pertinent information that the patient may not volunteer. To prevent unnecessary complications, the electromyographer should consult with the referring physician to weigh the diagnostic benefits against the risks. A patient taking anticoagulants should have appropriate laboratory tests for bleeding tendency prior to a needle study. With heparin infusion, partial thromboplastin time should not exceed $1\frac{1}{2}$ of control value. With warfarin (Coumadin) therapy, patients should have an international rating (INR) less than 2.0. The same precautions should apply to those with other coagulopathy, such as hemophilia.[214] For thrombocytopenia, unless the platelet count falls below 20,000/mm,[27] local pressure can usually counter the minimal hemorrhage. Testing the degree of bleeding tendency with a superficial muscle helps determine the feasibility of further study of deeper muscles, which cannot be compressed adequately to accomplish hemostasis. Transient bacteremia following needle examination could cause endocarditis in the presence of valvular disease or prosthetic heart valves. Although these patients must avoid needle studies unless clearly indicated, few electromyographers recommend prophylactic administration of antibiotics for the procedure.[1]

Some muscles considered for needle studies overlie the pleural cavity. These include the diaphragm, intercostal and abdominal muscles and, to a lesser extent, the supraspinatus muscle.[203] When performing needle studies of these muscles, a prior review of the pertinent anatomy minimizes the risk of pneumothorax. Allergens from rubber gloves, introduced under the skin during the

study, may cause local or systemic acute hypersensitvity reaction. In fact, the use of latex gloves has occasionally caused anaphylaxis and local hypersensitivity, especially in patients with myelodysplasia. A history of rubber allergy, therefore, should prompt the use of vinyl gloves.[162]

Electromyography, 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 preclude the confirmation of a clinical diagnosis, which often requires a muscle biopsy. With the anticipated need for pathologic exploration, needle examination must spare the muscle under consideration.

Serum creatine kinase (CK) increases in certain muscle diseases, such as muscular dystrophy and polymyositis, 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 electromyography, diurnal variation, and prolonged exercise.[29,190] Needle examination by itself, however, should not elevate CK to a misleading level in normal persons. In one series, no significant changes occurred within 2 hours after electromyographic studies.[45] The value reached a peak of $1\frac{1}{2}$ times baseline in 6 hours and returned to baseline 48 hours after the needle examination. 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

Electromyographic examination of skeletal muscle has four components:

1. insertional activity caused by movement of a needle electrode in the muscle
2. spontaneous activity recorded with the muscle at rest, that is, with the needle stationary in a relaxed muscle
3. motor unit potentials evoked by isolated discharges of motor neurons during mild voluntary contraction
4. recruitment and interference pattern during progressively increasing levels of contraction to a maximum level

Routine oscilloscope 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 motor unit potentials. 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 waveform of motor unit potentials.

The needle electrode registers muscle action potentials 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.

3 INSERTIONAL ACTIVITY

Origin and Characteristics

Insertion of a needle electrode into the muscle normally gives rise to brief bursts of electrical activity. The same discharges also occur 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,[72,259] 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 stimulated by the penetrating

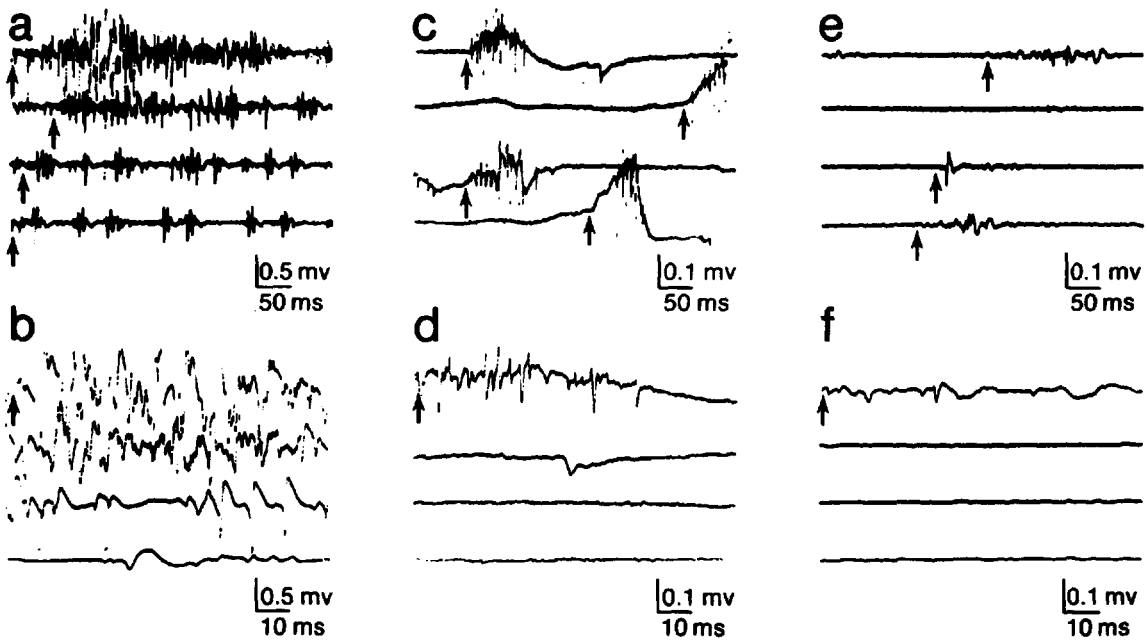

Figure 13–2. Increased (*a, b*) normal (*c, d*), and decreased (*e, f*) insertional activities (*arrows*) from the first dorsal interosseus in tardy ulnar palsy, tibalis anterior in a control, and fibrotic deltoid in severe dermatomyositis.

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 intended target.

Clinical Significance

The waveforms seen on the oscilloscope and, perhaps more importantly, the sounds over the loudspeaker allow a somewhat loose but useful categorization of the insertional activity into normal, decreased, and increased 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 excitability, being typically 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 electromyographer toward the proper course of examination. As mentioned earlier, a complete study consists of sampling the activities at several locations in each muscle by shifting the electrode from one point to another. Otherwise, patchy areas of hyperexcitability, if present, may escape detection.

In denervated muscles, insertion of the exploring needle may provoke positive sharp waves and, less frequently, fibrillation potentials. 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 the insertional activity.[258] None of these potentials, however, fired repetitively or in a train, or in a reproducible fashion with further insertions. Their audio characteristics lacked the typical pitch of positive sharp waves associated with denervation. These findings suggest the 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 END-PLATE ACTIVITIES

With the needle held stationary, normal resting muscles show no electrical activity except at the end-plate region. Here, irritation of the small intramuscular nerve terminals by the tip of the electrode causes end-plate activities that consist of two components: low-amplitude, undulating end-plate noise (Fig. 13–3) and high-amplitude intermittent spikes (Fig. 13–4). These two types of potentials occur conjointly or independently. The patient usually experiences a dull pain, which dissipates with slight withdrawal of the needle. End-plate activities, although physiologic in nature, tend to become excessive in denervated muscles.

End-Plate Noise

The background activity in the end-plate 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. It represents extracellularly recorded miniature end-plate potentials (MEPP), that is, nonpropagating depolarizations caused by spontaneous release of acetylcholine (ACh) quanta.[36,260] The

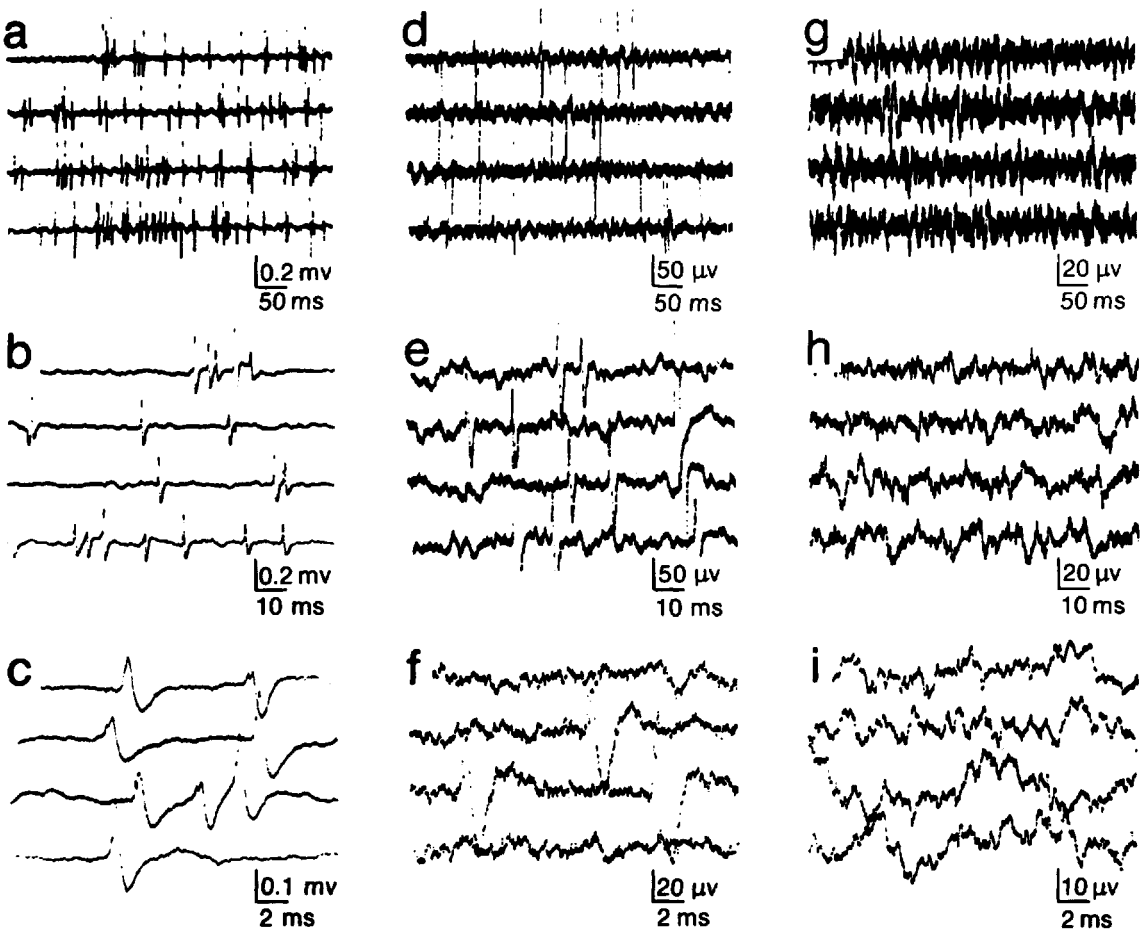

Figure 13–3. End-plate activities recorded from the tibialis anterior in a healthy subject. Two types of potentials shown represent the initially negative, high-amplitude end-plate spikes (*a, b, c*) and low-amplitude end-plate noise (*g, h, i*). The spikes and end-plate noise usually, though not necessarily, appear together (*d, e, f*).

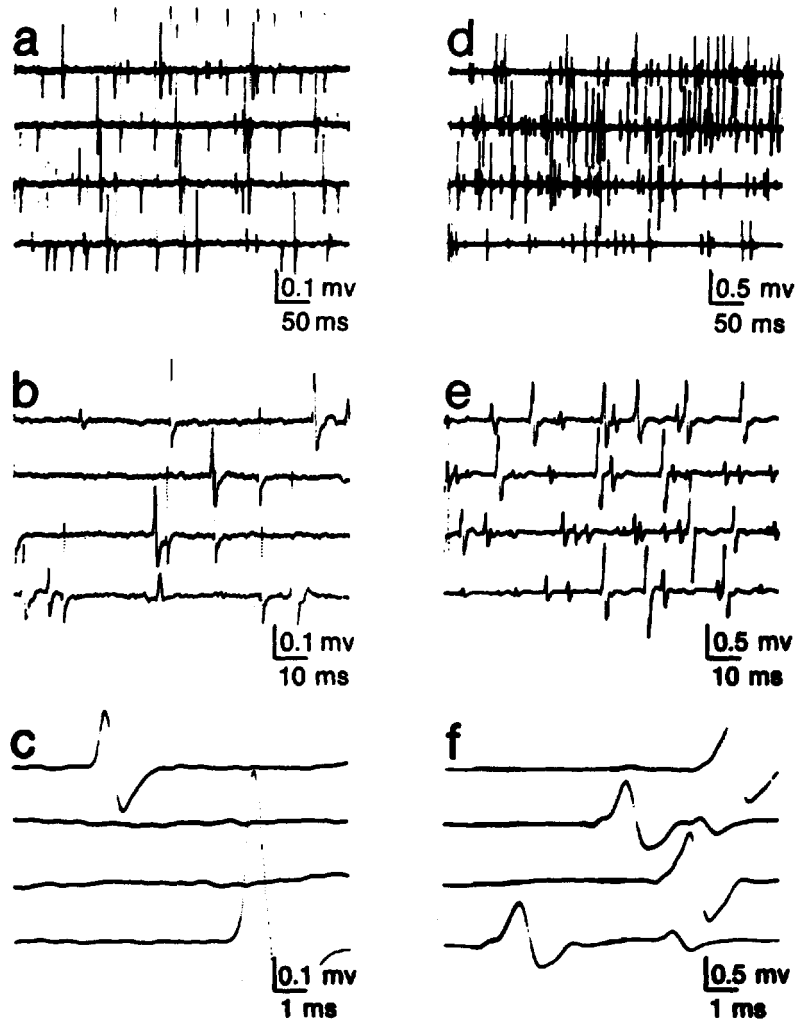

Figure 13–4. End-plate spikes recorded from the abductor pollicis brevis in a normal subject (*a*, *b*, *c*) and in a patient with the carpal tunnel syndrome (*d*, *e*, *f*). An unusual prominence of end-plate activity in denervated muscle, although common, carries little diagnostic value.

corresponding potentials recorded intracellularly with microelectrodes show monophasic positivity, about 1 mV in amplitude—that is, opposite in polarity and much greater in amplitude.[85] End-plate noise has had some limited clinical application. Its enhancement combined with the absence of end-plate spikes characterizes an attack of periodic paralysis.[81] This finding supports the notion that normal neuromuscular transmission sufficient to generate adequate end-plate potential (EPP) fails to generate propagating action potential in this disorder.[75] Power spectral analysis of end-plate noise permits rapid estimation of the dominant acetylcholine receptor ion channel kinetics.[161] Thus, the technique may provide a useful measure for possible identification of myasthenic syndrome.

End-Plate Spike

The end-plate spikes result from discharges of single muscle fibers excited by the needle.[31,36,120] 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. In fact, they have the same waveform as fibrillation potentials, which also show an initial negativity when recorded at the end-plate region. In contrast, fibrillation potentials,

recorded elsewhere, have a small positive phase preceding the major negative spike. Similarity of their firing patterns to discharges of muscle spindle afferents led some investigators to postulate their origin in the intrafusal muscle fibers,[188] but without subsequent confirmation.

Repositioning of the recording needle may injure the cell membrane at the end-plate region. Slight relocation of the needle tip near the source of discharge may then reverse the polarity of the ordinarily negative end-plate spikes. Small, irregularly occurring positive potentials also appear in the end-plate region when recorded with a concentric needle electrode. Here, the positive discharges probably represent cannula-recorded end-plate spikes, hence reversed in polarity and reduced in amplitude.[197] These positive potentials favor the more distal muscles, perhaps because of their higher innervation ratios.[198] The irregular pattern of firing and shorter duration distinguish the physiologic positive discharges at the end plate 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). It has anatomic and physiologic properties based on the innervation ratio, fiber density, propagation velocity, and integrity of neuromuscular transmission. These factors vary not only from one muscle group to another but also

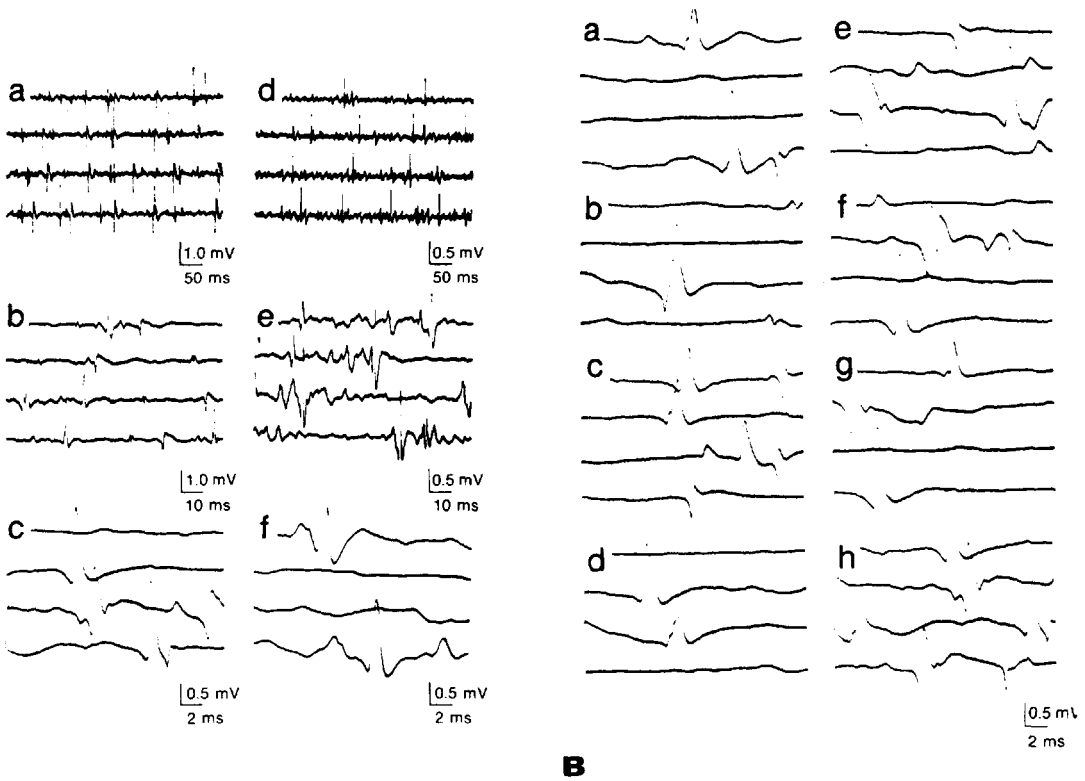

Figure 13–5. A. Normal motor unit potentials from minimally contracted biceps in a 40-year-old healthy man (*a*, *b*, *c*) and maximally contracted tibialis anterior in a 31-year-old woman with hysterical weakness (*d*, *e*, *f*). In both, low firing frequency indicates weak voluntary effort. **B.** Normal variations of motor unit potentials from the same motor unit in the normal biceps. Tracings *a* through *h* represent eight slightly different sites of recording with the patient maintaining isolated discharges of a single motor unit.

with 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. Principal components analysis shows three elements that contain 90 percent of the variance of the data set: changes in the size of the motor units, variations in the arrival time at the recording electrode, and loss of muscle fibers within the motor unit territory.[181] Refined techniques for longitudinal tracking of the same motor unit enables serial measures of these aspects for quantitative assessment of the disease process.[39,40,63,104] Surface recording, though not suitable for routine use,[111] may suffice to characterize enlarged motor units after reinnervation, as may be seen in poliomyelitis.[206]

Motor Unit Profile

The shape of motor unit 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.[21,60] The amplitude decreases slightly with hypothermia, despite the local facilitatory effect on the muscle membrane, because differential slowing and desynchronization more than counter the anticipated change. Cooling from 37° to 30° C, for example, causes the duration to increase by 10–30 percent, but the amplitude decreases by 2–5 percent per 1° C. The number of polyphasic potentials increases as much as tenfold with a 10° C decrease.[35]

Finally, a number of nonphysiologic factors 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.[33] 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 properties of the amplifier, choice of oscilloscope sensitivity, sweep or filters, and the methods of storage and display. These factors together dictate the amplitude, rise time, duration, number of phases, and other characteristics.[52]

Amplitude and Area

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 amplitude of a motor unit potential (Fig. 13–6). Single muscle fiber potentials fall off in amplitude to less than 50 percent at a distance of 200–300 μm from the source and to less than 1 percent a few millimeters away[74,107] with the use of an ordinary concentric needle. Fewer than 5–10 muscle fibers lying within a 500 μm radius of the electrode tip contribute to the high-voltage spike of the motor unit potential.[235,246] In fact, computer simulation indicates that the proximity of the electrode to the closest muscle fiber determines the amplitude.[70,183,236] Therefore, the same motor unit can give rise to many different profiles, depending on the recording sites. 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.[142] In one study using simultaneous recording by two types of electrodes,[41] 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 with concentric needles.

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

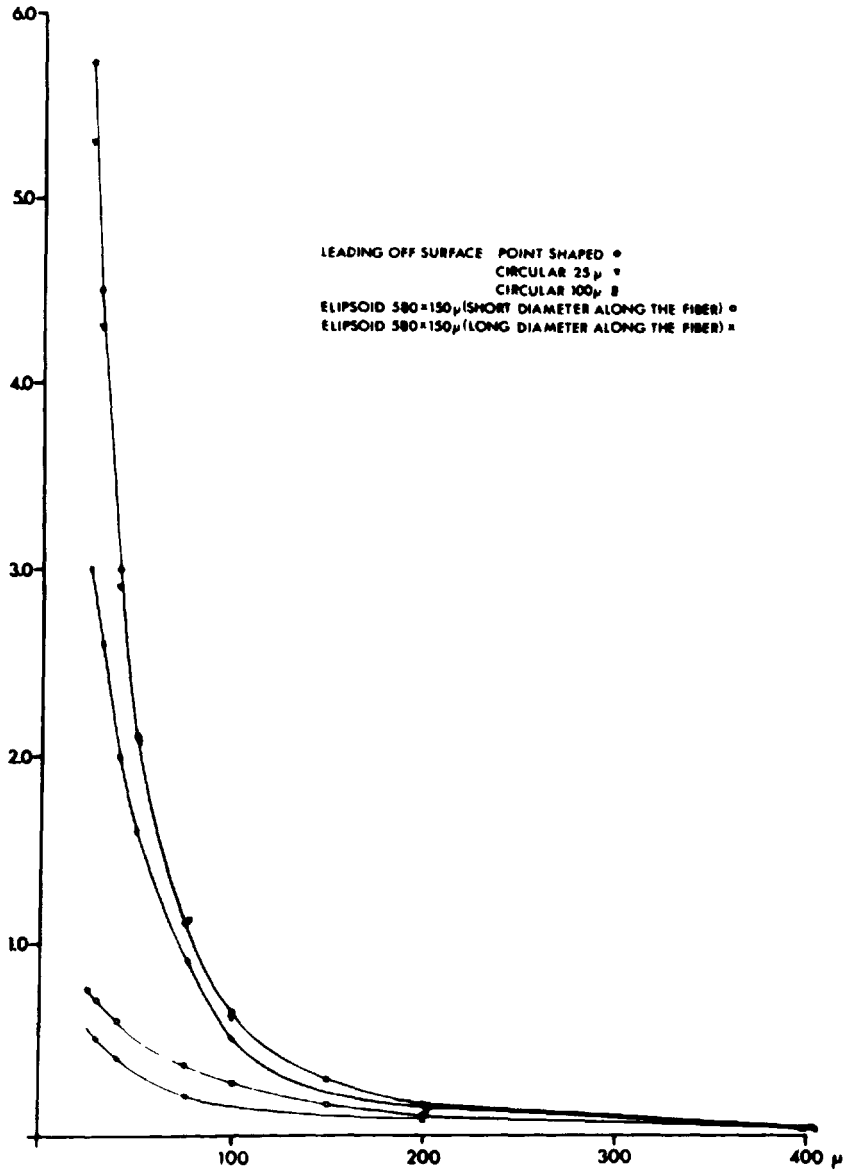

Figure 13–6. Reduction in amplitude of recorded response with the relocation of the electrode away from the source. The needle with a large leading-off surface registers a low amplitude even near the spike generator, showing only minor reduction as the distance between the electrode and the source increases. In contrast, amplitude declines per unit distance steeply with a smaller leading-off surface (see Fig. 16–1). [From Ekstedt and Stalberg,[74] with permission.]

"thickness" of the potential, which varies much less with changes in electrode position.[179] The combination of amplitude and area/amplitude ratio improves discrimination considerably,[228] detecting around 70 percent of neurogenic changes, compared to only 15–30 percent by duration criteria alone.

Rise Time

The rise time, measured as a time lag from the initial positive peak to the subsequent negative peak (see Fig. 2–6), 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 is accompanied by a dull sound, indicating 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,[129] but some argue for less restrictive criteria.[14] Such a motor unit produces a sharp, crisp sound over the loudspeaker, which provides an important clue to the proximity of the unit to the electrode. The measurement of the rise time confirms the suitability of the recorded potential for quantitative assessment of the amplitude.

Duration

Duration measured from the initial takeoff to the return to the baseline (Table 13–1) indicates the degree of synchrony among many individual muscle fibers with variable conduction velocity, membrane excitability and fiber length.[69] Unlike the spike amplitude, exclusively determined by a very small number of muscle fibers near the electrode, the duration of a motor unit potential 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.[183,235] Therefore, a slight shift or rotation of the needle influences the duration much less than the amplitude.[180] The duration normally varies from 5 to 15 ms, depending on the age of the subject. In one study,[32] 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[23] 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 a macroelectrode. Under this circumstance, the total time of single action potential from end-plate zone to musculotendinous junction may dictate overall duration of motor unit action potential.[71]

Phases

A phase is defined as that portion of a waveform between the departure from and return to the baseline. 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, motor unit potentials have four or fewer phases. Polyphasic motor unit potentials with more than four phases result from desynchronized discharges of individual muscle fibers, probably reflecting fiber size variability more than random loss of fibers. These potentials do not exceed 5–15 percent 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. These serrated action potentials or, less appropriately, complex or pseudopolyphasic potentials, also indicate desynchronization among discharging muscle fibers. In one study,[270] irregular potentials appeared more commonly during acute stages.

6 QUANTITATIVE MEASUREMENTS

Methods of Assessment

In clinical tests, electromyographers assess various features of a motor unit by oscilloscope displays of waveforms and 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 not suf-

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 Communis	Opponens Pollicis; Interosseus	Abductor Digiti Quinti	Biceps Femoris; Quadriceps	Gastroc-nemius	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 percent (20 potentials for each muscle). Therefore, deviations up to 20 percent are considered within the normal range when comparing measurements in a given muscle with the values of the table.

Source: From Buchthal,[32] with permission.

fice to delineate less obvious deviations or mixed patterns of abnormalities. These ambiguous circumstances call for objective measurement of motor unit potentials.[34,234,235] 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.[82]

Physiologic properties that characterize the motor unit potentials include duration, spike amplitude, spike area, phases, turns, number of satellites, and degree of waveform variability.[229] Additional measures of interest include spike duration, thickness[179] and size index,[228] 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.[230] 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,[146] two-channel recording using a concentric needle for pick-up and a single-fiber electrode for trigger,[149] template matching,[7] and decomposition technique based on multiple template matching.[15,24,131,165,178]

Selection and Analysis

In quantitative analysis,[20] most investigators use the standard concentric needle electrode with a lead-off surface of about 0.07 mm^2. The optimal recording requires an amplifier frequency range of 10 Hz–10 kHz and standard sensitivity of 100–500 $\mu V/cm$. The motor unit action potentials selected for assessment must have 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. An ideal quantification calls for counting at least 20 different units in each muscle, using multiple needle insertions.[32] In one study,[76] the 95 percent 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 results for duration supported the presence of myopathy in 2 of 10 patients with analysis of 5 units and in 9 patients with analysis of 20 units. Thus, compared to the analysis of 5 units, which may suffice in diagnosing some cases, studying 20 potentials narrows tolerance limits, reduces intertrial variability, and improves diagnostic sensitivity.

Table 13–1 summarizes the duration of motor unit potentials recorded with a concentric needle in normal subjects of different ages.[32] These values, measured from the point of takeoff to return to the baseline, exclude late or satellite components seen as a separate peak.[150] As discussed earlier, the normal ranges depend on many factors other than simply the characteristics of the motor unit itself. Hence, each laboratory should construct its own table of normal values to avoid indiscriminate application of published data.

Automated Methods

Different investigators have explored the possibility of automatically analyzing motor unit action potentials using analog[175] or digital techniques.[189,200,239] Such a system converts a motor unit potential 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 motor unit potentials by visual inspection, using a monitor scope, before processing them for automated analysis.[200] With another technique, motor unit potentials qualified automatically if their peak-to-peak amplitudes exceeded 100 μV.[145] Some investigators advocated lowering the cutoff to less than 50 μV for inclusion of a greater

number of motor unit potentials.[124] 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 time-consuming manual quantification and quick automatic analysis.[144,147,152,239] Indeed, the computer can accurately and efficiently discriminate typical neuropathic and myopathic changes.[220,269] 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 statistically significant differences between the two as a group.[250]

Routine studies rarely include quantitative analysis, which takes time to select and measure 20 individual motor unit potentials. Of various approaches discussed earlier, decomposition techniques are probably best suited for automatic analysis, as they avoid a time-consuming quantification process.[24,65,160,178,237] Although pilot studies show promising results, none of the techniques are widely used or tested. Their implementation and evaluation must await for further dissemination of special computer algorithms as part of commercially available software. Some authors recommend visual inspection and remarking of each motor unit potential before making clinical judgement from the data.[28]

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 motor unit potentials. This type of analysis reveals that the shorter the duration of the motor unit potential, the greater the high-frequency components. Several investigators have studied frequency spectra, or a histogram of activities against frequency, in normal and diseased muscles.[42,136,163] The highest peak seen during maximal contraction falls between 100 and 200 Hz in normal subjects.[256] This peak shifts to a higher frequency in subjects with myopathy,[204] and to a lower frequency in subjects with anterior horn cell lesions.[86] Frequency analysis may also help characterize fatigue trends in normal subjects,[12,110] and in those with myasthenia gravis[266] or other neuromuscular disorders.[267] In Duchenne muscular dystrophy, the isometric contraction causes an increase of the total power, showing a progressive increase in lower frequencies and a decrease in higher frequencies, with a shift downward of the median frequency.[93] These findings suggest decrement of the firing rate of the damaged fast-twitch motor units, compensated for by a predominance of activity of relatively spared slow-twitch motor units. The clear difference seen in typical cases does not imply its practical value as a diagnostic test, which depends primarily on controlling the variables, such as needle position or level of muscle contraction, that appreciably influence the results.[51]

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.[121] The units activated early consist primarily of small, type I muscle fibers according to the size principle.[58,78,122,215] These motor units discharge at a rate of five to seven impulses per second, typically semi-rhythmically, with slowly increasing, then decreasing interspike intervals, despite constant contraction. At such minimal levels of muscle contraction, changes in firing rate grade the muscle force (rate coding). Greater muscle force brings about two separate but related changes in the pattern of motor unit discharge: (*1*) recruitment of previously inactive units and (*2*) more rapid firing of already active units (Fig. 13–7). Which of the two plays a greater role is not known, but both mech-

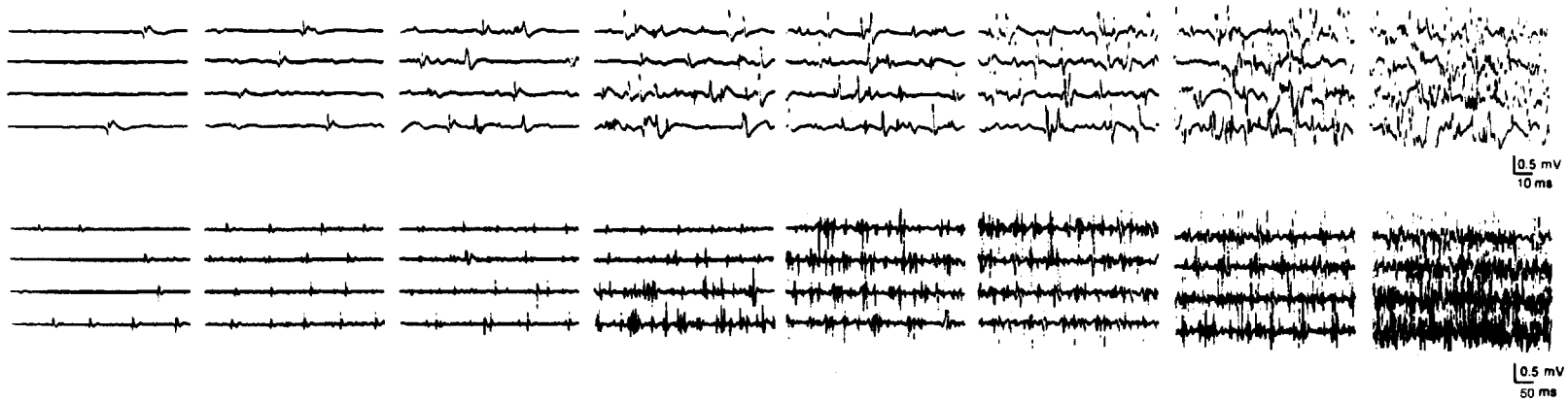

Figure 13–7. Normal recruitment and full interference pattern with increasing strength in the same healthy subject shown in Figure 13–5A. The tracings show the same activity recorded with fast (*top*) and slow (*bottom*) sweep.

anisms operate simultaneously. The physiologic rank order during slowly graded or ballistic increase in force (see Chapter 12–6) depends, in addition to soma diameter, on other factors contributing to its selectivity, such as synaptic density and efficacy as well as specific membrane resistance.[195] Ranking of recruitment also relates to the type of motor units: slow, fatigue resistant, and fast fatigue, in this order. With increasing tension by activation of large high threshold type II motor units, the force of single units enlarges exponentially compared to the size of motor unit potentials measured by macrotechnique.[254]

Recording with a monopolar or concentric electrode cannot readily confirm the size principle from low to high threshold motor units, because the small uptake areas of those electrodes fail to assess the motor unit territory.[80] The sizes of consecutively recruited motor unit potentials vary considerably at individual recording sites, primarily reflecting their fiber density rather than their motor unit size. A normal recruitment pattern thus implies the discharge of an appropriate number of motor units for the effort (Fig. 13–8A). A reduced or increased pattern indicates a smaller or greater number of discharging units than expected (Fig. 13–8 B and C). A loss of motor units results in late and sparse recruitment with increased rates of firing at all levels of effort. In contrast, a random loss of muscle fibers from each motor unit gives rise to early and excessive recruitment at minimal and moderate levels of effort. For accurate assessment, the examiner must know the approximate number of active motor units expected for a given force being exerted. Motor units may fire irregularly in basal ganglia disorders such as parkinsonism or chorea at or above physiologic tremor rate.[59] Upper motor neuron lesions such as spinal cord injury may alter motor unit forces and recruitment patterns.[248]

The recruitment frequency, defined as the firing frequency of the initially activated unit at the time an additional unit is recruited, measures the pattern of motor unit discharge. Normal values determined during mild contraction average 5–10 impulses per second, depending on the types of motor units under study.[109,194,195] The reported ranges show a considerable overlap between healthy subjects and patients with neuromuscular disorders.[99] 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.[53] If two units are firing over 20 impulses per second, the ratio exceeds 10, indicating a loss of motor units. Studying the temporal discharge pattern of single motor units may help distinguish firing behavior in normal subjects and in patients with upper motor neuron lesions.[84]

Interference Pattern

With greater contraction, many motor units begin to fire very rapidly (Fig. 13–9). Simultaneous activation of different units precludes recognition of individual motor unit potentials; 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 motor neurons 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 parentic muscles shows frequent lapses in the interference pattern and inability to sustain muscle activity as quantitative confirmation of clinical motor impersistency.[92] Computer simulation may help automatic analysis of interference patterns.[84,133] A special type of methodology permits the decomposition of interference patterns into their constituent motor unit potentials for measurement of their configurational and behavioral properties.[48,58,134,226] Such analysis shows increased amplitudes, firing rates, and firing variability in motor neuron disease, and reduced amplitudes, du-

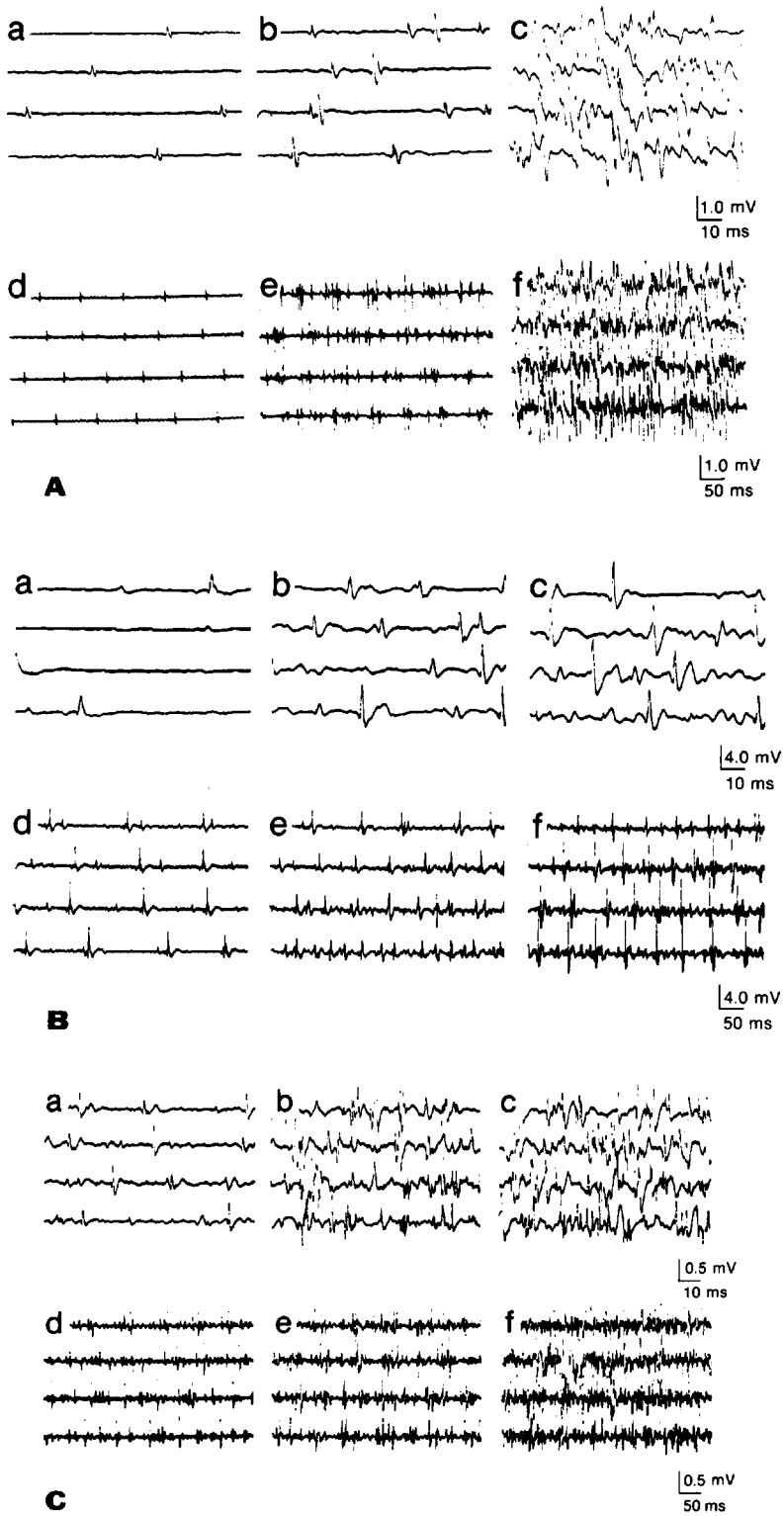

Figure 13–8. A. Normal recruitment in the triceps of a 44-year-old healthy man. The tracings show the same activity recorded with fast (*top*) and slow sweep (*bottom*) during minimal (*a, d*), moderate (*b, e*), and maximal contraction (*c, f*). **B.** Reduced recruitment in the tibialis anterior of a 44-year-old man with amyotrophic lateral sclerosis. A single motor unit discharged rapidly during 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 an excessive number of motor units for the amount of muscle force exerted during weak contraction.

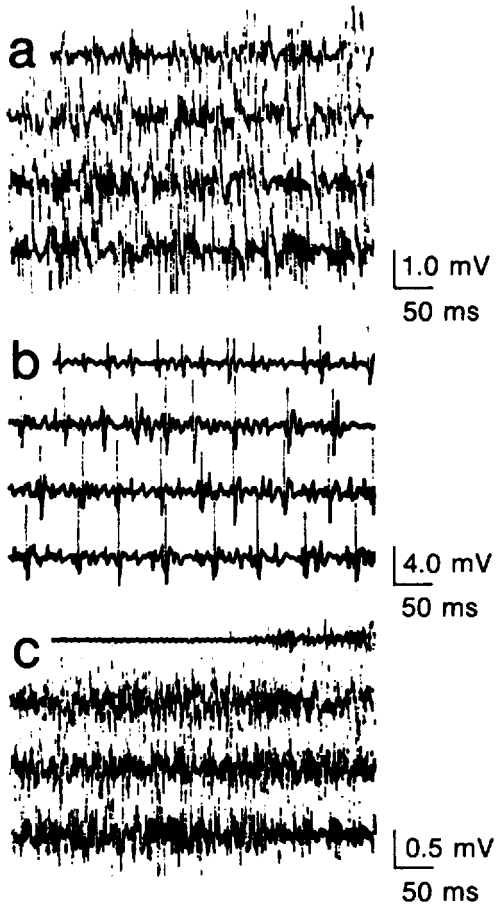

Figure 13–9. Interference patterns seen in the triceps of a 44-year-old healthy man (*a*), tibialis anterior of a 52-year-old man with amyotrophic lateral sclerosis (*b*), and quadriceps of a 20-year-old man with limb-girdle dystrophy (*c*). Discrete single motor unit discharge in *b* stands in good contrast to abundant motor unit potentials with reduced amplitude in *c*.

ration, and firing rates in myopathies, confirming many of the traditional criteria.[65]

Measurements of Turns and Amplitude

Examination of individual motor unit potentials during weak voluntary effort only relates to low-threshold type I muscle fibers. Studies of the interference pattern induced by strong muscle contraction allows quantitative assessment over a wider range.[219] 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.[263] 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.[118,119] During a fixed time epoch, the subject must maintain constant levels of muscle contraction. Turns and spectral analyses of interference pattern, though efficient, only indirectly relate to the physiologic properties of the motor units.[67] Reported measures include turns frequencies,[135] the maximal ratio of turns to mean amplitude, or peak ratio, and the number of time intervals between turns.[154] In this type of analysis, a decreased peak ratio and a decreased incidence of time interval supplement each other in identifying patients with neurogenic involvement.[88,89,155]

After automatic analysis, a special-purpose digital computer displays the total number of reversals, histograms of the intervals between potential reversals, and cumulative amplitude of all potentials during a fixed time period.[68] In one study,[96] the number of turns and mean amplitude had 10–25 percent variability on repeated trials. Interindividual differences diminished with the use of a relative, rather than absolute, force in each subject. Diagnostic yield reached an acceptable level at muscle contraction producing 20–50 percent of the maximum force, with the best reproducibility at 10–30 percent.[115]

As the force of voluntary contraction increased from low to moderate levels, the number of turns in the signal increased faster than did the mean amplitude change between turns. At higher force levels, the pattern was reversed.[182] The overall shape of the so-called normal cloud of the turns and amplitude measurements thus critically depends on the level of effort at which recordings are made. The increment from 10 percent to 30 percent maximal voluntary contraction led to highly significant increases in mean firing rate, number of turns, amplitude, and rise rate.[64] Clinical studies, therefore, must control contractile force precisely as a ma-

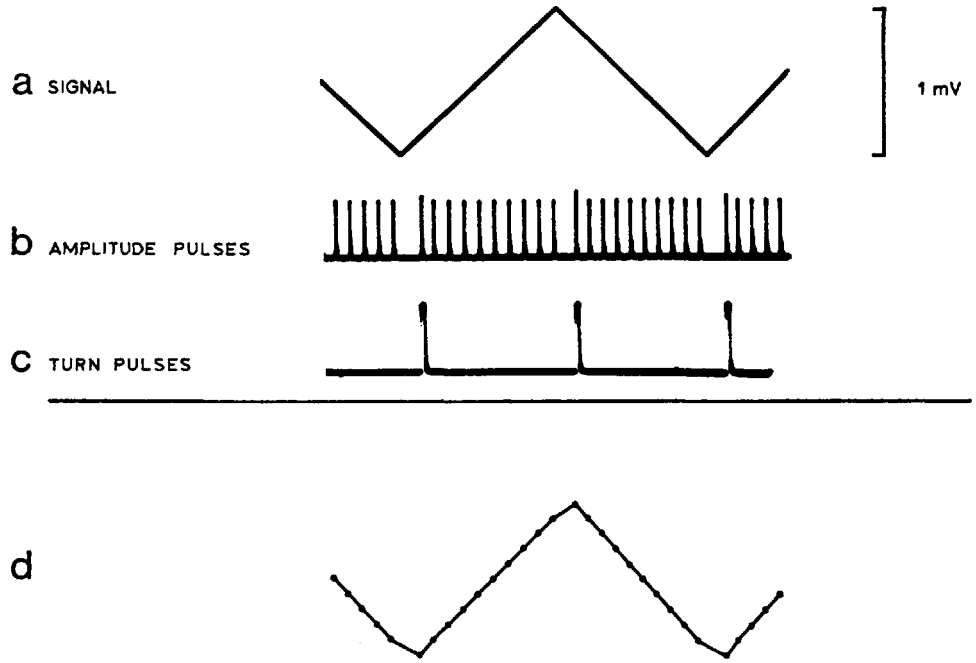

Figure 13–10. Conversion of calibration wavefom (*a*) into two serial pulse trains: amplitude (*b*) and turns (*c*). The outputs of these two pulse generators characterize the original input accurately, as evidenced by graphical reconstruction of the waveform (*d*) from *b* and *c*. [From Hayward and Willison,119 with permission.]

jor determinant of waveform and firing properties. The use of a calculated index independent of force may improve the diagnostic sensitivity.[37]

In one study,[127] mean amplitudes, durations, and numbers of turns all increased linearly with age in both low-threshold and high-threshold motor units, suggesting an ongoing process of denervation and reinnervation. The method also helps differentiate primary muscle disease from neurogenic lesions in infants and young children.[224,225] An increased ratio of turns to mean amplitude in myopathy, especially at 10–20 percent of maximum force, stands in contrast to a decreased ratio in neurogenic disorders, mainly at a force of 20–30 percent.[97] Conversely, the ratio of root mean square voltage to turns increased in chronic neuropathies.[90]

Quantitative measurements of recruitment patterns complement studies of single motor units. Evaluation of individual potentials allows 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 motor units. These methods, though not widely used at this time, hold promise as supplements to routine electromyography.[87,90,91,95,98,114,157,159,164,166,232]

8 OTHER MEASURES OF MUSCLE FUNCTION

Integrated Electrical Activity and Muscle Force

During maximal effort, motor units discharge at frequencies up to 50 impulses per second. This gives rise to a tetanic contraction, which, generated by a high degree of fusion, produces 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, can be used to estimate overall motor unit activity.[126,130] 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 motor performance, which in turn aids in the identification of unusual patterns—for example, those seen in hysterical paresis.[143]

Different surface measures of electrical activity have been proposed for quantifying muscle fiber conduction velocity,[174] (see Chapter 12–2) and other muscle function,[62,113] and assessing discharge pattern of motor units.[8,49,50,216,268] Waveform integration helps correlate the muscle force and the electrical activity, but, with repeated trials, the result may vary considerably.[167,221,222] 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.[13,170] 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.[148,172,249] Muscles of mixed fiber composition, however, may show a nonlinear relationship.[265] Surface recording can also provide useful information in estimating motor unit size.[207] Diagnostic yield of surface studies[57] may improve with the use of high spatial resolution recording in various neuromuscular disorders.[128]

Studies of muscle force in the management of neuromuscular diseases[3,261] require rigorous quality control measures to assure test reliability, especially in multicenter trials.[5,125] During dynamic contraction, power spectra of surface myoelectric signals change depending on the applied torque, muscle length, and velocity of contraction, whereas the median frequency varies with the torque and the muscle length, but not with the velocity.[217] The use of special quasi-trapezoidal-shaped pulses makes selective activation of small motor axons possible to achieve a physiologic recruitment order of small-to-large motor units. With this stimulation technique, force modulation proceeded more gradually and contraction fused at lower stimulation frequencies.[83] With some exceptions,[106] muscle force declines with age in both sexes.[209] Fallout of motor units contributes to the reduction in torque when compensatory reinnervation begins to fail.[231] Aged muscle is weaker, slower, and tetanized at lower fusion frequencies but, paradoxically, it is more resistant to static fatigue.[184] Other factors that influence muscle force include muscle fiber contractility, metabolic changes, and central mechanisms.

Collision Technique

A collision technique helps determine the relationship between the electrical potential and the force produced by voluntary contraction of the first dorsal interosseous muscle. Shocks of supramaximal intensity, delivered at either the wrist or the axilla, evoke nearly identical compound muscle action potentials, M(W) or M(A) (Fig. 13–11). Shocks applied simultaneously at the wrist and axilla with the subject at rest elicit 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. 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 magnitude of the voluntary impulse. This technique produces, in effect, a synchronized equivalent to the asynchronous motor neuron activity associated with voluntary contraction.[141] The amplitude M(V) relates linearly to the force of contraction under isometric conditions (Fig. 13–12).

Needle study during weak voluntary contraction best characterizes the recruitment and discharge pattern of individual motor units.[173,192,193,245] Strong muscle contraction interferes with the identification of single motor units in the

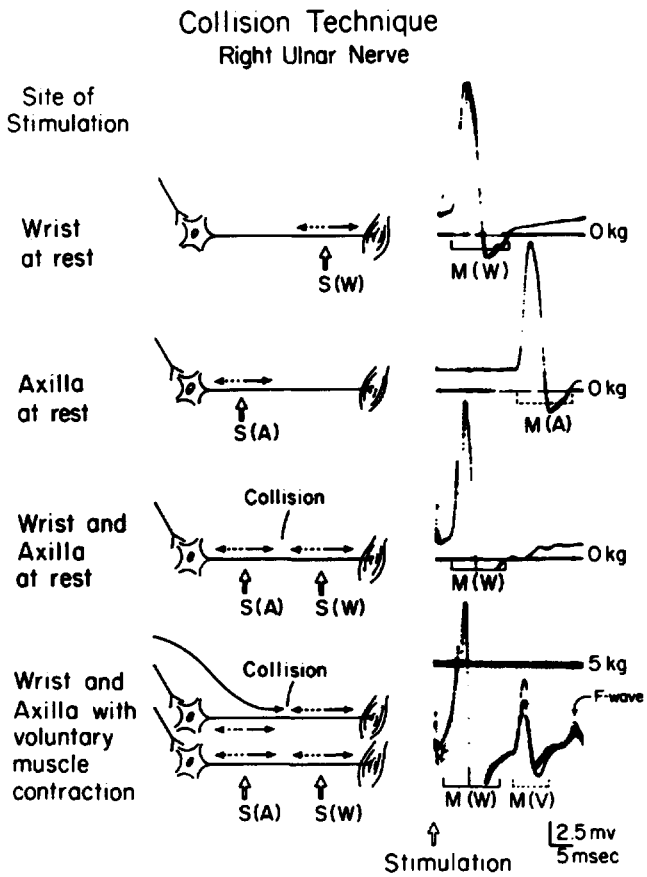

Figure 13–11. Compound muscle action potentials, M(W) and M(A), from the first dorsal interosseous and muscle force (*straight line*). At rest, the antidromic impulse from stimulation at the wrist eliminated the orthodromic impulse from the axilla by collision. With muscle contraction (*bottom tracing*), M(V) appeared in proportion to the number of axons in which the voluntary impulse first collided with the antidromic impulse from the wrist. [From Kimura,[141] with permission.]

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 motor neurons. The collision technique provides a direct means of elucidating the relationship between the discharge pattern of the motor neuron pool and muscle force over a wide range of voluntary contractions. This method also serves as a good measure of the central drive to assess supraspinal components of human muscle fatigue.[100]

Muscle Contraction and Fatigue

Compound muscle action potentials, though reduced in amplitude, change little in area after fatigue despite substantial reduction in torque.[218] During fatiguing contractions, electromyographic activities gradually decline not only in the contracted muscle but also to a lesser extent in the synergists, suggesting the existence of an inhibitory reflex.[212] The power spectrum shifts during fatigue, a phenomenon best explained by accumulation of extracellular potassium (K^+).[171] In one study using automated analysis,[66] motor unit potentials derived from contractions of 30 percent maximal voluntary contraction showed (*1*) short-lasting decline and stabilization of onset firing rate, followed by (*2*) progressive increase in mean firing rate and amplitude, and (*3*) recruitment of additional larger motor units prior to the development of fatigue. The last two elements result in the well-known increase in total surface electromyogram, compensating for a loss of force generated by fatiguing individual muscle fibers. Single human motor units recording during fatigue also showed a similar dissociation between the electrical and contractile properties.[3]

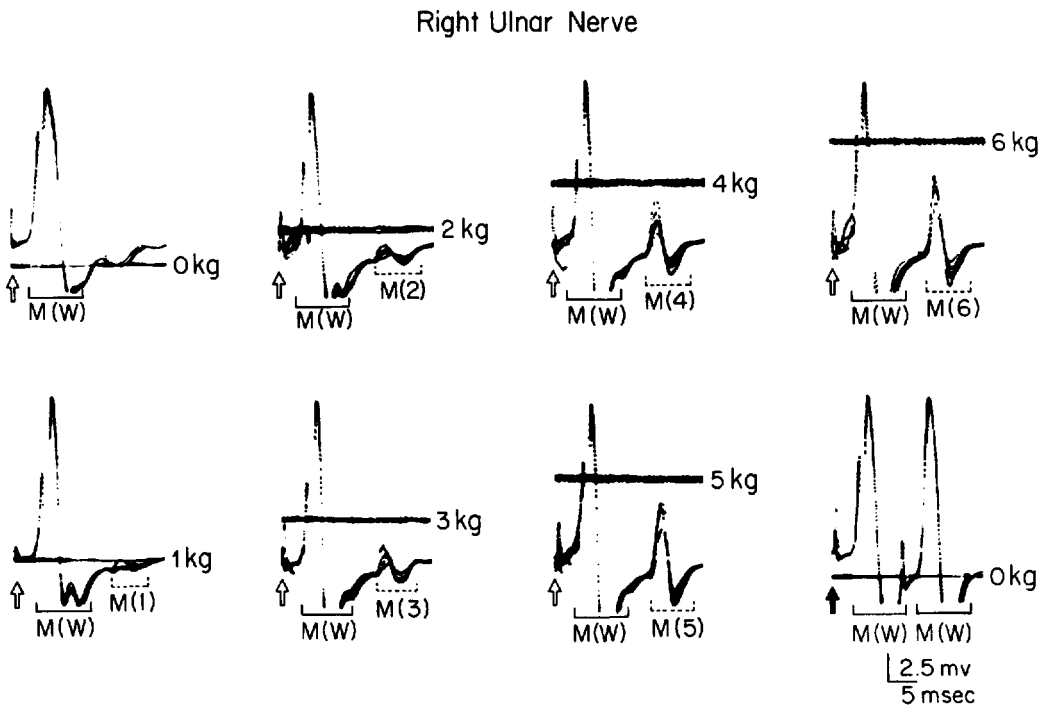

Figure 13–12. Correlation between muscle force and electrical activity, with the same stimulation (*open arrow*) and recording as in the bottom tracing of Figure 13–11. Muscle force ranged from 0 to 6.0 kg (*straight line*). In the last tracing, paired stimuli (*closed arrow*) delivered at the wrist 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. [From Kimura,[141] with permission.]

Fatigue decreases the contraction-relaxation rate of muscle fibers, lowering fusion frequency. Thus, lower rates of motor unit activation can result in the maintenance of constant force. In most studies, the number of motor unit spikes needed to maintain a constant force declined after maximal contraction, causing reduction in the surface recorded integral of the rectified electrical activities.[105,273] In another experiment,[46] the first 10 minutes of the 10 percent sustained contraction showed a most pronounced decrease in mean power frequency and increase in root mean square amplitude. Thereafter, frequency remained the same despite a continued increase in amplitude, indicating recruitment of new motor units. During sustained maximal effort, the mean and median power frequency declined exponentially with time. Fatigued muscles show a decrease in number of spikes and amplitude, in part reflecting a dropout of some motor units and a decrease in firing rate.[47] In four patients with congenital myopathies characterized by a 100 percent type I predominance, the power density frequency spectrum showed a shift to lower frequency and a greater electrical discharge per unit force compared with those of control subjects.[156]

Isometric measure shows a decrease in both the maximum voluntary and tetanic force after stimulation with a uniform rate at 10 per second but not with a nonuniform pattern containing a few high-frequency bursts.[211] During fatigue, as well as during recovery, changes in maximum voluntary contraction correlate best with H_2PO_4, implicating this metabolite as an important factor in human muscle fatigue.[26,168] Alteration in intracellular calcium (Ca^{2+}) exchange may play a major role in the fatigue process.[262]

Human muscle fatigue may also result from failure of central motor drive, which results in less than maximal activation of muscle.[100,139] The technique termed *twitch*

interpolation provides a quantitative estimate of the amount of volitional effort by superimposing electrical stimulation during voluntary contraction.[5,6,11,169,244,251] In one study using this method, corticomotor excitability increased during a sustained submaximal voluntary contraction followed by progressive intracortical inhibition as fatigue developed.[213] In some central nervous system disorders such as multiple sclerosis, motor unit activation may require a relatively greater central motor drive.[186] Patients with chronic fatigue syndrome complain of persistent asthenia that cannot be accounted for by any known medical disease. Careful analysis of symptoms should facilitate the clinical evaluation, often preventing unnecessary physiological or biochemical procedures.[151]

Kinesiology and Motor Control

Electromyography plays a unique role in kinesiology, measuring the output of α-motoneurons, which can be readily recorded in normal subjects and in patients with a variety of motor disorders.[238] Electrical signals and twitch torque recording have provided insight into the function of the normal and the disordered neuronal system as it relates to motor control.[201] This type of application includes studies of coordination,[112,252] locomotion,[44,79,132,176,242] spinal cord injury,[61,102,137,247] stretch reflex,[187,208] dynamic muscle fatigue,[9,10,73,138,272] effect of activation pattern on muscle force,[22,210,223] endurance,[30,77,227,271] skilled motor performance,[153,177] exercise-damaged muscle,[56] contracture,[199] task-oriented pattern of activity,[264] diurnal force fluctuation,[158] and motor performance by patients with a reduced number of motor neurons[25] or uppermotor neuron lesions.[94]

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 piezoceramic transducer glued to a flexible printed circuit board etched to form three copper strips taped firmly onto the skin.[2,43] Fourier analysis of sounds or vibrational signals shows presence of predominantly low-frequency components below 60 or 70 Hz.[257] 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.

Stimulated muscle sounds suffice when artifacts such as tremor preclude recording of voluntary muscle sounds. An accelerometer may be used to record muscle vibration induced by twitches after stimulation of the nerve. This approach not only eliminates motivational artifacts but also allows the use of fundamental, non-transducer-dependent units. It also provides quantitative data to relate electric signal to contractile muscle activity.[16,253] One study[17] reported latencies of 5.7 ± 0.6 and 5.1 ± 0.6 ms (mean $\pm$ 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,[196] phrenic nerve stimulation at the neck induced a diaphragmatic acoustic signal with a latency of 12.4 ± 0.6 ms as compared to an electrical response with a latency of 7.3 ± 0.7 ms.

The vibration amplitude from evoked muscle twitches provides a direct measure of evoked twitch force from fatiguing muscle.[19] Thus, both potentiation and reduction of force with exercise accompany parallel changes in vibration amplitude. 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. In children with muscle diseases, this ratio yielded an abnormal results in 13 of 16 patients, for a sensitivity of 82 percent and a specificity of 91 percent and normal results in 10 of 11 control subjects, indicating possible diagnostic values.[18] In a study of seven healthy adults, integrated acoustic and electromyographic activity increased linearly up to the maximal voluntary isometric force in

the quadriceps muscle.[240] After fatiguing activity, the slopes of the regression lines increased for electrical activities but remained the same for acoustic signals.[241] This technique may have some value in the assessment of muscular fatigue[123,205] and spastic contraction.[4] Its clinical application as a diagnostic test, however, needs further scrutiny.

Sonographic Imaging

Sonographic imaging of muscle may help evaluate the location and type of pathology. In 30 patients with partially or completely denervated muscles, initial pathologic ultrasound changes could be detected as soon as 2 weeks after an acute neurogenic lesion.[108] In 70 patients with histologically proven myositis, different types of inflammatory myopathies showed typical, but not specific, ultrasound features.[202] This test improves clinical assessment of patients by supplying precise muscle size measurements and identification of structural abnormalities. Sonography also effectively images fasciculations, demonstrating them in both resting and actively contracting extremity muscles and in less accessible muscles such as the tongue.[255]

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Chapter 14

TYPES OF ELECTROMYOGRAPHIC ABNORMALITIES

1 INTRODUCTION

Electromyographic studies analyze the propagating muscle action potentials extracellularly (see Chapter 13–2). Except for the end-plate activities and brief injury potentials coincident with the insertion of the needle, a relaxed muscle is electrically silent. Several types of spontaneous discharges seen at rest, therefore, all signal diseases of the nerve or muscle, although they do not necessarily carry the same clinical implications. Both fibrillation potentials and positive sharp waves result from excitation of individual muscle

fibers, whereas complex repetitive discharges comprise high-frequency spikes derived from multiple muscle fibers; these discharge sequentially and maintain a fixed order.

A motor unit is the smallest functional element of volitional contraction. In conventional electromyography, isolated discharges of single motor axons give rise to motor unit potentials. 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 motor unit potentials provides information useful in elucidating the nature of the disease.

Electromyography serves as a clinical tool only if the examiner interprets the findings in the light of the patient's history, physical examination, and other diagnostic studies. In fact, the study constitutes an extension of physical examination, rather than an independent laboratory test. The four steps of electromyography (see Fig. 13–1) help categorize motor dysfunction into upper and lower motor neuron disorders and myogenic lesions. Each entity has typical findings, as shown in Figures 14–1, through 14–3 and summarized in Figure 14–4. As a means of introduction, the illustrations 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.

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). Functionally inexcitable muscle fibers will also show the same abnormality during attacks of familial periodic paralysis. Absence of any activity, however, more often than not signals technical problems such as a broken lead wire, a faulty needle, or

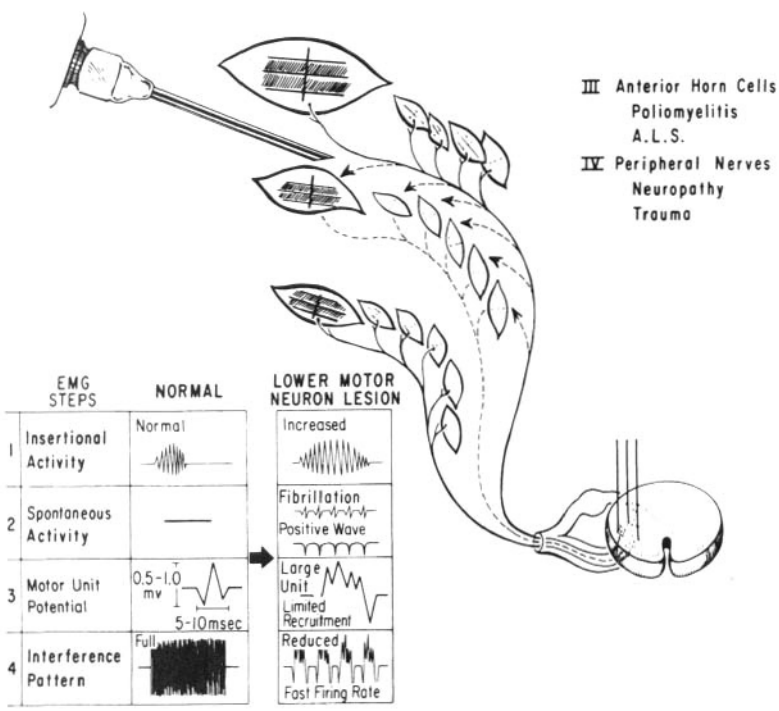


Figure 14–1. Typical findings in lower motor neuron lesions. They include (*1*) prolonged insertional activity, (*2*) spontaneous activities in the form of fibrillation potentials and positive sharp waves, (*3*) large-amplitude, long duration polyphasic motor unit potentials, and (*4*) discrete single 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, regeneration increases muscle fiber density, but not necessarily motor unit territory.

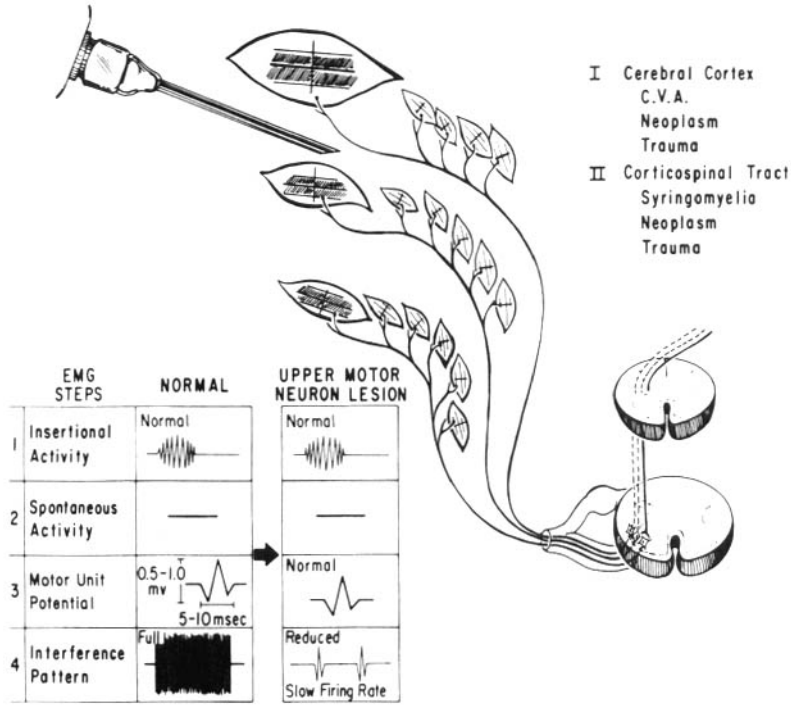


Figure 14–2. Typical findings in upper motor neuron lesions. They include (*1*) normal insertional activity, (*2*) no spontaneous activity, (*3*) normal motor unit potential if detected in an incomplete paralysis, and (*4*) reduced interference pattern with slow rates of firing of individual motor unit potentials. 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.

inadvertent exploration of the subcutaneous fat instead of muscle tissue by the examiner (underestimating the depth of obesity, for example). Abnormally prolonged insertional activity, outlasting the cessation of needle movement, indicates irritability of the muscle or, more specifically, instability of the muscle membrane (see Fig. 13–2 and 14–1). This type of activity often develops in conjunction with

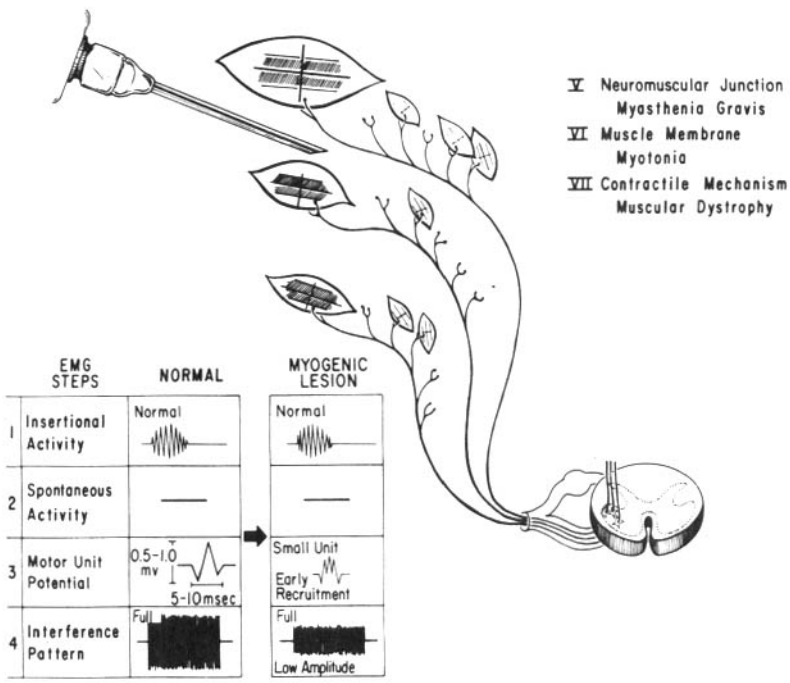


Figure 14–3. Typical findings in myogenic lesions. They include (*1*) normal insertional activity, (*2*) no spontaneous activity, with some notable exceptions, (*3*) low-amplitude, short-duration, polyphasic motor unit potentials, and (*4*) early recruitment leading to a low-amplitude, full-interference 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.

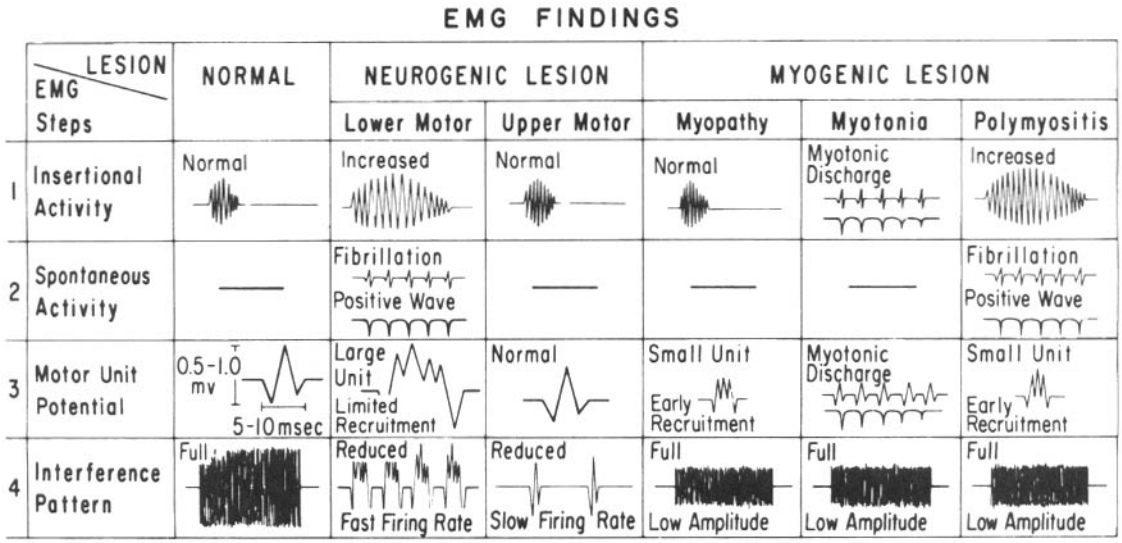


Figure 14–4. Typical findings in lower and upper motor neuron disorders and myogenic lesions as shown in Figures 14–1 through 14–3. Myotonia shares many features common to myopathy in general in addition to myotonic discharges triggered by insertion of the needle or with voluntary effort to contract the muscle. Polymyositis shows combined features of myopathy and neuropathy, including (*1*) prolonged insertional activity, (*2*) abundant spontaneous discharges, (*3*) low-amplitude, short-duration, polyphasic motor unit potentials, and (*4*) early recruitment leading to a low-amplitude, full-interference pattern.

denervation, myotonic disorders, or certain other myogenic disorders such as myositis.[84] In addition, in some healthy individuals one or two isolated positive potentials may occur at the end of the discharge.[157] The lack of reproducibility distinguishes this variant of normal insertional activity from qualitatively similar insertional positive waves, described below.

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. 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 from frankly denervated muscles at rest. In fact, abnormal insertional activity of this type commonly appears in the early stages of denervation, 10 days to 2 weeks after nerve injury, before the appearance of spontaneous activity. It may also occur in chronically denervated muscles or in association with rapidly progressive degeneration of muscle fibers in acute polymyositis. In these cases, positive sharp waves also appear 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 occur without apparent triggering mechanisms. Needle movement also enhances spontaneous activity, making differentiation between insertional and noninsertional activities somewhat arbitrary.

Insertional positive waves seen in denervated muscles have an abrupt onset and termination without a waxing and waning quality. Nonetheless, a few positive waves in the first seconds after insertion of the needle may mimic a mild form of myotonic discharge; hence the now-abandoned term *pseudomyotonia*. Similarly, an abortive form of myotonic discharge seen immediately after prolonged exercise resembles insertional positive waves of early denervation. This finding in otherwise asymptomatic subjects suggests a forme fruste of myotonia congenita of autosomal

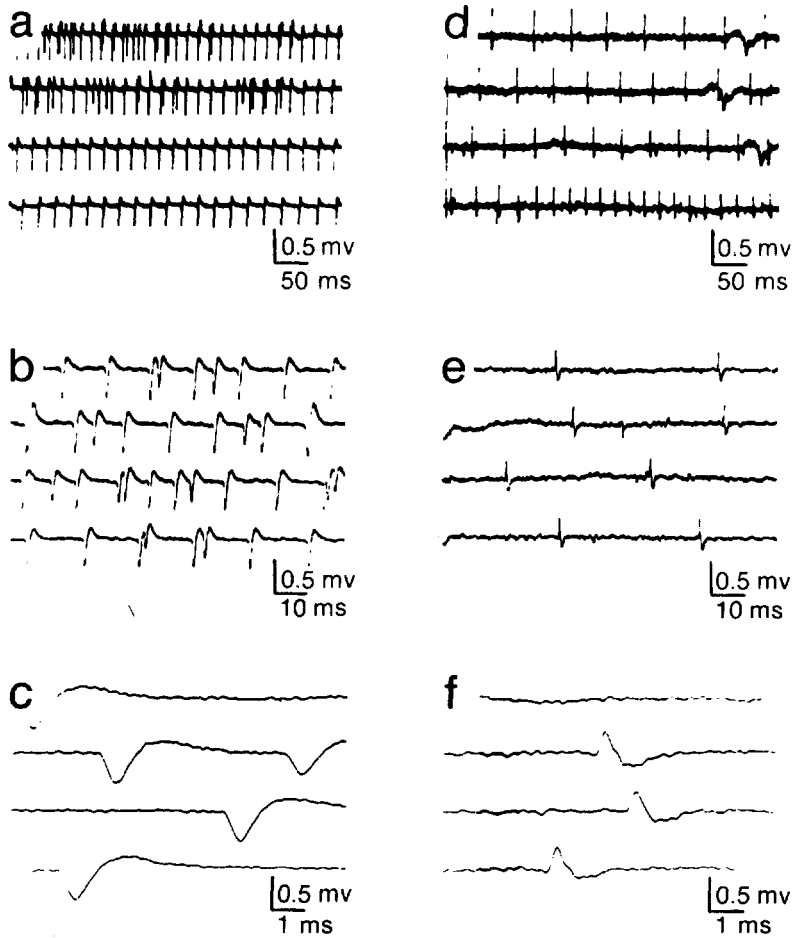


Figure 14–5. Spontaneous single-fiber discharges from the right paraspinal muscle in a 62-year-old woman with polymyositis. The tracings show two types of discharges: trains of positive sharp waves (*a,b,c*) and negative spikes (*d,e,f*) initiated by insertion of the needle electrode. The lack of initial positivity indicates the recording of the negative spikes near the end plate region, although their rhythmic pattern speaks against the physiologic end-plate spikes. Note the absence of waxing and waning quality typically associated with myotonic potentials. (cf. Figure 14–7).

dominant inheritance.[152,159] Exaggerated insertional positive waves may also accompany some metabolic disorders, such as myopathies associated with hypothyroidism (Fig. 14–6).

3 MYOTONIC DISCHARGE

A sustained contraction of the muscle follows voluntary movement or electrical or mechanical stimulation in myotonia congenita, myotonia dystrophica, paramyotonia congenita,[154] or hyperkalemic periodic paralysis[20,45,100] (see Chapter 29–2). The electromyographic correlates of clinical myotonia consist of rhythmic discharges that are triggered by insertion of the needle electrode but that outlast the external source of excitation. Myotonic discharges do not necessarily accompany clinical myotonia when seen in polymyositis, type II glycogen storage disease with acid maltase deficiency,[65] some form of myopathy such as cytoplasmic body myopathy resembling myotonic dystrophy[101] or other disorders characterized by chronic denervation.

Positive versus Negative Discharge

Myotonic discharges take two forms, depending on the spatial relationship between the recording surface of the needle electrode 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. 14–7). These waveforms, like those of denervation, represent recurring single-fiber

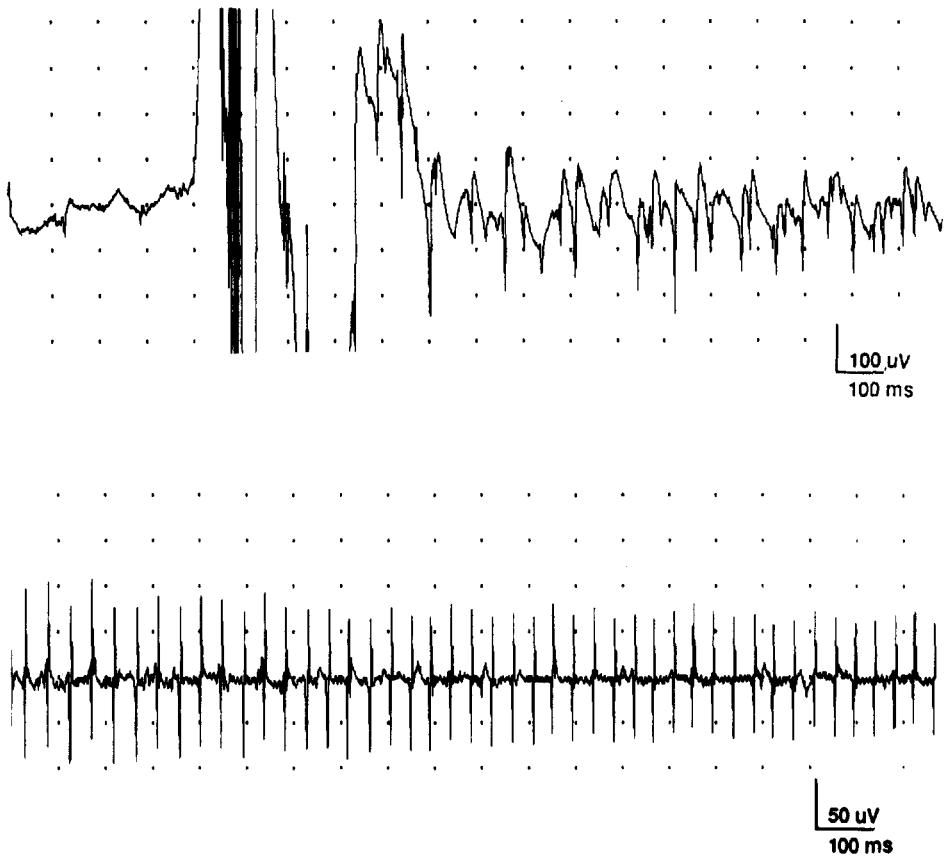


Figure 14–6. A 40-year-old woman with hypothyroidism. Electromyography showed increased insertional activities followed by sustained repetitive positive sharp waves, at times generating a transient myotonic discharge.

potentials recorded from an injured area of the muscle membrane. A second type of myotonic discharge consists of a sustained run of negative spikes with a small initial positivity. These spikes resemble the fibrillation potentials seen in denervation. 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 50–100 impulses per second, giving rise to a characteristic noise over the loudspeaker that is reminiscent of an accelerating or decelerating motorcycle or chain saw. Despite common belief, a myotonic discharge does not closely simulate the sound of a dive-bomber, judged from my extensive personal experience (with dive-bombers).

Pathophysiology

The pathophysiology of myotonic discharge, although not yet established in humans, relates to abnormalities of chloride (Cl^-) and sodium (Na^+) channels.[67] A decrease in resting chloride conductance results in repetitive electrical activity in isolated frog[52] and mammalian skeletal muscles.[92] Electrophysiologic studies show abnormalities attributable to decreased density of chloride channels in hereditary myotonia of goats.[91] In normal fibers, the presence of chloride conductance stabilizes the membrane potential

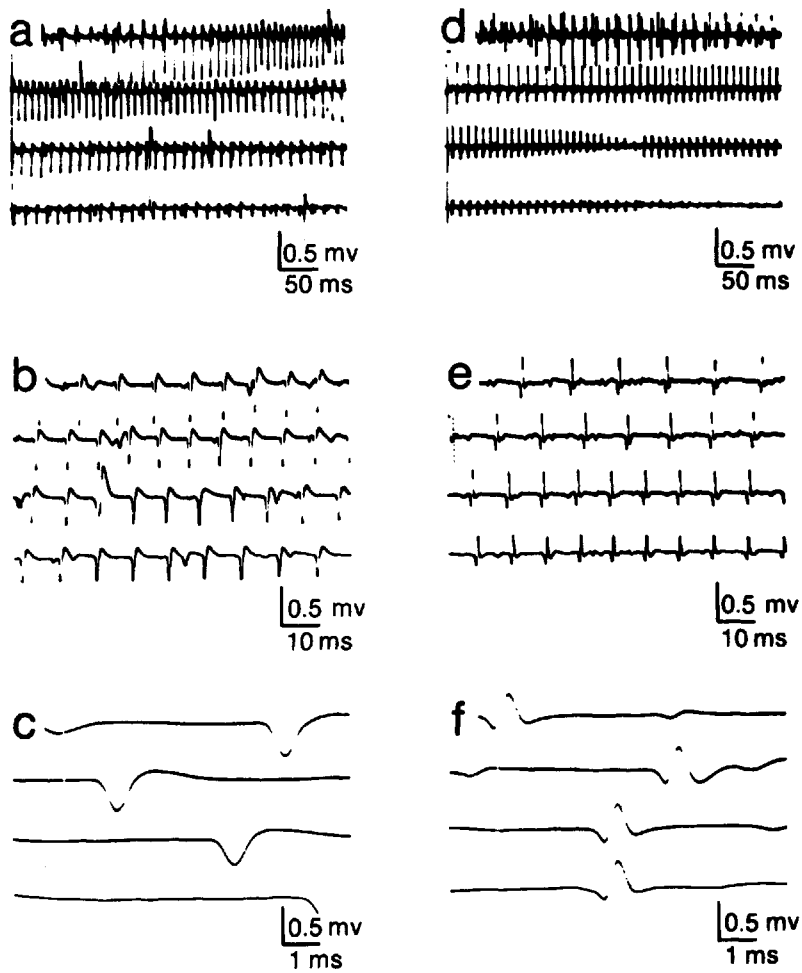


Figure 14–7. Myotonic discharges from the right anterior tibialis in a 39-year-old man with myotonic dystrophy. The tracings show two types of discharges: trains of positive sharp waves (*a,b,c*) and negative spikes with initial positivity (*d,e,f*). The discharges in *a* and *d* reveals waxing and waning quality.

by shunting the depolarizing current and dampening its effect. Conversely, the absence of chloride conductance in effect raises the resistance of the membrane. According to Ohm's law (E = IR) increased resistance, R, will reduce the amount of current, I, necessary to initiate a threshold depolarization, E.

The critical level of depolarization opens the sodium channel with a rapid change in sodium conductance, which in turn initiates an action potential. The action potential falls with inactivation of sodium conductance and delayed activation of potassium (K^+) conductance, which 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.[14] 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.[85] Pharmacologic blocking of the acetylcholine receptor or atropine binding site effectively silences fibrillation potentials, but not myotonic discharges.[12]

Paramyotonia and hyperkalemic periodic paralysis result from a number of mutations in the adult skeletal muscle sodium channel gene, which is located on chromosome 17q 23–25.[115] For reasons not completely understood, patients with the same mutation may have variable clinical findings (see Chapter 29–3). Con-

versely, 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.[154] 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.[126] Inactivation of normally functioning sodium channels by further cooling or exercise results in inexcitability of the muscle fiber and paralysis.

4 SPONTANEOUS ACTIVITY

Types of Spontaneous Discharges

Basic types of spontaneous activity comprise fibrillation potentials, positive sharp waves, complex repetitive discharges, fasciculation potentials, and myokymic discharges. Isolated visible muscle twitches over a localized area may accompany fasciculation potentials and complex repetitive discharges, but not fibrillation potentials or positive sharp waves. Myokymic discharges seen in cramp syndromes cause sustained segmental contraction (see Chapter 29–6). In contrast, more generalized muscle spasms characterize the syndrome of neuromyotonia representing peripheral nerve hyperexcitability. Patients with the stiff-man syndrome also suffer from similar involuntary muscle contraction, although the discharges responsible originate in the central nervous system.

Both fibrillation potentials and positive sharp waves represent single-fiber activation.[32,33,41,44,82,83] In contrast, complex repetitive discharges result from rapid firing of many muscle fibers in sequence, driven ephaptically at a point of lateral contact.[48,137] A spontaneously activated single fiber serving as a pacemaker regulates the frequency and pattern of discharge by two different, usually independent, mechanisms: rate of rhythmic depolarization of the denervated muscle fiber and circus movements of currents among muscle fibers.[71]

Fasciculation potentials are isolated spontaneous discharges of a motor unit. In contrast, myokymic discharges represent repetitive firing of a motor unit, as the name *grouped fasciculation* indicates.

Numeric grading serves to semiquantitate each of these spontaneous activities:

+1—Rare spontaneous potentials recordable at one or two sites only after some search. This category includes positive discharges elicited after moving the needle electrode (i.e., insertional positive sharp waves).
+2—Occasional spontaneous potentials registered at more than two different sites.
+3—Frequent spontaneous potentials recordable regardless of the position of the needle electrode.
+4—Abundant spontaneous potentials nearly filling the screen of the oscilloscope.

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.[94,144] This phenomenon, known as *denervation hypersensitivity*, may explain spontaneous discharges of denervated muscle fibers in response to small quantities of circulating ACh.[38,141] The disappearance of fibrillation potentials after artificially induced ischemia[64] and in isolated muscle fibers[141] also supports the presence of some circulating substance. In rats, fibrillation potentials cease after application of alpha-bungarotoxin or atropine sulfate.[12] Therefore, the receptor molecules for these agents must play an essential part in the production of spontaneous activity. In experiments using rat soleus muscles, fibrillation potentials appeared earlier after complete denervation than after partial denervation. The time difference seemed to reflect a more gradual increase in the number of acetylcholine receptors and a greater sensitivity to tetrodotoxin of the partially denervated muscles.[3]

Experimental data have been marshaled against the ACh hypersensitivity hypothesis: (*1*) The large amount of circulating ACh reaching the end plate combines with acetylcholinesterase 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,[147] rather than a specific change localized to the end-plate region.[5] Spontaneous activity, however, seems to originate only in the end-plate zone and not elsewhere along the nonjunctional membrane.[6] Further, the infusion of curare blocks the end-plate receptors but fails to abolish spontaneous discharges. (*3*) Denervation of frog muscle may cause increased sensitivity to ACh but produces no spontaneous activity.[96] 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,[141] denervation–induced alteration of the mechanisms that control refractory periods of sodium channels,[79] and reduction of extracellular calcium (Ca^{2+}) concentration based on suppressing effects of dantrolene sodium on fibrillation potentials.[70]

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.[23] These potentials usually have diphasic or triphasic waveforms with initial positivity (Fig. 14–8), unless the tip of the needle electrode faces the end plate zone, registering an initial negativity. Physiologic end-plate spikes also have an initial negativity, but unlike spontaneous activity recorded at the end plate, they fire irregularly at a very high rate. 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) or 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 impulses per second, with an average frequency of 13 impulses per second.[23,141] The firing rate may be proportional to oxygen supply, presumably reflecting the rate of aerobic metabolism.[69] The decreased resting membrane potential in the denervated muscle plays a critical role as the cause of the oscillations.[142] Fibrillation potentials originating from the same muscle fiber may occasionally fire irregularly in the range of 0.1–25 impulses per second.[19,97] These potentials result from random, discrete, spontaneous depolarization of nearly constant amplitude.[19] A very irregular firing pattern, however, usually represents discharges from more than one fiber. A new class of sodium channels that develops after denervation may cause reduced sodium inactivation. Increased sodium conductance presumably accounts for progressive lowering of the firing threshold, giving rise to cyclical activities.[116]

Voluntarily activated single-fiber potentials and fibrillation potentials have the same shape and amplitude distribution when studied with single-fiber electromyography (SFEMG).[135] 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.[38,72] The now-abandoned concept of the subunit led to the earlier erroneous belief that 10–30 muscle fibers must discharge to generate a single potential.[23,24]

Positive Sharp Waves

Positive sharp waves, which also represent single-fiber activation, have a saw-

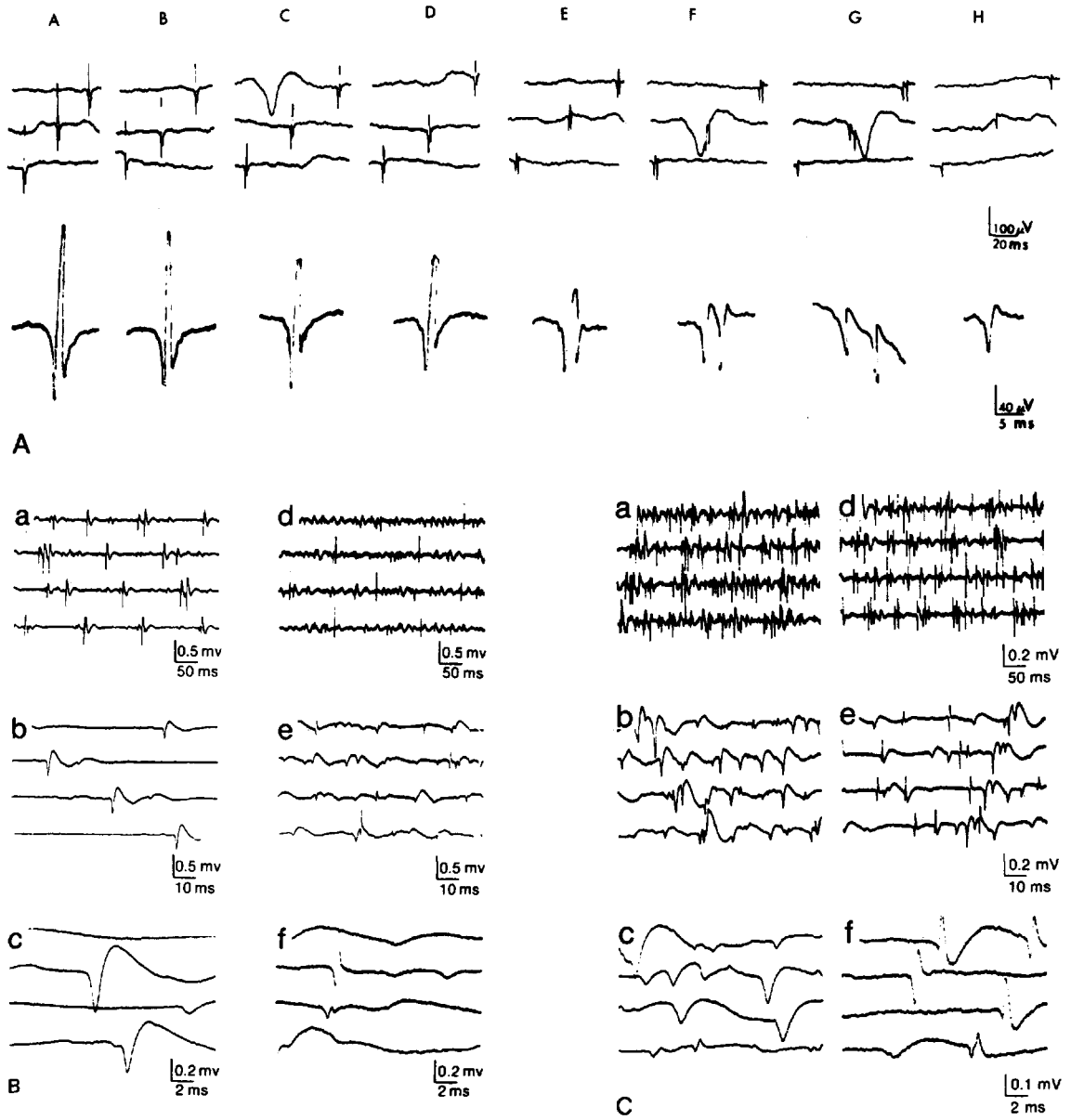


Figure 14–8. A. Single-fiber discharges recorded from the denervated tibialis anterior in a 67-year-old man with acute onset of a footdrop (cf. Fig. 5–6). Note gradual alteration of the waveform from a triphasic spike with major negativity to paired positive potentials and finally to a single positive 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. [From Kimura,[76] with permission.] **B.** Spontaneous single-fiber activity of the anterior tibialis in a 68-year-old woman with amyotrophic lateral sclerosis. The tracings show two types of discharges: positive sharp waves (*a,b,c*) and fibrillation potentials (*d,e,f*). **C.** Spontaneous single-fiber activity of the paraspinal muscle in a 40-year-old man with radiculopathy, consisting of positive sharp waves (*a,b,c*) and fibrillation potentials (*d,e,f*).

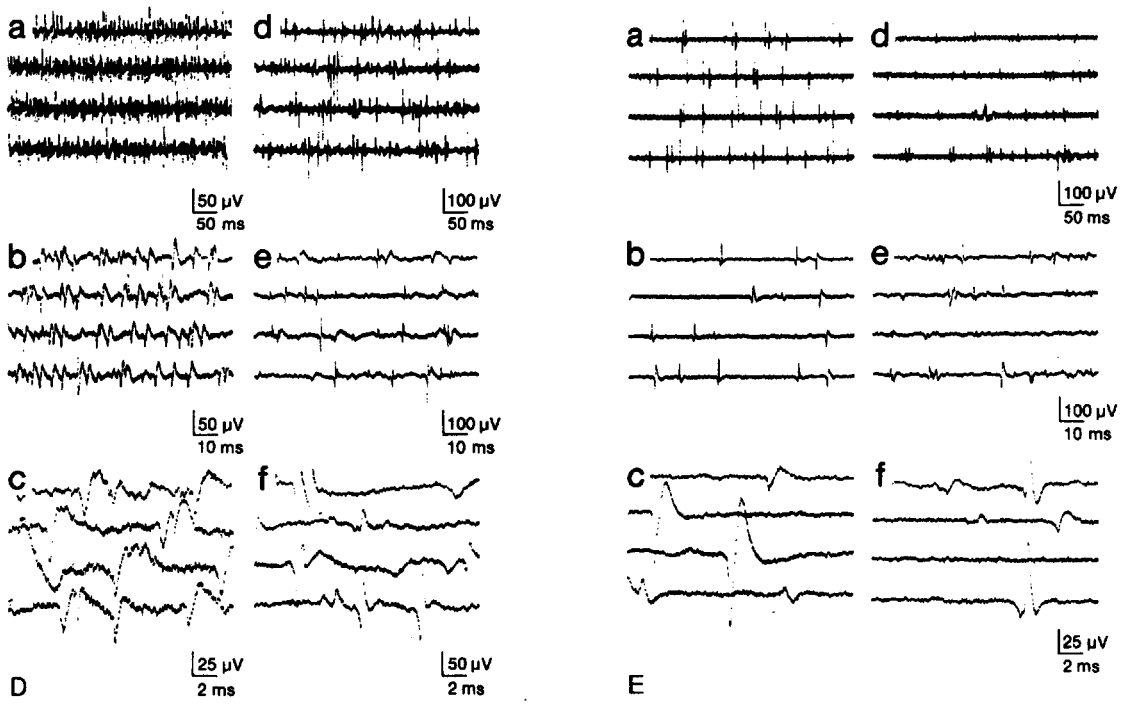


Figure 14–8. (*cont.*) D. Spontaneous single-fiber activity of the deltoid (*a,b,c*) and tibialis anterior (*d,e,f*) in a 9-year-old boy with a 6-week history of dermatomyositis, with two types of discharges: positive sharp waves (*a,b,c*) and fibrillation potentials (*d,e,f*). **E.** Spontaneous single-fiber activity of the tibialis anterior in a 7-year-old boy with Duchenne dystrophy, showing positive sharp waves (*a,b,c*) and fibrillation potentials (*d,e,f*).

tooth appearance with the initial positivity and a subsequent slow negativity, much lower in amplitude but longer in duration. They often follow insertion of the needle but also fire spontaneously at regular intervals (Fig. 14–8). The physical relationship between the generator and the recording electrode dictate the waveform of the potential.[42] If the tip of the needle damages the membrane, then 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 gives rise to a sharp positive discharge followed by a low-amplitude negative deflection. Therefore, the absence of a negative spike implies recording near the damaged part of the muscle fiber. Although usually seen together after nerve section, the appearance of fibrillation potential often lags behind that of positive sharp waves, which can be triggered by the insertion of a needle.[156] As discussed earlier, positive sharp waves may form part of myotonic discharges, triggered by insertion of the needle or by mild voluntary contraction. Despite the close resemblance in waveform, myotonic discharges, which characteristically wax and wane, do not appear spontaneously.

Spontaneous Single-Fiber Discharges in Clinical Domain

Spontaneous activity, if reproducible at a minimum of two muscle sites, provides an unequivocal sign of abnormality and is one of the most useful findings in clinical electromyography. It usually suggests lower motor neuron disorders, such as diseases of anterior horn cells, radiculopathies, plexopathies, and axonal polyneuropathies. Because of the latency period of 2–3 weeks, however, the absence of spontaneous activity does not preclude

denervation during the early weeks of nerve injury. When found in disorders of the lower motor neuron, the distribution of spontaneous potentials can aid in localizing lesions of the spinal cord, root, plexus, or peripheral nerve.

Fibrillation potential amplitude seems to relate to muscle atrophy after peripheral nerve injury. In one study,[81] the maximum peak-to-peak amplitude measured in 69 subjects declined from 612 μV during the first 2 months after injury to 512 μV during the third and fourth months and 320 μV during the fifth and sixth months. After the first year, all fibrillation potentials were reduced to less than 100 μV in amplitude.

Spontaneous discharges also characterize certain myopathic processes such as muscular dystrophy, dermatomyositis, and polymyositis. Less consistently, diseases of the neuromuscular junction give rise to fibrillation potentials, as do many other disorders,[58,111] such as facioscapulohumeral dystrophy, limb-girdle dystrophy, oculopharyngeal dystrophy,[62] myotubular, or centronuclear, myopathy,[133] and trichinosis.[152] Fibrillation potentials found in 25 percent of patients with progressive muscular dystrophy[23] result at least in part from denervation secondary to muscle necrosis.[39] Spontaneous activity in polymyositis suggests increased membrane irritability,[9] inflammation of intramuscular nerve fibers,[119] or focal degeneration separating a part of the muscle fiber from the end-plate region.[130] In support of postulated functional denervation, SFEMG and histochemical techniques revealed evidence of reinnervation in the terminal innervation pattern.[63] Like fibrillation potentials, positive sharp waves are seen not only in denervated muscles but also in a variety of myogenic conditions. The latter group includes polymyositis, dermatomyositis, trichinosis, ischemic myositis, and progressive muscular dystrophy.

Spontaneous discharges also occur, though not consistently, in otherwise uninvolved paretic limbs between 6 weeks and 3 months after the onset of acute upper motor neuron lesions.[29,73,74] One study[78] reported spontaneous activity in 68 percent of the arms and 70 percent of the legs on the affected side in 50 hemiplegic patients without apparent plexus injury. In another study,[25] 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 with 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 motor neurons.[26] As a rule, no spontaneous activity develops in disuse atrophy. Spontaneous activity may also appear in the paraspinous muscles after myelography or lumbar puncture, developing by the first day after the procedure and resolving by the second through the fourth day.[30,153]

In addition, fibrillation potentials and positive sharp waves may occasionally appear in otherwise healthy muscles. An isolated incidence, therefore, cannot serve as absolute evidence of a specific abnormality. Spontaneous discharges can occur in the absence of clinical signs or symptoms, presumably reflecting subclinical nerve injury. For example, 9 of 62 asymptomatic subjects had spontaneous discharges in lumbosacral paraspinal muscles.[31] Similarly, 7 of 21 asymptomatic subjects showed abnormalities in the extensor digitorum brevis or abductor hallucis muscles.[99] These changes alone, therefore, are of limited clinical importance, unless corroborated by other means.

Complex Repetitive Discharges

The complex repetitive discharges range from 50 μV to 1 mV in amplitude and up to 50 to 100 ms in duration, representing a group of muscle fibers firing in near synchrony (Figs. 14–9 and 14–10). 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

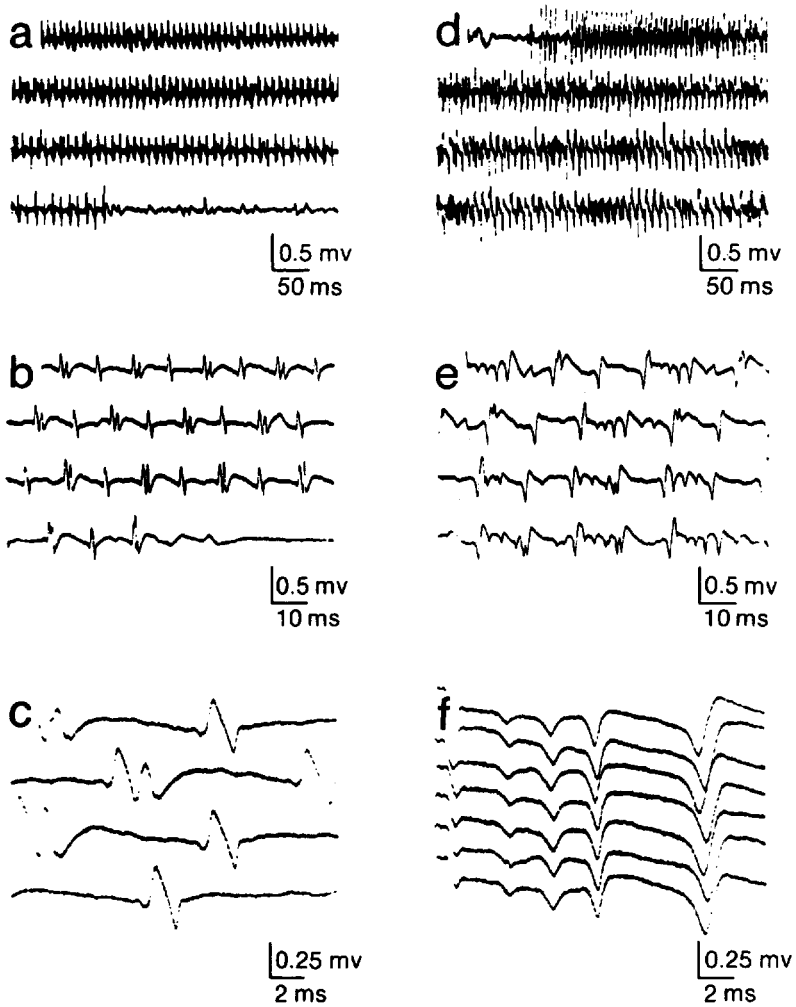


Figure 14–9. Complex repetitive discharges of the left quadriceps in a 58-year-old man with a herniated lumbar disc. The tracings show two types of discharges: trains of single- or double-peaked negative spikes (*a,b,c*) and complex positive sharp waves (*d,e,f*). In *f*, each sweep, triggered by a recurring motor unit potential, shows remarkable reproducibility of the waveform within a given train.

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 the firing pattern—showing an identical waveform from one burst to the next—make the complex repetitive discharges distinct from myokymia, neuromyotonia, and cramp syndromes, despite their superficial resemblance (see Chapter 29–4, 29–6, 29–11).

In single-fiber recordings,[137] complex repetitive discharges often consist of 10 or more distinct unit potentials separated 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. One fiber in the complex serves as a pacemaker, initiating the burst and driving one or several other fibers ephaptically.[137,147] In successive cycles, one of the remaining fibers activated late in the previous cycle, reexcites the principal pacemaker to repeat the cycle until the pacemaker fibers eventually fail. The electrical field associated with this repetitive pattern must effectively induce ephaptic activation of neighboring muscle fibers. Thus, complex repetitive discharges often give rise to high-amplitude spikes, compared with fibrillation potentials.

This discharge is seen in some myopathies, such as muscular dystrophy or polymyositis, and in a wide variety of

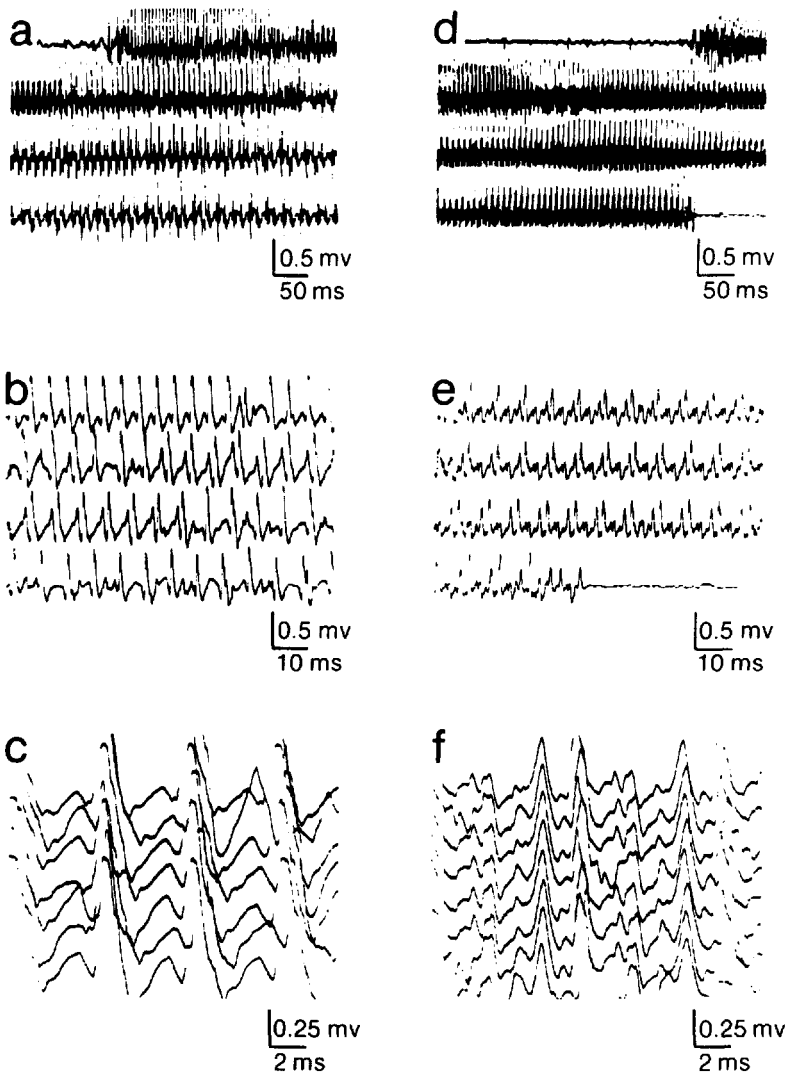


Figure 14–10. Complex repetitive discharges with trains of negative spikes from the same muscle shown in Figure 14–9. Note gradual decline of discharge frequency in one train (*a,b,c*) but not the other (*d,e,f*), and the characteristically abrupt onset and cessation (*a,d,e*). In *c* and *f*, each sweep, triggered by a recurring motor unit potential, shows a detailed waveform of the repetitive patterns.

chronic denervating conditions, such as motor neuron disease, radiculopathy, chronic polyneuropathy, myxedema, and the Schwarz-Jampel syndrome sometimes associated with neurogenic muscle hypertrophy.[125] In a large series,[48] overall analysis of the prevalence revealed its highest incidence in Duchenne muscular dystrophy, spinal muscular atrophy, and Charcot-MarieTooth disease. Women with urinary retention may have profuse activity of this type in the striated muscle of the urethral sphincter.[56] Apparently healthy subjects may occasionally show the complex repetitive discharges 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 and Myokymic Discharges

Clinicians once referred to visible twitching of muscle bundles as *fibrillation*, a term now reserved for the electromyographic description of spontaneously firing single muscle fibers. To avoid confusion, the term *fasciculation* was proposed to describe the spontaneous contraction of motor units.[38] Fasciculation potentials

result from spontaneous discharges of a group of muscle fibers representing either a whole or possibly part of a motor unit (Fig. 14–11). Motor unit potentials deep within the muscle may not necessarily induce visible twitches. In such instances, electromyography allows detection of this spontaneous activity, which would otherwise remain unrecognized.

Unlike normal voluntary motor unit potentials, 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 existing evidence favours a very distal site of origin at or near the motor terminals.[87] The neural discharge, however, may originate in the spinal cord or anywhere along the length of the peripheral nerve.[155] In one study using a collision method and F-wave analysis, nearly all fasciculations had an axonal origin.[121] Fasciculations may appear transiently after administration of an anticholinesterase medication or a depolarizing neuromuscular blocker.[114] Fasciculation potentials may sometimes persist despite distal nerve block. After total removal of the nerve supply to the muscle, they remain for about 4 days and then disappear.[55]

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 29–6).[28] Repetitive firing of the same motor units usually occurs in bursts at regular intervals of 0.1–10 seconds, with 2–10 spikes discharging at 30–40 impulses per second in each burst (Fig. 14–12). Myokymic discharges commonly, though not specifically, involve facial muscles in patients with brainstem glioma or multiple sclerosis. Myokymic discharges also favor certain chronic neuropathic processes, such as Guillain-Barré syndrome[95] and radiation plexopathies.[1,2,35] Hyperventilation induces hypocalcemia, which in turn amplifies axonal excitability and myokymic bursts, generated ectopically in demyelinated motor fibers.[11]

Fasciculation potentials, although typically associated with diseases of anterior horn cells, also occur in radiculopathy, entrapment neuropathy, and the muscular pain–fasciculation syndrome.[66] In patients with cervical spondylotic myelopathy, fasciculation 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.[75,77] Fasciculation potentials also accompany some metabolic derangements such as tetany, thyrotoxicosis, and overdoses of anticholinesterase medication.[35] Grouped occurrence of fasciculation potentials from multiple units tends to show frequent association with amyotrophic lateral sclerosis and progressive spinal muscular atrophy. They do not necessarily imply an ominous prognosis, however, because they are also seen in other degenerative diseases of the anterior horn cells, including poliomyelitis and syringomyelia. Synchronous fasciculations seen in muscles supplied by different nerves or in homologous muscles on opposite sides possibly suggest an intraspinal mechanism[105] or a reflex origin via spindle afferent triggered by the arterial pulse.[123]

Either single or grouped spontaneous discharges occur commonly in otherwise normal muscle,[98] sometimes, but not always, causing cramps. These benign fasciculations are not a prelude to progressive motor neuron disease. Data obtained from a questionnaire survey of a group of 539 healthy medical personnel indicate that 70 percent have experienced some type of muscle twitch.[117] Long-term follow-up of 121 patients with benign fasciculations revealed no incidence of motor neuron disease.[8] Because of the serious implications, a number of investigators have sought to differentiate this form of fasciculation potential from that associated with motor neuron disease, 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.[118,146] The frequency of discharge, however, may separate the two categories;

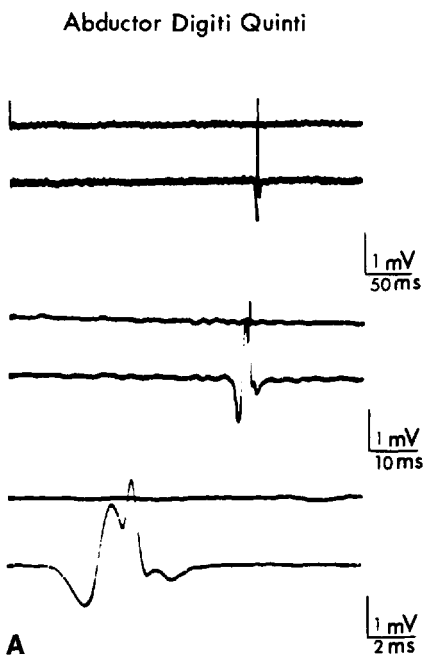
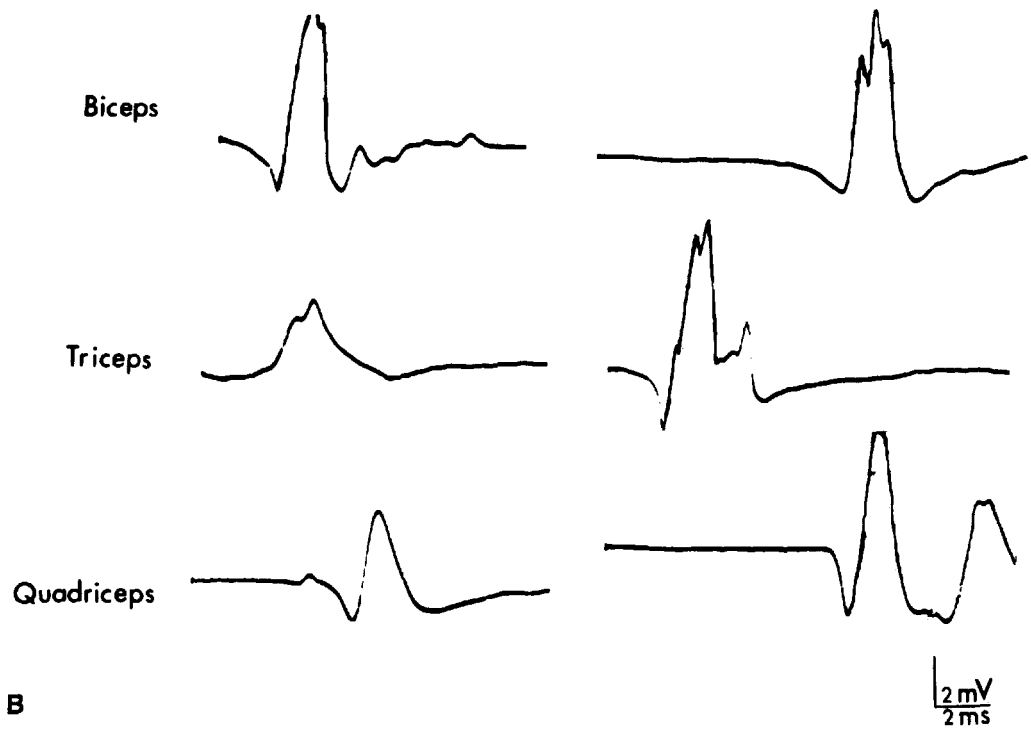


Figure 14–11. A. A 59-year-old man with pain in the posterior calf after a fall from a ladder, landing on his feet. Electromyography showed fibrillation potentials and sharp positive waves in the abductor hallucis and only fasciculation potentials in the abductor digiti quinti. [From Kimura,[76] with permission.] **B.** A 58-year-old man with muscular pain fasciculation syndrome of 1 year's 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. [From Kimura,[76] with permission.]



irregular firing at an average interval of 3.5 seconds in patients with motor neuron disease compared with 0.8 seconds in asymptomatic individuals.[37,146] The discharges in amyotrophic lateral sclerosis characteristically arise proximally early in the disease and distally in the later stages.[37]

In conclusion, fasciculation potentials by themselves cannot provide absolute proof of abnormality, unless they are accompanied by either fibrillation potentials or positive sharp waves. Excluding those seen in healthy subjects, fasciculation potentials suggest disease of the lower motor neuron 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

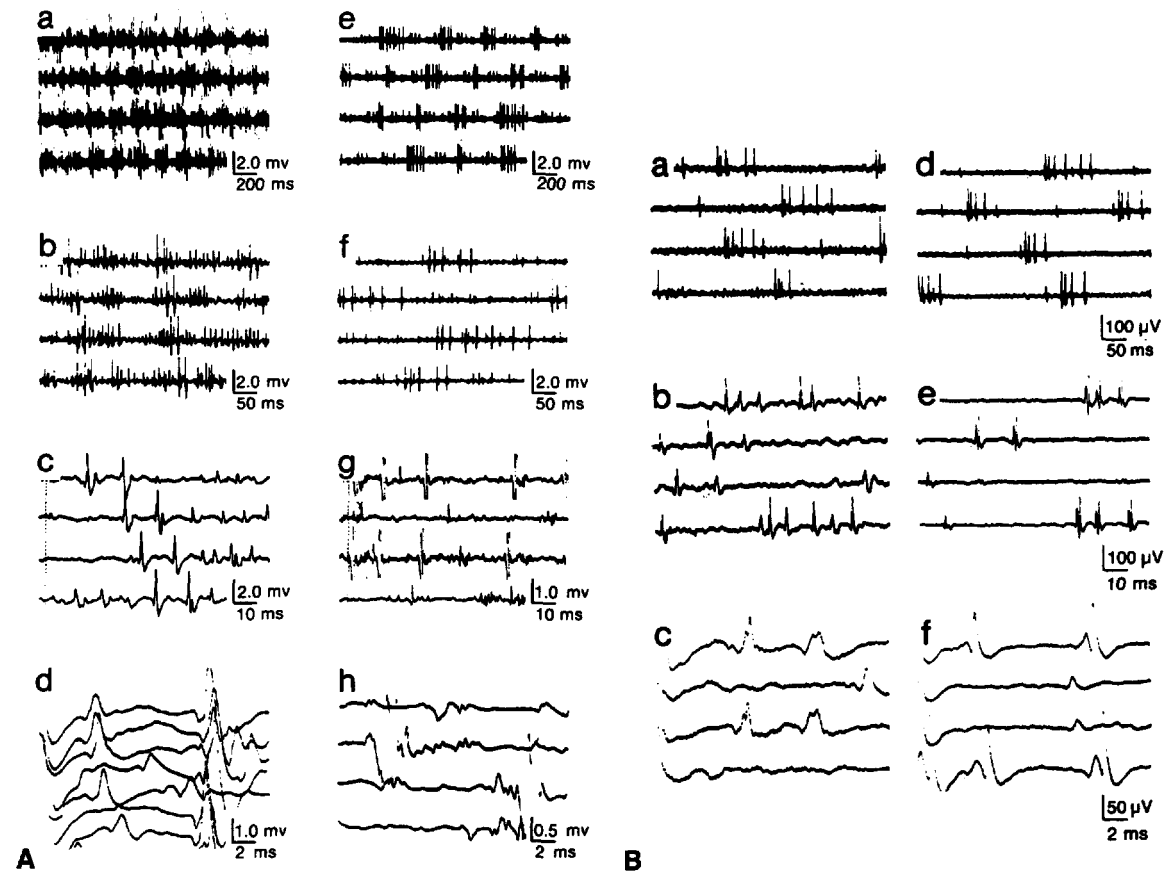


Figure 14–12. A. Myokymic discharges in a 21-year-old woman with multiple sclerosis. The patient had visible undulating movement of the facial muscles on the right associated with characteristic bursts of spontaneous activity recorded from the orbicularis oris (*a,b,c,d*) and the orbicularis oculi (*e,f,g,h*). 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 Guillain-Barré syndrome and 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.

normal muscle and "malignant" forms associated with motor neuron disease. The dichotomy, therefore, serves no useful purpose in the clinical domain. To characterize a recorded discharge, the description should consist of its waveform, amplitude, duration, firing pattern, and frequency of occurrence.

Continuous Muscle Fiber Activity

Continuous muscle fiber activity refers to the diffuse, sustained spontaneous motor unit activity seen in a heterogeneous group of central or peripheral disorders.[46] Stiff-man syndrome represents a rare but well-recognized entity characterized by sustained involuntary discharges of central origin (see Chapter 29–10). A needle recording reveals normal motor unit potentials that produce a sustained 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, also abolishes or attenuates the activity.

A descriptive term, *neuromyotonia*, probably serves best to describe continuous muscle fiber activity of peripheral origin.[59] Other names used include Isaacs' syndrome, quantal squander, generalized myokymia, pseudomyotonia and normocalcemic tetany[68,104] (see Chapter 29–4). These syndromes probably constitute different diseases that vary in their clinical and electrophysiological presentations despite the shared feature of sustained involuntary motor activity. The sites of generator responsible for different discharges vary from proximal segments of the nerve to the intramuscular nerve terminals.[93,122,143] Excess motor unit activity remains during sleep and after general or spinal anesthesia. Nerve block will be effective if abnormal discharges originate more proximally. 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, thus the name *neuromyotonia*. Needle studies demonstrate motor unit discharges with frequencies up to 300 Hz associated with a characteristic "pinging" sound. The firing motor unit potentials decline in amplitude slowly or rapidly as increasing numbers of muscle fibers fail to follow the high rate of repetitive pattern. 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.

Cramps

Cramp constitutes the sustained involuntary contraction of a muscle in part or in entirety, either as a normal phenomenon or as a sign of abnormality in pathologic conditions (see Chapter 29–11). The responsible impulses originate in the peripheral nerve, but the exact underlying mechanism of cramping remains unknown. Some studies suggest cramps may result from mechanical excitation of motor nerve terminals during muscle shortening.[87,88,89,106] Peripheral nerve block often abolishes the activity, but spinal or general anesthesia has no effects. After severe cramps, the pain may persist for days. Needle recording consists of repetitive discharges of normal motor unit potentials 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 sites may be activated simultaneously or sequentially. The discharges wax and wane for several minutes, then abate spontaneously.

5 MOTOR UNIT POTENTIALS

The measures to define a motor unit potential comprise amplitude, rise time, duration, phases, stability, and territory. A wide range of neuromuscular disorders alters the waveform in different but characteristic combinations. Hence, such abnor-

malities help distinguish primary muscle diseases from disorders of neuromuscular junction and lower motor neurons. A decrease in spike duration and amplitude characterizes motor unit potentials in myopathies associated with random loss of individual fibers.[22] In neuropathies or anterior horn cell diseases, a loss of axons results in a reduced number of units, although surviving fibers with sprouting give rise to a larger potential than normal. Thus, taken together with abnormalities of insertional and spontaneous activities, changes in the size and recruitment pattern of the motor unit potential play an essential role in the classification of weakness in diseases of the nerve and muscle.[49,61] In addition, assessing motor unit potentials serially helps monitor the disease process based on sequential physiologic changes which correlate with histologic alteration of the motor unit.[134]

Abnormalities of Motor Unit Potentials

The following discussion deals with the contrasting features of the motor unit potential seen in myopathies and lower motor neuron disorders. Each type of change occurs as a common feature 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 23 through 29). 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 a motor unit potential 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 muscle fibers lying closer together near the recording surface give 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 duration of the motor unit potential serves as a measure of a larger part of the muscle fiber population lying within some 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.[15,43]

Diphasic or triphasic motor unit potentials abound in normal muscles, with only 5–15 percent having four or more phases. The number of polyphasic units increases in myopathy, in neuropathy, or in motor neuron 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 or

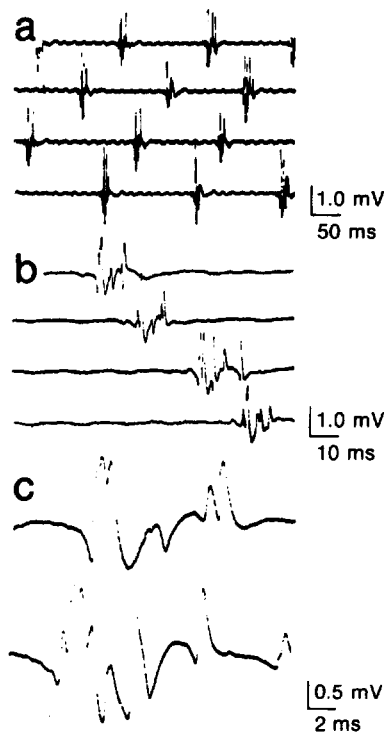


Figure 14–13. Polyphasic motor unit potentials from the anterior tibialis in a 52-year-old man with amyotrophic lateral sclerosis. Temporal variability of repetitive discharges in waveform suggests intermittent blocking of some axon terminals.

over the muscle fiber membrane. Extrapotentials clearly separated from the main unit constitute a satellite potential.[34,53,145] Its presence suggests neuropathy or myopathy: both have a five times higher incidence of such outliers than normal muscle.[54] During neurapraxia or an acute stage of axonotmesis, motor unit potentials, if recorded at all, show normal waveforms, indicating the integrity of the surviving axons (Fig. 14–14).

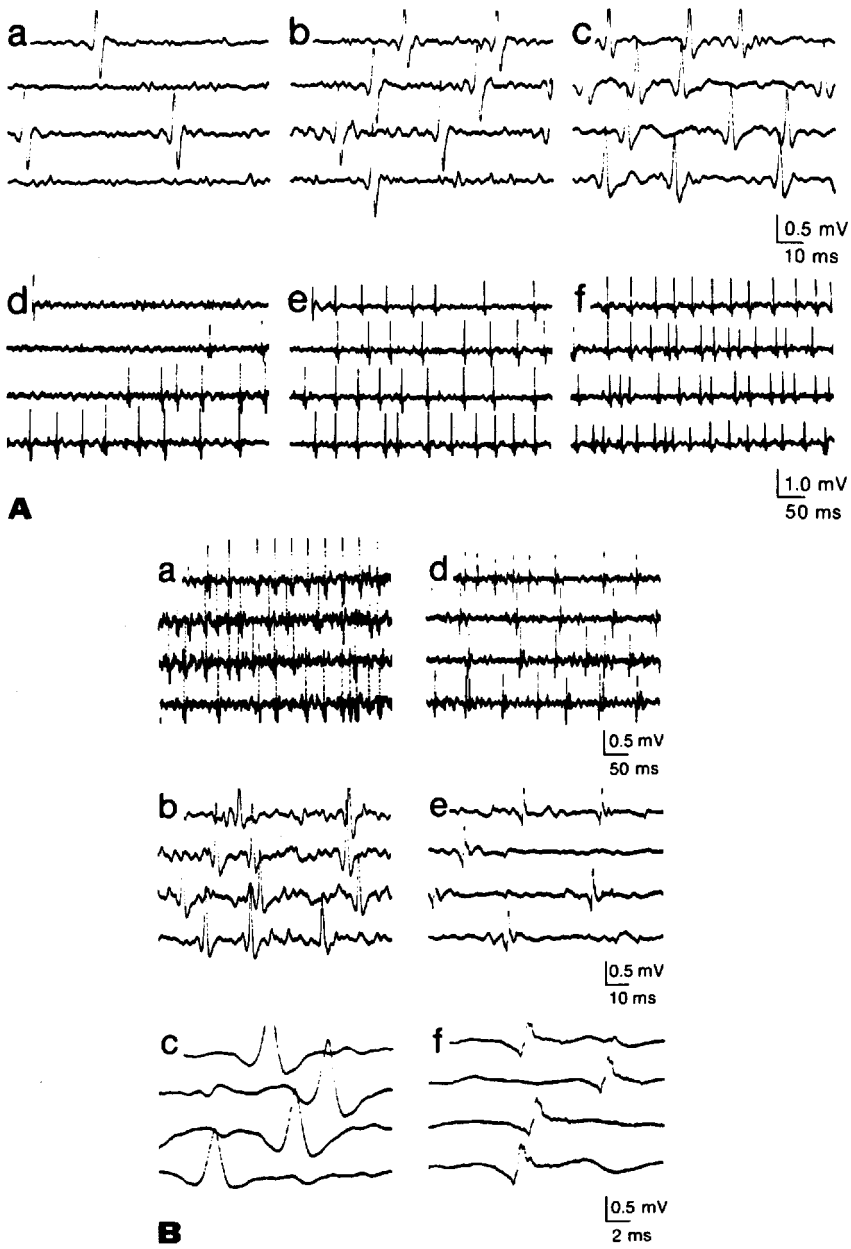


Figure 14–14. A. Motor unit potentials from the extensor digitorum communis in a 20-year-old man with partial radial nerve palsy. Minimal (*a,d*), moderate (*b,e*) and maximal voluntary contraction (*c,f*) recruited only a single motor unit, which discharged at progressively higher rates. **B.** Motor 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.

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 neuromuscular transmission, 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 acetylcholine (ACh). Waveform variability of a repetitively firing motor unit potential, termed *jiggle*, serves to document deficient neuromuscular transmission,[136] especially in muscles not accessible by conventional nerve-stimulation techniques (see Chapter 11–3). Increased jitter of the constituent single fiber potentials increase the waveform variability of the motor unit potential.[110] Such an instability of motor unit potential may imply a large group of disorders affecting the neuromuscular transmission. These include myasthenia gravis, myasthenic syndrome, botulism, motor neuron disease, poliomyelitis, and syringomyelia, as well as the early stages of reinnervation. In myotonia congenita, a characteristic decline in amplitude of the 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 discharges 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. They tend to accompany latent tetany, hyperventilation, and other metabolic states associated with hyperexcitability of the motor neuron pool.[127] Other possibilities include poliomyelitis,[149] motor neuron disease,[140] Guillain-Barré syndrome,[120] radiculopathy, and myotonic dystrophy.[107] Doublets may also occur at the beginning and end of voluntary contraction in normal muscles.[109] In Parkinson's disease, paired discharges with shorter intervals preceded higher tremor beats, possibly suggesting their mechanical contribution to pathologic movement.[47] Patients with fasciculation potentials do not necessarily have a higher incidence of double discharges during voluntary activation of motor unit potentials.[108]

A fraction of the motor unit potential 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. The results of a study using double stimulation technique revealed an ephaptic reexcitation of the axonal branch by a sprout rather than an ectopic focus as their origin.[131] The generation of ephaptic discharges suggests a hyperexcitable axon sprout typical of a heterogeneous group of chronic neurogenic disorders, which include neurotonia,[151] neuromyotonia,[4] entrapment syndrome,[139] and the syndrome of familial ataxia and myokymia.[13]

Lower Motor Neuron versus Myopathic Disorders

Increased amplitude and duration (Fig. 14–15) generally suggest disorders of the lower motor neuron, such as motor neuron disease, poliomyelitis, and syringomyelia, or diseases of the peripheral nerve, such as chronic neuropathy and reinnervation after nerve injury.[132] In these disorders, the increased size of motor unit potential 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, the consequences of reinnervation relate primarily to an increased number of muscle fibers, with incorporation of denervated fibers within the territory of the surviving axon (see Fig. 14–1). Thus, increased amplitude indicates a greater muscle fiber density, whereas an increased duration probably results from abnormal variability in length

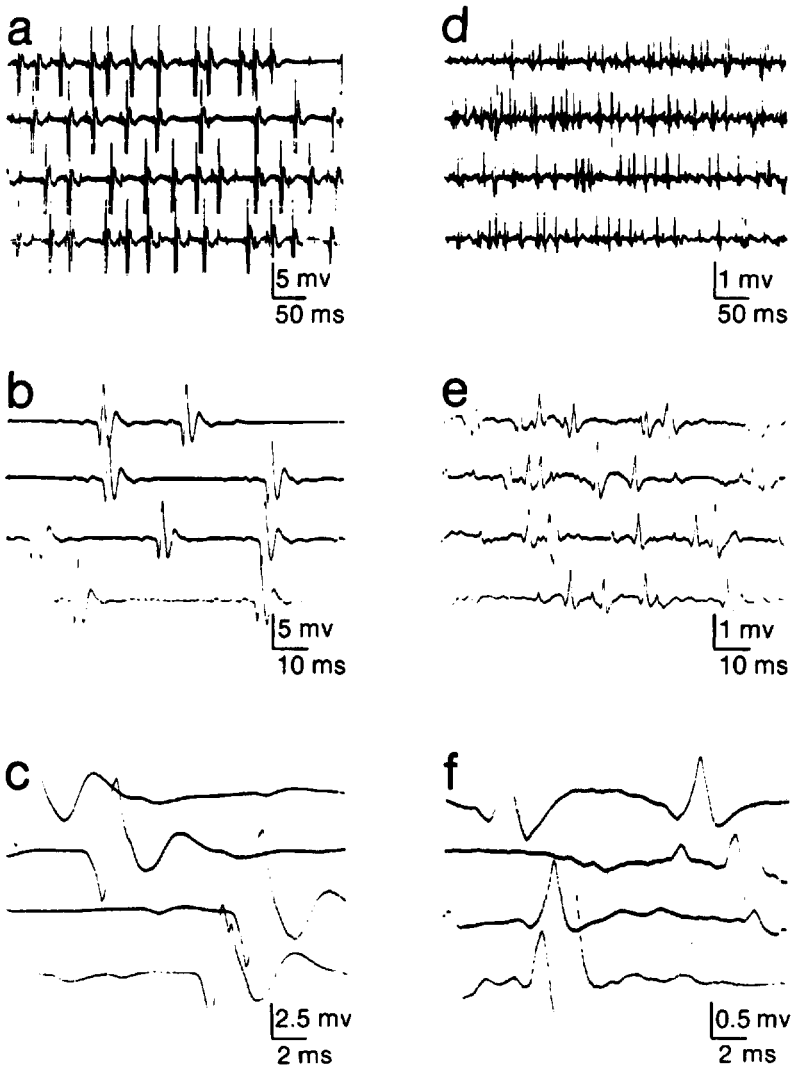


Figure 14–15. High-amplitude, long-duration motor unit potentials from the first dorsal interosseus (*a,b,c*) compared with relatively normal motor unit potentials from orbicularis oculi (*d,e,f*) in a patient with polyneuropathy. Note a discrete single unit interference pattern during maximal voluntary contraction.

and conduction time of regenerating axon terminals, as might be predicted by computer simulation.[90] 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.[124] Even then, a monopolar or concentric needle, inherently restricted by its small recording radius, fails to identify the enlarged territory of simultaneously firing motor unit potentials. A macrostudy serves better for delineating the size of discharging units.

Studies on the time course of reinnervations[10] have revealed characteristic changes of motor unit potentials following traumatic nerve injury. Complete nerve transection leads to increased polyphasicity and temporal instability, with intermittent segmental conduction block of regenerating motor axons. After a partial nerve lesion, healthy motor axons give rise to extensive collaterals for reinnervation of the denervated muscle fibers. Late potentials 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. Here, a recurring motor unit potential itself initiates the sweep, but a delay line allows display of the potential in its entirety (see Chapter 3–4).

In general, reduction in amplitude and duration of the motor unit potential (Fig.

14–16) suggests primary myopathic disorders such as muscular dystrophy, congenital or other myopathies, periodic paralysis, myositis, and disorders of neuromuscular transmission, including myasthenia gravis, myasthenic syndrome, 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 of motor unit potentials. In extreme cases, voluntary contraction activates only a single muscle fiber, displaying a motor unit potential 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.[16] Mild metabolic and endocrine myopathies characteristically show little or no alteration in duration or amplitude of the motor unit potential.

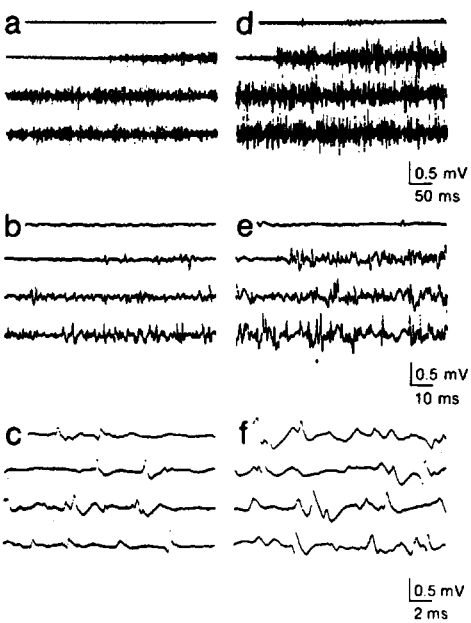


Figure 14–16. Low-amplitude, short-duration motor unit potentials from the biceps (*a,b,c*) and tibialis anterior (*d,e,f*) in a 7-year-old boy with Duchenne dystrophy. (cf. Fig. 14–8E). Minimal voluntary contraction recruited an excessive number of motor units in both muscles.

Contrasting changes in the waveform of motor unit potentials generally help differentiate myopathies from lower motor neuron disorders.[17,18] Electromyography and histochemical findings from muscle biopsies have an overall concordance of 90 percent or greater,[7,17,18,61] although the distinction may not always be unequivocal.[50] 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. Motor unit potentials may then become polyphasic, of low amplitude, and of short duration. In either instance a neuropathic process will produce changes classically regarded as consistent with a myopathy.[102]

Conversely, in myopathies with regenerating muscle fibers, motor unit potentials may have a long duration, erroneously suggesting a neuropathic process.[39,86,113] These potentials commonly appear quite distinct from the main unit, giving rise to the terms *satellite* or *parasite potentials*, now abandoned in favor of the more descriptive name *late component*. In one study dealing with 41 patients with different myopathies,[148] quantitative analyses revealed reduction of the mean duration in 64 percent and 95 percent of patients, depending on whether the late potentials were included or excluded. This observation confirms the need to exclude the late components in calculating the mean duration for diagnostic purposes. Complex potentials with normal or increased duration may appear in myopathy, reflecting increased variability of fiber diameter.[103] Additionally, if the fiber density increases during regeneration, so does the amplitude, to a range much greater than ordinarily expected in myopathy. Hence, the oversimplified dichotomy between myopathy and neuropathy may not hold in interpreting abnormalities of motor unit potentials and correlating them with clinical diagnoses.[51,150]

Despite these uncertainties, the electromyographic studies allow division between myogenic and lower motor neuron involvements in most patients with defi-

nite weakness.[21] Findings often vary among different muscles in the same patient or even from one site to another within a given muscle. An adequate study consists of exploration in 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 analysis of motor unit potentials may improve diagnostic yields in distinguishing myopathic and neuropathic changes.[112,134]

6 RECRUITMENT PATTERN

Lower and Upper Motor Neuron Disorders

The number and the average force contributed by each functional motor unit dictates the recruitment pattern. In disorders of the motor neuron, 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 motor neurons must fire at an inappropriately rapid rate to compensate for the loss in number. In extreme instances, a single motor unit potential may discharge at frequencies as high as 50 Hz, producing a discrete "picket fence" interference pattern with maximal effort (Fig. 14–17).

In late recruitment caused by failure of descending impulses seen in upper motor neuron lesions, the excited motor units discharge more slowly than expected for normal maximal contraction and may show characteristic firing patterns[160] (Fig. 14–18). 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.[57] Patients with hemiparesis also showed a compression in the range of motor neuron recruitment forces, and a failure to discharge motor units at a higher rate during increased voluntary effort to contract the paretic muscles.[60] Thus, a lower motor neuron weakness with a rapid rate of discharge stands in good contrast to an upper motor neuron 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 essential or other type of tremor. Thus, isokinetic measurements of muscle strength reveal increased variability of tonus in repeated tests and

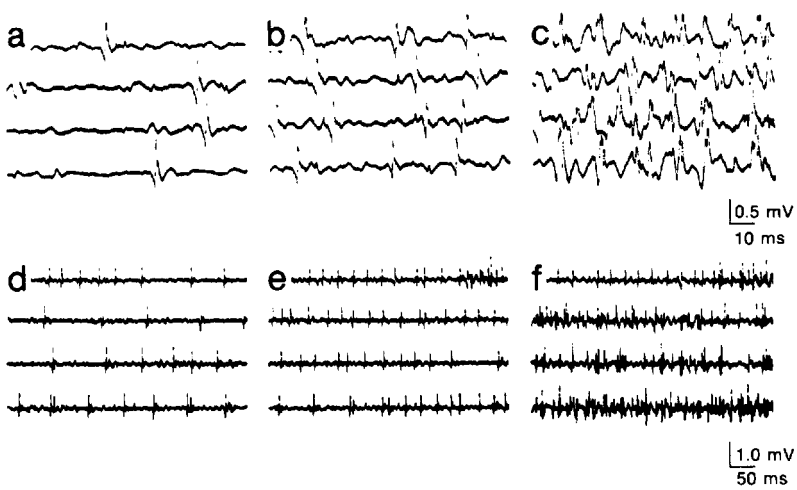


Figure 14–17. Reduced recruitment and incomplete interference pattern of the mildly paretic extensor carpi radialis in a 20-year-old man with partial radial nerve palsy. The rate of firing rather than the number of discharging motor units increased during minimal (*a,d*), moderate (*b,e*), and maximal voluntary contraction (*c,f*) (cf. Figure 14–14).

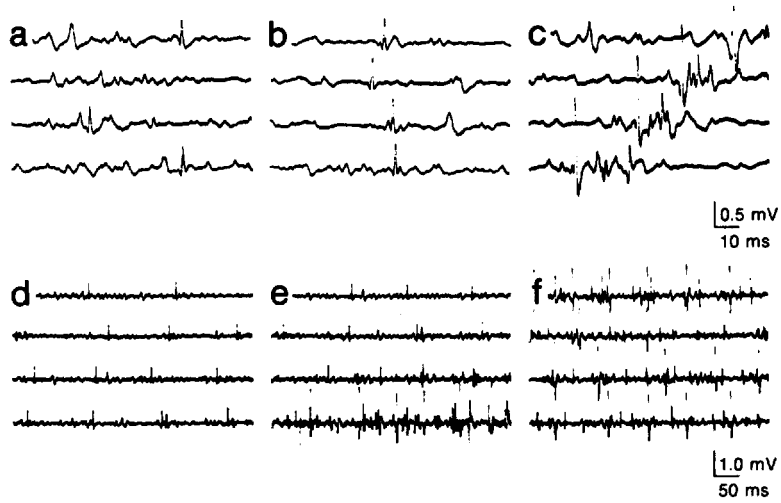


Figure 14–18. Reduced recruitment and incomplete interference pattern of the tibialis anterior in a 31-year-old woman with hysterical weakness. Minimal (*a,d*), moderate (*b,e*), and maximal (*c,f*) effort to contract the muscle altered neither the rate of firing nor the number of discharging motor units appreciably.

other signs of inconsistency and contradictory motor performance.[80]

Electromyography has value in quantitatively assessing paresis caused by upper motor neuron 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.[40] Conversely, it may detect changes in single motor unit firing characteristics caused by an upper motor neuron lesion early at a time when clinical examination shows no evidence of increased tone or spasticity.[128] Increased discharge variability in muscles just above the level of spinal cord injury also suggests that subtle effects extend beyond the clinically apparent segments of involvement.[158] In incomplete spinal cord injury, an increase in the surface electromyography during biofeedback depends on higher rates of firing of the already activated motor units rather than recruitment of previously unavailable motor units.[138] Section of the spinal cord results 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.[36]

Myopathy

If each motor unit potential, low in amplitude and short in duration, contributes less, many units must discharge early to functionally compensate in quantity for the smaller force per unit. 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 (Fig. 14–19). A full interference pattern develops at less than maximal contraction, although its amplitude remains low, reflecting the decreased fiber density of individual motor units. For the same reason, the motor units also show early recruitment, reaching full interference prematurely in diseases of neuromuscular transmission. This general rule may not apply in advanced myogenic disorders with loss of whole motor units instead of individual muscle fibers. Here, limited recruitment leads to an incomplete interference pattern, mimicking a neuropathic change; it reflects a reduced number of motor units rather than a random loss of individual muscle fibers.

Involuntary Movement

Electromyographic findings associated with involuntary motor symptoms and neuromyotonia may resemble changes seen in a lower motor neuron disease (see Chapter 29). Tremors show characteristic bursts of motor unit potentials repeating at a fairly constant rate. Although many motor units fire in a group during each

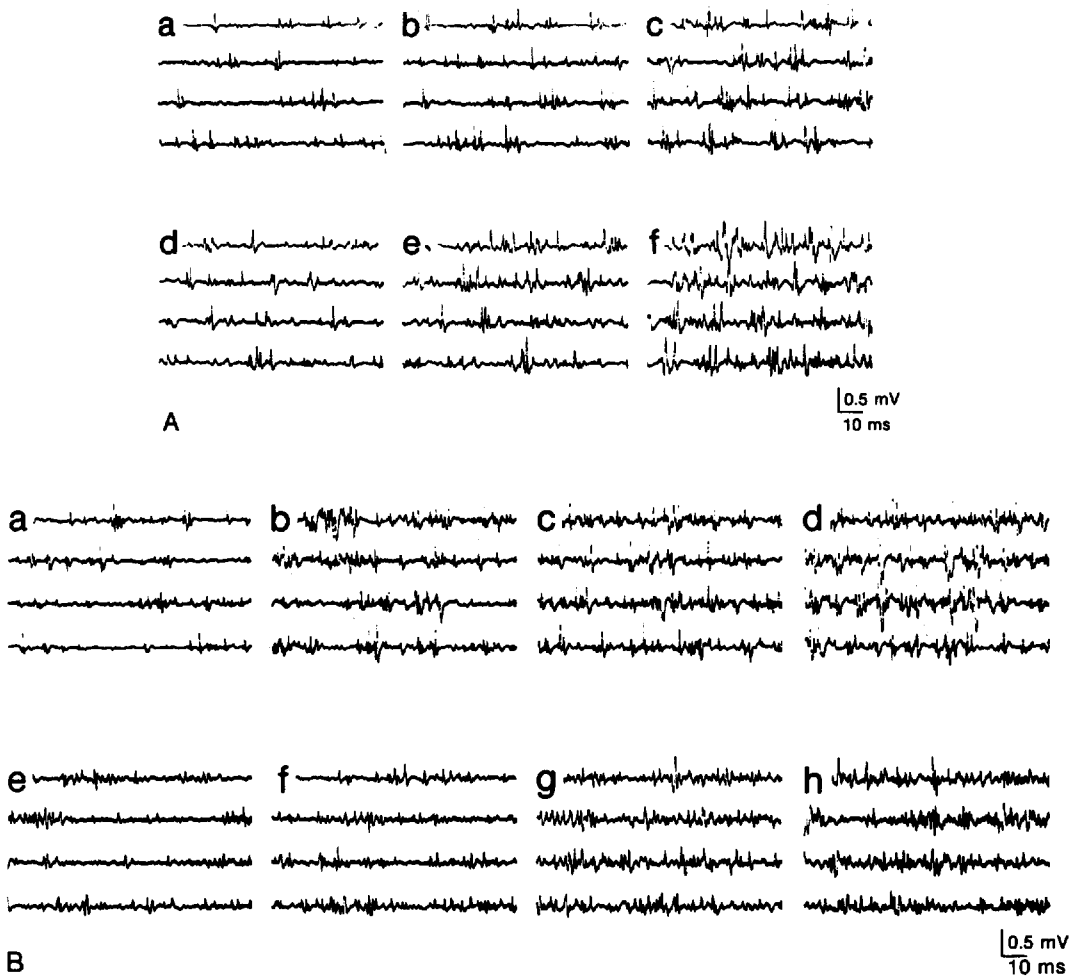


Figure 14–19. A. Early recruitment of the deltoid (*a,b,c*) and tibialis anterior (*d,e,f*) in a 9-year-old boy with a 6-week history of dermatomyositis. (cf. Fig. 14–8D). Note abundant motor units discharging with increasing effort from *a* through *c* and *d* through *f* during minimal muscle contraction. **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. Figure 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*).

burst, no fixed temporal or spatial relationships emerge among them. Thus, successive bursts vary in amplitude, duration, waveform, and number of motor unit potentials. A subclinical tremor burst could masquerade as a polyphasic motor unit potential of long duration, despite the varying appearance and rhythmic pattern. Electromyographic recordings help characterize different types of tremor on the basis of their rate, rhythm, and distribution.[129] Synkinesis seen in hemifacial spasm or following aberrant regeneration gives rise to unintended activation of motor units in the muscles not under voluntary control (see Fig. 15–1). Simultaneous recording from multiple muscles confirms the presence of time-locked discharge of aberrant motor unit potentials, thus differentiating associated voluntary activity from involuntary synkinetic discharges.

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Chapter 15

EXAMINATION OF NONLIMB MUSCLES

1 INTRODUCTION

Nonlimb muscles readily accessible to needle examination include the muscles of mastication, face, soft palate, and tongue. Electromyographic evaluation of laryngeal muscles requires 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 requisite 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.[14]

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, which are beyond the scope of this book.

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 exception of the laryngeal and extraocular muscles, as discussed below. The most commonly tested muscles in the face and neck include the masseter, temporalis, orbicularis oculi, orbicularis oris, tongue, trapezius, and sternocleidomastoid. In the study of these muscles, holding their belly between the index finger and thumb for firm immobilization generally facilitates the insertion of a needle electrode.

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 show low amplitude and short duration; reported values range from 2.28 ± 0.3 ms (mean ± SD)[60] to 5 or 6 ms.[19] 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.[17]

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 functional block in patients with peripheral facial palsy. The brevity and small amplitude of normal motor unit potentials 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

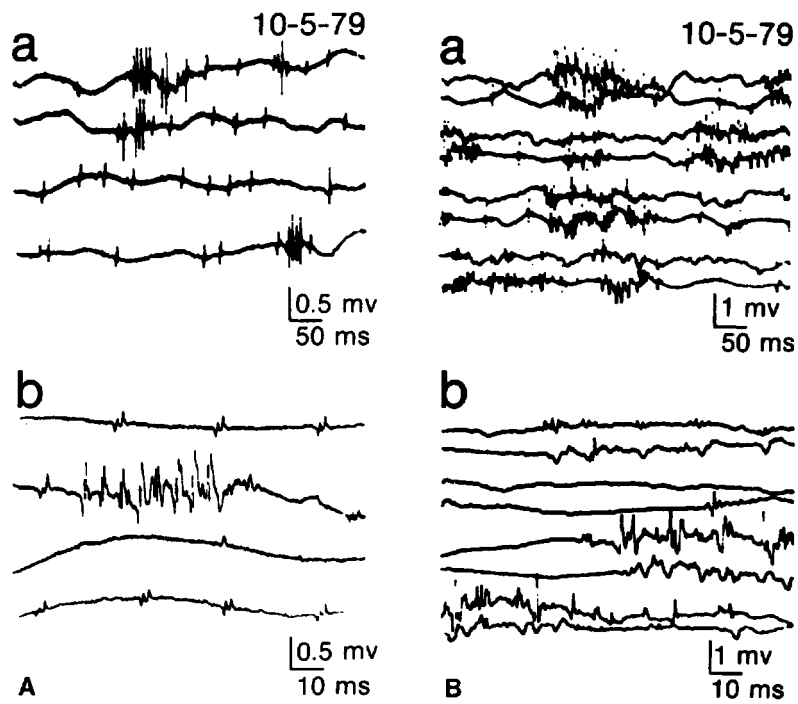

Figure 15–1. Motor unit potentials recorded in a 54-year-old woman with hemifacial spasm. **A.** Recurrent spontaneous bursts of high-frequency discharges from the orbicularis oris shown at a slow (*a*) and fast sweep (*b*). **B.** Simultaneous recording from the orbicularis oculi (*top tracing in each pair*) and oris (*bottom*). The patient blinked quickly several times to show synkinesis involving the two muscles.

nascent units precedes the clinical return of voluntary movement as the electrical evidence of reinnervation. Aberrant regeneration is the rule, not the exception, after the degeneration of the nerve from the proximal trunk (see Fig. 17–11).[48] Random misdirection may involve two branches of the facial nerve or two distinct but anatomically close nerves, such as the facial and trigeminal nerves. In these cases, simultaneous recording from the affected muscles substantiates the presence of synkinesis.

Laryngeal and Nuchal Muscles

The glossopharyngeal nerve and the recurrent branches of the vagal nerve subserve the same motor function in the larynx. Electromyographic studies can characterize the paralytic involvement of the vocal cord, palate, and pharyngeal and laryngeal muscles.[68,82] In one study with seven healthy subjects,[64] 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. As in skeletal muscles, electromyographic abnormalities of the pharyngeal and laryngeal muscles generally show better correlation with clinical findings of lower motor neuron than upper motor neuron involvement.[57] Pharyngeal electromyography, though technically feasible, lies outside the routine studies conducted in an ordinary laboratory.[58] In patients with vocal cord paralysis, the absence of motor unit potentials indicates poor outcome, although the reverse does not necessarily hold.[32] 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.[33]

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. 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. 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 generates the motor unit potentials, 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. The sternocleidomastoid has unique ipsilateral supranuclear control, unlike most other muscles, which receive crossed input from the contralateral cerebral hemisphere.[4] 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 from C2, C3, and C4 roots.[55]

Diaphragm

The sternal origin of the diaphragm arises from the xiphoid process. Here, the muscle is easily accessible to a needle electrode inserted behind the bone slightly off midline to either side.[38] An alternative 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.[65] Insertion of the needle perpendicular to the upper border of the ninth or tenth rib avoids the intercostal nerves and arteries, which run along the lower border of the respective ribs. The needle

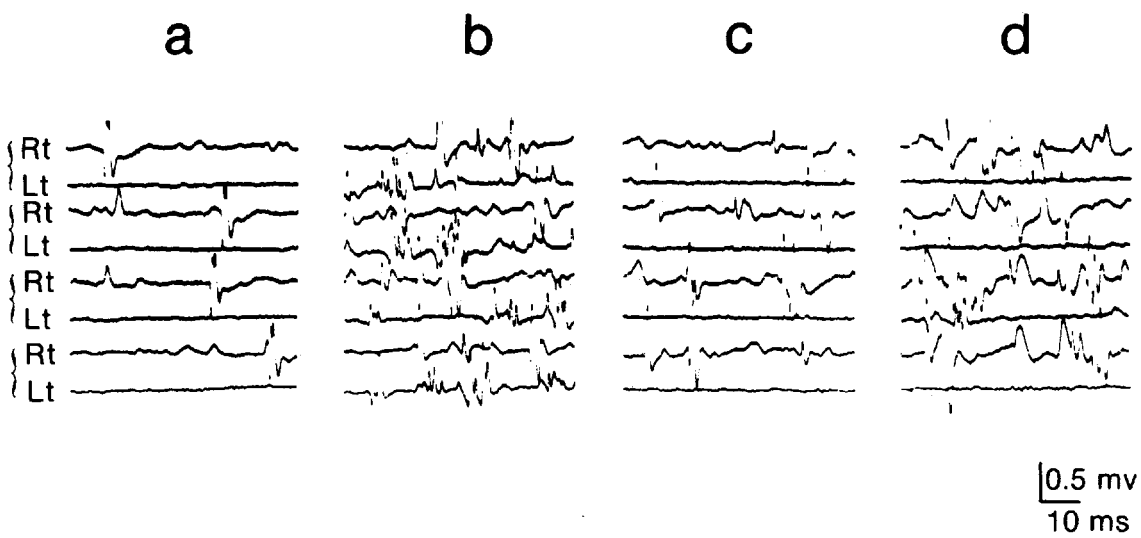

Figure 15–2. Torticollis on the right in a 30-year-old woman. Each pair of recordings shows muscle action potentials registered simultaneously from right (*upper tracing*) and left (*lower tracing*) sternocleidomastoid. During the sequential recordings, the patient either faced straight ahead (*a* and *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*).

must pass the intercostal muscle to reach the diaphragm, which can be readily identified by rhythmical discharges synchronous with respiration. Different types of neuromuscular diseases may involve the diaphragm, causing respiratory symptoms.[2,29,30,31,51] In addition to phrenic nerve conduction, needle study of the diaphragm provides great assistance in identifying the nature and site of a disorder.[12,24] 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,[53] turns analysis demonstrated a substantial overlap between neuropathic and myopathic involvement.

3 EXTRAOCULAR MUSCLES

Early work[9,50,71] provided detailed descriptions of electromyography in the extraocular muscles, and indicated its usefulness in differentiating causes of paralytic squint, such as denervation, ocular myopathy, and myasthenia gravis. Ocular studies also help detect abnormalities of eye movements attributable to mechanical limitations, such as 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.

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 0.005–0.015 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 must be awake during the examination and 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 searching, 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 subconjunctivally into the belly of a muscle along its long axis. Most patients tolerate the procedure well and 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.

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. The eye muscles can discharge at a rate of up to 200 Hz,[9] which stands in sharp contrast to the usual rates of firing of less than 50 impulses per second in the skeletal muscles. Extraocular muscle fibers range from 10 to 50 μm in diameter.[15] The motor units consist of a small number of muscle fibers, averaging 23 in one study[26] and numbering 6–12 in others.[73] These numbers fall considerably below the average value for the limb muscles, which varies from 100 to 2000.[18,69] 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.[16]

Despite electromyographic similarity to skeletal muscles, a certain electrophysiologic peculiarity characterizes the extraocular muscles. Placement of the needle electrode causes a brief insertional activity, presumably representing an injury potential. Unlike the limb musculature, the extraocular muscles show constant electrical discharges following the cessation of needle movement. The tonic activity maintains 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 motor unit potentials lower in amplitude and shorter in duration in the extraocular muscles than in the limb muscles. Reported normal values (mean ± SD) include an amplitude of 108 ± 9.2 μV and a duration ranging from 1.60 ± 0.06 ms[9] to 2.8 ± 0.1 ms.[34] Another study[16] 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, the motor unit potentials discharge at a rate of up to 200 Hz.[9] Spectral analysis also demonstrates greater power in the higher frequency domain in the extraocular muscles than in the limb muscles.[47]

Neurogenic Extraocular Palsy

A neurogenic extraocular palsy results from lesions of the third, fourth, or sixth

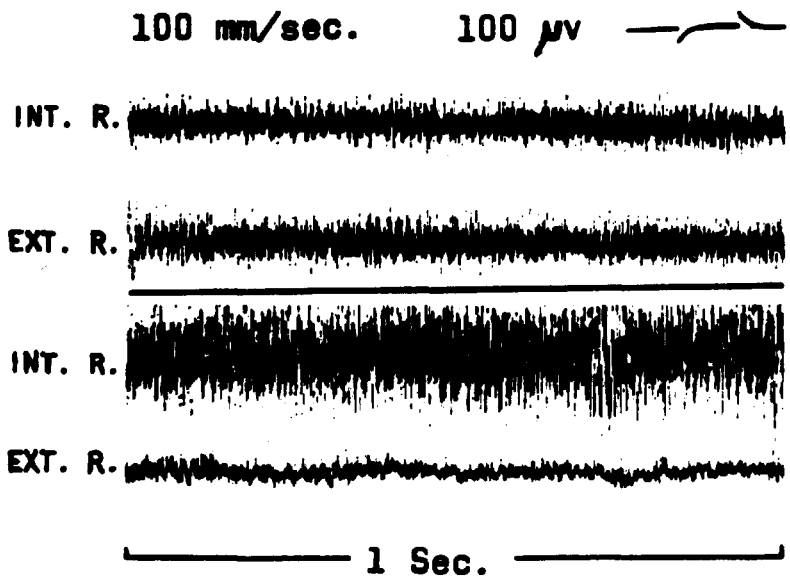

Figure 15–3. External and internal rectus of the left eye in a normal subject, recorded simultaneously for comparison. Upper tracing shows nearly equal and constant activity of normal amplitude in both muscles. *Lower tracing,* taken with the eye turned strongly into field of action of internal rectus, reveals increased motor unit activity of this muscle and corresponding reciprocal decrease in activity of external rectus. [From Van Allen and Blodi,[76] with permission.]

nerve. Electromyography, in principle, 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, the normally brief motor unit potentials resemble 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 high-amplitude motor unit potentials of long duration with increased polyphasic activities, but to a lesser extent than in skeletal muscles. Large motor unit potentials frequently accompany aberrant regeneration of oculomotor nerves.[16]

As in limb muscles, slow recruitment of motor unit potentials suggests neurogenic weakness of the extraocular muscles with a reduction of the interference pattern approximately in proportion to the degree of paresis. Examination shows no motor unit potentials in a totally paretic muscle with attempted maximal contraction, although rarely to the extent of complete electrical silence, even in severe palsies. The interference pattern may consist of repetitive discharges from a single motor unit in severe, but incomplete, paralysis. Patients without definite limitation of rotation may have abundant electrical activity in the remaining normal units despite mild palsies. This finding will mimic those seen in patients with ordinary strabismus, who also have nearly normal motor unit activity on attempted rotation despite limitation of movement.

Myopathy and Myasthenia Gravis

Electromyography in ocular myopathy, unlike that seen in neurogenic paralysis, shows preservation of a normal interference pattern with no evidence of denervation.[10] The abundance of brief, low-amplitude motor unit potentials suggests random loss of individual muscle fibers without major loss in the number of functional motor units.[35] Except in advanced cases, myopathic features may escape detection because normal extraocular muscles show a similar pattern. Myasthenia gravis affects the ocular muscles early, causing diplopia and abnormal fatigue of eye movements. Thus, needle studies of the extraocular muscles may help establish the diagnosis in patients with normal limb muscles. In myasthenia gravis, the amplitude of a motor unit potential fluctuates or steadily declines during sustained contraction. Progressive decrease

in the 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 as the presenting sign, studies of the levator palpebrae may reveal abnormality, despite the technical difficulty in localizing the muscle.

Other Types of Gaze Palsy

Musculofascial anomalies generally result in limitation of gaze in one direction, either vertically or horizontally. During contraction of an apparently paretic muscle for mechanical reasons, studies reveal normal motor unit potentials and a complete interference pattern disproportionate to the failure of rotation. In a blowout fracture of the orbit, for example, incarceration of the extraocular muscle in the fracture line may prevent the globe from normal rotation. In such a case, ocular electromyography establishes the presence of normally innervated muscles by demonstrating abundant activity with the effort to rotate the eye. Conversely, the detection of unequivocal abnormalities in patients with limited rotation suggests a direct injury to the nerve or muscle.

In Duane's syndrome, a deficiency of ocular motility results from congenital absence of the sixth nucleus with aberrant innervation of the lateral rectus by the third nerve.[54] The syndrome typically consists of impaired abduction of one eye and retraction and ptosis on attempted adduction of the same eye. A fibrotic lateral rectus muscle presumably neither contracts on abduction nor relaxes on adduction. Thus, the muscle shows a reduced number of motor unit potentials when activated and fails to produce electrical silence when reciprocally inhibited. In addition, a central supranuclear lesion may disrupt normal reciprocal inhibition (Fig. 15–4), contributing to the ophthalmoplegia in this condition.[11]

Limitation of eye movements may occur on a central basis, as in internuclear ophthalmoplegia. In this syndrome, caused by a lesion of the medial longitudinal fasciculus, the eye on the side of the lesion fails to adduct, despite the integrity of

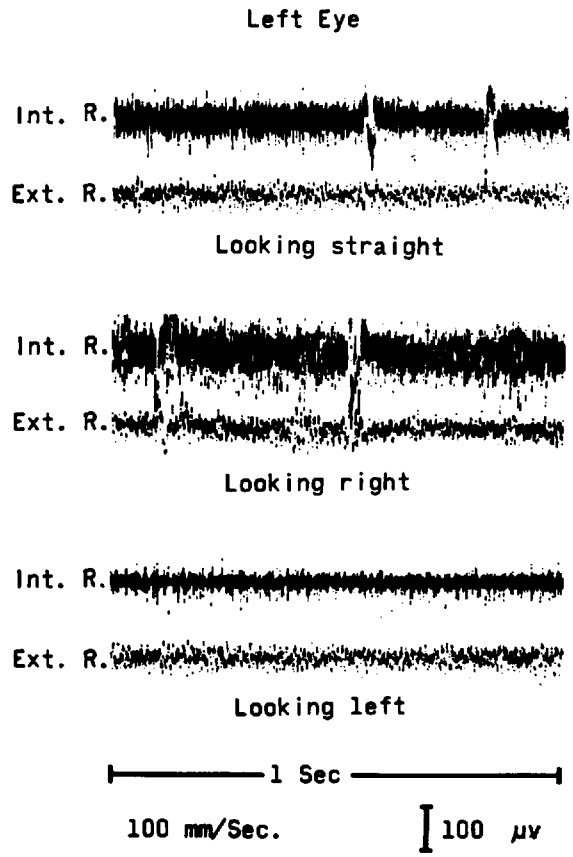

Figure 15–4. External and internal rectus of the left eye, recorded simultaneously in a patient with Duane's syndrome. The tracings show a normal innervation pattern of the internal rectus, but neither increment nor decrement of the external rectus on attempted gaze to the left or to the right. Note the normal electrical activity of this muscle in the primary position. [From Blodi, Van Allen and Yarbrough,[11] with permission.]

the peripheral motor system. In such supranuclear disturbances, extraocular electromyography reveals an altered pattern of innervation. The medial rectus has normal electrical discharges with the eyes in the primary position but shows neither an increase in activity on attempted adduction nor reciprocal inhibition on attempted abduction.

The Möbius syndrome consists of facial diplegia and restriction of horizontal eye movements. Electromyographic studies show synchronous bursts of activity from the medial and lateral rectus, instead of the normally expected reciprocal pattern of innervation (Fig. 15–5). These findings

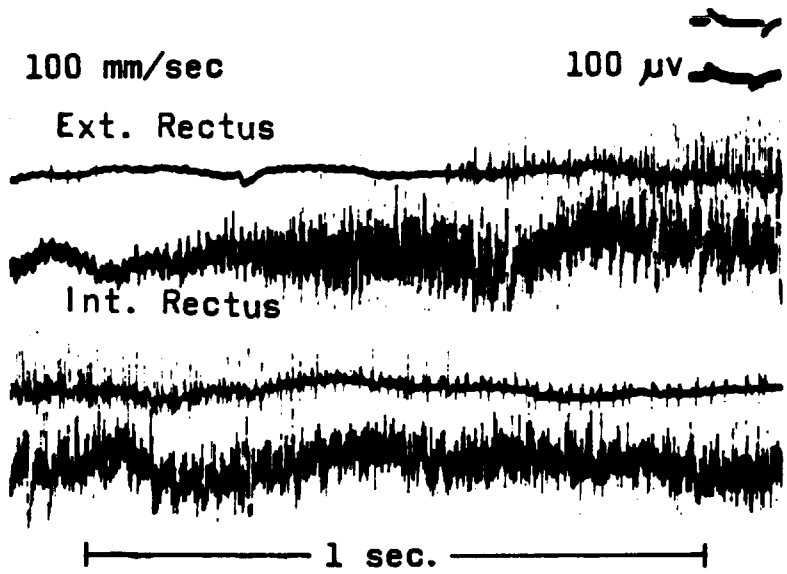

Figure 15–5. External and internal rectus of the left eye, recorded simultaneously in a patient with the Möbius syndrome. Note spontaneous volley in external rectus with simultaneous waxing of activity in internal rectus, indicating the lack of physiologic reciprocal innervation. [From Van Allen and Blodi,[76] with permission.]

suggest supranuclear abnormalities responsible for the abnormal ocular motility in affected patients, despite the designation of the syndrome as *congenital nuclear agenesis of the sixth and seventh nerves.* A pair of electrodes inserted into the extraocular muscles can elucidate the pattern of various types of nystagmus.[16] Electromyographic techniques also help explore the reciprocal relationship between orbicularis oculi and levator palpebrae.[76]

4 TRUNCAL MUSCULATURE

Abdominal Muscles

The anterior rami of the cervical spinal nerves supply the upper limb muscles; those of the lumbosacral spinal nerves, the lower limb muscles. 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.[37]

The electromyographic study of the abdominal muscles also helps 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.[39] The considerable overlap in segmental representation, however, precludes the exact localization of the involved cord level. Each segmental level receives at least two adjoining intercostal nerves in both thoracic and abdominal regions.

Electromyographers can study the abdominal musculature with a needle just as easily as the limb muscles. The external oblique is tested at the anterior axillary line, 5–10 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 analysis of motor unit potentials, the patient contracts the muscle by bending the upper trunk forward.

The abdominal rectus is tested 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.[38] The patient bends forward against resistance to contract the muscle for the assessment of motor unit potentials.

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 electromyographic 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 Figs. 1–7 and 14–8C). A more distally located lesion at the level of the plexus or the peripheral nerve would entirely spare the paraspinal muscles without the involvement of the posterior rami. Hence, the examination of paraspinal muscles plays a critical role in the investigation of cervical or lumbar disc herniation.[40,45,46] In fact, patients in early stages of radiculopathy within 1–2 weeks after the onset may have electrical abnormalities limited to this region. Some systemic disorders, most notably polymyositis, may affect the paraspinal muscles preferentially and sometimes exclusively.[1,72] Relatively selective denervation in this region also develops in degenerative joint disease, arachnoiditis, diabetic polyradiculopathy, and rare local metastasis to the muscles.

The erector spinae consists of two portions, short spinal muscles, or multifidus, originating from different spinous processes, and long spinal muscles, or longissimus dorsi. The short spinal muscles, located deep, immediately posterior to the transverse process, receive a fairly discrete segmental nerve supply from corresponding posterior rami.[20] A needle inserted deeply, just lateral to the spinal process, toward the transverse process reaches this portion of the muscle. Some authors advocate paraspinal mapping to quantify needle study, incorporating the concept of unisegmental innervation of medial multifidus muscles,[41,43] but its clinical utility awaits further documentation.[28] The long spinal muscles, located more superficially, extend several centimeters to either side of the spinous process and the ligamentum nuchae.[38] Their nerve supply overlaps at least one to two segments caudally and rostrally.[49,80] 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. In one study,[42] cadaveric dissection confirmed accurate needle placement into specific fascicles for 91 of 112 injections into multifidus, 39 of 43 injections into longissimus, and 35 of 44 injections into iliocostalis. Another study[70] using percutaneous injection of colored latex into cadavers confirmed the ability to make appropriate needle placement.

To achieve complete relaxation, the subject lies in the prone position with pillows under the abdomen for lumbar studies and under the neck for cervical examination. For relaxation of the lumbar paraspinal muscles, the patient raises the hips slightly toward the ceiling. The cervical paraspinal muscles usually relax if the patient bends the neck forward, pressing the forehead against the table. In some subjects, lung tissue extends above the clavicle with a distance from skin surface of approximately 3.3 cm.[44] Thus, directing the exploring needle in a direction perpendicular to the spine or slightly upward minimizes the risk of inducing pneumothorax, especially in the patient with a long neck.

Patients generally have less control for voluntary activation of paraspinal muscles, making assessment of motor unit po-

tentials difficult, especially for quantitative measure of phases, turns, and other characteristics.[5,74] Motor unit potentials of low amplitude and short duration seen in the cervical or lumbar region may mimic fibrillation potentials. Transient positive sharp waves may appear in the paraspinal muscles by the end of the first day and last up to 4 days after myelography[79] or lumbar puncture.[27] Paraspinal studies help evaluate not only segmental pathology but also diffuse processes such as myopathy and motor neuron disease. For example, vacuolar myopathies affect paraspinal muscles more than limb muscles.[61] In amyotrophic lateral sclerosis, detection of profuse spontaneous discharges confirm denervation unrelated to nerve entrapment. In one study,[28] however, up to 15 percent of asymptomatic subjects may have positive sharp waves and fibrillation potentials in lumbosacral paraspinal muscles.

5 ANAL SPHINCTER

Indications and Technique

The anal sphincter receives the innervation of the pudendal nerve, which derives from the anterior division of the 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 is under volitional control, shares similar physiologic properties with the skeletal muscles of the limbs. Since an initial attempt in 1930,[7] electromyography 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 record reflex contraction induced by digital stretching of the sphincter. The conventional concentric or monopolar needle suffices for routine clinical use.

Electromyographic studies quantitate sphincter dysfunction in neurologic disorders.[52,56] 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, if it is present, 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. Electromyography helps determine the extent of damage in such cases and aids in differential diagnosis of fecal incontinence.[25] 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. Electromyography of the urethral sphincter ideally involve the help of urologists working in a laboratory equipped with tools for urodynamic investigations.

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, 0.5–1 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 while contracted voluntarily or reflexively.

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 firing of isolated motor unit potentials at a low rate. This activity varies considerably with changes in subject position. The activity continues during sleep, although the discharge rate drops substantially compared with that 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, as in any denervated limb muscles.

To test voluntary activity, the patient contracts the sphincter as though attempting to hold a bowel movement. The motor unit potentials range from 5.5 to 7.5 ms in duration and from 200 to 500 μV in amplitude.[21,59] In one study,[6] patients with fecal incontinence exhibited prolongation of mean motor unit potential duration, compared with matched controls. Digital examination of the anus, 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.[78] Some subjects can neither relax nor contract the sphincter during the test, as instructed by the examiner. In these cases, an appraisal of sphincteric

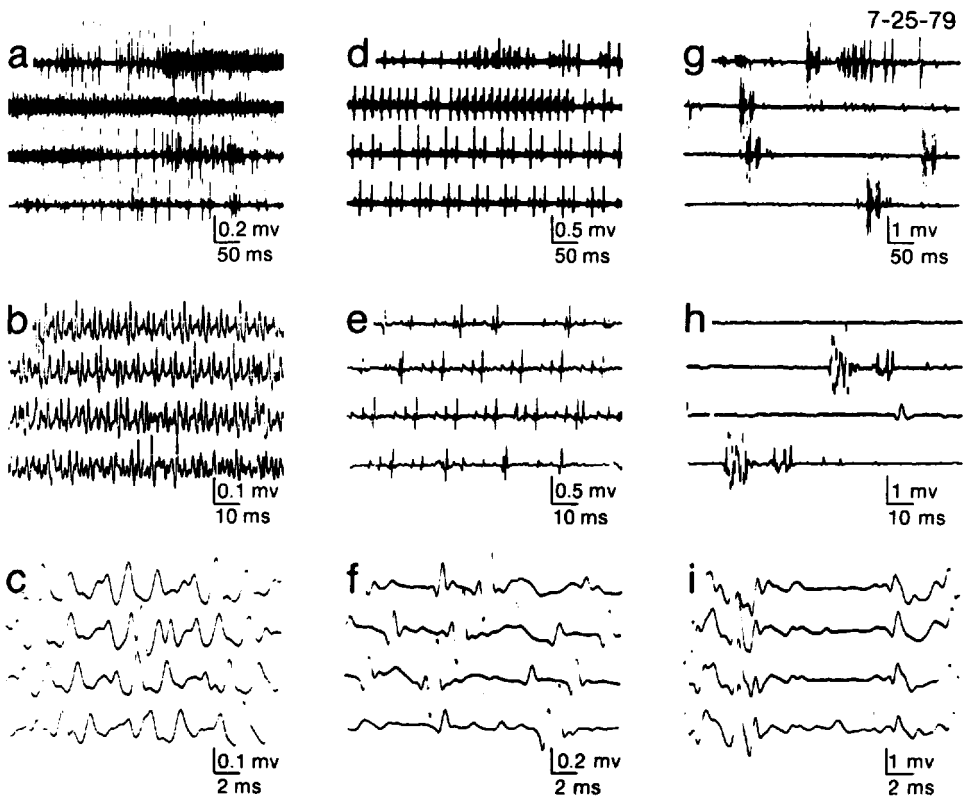

Figure 15–6. Recording from anal sphincter in a 16-year-old girl with incontinence. Tracings include continuous discharge at high frequency, resembling very prominent end-plate noise (*a,b,c*), complex repetitive discharges (*d,e,f*), and very polyphasic fasciculation potentials (*g,h,i*), all recorded 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.

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. The interference pattern is incomplete, with motor unit potentials of normal amplitude discharging 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 suggests lesions in the cauda equina or in the sacral or pudendal plexus. In an incomplete paralysis, volitional effort recruits a few motor units that fire at a high frequency. In contrast to central paralysis, the surviving units show a polyphasic waveform and a long duration. In an acute cauda equina syndrome, the initial paralysis may result from a functional block. Axonal degeneration, if present, gives rise to fibrillation potentials, positive sharp waves, and complex repetitive discharges (Fig. 15–6).

Patients often have a mixture of central and peripheral paresis in congenital malformation, vascular disease, or traumatic injury of the conus medullaris.[13] Spina bifida with meningomyelocele characteristically affects both upper and lower motor neurons.[22] Electromyography of the anal sphincter in these cases 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 conus medullaris precludes sphincter response either voluntarily or reflexively. Spontaneous potentials recorded in these cases indicate the involvement of the anterior horn cells.[23]

Amyotrophic lateral sclerosis typically spares the sphincter, even when the limb muscles show evidence of conspicuous denervation.[66] In contrast, abnormal spontaneous activity serves as a specific marker for neuronal degeneration of Onuf's nucleus in multiple system atrophy[63,67] and progressive supranuclear palsy.[75] In one series of 126 patients with suspected multiple system atrophy, 82 percent of those with definite diagnosis had an abnormal sphincter studies.[36,56] This finding also helps differentiate multiple system atrophy from Parkinson's disease.[3,8,77]

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Chapter 16

SINGLE-FIBER AND MACRO ELECTROMYOGRAPHY

1 INTRODUCTION

The concentric needle electrode[2] and other bipolar or monopolar needles record single motor unit potentials that represent the smallest functional unit of muscle activation. They fail to discriminate potentials from different muscle fibers within a motor unit, all of which fire more or less synchronously.

In contrast, the single-fiber needle[17] allows extracellular recording of individual muscle fiber action potentials during voluntary contraction.[6,85,103,108] Termed *single-fiber electromyography* (SFEMG), this technique has contributed substantially to the understanding of muscle physiology and pathophysiology.[8,32,117] In the clinical domain, the SFEMG supplements conventional electromyography by determining (*1*) fiber density—the number of single-fiber action potentials within the recording radius of the electrode—and (*2*)

electromyographic jitter—the variability of the interpotential interval between two or more single muscle fibers belonging to the same motor unit.[108,116,127]

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.[15] In addition, a smaller pick-up 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. Here, the action potential decreases almost exponentially as the recording electrode moves away from the origin.[30] Thus, the recorded amplitude declines very steeply as the distance between the electrode and the source increases (see Fig. 13–6). 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 of 25–30 μm has proven to be optimal for this purpose, considering the average muscle fiber diameter of 50 μm.[19] Most SFEMG needles have an active recording surface of 25 μm in diameter, located 3 mm from the needle tip along the side port. This arrangement minimizes the chance of recording from 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

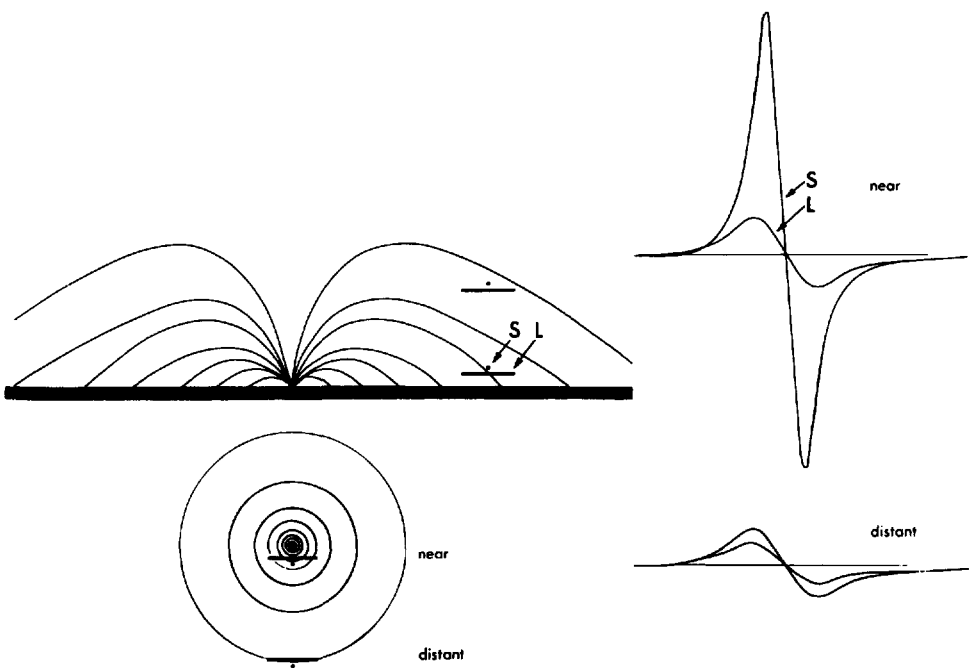

Figure 16–1. Electrical field around a muscle fiber recorded with a small (*S*) and a large (*L*) leading-off surface. The size of the recording area primarily determines the magnitude of shunting across the high- density isopotential lines near the generator source, but to a lesser degree further in the periphery. This in turn dictates the relationship between the amplitude recorded and the electrode distance from the source—a much steeper decline in potential per unit radius with a smaller leading-off surface (see Figure 13–6). [From Stålberga and Trontelj,[115] with permission.]

monopolar arrangement with a reference electrode outside the muscle (see Fig. 3–1). The suggested interelectrode distance of 200 μm provides enough separation for optimal amplification of a single discharge but precludes recording from two independent sources.[116]

In comparison, the conventional needle electrode has a leading-off surface of about 150 × 600 μm, which records from an area within a 500 μm to 1 mm radius (see Fig. 3–1). 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 lower gradient of the electrical field. With large leading-off surfaces, therefore, the action potential does not decrease exponentially with increasing recording distance.[28] Consequently, potentials derived from near and distant fibers show relatively little difference in amplitude.

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. This helps maintain an adequate common mode rejection ratio or differential amplification between the signal and the interference potential.[116] The initial amplifier settings include a sensitivity of 0.2–1 mV/cm and a sweep speed of 0.5–1 ms/cm.

Short-duration, high-amplitude single-fiber action potentials, recorded near the generator, consist 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 percent.[29,30] 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 Hz. 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.[14] 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.[30] 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.[28]

Recording Procedures

Either electrical or voluntary activation can suitably generate motor unit potentials for SFEMG. Surface stimulation of the motor fibers evokes many motor units simultaneously, making single-fiber recording difficult. In contrast, stimulation of an end plate zone with a bipolar needle electrode can excite only a few terminal twigs of a motor neuron. 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.[95,114] This allows recording of the SFEMG from a single motor unit firing in response to electrical stimulation. In cooperative subjects, slight, steady voluntary muscle contraction also reliably generates isolated motor unit potentials, a preferred method of studying SFEMG.

The recommended recording procedure[20,116] calls for amplifier sensitivity of 0.2–1 mV and sweep of 0.5–1 ms/cm for initial exploration. The needle is inserted into the slightly contracting muscle with the subject comfortably lying down or seated. Optimal acquisition of single-fiber potentials depends primarily on maintaining the needle at the critical area with a steady hand. Small shifts in position result in radical changes in the waveform and amplitude of the recorded response. 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 of 20 μs/cm. A constant waveform of the successive tracings confirms a single muscle fiber discharge, whereas varying waveforms 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 above 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 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.[7] In this situation, even regular needle electrodes register the activity selectively from a few muscle fibers located nearby. Thus, low-frequency attenuation helps record single-fiber potentials with the monopolar or concentric needle. Although this type of recording does not accurately distinguish single-fiber responses from summated potentials of more than one fiber, it sometimes reveals abnormal complexity and instability of the motor unit not otherwise appreciated. This approach may bridge the gap between SFEMG and conventional electromyography.[74,116,135]

4 FIBER DENSITY

Definition and Clinical Significance

A 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 electromyographic 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.[116] 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 mo-

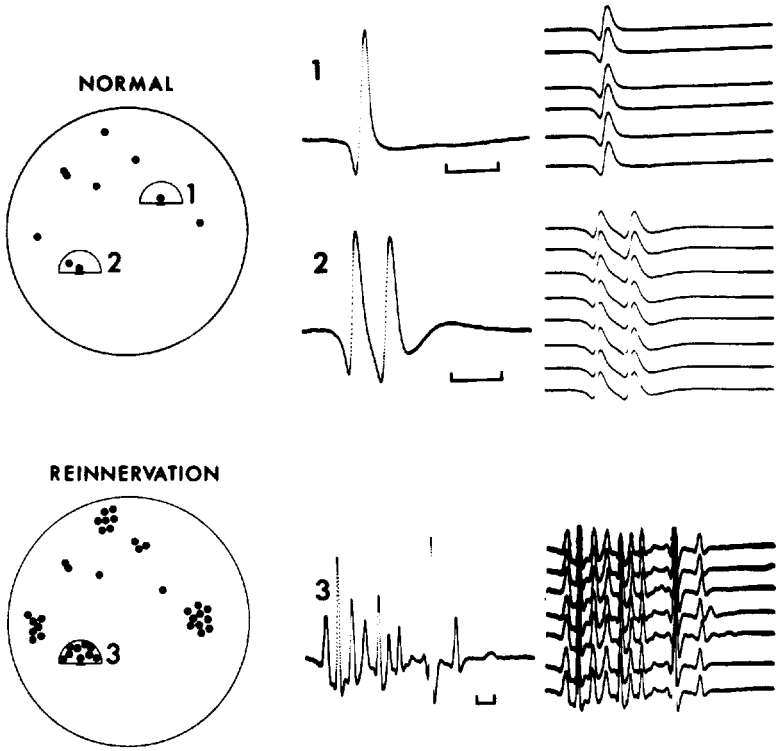

Figure 16–2. Fiber density in normal and reinnervated muscles. All muscle fibers belonging to one motor unit (*small closed circles*) discharge synchronously, but the recording radius of the single-fiber electrode (*half circle*) normally contains only one (*1*) or two (*2*) muscle fibers. Following reinnervation, however, a large number of fibers (*3*) cluster within the same radius, reflecting an increase in fiber density. Time calibration is 1 ms. [From Stålberg and Trontelj,[115] with permission.]

tor 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.[25,68,116] Studies have shown a slightly higher density in the frontalis and lower values in the biceps brachii. Subjects under the age of 10 years and over the age of 60, in general, have slightly higher counts (Table 16–1). Fiber density increases slowly throughout life, with faster progression after the age of 70 years, perhaps indicating degenera-

Table 16–1 Fiber Density in Normal Subjects*

	Ages											
	10–25 Years			26–50 Years			51–75 Years			Above 75 Years		
Muscles	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**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	1.57	0.17	59	2.13	0.41	21
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	1.77	0.12	4	3.8		1
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.
Source: From Stålberg and Trontelj,[115] with permission.

tion of motor neurons 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 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. The needle is then further advanced to identify another single muscle fiber potential. This procedure, repeated at 20 different sites in the muscle, allows calculation of the fiber density as the average number of simultaneously firing single muscle fibers within the recording radius of the single-fiber electrode. For example, isolated discharges of a single muscle fiber at ten different recording sites and two fiber discharges at ten 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 a single fiber occur in 65–70 percent of random insertions in the normal extensor digitorum communis muscle. Only two fibers discharge in the remaining 30–35 percent, and triple potentials appear in 5 percent or less.[113]

Duration and Mean Interspike Intervals

The duration of the action potential complex determined 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 recorded at each random insertion, reflects the difference in nerve terminal conduction, neuromuscular transmission, 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 percent 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, polymyositis, and early reinnervation.[116]

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 electromyographic *jitter* (Fig. 16–3), the term previously used in the engineering literature to denote instability of a time base generator.[18] Repetitive discharges of a single muscle fiber when evoked as H reflex show a greater latency variability than direct responses. H reflex jitter, largely derived from synaptic transmission between the Group IA afferent and the motor neuron, in addition to the neuromuscular junction,[50,122] shows a correlation with age, motor unit size, and recruitment threshold.[1,48] Antidromic rather than reflexive activation of a single motor neuron results in F wave with jit-

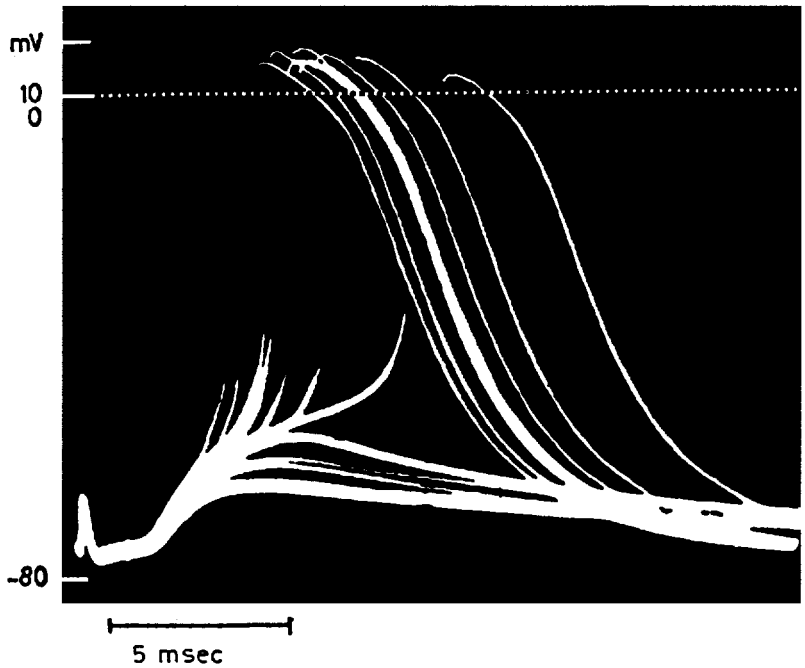

Figure 16–3. End-plate potentials (EPP) and action potentials recorded intracellularly from the end-plate region of a human muscle fiber. The inconsistency of neuromuscular transmission time (jitter) results primarily because amplitude and slope of EPP vary from one discharge to the next. [From Elmqvist, Hofmann, Kugelberg et al,[22] with permission.]

ter values less than an H reflex but more than a direct response.

Axonal microstimulation serves as a convenient alternative to study the jitter at the individual motor end plates.[58,117,125,127] 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, including pauses in activity, for quantitative estimation of the neuromuscular defect.[4,117] It obviates the need to search for muscle fiber pairs. It enables testing of young children and comatose or uncooperative patients, as well as those with impaired voluntary motor control.[127] Stimulation technique occasionally reveals abnormalities that otherwise escape detection. For example, bimodal latency distribution seen in patients with myasthenia gravis[120,127] implies the presence of dual neuromuscular junction supplied either by a single or two different motor neurons.[128]

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, electromyographic jitter equals the degree of variability in the interval, that is, 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 equal $\sqrt{2}$ times the stimulated single fiber jitter.[117] 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

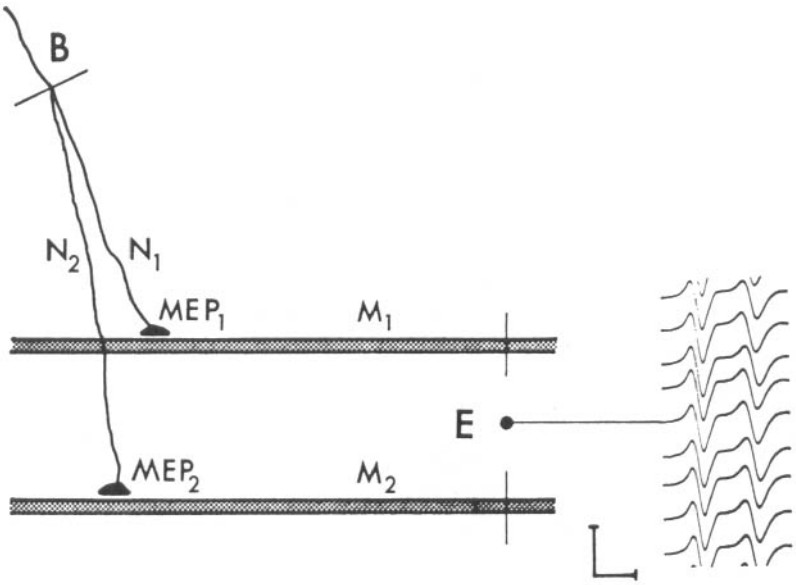

Figure 16–4. Determination of jitter by simultaneous recording from two muscle fibers, M_1 and M_2, within the same motor unit. The potential from M_1 triggers the sweep, although the use of a delay line allows its display from the onset. The potential from M_2 appears after a short interpotential interval 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 end-plates, 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 Stålberg,[11] with permission.]

paired potentials show an excessive interval or very rapid firing, as discussed below. Thus, the motor end plate constitutes the main source of jitter in normal muscles.[85,110] A slight change in the rising slope of the end plate potential (see 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 transmission time at the neuromuscular junction.[59]

When jitter increases excessively, the second potential fails. This phenomenon, referred to as "blocking," occurs more commonly in pathologic conductions such as in myasthenia gravis, but also, to a lesser extent, in normal subjects, especially after age 50.[21]

Determination of Jitter

Jitter measurement 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 trigger, measurement of a potential pair separated by less than 150 μs, and determination of jitter in potentials on the descending phase of the triggering discharge.

Most investigators express electromyographic jitter as the mean value of consecutive differences (MCD),[16] 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 compar-

ison of sequential discharges measures only the short-term variation. A series of consecutive differences has the additional advantage of being more easily computed. Jitter values expressed by this method remain the same during continuous activity lasting up to 1 hour.[16]

Most digital instruments offer software for automatic analysis of jitter and display of the results by numeric or graphic means. Without such a program, manual determination of jitter depends on photographic superimposition of 50 sweeps in groups of 5 or 10 discharges with a sweep speed of 200 μs/cm or faster (Fig. 16–5). If the first potential triggers the oscilloscope, then the jitter equals the variability of a series of second potentials, which follows within approximately 1 ms. After superimposition of 10 paired discharges, the latency difference between the baseline intersection points of the earliest and latest second potentials provides the time range of 10 discharges. The average value of this measure from five different sampling sites in the same muscle gives the mean range of 10 discharges. Multiplying it by a factor of 0.37 yields an estimated MCD.[14] Similarly, another conversion factor of 0.49 applies for the mean range of 5 discharges from ten different sites. The value obtained by these formulas gives a good approximation of the actual jitter value calculated by a computer program.[65,79]

Muscle fiber propagation slows substantially upon rapid firing, because suc-

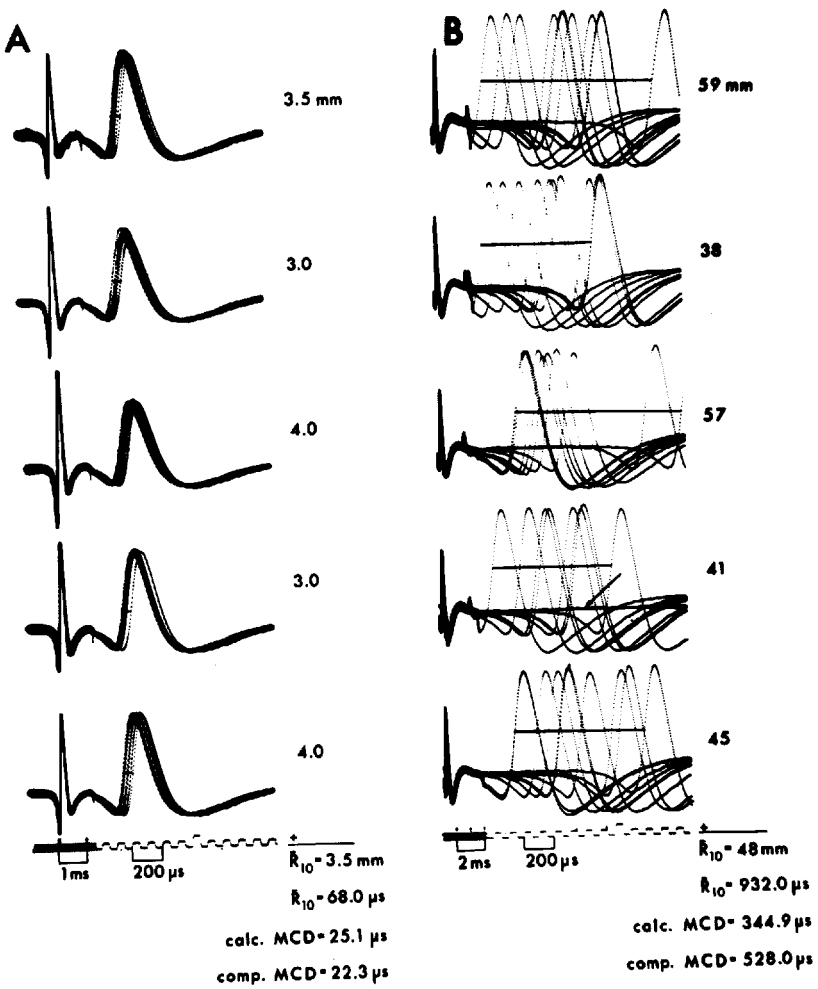

Figure 16–5. Manual calculation of jitter in a normal (*A*) and abnormal (*B*) action potential pair. The tracings show five groups of 10 superimpositions to measure the ranges of variability for the interpotential interval (IPI) in each group. The mean value of the IPI variability multiplied by 0.37 equals the calculated mean value of consecutive difference (*calc MCD*), which approximates very closely the result determined by a computer (*comp MCD*). [From Stålberg and Trontelj,[115] with permission.]

cessive 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). The rate-dependent jitter contributes on the average less than 10 μs but can be so large as to produce false abnormality at more irregular firing, longer interval, and pronounced differences in velocity recovery function.[129] 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. In calculating jitter without a computer, selection of an interpotential interval of less than 4 ms omits the effect of firing rate, and the use of MCD accommodates slow trends.

Normal and Abnormal Jitter Values

Different investigators have applied the technique to various conditions including studies of laryngeal muscles.[90] Table 16–2 summarizes the jitter values for various muscles determined at a very fast sweep speed with the time resolution of 0.3 μs.[116] Jitter measurements may show a different range and higher mean value than those listed if recorded with less time resolution. Jitter value varies, depending on the age of the subjects, 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 end plates and 18 μs for the median of 20 motor end plates.[124] In general, stimulation technique yields smaller jitter values and fewer percentages of abnormal fibers, as expected from the measurement of one end plate versus two end plates tested with voluntay contraction.[47] Despite these variabilities, blocking in more than one fiber or jitter values exceeding 55 μs constitute an abnormality in any muscle. In the extensor

Table 16–2 Jitter in Normal Subjects*

Muscles	Number of Potential Pairs	MCD—Pooled Data Mean	MCD—Pooled Data SD	SD of MCD Values from Individual Subjects Mean	SD of MCD Values from Individual Subjects SD	Upper Normal Limit Close to Mean + 3 SD
Frontalis (range of individual means	258	20.4 (15.7–29.2)	8.8	6.2 (5.5–8.7)	2.3	45
Biceps	125	15.6	5.9			35
Extensor digitorum communis (range of individual means)	759	24.6 (16.5–32.0)	10.6	8.3 (2.3–12.4)	3.2	55 (65)†
Rectus femoris	73	31.0	12.6			60 (75)†
Tibialis anterior	153	32.1	15.0			60
Extensor digitorum brevis	29	85.3	68.6			None

*Jitter (MCD) measured with voluntary activation in normal subjects aged 10 to 70 years.

†Because of some extreme high values, the data deviate from a Gaussian distribution. Thus, a more appropriate upper normal limit is 60 μs. In no one normal subject was there more than one value exceeding this limit.

Source: From Stålberg and Trontelj,[115] with permission.

digitorum communis, jitter remains relatively constant in persons younger than 70. It increases around the age of 50 in the tibialis anterior, probably secondary to neurogenic change.[114] Normal muscles show the same jitter regardless of the innervation rates or the recording site relative to the end-plate zone. Abnormal jitter, when found in normal muscle, usually occurs as part of a triplet or multiplet.[57] Neuromuscular jitter may increase during continuous voluntary activation in patients with myasthenia gravis, spinal muscular atrophy, or motor neuron disease, but not in normal subjects.[45] Occasional bimodal distribution of response latencies obtained during axonal microstimulation suggests multiple innervation of muscle fibers by the coexisting neuromuscular junctions from the same or different motor neurons.[128]

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, jitter results primarily from variability in neuromuscular transmission. To support this view, nonparalytic doses of tubocurarine, known to block end plate depolarization, cause jitter to increase without changing the shape and amplitude of the single muscle fiber potentials.[18] 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 firing rate may reflect this type of underlying pathology. In myasthenia gravis characterized by postsynaptic defect, the rapid firing rate increases jitter, even with an interval of less than 4 ms. In presynaptic disorders such as myasthenic syndrome and botulism, jitter increases at slow firing rates and decreases at fast rates.

Jitter increases 2–3 μs per degree centigrade as the temperature of the muscle falls from 36° to 32° C, followed by a more rapid change of about 7.5 μs per degree centigrade thereafter.[106] Despite an increase in the jitter value, a train of stimuli shows a less decrement of the compound muscle action potentials with cooling. A number of factors may contribute to the apparent discrepancy. Defective release of transmitters at low temperatures would explain increased jitter and paradoxically smaller decrement; fewer quanta released by the first impulse leave more quanta available for subsequent release. Increases in temperature between 35° and 38° C do not normally change 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 myasthenia gravis.[64] Abnormal jitter occurs not only in diseases of neuromuscular transmission[21] but also in many other conditions associated with conduction defects of nerve and muscle.[19,20,51] It may also result from unusually low end-plate potentials or from a high threshold of the muscle fiber membrane. In general, an increase in jitter values, typically beyond 80–100 μs, precedes the transmission block. Blocking of single muscle fiber discharges results in a reduction amplitude of the compound muscle action potential with repetitive nerve stimulation.[33] SFEMG can detect increased jitter before blocking and impulse blocking at levels below the resolution of surface recording of compound potential.[33,81] Chronic muscular activity also leads to increased jitter and other minor SFEMG abnormalities, presumably as the result of mild denervation and reinnervation of nerve terminals.[93]

6 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 10 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 electromyography (EMG) using a

specially constructed needle circumvents this difficulty by means of an averaging technique.[99,100]

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 pick-up with a bare cannula 15 mm in length (Fig. 16–6). 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.

The resultant response differs substantially from the ordinary motor unit potential. A monopolar or concentric needle registers the activities generated by only a few muscle fibers within a 500 μm to 1 mm radius. In contrast, macro EMG motor unit potentials receive contributions from many more muscle fibers located outside the range of the conventional recording,[67] showing good short-term stability on repeated recording every 15 minutes during a 2-hour period.[37] Thus, macro EMG signals give information about a greater part of the motor unit, in contrast to the regional electrical activity measured in conventional studies, or the focal pick-up recorded in SFEMG (Fig. 16–7). Macrorecording serves better in correlating the size of single motor units to their functional characteristics such as twitch properties.[130,131] For example, successively recruited motor units show a progressive increase in macropotential and a decrease in firing frequency, confirming the size principle.[49] In juvenile myoclonic epilepsy, macrorecording shows an increase in the amplitude of motor unit potentials, suggesting an enlargement of motor units.[24] Macro- and surface-recorded motor unit potentials show high positive correlations in area and in peak-to-peak amplitude.[77]

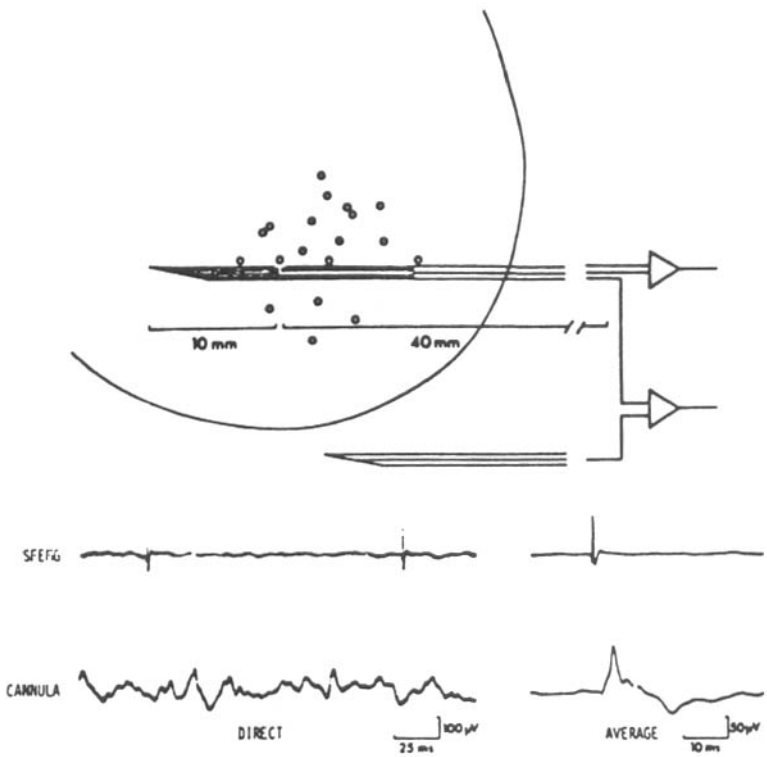

Figure 16–6. Principles for macro EMG (*A*). Single-fiber action potentials (*B*) recorded by the small lead-off surface provide triggers to average cannula activities (*C*) time-locked to the discharge from one muscle fiber (*D*). [From Stålberg,[99] with permission.]

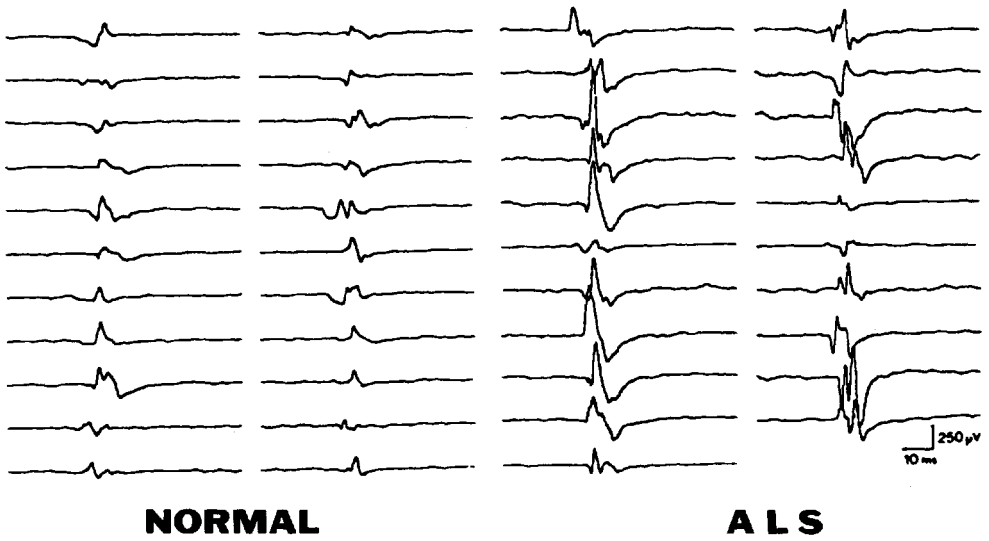

Figure 16–7. Examples of macro motor unit potentials recorded in normal muscle and amyotrophic lateral sclerosis. [From Stålberg,[100] with permission.]

A specially constructed needle records macropotential simultaneously with concentric recording, which serves as the trigger.[46] With this technique, macrorecording correlated better with the area than the amplitude of motor unit potential recorded by concentric electrodes in normal subjects, as well as in patients with myogenic or neurogenic disorders.[5,27] The macropotential has a 40–50 percent smaller amplitude and area when triggered with concentric as compared to single-fiber needle recording.[69] This difference probably results from variant spatial orientation of the macroneedle to the motor unit in the two recording methods.

A variant of macrostudy 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. This technique has verified the rearrangement of muscle fibers in disease states, showing the presence of long polyphasic sections as the most striking finding.[104] In one study,[35] most patients with myogenic disorders had motor unit territory smaller than 4 mm, whereas those with neurogenic processes showed larger values. The sizes of the abnormal units, however, only occasionally exceeded the lower and upper limits of normal, ranging from 2 to 8 mm. Thus, the size of the motor unit territory fails to provide a useful measure for detecting pathology.[104] In the process of reinnervation, the terminal sprouts from a surviving motor unit probably reach only those territorially overlapping denervated muscle fibers from another unit without extending beyond that unit's original boundary.

In summary, with a modified SFEMG electrode, single-fiber action potentials provide the trigger for selective averaging of the intended motor unit potential. Based on this principle, macrotechnique 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.[99] During the reinnervation process, SFEMG reveals the dynamics, whereas macro EMG uncovers the topography.[102] The factors that determine the characteristics of macro EMG include number of fibers, fiber diameter, end plate scatter, pattern of nerve branching, motor unit territory, and electrode position. Table 16–3 summarizes the suggested normal data for the different age groups. Macro motor unit potentials increase in size after age 60, in part reflecting reinnervation following physiologic loss of anterior horn cells with age.[12,109]

Table 16–3 Macro EMG in Normal Subjects

	Suggested Amplitude Limits (μV)											
	Biceps				Vastus Lateralis				Tibialis Anterior			
	Median		Individual Macro-MUP		Median		Individual Macro-MUP		Median		Individual Macro-MUP	
Age	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

Source: From Stålberg,[100] with permission.

7 CLINICAL VALUES AND LIMITATIONS

SFEMG has become available in most laboratories with a dedicated system or with minor modification of the conventional units. A computer-assisted method has rendered the technique simple enough to conduct as part of routine studies with a little extra training.[116] The method has clinical and research applications for lower motor neuron disorders and diseases of muscle in general, and of neuromuscular transmission in particular.[136] It has proven most useful, from an electrodiagnostic point of view, as a test for myasthenia gravis and myasthenic syndromes,[21,98,107] and, to a lesser degree, for a variety of peripheral nervous system disorders, especially in assessing patterns of nerve regeneration.[101] 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 neuromuscular transmission jitter results from intrinsic noise rather than from deterministic chaos.[34] Table 16–4 summarizes the normative data reformatted for simplified presentation.[8]

Motor Neuron Disease

Disorders associated with abnormal SFEMG include degenerative processes affecting the anterior horn cell[111] and tetanus.[26] The chronic processes with marked collateral sprouting, such as spinal muscular atrophy, show the highest fiber density among motor neuron diseases. Clinical studies have revealed an inverse relationship between muscle strength and fiber density.[119] The increased duration of the action potential found in this entity suggests a mixture of hypertrophic and atrophic fibers and slowly conducting, regenerated nerve sprouts, forming collateral reinnervation but not as effectively as in other neurogenic disorders.[119] In contrast, rapidly progressive diseases such as amyotrophic lateral sclerosis show increased jitter and blocking. The SFEMG characterizes the functional status of the motor unit and may help establish the diagnosis and prognosis. Detecting abnormalities not apparent clinically or with conventional electromyography provides early evidence of motor neuron involvement.

Peripheral Neuropathy

Disorders of the peripheral nerves also show increased jitter, occasional blocking, and increased fiber density.[105] These findings become particularly prominent during the process of reinnervation, having been observed, for example, up to 1 year after autogenous facial muscle transplants.[38] Mean jitter values usually return to normal approximately $1\frac{1}{2}$ years after the onset of reinnervation, although some individual recordings may remain abnormal permanently.[134] Abnormalities of the SFEMG result in part from reinnervation, when seen in patients with polyneuropathies and motor neuron disease, and

Table 16–4 Single-Fiber EMG Reference Values

	Jitter Values (μs): 95% Upper Confidence Limit of Normal Mean Consecutive Difference (MCD)/Single Fiber Pairs								
Muscle	**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 oris	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		
Sternocleidomastoid	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 comminis	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

	Fiber Density Values: 95% Upper Confidence Limit of Normal for Mean Fiber Density								
Muscle	**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		
Sternocleidomastoid	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 comminis	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	

Recommended criteria for an abnormal study: *Jitter is abnormal if either: (1) value for mean MCD of 20 fiber pairs greater than the 95% upper confidence limit; or (2) jitter values in more than 10% is greater than the 95% upper confidence limit for action potential pairs. Fiber density is abnormal if mean value of 20 observations is greater than 95% of upper confidence limit.*

Source: From Bromberg, Scott, and AD HOC Committee of the AAEM Single Fiber Special Interest Group (1994),[8] with permission.

perhaps also in those with polymyositis and muscular dystrophy. Not all the polyneuropathies show similar changes. Studies of the extensor digitorum communis[121] showed abnormalities of fiber density, jitter, and blocking in patients with alcoholic neuropathy, but not in those with diabetic or uremic neuropathy. Another study, however, revealed an increased fiber density and jitter not only in diabetic patients with neuropathy but also in diabetic controls without overt neuropathy. Persistent changes may reflect ongoing reinnervation in certain types of neuropathy.[92] Jitter values in chronic renal failure improve after intermittent hemodialysis.[54] Other disorders sometimes associated with increased jitter include multiple sclerosis,[132] chronic demyelinating neuropathy,[71] idiopathic fecal incontinence,[94] critical-illness polyneuropathy,[87] and peripheral sprouting after acute quadriplegia.[61]

Macro EMG study in chronic demyelinative neuropathy showed an increase in average amplitude, probably resulting from the loss of smaller motor units rather than reinnervation.[56] One study of diabetic neuropathy[3] showed a greater increase in amplitude of macro motor unit potential and fiber density in patients with weakness as compared to those with normal strength, suggesting incomplete reinnervation as the cause of the functional loss.

Disorders of Neuromuscular Transmission

Normal muscles show increased jitter in 1 of 20 recorded pairs of potentials.[106] Increased jitter or blocking, if found in 2 or more of 20 pairs of potentials, provides evidence of defective neuromuscular transmission. A patient with myasthenia gravis may have normal or increased jitter values within any one muscle. Jitter exceeding 100 μs usually leads to intermittent blocking.[118] In generalized myasthenia gravis, more than 30 percent 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.[82,118] About 25 percent of patients with myasthenia gravis have fiber density increased slightly above the normal range. Statistical analyses showed no correlation between this abnormality and disease severity or duration, but patients treated with cholinesterase inhibitors had a significantly greater increase in jitter value.[43] In one study of 15 myasthenic patients, voluntary activation demonstrated greater increase in jitter value and proportion of blocking than stimulation technique, probably because of different sampling bias between the two methods.[66]

SFEMG can detect disturbances of neuromuscular transmission before the appearance of clinical symptoms. Thus, normal jitter in a clinically weak muscle tends to exclude the diagnosis of myasthenia gravis.[83] In one series,[118] SFEMG showed increased jitter or blocking in the hypothenar muscles in all 40 patients with mild to moderate generalized myasthenia gravis, even though the repetitive nerve stimulation technique revealed equivocal results in 40 percent of these patients. In another series,[82] 127 of 131 patients demonstrated defective neuromuscular transmission by SFEMG, whereas less than 50 percent of these patients had an abnormality by the conventional nerve stimulation technique. SFEMG of the extensor digitorum communis showed abnormality in 8 of 24 first-degree relatives of 12 patients with juvenile myasthenia gravis. In this asymptomatic group, increased jitter occurred, on average, in 5 of 20 potential pairs. Hence only 25 percent of all recordings showed abnormalities, in contrast to 75 percent in clinically symptomatic patients.[118] In a study of 17 patients with pure ocular myasthenia gravis,[53] SFEMG showed abnormalities in all superior rectus and levator palpebralis muscles, and in 62 percent of orbicularis oculi muscles.[75] In patients with restricted extraocular muscle weakness, 58 percent developed generalized symptoms if the extensor digitorum communis showed increased jitter initially as compared to 18 percent of those without such abnormalities.[133]

The SFEMG abnormalities correlated well with the clinical course in serial studies of individual patients.[63,81] Adminis-

tration of edrophonium (Tensilon) shortens abnormal jitter and decreases the incidence of blocking, without affecting the initially normal jitters. A therapeutic dosage of anticholinesterase medication may correct jitter in myasthenia. In some cases, recovery from blocking in a number of fibers may give an apparent increase in jitter values after treatment. In a healthy subject, anticholinesterase 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 myasthenia gravis.[116] SFEMG may occasionally return to normal during spontaneous remission or after thymectomy, but most of these patients still have increased jitter without blocking.[116]

In the myasthenic syndrome, a slight increase in fiber density[116] probably results from type II fiber grouping.[39] In this syndrome, blocking tends to occur at greater jitter values than in myasthenia gravis. 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.[88,89] Both jitter values and the degree of blocking decrease as the stimulation rate increases, and these transmission abnormalities worsen after rest.[10,80] These findings stand in sharp contrast to those typically seen in patients with myasthenia gravis, but improvement of jitter and blocking at higher rates of stimulation, unless dramatic, does not necessarily suggest a presynaptic abnormality.[126] Serial studies show a corresponding improvement with remission or after therapy, providing a quantitative measure of the changing clinical status.[70,72,78]

Jitter values usually improve at high rate of stimulation in presynaptic disorders.[9,76] SFEMG in human botulism,[73,86] however, may yield a different pattern of abnormality, depending on the type of toxin and the stage of illness. In two patients with wound botulism, for example, stimulated SFEMG showed increased jitter at high stimulation frequency,[60] countering the general principle. In four patients who received periocular injections of botulinum toxin for blepharospasm, SFEMG demonstrated abnormal neuromuscular transmission of the arm muscles.[84] 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 muscle in general shows increased fiber density and jitter; it also occasionally shows decreased jitter in some recordings. Macro EMG studies indicate a normal diameter of motor units with no signs of abnormal volume conduction.[41,42] These findings suggest a remodeling of the motor unit as the result of fiber loss, fiber regeneration, and reinnervation, but the exact pathophysiology underlying the process remains unclear. 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 end plate by transverse lesions, as shown in Duchenne dystrophy.[13] Alternatively, fiber density may reflect new innervation of regenerating muscle fibers or splitting of muscle fibers.[96] Increased jitter may result from altered propagation time in the muscle fibers.[95]

In one series,[98] patients with Duchenne dystrophy had 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 percent of the recordings in each muscle and occasional blocking in 10 percent 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.[44] In support of this view, pairs with reduced jitter always block simultaneously when subjected to tubocurarine or other agents that inhibit neuromuscular transmission. Ordinary potential pairs would show clear dissociation with this type of inhibition. Fiber density also increases in limb-girdle dystrophy, but to a lesser degree than in Duchenne dystrophy. In one series,[97]

studies of clinically weak muscles showed increased jitter in 54 percent of the recordings and blocking in less than 10 percent. In another series of 20 patients, SFEMG confirmed the original diagnosis in 16 unequivocal cases and helped differentiate the four indeterminate cases into myopathic and neurogenic categories.[91] Patients with facioscapulohumeral dystrophy[97] and chronic progressive external ophthalmoplegia[55] had findings similar to those reported in limb-girdle dystrophy.

Another study of 56 patients correlating SFEMG with histochemistry revealed slightly increased fiber density in the majority of patients with acid maltase deficiency, limb-girdle dystrophy, and polymyositis and in nearly half of those with mitochondrial myopathy.[6] In contrast, patients younger than 40 with muscle phosphorylase deficiency, myotonia congenita, or hypokalemic periodic paralysis had no abnormality. In polymyositis, a segmental degeneration separates a portion of the affected muscle fiber from its motor end plate. 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, high-frequency discharges recorded in SFEMG progressively decrease in amplitude and increase in rise time. In one series,[62] fiber density exceeded the normal range in 84 percent, and jitter in 20 percent, of the measurements.

Other Applications

SFEMG has revealed abnormalities in other disorders not overtly associated with neuromuscular diseases, possibly implicating subclinical disturbance of muscle fibers. These include idiopathic scoliosis,[123] postviral fatigue syndrome,[52] and healthy muscles following a period of disuse.[36]

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Part V

SPECIAL TECHNIQUES AND STUDIES IN CHILDREN

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Chapter 17

THE BLINK REFLEX

1 INTRODUCTION

The use of an oscilloscope display allows quantitative analysis for meaningful assessment of the corneal reflex responses tested in clinical practice.[1,108] The mechanical or electrical stimulation of the trigeminal nerve also elicits a blink reflex that bears a resemblance to the corneal reflex.[9,25,27,69,76,106,120,130,131,134] Electrical stimulation of the supraorbital nerve elicits two or more temporally separate responses of the orbicularis oculi muscles, an ipsilateral early (R_1) component and bilateral late (R_2 and R_3) components

(Fig. 17–1). R_1, usually evoked only on the side of stimulation via a pontine pathway,[53,130] may also appear contralaterally if primed[153] or after facial nerve palsy.[97] These findings suggest unmasking of a preexisting crossed pathway. Unilateral stimulation always elicits R_2 bilaterally, presumably relayed through a more complex route, including the pons and lateral medulla.[20,42,44,67,80,107,142] A greater shock may evoke R_3 probably by activation of small-diameter, high-threshold afferent fibers.[6,29,77–79,117,119] Painful laser stimulation also elicits bilateral responses at around 70 ms, and occasionally at 130 ms as well.[28] Assuming the nociceptor activation time of about 40 ms, these onset latencies fall within the range of electrically evoked R_2 and R_3.

The more reproducible R_1 serves as a reliable measure of nerve conduction along the reflex pathways. Analysis of R_2 helps localize the lesion to the trigeminal nerve, the facial nerve, or the brainstem.[38,67] Involvement of the trigeminal nerve causes an afferent pattern with delays or diminution of R_2 bilaterally after stimulation of the affected side. In diseases of the facial nerve, the pattern indicates an efferent abnormality with alteration of R_2 only on the affected side, regardless of the side of stimulation. Afferent and efferent delays of R_2 conceptually resemble the two types of abnormality in the pupillary light reflex, which, therefore, serves as a good analogy. Neither pupil constricts in response to light stimuli given to the affected eye in an afferent defect, whereas the affected eye shows no pupillary constriction regardless of the side stimulated in an efferent defect.

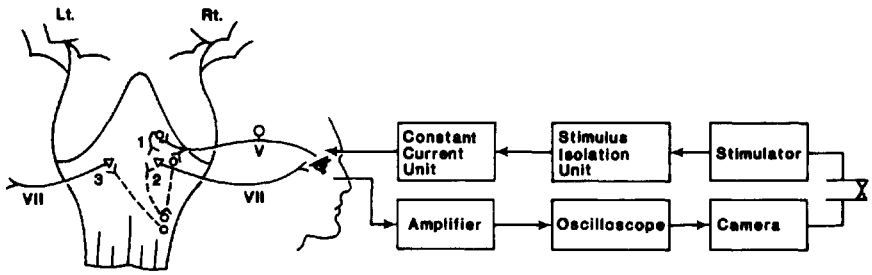
2 DIRECT VERSUS REFLEX RESPONSES

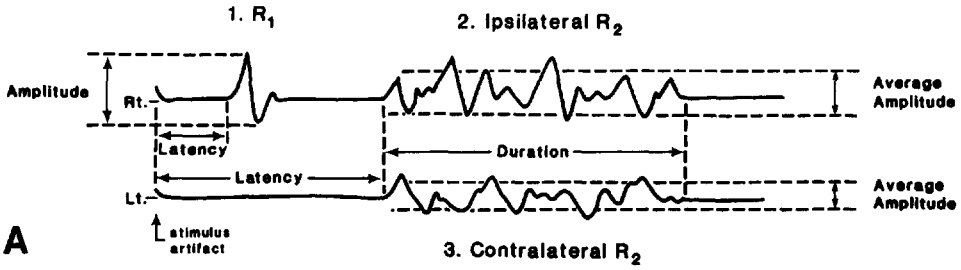
Stimulation of the Facial Nerve

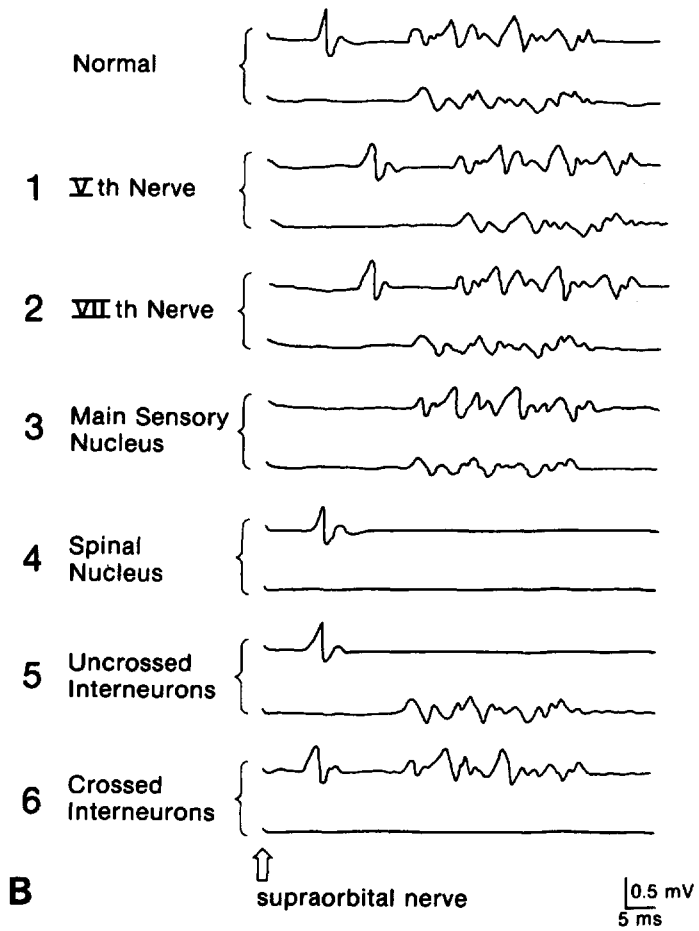
The test of nerve excitability consists of applying shocks of increasing intensity and observing the resulting contraction of the facial muscles. The normal threshold ranges from 3.0 to 8.0 mA, depending on skin resistance, skin temperature, and the anatomic course of the facial nerve. Comparisons with the unaffected nerve on the opposite side reduce the number of variables to a minimum. In healthy subjects, differences between left and right should not exceed 2.0 mA. A complete section of the nerve at a proximal site results in loss of distal excitability by the end of the first week, but not during the first few days before the emergence of wallerian degeneration. Hence, a normal distal response at the end of the first week after damage suggests a good prognosis.[36]

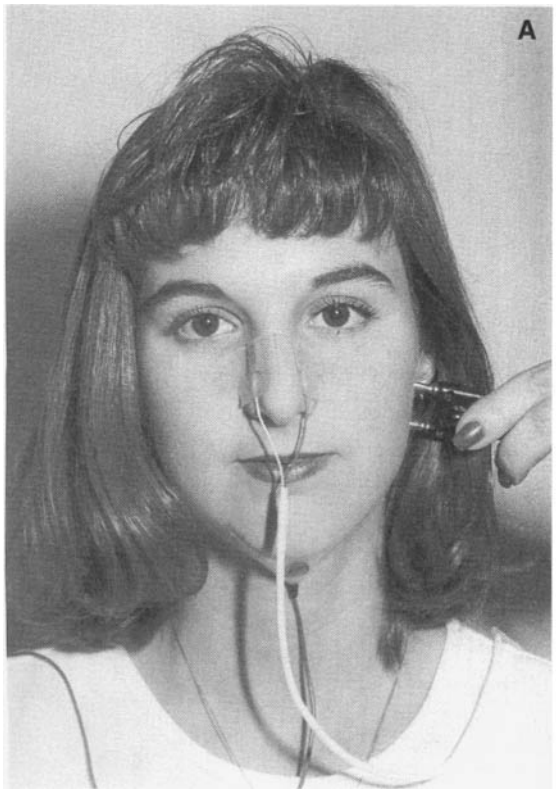
Recording of muscle action potentials provides a more quantitative assessment of nerve excitability than visual inspection of contracting muscle. Stimulating the facial nerve just below the ear and anterior to the mastoid process[151] or directly over the stylomastoid foramen[141] elicits compound muscle action potentials in the facial muscles. Placing the stimulating electrodes more distally along a branch of the facial nerve (see Fig. 1–2) results in more selective activation of the target muscles (Fig. 17–2A). Its designation as direct response, or M response, distinguishes it from the reflex activation of the orbicularis oculi by stimulation of the trigeminal nerve.

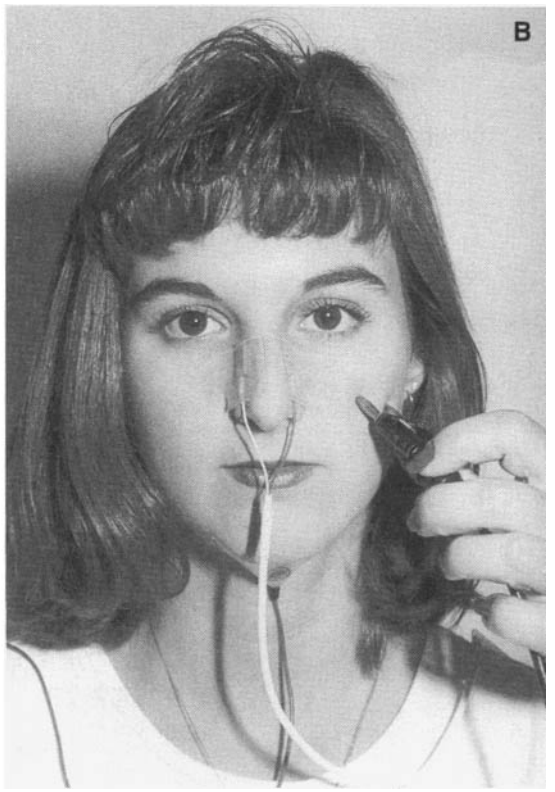
Figure 17–1. A. *Top.* Stimulation and recording arrangement for the blink reflex, with the presumed pathway of R_1 through the pons (*1*) and ipsilateral and contralateral R_2 through the pons and lateral medulla (*2* and *3*). The schematic illustration shows the primary afferents of R_1 and R_2 as one fiber, as details of polysynaptic central connections of these reflexes are unknown. *Bottom.* A typical oscilloscope recording of the blink reflex after right-sided stimulation. Note an ipsilateral R_1 response and bilateral simultaneous R_2 responses. [Modified from Kimura,[59] with permission.] **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; (*2*) efferent pathway along the facial nerve; (*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 R_1 usually indicate the involvement of the reflex arc itself, whereas the loss or diminution of R_1 or R_2 may result not only from lesions directly affecting the reflex pathway but also from those indirectly influencing the excitability of the interneurons or motor neurons.


Lt.
Rt.
1
2
3
V
VII
VII
Constant Current Unit
Stimulus Isolation Unit
Stimulator
Amplifier
Oscilloscope
Camera


1. R_1
2. Ipsilateral R_2
Amplitude
Rt.
Latency
Latency
Duration
Average Amplitude
Average Amplitude
Lt.
stimulus artifact
3. Contralateral R_2
A


Normal
1 Vth Nerve
2 VIIIth Nerve
3 Main Sensory Nucleus
4 Spinal Nucleus
5 Uncrossed Interneurons
6 Crossed Interneurons
B
supraorbital nerve
0.5 mV
5 ms





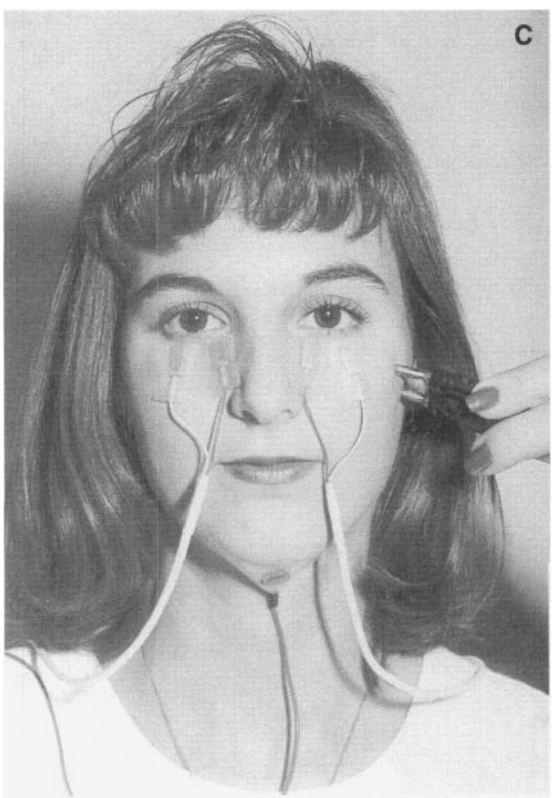


Figure 17–2. Technique for recording the direct response. **A.** Stimulation of the facial nerve trunk with the cathode placed just anterior to the mastoid process elicits compound muscle action potentials in all mimetic muscles of the face ipsilaterally. Stimulation of buccalis (**B**), zygomaticus (**C**), or other branch activates the target muscle more selectively, minimizing movement artifact. Recording from the nasalis with G_1 placed on the ipsilateral side of the nose and G_2 on the other side often gives rise to a discrete compound muscle action potential (**A** and **B**). The test performed in conjunction with the blink reflex uses the active electrode (G_1) and the reference electrode (G_2) placed on the lower portion of the orbicularis oculi (**C**) (see Fig. 1–3).

The amplitude of the direct response varies with the number of functional motor axons, whereas the onset latency reveals the distal conduction of the fastest fibers.

Recording electrodes consist of G_1 placed on the orbicularis oculi, orbicularis oris, quadratus labii, or nasalis, and G_2 on the same muscle on the opposite side or on the nose. When necessary, selective stimulation of a given branch of the facial nerve elicits an isolated response from any of the muscles of the face (Fig. 17–2B,C), including the posterior auricular muscle.[21] Some investigators prefer to record from a needle placed in the orbicularis oris just superior to the corner of the mouth or in the orbicularis oculi at the lateral epicanthus. Surface electrodes are generally better for assessment of compound muscle action potentials, although needle study is useful for selective recording from a small or atrophic muscle. The coaxial needle gives a slightly better endpoint than the monopolar needle used in conjunction with a reference electrode placed on the side of the nose. A larger electrode placed on the forehead or under the chin serves as the ground.

Reported normal values for facial nerve latencies (mean ± SD) in adults range from 3.4 ± 0.8 to 4.0 ± 0.5 ms.[141] Table 17–1 summarizes the normal values measured to the onset of the negative deflection of the evoked potential in 78 subjects divided into different age groups.[151] For the assessment of a proximal lesion in Bell's palsy, the latency of the direct response rarely provides useful information. Even with substantial axonal degeneration, the remaining axons tend to show a normal or only slightly increased onset latency. In contrast, the amplitude of the direct response determines the degree of axonal loss for accurate assessment of prognosis. Comparison between the sides in the same individual provides a more sensitive measure than the absolute value, which varies substantially from one subject to the next. An amplitude reduction to one half that of the response on the normal side suggests distal degeneration.

Table 17–1 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

From Waylonis & Johnson (1964),[151] with permission.

More importantly, serial determinations reveal progressive amplitude changes as an increasing number of axons degenerates in time (Fig. 17–3). Distal stimulation elicits a normal response for a few days, even after complete separation of the nerve at a proximal site. By the end of the first week, however, the amplitude drops abruptly, coincident with the onset of inexcitability of neuromuscular junction followed by nerve degeneration, Thus, a normal direct response during the first week after injury promises a good prognosis. With shocks of very high intensity, a stimulating current may inadvertently activate the masseter muscle at its motor point (see Fig. 7–1). A volume conducted potential from this muscle can erroneously suggest a favorable prognosis when in fact the facial nerve has already degenerated. Close visual inspection of the contracting muscle clarifies the otherwise confusing results (see Chapter 7–3).

Stimulation of the Trigeminal Nerve

Stimulation of the trigeminal nerve elicits reflex contraction of the orbicularis oculi. In contrast to the direct response that provides a measure of distal nerve excitability, the blink reflex reflects the integrity of the afferent and efferent pathways, including the proximal segment of the facial nerve. As mentioned earlier, a single shock to the supraorbital nerve evokes two separate contractile responses of the orbicularis oculi. The latency of R_1 represents the conduction time along the trigeminal and facial nerves and pontine relay. Inherent latency variability from

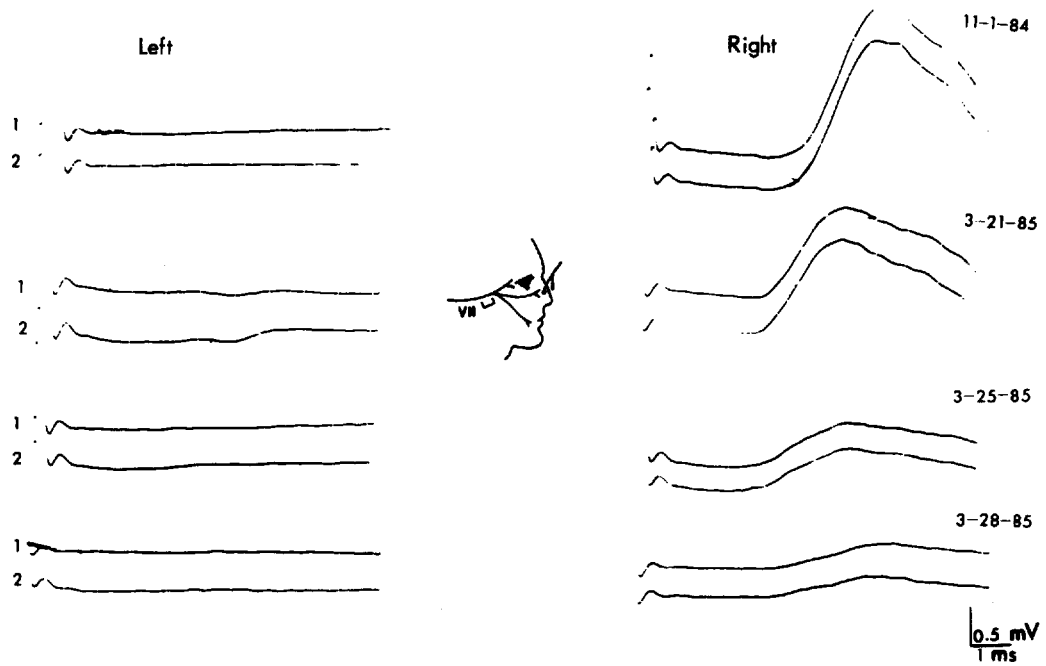


Figure 17–3. A 63-year-old man with acute facial palsy on the left in November 1984 and on the right in March 1985. Stimulation of the left facial nerve elicited no response in the nasalis at the initial evaluation, and there was no recovery thereafter. Stimulation on the right evoked a normal response 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. [From Kimura,[62] with permission.]

one trial to the next makes R_2 less reliable for diagnostic purposes. Furthermore, the latency of R_2 reflects the excitability of interneurons and the delay for synaptic transmission, in addition to the axonal conduction time.

The subject lies supine on a bed in a warm room with the eyes open or gently closed for surface stimulation with the cathode placed over the supraorbital foramen and the anode placed 2 cm rostrally.[69] Shocks applied here evoke R_1 and R_2, which are best recorded with two pairs of recording electrodes (G_1) and reference (G_2) electrodes placed 2 cm apart on the lower aspect of the orbicularis oculi muscle on each side, with a ground electrode under the chin or around the arm (Fig. 17–4). Additional studies consist of stimulation of the infraorbital and mental nerve with the cathode placed over the respective foramen on one side and recording from the orbicularis oculi on both sides. Assessment of facial synkinesis, described later in this chapter, requires two pairs of recording electrodes on the same side of the face, one pair over the orbicularis oculi and the other over the orbicularis oris or platysma.[3,70]

Shocks of 0.1 ms duration and optimal intensity ranging from 50 to 100 V or 5 to 10 mA elicit a nearly stable R_1 response with repeated trials. In 5–10 percent of healthy subjects, single shocks of appropriate intensities may not elicit a stable R_1 with stimulation on either side. In these cases, mild voluntary contraction of the orbicularis oculi may facilitate the response. A higher shock intensity may only cause the patient discomfort without satisfactory results. Applying paired stimuli with an interstimulus interval of 3–5 ms, however, usually gives rise to an acceptable response. For accurate determination of the shortest latency, a pair of stimuli ideally comprises a subthreshold conditioning shock to subliminally excite the motor neurons and a supramaximal test

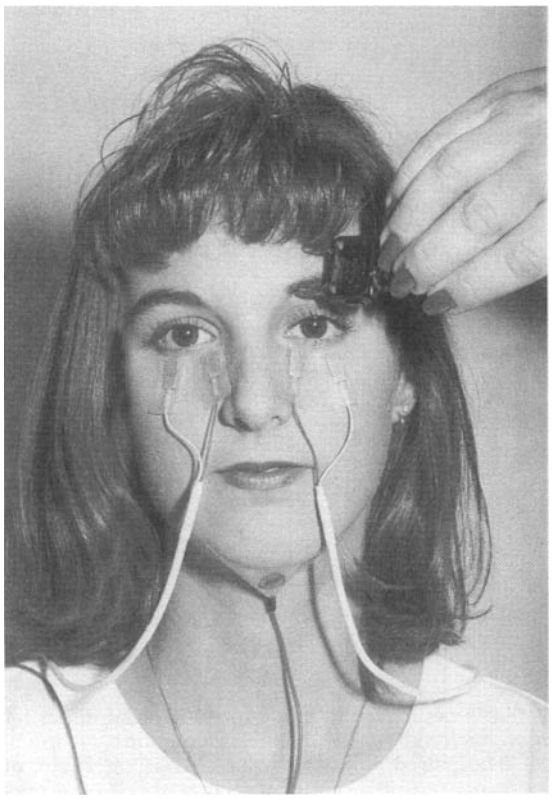


Figure 17–4. Technique for recording the blink reflex. Unilateral stimulation of the supraorbital nerve with the cathode placed at the supraorbital foramen elicits R_1 ipsilaterally and R_2 bilaterally in the orbicularis oculi muscles. Recording leads consists of the active electrode (G_1) placed over the inferior portion of the orbicularis oculi near the inner canthus and the reference electrode (G_2) placed 2 cm laterally. Rotation of the anode around the cathode helps establish the optimal position of the stimulating electrodes to minimize the shock artifact.

stimulus to evoke the response (Figs. 17–4 and 17–5). In this case, the diagnostic assessment depends on the latency measured from the second shock artifact that elicits the recorded reflex. The reflex latency of R_1, measured to the initial deflection of the evoked potential, corresponds to the minimal conduction time of the reflex pathway. Running several trials on each side ensures recording of the shortest latency response. The latency ratios of R_1 to the direct response (R/D ratio) provide a measure for comparison of the conduction through the distal segment of the facial nerve with that of the entire reflex arc, which includes the trigeminal nerve and the proximal segment of the facial nerve.

Because G_1 and G_2 lie only a few centimeters away from the cathode, R_1 tends to overlap 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 with a short blocking time (0.1 ms) and low internal noise (0.5 μV RMS at a bandwidth of 2 kHz) minimizes the problem of stimulus artifact.[148] Most modern electromyography instruments offer a similar fast recovery feature, requiring no additional special devices for routine recording of R_1. A frequency response in the range of 20–10 kHz suffices for recording either the R_1 or R_2 component.

In addition to electrical stimulation of the supraorbital nerve, mechanical, visual, or auditory stimuli also elicit the blink reflex. A mechanical tap[35,72,76,130,136] 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 R_1 only ipsilaterally, similar to unilateral electrical stimulation. In contrast, a glabellar tap, stimulating the trigeminal nerves on both sides, elicits the R_1 component bilaterally, allowing instantaneous comparison of the two sides (see Fig. 17–6C). A mechanically elicited R_1 has a latency 2–3 ms greater than the electrically evoked response. The longer latency results in part from 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. This stands in contrast to magnetic coil stimulation, which also elicits R_1 bilaterally, but with latencies equal to those following electrical shocks.[10]

The R_2 component elicited by a glabellar tap provides confirmation of an afferent or efferent abnormality of the electri-

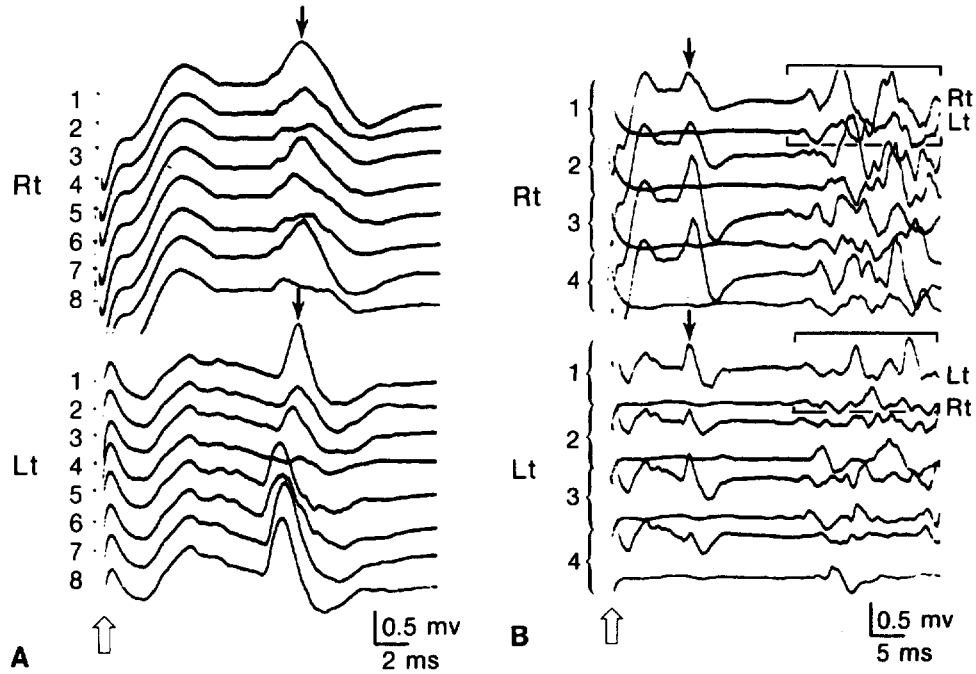


Figure 17–5. A. R_1 components recorded from the orbicularis oculi after stimulation of the supraorbital nerve by individual supramaximal stimuli (*top four trials on each side*) or by paired stimuli with an interstimulus interval of 5 ms (*bottom four trials on each side*). The paired stimuli consist of the first shock of subthreshold intensity, which subliminally primes the motor neuron pool, and the second shock of supramaximal intensity, which activates the reflex and triggers the oscilloscope sweep. [From Kimura,[60] with permission.] **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, which triggers the oscilloscope sweep. Note unilateral R_1 (*arrows*) recorded only in the *upper tracing* in each frame and bilateral R_2 (*brackets*) in both *upper* and *lower tracings*. [From Kimura,[60] with permission.]

cally elicited R_2. A glabellar tap stimulates the right and left trigeminal nerves simultaneously, and these nerves activate the facial nuclei on both sides to elicit bilateral R_2 responses. A consistent latency or amplitude difference between simultaneously recorded right- and left-sided R_2 indicates a delay or block in the facial nerve that constitutes the final common path. A lesion affecting the afferent arc unilaterally does not alter R_2 on either side, because the crossed afferent input from the unaffected side compensates for the loss (see Fig. 17–6C). A glabellar tap or magnetic coil stimulation[10] renders less discomfort to patients and causes no shock artifacts. In our experience, however, electrical stimulation of the supraorbital nerve generally provides more precise information.

3 NORMAL VALUES IN ADULTS AND INFANTS

Latencies of the Direct and Reflex Responses

Table 17–2 shows the normal latency range of the direct response, R_1, the R/D ratio, and R_2 elicited by stimulation of the supraorbital nerve in 83 healthy subjects 7–86 years of age (average age, 37 years)[59] and R_1 elicited by a midline glabellar tap in another group of 21 healthy adult subjects.[72] In a comparable study of infants, R_1 was present in all but 3 of the 113 subjects.[63] Despite a considerably shorter reflex arc, the neonates have a significantly greater latency than the adults (Fig. 17–7). Stimulation of the supraorbital nerve

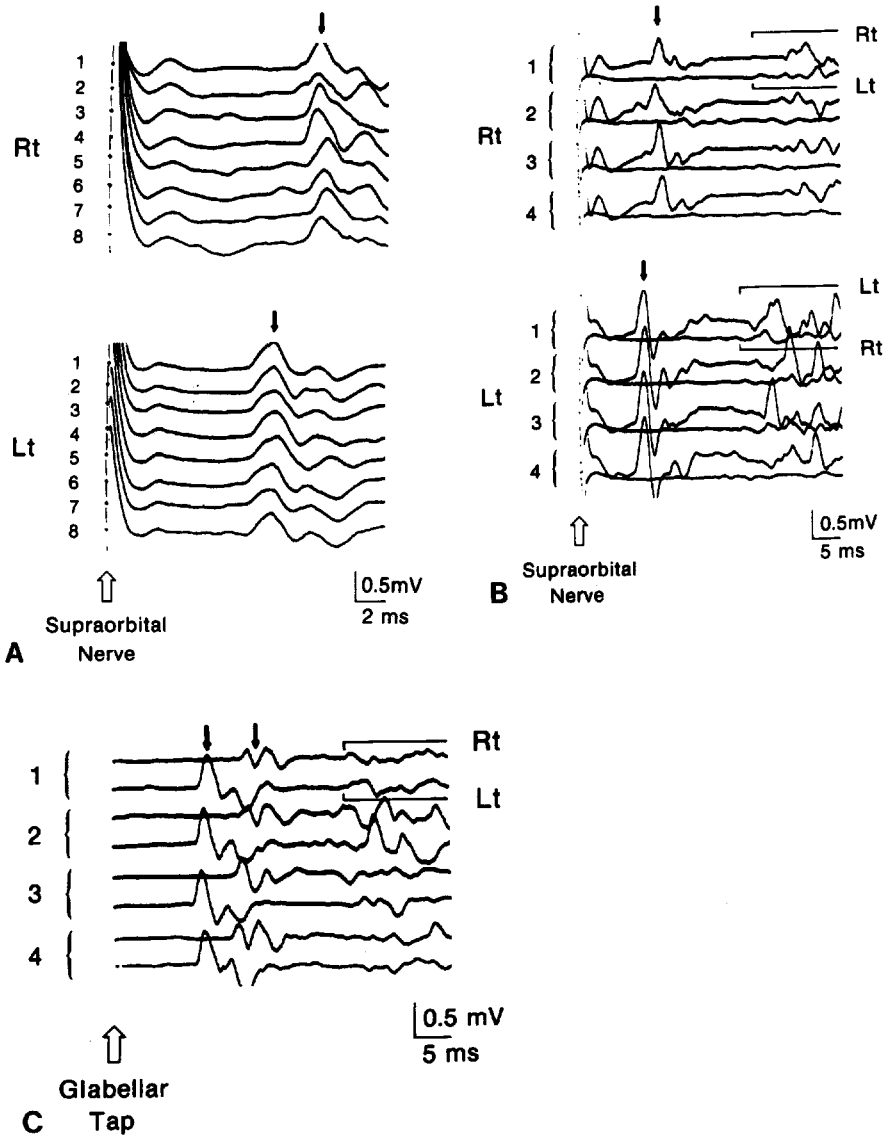


Figure 17–6. A. Delayed R_1 (*arrows*) in a 68-year-old man with a mass lesion involving the right anterior cavernous sinus (cf. Fig. 17–5A). **B.** Delayed and diminished R_2 (*bracket*) on both sides after stimulation on the right in the same patient as in **A.** Stimulation on the left elicited normal R_2 on both sides. These findings suggest a lesion involving the afferent arc of the reflex pathway on the right (cf. Fig. 17–13B). **C.** R_1 (*arrow*) and R_2 (*bracket*) after a midline glabellar tap in the same patient as in **A** and **B**. Note a delayed R_1 on the right in conjunction with a normal R_2, bilaterally. Because of crossed input from the intact trigeminal nerve, a unilateral lesion involving the afferent arc results in little alteration of R_2 when elicited by a midline glabellar tap.

elicited R_2 bilaterally in all adults but in only two thirds of neonates, mostly on the side ipsilateral to the stimulus (Fig. 17–8)[11,16,63] and rarely in premature babies.[40,49,137] Both direct and reflex responses vary considerably in amplitude from one individual to the next. In 60 nerves from 30 healthy subjects 7–67 years of age, the values averaged 1.21 mV for direct response, 0.38 mV for R_1, 0.53 mV for ipsilateral R_2, and 0.49 mV for contralateral R_2.[69]

In another 50 healthy subjects 12–77 years of age (average age, 40 years), stim-

Table 17–2 Blink Reflex Elicited by Electrical Stimulation of Supraorbital Nerve in Normal Subjects and Patients with Bilateral Neurologic Diseases (Mean ± SD)

Category	Number of Patients	Direct Response Right and Left Combined			R_1 Right and Left Combined			Direct Response (ms)	R_1 (ms)	R/D Ratio	Ipsilateral R_2 (ms)	Contralateral R_2 (ms)
		Abs	*Delay*	*Nl*	*Abs*	*Delay*	*Nl*					
Normal	83 (glabellar tap 21)*	0	0	166	0	0	166	2.9 ± 0.4	10.5 ± 0.8 (12.5 ± 1.4)*	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; N1 = normal.

*R_1 elicited bilaterally by a midline glabellar tap in another group of 21 healthy subjects.

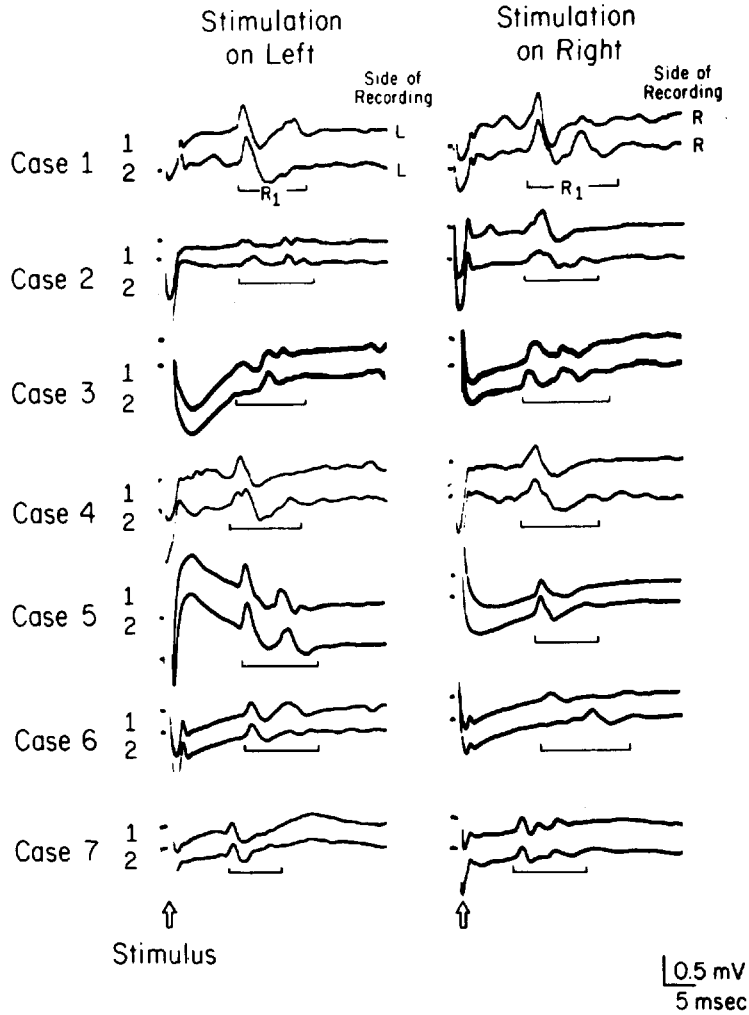


Figure 17–7. R_1 component (*brackets*) of electrically elicited blink reflex in seven newborn infants, recorded from the orbicularis oculi muscle on the side of the stimulus (*arrows*). Two successive trials in each subject show consistency of R_1 response. Neonates often have polyphasic R_1 with prolonged 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 R_1, measurements to the second peak may show an erroneously increased latency (case 6, *right, second tracing*). [From Kimura, Bodensteiner and Yamada,[63] with permission.]

ulation of the supraorbital nerve elicited both R_1 and R_2 regularly, whereas that of the infraorbital nerve evoked R_1 in some cases and R_2 in all. Both R_1 and R_2 had similar latencies regardless of the nerve tested. Shocks applied to the mental nerve elicited R_1 rarely and R_2 inconsistently, showing considerably prolonged latency. Stimulation of the lingual nerve on one side also elicits R_2 in the orbicularis oculi bilaterally, as a possible test for lingual neuropathy.[96,112]

Upper and Lower Limits of Normal Values

The upper limits of normal, defined as the mean latency plus 3 SD include 4.1 ms for direct response, 13.0 ms for electrically elicited R_2, and 16.7 ms for mechanically evoked R_1. Additionally, the latency difference between the two sides should not exceed 0.6 ms for direct response, 1.2 ms for electrically elicited R_1, and 1.6 ms for mechanically evoked R_1. The R/D latency ratio should not fall outside the range of 2.6–4.6, 2 SD above and below the mean in normal individuals.

With stimulation of the supraorbital nerve, R_2 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 R_2 simultaneously evoked by stimulation on one side should not vary more than 5 ms in latency. A latency difference between R_2 evoked by right-sided stimulation and cor-

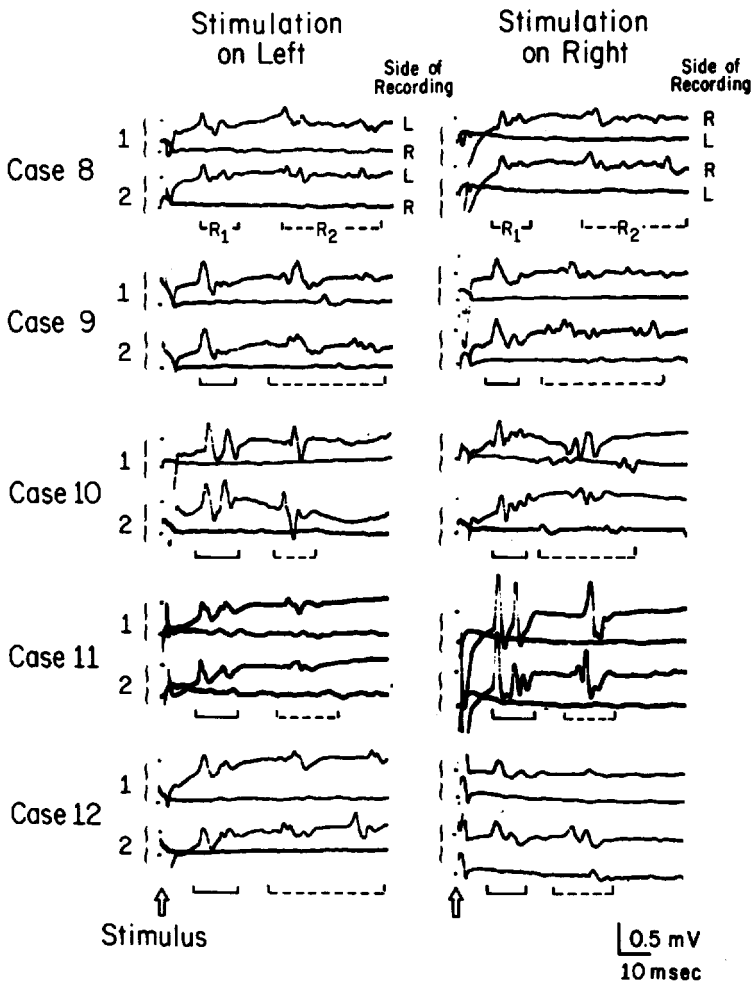


Figure 17–8. R_1 (*solid brackets*) and R_2 (*broken brackets*) components of electrically elicited blink reflex in five newborn infants, recorded from orbicularis oculi muscle on both sides after unilateral stimulation (*arrows*). Each subject had two successive right-sided stimuli (*right half of figure*) followed by two successive left-sided stimuli (*left half*) to show consistency of reflex responses. All five infants showed R_1 and ipsilateral R_2 with small or absent contralateral R_2 (cases 9 and 11, *left*; cases 10 and 12, *right*). [From Kimura et al,[63] with permission.]

responding R_2 evoked by left-sided stimulation may show a slightly greater value, but not more than 7 ms. With stimulation of the infraorbital nerve, the upper limit is 41 ms on the side of the stimulus and 42 ms on the contralateral side. Studies of the mental nerve provide less consistent results, but R_2 response rarely exceeds 50 ms in latency.

4 NEUROLOGIC DISORDERS WITH ABNORMAL BLINK REFLEX

Tables 17–2 through 17–4 summarize a 10 year experience with the blink reflex in our laboratory.[54–57,59,63,64,67,71,84,85] 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.[32,71,73,106,132] In our own series, only 7 of 93 patients with trigeminal neuralgia had absent or slowed R_1 (see Table 17–3). Excluding 3 patients who had undergone nerve avulsion before the test, only 4 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.[19]

Table 17–3 Blink Reflex Elicited by Electrical Stimulation of Supraorbital Nerve on the Affected and Normal Sides in Patients with Unilateral Neurologic Diseases (Mean ± SD)

Category and Side of Stimulation	Number of Patients	Direct Response (ms)	R_1 (ms)	R/D Ratio	Ipsilateral R_2 (ms)	Contralateral R_2 (ms)
Trigeminal 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
Compressive 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

In contrast, 10 of 17 patients with tumor, infection, or other demonstrable causes of facial pain showed an unequivocal delay of R_1 on the affected side (see Fig. 17–6A). In these patients, reproducible delay of R_2 bilaterally with stimulation on the affected side indicated involvement of the afferent arc of the blink reflex (see Fig. 17–6B). The

Table 17–4 Direct Response and R_1 and R_2 of the Blink Reflex

Disorders	Direct Response	R_1	R_2
Trigeminal neuralgia	Normal	Normal (95%)	Normal
Compressive 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 trigeminal 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

R/D ratio increased, reflecting normal conduction along the distal segment of the facial nerve, combined with a delay along the trigeminal nerve.

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.[64,69,113,114,125] All 144 patients studied showed either absence or slowing of R_1 during the first week of Bell's palsy, although the abnormalities did not necessarily emerge at the onset. Delayed or absent R_2 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 R_1 or R_2 returned, with preservation of the direct response throughout the course. This finding implied recovery of conduction across the involved segment without substantial distal degeneration (Fig. 17–9). These patients generally showed a good clinical recovery within a few months after onset. The latency of R_1, initially delayed by more than 2 ms on average, decreased during the second month and returned to normal during the third or fourth month (Fig. 17–10). The magnitude of latency change at the onset and the subsequent time course of recovery indicated a demyelinative nature of the responsible lesion. The R/D ratios increased as expected from abnormalities involving the proximal segment of the facial nerve. In the remaining 27 patients, marked diminution of the direct response without return of the reflex response during the first 2 weeks indicated axonal degeneration.[70] This group of patients had a slow and usually incomplete recovery associated with synkinesis. In some of them, R_1 may return on the affected side, albeit with a delayed latency, even though stimulation of the facial nerve fails to evoke a direct response of the orbicularis oculi. This discrepancy

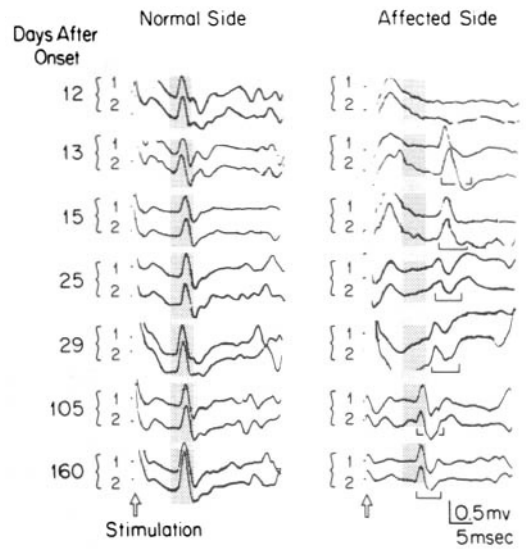


Figure 17–9. Serial changes of R_1 in a 16-year-old girl with Bell's palsy on the right. Two consecutive tracings recorded on each side show consistency of R_1 on a given day. On the affected side, delayed R_1 first appeared on the thirteenth day after onset, recovering progressively thereafter. *Shaded areas* indicate normal range (mean 3 SD in 83 subjects). [From Kimura,[61] with permission.]

implies an abnormally increased threshold of the regenerated facial nerve segment to locally applied stimuli despite propagation of impulses following reflexive activation of the motor neurons (see Fig. 7–16).

Synkinesis of Facial Muscles

The R_1 and R_2 components of the blink reflex both normally involve the orbicularis oculi alone and only rarely, if at all, other facial muscles.[130] During axonal regeneration, however, the fibers that originally innervated the orbicularis oculi may supply other facial muscles by misdirection.[70] Under such circumstances, the blink reflex elicited elsewhere serves as a sign of aberrant reinnervation (Fig. 17–11).

Recording an aberrant blink reflex helps identify time-locked discharges involving two independent muscles showing synkinetic movements. In contrast, volitional, associated movements that clinically mimic synkinesis lack the exact temporal relationship between the two co-contracting

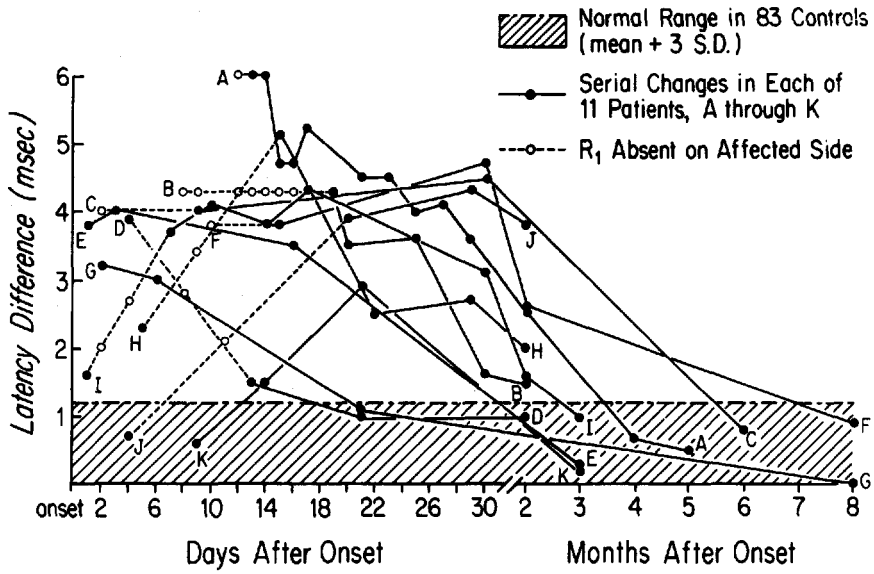


Figure 17–10. Serial changes in latency difference of R_1 between normal and paretic sides in 11 patients recovering without nerve degeneration (*A* through *K*). *Shaded area* indicates the normal range (mean 3 SD in 83 subjects). The response, if present at onset, showed relatively normal latencies but rapidly deteriorated during the first few days. Delayed R_1 usually returned during the second week, plateaued for 2 to 4 weeks, and progressively recovered in latency during the next few months. [From Kimura, Giron, and Young,[64] with permission.]

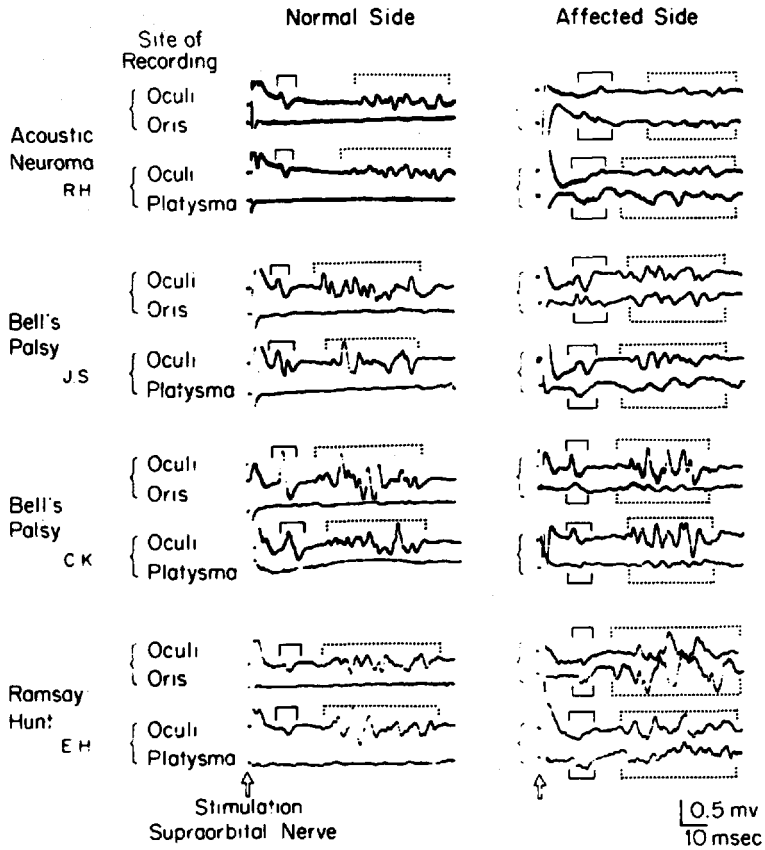


Figure 17–11. The blink reflex in the orbicularis oris and platysma in four patients following various diseases of the facial nerve. Stimulation on the affected side of the face elicited both R_1 (*small bracket*) and R_2 (*dotted bracket*) not only in the orbicularis oris but also in the platysma, indicating widespread synkinesis. The blink reflex elicited only in the orbicularis oculi on the normal side of the face served as a control in each patient. [From Kimura et al,[70] with permission.]

muscles. Measurement of the size of the blink reflex elicited in muscles other than orbicularis oculi also elucidates the extent of aberrant reinnervation. In one 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.[70] One of the remaining 3 patients had injury only to a peripheral branch of the facial nerve and experienced return of function with no evidence of synkinesis. In the other 2 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 29–7) also exhibit clinical and electrical evidence of synkinetic movements.[3,13,33,59,86,149] 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.[92,101,102,140] Unlike the constant responses seen after peripheral facial paresis,[70] successive responses in hemifacial spasm may vary in latency and waveform, a finding supportive of ephaptic transmission.[3] Inhalation of anesthetics during surgery completely suppresses R_1 or R_2 in normal subjects, but not on the affected side of patients with hemifacial spasm.[93–95] 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,[27,68,84,103,111,118,129] the blink reflex provides unique diagnostic value. In 33 patients studied, stimulation of the facial nerve elicited no direct 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 R_1 in 5, delayed R_1 in 17, and normal R_1 in 4. Analyses of R_2 revealed 6 efferent, 6 afferent, 7 mixed patterns, and 7 normal responses.

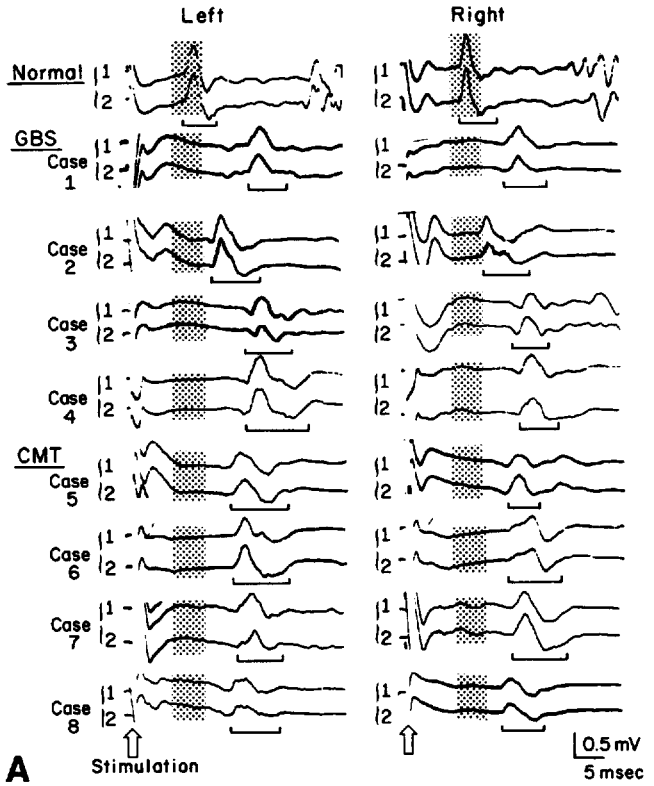
Polyneuropathy

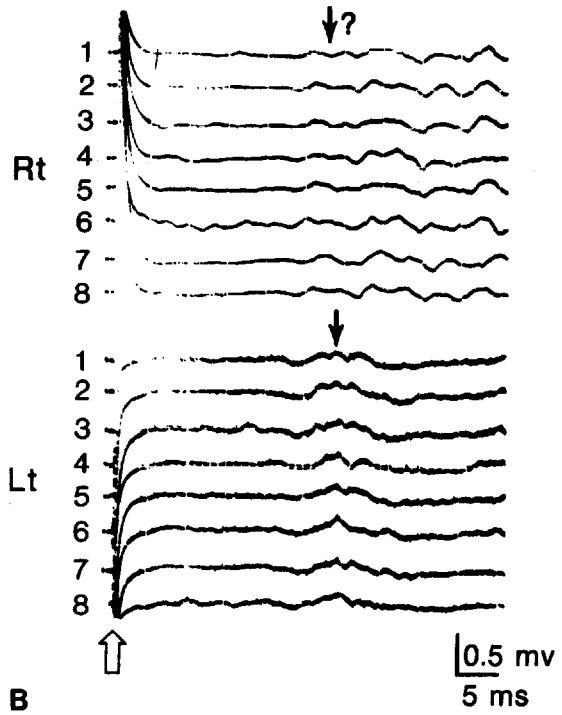
Facial or trigeminal nerve involvement in various polyneuropathies affects the blink reflex (Fig. 17–12A). Unlike the two clearly separated components seen normally, a delayed and temporally dispersed R_1 tends to merge with R_2 in a demyelinative neuropathy (Fig. 17–12B). In such cases, bilateral recording can delineate the onset of R_1 as the response clearly preceding the onset of the contralateral R_2, which should approximately coincide with the ipsilateral R_2 (Fig. 17–12C).

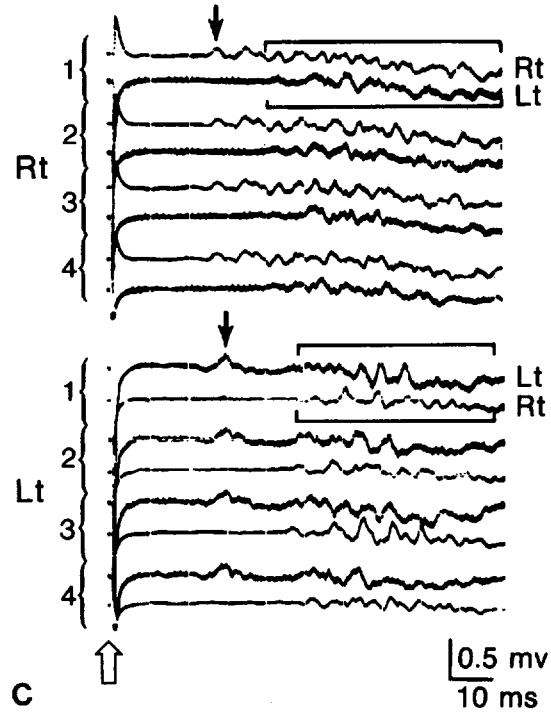
Different categories of neuropathy show distinct abnormalities, as briefly described below.[18,37,60,61] Most patients have either absent or delayed direct and R_1 responses in the Guillain-Barré syndrome (GBS), chronic inflammatory demyelinative polyradiculoneuropathy (CIDP), and hereditary motor and sensory neuropathy (HMSN) type I or the hypertrophic type of Charcot-Marie-Tooth disease (CMT1). Patients with diabetic 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 R_1 on the affected side. The blink reflex usually shows no abnormalities in HMSN type II or the neuronal type of Charcot-Marie-Tooth disease (CMT2). Patients with chronic renal failure have an abnormal blink reflex, which often improves after hemodialysis.[135] Exposure to trichloroethylene, known to have specific toxic effects on the trigeminal nerve, also delays R_1 latency.[32] Abnormalities of mechanically induced blink reflexes seen in patients with diabetes showed a correlation with the degree of hyperosmolality.[136]

Statistical analyses of the direct response

Figure 17–12. A. Bilateral delay of R_1 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. [From Kimura[61].] **B.** R_1 in a 55-year-old woman with chronic peripheral neuropathy and a monoclonal gammopathy (cf. Fig. 17–5A). Note a substantially delayed and temporally dispersed R_1 recorded by the slower 5 ms/division sweep instead of the 2 ms/division normally used to obtain this response. **C.** R_1 and R_2 in the same patient as in **B.** Note delayed R_2 recorded by the slower 10 ms/division sweep instead of the usual 5 ms/division. The continuity between R_1 and R_2 precluded accurate latency determination of R_2 on the right. Nonetheless, the contralateral R_2 recorded simultaneously allows approximate separation between R_1 and R_2 on the affected side.







and R_1 latencies revealed a marked increase in GBS, CIDP, and CMT1, a much lesser degree of slowing in diabetic polyneuropathy, and no change in the Fisher syndrome or CMT2 (Table 17–2). The latency ratio of R_1 to the direct response showed a mild increase in GBS, a moderate decrease in CMT1 and CIDP, a mild decrease in diabetic polyneuropathy and a normal value in CMT2. The latencies of R_2, although commonly within the normal range when analyzed individually, had a significantly greater average value in the neuropathies than in the controls.

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[2,43,105,138] and spinal cord.[104] 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).[68] The R_1 showed a delayed latency in all but three cases of medullary tumors and one case of cerebellar tumor. Alteration of R_1 by posterior fossa tumors reflects either intrinsic or extrinsic pontine lesions or trigeminal or facial nerve involvement by tumor. The R_2 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 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 R_1,[50,53,81,85,100,109] as expected from the effect of demyelination on impulse propagation.[88,127,150] The incidence of blink reflex abnormality varies greatly, depending on the selection of patients. In general, patients with a longer history of clinical symptoms have a higher incidence of abnormality.

An earlier study of 260 patients with long-standing disease[59] showed a delayed R_1 in 96 of 145 patients (66%) who clinically had disseminated lesions as well as episodes of remission and exacerbation (Fig. 17–13). The study showed an abnormality in 32 of 57 patients (56%) who had either multiple sites of involvement without relapse or a history of recurrence of a localized lesion. The test revealed alteration of R_1 in 17 of the remaining 58 patients (29%) in whom the diagnosis of multiple sclerosis was suspected but not clinically established. In the same 260 patients, R_1 was abnormal in 49 of 63 patients (78%) with clinical evidence of pontine lesions, 50 of 104 (57%) with other brainstem lesions, and 37 of 93 (40%) with neither brainstem signs nor symptoms.

In the 63 patients with clinical signs of pontine lesions, the average latency of R_1 substantially exceeded the normal value but fell short of the delay seen in GBS or CMT1 (Fig. 17–14). The normal direct response, combined with delayed R_1, markedly increased the 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.[116]

Subsequent studies showed comparable results.[81,85,109,122,143] Another series revealed a lower incidence of abnormalities: a delayed R_1 in 41 percent of patients with definite diagnosis and 18 percent in those with possible diagnoses.[50] Other investigators reported similar rates of abnormality in patients referred for electrophysiologic testing soon after the onset of their symptoms.[48,123] The blink reflex detects only those lesions that affect the short pontine pathway. Thus, a delayed R_1, although less frequent than visual, somatosensory, or brainstem auditory evoked potentials, helps localize a lesion to the

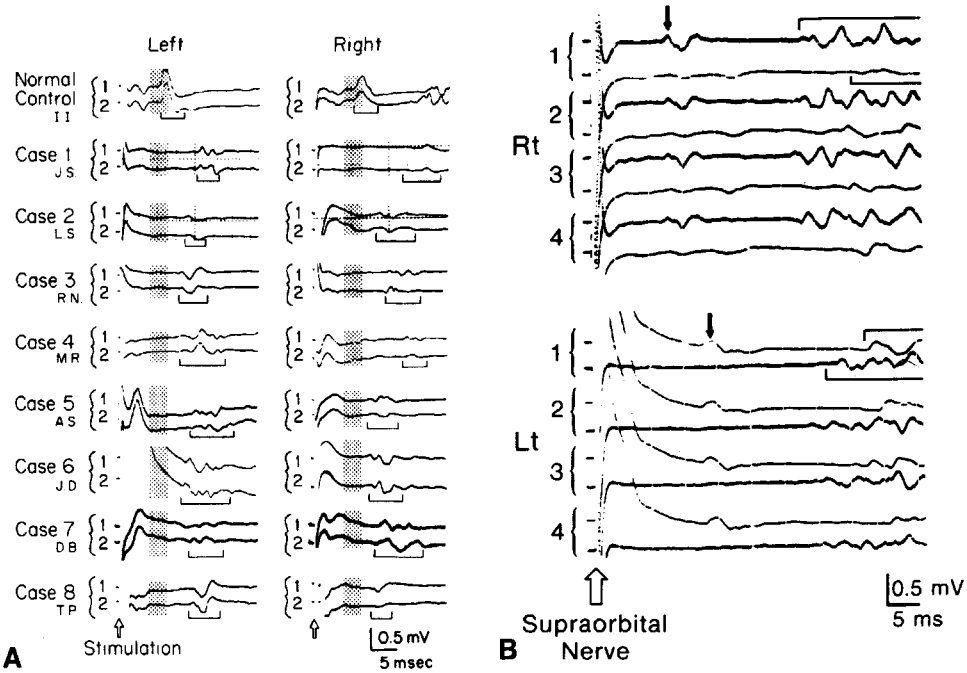


Figure 17–13. A. Delayed R_1 on both sides in multiple sclerosis. Two tracings recorded on each side in each subject show consistency of R_1 response. The *top tracings* from a healthy subject serve as a control, with *shaded areas* indicating the normal range (mean 3 ± SD in 83 subjects). In addition to increased latency, R_1 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. [From Kimura,[59] with permission.] **B.** R_1 and R_2 in a 35-year-old woman with multiple sclerosis and mild facial and abducens paresis on the left (cf. Fig. 17–5B). Stimulation on the right elicited normal R_1 and delayed R_2 contralaterally, whereas stimulation on the left evoked delayed R_1 and delayed R_2 ipsilaterally. This finding suggests a lesion involving the efferent arc of the reflex on the left, that is, the intrapontine portion of the facial nerve (cf. Fig. 17–6B). [From Kimura,[61] with permission.]

pons when establishing subclinical dissemination in multiple sclerosis.[51]

Wallenberg Syndrome

Patients with the Wallenberg syndrome have selective alteration of R_2 as expected from lesions affecting the lateral medulla.[67,107,146] Unless the infarct extends to the pons, the latency of R_1 falls within the normal range, but when analyzed individually, the values on the affected side may slightly exceed those on the normal side (see Table 17–3). In a series of 23 typical cases, stimulation on the affected side of the face elicited no R_2 on either side in 7, low-amplitude R_2 in 6, and delayed R_2 in 10 (Fig. 17–15). In contrast, stimulation on the normal side of the face evoked normal R_2 bilaterally in 20 of 23 patients. The remaining 3 patients showed normal R_2 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 in lateral medullary infarction.[52,98,121,147]

Facial Hypoesthesia

Patients with contralateral hemispheric lesions also develop an afferent delay of R_2 indistinguishable from that seen in the Wallenberg syndrome.[22,35,58,91] This type of abnormality commonly, although not ex-

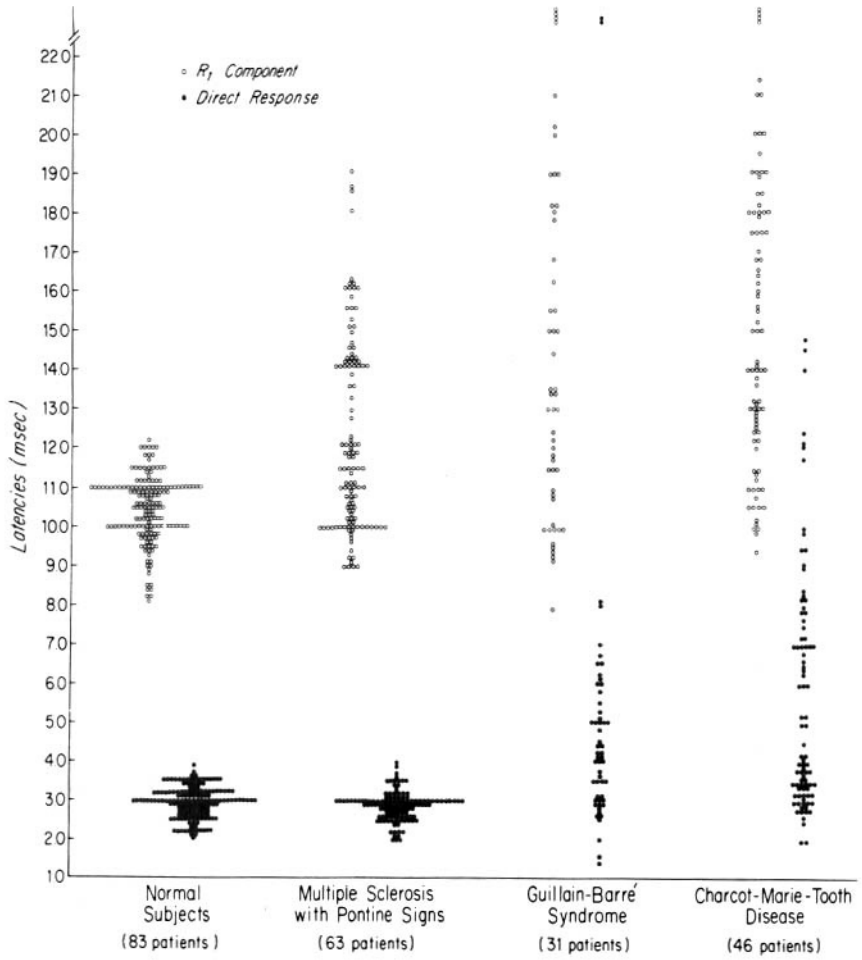


Figure 17–14. Latency distribution of the direct response and R_1 of the blink reflex in normal subjects and in patients with central or peripheral demyelination of the reflex pathways. The histogram shows delayed direct response in Charcot-Marie-Tooth disease, and to a slightly lesser extent in Guillain-Barré syndrome, and normal response in multiple sclerosis. The R_1 response is delayed equally in the two polyneuropathies, but to a lesser degree in multiple sclerosis. [From Kimura,[61] with permission.]

clusively, accompanies sensory disturbances of the face. Thus, the electrically elicited blink reflex provides a means of quantitating facial sensation. In equivocal cases, repetitive stimulation of the right and left sides of the face alternately every 5–10 seconds reveals consistent asymmetry beyond random variations that follow no predictable pattern. In 6 patients with bilateral trigeminal neuropathy, blink reflex studies revealed slowed or absent R_1 bilaterally in 3 and delayed or diminished R_2 regardless of the side of stimulation in 4. In 19 patients with unilateral disease of either the trigeminal nerve[17] or the brainstem,[16] stimulation on the affected side of the face elicited absent R_1 in 6, delayed R_1 in 7, and various combinations of R_2 abnormalities in the others (Fig. 17–16). Generally, a smaller response indicated more complete sensory loss, and stimulation on a totally anesthetized part of the face failed to elicit any response at all.

Other Disorders

A high incidence of blink reflex abnormalities in handicapped children implies the prevalence of brainstem lesion.[138] Blink re-

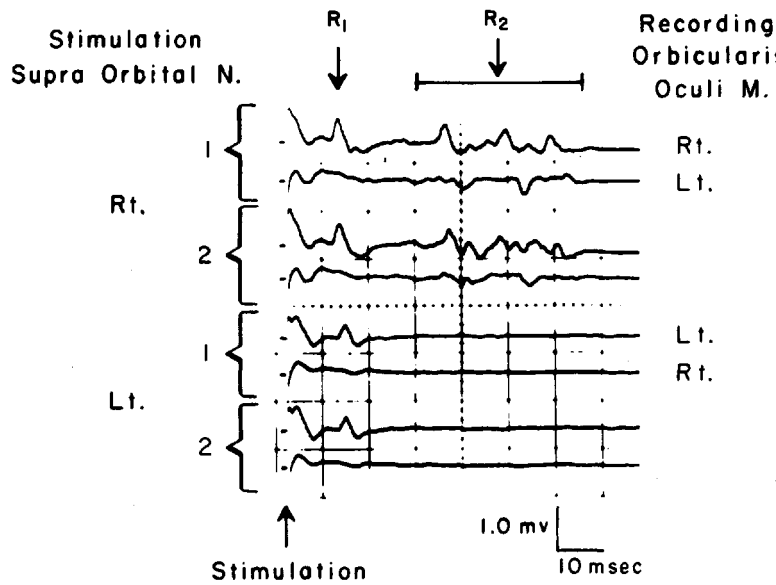


Figure 17–15. Left lateral medullary syndrome. Two successive stimuli given on the right (*top two pairs*) elicited a normal R_1 and R_2 bilaterally. Two successive stimuli on the left (*bottom two pairs*) evoked normal R_1 but absent R_2 bilaterally (cf. Fig. 17–19). [From Kimura and Lyon,[67] with permission.]

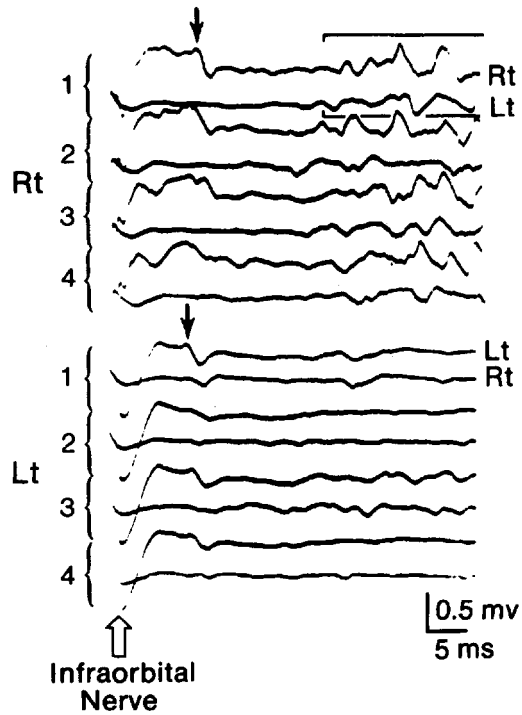


Figure 17–16. R_1 and R_2 elicited by stimulation of the infraorbital nerve in a 39-year-old woman with syringobulbia and facial numbness on the left (cf. Fig. 17–5B). Stimulation of the right side of the face elicited normal R_1 and R_2 bilaterally, but stimulation on the left evoked only the R_1 component.

flex studies also show abnormalities in Millard-Gubler syndrome caused by a lesion at the level of the facial nucleus.[39]

5 ANALYSIS OF THE R_1 COMPONENT

Direct Involvement of the Reflex Arc

A substantial increase in latency of R_1 usually implies demyelination of either the central reflex pathway in the pons[53,56,59,81,99] or of the peripheral pathway along the trigeminal nerve,[41,71,106] the facial nerve,[64,69,113,114,125] or both.[7,27,55,68,85] Posterior fossa tumors may affect R_1, either by compressing the cranial nerves extra-axially or by involving the brainstem itself.[17,54,68]

Effect of Lesions Outside the Reflex Pathway

Alteration of R_1 may also result from lesions indirectly affecting the brainstem and causing excitability changes.[59] A reversible block of R_1 seen in comatose patients usually indicates acute supratentorial lesions

or massive drug intoxication.[83] The latency of R_1 elicited by a glabellar tap shows a mild increase in patients with acute hemispheric strokes but recovers almost completely within a few days.[35] In some of these patients, single electric shocks may also elicit R_1 partially or not at all when given contralateral to the hemispheric lesion. An apparent increase in the latency of R_1 results if such a stimulus fails to activate the fastest conducting fibers. In this instance, paired stimuli with an interstimulus interval of 3–5 ms usually elicit a maximal R_1 with normal latency.[54,58,59]

Thus, electrically elicited R_1 has a normal latency even during acute stages of hemispheric disease, when elicited with paired stimuli or other facilitatory maneuvers[115] to compensate for reduced excitability.[22,46,58] As an inference, the latency of a fully activated R_1 indicates the conduction characteristics of the reflex arc itself, and a delay of fully activated R_1 beyond the normal range implies a lesion directly involving the pathway, rather than a remote process altering excitability. In these cases, smaller, slower conducting fibers may mediate the reflex response following the conduction block of the larger myelinated fibers, or the axons may have slowed conduction across the demyelinated area.

Degree of Slowing

In multiple sclerosis, central demyelination increases the latency of R_1 to 12.3 ± 2.7 ms (mean ± SD) compared with 15.1 ± 5.9 ms in GBS and 17.0 ± 3.7 ms in CMT1. 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, in Bell's palsy with focal involvement of the facial nerve the latency of R_1 increases only to 12.8 ± 1.6 ms. Patients with compressive lesions of the trigeminal nerve have a similar degree of delay of R_1.

Conduction abnormalities affect CMT1 and GBS to the same degree (see Figs. 17–12A and 17–14). A decreased R/D ratio found in CMT1 suggests distal slowing of facial nerve conduction, whereas a slightly increased R/D ratio in GBS indicates proximal involvement of the facial nerve, if the trigeminal nerve conducts normally. Other disorders with 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.

6 ANALYSIS OF THE R_2 COMPONENT

Direct and Remote Effect on Polysynaptic Pathways

As mentioned earlier, analysis of the R_2 component usually 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 (see Fig. 17–1B). Stimulation on one side may reveal unilateral abnormality of R_2 either ipsilateral or contralateral to the stimulus, whereas stimulation on the opposite side shows normal, absent, or delayed R_2 bilaterally or unilaterally, but not necessarily on the same side implicated by the contralateral stimulation.

Like R_1, changes of R_2 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. 17–17).[24,44,67,107,139] For example, any comatose state renders R_2 unelicitable or markedly diminished in size (Fig. 17–18), regardless of the site of lesion.[14,83,90,126] A hemispheric lesion (Fig. 17–19) also suppresses R_2, producing either an afferent or an efferent pattern of abnormality, perhaps based on the site of involvement.[8,23,35,46,58,72]

Level of Consciousness and Perception of Pain

A person's state of arousal alters the excitability of R_2 and, to a lesser extent, R_1.[5,12,25,34,65,66,128,133] Analysis of R_2 during sleep has shown marked reduction in stages II, III, and IV and substantial recovery during rapid eye movement (REM) sleep, when the excitability approaches

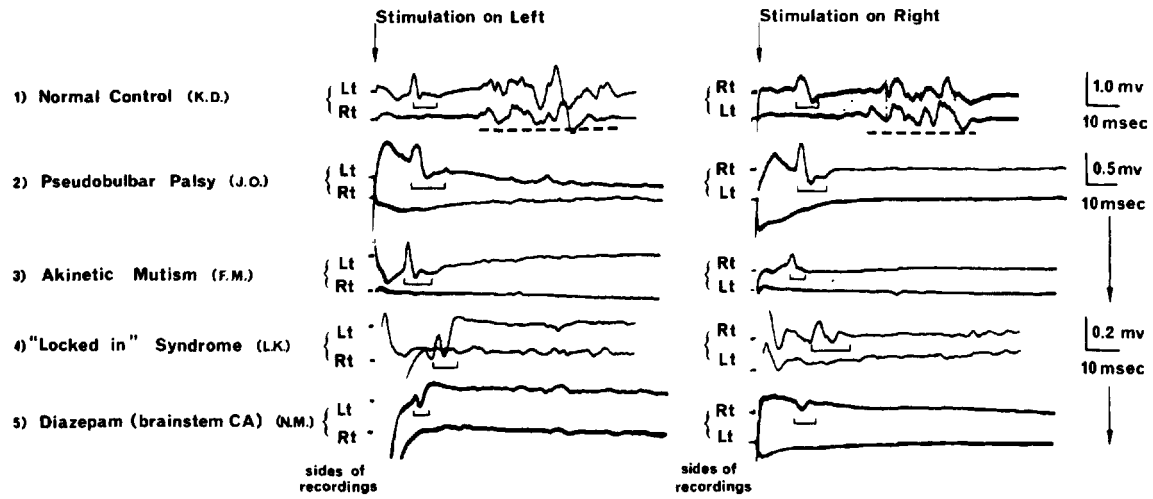


Figure 17–17. Various neurologic disorders associated with absent R_2 after stimulation of the supraorbital nerve. Shock intensity was slowly advanced up to 40 mA and 0.5 ms duration. Note virtual absence of R_2 regardless of the side of stimulation in cases 2 through 5, with normal R_1 in cases 2, 3, and 5 and delayed R_1 in case 4. [From Kimura,[56] with permission.]

that of full wakefulness, showing some unusual discharge characteristics. Blink reflex studies may show absent R_2 with normal or nearly normal R_1 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.[56] Com-

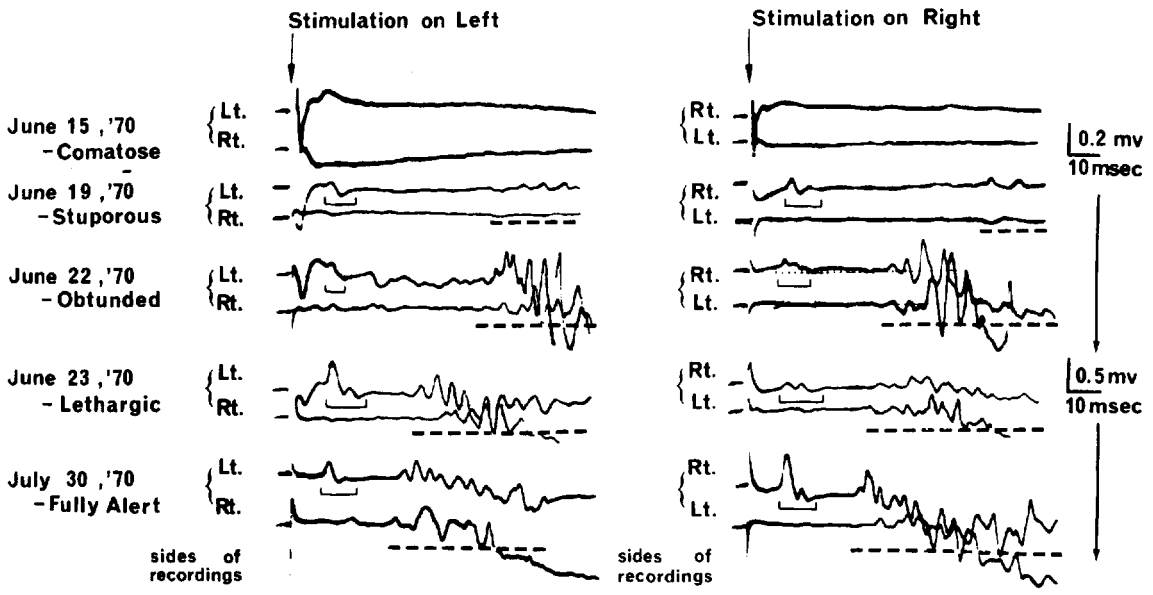


Figure 17–18. R_1 and R_2 in a patient recovering from herpes simplex encephalitis. The stimulus delivered to the supraorbital nerve elicited neither R_1 nor R_2 on June 9 (not shown) and on June 15 with the patient in coma. A repeated study on June 19 showed a normal R_1 but markedly delayed and diminished R_2. Note the progressive recovery in amplitude and latency of R_2 contemporaneous with the patients improvement to full alertness in July. [From Kimura,[56] with permission.]

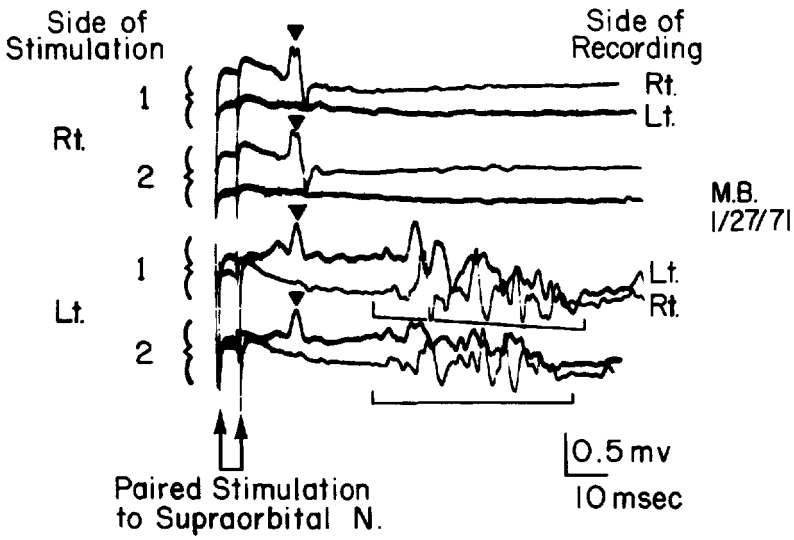


Figure 17–19. Left cerebral stroke (cf. Fig. 17–15). Paired stimuli delivered to the right supraorbital nerve elicited normal R_1 but no R_2 on either side. Stimulation on the left, however, evoked an ipsilateral R_1 and bilateral R_2. [From Kimura,[58] with permission.]

plex psychological events may also selectively affect different reflex pathways.[124]

Stimulation on a hypesthetic area of the face elicits a smaller R_2 than that evoked by a shock of the same intensity applied to the corresponding area on the normal side. Sensory deficits of the face often cause alteration of R_2; the reverse, however, does not hold, because a similar reduction of R_2 occurs in pure motor hemiplegia.[4,15,22,35,58] In such cases, clinical evaluation may have failed to detect minor sensory deficits, or supratentorial lesions outside the somatosensory pathways may have inhibited or failed to facilitate the excitability of the efferent pathway.

Altered Excitability of Interneurons

Of the two components, R_2 habituates readily in normal subjects but not in patients with Parkinson's disease, whether tested clinically, as with the glabellar taps, or electromyographically.[74,82,89,114,120] Similarly, the blink reflex fails to show physiologic habituation in nocturnal myoclonus, a syndrome associated with additional reflex components after R_2. These findings suggest a disorder of the central nervous system producing increased excitability of segmental reflexes.[152]

The paired-shock technique reveals the effect of a single cutaneous conditioning stimulus on this reflex (Fig. 17–20). Healthy subjects show a greater suppression of R_2 than of R_1 following a conditioning stimulus. Dissociation between the recovery curves of the oligosynaptic R_1 and the polysynaptic R_2 presumably results from excitability changes at the interneuron level.[57,144] A conditioning stimulus delivered anywhere on the face or neck suppresses the test R_2 response elicited by a subsequent stimulus when the two stimuli are applied to the same or different ipsilateral or contralateral trigeminal cutaneous fields.[57] Thus, the physiologic inhibition must involve the interneuronal network diffusely, even in response to remote segmental input.

In Parkinson's disease, the recovery of R_1 follows a normal time course, whereas the physiologic suppression of R_2 by a conditioning stimulus lasts substantially less than the normal range.[68,87] Unlike in normal subjects, the recovery curve of R_2 in Parkinson's disease indicates that a cutaneous conditioning stimulus fails to inhibit interneurons. Interestingly, dyskinetic patients show more physiologic inhibition of R_2, presumably reflecting the reinstatement of dopaminergic suppressive control over the multisynaptic pathway.[45] Additional evidence of a change in excitability includes an abnormally short latency of R_2 in response to a single maximal stimulus in advanced cases. These findings

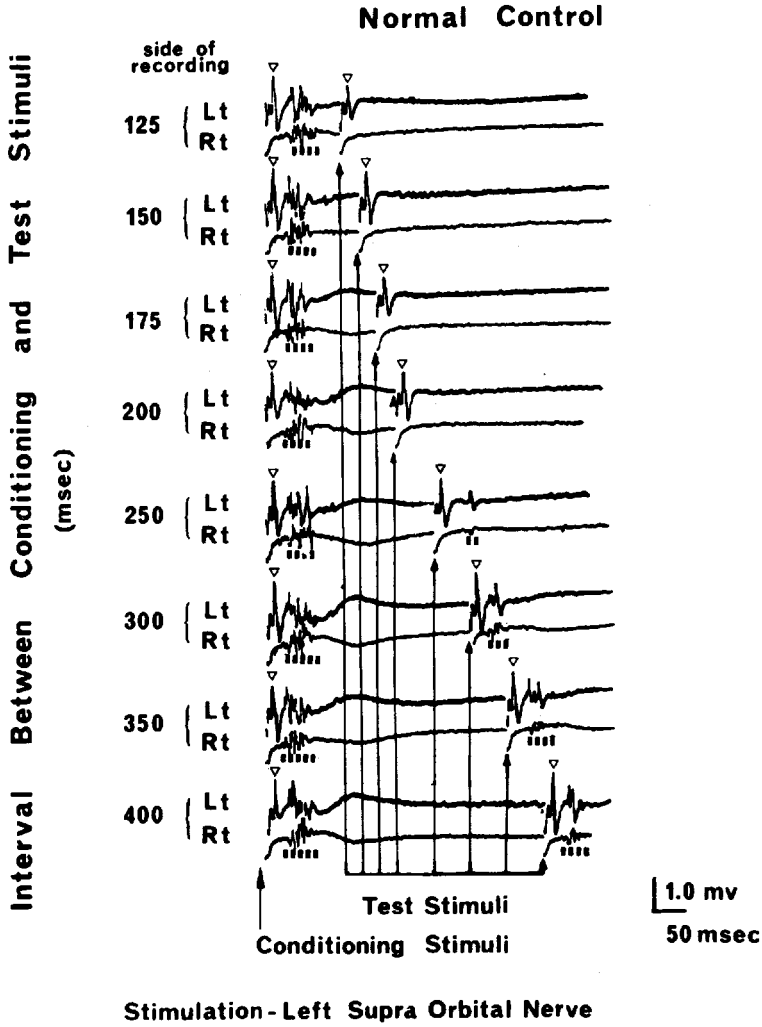


Figure 17–20. Normal responses to paired shocks (*arrows*) delivered to the left supraorbital nerve with time intervals ranging from 125 to 400 ms between test and conditioning stimuli. R_1 of the test response, although slightly suppressed at time intervals of 125 to 175 ms, remained relatively constant thereafter with the amplitude equal to the conditioning response. The test stimuli failed to elicit R_2 up to the time interval of 200 ms with gradual recovery thereafter. [From Kimura,[57] with permission.]

imply facilitation or disinhibition of the interneurons, rather than the motor neurons, as the primary cause of motor dysfunction in this disease.

In contrast, diminution of the R_2 component in Huntington's chorea represents the opposite extreme and probably represents a decrease in interneuronal activity.[30,31] The recovery curves in premature infants show little or no evidence of inhibition.[40] Similarly, the recovery curves show decreased inhibition in patients with cranial, cervical, and generalized dystonia[26] but not in patients with extracranial segmental dystonia.[110] The test may also provide an objective means for evaluating the reactivity in brainstem pathways in such disorders as olivopontocerebellar atrophy,[145] mitochondrial myopathy,[75] and hemifacial spasm[26] and blepharospasm.[47]

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Chapter 18

THE F WAVE AND THE A WAVE

1 INTRODUCTION

The F wave results from the backfiring of antidromically activated anterior horn cells. Thus its measurement helps in assessing motor conduction along the entire length of the peripheral axons, including the most proximal segment. Explored first in patients with Charcot-Marie-Tooth disease[80] and motor neuron disorders,[127] the method has since gained popularity in evaluation of a variety of neurologic conditions as part of routine nerve conduction studies.[12,14,49,89,133–135,144,180]

The inherent variability of the latency and configuration makes use of the F wave technically more demanding than that of the direct compound muscle action potential, or M response determina-

tion. Nonetheless, this response usefully supplements the conventional nerve conduction studies in characterizing neuropathic disorders in general and demyelinating polyneuropathies in particular. 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.[85,87] The F wave also provides a measure of motor neuron excitability, which presumably dictates the probability of backfiring in individual axons. This section reviews the available methods of F wave determination and discusses its clinical value and limitations in the clinical context.

2 PHYSIOLOGY OF THE F WAVE

Recurrent versus Reflexive Activation of the Motor Neuron

A supramaximal electric shock delivered to a nerve often elicits a late muscle response that follows the direct motor potential, or M response. Since the original description by Magladery & McDougal in 1950, when they designated it the F wave (presumably because they initially recorded it from intrinsic foot muscles), 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. 18–1). 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 a reflex hypothesis[70,105,111] or a theory based on recurrent discharge of antidromically activated motor neurons,[21,114,115,166] or both.[63,65]

The presence of the F wave in deafferentated limbs[57,114,115] and after transverse myelotomy[117] implies that it depends on backfiring of motor neurons. Studies using single-fiber electromyography[171] have also shown that the occurrence of the F wave requires prior activation of the motor axon. The evidence of its recurrent nature, however, does not necessarily preclude the presence of reflex components that may still contribute. F-wave amplitude and persistence serve as a measure of motor neuron excitability, as does the H reflex. Contrary to the general belief, comparison between the two modes of motor neuron activation may not help differentiate whether the observed change involves the presynaptic or postsynaptic pathway. This uncertainty relates primarily to possible differences in inherent sensitivity between antidromic and reflexive activation, which would bias the result (see Chapter 19–2).[18,50,77,103,104]

Block of Antidromic or Orthodromic Impulses

Motor neurons subject to recurrent activation fire only infrequently after a series of direct motor responses.[154] Thus, although antidromic activation and orthodromic activation of motor neurons usually follow the same physiologic principles,[28] additional mechanisms must prevent the motor neurons from generating the recurrent response with every stimulus.[28,141] 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 motor neurons.[107] 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. In addition, H-reflex discharges, if elicited by simultaneous stimulation of the group IA afferent fibers, prevent antidromic invasion by collision. This possibility may paradoxically reduce the F wave amplitude and frequency when a higher excitability results in a greater reflexive activation of the motor neurons.

The spike potential generated in the soma-dendrite membrane (SD spike) faces a very narrow window for transmission. On the one hand, the generation and propagation of SD spike must precede the inhibition via the Renshaw cell, activated antidromically with a synaptic delay of

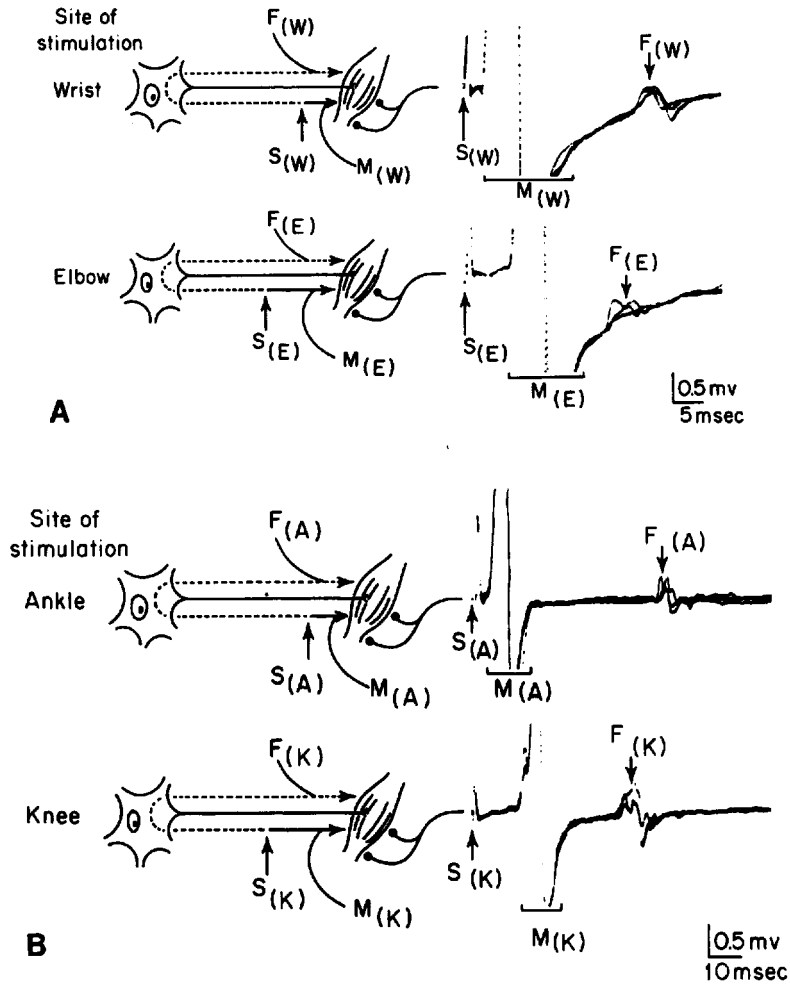


Figure 18–1. A. Normal M response (horizontal brackets) and F wave (small arrows) recorded from the thenar muscles after supramaximal stimulation of the median nerve at the wrist (*top*) or elbow (*bottom*). The shift of stimulus point proximally increased the latency of the M response and decreased that of the F wave. The schematic diagrams illustrate the centrifugal (*solid arrows*) and centripetal impulses (*dotted arrows*). [Modified from Kimura,[80] with permission.] **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*) or knee (*bottom*). With a shift of stimulus site proximally, the latency of the M response increased, whereas that of the F wave decreased. [From Kimura, Bosch, and Lindsay,[88] with permission.]

1 ms. On the other hand, the impulse, if activated too early, cannot travel orthodromically through the axon hillock during its refractory period, which lasts for 1 ms or so after the passage of the antidromic impulse. Thus, only the recurrent discharges confined to this short time interval will have any chance to be sustained. This explains in part why only a small percentage of the axons give rise to F waves even if the antidromic impulses invade the entire motor neuron pool. Because of a particular set of physiologic conditions required for generation and propagation of a recurrent discharge, the latency of successive F waves from a single motor axon varies only narrowly between 10 and 30 μs.[154] 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 19–2).

Slight voluntary contraction may subliminally excite soma-dendrite membrane and facilitate antidromic activation of the SD spike, resulting in increased probability of a recurrent response. Conversely, subliminal depolarization of the soma-dendrite membrane may prematurely generate the recurrent impulse, which cannot propagate across the still refractory axon hillock. It may also facilitate reflexive activation of motor neurons, blocking antidromic impulses by collision. The two opposing effects of subliminal depolarization of motor neurons render the excitability change unpredictable, but slight voluntary

muscle contraction usually enhances F wave activation. Excessive effort, however, may have the reverse effect because, if the descending facilitation reaches the threshold and generates an action potential, it will protect the motor neuron from antidromic invasion by collision, precluding the possibility of recurrent discharge.

Up to 5 percent of antidromically invaded motor neurons give rise to an F wave, regardless of their peripheral excitability or conduction characteristics.[23] In normal subjects, F-wave frequency varies, with a mean of 79%, most responses occurring only once during a train of 200 stimuli.[137] 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.[42,75,79] Furthermore, 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.[92] Studies of twitch contraction by intramuscular microstimulation also show that recurrent discharges occur not only in the larger motor neurons with greater twitch force but also in the smaller motor neurons with lesser twitch force.[22]

For clinical studies in which both large and small axons are activated simultaneously rather than selectively, anatomic or physiologic properties might predispose a given fraction of the more excitable motor neuron pool to backfiring.[69] In one study designed to analyze the constitution of the F wave, additional motor units contributed a greater potential when recruited at higher stimulus intensities.[179] In another study, however, no consistent correlation emerged between the latency and amplitude of the F wave.[44,45] The recurrent discharges probably encounter blockage at the initial segment more frequently in the smaller, lower threshold motor neurons, which rapidly depolarize.[72,79] Preferential activation of the larger motor neurons may result if Renshaw cells inhibit the smaller motor neurons more effectively.[29,30,68] Hence, the incidence of the F wave may, at least in theory, favor the larger motor neurons 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. This in turn provides a rationale for using the minimal latency of the F wave selected from a relatively small number of trials as a measure of the fastest conducting fibers. The incidence of repeater F waves increases with loss of motor axons, as seen, for example, in median nerve studies of the carpal tunnel syndrome.[109]

Latency and Amplitude of the F Wave

A few-millisecond interval between the earliest and latest F wave results, in part, from the difference between fast and slow motor conduction.[140] The 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 unmyelinated terminal branch, however, may result in a substantial latency difference. Another unknown variable is 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.[92]

As described above, motor neuron excitability influences the amplitude and persistence of the F wave based on complex physiologic mechanisms.[33,41,42,54,55] The F wave fails in hypoexcitable cells if an antidromic impulse produces only subliminal depolarization. It also fails in hyperexcitable cells if a voluntarily or reflexively evoked discharge eliminates the antidromic invasion by collision. In addition, backfiring that occurs too rapidly during hyperexcitable states may abate, facing the refractory period of the initial axon segments. Stimulation of afferent fibers may alter central motor neuron pool excitability, inhibiting F waves ipsilaterally[48] and facilitating them contralaterally.[175] Subthreshold transcranial mag-

netic stimulation, if appropriately timed to collide at the motor neuron, 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.[116] Electrical stimulation of the dentate nucleus also reduces the size of the F wave in humans.[56]

3 THE A WAVE AND OTHER LATE RESPONSES

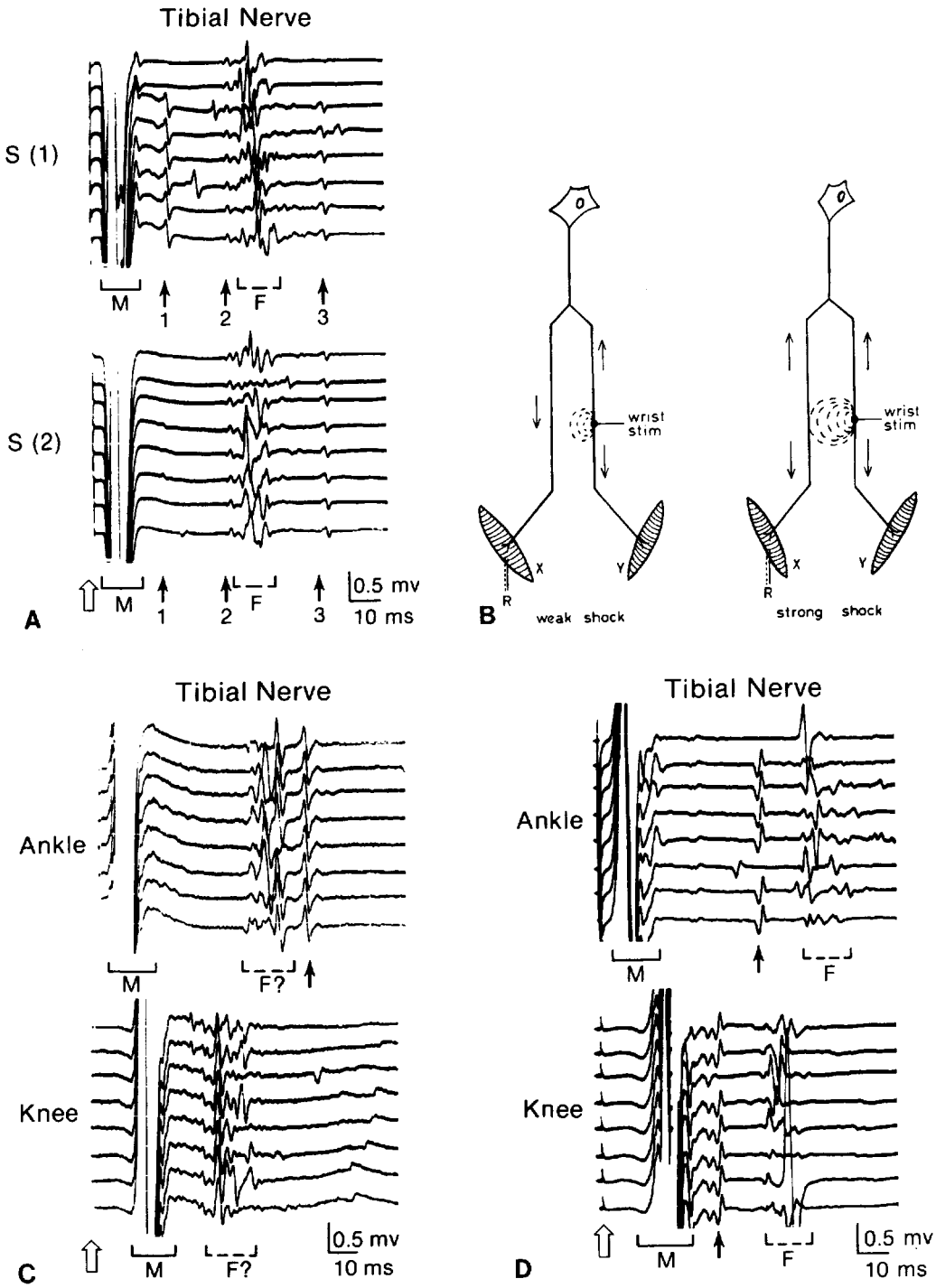
Physiologic Characteristics

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, giving rise to a constant late response, called the *A wave*. This newer designation has replaced the traditional name *axon reflex* to avoid the implication of its reflexive origin. As suggested by its original description, the *intermediate latency response*, the A wave usually, although not always, appears between the M response and the F wave.[61] Possible pathophysiologic mechanisms include, in addition to collateral sprouting, ephaptic or ectopic discharges generated in the proximal portion of the nerve.[9,110] Analogous to the F wave, A wave latencies decrease with more proximal stimulation, indicating an initially antidromic passage of the impulse.

With the A waves generated by collateral sprouting shocks of higher intensity, activating both branches distally, eliminates the response, because two antidromic impulses collide as they turn around at the branching point (Fig. 18–2A and B). Thus, supramaximal stimuli normally abolish the collateral A wave altogether, unless surrounding fibrosis or other structural change prevents the current from reaching one of the branches. In many instances, the ephaptic A wave may persist despite the use of very high-intensity stimuli. The antidromic impulse of the fast conducting axon may have already passed the site of ephaptic transmission induced by a slow conducting demyelinated axon, thereby preventing 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 a nerve branch. 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 every other stimulus gives rise to an ectopic A wave, because even-numbered shocks cause collision.

Distal stimulation of the median or ulnar nerve at the wrist or of the peroneal or tibial nerve at the ankle evokes an A wave most commonly, whereas proximal stimulation above the origin of the collateral sprout or cross talk produces only an M response. Thus, a series of stimuli applied along the course of the nerve may localize the site of bifurcation or the point of ephaptic transmission. Collateral sprouting, however, does not always develop at the level of the lesion, but frequently well below the actual site of involvement.[61,167] Distal and proximal stimuli may elicit the same A wave, allowing determination of conduction velocity for the short intersegment of that particular motor fiber. The point of origin and the conduction velocity of the two branches of the axon involved determine the latency of the A wave. The unmyelinated regenerating collateral sprout may conduct the ascending or descending impulses much slower than the nearby intact axons that relay the F wave. Hence, occasional A waves follow, rather than precede, the F wave (Fig. 18–2A,C), making the designation, intermediate latency response, not universally appropriate.

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 a hyperexcitable site vulnerable to ephaptic transmission or ectopic discharge. In the absence of synaptic connection along the pathway, the impulse can usually follow a high rate of repetitive stimulation up to 40 Hz. Less frequently, repetitive A waves (or an A wave multi-



plex) occurs after the M response, probably representing reverberating ephapsis or multiple ectopic discharges.[95] Repetitive A waves usually fail at high rates of stimulation and tend to vary in latency and waveform even if they originate from a single axon. If repetitive potentials originate distally by the orthodromic impulse, their latencies change with M response, shortening with more distal stimulation. High-

Figure 18–2. 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 weak shocks S (1), stronger shocks 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. [From Fullerton and Gilliatt,[61] with permission.] **C.** A waves after stimulation of the left tibial nerve at the ankle or knee in the same patient as in **A.** Proximal stimulation eliminated the A wave (*arrow*) that followed the F wave with distal stimulation. **D.** 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.

frequency responses probably result from ephaptic or ectopic discharge at a focal point of an axon, leading to repetitive reexcitation of the same site through complex neural pathways.[149,159]

A late motor response presumably mediated by an axon loop along the nerve may mimic the A wave.[150] Other pathophysiologic mechanisms for this type of discharge include reflection of an impulse and ephaptic transmission distal to the site of stimulation.[66,168] A late potential may also result from a scattered motor response with slow conduction in pathologic nerves. Again, with proximal stimulation, the latency of the A wave decreases, whereas that of a temporally dispersed M response increases (Figs. 18–2D and 18–3). Analyses of recorded responses using various models usually prove or disprove the ephaptic hypothesis in each case.[110] The electric field of the muscle action potential could also ephaptically reexcite an intramuscular axon, producing a muscle–nerve reverberating loop.[155] In either case, the original muscle potential and the repetitive discharge maintain the same interval regardless of the nerve stimulation point.

Clinical Applications

A waves occur in a heterogeneous group of patients with peripheral neurogenic disorders and rarely, if at all, in healthy individuals. As a sign of neurogenic abnormality it abounds in acute and chronic neuropathies, widely varying in pathophysiology from nerve regeneration to demyelination. The disease entities commonly associated with the A wave include various entrapment syndromes, tardy ulnar palsy, brachial plexus lesions, diabetic neuropathy, hereditary motor sensory neuropathy,

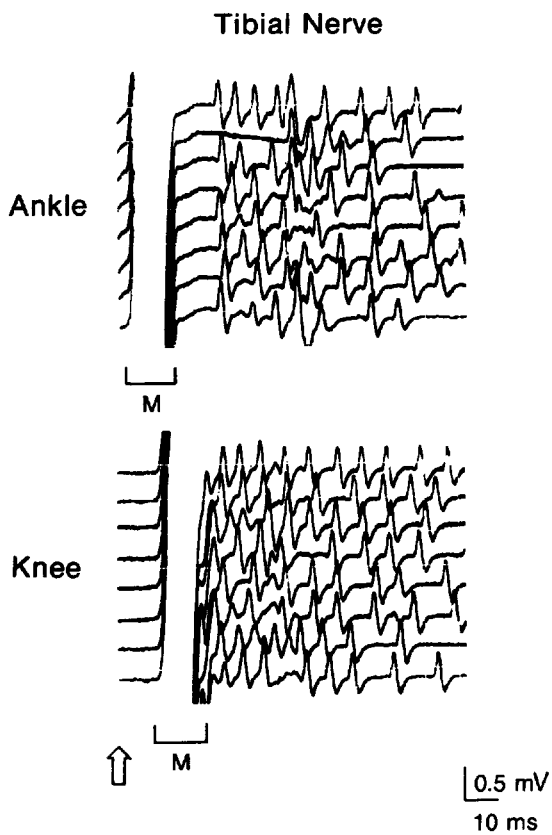


Figure 18–3. Incidental finding of unusual repetitive discharges resembling A waves in a 38-year-old man with a history of right pelvic fracture. Stimulation of the right tibial nerve at the ankle or knee elicited the repetitive discharge. Its onset latency shortened with proximal as opposed to distal stimulation, as expected in an A wave.

facial neuropathy, amyotrophic lateral sclerosis, Guillain-Barré syndrome, and cervical root lesions.[60,95,96,146–148,151,152]

4 DETERMINATION OF F-WAVE LATENCY

Recording Procedures

A supramaximal stimulus applied at practically any point along the course of a nerve elicits the F wave. In theory, placing the anode proximal to the cathode may cause anodal block of the antidromic impulse. In clinical practice, however, the effect of anodal hyperpolarization mostly abates before the arrival of the propagating impulse with the use of an ordinary stimulator having two poles separated by 2–3 cm. Thus, the reversal of stimulator orientation provides no added advantage in the study of F-wave conduction.[181] Besides, the importance of maintaining the same cathodal position in eliciting M response and an F wave outweighs the theoretical concern of anodal inhibition. A surface electrode placed over the motor point of the tested muscle serves as the active lead (G_1) against the reference electrode (G_2) over the tendon. An optimal setting for display of F waves consists of an amplifier gain 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 provide an option to display the M response and F wave simultaneously, but separately, using two optimal gains.

F-wave latencies measured from the stimulus artifact to the beginning of the evoked potential vary by a few milliseconds from one stimulus to the next. Automatic vertical shifting of successive sweeps helps identify the number of F waves out of 16–20 trials and other characteristics of the waveform (Fig. 18–4). Determination of the minimal and maximal latencies reveals not only the fastest conducting fiber but also the degree of scatter among consecutive responses, providing a measure of tem-

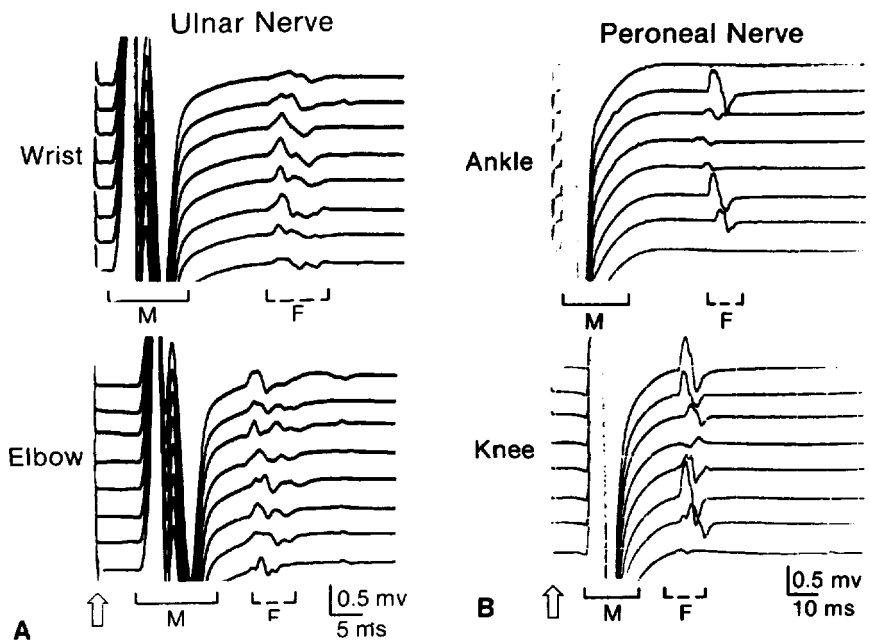


Figure 18–4. A. Eight consecutive tracings showing normal M responses and F waves recorded from the hypothenar muscles after stimulation of the ulnar nerve at the wrist and elbow. **B.** Eight consecutive tracings showing normal M responses and F waves recorded from the extensor digitorum brevis after stimulation of the peroneal nerve at the ankle and knee.

poral dispersion. Electronic averaging of a large number of responses permits easy analysis of mean latency, although phase cancellation sometimes defeats its own purpose.[31,43,45,73,74,112]

Slight voluntary contraction enhances the incidence of the F wave, thus facilitating the analysis, especially if the trial at rest yields only a few responses. During this maneuver, only a small number of axons carry a voluntary impulse at any given moment.[83] Despite the orthodromic activation in a few motor fibers, the antidromic impulse will reach the cell body in most of the axons and generate recurrent discharges. Therefore, the late responses recorded during mild voluntary contraction consist primarily of F waves through motor conduction to and from the spinal cord. With greater effort to contract the muscle, voluntary impulses collide with antidromic activity in many axons, inhibiting the generation of the F wave. In this case, reflexively activated impulses, propagated along the motor axons cleared of the antidromic impulse, may give rise to a late response analogous to the H reflex.[71,174]

Distal versus Proximal Stimulation

The F wave elicited by distal stimulation at the wrist or ankle serves as a measure of the motor conduction time along the entire length of the nerve. With diffuse or multisegmental lesions, the delay in nerve conduction increases in proportion to the length of the tested pathway. Thus, relatively mild slowing not identifiable by conventional motor nerve conduction studies may lead to a delayed F wave. In the study of F waves, an increased latency detected by distal stimuli results from conduction delay anywhere along the course of the nerve (see Chapter 7–6). In contrast, comparison of F wave and M response latencies with stimulation at the elbow or knee can distinguish between distal and proximal slowing.

The F wave first travels in the centripetal direction toward the spinal cord before it turns around distally to activate the muscle. With more proximal stimulation, the F wave moves closer to the M response, because the latency of the M response increases, whereas that of the F wave decreases. With stimulation at the wrist, elbow, ankle, and knee, the F wave clearly occurs after the M response. Axillary stimulation, however, elicits the F wave superimposed on the M response.[80,81] 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, leaving the M response from the wrist and the F wave from the axilla intact. These two remaining evoked muscle potentials do not overlap, allowing detection of the F wave elicited by axillary stimulation.[80]

On average, the decrease in latency of the F wave equals the increase in latency of the M response, when the stimulating point moves from the wrist to the elbow and then to the axilla. Thus, the sum of F wave and M response latencies remains the same regardless of the site of nerve stimulation, providing twice the conduction time along the entire length of the axon, plus 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.[89] That is,

$$F(A) = F(W) + M(W) - M(A)$$

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) represent latencies of the corresponding M response.[6]

For clinical studies, routine procedures include stimulation of the median and ulnar nerves at the wrist and elbow, and of the tibial and peroneal nerves at the ankle and knee. When necessary, the equation described above provides the estimated latency of the F wave from any proximal site. Stimulation of the facial nerve also elicits F waves,[153] although superimposition of the M response usually makes its recognition difficult. Furthermore, inadvertent stimulation of neighboring trigeminal afferent fibers may simultaneously activate reflex responses,[172] which may mimic the late response.

5 MOTOR CONDUCTION TO AND FROM THE SPINAL CORD

Central Latency

Central latency or conduction time from the stimulus point to and from the spinal cord equals F − M, where F and M are latencies of the F wave and the M response, respectively (Fig. 18–5). Subtracting an estimated delay of 1.0 ms for the turnaround time at the cell and dividing by two, (F − M − 1)/2 represents 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 cells in humans, animal data indicate a delay of nearly 1.0 ms.[64,107,141] The absolute refractory period of the fastest human motor fibers lasts about 1.0 ms or slightly less.[82,90] 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 unless it is propagated orthodromically before the inhibition of Renshaw cells activated by an antidromic impulse with a synaptic delay of 1.0 ms. In evaluating the minimal latency, therefore, it seems appropriate to assume a turnaround time of 1.0 ms.

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

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

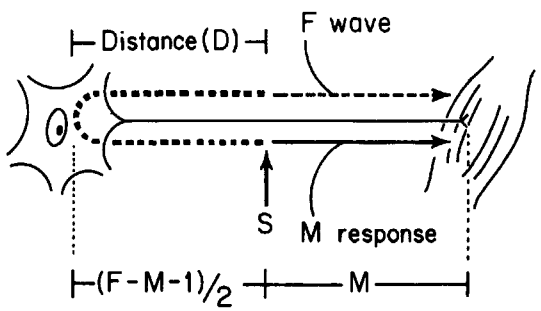


Figure 18–5. The latency difference between the F wave and the M response represents the passage of a motor impulse to and from the cord through the proximal segment. Considering an estimated minimal delay of 1.0 ms at the motor neuron pool, the proximal latency from the stimulus site to the cord equals (F − M − 1)/2, where F and M are latencies of the F wave and M response. In the segment to and from the spinal cord, FWCV = (D × 2)/(F − M − 1), where D is the distance from the stimulus site to the cord, (F − M − 1)/2 is the time required to cover the length D, and FWCV is F-wave conduction velocity. Dividing the conduction time in the proximal segment to the cord by that of the remaining distal segment to the muscle, the F ratio = (F − M − 1)/2M, where (F − M − 1)/2 and M are proximal and distal latencies. [From Kimura,[85] with permission.]

A given F wave represents only a portion of the motor axons available for activation of the M response. The interval of a few milliseconds between the earliest and latest F wave results from the difference between the fast and slow conducting motor fibers. The minimal-latency F wave selected out of many trials usually, although perhaps not always, reveals the conduction properties of the fastest fibers.[17,34,80,88,93,134] In some diseased nerves all the surviving fibers that contribute to the M response may not propagate antidromic impulses centripetally. In this instance, the stimuli that elicit an M response fail to evoke F waves. If the fast conducting fibers show proximal, but not distal, conduction block, the M response and minimal-latency F wave represent two separate groups of motor fibers, not directly comparable for calculation of conduction velocity. This possibility diminishes if the increase in latency of the M response elicited by a proximal stimulus equals the decrease in latency of the F wave.[80,88,114,134] Comparison of the sums of the F latency and M latency at distal and proximal stimulus sites tests this relationship. If the sums remain the same, the minimal-latency F wave and the earliest portion of the M response represent the same group of motor fibers, or at least those with the same conduction characteristics. This, in turn, provides a rationale for directly comparing the latencies of these two muscle potentials in various assessments of proximal versus distal conduction characteristics.[84]

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.[80,85] In the lower limbs, 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.[88] 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:

$$FWCV = (2D)/(F - M - 1)$$

where D represents the distance from the stimulus site to the cord, and $(F - M - 1)/2$, the time required to cover the length (see Fig. 18–5).

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[106] as well as the lower limbs.[88] F wave latencies may provide a useful measure in studying limbs of average length[20] 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[162] or the patient's height with the use of a nomogram.[169] 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 provides the best yield of abnormality (Tables 18–1 and 18–2).[84,178]

The F Ratio

Two latency ratios compare proximal and distal nerve conduction: the F/M ratio,[34,35] where F represents the latency of the F wave and M, that of the M response, and the F ratio, which is $(F - M - 1)/2M$, where $(F - M - 1)/2$ represents the conduction time from the cord to the stimulus site, and M, that of the remaining distal nerve segment to the muscle. Circumventing the need for determining the nerve length, the F ratio provides a simple means of evaluating conduction characteristics of the proximal versus distal segment (see Fig. 18–5). Clinical use of this ratio assumes that the various limbs of different lengths have the same proportions for the proximal and distal segments.[84] Because of individual variability, the F ratio has proven less useful than theoretically expected as a diagnostic test. It has, however, provided an important means to characterize the conduction abnormalities in various neuropathic conditions based on statistical comparison between patients and control subjects as a group.

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, the tibial nerve at the popliteal fossa, and the peroneal nerve immediately above the head of the fibula (see Table 18–1). With stimulation at these sites, therefore, the latency of the F wave equals three times the latency of the M response plus 1.0 ms for turn around time. Thus, the stimulus sites at the elbow or knee 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.[88] In fact, calculated FWCV indicates faster conduction proximally than distally, which compensates for the difference in nerve length.[17,80,88,89,93,121,134]

6 THE F WAVE IN HEALTH AND DISEASE

Clinical Value and Limitations

Clinical uses of the 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,[15] a sample size of 10, as compared with 100, underestimated 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.[52] In group comparison of ulnar nerve F waves, the lower limit of sample size showing valid results included 16 stimuli or 10 waves

Table 18–1 F Waves in Normal Subjects*

Number 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 (0.82–1.14)**,††
	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)	1.0 ± 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 (0.87–1.23)
	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 (0.87–1.23)
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 (0.89–1.33)

*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 are latencies of the F wave and M response, respectively.

‡Conduction velocity = 2D/(F − M − 1), where D is 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 fibula (peroneal), and in the popliteal fossa (tibial).

¶F(A) = F(E) + M(E) − M(A), where F(A) and F(E) are latencies of the F wave with stimulation at the axilla and elbow, respectively, and M(A) and M(E) are 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 18–2 Comparison Between Two Nerves in the Same Limb*

Number 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 are latencies of the F wave and M response, respectively.
‡Upper limits of normal calculated as mean + 2 SD.

for minimal and maximal latencies and 20 stimuli or 16 waves for chronodispersion.[125] Recording as many as 40–100 F waves at each stimulus site proved useful in special studies,[130,135] but not in a routine clinical test. 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 suit better for evaluating the same subjects sequentially, as is done in drug trials (see Chapter 7–6). Calculation of the

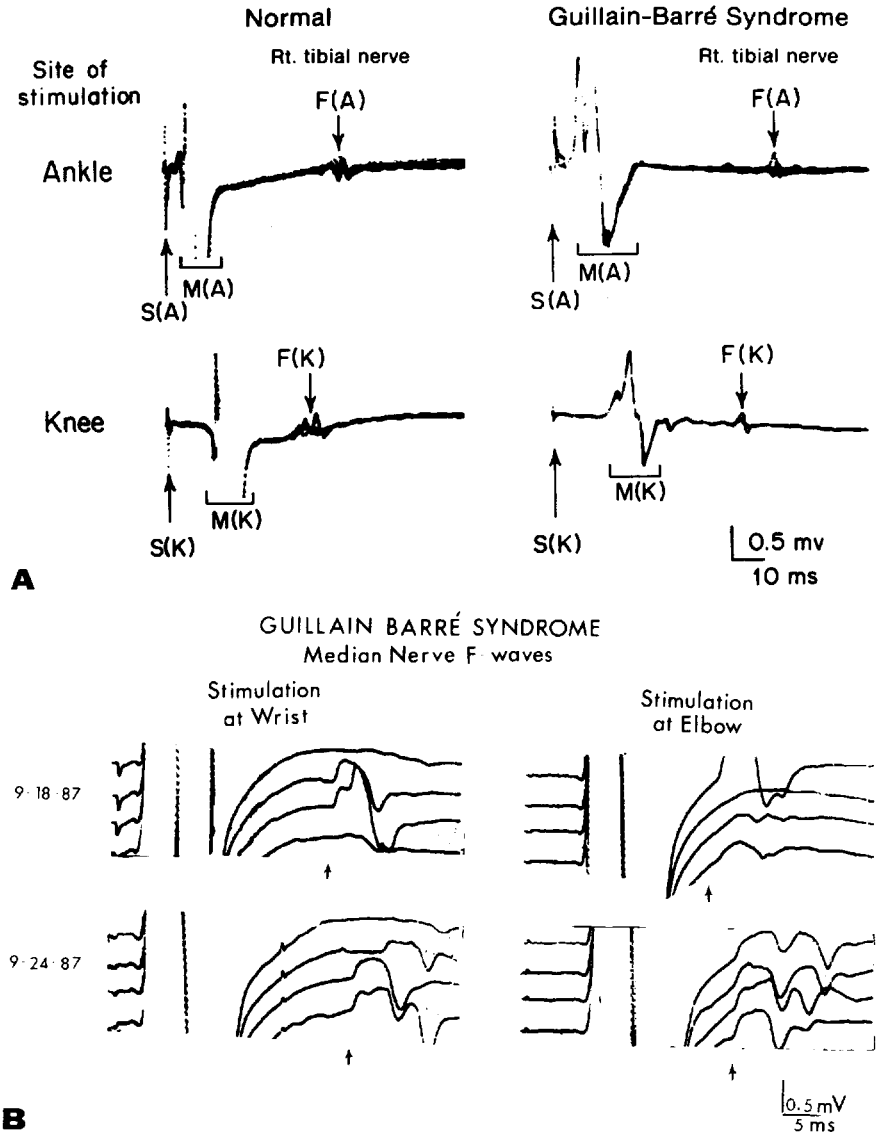


Figure 18–6. A. M response (*open brackets*) and F wave (*small arrows*) recorded from the abductor hallucis in two subjects. The patient with Guillain-Barré syndrome had increased F wave latency. The M response was normal in latency, although reduced in amplitude. **B.** A 26-year-old man with progressive generalized weakness of 2 weeks' duration. He had difficulty rising from the chair or climbing stairs. Electrophysiologic studies on September 18 revealed normal nerve-conduction studies, although the patient was unable to recruit motor unit potentials. On September 24, the minimal F wave latency was increased by 4 ms from the previous measures with stimulation of the median nerve either at the wrist or at the elbow. Prolongation of minimal F latency to this degree, if reproducible, suggests a proximal conduction delay. This may be the only abnormality in some patients with Guillain-Barré syndrome during an acute stage.

central latency, the FWCV, and the F ratio provides additional information not otherwise available, especially in the comparison of proximal and distal segments (see Tables 18–1 and 18–2).

Other measures advocated include F chronodispersion based on the degree of scatter between minimal and maximal latencies.[129,131] As a related matter, F tacheodispersion plots the distribution of the conduction velocities of individual nerve fibers or small groups of nerve fibers estimated from a large number of consecutively recorded F waves.[13] This value may show an abnormality in some patients with neuropathy despite normal conventional nerve conduction studies.

The F-wave studies show consistent abnormalities in patients with hereditary motor sensory neuropathy,[80,88,128] acute or chronic demyelinating neuropathy,[85,89,93] diabetic neuropathy,[17,91] uremic neuropathy,[1,132,133] alcoholic neuropathy,[101] and a variety of other neuropathies.[99] Other categories of disorders associated with F wave changes include entrapment neuropathies,[34,178] amyotrophic lateral sclerosis,[5] and radiculopathies.[35,55] Some patients with cervical syringomyelia may have increased F-wave latencies of the median or ulnar nerve with normal peripheral conduction velocities.[138,145]

Studies of the F wave help characterize polyneuropathies in general and those associated with prominent proximal disease in particular (Figs. 18–6 to 18–8). 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 may reduce the F wave persistence but rarely alter the F wave latency beyond its inherent variability (see Chapter 7–6). In fact, in experimental allergic neuritis with demyelination of the ventral root, only 14

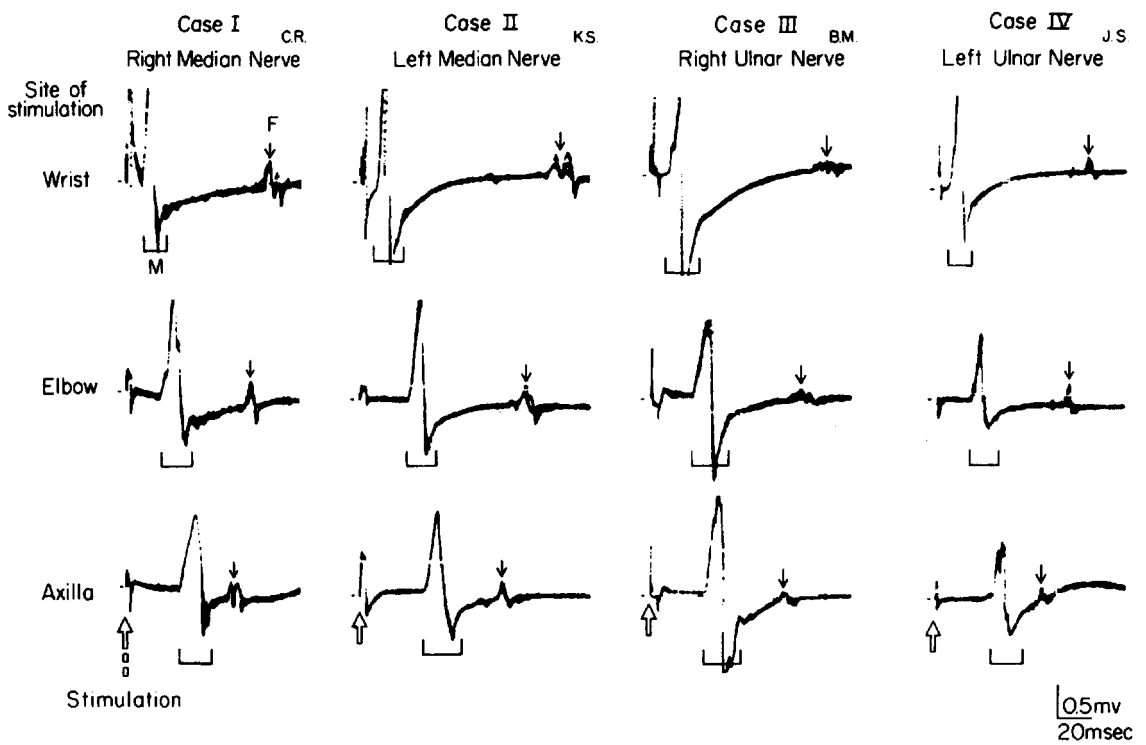


Figure 18–7. M response (*horizontal brackets*) and F wave (*small arrows*) recorded from the thenar muscles (cases 1 and 2) and hypothenar muscles (cases 3 and 4) in patients with hereditary motor sensory neuropathy type I. Three consecutive trials in each showed markedly increased latencies of the M response and F wave, requiring a slower sweep speed of 20 ms/cm instead of the usual 5 ms/cm. Because of slowed conduction, the M response and F wave were separated even with proximal stimulation at the axilla, rendering the collision technique unnecessary. [From Kimura,[80] with permission.]

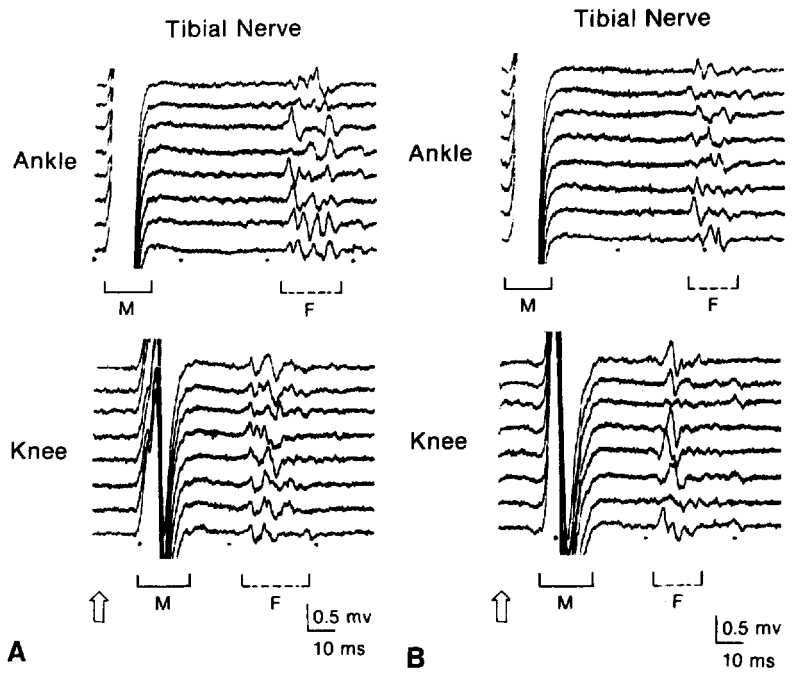


Figure 18–8. A 44-year-old man with adrenoleukodystrophy and diffuse weakness. Stimulation of the tibial nerve at the ankle or knee on the right (**A**) or left (**B**) elicited the F waves in the abductor hallucis. An increase in latency and duration and a marked temporal dispersion of the F wave stand in sharp contrast to the normal M response (cf. Fig. 18–4B).

percent of the guinea pigs and 7 percent of the rabbits showed an abnormal increase in F-wave latency in fibers with normal motor nerve conduction velocity.[173]

F-wave characteristics are altered in some patients with upper motor neuron symptoms, implying the importance of central interaction.[38,46,118] As a test of motor neuron excitability,[113] however, the F wave provides a less sensitive measure than the H reflex.[76] Nonetheless, patients with lower limb spasticity show increased mean amplitude and duration of the F waves elicited by stimulation of the tibial nerve.[8] In one study,[33] the largest F wave, 4.5 percent of the M response in normal subjects, remained the same in the patient group with chronic paraparesis. In patients with spasticity, however, the F wave became more persistent, making the average amplitude of 32 F waves significantly greater than 1 percent of the M response seen in normal subjects. Another study of patients with spasticity showed paradoxical reduction in the average F wave frequency in motor neuron disease together with an increased incidence of repeater F waves.[139]

A higher rate of stimulation tends to increase F wave amplitude and persistence in normal persons[39] and to a lesser degree in patients with spasticity.[40] Reflex components may contribute to the late response, especially if the patient has prominent hyperreflexia. The degree, duration, and type of spasticity may determine average as well as maximal amplitude of the F wave.[62] Unusually large F waves may appear in association with clinical spasticity and other upper motor neuron signs (Fig. 18–9).[47] Patients with upper motor neuron disorders show less facilitation of F waves with voluntary muscle contraction partly because already enhanced baseline values have no room for further increase.[123] The amplitude of the F wave also increases in disorders of the lower motor neuron, presumably because regenerated axons supply an increased number of muscle fibers.[51,156]

Normal Values

Tables 18–1 and 18–2 summarize the ranges and the upper and lower limits of normal latency, defined as 2 SD around the mean, and other aspects of the F wave established in the same control subjects as described in the preceding section for nerve conduction studies. Placement of the cathode 3 cm more proximally in this study of the median and ulnar nerves has

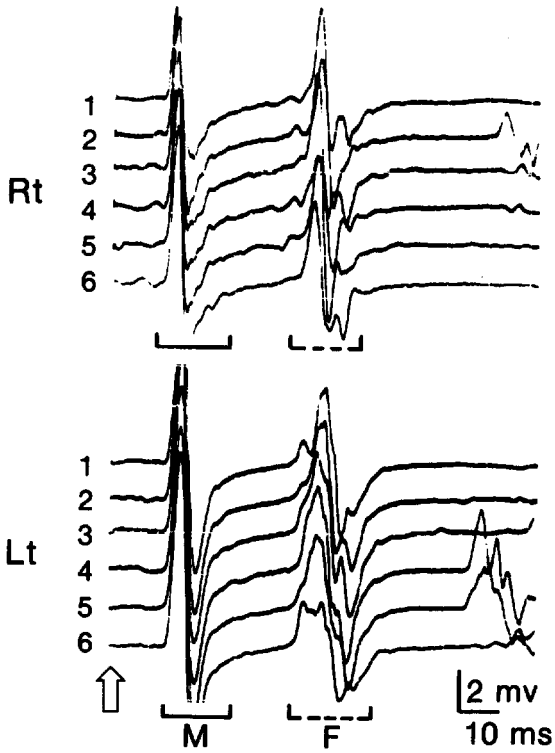


Figure 18–9. A 39-year-old man with chronic tetanus, diffuse hyperreflexia, and rigidity. Supramaximal stimulation of the peroneal nerve at the knee elicited large F waves in the extensor digitorum brevis. Six consecutive trials obtained on each side show consistency of the response. The average amplitude of the F wave was 57% of 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,[142] with permission.]

shortened the average F latency in this series compared with previous studies.[80,88] In addition, an attempt to elicit three times as many F waves at each stimulus site and slight voluntary facilitation routinely employed also increased the chance of recording the fastest conducting fibers.

Neonates and infants tend to have large F waves, probably reflecting the immaturity of physiologic inhibition.[120] 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 (see Chapter 22). For example, 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 1 year), and 16 ms in children (2 to 12 years) in one study.[119] The F-wave latency then increases until about the twentieth year of life, when it reaches 95 percent of its maximal value.[98] An older group of subjects have longer F-wave latencies than young healthy subjects.[124]

Hereditary Motor Sensory Neuropathy

Patients with advanced illness have neither an M response nor an F wave in the lower limbs,[88,128] but they have relatively preserved responses in the upper limbs. These findings support the clinical impression that the disease affects the lower limb more severely (Table 18–3). Mildly diseased

Table 18–3 Hereditary Motor Sensory Neuropathy (mean ± SD)

Number 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	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	38.9 ± 20.2	38.4 ± 16.8
31 ulnar nerves	Wrist	5.2 ± 2.9	55.5 ± 35.1	38.0 ± 18.3	39.2 ± 18.7
	Below elbow	13.1 ± 7.9	48.2 ± 29.8	36.6 ± 19.3	40.2 ± 19.0
	Above elbow	18.0 ± 10.6	40.7 ± 27.2	42.5 ± 22.1	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
2 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.

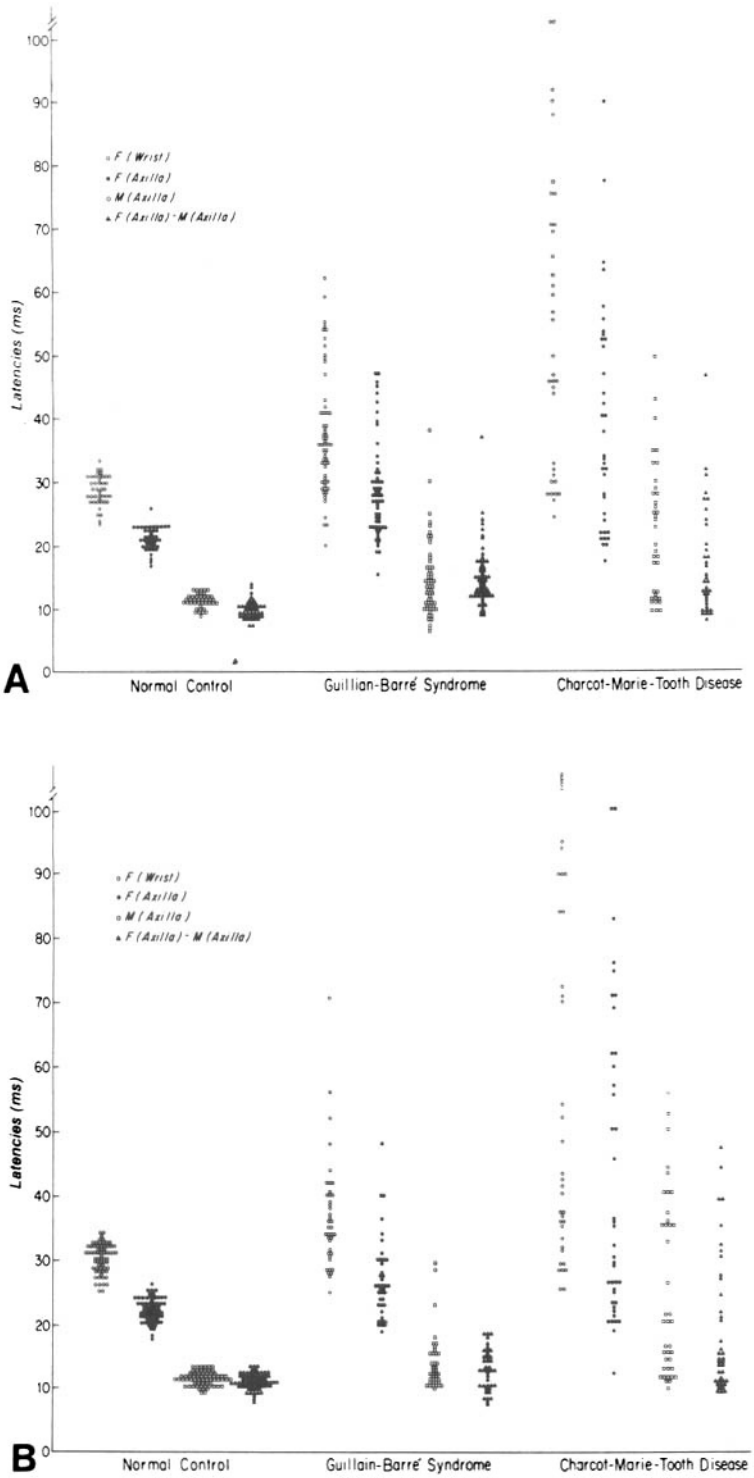


Figure 18–10. Latencies of F waves and M responses for median (**A**), ulnar (**B**), peroneal (**C**), and tibial nerves (**D**) in control, Guillain-Barré syndrome, and Charcot-Marie-Tooth disease. The histogram includes only those nerves whose stimulation elicited both an M response and an F wave 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. [From Kimura,[87] with permission.]

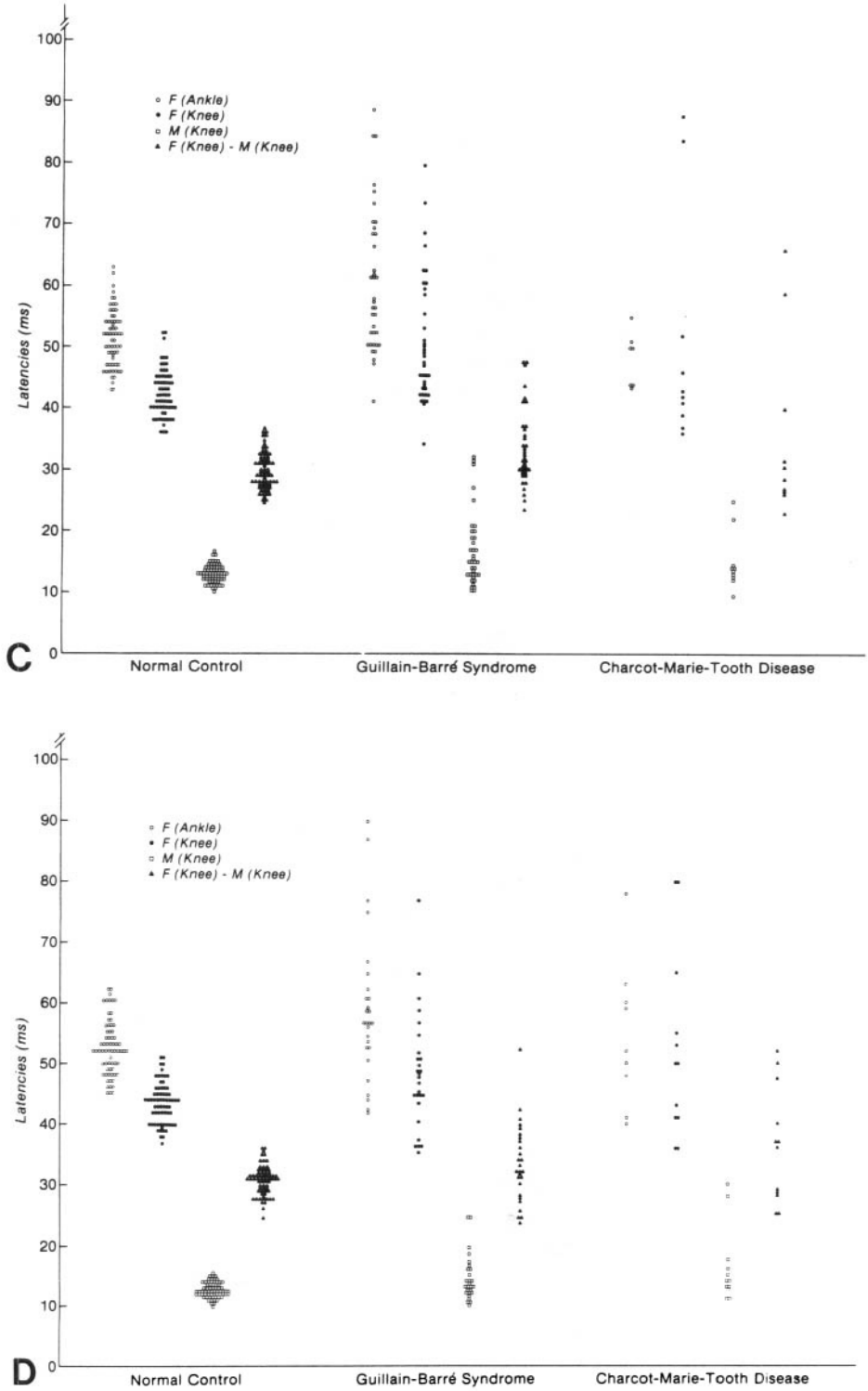


Figure 18–10 (*cont.*).

nerves may show slow motor conduction in the distal segment and normal conduction in the proximal segment.[80] In advanced cases, conduction abnormalities affect both segments equally. A bimodal distribution of motor nerve conduction velocities[165] supports the dichotomous separation into hypertrophic and neuronal types, or Charcot-Marie-Tooth disease (CMT) 1 and CMT 2 (see Chapter 25–5). Intermediate F-wave latencies seen in the present series probably reflect extreme variability of conduction over a wide spectrum in each group (Fig. 18–10).

Guillain-Barré Syndrome

Conduction abnormalities may involve any segment of the peripheral nerve in this syndrome (Table 18–4). 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 in early stages (see Chapter 25–3).[85,89,93] The routine conduction studies may show normal results in 15–20 percent of cases tested within the first few days of onset.[32] Some of these patients may have axonal neuropathies, but others probably have the lesion too proximal for detection with the use of ordinary techniques. 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 suggests demyelination of the involved segment (see Fig. 18–10).[58]

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 increase in terminal latency compensated 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 25–2). In fact, probability models can reproduce the same sensory deficit on the basis of randomly distributed axonal dysfunction.[176] Diabetic neuropathy shows notable F-wave changes, reflecting conduction abnormalities over both proximal and distal segments,[17,26,58,91,170] although not as a universal finding in mild cases.[122] In fact, minimal F wave latency serves as the most sensitive and reproducible measure of conduction slowing in

Table 18–4 Guillain-Barré Syndrome (mean ± SD)

Number 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		49.1 ± 11.4
	Axilla	14.5 ± 5.7	29.4 ± 9.5	55.5 ± 14.1	47.5 ± 14.5
40 ulnar nerves	Wrist	4.0 ± 2.0	36.8 ± 8.6		48.1 ± 9.7
	Below elbow	8.3 ± 2.5	32.1 ± 7.1	52.2 ± 10.7	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.

patients with diabetes mellitus (see Chapter 7–6).[4,94] The average value and distribution of the F ratio indicate distally prominent conduction abnormalities despite slowing along the entire length of the nerve (Fig. 18–11). In contrast, patients with proximal amyotrophy may have an increased F ratio in the lower limbs.[11]

Patients undergoing hemodialysis for chronic renal[112] or hepatic[37] failure have an increased F wave latency and a latency difference between the minimum and maximum values. In some of these patients, an increased F ratio implies predominant affection of the proximal nerve segment;[10] in others, slowing of nerve conduction involves both segments to the same extent.[36]

Entrapment Syndromes

In general, the F wave latency fails 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 7–6). Nonetheless, a reduced F ratio of the median nerve in the carpal tunnel syndrome rivals that in diabetic neuropathy (see Fig. 18–11).[91] F waves may also show abnormalities in compression neuropathies of the ulnar nerve. Differences between minimum and maximum F-wave latencies may provide a sensitive indicator for early detection of this syndrome.[157,158] In the carpal tunnel syndrome, unaffected neurons backfire at higher than normal frequencies, resulting in an increased percentage of repeater F waves.[109]

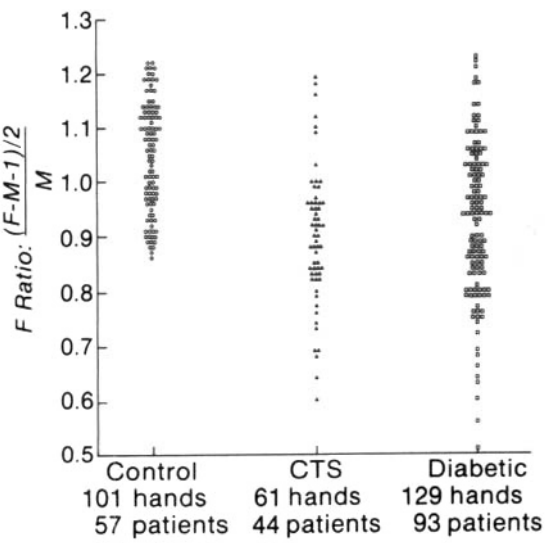


Figure 18–11. F ratio of the median nerve in the control group, carpal tunnel syndrome (CTS), and diabetic polyneuropathy. Statistical analysis showed significantly (p 0.01) reduced ratios in both disease groups, indicating disproportionate slowing of motor conduction distally. [From Kimura,[86] with permission.]

Plexopathy and Radiculopathy

A number of reports have suggested clinical value in assessing patients with root injuries.[34,35,53,78,126,164,169] The F wave usually remains normal in latency in most cases of radiculopathy, even if the lesion affects the motor fibers. Thus, normal studies do not preclude the presence of radicular lesions. In the thoracic-outlet syndrome, the F wave latency may increase in the classic type with neuronal involvement,[24,67,177,178] but rarely if vascular symptoms predominate.[84,157,158] F-wave changes render useful information in some children with brachial plexus injury at birth,[97] but the results may remain normal in clinically established cases of brachial or lumbosacral plexopathy.[2]

In general, the F-wave determination provides only limited help as might be expected on theoretical grounds in the early diagnosis of focal abnormalities.[51,143] An unequivocal delay or absence of the F wave in conjunction with normal motor conduction distally, however, indicates a proximal lesion (Fig. 18–12). Right-sided versus left-sided comparison is usually a reliable means of assessing unilateral lesions, although even this measure often falls short of documenting small latency change.[84] The F-wave persistence declines on the affected side, compared with the normal side, when the proximal lesion induces partial conduction block. F chronodispersion shows a more postural effect than the minimal latency in patients with lumbosacral root compression and canal stenosis.[163] In some patients with neurogenic claudication, serial studies before

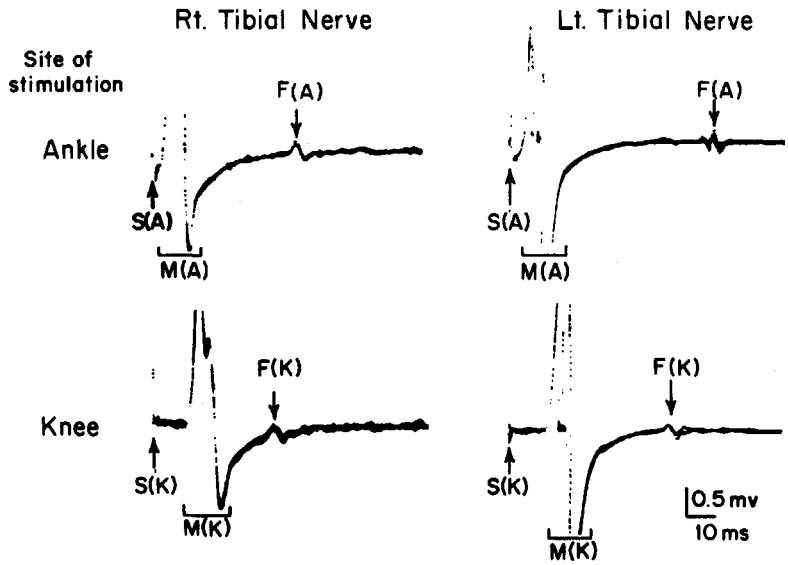


Figure 18–12. A patient with a sacral plexus lesion on the left. Stimulation of the tibial nerve at the ankle and knee elicited an M response (*open brackets*) and F wave (*small arrows*) in the abductor hallucis. Note the increased F wave latency on the affected side despite a normal M response.

and after ambulation reveal dynamic alterations in F-wave persistence and latency.[108,136,161] These reversible changes suggest ischemic conduction block and slowing in proximal motor axons, corroborating a neurologic origin for the symptoms.

States of Altered Excitability

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.[102] In one series,[19] 50 percent 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 motor neurons. This type of F-wave change can also occur in an evolving spinal cord lesion or conus medullaris,[3,16,160] mimicking the abnormalities seen in early stages of Guillain-Barré syndrome.[58]

Generally reduced F-wave excitability in acute flaccid hemiparesis recovers toward the normal range during chronic stages.[19,27,160] In one study of healthy subjects, simulating paresis for 6 hours by immobilizing the limb with a cast, F waves showed reversible declines in amplitude and persistence.[59] In our experience, hysterical paresis also reduces F-wave excitability, probably because of the lack of facilitatory drive.

Systematic administration of anesthetic agents intravenously affected F-wave excitability only little, if at all.[100] Intrathecal baclofen application, however, altered F-wave mean and maximum amplitude as well as mean duration, in a quantifiable manner.[25] Intravenous or subcutaneous injections of thyrotropin-releasing hormone rapidly increased the amplitude of the F waves.[7]

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Chapter 19

H, T, MASSETER, AND OTHER REFLEXES

1 INTRODUCTION

Traditional nerve stimulation techniques primarily assess the distal segments of the peripheral nerves. Methods of testing the proximal nerve segments or the central nervous system include, in addition to the blink reflex (see Chapter 17) and F wave (see Chapter 18), the H reflex, T reflex, tonic vibration reflex, and silent period. 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.

Extensive studies have proven the practical value of the H and T reflexes in certain neurologic disorders. Clinical applications of the other techniques mentioned here await further confirmation, even though they have contributed substantially as a means of quantitating physiologic studies of motor and sensory systems. This chapter reviews the basic physiology and diagnostic usefulness of these techniques in evaluating the regions of the

nervous system not accessible by the conventional methods.

2 H REFLEX AND T REFLEX

Neurologic examination exploits the muscle stretch reflex to measure motor neuron excitability in spasticity and other related conditions. Clinical observation, however, falls short in objectively evaluating the briskness, velocity, or symmetry of these responses. Electrophysiologic recordings offer these advantages by quantitating the response after a mechanical tap to the Achilles tendon or electrical stimulation of the tibial nerve. The electrically elicited spinal monosynaptic reflex, called the *H reflex* after Hoffmann, bypasses the muscle spindles, although otherwise it is identical in many respects to the stretch reflex induced by a mechanical tap to the tendon (T) reflex.[163] 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 H reflexes only when applied to the median or tibial nerve. In contrast, mechanical stretch of any muscle evokes T reflexes. For example, tapping the voluntarily contracted erector spinae evokes two component stretch reflexes, short-latency R_1, considered segmental in origin, and long-latency R_2, induced by the suprasegmental pathway.[342] In one study,[215] mechanical stimuli to the ankle and patellar but not triceps tendon elicited the T reflex consistently in healthy subjects, suggesting their clinical value. The tendon jerk reflex elicited by a mechanical tap, however, provides an incomplete picture of the pathologic changes compared with more complex patterns of response following muscle stretch caused by active or passive movement.[114]

H Reflex versus F Wave

Stimulation of most nerves in the limb, including the ulnar nerve, elicits an H reflex in newborn infants and during the first year of life.[161,346] In adults, the reflex can be evoked in the soleus and plantar foot muscles after stimulation of the tibial nerve and less consistently in the flexor carpi radialis after stimulation of the tibial and median nerves at rest.[85,105,182,283,318] Stimulation of the femoral nerve also can elicit a reflex response of the quadriceps in some but not all subjects.[8,129] When necessary, mild voluntary contraction primes the motor neuron pool sufficiently to allow reflexive activation of other muscles such as biceps brachii, extensor digitorum longus, and tibialis anterior.[47,84,128,147,261,297,318,372] Under this condition, H-reflex latencies exceeded minimal F-wave latencies when evaluating the abductor pollicis brevis and tibialis anterior but not the soleus muscle.[37] Thus, the H reflexes elicitable only when primed by voluntary contraction may preferentially involve the low threshold slow conducting motor neurons, whereas the minimal latency F waves represent the high threshold fast conducting pools.

Despite the traditional emphasis on homonymous activation, IA afferents have a widespread projection to heteronymous motor neuron pools. For example, the biceps brachii receive monosynaptic excitation from afferents in the median nerve at the elbow as shown by poststimulus time histograms of voluntarily active motor units.[49] In fact, stimulation of the median nerve at the elbow elicits a reproducible heteronymous monosynaptic reflex in the contracting biceps brachii, producing a response smaller than the homonymous H reflex evoked by stimulation at Erb's point.[261] Similarly, stimulation of the median nerve at the elbow 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.[286] These findings offer physiologic evidence in humans of monosynaptic excitation from group IA afferents to heteronymous muscles.

The limited distribution of the H reflex at rest stands in contrast to an unrestricted elicitation of the F wave in practically any distal limb muscle. The effect of increasing stimulus intensity also distinguishes the two (Fig. 19–1). The H reflex amplitude increases initially as the stimulus changes from subthreshold to

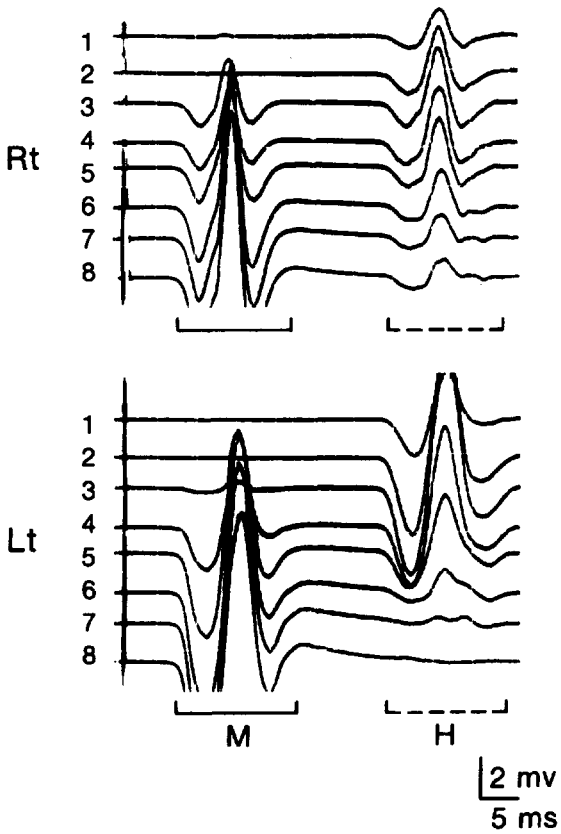


Figure 19–1. H reflex recorded from the soleus after stimulation of the tibial nerve at the knee. Shock intensity was gradually increased from subthreshold level (*1*) to supramaximal stimulation (*8*). Note the initial increase and subsequent decrease in amplitude of the reflex potential with successive stimuli of progressively higher intensity. The H reflex normally disappears with shocks of supramaximal intensity that elicit a maximal M response and F wave.

submaximal. With a higher shock intensity, the H reflex diminishes progressively, and the F wave appears instead with a slightly longer latency when the stimulus elicits a maximal compound muscle action potential or M response. The soleus H reflex, elicitable at rest, has a shorter latency than the minimal F wave, indicating the participation of the fast conducting afferent and efferent fibers. This stands in contrast to the slower conducting motor neurons activated reflexively only after priming with voluntary contraction.[37] An optimal elicitation of the H reflex requires maximal stimulation of the group IA afferent fibers without concomitant activation of motor fibers, although in practice few stimuli accomplish such selectivity. If the stimulus activates any motor axons eliciting an M response, the antidromic impulse in those axons can generate recurrent discharges. Thus, submaximal intensity does not guarantee the reflex origin of the late response. In contrast to these human characteristics, studies in rats show near-maximal H reflex elicited by shock intensities supramaximal for M response.[50]

Possible mechanisms for the extinction of the H reflex with increasing stimulus intensity include (*1*) collision of the reflex impulse with antidromic activity in the alpha motor axon, (*2*) refractoriness of the axon hillock after the passage of the antidromic impulse, and (*3*) Renshaw inhibition mediated by motor neuron axon collaterals via internuncial cells to the same and neighboring alpha motor neurons.[97,300,355] In humans, unlike in animals, the antidromic volley arrives after the monosynaptic excitation because the fast conduction of the IA afferents more than compensates for the synaptic delay.[96,178] Therefore, under normal conditions, the H reflex discharge protects the motor neurons

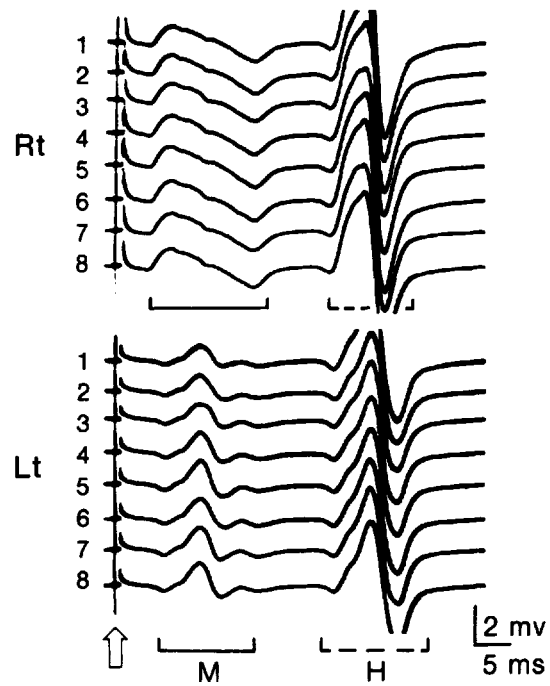


Figure 19–2. The H reflex from the soleus after stimulation (*arrow*) of the tibial nerve at the knee. Consecutive trials show consistency of the response on each side.

from antidromic invasion while at the same time being eliminated by collision. Gamma hydroxybutyrate, known to promote cataplexy, markedly suppresses the H reflex, presumably by presynaptic inhibition, without affecting the F wave.[240] A differential effect on the two responses may not serve as an indirect measure of presynaptic inhibition of IA fibers mediating the H reflex because changes in motor neuron excitability influence the F wave much less than the H reflex.[178]

Consecutive F waves characteristically vary in latency and waveform, because they represent recurrent discharges of different groups of motor neurons with variable conduction characteristics. In contrast, H reflexes remain relatively constant if elicited by the same stimuli because each trial activates the same motor neuron pool as long as motor neuron excitability remains the same[126] (Fig. 19–2). The amplitude of the H reflex, however, declines when activated repetitively.[120] The low-frequency depression seen at a stimulus rate of 1 pulse per second may result from processes intrinsic to the presynaptic bouton.[176] In testing individual axons with single-muscle-fiber recording, the latency variability of consecutive H reflexes far exceeds that of the F waves. As mentioned earlier, this reflects a greater variability in synaptic transmission at a motor neuron compared with a relatively constant turnaround time for a recurrent discharge.[183,315,355] 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.[355] In a similar study, H-reflex jitter showed a direct correlation with H-reflex latency, which, therefore, may serve as an indirect measure of the motor unit size and recruitment threshold.[184]

Recording Procedures of the Soleus H Reflex

The H reflex recorded with the patient supine or prone suffices in clinical determination of reflex latencies (Fig. 19–3). 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.[175] A soft cushion supports the knee, semiflexed at about 120 degrees. Maintaining the angle of the ankle joint constant at about 110 degrees helps establish optimal

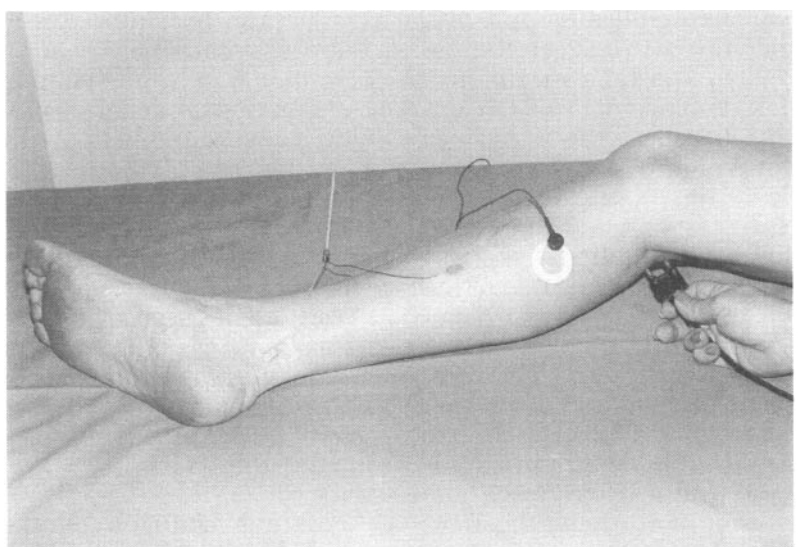


Figure 19–3. Recording of electrically induced H reflex from the soleus muscle with the active electrode (G_1) on the medial surface of the leg at the edge of the tibia, one half to two thirds of the way from the popliteal fossa to the ankle, and the reference electrode (G_2) over the Achilles tendon. Shocks of submaximal intensity and long duration (1 ms) applied at the popliteal fossa optimally activate the afferent fibers of the tibial nerve.

relaxation of the calf muscle. The traditional recording uses the active electrode (G_1) placed 2 cm distal to the insertion of the gastrocnemius on the Achilles tendon and the reference electrode (G_2), 3 cm further distally, with a ground electrode located between the stimulating and recording electrodes. An alternative, generally preferred, derivation consists of G_1 placed over the soleus just medial to the tibia, half the distance from the tibial tubercule to the medial malleolus, and G_2 over the Achilles tendon medial and proximal to the medial malleolus.[70] A second pair of electrodes, placed over the belly of the anterior tibialis muscle 3 cm apart, along the longitudinal axis and near midline, monitors the antagonistic muscle. Intramuscular studies reveal a substantially greater contribution of the soleus compared with either medial or lateral gastrocnemius in the surface-recorded H reflex.[247] Thus, the recorded H reflex varies in amplitude and waveform depending on the placement of the recording electrodes. It appears as a triphasic potential with initial positivity with electrodes placed over the gastrocnemius and as a diphasic potential with initial negativity when recorded from the soleus.

The effective modes of stimuli include (*1*) an electrical or magnetic stimulation applied to the tibial nerve at the S1 nerve root, sciatic nerve, or popliteal fossa (H reflex); (*2*) a tap of the Achilles tendon with a reflex hammer fitted to trigger the oscilloscope (T reflex), and (*3*) a mechanical stretch by quick displacement of the ankle. The ability to elicit the soleus H reflex from stimulation distally and proximally helps localize the site of involvement.[106,107,202,236,290,385,387] Standardization of stimulus conditions ensures reproducible results. The amplitude of the H reflex and its relationship to the M response change with stimulus duration. Based on the recruitment curves, a stimulus duration between 0.5 and 1 ms best elicits H reflexes.[268,287] Stepwise change of shock intensities helps determine optimal electrical stimuli for obtaining the maximal responses. In studying the T reflex, a handheld reflex hammer often gives acceptable results equal in reliability to complicated instrumental stimulators.[334]

Studies under isometric conditions should measure the force of induced muscle contraction with a transducer placed against the foot plate. In isotonic conditions, a potentiometer mounted on the axis of the foot plate determines the degree and rate of foot displacement. The common evaluation of muscle action potentials recorded reflexively from the soleus include the onset latencies of the H and T reflexes determined to the initial deflection, either negative or positive, H_{max}/M_{max} and T_{max}/M_{max}, where H_{max}, M_{max}, and T_{max} represent the maximal amplitude of the H reflex, M response, and T reflex. Submaximal M responses exceeding 5–10 percent of the maximal size closely resemble the waveform of the total response.[172] This provides 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 alter the H-reflex magnitude.[366] H_{max}/M_{max} is greater when recorded from the soleus than from the gastrocnemius.[271]

Excitability and the Recovery Curve

When elicited with an optimal mechanical or electrical stimulus, the amplitude of the H and T reflexes provides a measure of motor neuron excitability.[23,206,284,347,365,371] Suppression of the H reflex, however, may also result from presynaptic inhibition of IA afferents. In general, preservation of F waves associated with a suppressed H reflex suggests a reduction of excitatory input rather than decreased excitability of motor neurons.[227] As stated earlier in this chapter, however, methodological problems confound the comparison of the F wave and H reflex in elucidating the responsible physiologic mechanisms of excitability change.[179] Nonetheless, the H-reflex measurement helps in quantitatively evaluating supraspinal and segmental inputs on the alpha motor neurons.[13,80,81,117,225,229,376]

Postural changes play an important role.[82,98,190,205,223,270,273] For example, lateral tilting modulates the soleus H reflex through vestibular influences, showing ipsilateral suppression and contralateral facilitation.[5,6] These data indicate that,

in humans, as in the decerebrate cat, tonic labyrinth reflexes act asymmetrically. Caloric stimulation of the labyrinth facilitates the H reflex bilaterally.[79,83]

Sleep in general, and the rapid eye movement period in particular, depresses the reflex.[161] The background fusimotor activity has little or no influence in eliciting an Achilles' tendon jerk during complete relaxation,[41,42] although spindle discharges induced by shortening the homonymous muscle depress the monosynaptic reflexes.[377] Descending motor commands that produce patterned voluntary activity during pedaling normally causes facilitation during the downstroke and suppression during the upstroke. Loss of this supraspinal control over the spinal inhibitory mechanism may contribute to the functional disability in spasticity.[31]

Other related areas of interest include spasticity,[32,63,111,113,211,232,296,298,344,348,378] dystonia,[33] task-dependency,[45,94,95,319] drug effect,[238] anesthesia,[228,249,272] preparatory anticipation,[121] and selective rhizotomy.[55,71,234]

The paired-shock technique reveals the time course of alteration in motor neuron excitability by means of conditioning and test stimuli.[195,285,381] Shocks of suprathreshold intensity exert two opposing effects on the excitability of the motor neuron pool: On the one hand, those motor neurons that have discharged in response to the conditioning stimulus become less responsive to a subsequent stimulus because of the refractory period, the Renshaw effect, and other inhibitory mechanisms. On the other hand, the remaining motor neurons, activated subliminally by the conditioning stimulus, become more excitable in response to the test stimulus as the result of partial depolarization. The presence of these two competing factors complicates the interpretation of the result.[158] To further compound the problems, the size of the test H reflex also depends on the physiologic characteristics of the sampled motor neurons and syn-aptic effects on recruitment gain.[198] In experimental studies, single motor unit analysis circumvents these uncertainties, providing a tool to explore the effect of a conditioning stimulus on a unitary H reflex.[329,330]

If the conditioning stimulus gives rise to muscle contraction, motor neuron excitability may change as the secondary effect of group IA inflows caused by mechanical stretch of the ankle extensor muscles on relaxation of the flexor muscles.[61,176,188] Selective cutaneous stimulation of the peroneal or tibial nerve circumvents such ambiguity.[230,294] In normal subjects, it results in marked amplitude reduction of the test response at an interstimulus interval of about 100 ms.[130,131,173,174] This physiologic inhibition may not occur in the presence of parkinsonian rigidity.[246] Conditioning cutaneous stimulation may even facilitate the H reflex in patients with corticospinal lesions.

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. 19–4). Superimposed on this long-lasting suppression, interceding potentiation begins from 50 to 200 ms or sometimes up to 300 ms, peaking at 150 ms. Initial facilitation coincides with the excitatory postsynaptic potential in subliminally activated alpha motor neurons.[340] Subsequent depression presumably reflects presynaptic inhibition or transmitter depletion. The intervening relative facilitation, seen bilaterally with unilateral conditioning,[305] may result from interaction of segmental or long loop reflexes.[130,131]

The paired-shock technique also reveals the effects of reciprocal inhibition[19–21,46,62,196,266,269,379] and reflex interactions.[154,235] 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.[258,259] Conversely, the conditioning impulse from sciatic nerve afferents facilitates vastus medialis motor neurons at the joint time of arrival of the test volley via the H reflex or corticospinal pathways. Subsequent inhibition seen only in the H reflex implies presynaptic inhibition of the IA afferent terminals.[310,360,386] A selective voluntary contraction also produces H-reflex excitability changes by presynaptic and postsynaptic mechanisms.[2,37,43,176,239,375]

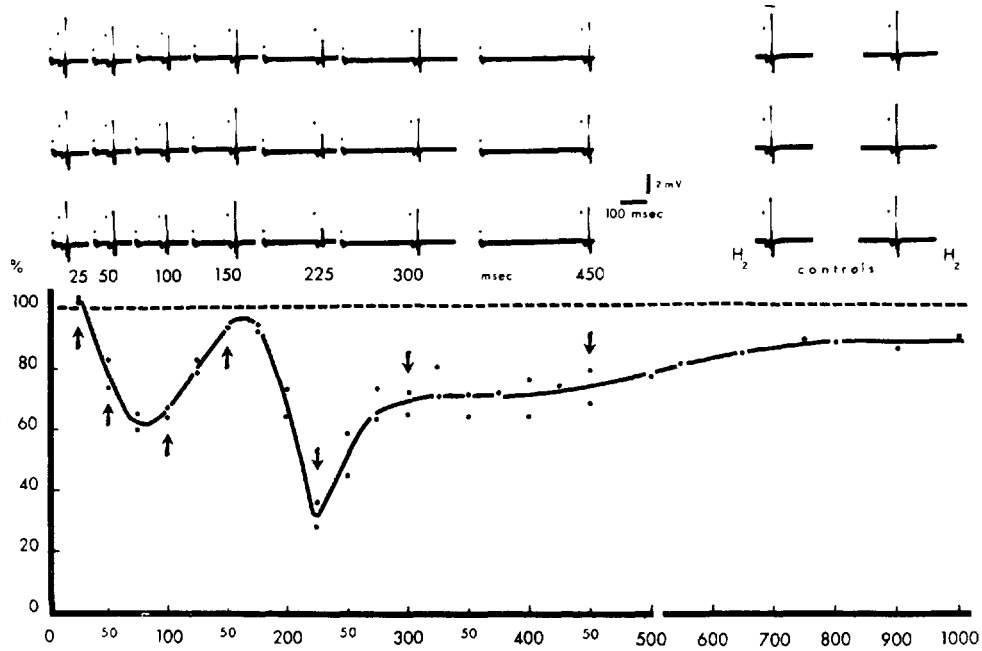


Figure 19–4. Conditioning of an H reflex by a subliminal H reflex stimulus. In the *upper half* are specimen records arranged in groups of three for each experimental situation. To the *right* are three H_2 control reflexes before and after the conditioning series. To the left are groups of three conditioned H_2 reflexes at testing intervals of 25, 50, 100, 150, 225, 300, and 450 ms as indicated in the *lower curve*. The S_1 stimulus was just below the threshold for evoking an H reflex whereas the S_2 stimulus was just below the threshold for an M response. The *lower curve* shows plotting of the mean of the three H_2 reflexes at each testing interval (abscissa), the mean sizes being expressed as percentages of the mean H_2 reflex controls. [From Taborikova and Sax,[340] with permission.]

Clinical Applications

H or T reflex latency of the tibial or median nerve provides a measure of nerve conduction along the entire length of the afferent and efferent pathways.[101,146] It increases in patients with alcoholic,[374] uremic,[152] and various other polyneuropathies,[318] and it decreases in the tethered cord syndrome, reflecting the lower location of the conus medullaris.[157] In patients with diabetes, this test rivals conventional nerve-conduction studies in detecting early neuropathic abnormalities and a clear-cut proximal-to-distal gradient of conduction slowing.[352,353] The test also helps establish maturational changes in the proximal versus distal nerve segment.[364]

The difference between the H-reflex and distal motor latencies equals the segmental conduction time along the reflex pathway.[76,352,353] Dividing the distance between the knee and T11 by the latency difference provides a mixed sensory and motor index or conduction velocity along the afferent and efferent fibers of the tibial nerve.[354] Segmental studies are better suited for evaluation of focal lesions like radiculopathy, eliminating the normal portions of the reflex pathway, which tend to dilute the conduction abnormality (see Chapter 7–6). As stated below, magnetic or electrical stimulation of the S1 nerve root provides a most sensitive measure of the very short proximal segment within the spinal canal.[106,107,236,290,385,387]

Early studies revealed abnormalities of the T reflex in patients with lumbar and sacral root compression[89,321] and demonstrated clinical applications of the H reflex as a test for radiculopathy.[34,290,303,312,322] A delay or diminution of the triceps surae reflex implicates the S1 root, like a depression of the ankle stretch reflex in the neurologic examination, especially if it is unilateral.[7,68,99,108,109,187,275,324,373] Analogous to clinical testing of phasic stretch reflexes elicited by tapping the dorsal side

of the foot,[333] the H reflex recorded from the extensor digitorum longus[84] or tibialis anterior[297] after stimulation of the common peroneal nerve may show abnormalities in patients with L5 or L4,5 radiculopathy. In patients with cervical radiculopathy, abnormality of flexor carpi radialis reflex may indicate lesions of the C6 or C7 root or both.[262,263,316,317]

The recruitment curve of the soleus H reflex may reveal an increased threshold of excitation during transient conduction abnormalities as might be seen in neurogenic claudication.[98,289] Other conditions associated with depressed stretch reflex such as neuropathy and Adie's syndrome[265] also show a diminished or absent H reflex. As with the F wave, H-reflex or T-reflex latencies along the entire pathway often fail to detect a focal abnormality, which results in only a limited percentage increase of the total conduction time.[242] This stands in contrast to the utility of reflex studies in assessing diffuse or multisegmental pathology like chronic demyelinating polyneuropathy, in which a longer pathway yields a greater latency increase.[216] To circumvent this problem, H–M intervals to S1 root stimulation provide more reliable measures of conduction across a short segment within the spinal canal comprising the proximal afferents, anterior horn cells and ventral roots. In one study of 100 healthy subjects (Fig. 19–5),[385] peak latency differences between the simultaneously recorded M response and H reflex were 2.6 ± 0.7 ms (mean ± SD) with stimulation at T12 to L1, 4.2 ± 0.6 ms at L2 to L3, and 5.5 ± 0.3 ms at L4 to L5 spinal processes and 6.8 ± 0.5 ms at the S1 foramen.

Table 19–1 summarizes the normal values found in our laboratory in healthy

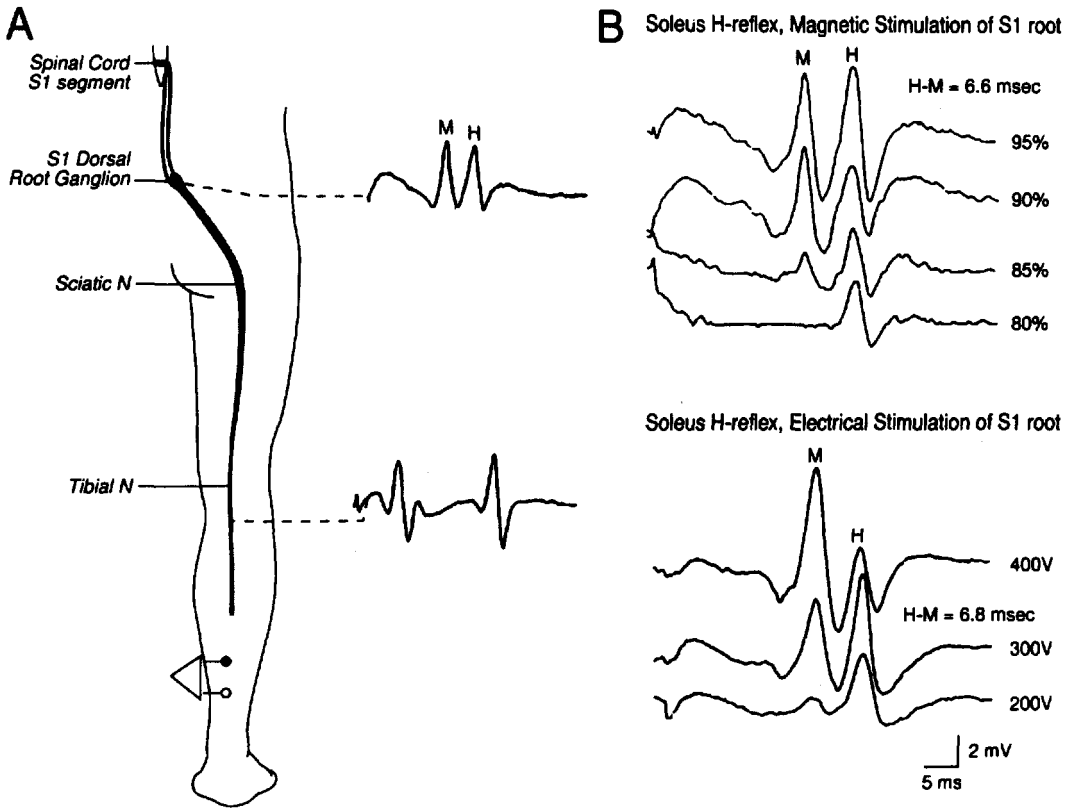


Figure 19–5. A. Schematic representation of soleus H reflexes elicited by electrical stimulation of the S1 root at the S1 foramen and of the tibial nerve at the popliteal fossa. **B.** The response complex of the H reflex and the M response elicited by magnetic stimulation (*upper traces*) and electrical stimulation (*lower traces*) of the S1 nerve root at the S1 foramen. The intensity of the nerve stimulus is shown to the right of the traces. [From Zhu, Starr, and Haldeman et al,[385]]

Table 19–1 H Reflex*

Amplitude† (mV)	Difference Between Right and Left (mV)	Latency‡ to Recording Site (ms)	Difference Between Right and Left (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.

adults. In evaluating a unilateral lesion, the latency difference between the two sides provides the most sensitive measure of the T or H reflex (Fig. 19–6).[34] Unilateral absence or a right–left latency difference greater than 2.0 ms supports the diagnosis of S1 radiculopathy in the proper clinical context but does not by itself constitute sufficient evidence of a herniated disc or of a need for laminectomy.[138] Preterm neonates have slower H reflex conduction velocity than full-term babies.[264] 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 31–34 weeks, 16.7 ± 1.5 ms for ages 35–39 weeks, and 15.9 ± 1.5 ms for 40–45 weeks.[36] These results reflect the degree of myelination in infants of increasing conceptional age, showing progressive latency diminution despite the longer reflex pathway associated with growth (see Chapter 22–5). In one study of 103 elderly subjects aged 60–80 years, the H reflex elicited in 92 percent of the population showed average latencies of 30.8 ± 2.6 ms (mean ± SD) on the right and 30.7 ± 26 ms on the left, with an upper limit of normal side-to-side difference of 1.8 ms.[112]

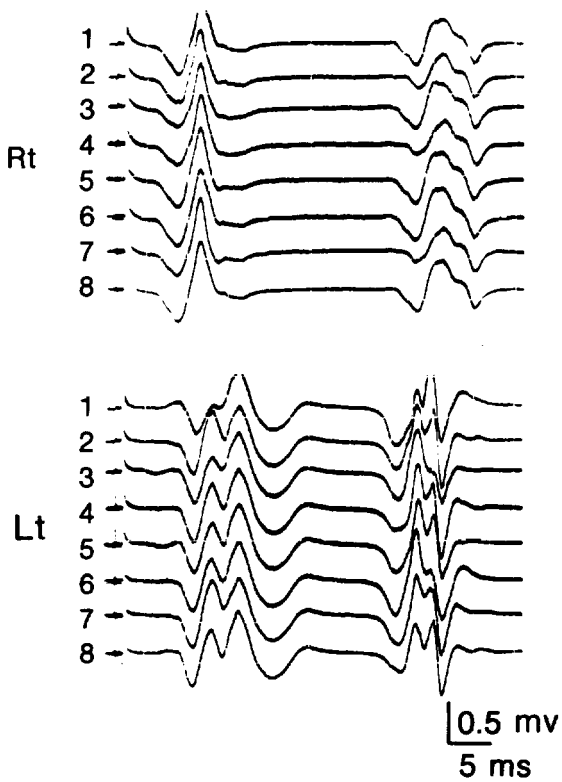


Figure 19–6. The H reflex in a 77-year-old man with cauda equina syndrome. The recording arrangement is the same as for Figure 19–2. The reflex was delayed by more than 2 ms on the right compared with the left. The central latency as determined by the latency difference between the M response and the H reflex was also considerably greater on the right than on the left side.

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.[140,167,213] Electrical stimulation of the masseter nerve elicits not only the direct motor responses[64] but also a masseteric H reflex.[66,135,136] This reflex, relayed via the mesencephalic nucleus of the trigeminal nerve, reflects conduction through the midbrain. The so-called motor root of the trigeminal nerve contains the sensory fibers of the muscle spindle that form the afferent arc of the masseter reflex and the motor axons to the extrafusal muscle fibers that form the efferent arc. The cell bodies of the proprioceptive spindle affer-

ents lie in the mesencephalic trigeminal nucleus. The collateral branches from these cells make a monosynaptic connection with the motor neurons of the trigeminal nerve located 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 T and H reflexes.[135,136] Some authors advocate the stretch reflex from the medial pterygoid as an additional electrophysiologic study for the trigeminal nerve.[166,168]

Methods and Normal Values

In eliciting the jaw reflex by a mechanical tap over the mandible, the closure of a microswitch attached to the percussion hammer triggers the oscilloscope sweep (Fig. 19–7). During repetitive testing, an increase in the weight supported by the mandible or Jendrassik's maneuver tends to facilitate the masseter reflex.[156] 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.[203] Thus, electrophysiologic evaluation depends on the side-to-side comparison of the reflex responses recorded simultaneously from the right and left masseter muscles, rather than on the absolute values.

In a study using a needle recording electrode,[282] 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. Table 19–2 summarizes normal values established in our laboratory.[203] For the pterygoid reflex, the normal values reported include a latency of 6.9 ± 0.43 ms (mean ± SD), with a side-to-side differ-

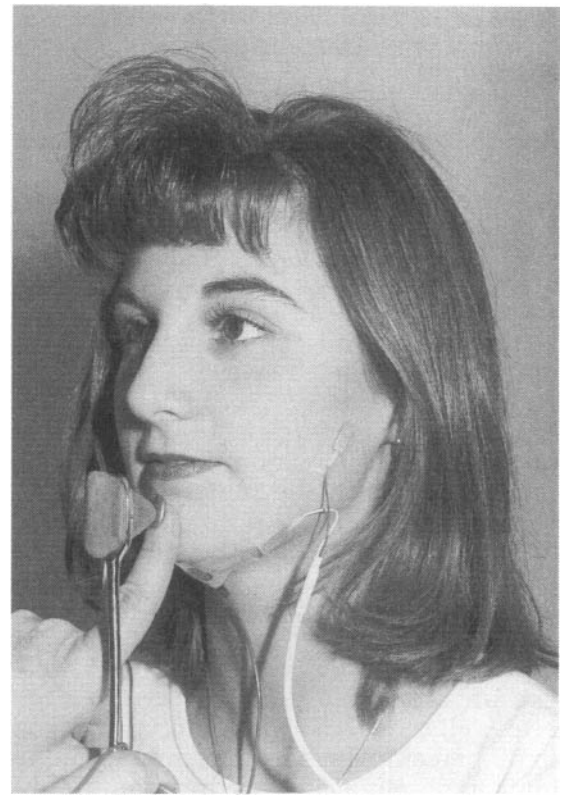


Figure 19–7. Jaw tap for simultaneous recording of mechanically induced masseter reflex from both sides with two pairs of electrodes placed over the belly of the masseter muscle (G_1) referenced to the chin (G_2). A modified reflex hammer has a built-in microswitch that triggers the oscilloscope sweep on contact.

Table 19–2 Latency and Amplitude of Masseter Reflex in 20 Normal Subjects

	Latency (ms)	Latency Difference (Large Value Minus Small Value)	Amplitude (mV)	Amplitude Ratio (Large Value Over Small Value)
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

From Kimura et al,[203] with permission.

ences of 0.29 ± 0.21 ms, in 23 healthy volunteers.[168]

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. 19–8). Nonetheless, an unequivocal unilateral delay or absence suggests a lesion of the trigeminal nerve or the brainstem.[203,313] Electromyographic study of the masseter muscle may document the presence of denervation, thus localizing the lesion within the motor pathway.[281] 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.[141,382] In another study of 51 patients with internuclear ophthalmoplegia, an abnormality limited to the masseter reflex, suggested a midbrain lesion in 59 percent whereas abnormal R_1 of the blink reflex indicated rostral pontine involvement in 35 percent.[169] In Friedreich's ataxia, which is characterized by absent or hypoactive stretch reflexes in the upper and lower limbs, the masseter reflex remains unaffected and may paradoxically show hyperactivity.[14,15,132] This discrepancy probably reflects a different location of the afferent nerve cell body, intra-axial mesencephalic nucleus, and extra-axial craniospinal ganglia. A normal masseter reflex in patients with pure sensory symptoms favors a diagnosis of ganglionopathy instead of axonal sensory neuropathy.[17]

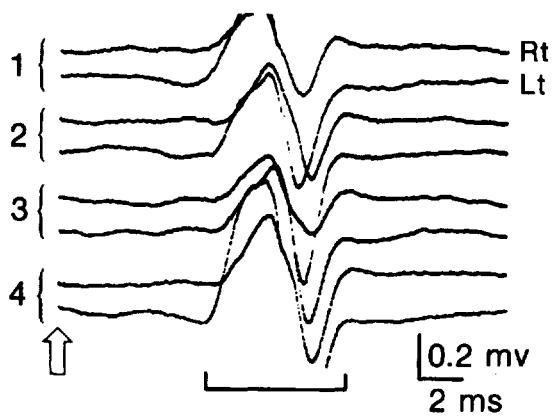


Figure 19–8. Jaw reflex recorded simultaneously from right (*top tracing of each frame*) and left (*bottom*) masseter after a mechanical tap on the chin (*open arrow*). Four trials are taken to show consistency of the response.

Masseteric Silent Period

A jaw reflex elicited during voluntary clenching gives rise to a brief pause in the electromyographic activity of the masseter muscle (Fig. 19–9). This inactivity, referred to as the masseteric silent period, lasts about 30 ms in normal subjects.[338,341] A similar masseteric silence also follows acoustic or electric stimulation of the tongue, gums, oral mucosa, or belly of the muscle.[135,136,255,325] A unilateral stimulus suppresses the muscle activity on both sides, indicating the presence of crossed and uncrossed central pathways for this inhibition.[209,279,282] The masseteric silent period simulates an analogous phenomenon seen in limb muscles after electric stimulation of the nerve (see this chapter, part 5).

In one study assessing the effects of brainstem lesions on the two phases of silence, S_1 and S_2, evoked by stimulation of the mental nerve, abnormalities tended to implicate the pontine tegmentum between the midpons and the pontomedullary junction.[280] The afferent impulses for S_1 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 S_2 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.[67]

The force and direction of the tap and the magnitude of jaw clenching substantially influence the mechanically induced silent periods. In particular, a decrease in voluntary muscle contraction results in a

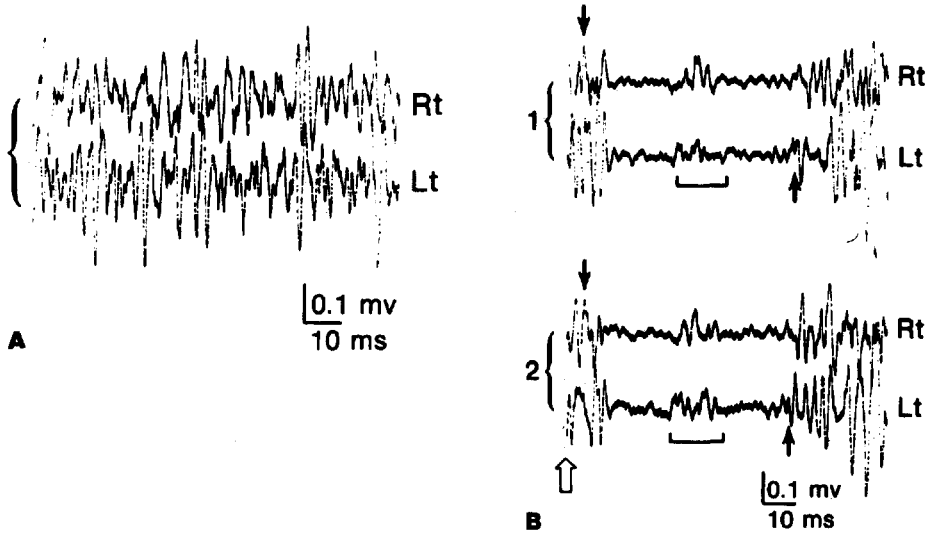


Figure 19–9. A. Voluntary contraction of the masseter. Electromyography was recorded simultaneously from right (*top tracing*) and left (*bottom*) sides using two pairs of surface electrodes placed on the belly of the muscle (G_1) and under the chin (G_2) on each side. **B.** Silent period (SP) of the masseter. The recording arrangement is the same as in **A**, but the mechanical tap was 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 volitional activity (*arrows from bottom*) approximately 80 ms after the tap.

major increase in its duration. Thus, stimulus and subject variables tend to limit its use as a clinical test of the masticatory system.[253] Some patients with tetanus lack the inhibition.[116,303,304] Conversely, its duration exceeds the normal range in patients with the temporomandibular joint syndrome.[25] Patients with Wallenberg syndrome show a variety of abnormalities in brainstem reflexes, including a masseter inhibitory reflex elicited by electrical stimulation (see Chapter 17–4).[361] The onset latency of the silent period may show a delay, reflecting proximal conduction abnormalities in a demyelinative polyneuropathy[16] and diabetic polyneuropathy.[65]

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.[38,39,93,185] This tonic vibration reflex in many respects simulates a tonic stretch reflex,[135–137,151,267] although skin mechanoreceptors may also contribute.[1,103] Hence, the vibration provides a means of testing motor neuron reaction to tonic, rather than phasic, stimuli.[86,160,217,362] Studies of the tonic reflex consist of stimulating the tendon with a small vibrator that oscillates at 150 Hz with an approximate amplitude of 0.5–1.5 mm and recording muscle responses with surface electrodes placed over the belly (G_1) and tendon (G_2). Intervals of at least 10 seconds should separate the stimuli to avoid cumulative depression of the reflex activities evoked segmentally.

Normal and Abnormal Responses

The motor effects of tonic vibration include (*1*) active and sustained muscle contraction,[4,149,217] (*2*) reciprocal inhibition of motor neurons innervating antagonistic muscles,[148] and (*3*) suppression of the T and H reflexes (Fig. 19–10).[78,206] Its generation involves more than a simple, spinal neural

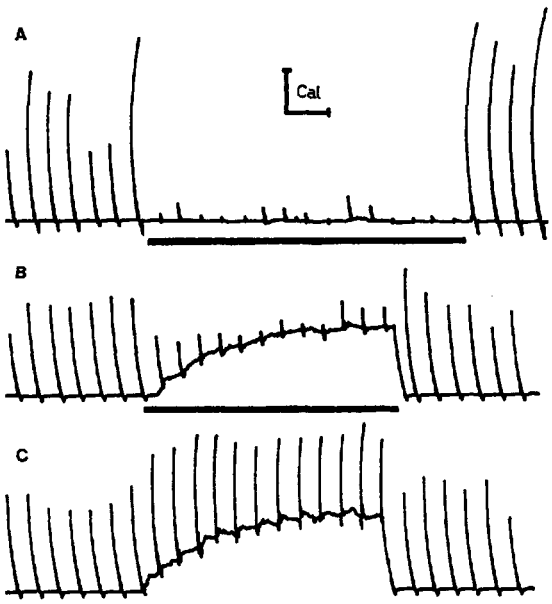


Figure 19–10. Effects of continuous muscle vibration in a normal subject showing suppression of phasic stretch reflexes with or without the generation of the tonic vibration reflex (TVR). **A.** Vibration of the quadriceps while knee reflexes are elicited every 5 s. Knee reflexes are depressed during the period of vibration (*black bar*) even without the development of tonic contraction, probably because of the spread of the vibration wave to flexor muscles. **B.** Suppression of knee reflexes accompanying a tonic contraction induced by vibration. **C.** Voluntary contraction of quadriceps in the same subject as in **B**, without suppression of knee reflexes. Calibration: Vertical 0.4 kg for **A**, 0.6 kg for **B** and **C**; horizontal, 10 s. [From De Gail et al,[75] with permission.]

arc.[159] 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 midcolliculus, (*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.[10,40]

Patients with a variety of motor disorders develop abnormalities of the tonic vibration reflex.[27,92,191,217,332] These changes include (*1*) absence or diminution of the response, (*2*) loss of voluntary control over the reflex, (*3*) more abrupt development and termination of the response than in normal persons, (*4*) loss or diminution in concomitant suppression of the T and H reflexes, (*5*) side-to-side asymmetries in corresponding muscles of the two limbs, and (*6*) imbalances in two antagonistic muscles within the same limb. The tonic vibration reflex has also helped in assessment of reciprocal inhibition,[52,54] presynaptic inhibition, an inhibitory effect of acupuncture on the motor neurons,[165] central control of voluntary movements,[118,189,308] spasticity,[51] ischemia,[51] and Parkinson's disease.[53,248]

Clinical Applications

Clinical applications include early detection of incipient weakness, subclinical rigidity, spasticity, and involuntary movements such as tremors, clonus, and choreoathetosis and dystonia.[149,189,217] The tonic vibration reflex varies from patient to patient, depending on the site of spinal cord lesions. Thus, the predictable pattern of abnormality, if clearly elucidated, would help localize the responsible lesion.[26–28]

A large number of papers have appeared describing the effect of tonic vibration on spasticity or rigidity.[149,164,217] 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.[26,27] Unfortunately, these positive effects last only for the duration of the vibration, which in practice cannot exceed a few minutes because of frictional generation of heat. Nonetheless, the technique holds promise as a diagnostic test for patients with spinal cord injuries and dystonia.

5 THE SILENT PERIOD, LONG-LATENCY REFLEX, AND CORTICAL RESPONSE

Silent Period

Despite continued effort, action potentials of a voluntarily contracting muscle undergo a transient suppression following electric stimulation of the mixed nerve in-

nervating that muscle[162] or a cutaneous sensory nerve.[44] This period of electrical inactivity, designated either the *mixed nerve* or *cutaneous silent period*, results from several physiologic mechanisms.[102,325] A number of investigators have studied it after stimulation of the nerve electrically[104,325,357] or unloading of the muscle spindles mechanically[337] in normal subjects[252] and in patients with neurologic disorders.[18,30,193,218,220] Transcranial magnetic stimulation during sustained voluntary muscle contraction also results in the silent period (see Chapter 21–3).[48,72,124,125,180,214,251,277,351,358]

Physiologic Mechanisms

The initial segment of muscle inactivity immediately after the M response results from collision in motor axons. Later phases reflect recurrent inhibition,[201,301] unloading of muscle spindles,[144] and activation of inhibitory group IB and cutaneous afferents.[221,325] Although recurrent inhibition[301] follows the passage of an impulse along the motor axon to either direction,[293] antidromic activities produce more effective suppression.[212,311]

Even with supramaximal stimulation, not all antidromic impulses reach the central motor neuron pool, because during muscle contraction they collide with voluntary orthodromic impulses in some motor fibers. Greater effort increases the chance of collision, because more axons carry orthodromic impulses.[199,200] Stimulation of the nerve distally also enhances this probability, which increases in proportion to the length of the nerve segment between the stimulus site and the cell body (Fig. 19–11). 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 motor neurons (Fig. 19–12). In addition to the Renshaw effect, other mechanisms such as the unloading of the muscle spindle[11,186,257] and activation of the Golgi tendon organ[143] contribute to the muscle inactivity.[325] Ascending cutaneous volleys also have an inhibitory effect, although a well-defined suppression on this basis results only from a high intensity volley.[210]

Sensory nerve stimulation could generate a reproducible inhibition, presumably through either group IB afferent fibers from tendon organs or through ascending

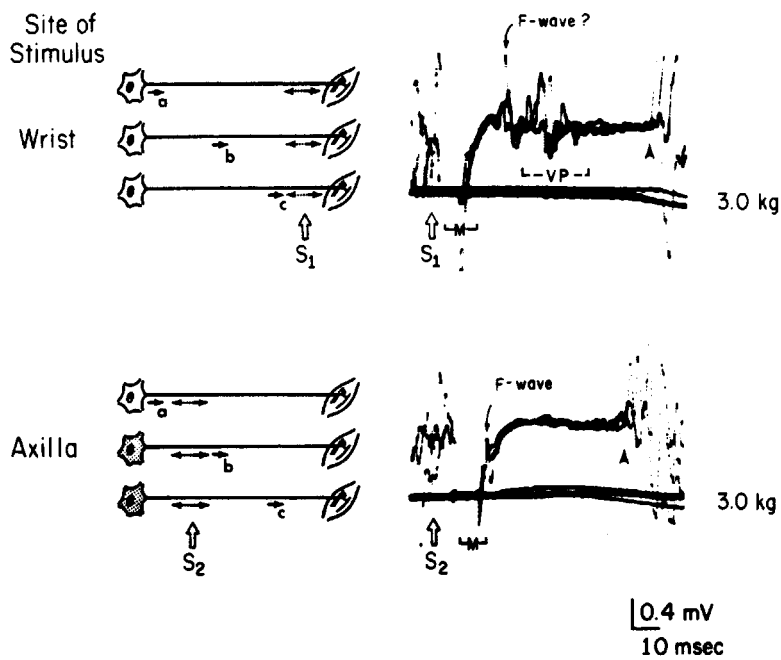
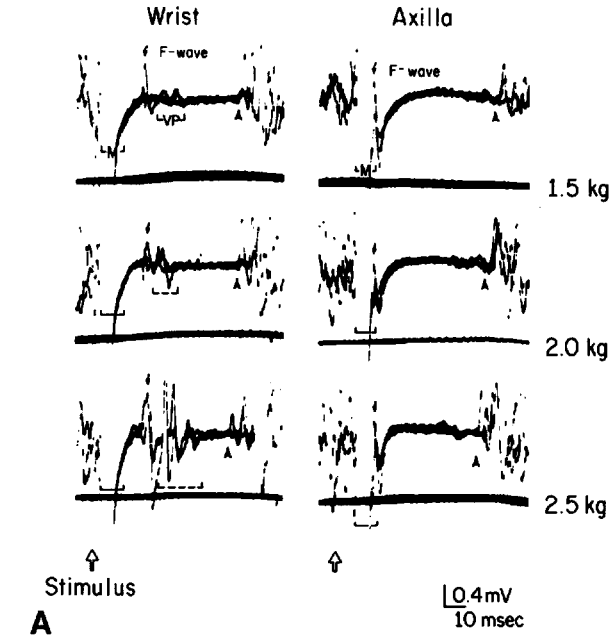


Figure 19–11. Simultaneous recording of muscle force of 3.0 kg (*straight line*) and the silent period (SP) from the voluntarily contracting first dorsal interosseous muscle (three trials superimposed). The SP was broken by the voluntary potential (VP) with a stimulus at the wrist but not with a stimulus at the axilla, indicating greater inhibition of motor neurons with proximal than distal nerve stimulation. With distal stimulation, most antidromic activity is extinguished by collision with voluntary impulses, *a*, *b*, and *c*, before reaching the motor neuron pool. With proximal stimulation, antidromic activity, escaping collision, presumably invades recurrent axon collaterals and inhibits the motor neurons (*shaded area*). [From Kimura,[201] with permission.]



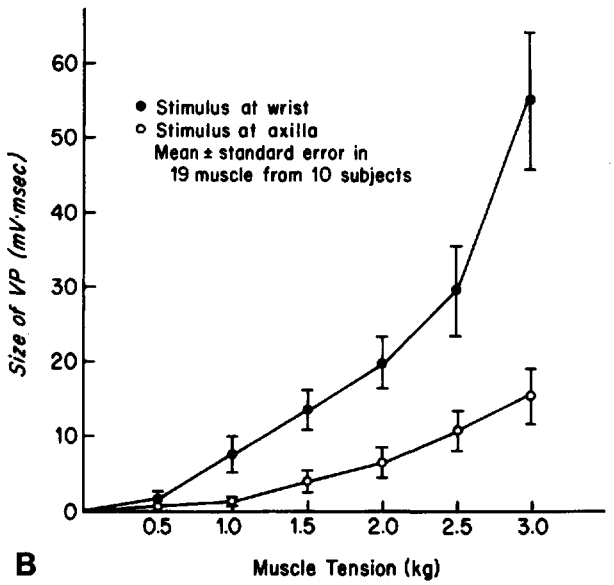


Figure 19–12. A. Stimulation and recording as in Figure 19–11 at muscle tensions ranging from 1.5 to 2.5 kg. With stimulation at the wrist, the voluntary potential (VP) became progressively greater in size at increasingly higher muscle forces. With stimulation at the axilla, no VP was recorded at any level of muscle force, but the duration of the silent period (SP) was shortened as the muscle force was increased. [From Kimura,[201] with permission.] **B.** Muscle tension and the size of the VP breaking through the SP. For muscle forces of 1.0 kg and above, the VP was significantly larger with stimulus at the wrist than at the axilla, indicating that motor neurons were more inhibited by proximal as opposed to distal nerve stimulation during voluntary muscle contraction. The difference in inhibitory effects of proximal versus distal stimulation became progressively larger as the muscle force was increased. [From Kimura,[201] with permission.]

reflex pathways.[142,170,181,224,226,326,357] When this is the case, proximal stimulation, which activates a greater number of afferent fibers, would inhibit the motor neurons more effectively. In contrast, the silent period may abate in cases of syringomyelia, which may interrupt the pathway through the posterior horn.[193] The physiologic mechanisms generating a cutaneous silent period remain elusive.[60,177,233,274] In one study, the F wave elicited during the cutaneous silent period showed normal or even increased excitability, in conjunction with a diminished H reflex compared with the control values.[222,227] These findings suggest presynaptic inhibition of group IA afferents, reducing the H reflex, and of descending corticospinal fibers, inducing the silent period, in the face of normally

excitable motor neurons. This interpretation may not necessarily hold, however,[241] if the discrepancy between the two responses simply results from a greater sensitivity of the H reflex than of the F wave as a measure of motor neuron excitability (see this chapter, part 2).[61,178]

Potentials That Break Through the Silent Period

Increasing voluntary muscle contraction can interrupt the silent period, which therefore must represent a relative, rather than an absolute, suppression. Two separate potentials, V_1 and V_2, appear.[359] At high levels of muscle contraction, where the antidromic activity collides with voluntary impulses in most axons, the first potential mainly comprises the H reflex.[250,335] At low levels of muscle contraction, based on few voluntary impulses, the first potential primarily represents the F wave, because substantial antidromic activity reaches the central motor neuron pool.[200] The second potential, V_2, also designated the *voluntary potential, long-latency reflex, long-loop response*, or *cortical (C) response*, interrupts the silence at approximately twice the latency of V_1. Despite presumed hypoexcitability of motor neurons, transcranial magnetic stimulation elicits large motor evoked potentials between the V_1 and V_2.[351,384] This intuitively paradoxical finding may result from activation of muscle afferents by mixed nerve stimulation, which increases cortical motor excitability.[69,87,208,237,243]

The middle portion of the silent period results at least in part from antidromic invasion of the Renshaw loop. Thus, the V_2 tends to occur with any maneuver that reduces the recurrent inhibition by axonal volleys arriving at the motor neuron pool.[201] For example, weaker stimuli, which activate fewer motor axons, favor the appearance of V_2.[325] Descending volitional inputs play an important role in the generation of V_2, normally seen only during tonic contraction of the muscle.[200] A similar activity can also be elicited at rest in patients with posthypoxic cortical myoclonus[383] and several other types of myoclonus,[197,327,328] presumably in response to segmental polysynaptic inputs to motor neurons.[359] Alternatively, some investigators equate V_2 with the transcortical reflex activity, or C response, elicited by brief stretching of arm muscles.[77,110,244,331]

In contrast to total or partial suppression of V_2 in hemiparetic patients and during cognitive tasks in normal subjects, repetitive trains of stimuli have a strong facilitatory effect.[59] In Huntington's disease, displacement of the index finger or electrical stimulation of the median nerve elicits V_1 but not V_2.[276] In parkinsonism, the median latency of V_2 in the stretched triceps surae muscle is increased.[320]

If V_1 occurs segmentally and V_2 cortically, the latency difference between them provides a measure of the central conduction along the spinal cord to and from the reflex center of V_2. The comparison between the arm and leg allows calculation of mean spinal conduction time between the seventh cervical and fifth lumbar spinous processes, as follows.[100] A large variability precludes its use as a diagnostic test, but this measure may serve as an estimate of the mean conduction characteristics in a group of subjects.

Spinal cord conduction time

$$= (V_2 - V_1)\text{leg}/2 - (V_2 - V_1)\text{arm}/2$$

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 M_1 and M_2, in the stretched triceps surae muscle and a long-latency response in its antagonist, the tibialis anterior muscle.[29,30,171,314] Stretch of the biceps brachii[114] and the quadriceps femoris[24] also produces M_1 and M_2 responses with a good intraindividual reproducibility. Of these, M_1 is transmitted segmentally by way of a spinal pathway, whereas the origin of M_2 remains to be determined.[47,73] Some authors have referred to M_2 as the "long-loop" reflex via transcortical pathways.[139,219,245,343] In agreement with this view, patients with multiple sclerosis, spinal tumor, or cervical stenosis may have a delayed long-loop reflex, a finding that implies the presence of a supraspinal pathway.[3,90,91,123] The long-latency reflex component also shows a

close relationship with the motor preparation and programming.[204]

Despite the prevailing view that M_2 travels via a cerebral pathway, some studies have provided contradictory findings. For example, these discharges may persist after spinal cord transection in cats and monkeys,[133,350] which suggests a segmental origin. Sudden stretching of the human wrist, eliciting long-loop stretch reflexes, accompanies a series of spindle discharges.[150] Repetitive segmental reflexes may result from these group IA afferent bursts, giving rise to a latency comparable with the transcortical pathways. In a patient with mirror movements, stretch reflexes of the hand, but not the arm, gave rise to contralateral M_2 responses, indicating the absence of transcortical mechanisms for the long-latency response in the proximal muscle.[115] The same physiologic mechanisms may underlie the late response elicited by cutaneous stimulation and long-loop reflex induced by stretching of the spindle.[22,35,295] Both may represent activity at the segmental level modulated by descending impulses from the higher center, such as the cerebellum.[122]

6 OTHER REFLEXES

The flexor reflex elicited by stimulation of the peripheral nerve consists of two or more components usually demonstrating excitation–inhibition cycles.[88,118,256,260,306] Analogous to the clinical Babinski sign, stroking the plantar surface with a blunt probe elicits a flexor reflex recordable from the extensor digitorum longus and the extensor hallucis longus with a latency ranging from 160 to 500 ms, depending on the intensity and speed of the mechanical stimulation.[307] Electrical stimulation of the sole of the foot[9] or of the fingers[119,134,326] elicits cutaneous withdrawal reflexes approximately coinciding with a silent period in active muscles. In standing humans, nociceptive stimulation induces a spinal reflex pattern without disturbing the support function of the limb.[12,74,309,336] In patients with spinal cord injuries, transcutaneous electrical stimulation of the sural nerve tends to suppress the flexor reflex.[145] Flexor reflex recordings may provide a useful measure for quantifying the benefit of antispastic therapy such as intrathecal baclofen.[288] Similar to the eye blink conditioning paradigm, the human flexion reflex can serve as a model in classical conditioning experiments.[207,292,349]

Analogous to flexor reflexes in the limb muscles, stimulation of perianal skin elicits a two-component response in the external anal sphincter.[291,339] Stimulation of penis or clitoris also evokes reflex responses with a typical latency of 33 ms in the external anal and urethral sphincters.[370] Similarly, stimulation of the dorsal genital nerve elicits reflex activation of the external anal sphincter with a latency of 38.5 ± 5.8 ms (mean ± SD). Patients with fecal incontinence may have absence or delay of this pudendoanal reflex.[363] With the active electrode (G_1) over the bulbocavernosus muscle beneath the scrotum and the reference electrode (G_2) 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 onset latency of 35.9 ± 9.0 ms.[153] Unilateral stimulation of the genital nerve also elicits two-component bulbocavernosus reflexes, R_1 and R_2, bilaterally via crossed and uncrossed spinal cord pathways.[299]

These techniques may prove useful in the evaluation of diabetic neuropathy,[127] impotence secondary to peripheral nerve involvement,[254] spinal cord injury, and neurogenic bladder.[194] The bulbocavernosus reflex may provide a more sensitive measure of the sacral nervous system than conventional or single fiber electromyography of external urethral and anal sphincters.[367–369] The voluntary act of micturition suppresses this reflex in normal persons, but not in patients with upper motor neuron lesions or voiding dysfunction.[323] Nerve conduction studies of the dorsal nerve of the penis and pudendal somatosensory evoked potentials complement the measurement of the reflex latency in diagnostic evaluation of bowel, bladder, and sexual function (see Fig. 20–20A).[192,380]

The auditory postauricular reflex gen-

erated in the posterior auricular muscle has two prominent components at latencies of 12 and 16 ms.[155] Voluntary contraction of the neck extensor or facial muscles enhances the response. A markedly enlarged reflex may help differentiate an upper motor neuron lesion in clinically equivocal cases. Click stimulation evokes a short-latency myogenic potential of vestibular origin in the neck muscles.[56-58] Click intensity and prestimulus tonic contraction of the sternocleidomastoid muscle jointly determine the amplitude of the vestibular click-evoked myogenic potential.[231] The corneomandibular reflex, not seen in healthy subjects, may appear with lesions involving the precentrobulbar tract.[278] Electromyographic studies help differentiate this reflex from clinically similar corneomental reflexes. The abdominal reflex, elicited bilaterally in patients with upper motor neuron lesions, shows an average latency ranging from 16.5 to 25 ms, with side-to-side variation not exceeding 3 ms.[345]

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Chapter 20

THE SOMATOSENSORY EVOKED POTENTIAL

1 INTRODUCTION

Conventional sensory nerve conduction techniques, primarily used in evaluating the more distal portions of the peripheral nerve, seldom contribute to the study of the less accessible proximal segments. In contrast, studies of somatosensory evoked potentials (SEPs) assess the entire length of the afferent pathways. Early work with SEPs emphasized changes in the amplitude and waveform of recorded potentials in diseases affecting the cerebrum or spinal cord. Other studies have focused on the evaluation of central neural conduction determined by the latencies of the SEPs recorded over the spine or scalp.

This chapter reviews recording techniques and neural sources of spinal-recorded and scalp-recorded SEPs and discusses their practical value and limitations in the diagnosis of certain disorders of the nervous system. Published studies have dealt mainly with the median or tibial nerves, 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 SEPs.[98,129,186,409,466] The common sites of stimulation include the median or ulnar nerve at the wrist, the tibial nerve at the ankle, and the peroneal nerve at the knee. A shock with intensity adjusted to cause a small twitch of the innervated muscle suffices to activate all the large myelinated, more easily excitable sensory fibers. 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. Subcutaneous shocks administered with a needle electrode inserted close to the nerve, require considerably less current.

The optimal frequency and number of stimuli vary a great deal, depending on the components under study.[195,265,285,332] Small spinal potentials and scalp-recorded short-latency SEPs need up to 4000 stimuli to achieve an adequate resolution. Most subjects tolerate the rate of stimulation exceeding 4 Hz poorly. Medium-latency and long-latency components in the range of 20–200 ms intervals require only 200–400 stimuli delivered randomly at lower rates of 1–2 Hz. With shocks given every 30 s or less, the initial stimuli of a train may give rise to a disproportionately larger response, presumably because of habituation.

Unilateral stimulation elicits short-latency components symmetrically over both hemispheres. Long-latency responses show obvious asymmetry with major contralateral components, which can vary considerably from one trial to the next.[472] 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.[473]

Recording

Somatosensory evoked potential components show no significant difference in amplitude or latency whether recorded by surface disc or subdermal needle.[118,121] The analysis of the SEP topography depends on multichannel recordings from 16 to 32 scalp areas. For clinical testing, two to four well-selected channels covering optimal recording sites suffice. The 10–20 International Electrode Placement system (Fig. 20–1A) designates the scalp positions according to their specific anatomic locations. It derives its name from spacing the electrodes 10–20 percent 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

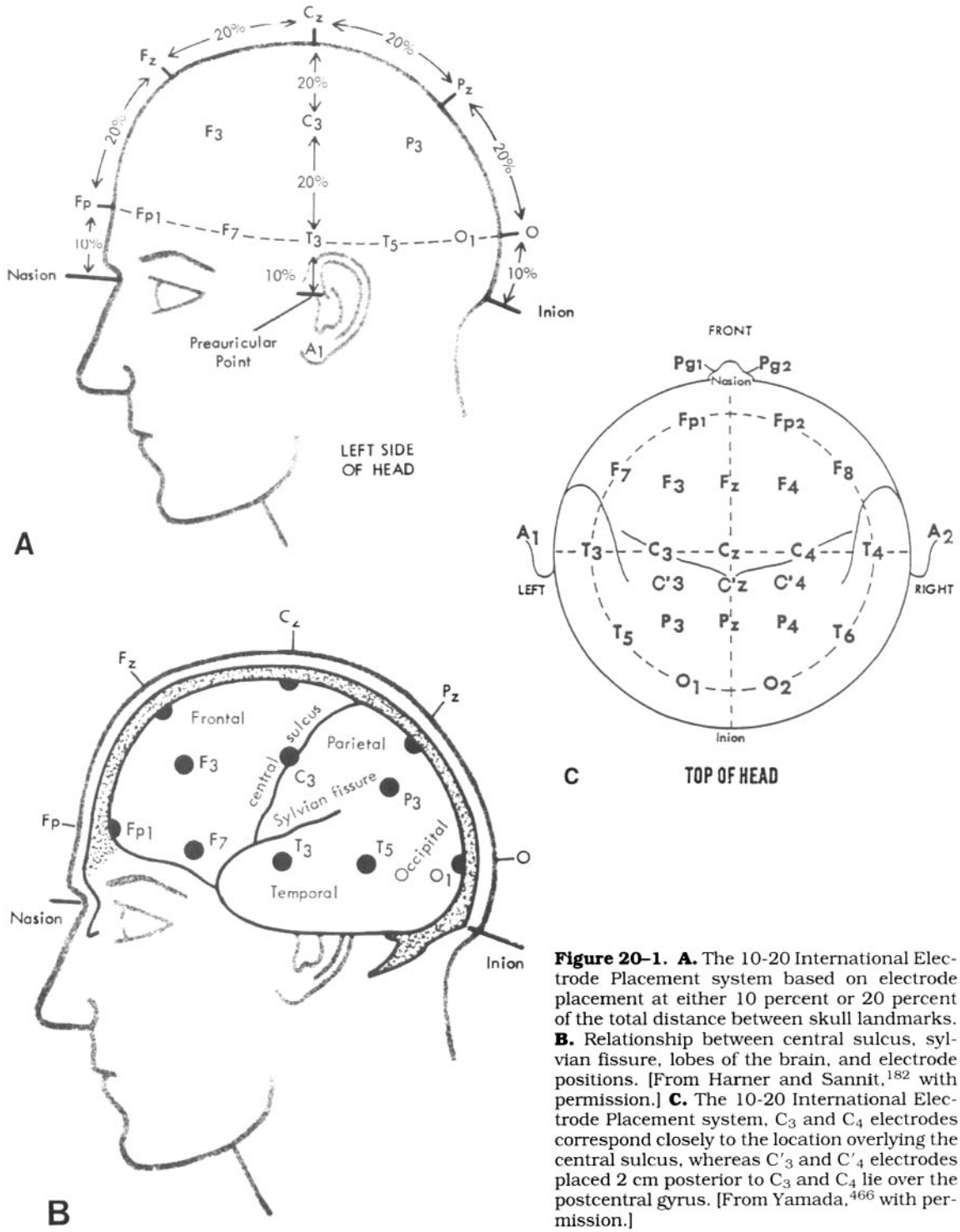


Figure 20–1. A. The 10-20 International Electrode Placement system based on electrode placement at either 10 percent or 20 percent of the total distance between skull landmarks. **B.** Relationship between central sulcus, sylvian fissure, lobes of the brain, and electrode positions. [From Harner and Sannit,[182] with permission.] **C.** The 10-20 International Electrode Placement system, C_3 and C_4 electrodes correspond closely to the location overlying the central sulcus, whereas C'_3 and C'_4 electrodes placed 2 cm posterior to C_3 and C_4 lie over the postcentral gyrus. [From Yamada,[466] with permission.]

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 C_3 electrode, for instance, lies within 1 cm of the central sulcus (Fig. 20–1B).

Optimal scalp electrodes (G_1) include P_3, P_4, C_3, or C_4 contralateral to the side of stimulus for median or ulnar SEPs and C_1, C_2, or C_z for peroneal or tibial SEPs. A common reference electrode (G_2) usually lies at F_z, the chin, or connecting the ears, A_1 and A_2. Far-field potentials (FFPs) typically affect all scalp points nearly equally. Thus, they tend to cancel if they are recorded between two cephalic leads. In contrast, a knee or other noncephalic reference provides good resolution in median or tibial SEPs.[474] Although the greater separation between G_1 and G_2 generally results in larger amplitude of the recorded response, background noises also amplify, thereby obscuring the signal. The size and shape of evoked potentials depend not only on the potential at G_1 but also on the activity of G_2. Superfluous peaks generated by an "active" G_2 may confuse SEP analyses, especially in assessing short-latency peaks. The activity of G_2, if opposite in polarity to G_1, helps enhance the signal under study. For example, short-latency median SEPs amplify substantially if registered with G_1 placed on the neck and G_2 connecting the ears. Here the recorded response represents summation of the negative field registered by G_1 and the concomitant positive potentials from the same source detected at G_2.

Most healthy subjects have recordable cervical potentials and short-latency scalp peaks after stimulation of the median or ulnar nerve at the wrist. Stimulation of lower limbs gives rise to less consistent cervical and short-latency scalp SEPs. Electrodes placed on the lumbosacral spinous process regularly register spinal potentials after unilateral or bilateral stimulation of the peroneal or tibial nerve.[75,345,462] In one study, the decreases in muscle artifact provided by diazepam improved recording of lumbar and neck SEPs.[342] The amplitude of evoked spinal potentials increases substantially if recorded with G_1 inserted in the subdural[140] or epidural space,[389] although surface recordings provide a more practical means for clinical use.

Averaging Procedure

Single-sweep SEPs may emerge from ongoing electroencephalography (EEG) either by filtering techniques[321] or by pharmacologic suppression of background activity with general anesthesia.[203,204] 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 cutoff 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.[287] A computer will then process the amplified potential, converting an analog signal into a digital one, for on-line measurement or for later off-line analysis of the stored data. In general, an adequate analysis will require 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 100–500 μs or 10–20 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 (500–1000 times/s).

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 a duration of 1 second at a 5 kHz cutoff, therefore, requires 10 K of memory, whereas only 5 K of memory would suffice for a shorter analysis time of 500 ms.

To exclude electrocardiogram (ECG) ar-

tifacts, 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. In our laboratory, the edit program at a sampling rate of 100–500 μs/address rejects any trials with five successive equipotential points, which usually indicates an overloaded response or mistrigger. A more 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 G_1 and G_2, 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.

The amplitude resolution of the computer system determines the degree of accuracy in analyzing small neural responses. 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. Other computer manipulations for optimal recording of unstable or rapidly changing evoked potentials include real-time reconstruction using a two-dimensional filter method that stacks successive responses for easy tracking[381] and weighted averaging to maximize the signal-to-noise ratio.[82]

3 FIELD THEORY

Near-Field Potential versus Far-Field Potential

The near field relates to the propagating action potentials recorded as the impulse passes under the pick-up electrodes, and the far field, a stationary potential generated by the signal away from the recording site (see Chapter 2–4). A referential montage preferentially detects the far-field activity, although it may also register the near field if the impulse passes near the active (G_1) or indifferent (G_2) electrode. Far-field recording has gained popularity in the study of evoked potentials for detection of a voltage source generated at a distance.[48,71,93,113,126,137,252,284,410] This section will review the current concept of far-field potentials (FFPs) as it pertains to recordings through a volume conductor (see Chapter 2–4).

Earlier studies suggested that synaptic discharges from the brainstem might account for short-latency auditory evoked potentials. This assumption led to the common belief that stationary peaks of cerebral evoked potentials generally originated from fixed neural generators, such as those that occur at relay nuclei. The initial positive peak of the scalp-recorded median (P_9) and tibial (P_{17}) SEP, however, occur before the propagating sensory nerve action potentials reach the second-order neurons in the dorsal column.[74,115,188,215,254,281,284,303,322,474] These peaks, therefore, must result from axonal volleys of the first-order afferents.[251,254] Why, then, does the far-field activity from a moving source appear as a nonpropagating potential at certain fixed points in time? This section reviews the accumulating evidence that volume conductors play an essential role in the generation of FFPs.

Animal and Human Studies of Peripheral Nerve Volleys

A series of important animal experiments[316] revealed interesting observations of the bullfrog's action potentials, recorded by fluid electrodes, that is, Ringer's solution containing a nerve immersed through

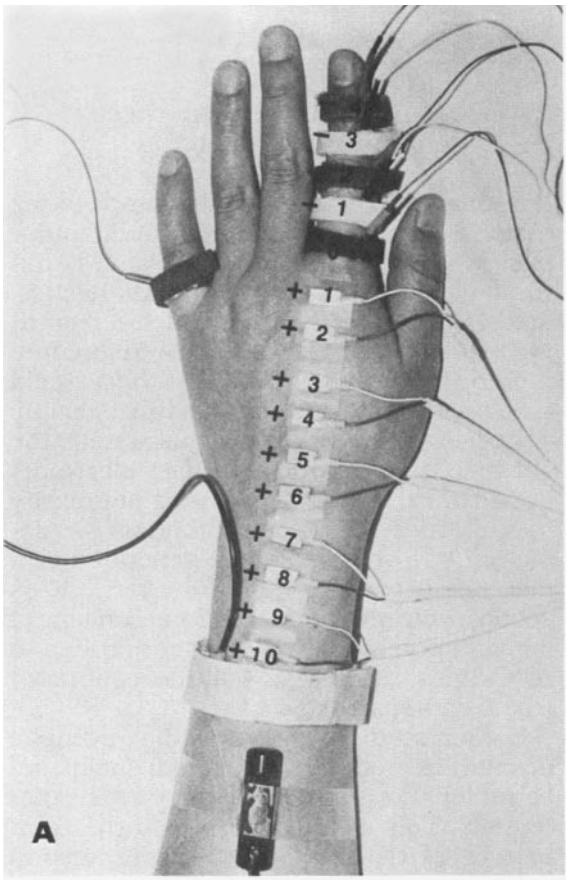
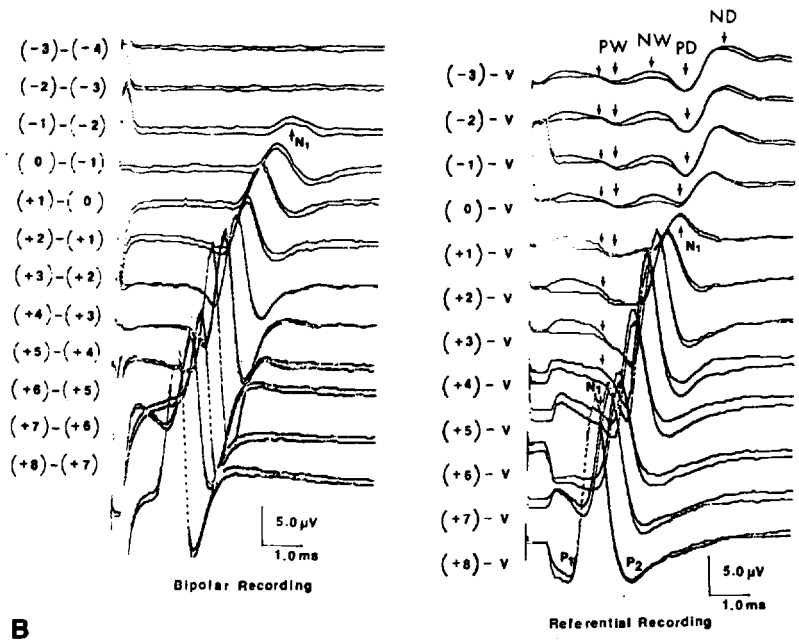


Figure 20–2. A. Stimulation of the radial nerve 10 cm proximal to the styloid process of the radius and serial recording of antidromic sensory potentials in 1.5 cm increments along the length of the radial nerve. The "0" level at the base of the second digit indicates the site where the volume conductor changes abruptly. In most hands, "+6" lies near the distal crease of the wrist, where another geometric transition takes place. The ring electrode around the fifth digit served as an indifferent lead for referential recordings. **B.** Sensory nerve potentials across the hand and along the second digit 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 (cf. **A**). In a bipolar recording using adjacent points as G_1 and G_2 (*left*), the initial negative peaks, NI (*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 fifth digit (V) as G_2 (*right*), biphasic peaks, P_W–N_W and P_D–N_D (*larger 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 (*smaller arrows pointing down*), whereas P_D first appeared at the base of the digit. [From Kimura, Mitsudome, Yamada et al,[250] with permission.]



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[315] 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.[247,249,250,475] In referential recording of the antidromic median sensory potentials along the third digit, for example, a stationary positive peak developed coincident with the entry of the propagating sensory potential into the palm–digit junction.[249] The same far-field activity may precede the M response as a premotor potential, depending on the electrode placement used for motor conduction studies.[116,336] In referential recording of antidromic radial sensory potentials (Fig. 20–2A), the digital electrodes detected two stationary FFPs, PI–NI and PII–NII.[247,250] 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. 20–2B). 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. 20–3).[247]

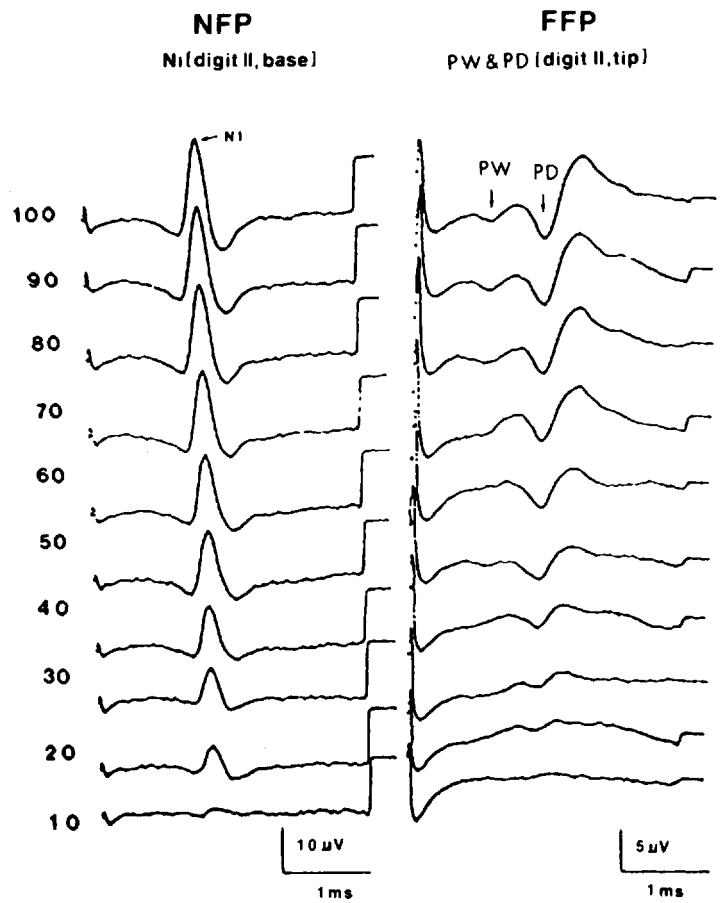


Figure 20–3. The far-field potential (FFP) recorded referentially with G_1 at the tip of the second digit and G_2 at the fifth digit, and near-field potential (NFP) registered bipolarly with G_2 at the base of the digit and G_1 1 cm proximally, after stimulation of the radial nerve. With reduction of 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 (N_1). [From Kimura, Kimura, Ishida et al,[247] with permission.]

The traditional concept of far-field activity implied that it is a monophasic positivity reflecting the approaching wavefront of depolarization.[207,277,463] 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.[111,115,188,189,247,250] On theoretical grounds, the direction of the traveling impulse in relation to the size of the volume being left and entered may determine the polarity of the FFP. A computer model[411] predicts that the volume entered becomes initially positive compared with the volume departed, regardless of the relative size of the adjoining conductors. In the case of a boundary constriction, a consensus has emerged that points on the far side begin to go positive when the generator approaches the boundary (Fig. 20–4).[79] Other major determining factors include the direction of axonal volleys as documented in the analysis of the median SEP.[95,234]

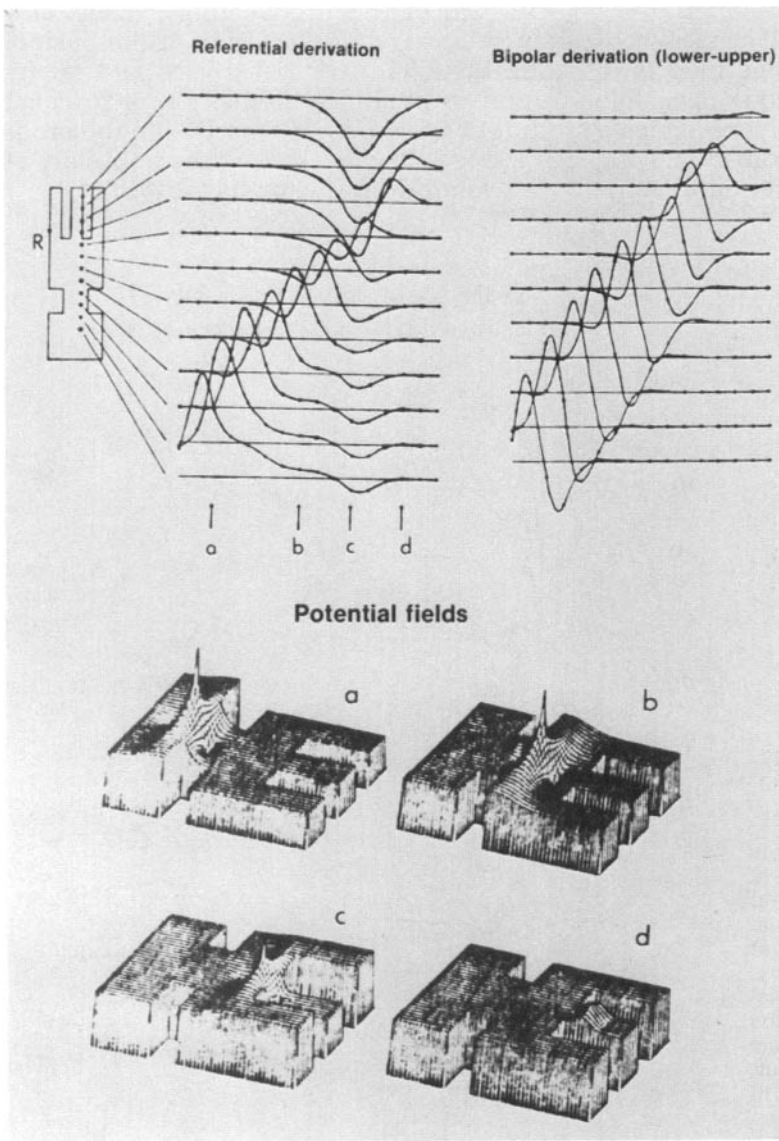


Figure 20–4. Representation of antidromic sensory action potentials propagating through a 3-"fingered" "hand" with independent attenuation of sources and sinks on propagation through the hand, such that the initial source reaches zero amplitude first. The examples include calculated potential fields (*left*), and referential (*middle*) and bipolar (*right*) waveforms of potential at 12 recording sites against generator position. By 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 is of negative polarity relative to the reference on the lateral digit, as in the actual recordings (cf. Fig. 20–2B). [From Cunningham, Halliday and Jones,[79] with permission.]

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 based on the geometric contour of the volume conductor entered.[28,206,249,250] Thus, FFPs may also originate in muscle tissue at the proximal and distal muscle tendinous junctions.[114,121] Studies using various models such as cylindrical and rectangular volume conductors have contributed in elucidating the sources of stationary potentials.[117] The waveforms recorded by surface electrodes in our model bear a great resemblance to those registered by fluid electrodes in an in vitro experiment.[314–316] 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. To draw an analogy, an oncoming train (axonal volley) becomes simultaneously visible (far field) to all bystanders at a distance (series of recording electrodes) 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.[247] The designation *junctional* or *boundary* potential specifies the source of the voltage step by location and differentiates this type of FFP from those originating in fixed neural generators. A pair of electrodes positioned only a short distance apart provides the best means of detecting such a stationary potential as long as they are placed across the partition in question.[246,403] This observation calls for reassessment of the commonly used dichotomy, equating a bipolar and referential montage with the near-field and far-field recording.

Clinical Implications

Despite common belief to the contrary, the complex waveform of short-latency SEPs reflects primarily the physical relationships between the nerve and the surrounding conducting medium. The animal and human data provide strong, albeit indirect, support for the contention 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, P_9 and P_{17} of the median and tibial SEPs arise when the propagating volleys enter the shoulder and pelvic girdles.[249,250] Similarly, the second positive peaks, P_{11} and P_{24} of the median and tibial SEPs reflect, at least in part, changes in geometry as the impulses reach the cervical cord and the conus medullaris. The latencies of these early components support this view.[133,148] A change in the position of the shoulder girdle slightly but significantly alters its latency and waveform.[95,187]

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 necessarily from the sensory pathways per se. Clinical studies of cerebral evoked potentials exploit far-field recording in the evaluation of subcortical pathways not otherwise accessible. In these instances, junctional potentials may render clinically useful information about the arrival of the impulse at a given anatomic landmark forming a partition of the volume conductor. This type of recording also provides an indirect measure of neural activities responsible for sensory transmission, which is linearly related to the amplitude of the stationary peak.[247]

4 NEURAL SOURCES OF VARIOUS PEAKS

Nomenclature

Considerable confusion exists in the analysis of SEPs because various authors use different nomenclature for the same waveforms (American EEG Society AEEGS Guidelines on evoked potentials).[8,199] Some describe the components by loca-

tion and sequence, that is, 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, that is, cervical N_{13} or scalp-recorded P_{14}, N_{17}, P_{20}, and N_{29}. 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.[59,302] Ideally, the names of the various components should indicate the respective neural sources, but the exact generator sites of most peaks are still unclear.

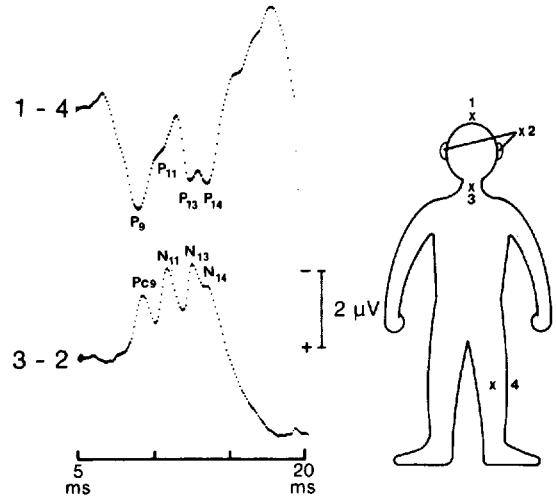


Figure 20–5. Simultaneous recording from C_z (1) referenced to knee (4) and low cervical electrode (3) referenced to ear (2) after stimulation of the median nerve at the wrist in a normal subject. Four positive peaks, P_9, P_{11}, P_{13}, and P_{14} recorded at C_z were nearly identical in latency to four negative peaks, N_9 (P_{C9}), N_{11}, N_{13}, and N_{14} recorded at the low cervical electrode [cf. Figs. 20–6 and 20–7]. [From Yamada, Kimura, and Nitz,[471] with permission.]

Median and Ulnar Nerves

Several studies have confirmed the presence of short-latency SEPs in adults and children.[55,71,74,92,138,266,284,426,433] The multi-channel SEPs recorded simultaneously from the scalp and cervical electrodes help delineate the field distribution of such short-latency components (Figs. 20–5 through 20–7, Table 20–1). Most of these studies relate to median SEPs, but studies of the ulnar nerve have revealed comparable results.[129,153,154,205] Some studies have dealt with normative data in children,[158,494] showing complex maturational changes, that complicate the interpretation.[159,162,292] Neurologically intact preterm and term infants present characteristic maturational changes in their topographic distribution of late SEP components (see Chapter 22–9).[237]

Stimulation of the median nerve at the wrist elicits cervical potentials consisting of four negative peaks (N_9, N_{11}, N_{13}, and N_{14}) when referenced to the tied ears (see Fig. 20–5).[471] The earliest component shows relative positivity if recorded with

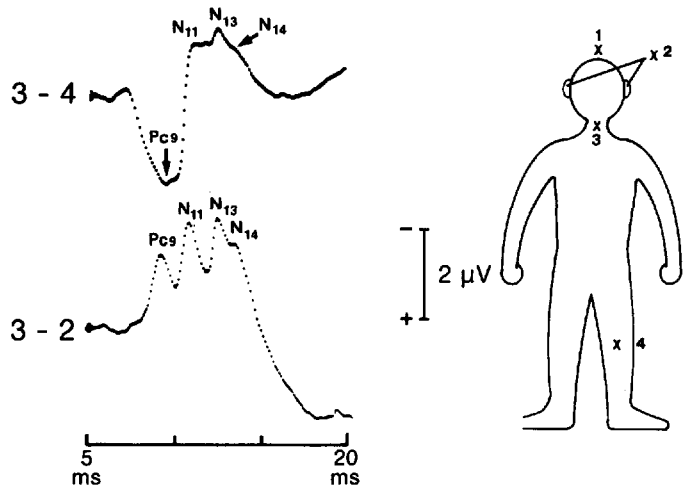


Figure 20–6. Simultaneous recording from a low cervical electrode (3) with knee (4) or ear (2) reference after stimulation of the median nerve at the wrist in a normal subject. The recording with a knee reference showed the initial positive peak, P_9, followed by three negative peaks, N_{11}, N_{13}, and N_{14}. The use of an ear reference reversed the polarity of the first peak and enhanced the subsequent negative peaks. [From Yamada, Kimura and Nitz,[471] with permission.]

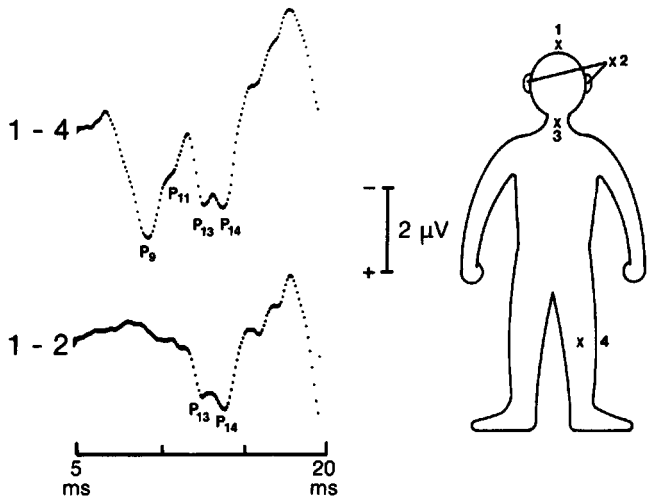


Figure 20–7. Simultaneous recording from C_z (1) with knee (4) or ear (2) reference after stimulation of the median nerve at the wrist in a normal subject. Of the four positive peaks, P_9, P_{11}, P_{13} and P_{14} recorded with a knee reference, only P_{13} and P_{14} appeared when referenced to the ear. [From Yamada, Kimura and Nitz,[471] with permission.]

a noncephalic reference (see Fig. 20–6). With the use of the knee reference, the initial positive potential of scalp-recorded SEPs contains four positive peaks: P_9, P_{11}, P_{13}, and P_{14} (see Fig. 20–7). Recording with ear reference (see Fig. 19–7), far-field peaks consist of P_{13} and P_{14} without earlier components, which make the scalp and ear equally positive. These four peaks of the cervical and scalp-recorded SEPs normally occur within the first 15 ms, followed by a small but distinct negative peak, N_{18}, recorded bilaterally in the frontal region as negative FFP. The medium-latency and long-latency components of scalp-recorded SEPs from the central areas during the next 100 ms consist of N_{19}, P_{22}, N_{30}, P_{40}, and N_{60}, or, according to another nomenclature, NI, PI, NII, PII, and NIII.

The earliest scalp potential, P_9,[74] which originates from a distal portion of the brachial plexus, corresponds to N_9 of the cervical potential as recorded by means of a scalp reference (see Figs. 20–5 and 20–8).[215] As mentioned above, the field distribution of the first component shows a diagonal orientation with negativity at

Table 20–1 Latency of Erb's Potential and Short-Latency Median Somatosensory Evoked Potential in 34 Normal Subjects

	Latency (Left and Right Combined)			Latency Difference (Between Left and Right)		
Components	**Number Identified**	**Mean ± SD (ms)**	**Mean + 3 SD**	**Number Identified**	**Mean ± SD (ms)**	**Mean + 3 SD**
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
Interwave peaks						
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

*Consistently measurable components and interwave peaks.
From Yamada et al.,[478] with permission.

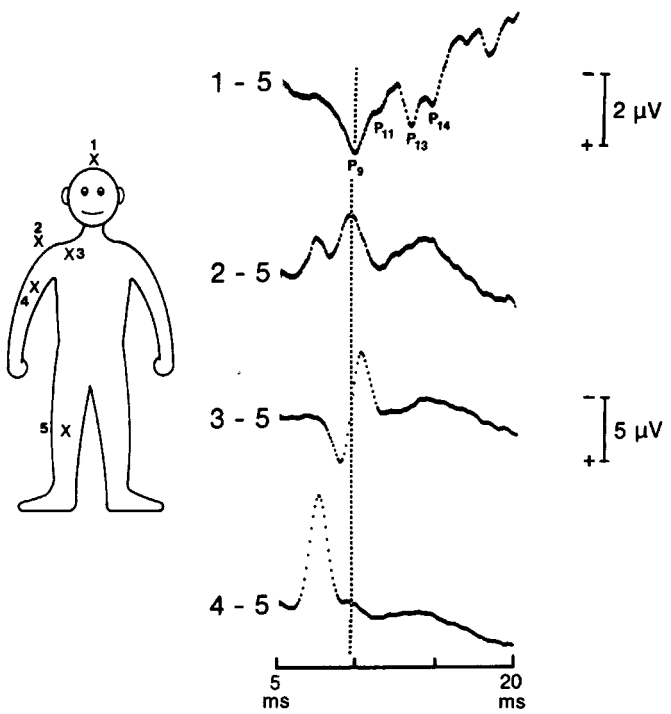


Figure 20–8. Relationship between potentials recorded at the scalp P_9 (1) and potentials recorded at the shoulder (2), Erb's point (3), and 5 cm distal to the axilla (4). The positive peak, P_9, at the scalp corresponded in latency to the negative peak recorded from the shoulder. [From Yamada, Kimura and Nitz,[471] with permission.]

the shoulder and axilla and positivity over the entire scalp and neck (see Figs. 20–6 and 20–8). The propagating impulse generates a junctional potential at this level, reflecting an abrupt geometric change of the volume conductor, anatomic orientation of the impulse, and branching of the nerve.[95,189,249,250,251,317,471]

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.[131,253] Thus, N_{11} starts upon arrival of the peripheral nerve volley at the spinal cord level.[92] It closely relates to the activity recorded from the side of the neck ipsilateral to the stimulation (Fig. 20–9). The characteristics of the refractory period indicate the presynaptic nature of this component.[143] The neural source of N_{11}, therefore, must lie near the entry zone, with scalp-recorded P_{11} reflecting the positive end of the same field.[471] Some investigators, however, have observed a delayed N_{11} in patients with cervical cord and medullary lesions. This finding would imply a more rostral origin.[18]

Despite considerable clarification during recent years, the origin and identity of the N_{13}/P_{13} components still rank among the most controversial SEP topics.[300,489] The negativity reaches a maximum at the cervical level with decreasing amplitude rostrally and caudally.[31,471] A slight delay of N_{13} at higher cervical electrodes suggests the presence of a traveling wave.[253] Recordings of N_{13} 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.[93,217] These findings suggest that the near-field N_{13} 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 N_{13}, while abolishing subsequent components.[299] Some investigators have recorded two subcomponents with different orientations, N_{13a}/P_{13a} and N_{13b}/P_{13b}, possibly corresponding to generators in the dorsal horns and the cuneate nucleus.[4,217,218] Epidural, pial, and subpial recording allows detection of additional low-amplitude high-frequency waves superimposed on P_9–N_{13}, presumably related to the cuneate fascicles.[101,348]

The third positive scalp potential consists of two different generator sources, P_{13} and

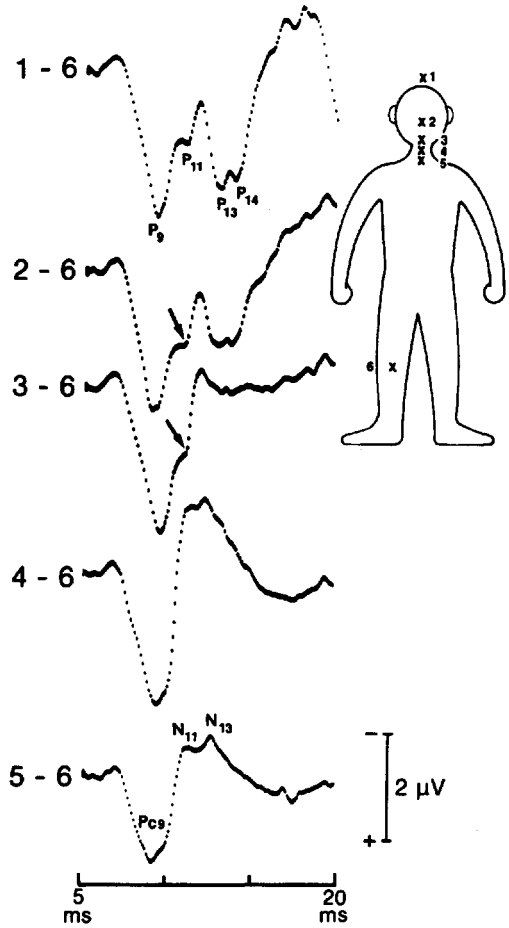


Figure 20–9. Responses recorded from a series of electrodes placed longitudinally at C_z (1), O_z (2), and high (3), mid (4), and low (5) cervical regions, with a reference lead at the knee (6). The amplitude of P_{11} decreased progressively from Cz to the high cervical electrode (arrows) with phase reversal to N_{11} at mid and low cervical electrodes. In contrast, the positive field of the first component (P_9) extended from C_z to low cervical electrode (P_{C9}). [From Yamada, Kimura, and Nitz,[471] with permission.]

P_{14}, as evidenced by its bilobed appearance.[74] Debates continue on whether scalp-recorded P_{13} represents the phase reversal of N_{13} from the dorsal horn[93] or corresponds to the ascending volley of the posterior column.[18,309,471] A small and at times equivocal P_{13}, recorded over the scalp stands in contrast to N_{13}, which represents the largest cervical potential. Some believe that P_{13} originates below the foramen magnum,[299,449] whereas others,[183,238] on the basis of intracranial recordings in humans, propose that P_{13}, like P_{14}, arises from volleys ascending in the medial lemniscus at the brainstem level. Although the origin of P_{13} remains uncertain, it probably corresponds to N_{13} arising from the cervical cord, which in turn consists of at least two subcomponents, as mentioned above.[219,406]

Earlier studies suggested that P_{14} might arise in the thalamus.[74] In fact, SEPs recorded in humans from the nucleus ventralis caudalis consisted of monophasic or diphasic potentials with a mean onset latency of 13.8 ms.[47] The preservation of P_{14} in patients with cerebral,[18] thalamic,[311] or mesencephalic lesions[55] suggests a more caudal location of the neural source. Furthermore, this component shows no phase reversal between scalp and nasopharyngeal recordings (Fig. 20–10),[471] as might be expected if it were generated in the thalamus. Unlike N_{11} and N_{13}, a cervical electrode barely detects N_{14} in most subjects, indicating its neural source rostral to the cervical spine. All of these observations together suggest that P_{14} originates rostral to the cuneate nucleus,[44,183,202,335] partially or entirely representing a junctional potential of the medial lemniscus impulse crossing the foramen magnum.[209,245,246]

The polarity characteristics of the short-latency SEPs suggest that a negative field

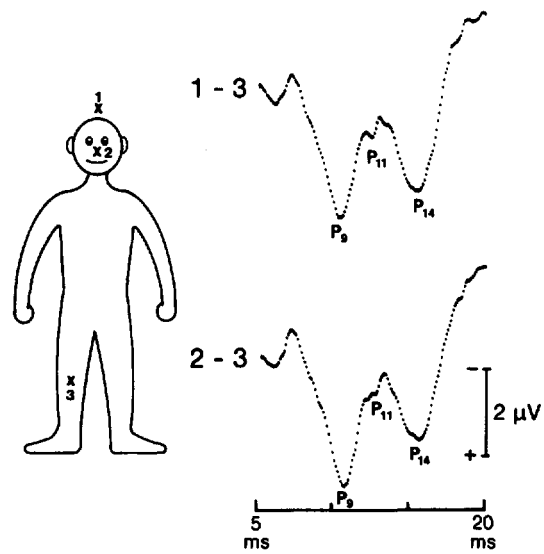


Figure 20–10. Responses recorded from C_z (1) and a nasopharyngeal electrode (2) using a knee reference. The identical waveform of P_{14} in both tracings indicates its generation source caudal to both recording sites, that is, below the base of the skull. (From Yamada et al.,[471] with permission.)

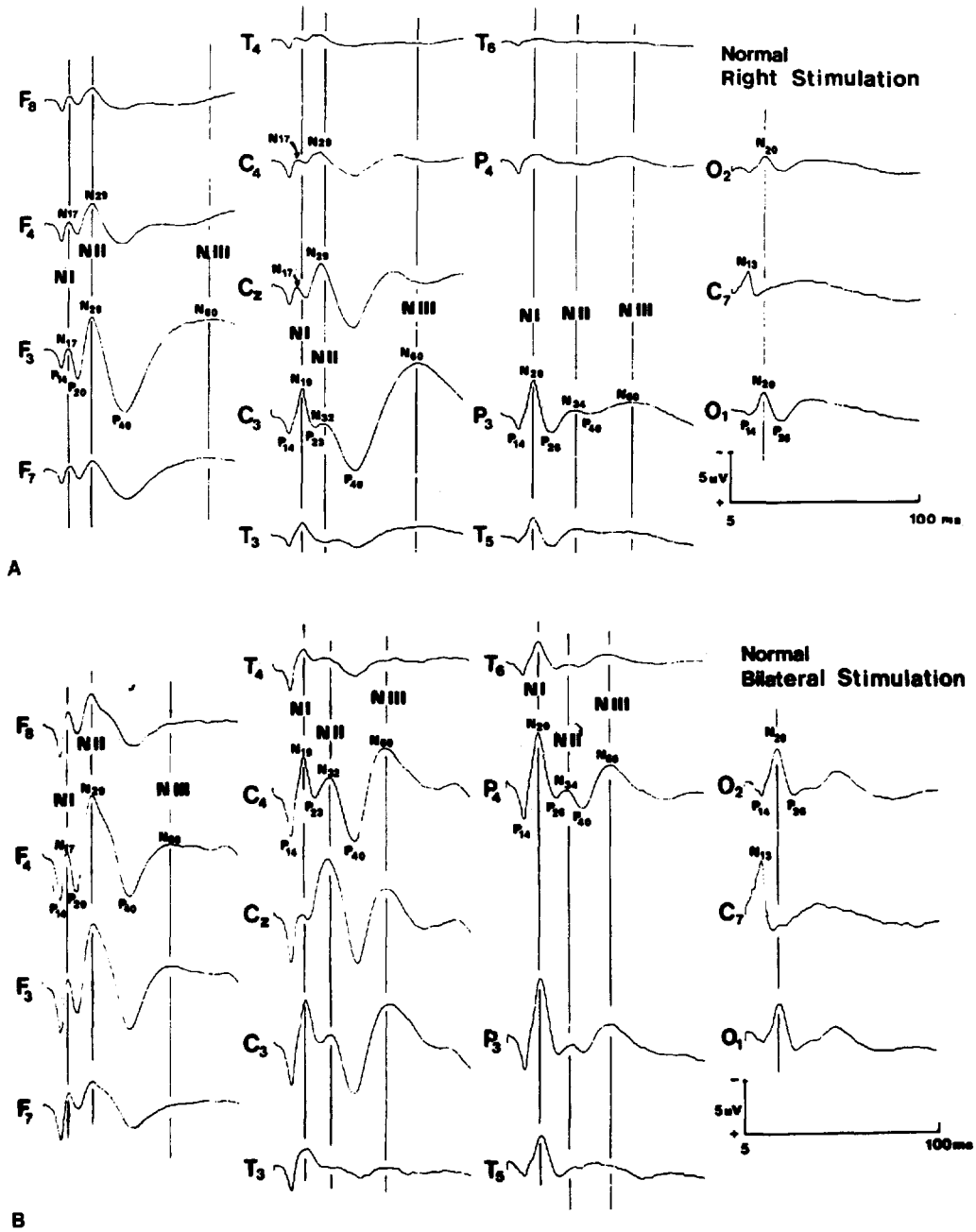


Figure 20–11. A. Median SEPs after unilateral stimulation on the right in a normal subject. Topographic analysis indicates N_{17}–P_{20}–N_{29} peaks distributed bifrontally and at ipsilateral central (C_4) and C_z electrodes, N_{19}–P_{23}–N_{32} at contralateral central electrode (C_3), and N_{20}–P_{36}–N_{34} at parietal and occipital electrodes. In this and in **B.** C_7 indicates a cervical electrode just above the C7 spinal process. **B.** Median SEP after bilateral stimulation in the same subject as in **A.** Potentials recorded over homologous electrodes in the two hemispheres show symmetric patterns that resemble contralateral responses elicited by unilateral stimulation. [**A** and **B** from Yamada et al[469] with permission.]

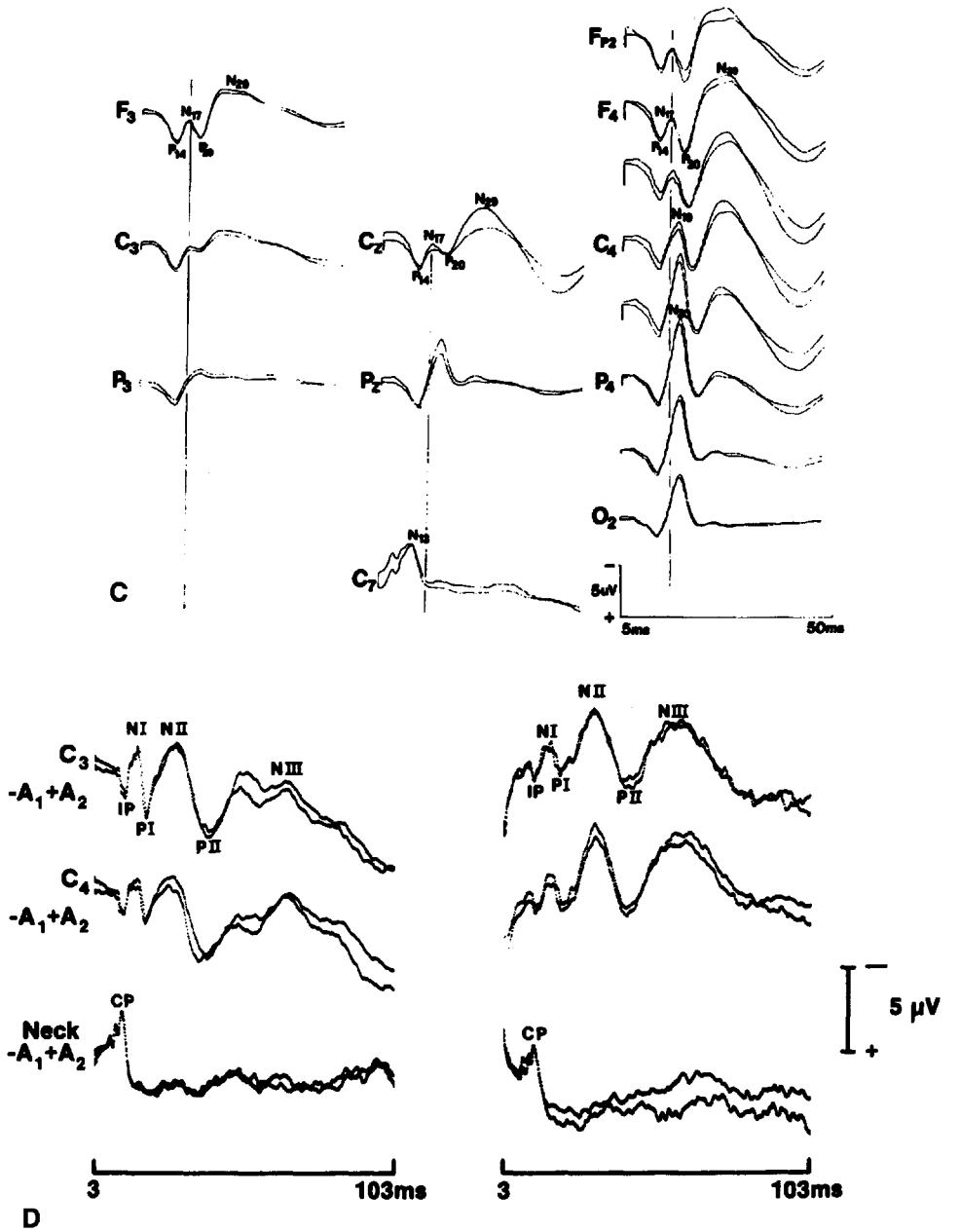


Figure 20–11 (*cont.*). C. Topographic display of scalp (10-20 International Electrode Placement system) and cervical potentials (C_7) to stimulation of the left median nerve. Frontal N_{17} (F_{Pa}, F_4) preceded central N_{19} (C_4) and parietal N_{20} (P_4) contralateral to the stimulus. N_{17} also appeared at the vertex (C_z) and frontal and central areas ipsilaterally (F_3, C_3). [From Kimura and Yamada,[251] with permission.] **D.** Cervical and scalp-recorded SEPs in two normal subjects after simultaneous bilateral stimulation. Tracings were recorded from the left (C_3) and right (C_4) central regions of the scalp and the mid-neck, all referenced to the connected ears. The initial positive potential (IP) consists of P_{13} and P_{14}, and the cervical potential (CP) consists of N_9, N_{11}, N_{13}, and N_{14}. The subsequent negative and positive peaks, NI, PI, NII, PII, and NIII, correspond to N_{19}, N_{22}, N_{32}, P_{40}, and N_{60}. [From Yamada, Machida and Kimura,[474] with permission.]

near the generator site gives rise to the cervical potentials and that scalp-recorded peaks reflect FFPs from the same source. Based on the polarity and mean latency, the presumed generator sites include (*1*) the entry to the brachial plexus at the shoulder (N_9 and P_9), (*2*) entry to the cervical cord at the neck (N_{11} and P_{11}), (*3*) dorsal column volley with possible contributions from dorsal horn interneurons and the cuneate nucleus (N_{13} and P_{13}), and (*4*) entry to the medial lemniscus at the foramen magnum (N_{14} and P_{14}). Of these, P_9, P_{11}, and P_{14} 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 SEPs (see Fig. 20–7).[465,471]

Negative–positive peaks, NI, PI, and NII, subsequent to P_{14} (Fig. 20–11 and Table 20–2) show the shortest latency at the frontal electrodes (N_{18}, P_{20}, and N_{29}), with a progressive delay toward the central (N_{19}, P_{22}, and N_{32}) and parietal (N_{20}, P_{26}, and N_{34}) areas. In contrast to a small N_{18} recorded bilaterally in the frontal region, the first major negative peaks, N_{19} and N_{20}, 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, N_{18}. In this case, N_{18} precedes N_{19} as an additional separate peak, suggesting the presence of two distinct components of separate neural origin. The appearance of N_{18} after P_{14}, which arises in the medial lemniscus, initially suggested its originate in a thalamic structure[297,447,448,452] or subthalamic structure. The slow negative component, N_{18}, however, appears on the scalp with a latency shorter than that of the negativity in the thalamus,[3] and an extensive thalamic[298] or pontine lesion[404] may spare N_{18}, abolishing N_{20} and subsequent components. A far-field theory predicts the generation of a slow negative rebound after positive peaks, P_9, P_{11}, P_{13}, and P_{14} as the ascending impulse crosses the shoulder and foramen magnum.[246,431,434] Documented cases with involvement of P_{14} without change in N_{18}[405] and dissociated effect of vibration on these two components[293] imply that the onset of N_{18} may be even more caudal, perhaps representing the slow negative sequelae of P_9 generated at the brachial plexus.

Topographic analyses have shown conflicting results regarding the possible dipole relationship between parietal N_{20} and frontal P_{20}.[5,88,96,407,443] Despite a similarity in latency, close scrutiny reveals that P_{20} has a slightly later onset than N_{20}.[92,251] The N_{20} and P_{20} show distinct amplitude changes with increasing stimulus frequency, indicating that these potentials arise from separate generators.[90] The dipole theory also falls short of providing an adequate explanation for some of the reported observations in clinical context. For example, patients with motor neuron disease show selective alteration of prerolandic potentials.[488] Conversely, those with anterior lesions may show preservation of the parietal N_{20} despite substantial loss of frontal P_{20}. These findings suggest a radially, rather than tangentially, oriented dipole mainly in the parietal area.[190] To further confound the issue, the central P_{22} may have yet another independent source, showing radial orientation over the precentral gyrus[96,450] or the postcentral gyrus.[41,43,45]

Table 20–2 Latency of Medium- and Long-Latency Median Somatosensory Evoked Potentials in 34 Normal Subjects

	Latency (Left and Right Combined)			Latency Difference (Between C3 and C4)		
Components	Number Identified	Mean ± SD (ms)	Mean + 3 SD	Number Identified	Mean ± SD (ms)	Mean + 3 SD
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
P_{60} (NIII)	64	62.8 ± 9.3	90.7	32	1.5 ± 1.1	4.8

From Yamada et al.,[478] with permission.

The origin of the subsequent component NII (N_{30}) remains undetermined. It is elicited by electrical stimuli applied to the proximal phalanx of the thumb having both deep and cutaneous afferents, but not by those applied to the distal phalanx containing only the cutaneous afferents.[357] Therefore, joint and tendinous input may evoke fontrocentral N_{30} in either precentral or postcentral areas.

The last negative peak, NIII (N_{60}), shows a wider distribution over the cortex, with greater temporal variability than the earlier peaks. In contrast to the medium-latency responses relayed by specific oligosynaptic routes, a nonspecific polysynaptic pathway probably mediates the long-latency component.

A number of models have been proposed to describe median SEPs as the result of a set of overlapping time-varying dipoles.[85] In fact, ascending and descending phases of N_{20} contain a number of wavelets that show different recovery functions, presumably reflecting the number of interspersed synapses.[139,468]

Tibial and Peroneal Nerves

The scalp-recorded potentials usually begin with P_{35} after stimulation of the peroneal nerve at the knee and P_{40} after stimulation of the tibial nerve at the ankle (Fig. 20–12).[106,253] The tibial SEP serves better for routine clinical use, showing larger amplitude and less intersubject variability in waveform and topography than the peroneal SEP.[339] The peroneal or tibial SEP also contains earlier peaks that correspond to the short-latency components of the median SEP.[229,281,308,362,403,430,453,474] Recording these small potentials requires particular attention to technical details and a substantial number of trials for averaging. Stimulation of the tibial nerve at the ankle evokes three regular components, P_{17}, P_{24}, and P_{31}, and three less consistent peaks, P_{11}, P_{21}, and P_{27}, diffusely over both hemispheres. Of these, only P_{31} is recorded with the use of the ear or shoulder as a reference; only P_{24} and P_{31}, with the iliac crest as a reference (Figs. 20–13 and 20–18, Table 20–3).

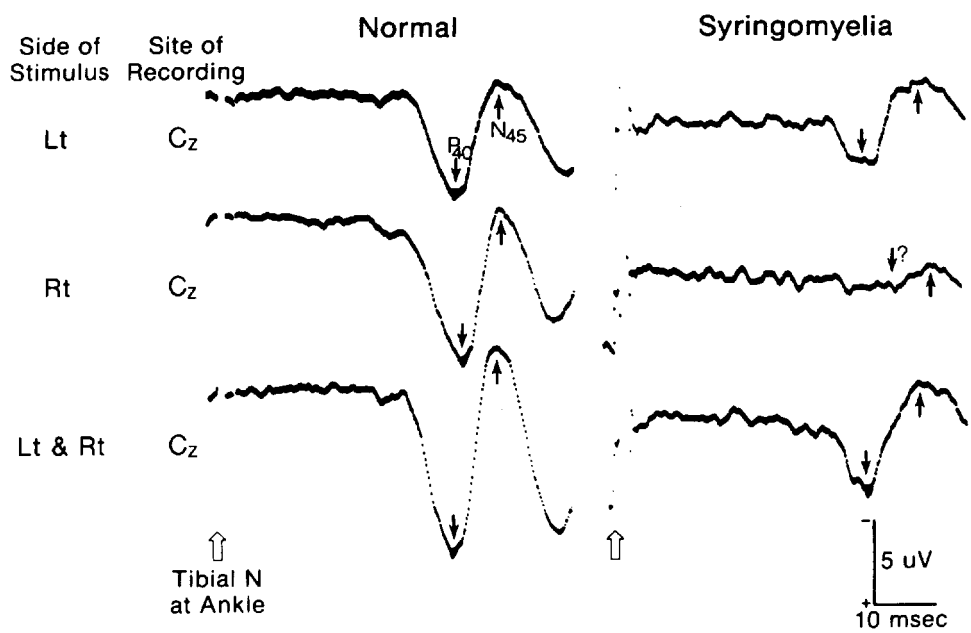


Figure 20–12. Tibial SEPs after stimulation at the ankle in a normal subject (*left*) and a patient with syringomyelia and loss of vibration sense in the right leg (*right*). Note markedly reduced P_{40} and N_{45} to right-sided stimulation in the patient (*middle tracing*). The use of an ear reference precluded the recording of short-latency positive peaks, P_{17} and P_{24}, and minimized P_{31} and the subsequent negative peak, N_{37}, preceding P_{40} (cf. Fig. 20–15.)

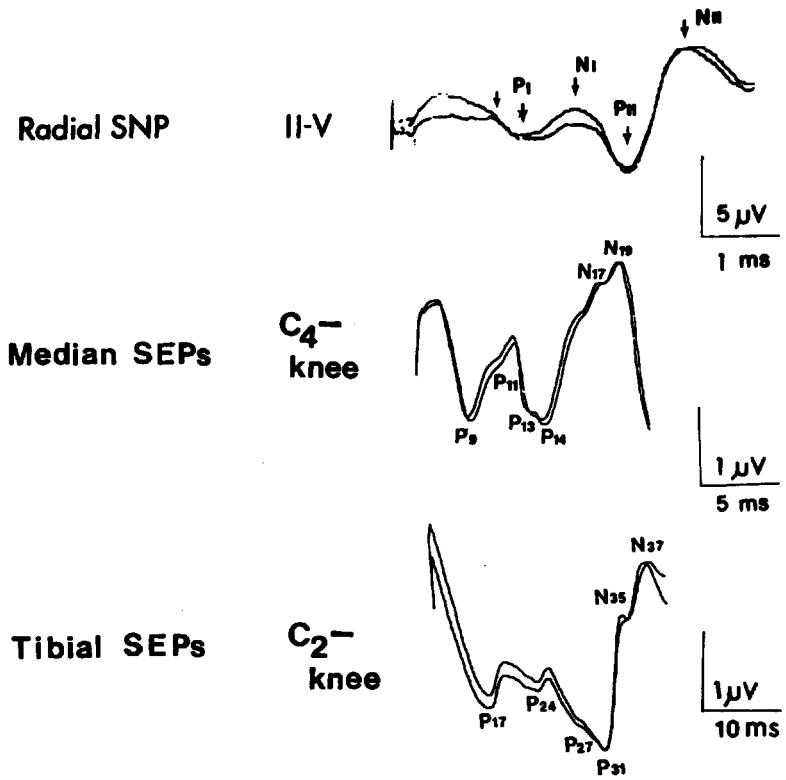


Figure 20–13. Scalp recorded SEPs using a noncephalic reference after stimulation of the median nerve at the wrist (*middle*) and the tibial nerve at the ankle (*bottom*). Both median and tibial SEPs consist of four positive peaks initially and two negative peaks thereafter, all within the first 20 and 40 ms following the stimulus, respectively. For comparison, the *top tracing* shows far-field potential, PI–NI, and PII–NII, recorded from digit II referenced to digit V, after stimulation of the radial sensory fibers at the forearm. [From Kimura, Yamada and Walker,[255] with permission.]

Simultaneous recordings from multiple levels along the somatosensory pathway suggest that P_{17} originates in the peripheral nerve, P_{24} in the spinal cord, and P_{31} in the brainstem (Fig. 20–14). The initial major component reverses its polarity near the pelvis, rendering the trunk and scalp more positive (P_{17}) than the leg, concomitant with the arrival of the propagating nerve potential at the gluteus (N_{16}). The second component shows the largest negativity over the T11 to T12 spinous processes (N_{23}) associated with stationary positive peaks rostrally (P_{24}), with a latency slightly longer than the estimated nerve conduction time from the ankle to the spinal cord. The last component, best recorded as a positive peak at the scalp

Table 20–3 Latency of Short-Latency Tibial Somatosensory Evoked Potentials (A) and Negative Peaks Along the Somatosensory Pathway (B) in 21 Healthy Subjects

Recording Site	**Scalp**					
(A) Components	**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	31.2 ± 2.1
Number recorded	22	40	21	39	30	40
Number tested	40	40	40	40	40	40
Recording Site		**Gluteus**	**L4**	**T12**	**C7**	**C2**
(B) Components		**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
Number recorded		20	40	40	18	25
Number tested		22	40	40	22	26

From Yamada et al.,[474] with permission.

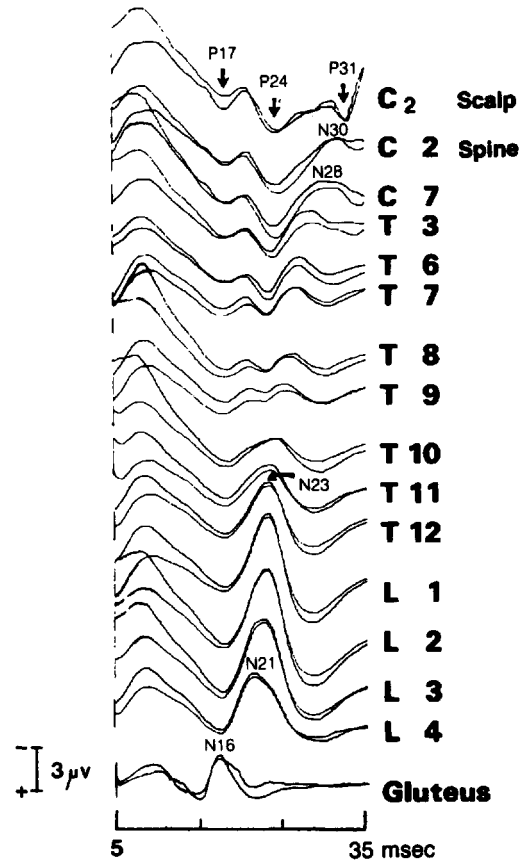


Figure 20–14. Tibial SEPs recorded from scalp lead and longitudinally placed electrodes over the spine. The first two positive peaks, P_{17} and P_{24}, appeared diffusely not only over the scalp but also along the entire spine. The gluteal lead registered a negative peak, N_{16}, which slightly preceded P_{17}. The second component, P_{24}, extended caudally to the T_{11} spine, corresponding to negativity, N_{23}, best recorded at the T_{12} spine. A negative peak, N_{30}, recorded at the C_2 spine slightly preceded P_{31}. [From Yamada, Machida and Kimura,[474] with permission.]

(P_{31}), coincides with the negative source located in the brainstem (N_{30}). The less consistent peaks, P_{11} and P_{21}, are generated with the arrival of the peripheral nerve potential, N_{11}, at the popliteal fossa, and the spinal potential, N_{21}, at the L4 spinous process. The other peak, P_{27}, coincides with the arrival of the negative cervical potential, N_{28}, at the C7 spinous process as recorded from the neck or the surface of the dorsal column nuclei.[310] A localized synapse-dependent negativity, N_{29}, can also be recorded at the level of the second cervical spine.[378]

In contrast to the diffuse distribution of the early positive components, the first negative peak shows interhemispheric asymmetry, with the ipsilateral response, N_{35}, appearing before the contralateral response, N_{37} (Fig. 20–15). These two peaks probably represent the subthalamic or subcortical responses generated by two independent sources in each hemisphere. In clinical studies, the subsequent positivity, P_{40}, is better suited for measuring the conduction time to the cortex because of its consistency. 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.[77,334,377,421,453] Intrathecal stimulation of the lumbosacral cord elicits similar cortical potentials, although 10–15 ms shorter in latency.[141]

Tibial or peroneal SEPs recorded over sacral, lumbar, or low thoracic levels correspond to median or ulnar SEPs at the cervical level.[91,282,345,482] With the reference electrode (G_2) placed at the T6 spinous process or the iliac crest, the lumbosacral potential usually attains the maximal amplitude with the active electrode (G_1) over the upper lumbar–lower thoracic vertebrae. Stimulation of the sciatic nerve in the monkey also elicits predominantly negative triphasic spinal potentials along the cauda equina and caudal spinal cord.[144]

The lumbosacral potentials recorded from the surface after stimulation of the peroneal or tibial nerve consist of two negative components (Fig. 20–16). The latency of the early peak increases from sacral to upper lumbar levels, but that of the second peak remains constant (Fig. 20–17). Thus, the latency separation between the peaks becomes maximal in recordings from the lower lumbar or upper sacral sites.[345] The first peak probably represents a traveling wave ascending through the nerve roots of the cauda equina (cauda peak, or R wave); the second peak, a standing potential generated in the conus medullaris, located at the level of the T12 spinous process (cord peak, or S wave). The stability of the cord peak in response to short-interval paired stimuli

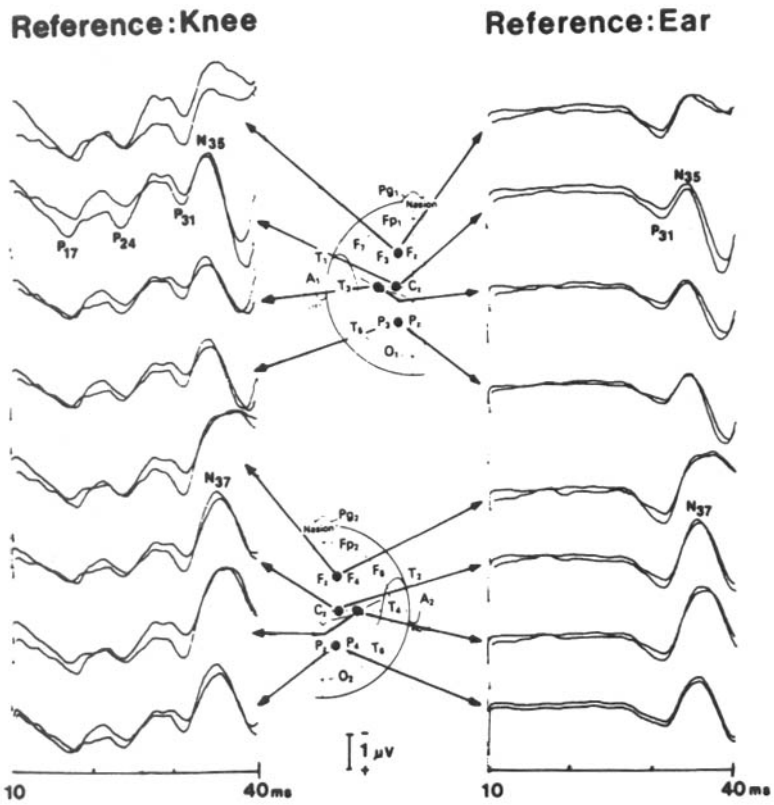


Figure 20–15. Tibial SEPs after unilateral stimulation on the left. The major components consist of symmetrically distributed P_{17}, P_{24}, and P_{31} recorded with the use of a knee reference (*left column*) and the subsequent asymmetric negative peak, ipsilateral N_{35} and contralateral N_{37}. The use of an ear reference precluded the recording of the short-latency positive peaks P_{17} and P_{24} (*right column*). [From Yamada, Kimura, and Machida,[470] with permission.]

suggests a presynaptic origin,[345] although postsynaptic potentials may also contribute. Intrathecal baclofen infusion for management of spasticity suppressed the postsynaptic conus medullaris responses, abolishing concomitantly recorded H reflexes without producing substantial changes in cortical SEPs.[256]

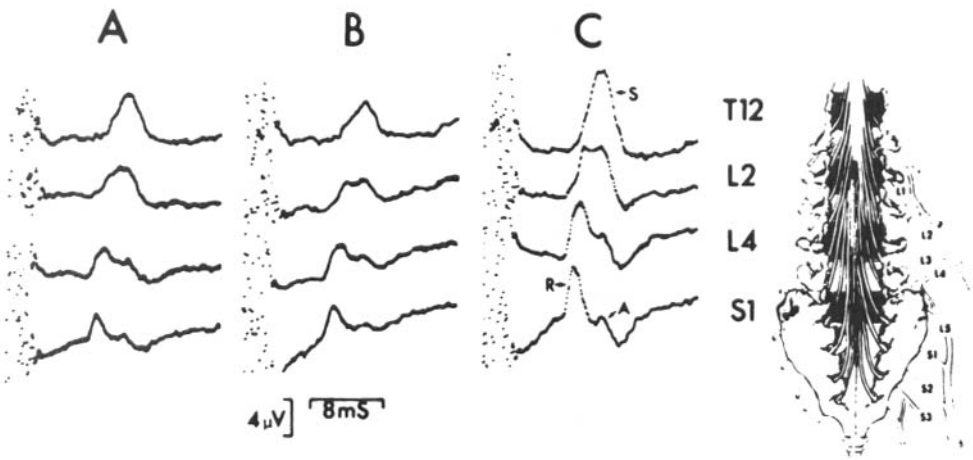


Figure 20–16. Surface recording of lumbosacral evoked potentials after stimulation of the right (**A**), left (**B**), and bilateral (**C**) tibial nerves at the popliteal fossa using a common reference electrode placed over the T6 spine. The responses consist of spinal (S) and double-peaked (R and A) cauda equina potentials as labeled in **C**. In the diagram of the lower spine and pelvis on the right, the *shaded areas* indicate the locations of recording electrodes at T12, L2, L4, and S1 vertebral levels. All traces represent averages of 64 responses. [From Dimitrijevic, Larsson, Lehmkuhl et al,[102] with permission.]

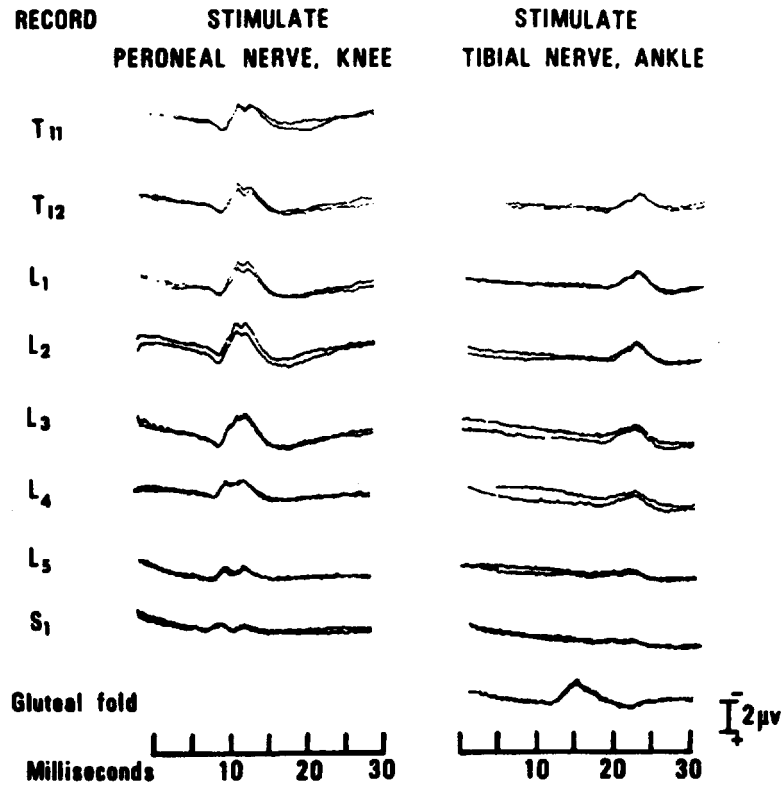


Figure 20–17. Cauda (first) and cord (second) peaks in spinal evoked potentials recorded from multiple spinal levels using a reference electrode over the iliac crest contralateral to the side of stimulation. Each of the superimposed traces represents the average of 128 responses. For comparison, the last trace of the right column shows a potential recorded from an electrode over the sciatic nerve at the gluteal fold in response to the tibial nerve stimulation. [From Phillips and Daube,[345] with permission.]

The cord peak recorded at the level of the T12 spinous process probably consists of several components, including volleys in the dorsal root and dorsal column,[94] orthodromic and antidromic discharges in the ventral roots,[351] and activities generated locally in interneurons. When recorded caudal to the T12 spinous process, the potential that occurs synchronously with the cord peak, and labeled as the A wave by some, may represent efferent motor activity in the anterior root.[91,102,351] It may also reflect a junctional potential recorded at the reference electrode, which becomes positive (P_{24}) when traveling volleys arrive at the conus medullaris (N_{23}) (Fig. 20–18). Such a positive field extends over the entire trunk, head, and arm, affecting any reference electrode placed rostral to the T12 spinous process.[494]

Trigeminal Nerve

In eliciting SEPs from the trigeminal nerve, the sites of stimulation include the peripheral nerve bundle,[268,369,394] the upper or lower lip,[146] the gums,[30,50] tongue,[6] and other parts of the face.[21] Each of these methods evokes a major triphasic waveform, which varies considerably depending on the technique used. In one study, scalp SEPs elicited by stimulation of the second division (upper lip) consisted of N_8, P_{14}, and N_{18}, whereas stimulation of the third division (lower lip) reversed the polarity to P_8, N_{13}, and P_{19}.[146] A bipolar recording between C_3 (G_1) and F_3 (G_2) also revealed an inverted sequence, NI, PI, and NII or N_{13}, P_{19}, and N_{26}, following simultaneous stimulation of both the upper and lower lips unilaterally (Fig. 20–19 and Table 20–4).[415] With an ear reference, stimulation of the gum above the first maxillary bicuspid elicited scalp responses N_{20}, P_{34}, and N_{51}.[29] Stimulation of the infraorbital nerve elicited three peaks over the scalp, W_1, W_2, and W_3, corresponding to the activity at the entry into the gasserian ganglion, into the pons, and into the trigeminal spinal tract. Awake subjects also had additional components P_4, N_5, P_6, and N_7 when recorded with the use of a noncephalic reference.[269] These

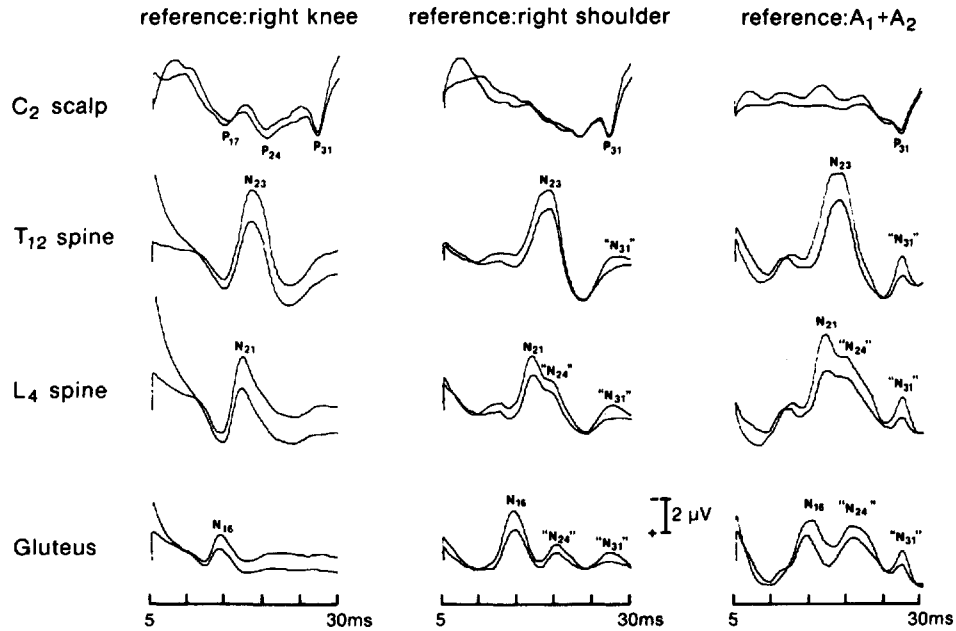


Figure 20–18. Far-field peaks (FFPs), recorded over the scalp, and near-field potentials (NFPs), recorded along the thoracic and lumbar spine and gluteal fold, after stimulation of the tibial nerve at the ankle. The scalp peaks consist of P_{17}, P_{24}, and P_{31} (*left, top*), which coincide with the arrival of NFP at the hip (N_{16}), conus medullaris (N_{23}), and brainstem, respectively. The first lumbar potential (N_{21}), which probably originates from the cauda equina, gives rise to an inconsistent FFP over the scalp. The second ("N_{24}") and the third ("N_{31}") peaks in the right and middle columns represent FFPs registered by an "active" reference electrode. In the left column, the use of the "inactive" knee reference eliminated the superfluous peaks.

peaks probably correspond to FFPs generated at the mandibular foramen, foramen ovale, and gasserian ganglion or trigeminal root after stimulation of the mandibular nerve in cats.[2]

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 selected, surface current readily spreads to the pick-up 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[29] and paratrigeminal syndromes.[267] Air puff stimulation induces neither stimulus nor muscle artifacts.[185] 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 SEPs over the sensory cortex and spinal cord.[177,420] The concurrent measurement of the cortical and spinal potentials and bulbocavernosus reflexes (see Chapter 19–6) permits the evaluation of the peripheral and central sensory and motor pathways. Stimulation of the vesicourethral junction also elicits cerebral evoked responses with a late prominent

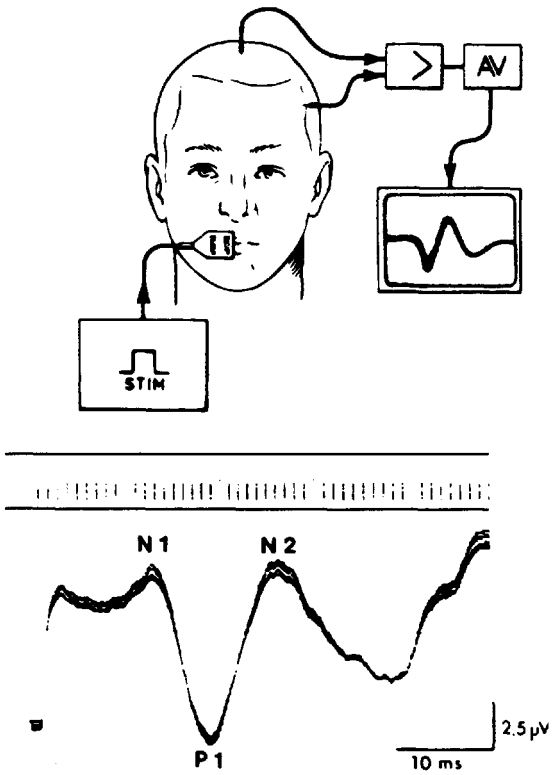


Figure 20–19. A cortical SEP of the trigeminal nerve elicited in a healthy subject following stimulation of the lips. [From Stohr, Petruch and Scheglmann,[416] with permission.]

negativity.[373] In contrast to distal urethral or pudendal nerve stimulation that activates the somatic afferents,[181] this technique probably excites the visceral afferents arising from the vesicourethral junction. Rectal stimulation may elicit two distinctly different potentials, presumably representing excitation of either the pudendal nerve or the visceral afferents.[275] Most patients with detrusor acontractility from suprasacral cord lesions have normal lumbosacral SEPs, indicating the multifactorial nature of neurogenic bladder dysfunction.[280]

The pudendal SEPs recorded with G_1 2 cm behind C_z and G_2 over the forehead resemble those of the tibial SEPs (Fig. 20–20A), with an initial positive deflection and subsequent negative and positive sequences.[177] Table 20–5 summarizes the mean latencies and standard deviations of these waves in each of the populations studied. 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 SEP. After stimulation of the pudendal nerve, the spinal potential recorded by G_1 over the L1 and G_2 over the L5 spinous process consists of a dominant negative peak with the onset latency of 9.9 ± 3.4 ms (mean ± SD) (Fig. 20–20B).[177] 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 to 1 μV.

Based on the latency of spinal potentials, the impulses arrive at the L1 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 SEPs over the scalp, however, show similar latencies, presumably because the muscle afferents of the tibial nerve conduct much faster than the cutaneous afferents of the pudendal nerve.

Other Nerves

Typical short-latency femoral nerve SEPs consist of widely distributed P_{15} and N_{19}

Table 20–4 PI Latency and NI/PI Amplitude of Trigeminal Somatosensory Evoked Potentials in 82 Healthy Subjects

Latency (ms) (Mean ± SD)	Upper Limit (ms) (Mean + 2 SD)	Side-to-Side Latency Difference (ms) (Mean ± SD)	Upper Limit (ms) (Mean + 2 SD)	Amplitude (μV) (Mean)	Side-to-Side Amplitude Difference (μV) (Mean)
18.5 ± 1.51	22.3	0.55 ± 0.55	1.93	2.6	0.51

Modified from Stohr and Petruch.[415]

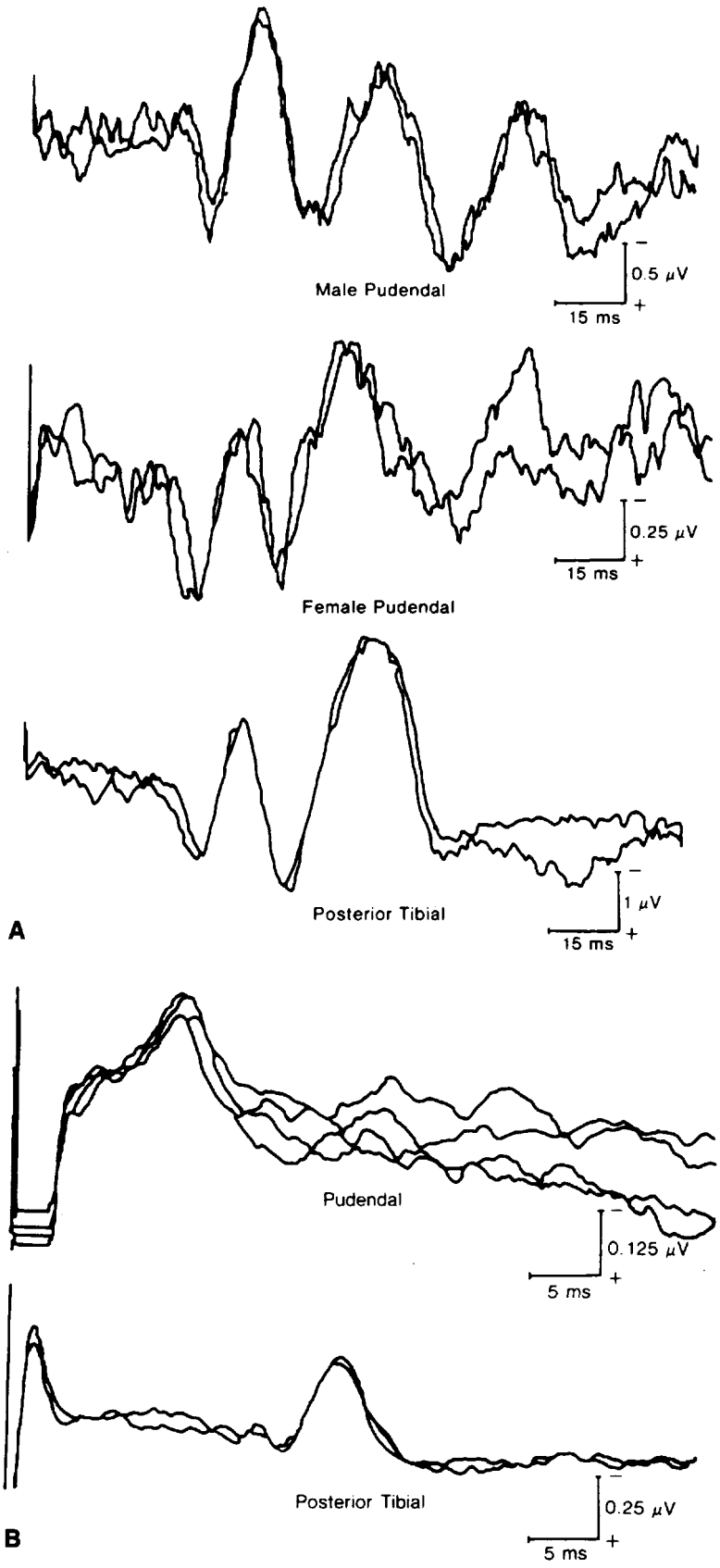

Male Pudendal
0.5 μV
15 ms
Female Pudendal
0.25 μV
15 ms
Posterior Tibial
1 μV
15 ms
A
Pudendal
0.125 μV
5 ms
Posterior Tibial
0.25 μV
5 ms
B

Figure 20–20. A. Somatosensory evoked potential recorded 2 cm behind C_z on stimulation of pudendal and posterior tibial nerves. **B.** Spinal somatosensory evoked responses recorded at the L1 vertebral spinous process on stimulation of pudendal (*top*) and posterior tibial nerves (*bottom*). [From Haldeman, Bradley, Bhatia et al,[177] with permission.]

and localized scalp components P_{26}, N_{34}, P_{44}, and N_{56}.[460] Percutaneous stimulation of the phrenic nerve in the supraclavicular fossa[35] evokes, over the scalp, 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.[497] Stimulation of the intercostal nerve also elicits SEPs, which may assist in the diagnosis of both central and peripheral thoracic neural compromise.[109] Other nerves of interest include medial and lateral plantar and calcaneal nerves for plantar neuropathies,[112] lateral femoral cutaneous nerve for meralgia paresthetica,[346] and saphenous nerve for entrapment neuropathies.[436]

Dermatomal Stimulation

Stimulation of the cervical or lumbosacral dermatomes elicits SEPs used to evaluate radiculopathies.[273] Paraspinal stimulation excludes most of the peripheral nervous system, thus eliciting SEPs that serve as a measure of spinal lesions.[167] Spinal SEPs following segmental sensory stimulation provide a direct measure of dorsal root function.[379] Dermatomal SEPs may also serve in monitoring individual nerve root functions during degenerative spinal surgery despite considerable variability of innervation patterns.[333]

5 PATHWAYS FOR SOMATOSENSORY POTENTIALS

Peripheral Inputs and Their Interaction

Early clinical studies revealed abnormal SEPs only in patients with impaired vibration or position sense, whether the lesions involved the spinal cord, cerebral hemisphere, or brainstem. More recent findings suggest a better correlation of SEP abnormalities with the loss of position than vibration sense in patients with selective involvement of either modality.[484] 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 SEPs, which attenuate by vibration applied locally or by voluntary contraction of the muscle.[495] These findings confirm that muscle spindle receptors at least in part provide the afferent input responsible for early components of SEPs. Brief air puff and electric stimuli applied to the tip of the index finger produce SEPs of similar morphology.[184] 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.[186] Mechanical stimuli also

Table 20–5 Latency Comparison Between Tibial and Pudendal Evoked Potential 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

From Haldeman et al.,[177] with permission.

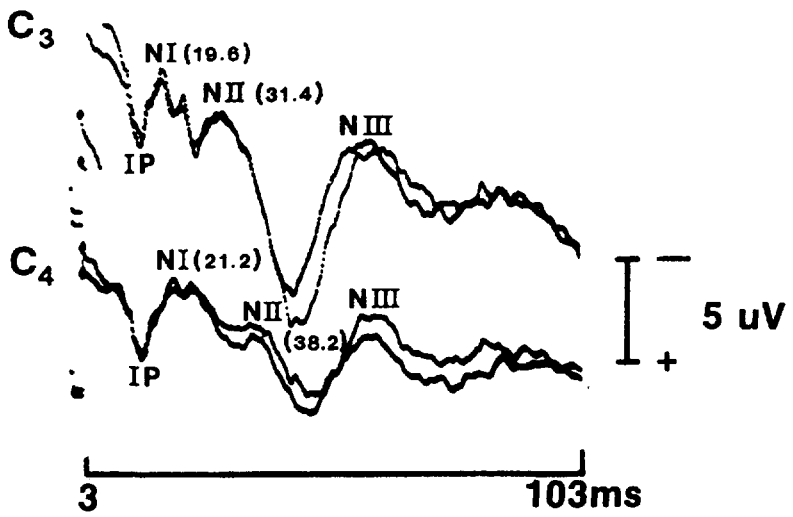


Figure 20–21. Scalp-recorded potential to bilateral stimulation of the median nerve in a 33-year-old man with traumatic avulsion of C8, T1, and probably T2 roots on the left. Myelography demonstrated a large meningocele at C7. Interhemispheric comparison revealed no asymmetry for IP, NI, and NIII despite an obvious delay of NII on the right (C_4).

evoke lower amplitude responses with fewer components than electric stimulation, which activates more fibers synchronously.[65,150] Passive plantar flexion of the ankle can also elicit cerebral potentials in humans, presumably via the afferent fibers that originate from muscle mechanoreceptors.[409] Thus, the fast-conducting, large, myelinated sensory fibers of the dorsal column–medial lemniscal system, via either cutaneous afferents[5] or muscle afferents[152] primarily, although not exclusively, mediate SEP components.

Activity carried in the anterolateral column, however, also reaches the cortex in monkeys as well as in humans.[15,498] Indeed, stimulation with an intensity great enough to activate both large- and small-diameter fibers in the peroneal nerve produces SEPs even after transection of the dorsal column and spinocervical tract in cats.[242] These findings all support the contention that first-order afferent fibers outside the posterior column contribute to some of the SEP peaks. Clinical observations also support the experimental evidence in favor of separate sensory pathways mediating various SEP peaks. Similarly, 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. 20–21 and 20–22).[473] Conversely, lesions of the brainstem, cervical cord, or brachial

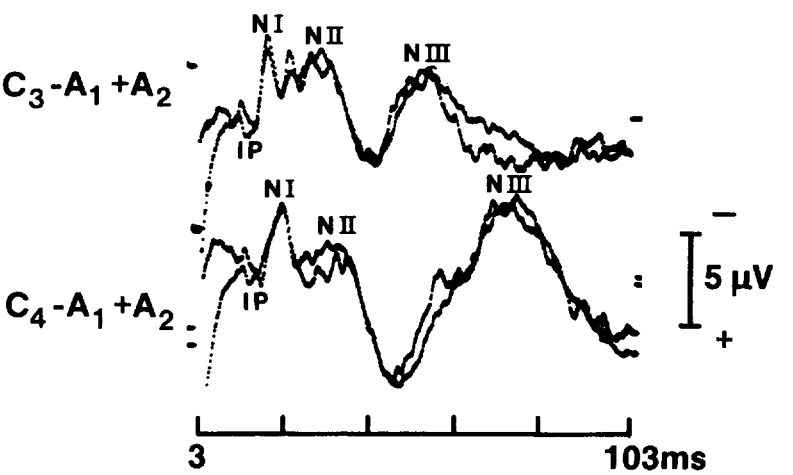


Figure 20–22. Scalp-recorded potential to bilateral stimulation of the median nerve in a 46-year-old woman with multiple sclerosis. Interhemispheric comparison showed a slight delay of IP and NI and far greater delay of NII and NIII on the right (C_4). [From Yamada, Kimura, Young, et al.[473] with permission.]

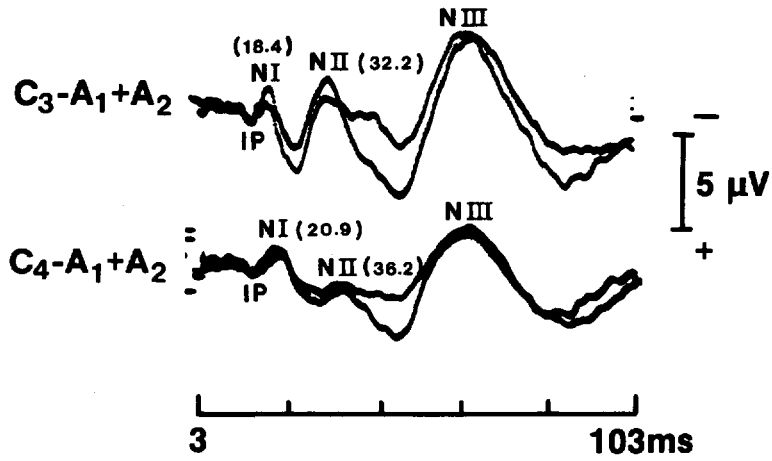


Figure 20–23. Scalp-recorded potential to bilateral stimulation of the median nerve in a 59-year-old woman with multiple sclerosis. Despite a delay of NI and NII on the right (C_4) following a normal IP, NIII showed no difference between the two hemispheres. [From Yamada, Kimura, Young, et al.[473] with permission.]

plexus[479] may affect NI and earlier peaks selectively, sparing NII and subsequent components (Figs. 20–23 to 20–25). Such dissociated abnormalities of early or 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. A high-intensity stimulation elicited cortical SEPs with a latency of 84 ms for an estimated propagation velocity of 12 m/s in a man with a complete loss of large myelinated sensory fibers.[68]

A pinprick, but neither touch nor tactile tap, elicits SEPs in patients with loss of vibration and touch sensations.[387] Brief heat pulses applied to the skin excite the afferent pathway of pain and temperature sensitivity.[439] In normal subjects, stimulation with CO_2 laser radiant heat elicits a large P_{320}, maximal at vertex but distributed widely over the scalp.[222,231,437] Its amplitude decreases and latency increases with reduction in stimulus intensity. Calculations using this method revealed an estimated conduction velocity of 9 m/s for the Aδ fibers in the peripheral nerve,[223] and 8–10 m/s for the slowly conducting spinothalamic tract in humans.[228] Clinical studies showed a positive relationship between pain SEP and densities of small myelinated fibers of the sural nerve in neuropathies,[283] a drasti-

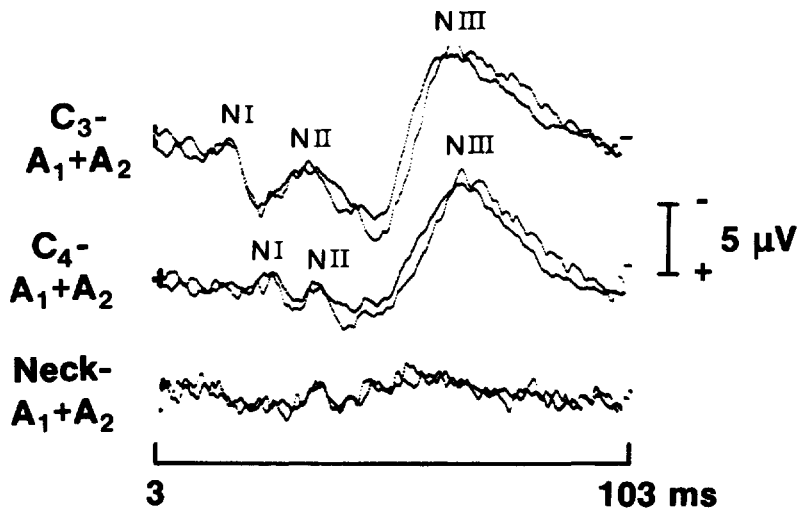


Figure 20–24. Scalp-recorded potential to bilateral stimulation of the median nerve in a 55-year-old woman with multiple sclerosis. The tracings consisted of bilaterally absent IP, substantially delayed NI, borderline NII, and normal NIII on the right.

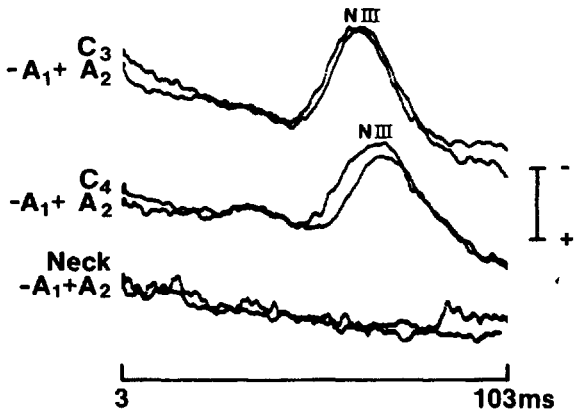


Figure 20–25. Scalp-recorded and cervical potentials to bilateral stimulation of the median nerve in a 47-year-old man with multiple sclerosis. A well-preserved NIII occurred as the initial potential in the absence of preceding peaks, IP, NI and NII. [From Yamada, Kimura, Young, et al.[473] with permission.]

cally increased latency consistent with delayed pain perception in neurosyphilis,[441] and normal pain SEPs in hereditary motor and sensory neuropathy with the preservation of C-fiber function.[264] Other conditions evaluated by this technique include cortical reflex myoclonus,[232] dissociated sensory loss of pain and temperature,[39,438] carpal tunnel syndrome,[20] syringomyelia[350,440] stroke,[480] and facial hypesthesia.[76]

The brief effect of an inflated cuff on the nerve, caused by ischemia rather than by mechanical compression, involves the largest myelinated fibers first. Such tourniquet-induced ischemia diminishes the short-latency SEP peaks, P_9, P_{14}, and the first cortical response, NI, along with the nearly parallel loss of the potential recorded at Erb's point.[476] Thus, the large myelinated fibers responsible for nerve action potentials must subserve the early SEP components. Relative sparing of the later components, PII, NII, PIII, and NIII, implies the presence of independent routes, possibly involving different peripheral axons, for example, smaller myelinated fibers. Interestingly, ischemia prolongs the latencies of PII and later peaks more than those of the earlier peaks (Fig. 20–26), again indicating the heterogeneity of the afferent fibers contributing to the SEPs.

Central Mechanisms for Integration

During gating experiments, which test input interactions, different kinds of movement primarily affect the late cortical SEP, more than early cortical responses with minimal change in subcortical components.[17,52,363,367,451] In one study, movement of the first digit, but not the fifth digit, attenuated P_{27} cerebral potentials elicited by stimulation of the first and second digits, or the median nerve. Conversely, movement of the fifth digit, but not of the first digit, attenuated the component evoked by stimulation of the fifth digit, or the ulnar nerve. These findings suggest selective gating of SEPs with movement that involves the areas of stimulation.[424] In one study, aged healthy subjects had a larger SEP amplitude at rest and showed greater amplitude reduction by voluntary movement than younger controls.[435] Thus, the magnitude of gating may depend on SEP amplitude at rest. Pre-movement gating of frontal N_{30} with no effect on N_{20} suggests a rostral projection from the primary somatosensory area or direct projection from the thalamus to the motor cortices.[388] Mental movement simulation also affects the N_{30} frontal component.[53,360] Vibration attenuates spinal and cerebral potentials evoked by stimulation of the mixed nerve or muscle spindle but has no effect on cutaneous input.[63,64] Prior stimulation of the same or other nerve also modifies SEPs.[169,319,331,353] The final waveform of the recorded potential depends on a complex interaction of varied sensory inputs from different sources, some facilitatory and others inhibitory.[220,224,225] Cognitive components also alter the later components of SEP, which therefore serve as a measure of cortical function.[99]

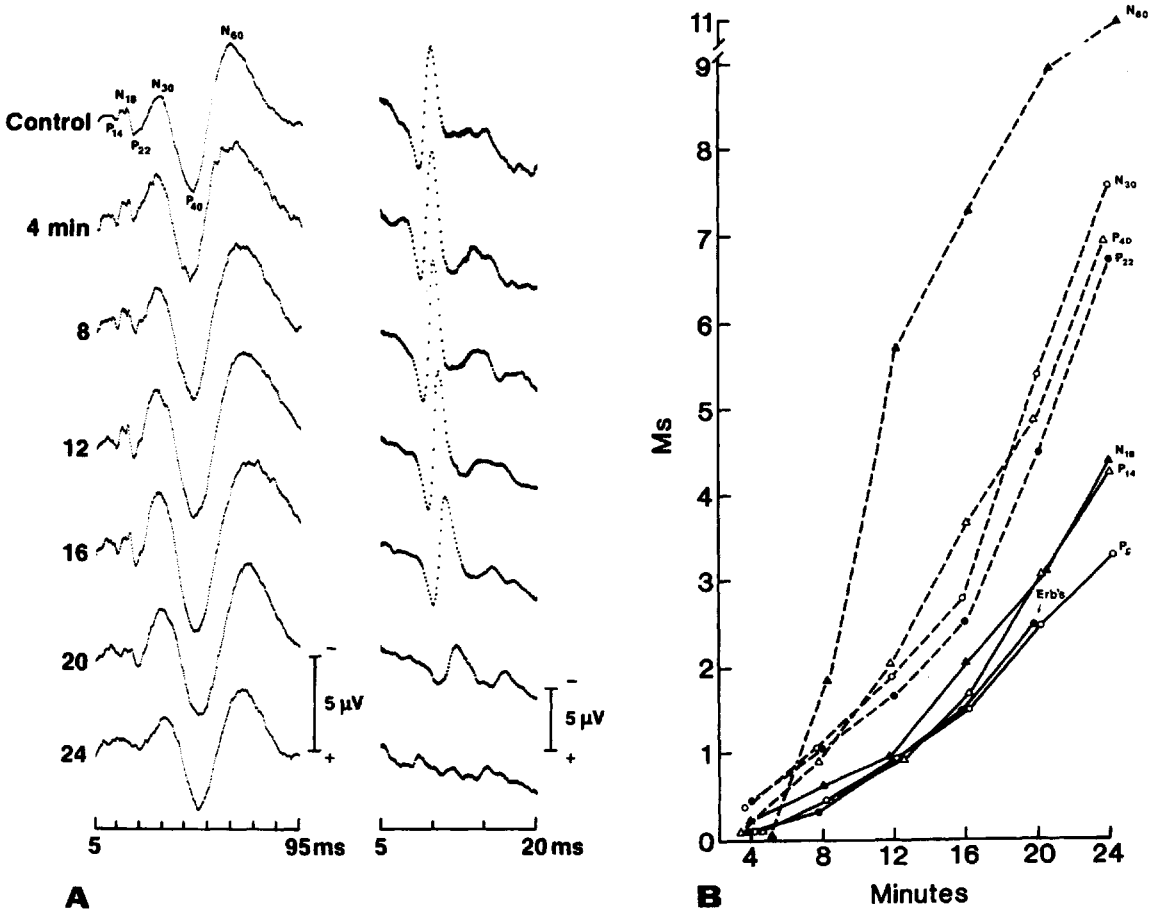


Figure 20-26. A. Sequential changes of scalp-recorded SEPs (*left*) and Erb's potential (*right*) during mechanical application of a pressure cuff around the upper arm in a normal subject. Ischemia affected the initial positive and negative components, P_{14} and N_{18}, along with Erb's potentials earlier than the subsequent components P_{22}, N_{32}, P_{40}, and N_{60}. A 24 minute compression abolished the "ischemia-sensitive" peaks while preserving the "ischemia resistant" peaks relatively intact. **B.** Effect of ischemia on the SEPs and Erb's potential. 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. [From Yamada, Muroga and Kimura,[476] with permission.]

Despite this complexity, SEPs generally favor 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 would explain the generation of relatively preserved SEPs despite a very abnormal sensory nerve action potential in patients with peripheral neuropathies. Such discrepancy may also result from central amplification that compensates for peripheral conduction block.[134] In one study, early components of SEPs attained a maximum amplitude before the responsible muscle afferent volley reached 50 percent of its maximum.[152] 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 7–5).[248] Similarly, the diminution of early SEPs may initially result from temporal dispersion of axonal volleys rather than from conduction

block. If so, the cortex, operating as an integrator, may generate a sizeable evoked response 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. These disorders may affect the amplitude of the initial SEP peaks selectively without concomitant diminution of the later components. More importantly, 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 SEPs, two separate trials with the same stimulus setting serve to confirm the consistency of the recorded response. Repeat studies on successive occasions show better stability for SEPs elicited by stimulation of the upper limbs than of the lower limbs. The usual measurements include onset and peak latencies and peak-to-peak amplitudes (see Tables 20–1 to 20–3). Available data suggest a linear relationship between the subject's height and the latency of a given peak elicited by stimulation of a lower limb.[239] SEP latencies, which include synaptic delay, also change as a function of body temperature, affecting central, more than peripheral, conduction times.[192,295]

Group means of the median SEPs indicate minor differences in waveform and latency between the genders.[197] During normal postnatal development up to 8 years of age, scalp-recorded tibial SEPs show latency changes that reflect complex maturation of central pathways. In contrast, the latencies of the peripheral and lumbar potentials correlate positively with age and height, yielding a predictable nomogram.[163] Short-latency SEPs in infants and children resemble those of adults but show great maturational changes until adolescence. The peripheral part of the sensory pathway reaches the adult range at 3–4 years of age and the central part, at school age.[432] The central conduction time (mean ± SD), measured from the cervical area (N_{13}) to the primary cortical response (NI), remains relatively constant (5.66 ± 0.44 ms) between 10 and 49 years of age. It increases by approximately 0.3 ms between the fifth and sixth decades, with no further change thereafter.[191]

The somatosensory latency has two parts, peripheral conduction from the stimulus site to the spinal cord entry and 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 reveals 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.[107,127] 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.[32] 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. Changes in conduction characteristics of slower conducting fibers not assessed by conventional nerve conduction studies, could alter the SEP latency and waveform. Analysis with correlation co-

efficients can determine their reproducibility and side-to-side asymmetry.[262]

6 CLINICAL APPLICATIONS

Studies of SEPs have made steady progress since the original description by Dawson[84] more than half a century 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 SEPs and other evoked potential studies in the clinical domain, and a great number of patients undergo such a test as a routine procedure. Important questions remain, however, to delineate the practical scope of the SEP and its proper usage.[13,244,260] These include standardization of the technique and nomenclature, precise localization of neural generators, and elucidation of various factors that affect the measurements.[178]

Common Derivations and Normal Values

Median SEPs generally have larger and better defined responses than the corresponding peaks of ulnar SEPs 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 (channels 1 and 2) (Figs. 20–27 and 20–28 and Tables 20–6 to 20–8). Channel 4 records N10, or the nerve potential at Erb's point, with a mean latency of 10 ms, which serves as a monitor of the peripheral nerve. 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.

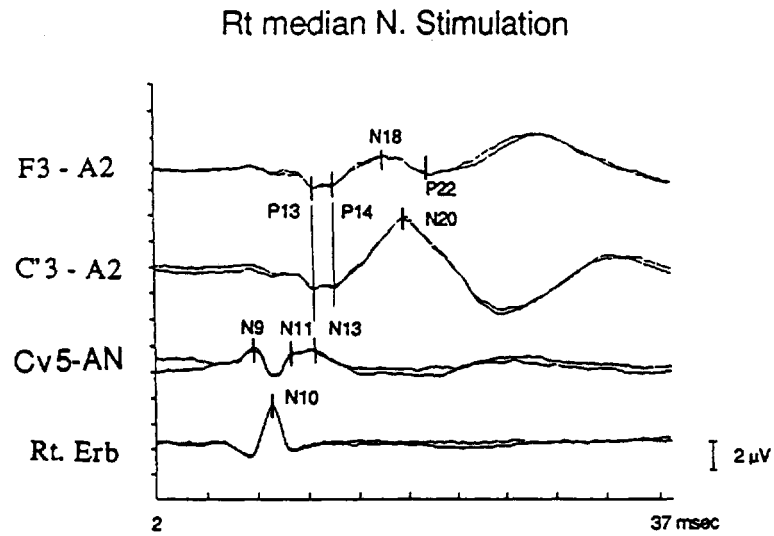


Figure 20–27. Four-channel recording of median SEPs showing P_{13} and P_{14} recorded at F_3 and C'_3 electrodes, N_{18} at F_3 electrode and N_{20} at C'_3 electrode. C_{V5}–AN derivation registers mixed near-field and far-field potentials, N_9, N_{11}, and N_{13}. Of these, N_{13} matches P_{13} in latency despite a different generator source. The propagating signal, N_{10}, recorded at Erb's point falls in between N_9 and N_{11}, representing far-field activities. [From Yamada 1994,[466] with permission.]

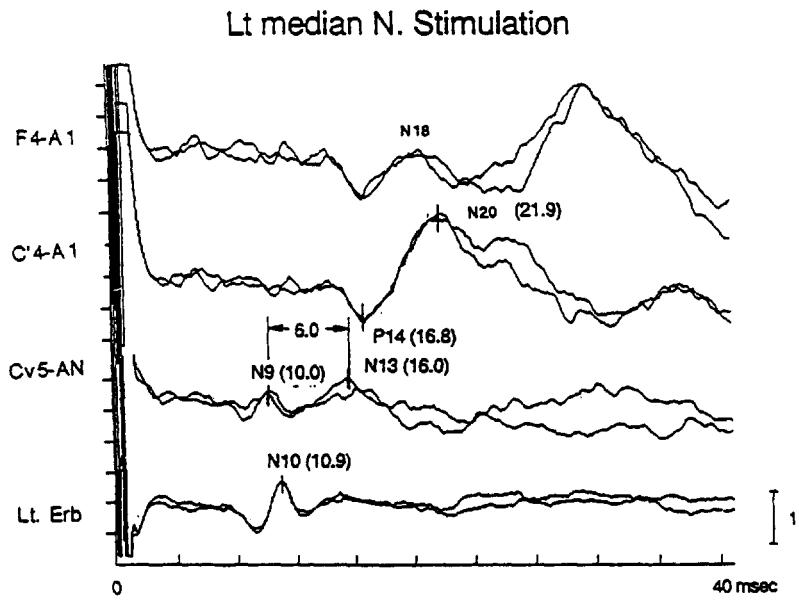


Figure 20–28. An abnormal median SEP with normal N_9 and N_{10} and delayed N_{13}, P_{14}, and N_{20}. A prolonged N_9 to N_{13} interwave peak latency beyond the upper limit of normal (5.3 ms) indicates a lesion involving either the proximal segment of the peripheral nerve or the cervical cord. [From Yamada,[466] with permission.]

The FFPs of clinical interest include four positive peaks, P9, P11, P13, and P14, recorded from C'3 or C'4 scalp electrodes usually by means of a non-cephalic reference (see Fig. 20–1). 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 lead from the frontal but not parietal region registers a negative FFP, N18, following positive FFPs, 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 FFPs. 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, 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 N32, 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 physiologic

Table 20–6 Four-Channel Derivation for Median Somatosensory Evoked Potential

Stimulation of Left Median Nerve		Stimulation of Right Median Nerve	
Channel 1:	F_4–A_1	Channel 1:	F_3–A_2
Channel 2:	C'_4–A_1	Channel 2:	C'_3–A_2
Channel 3:	C_{v5} to anterior neck	Channel 3:	C_{v5} to anterior neck
Channel 4:	Lt Erb to Rt Erb	Channel 4:	Rt Erb to Lt Erb

F_3, F_4, C'_3 and C'_4 refer to the 10–20 International Electrode Placement system (Fig. 20–1). C'_3 or C'_4 is 2 cm posterior to the C_3 or C_4, respectively. C_{v5} refers to a point just below the C5 spinous process. Lt = left; Rt = right.

Table 20–7 Peaks of Median Somatosensory Evoked Potential and Their Origins

	Peaks	Anatomic Origin
Channel 1:	P_{13}–P_{14}	Brainstem (median lemniscus)
	N_{18}	Perpheral nerve of brainstem
Channel 2:	P_{13}–P_{14}	Brainstem (medial lemniscus)
	N_{20}	Thalamocortical projection or cortex
Channel 3:	N_9	Distal portion of brachial plexus
	N_{11}	Root entry zone or dorsal column
	N_{13}	Cervical cord or cuneate nucleus
Channel 4:	N_{10}	Erb's potential

substrates for cortical sensory processing. Thus, these late waves may provide useful information in the evaluation of higher cortical functions, although their clinical value is limited.

NERVES OF THE 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 four-channel recording of the tibial SEP, which shows less intraindividual and interindividual variability than peroneal nerve SEPs (Figs. 20–29 and 20–30 and Tables 20–9 and 20–10).

Channel 4 registers N_8, or the peripheral potential with a latency of about 8 ms. Channel 3, similar to its counterpart in median nerve SEPs, registers a combination of near-field and far-field activities. Of these, N_{24}, recorded at L1 and T12 spinal processes, derives from the conus medullaris and N_{21} from the cauda equina, which in some cases appears as a small notch over the rising phase of N_{24}. These two components correspond to N_{11} and N_{13} 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 C'_z referenced to the ear registers P_{31}, N_{35}, and P_{40}. Of these, P_{31} corresponds to P_{13}/P_{14} of the median nerve SEP, arising from medial lemniscus. Like P_{13}/P_{14}, P_{31} remains stable under anesthesia, providing a useful measure for spinal cord monitoring. The onset of N_{35} probably in part represents a negative FFP equivalent to N_{18} of the median nerve SEP.

Unlike N_{20} of the median SEP, its counterpart, N_{35} of the tibial SEP, generally shows a small amplitude even in normal subjects. Channel 1 with C'_z–F_z (F_{pz}) derivation suites best for defining P_{40}, 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 N_{24}–P_{31} and N_{24}–P_{37} 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 in both children and adults (Figs. 20–31 and 20–32).

Table 20–8 Upper Limit of Normal Values for Median Somatosensory Evoked Potentials, Mean + 2 SD

	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
	Latency Differences	
N_9–N_{13}	5.3	1.0
N_{13}–P_{14}	2.2	0.8
N_{13}–N_{20}	7.4	1.0

Peripheral Nerve

The studies of SEPs 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

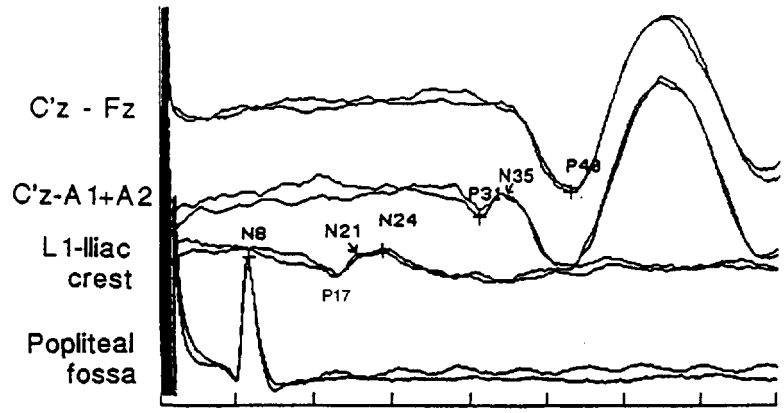


Figure 20–29. Four-channel recording of tibial SEP showing a cortical potential, P_{40}, in scalp-to-scalp derivation and preceding far field potential P_{31}–N_{35} when referenced to the ears. L1 iliac crest derivation registers a far-field potential, P_{17}, and near-field peaks N_{21} and N_{24} from cauda equina and conus medullaris. The latency difference between P_{31} and N_{24} approximates the spinal conduction time. The propagating signal, N_8, recorded at the popliteal fossa, monitors the peripheral nerve. [From Yamada,[466] with permission.]

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. Selective stimulation of the first, third, and fifth digits elicit SEPs corresponding to the C6, C7, and C8 roots in the differentiation of radicular lesions.[418]

Disorders commonly tested by this means include lesions involving the root, plexus, or thoracic outlet (see Fig. 20–21).[130,257,341,483,487] A number of studies explored the use of segmental and dermatomal SEPs in the diagnosis of cervical

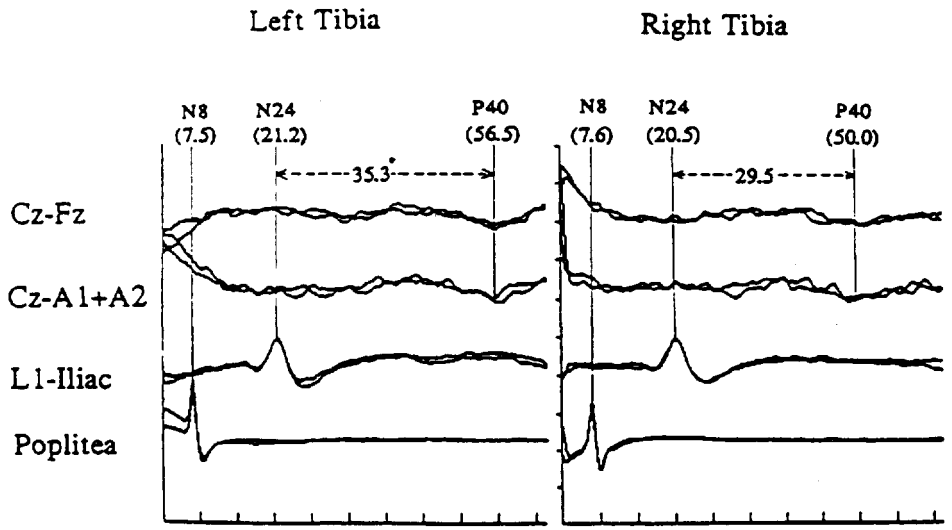


Figure 20–30. An abnormal tibial SEP in a patient with thoracic spinal cord injury, showing normal N_8 and N_{24} and diminished and delayed P_{40}. A prolonged N_{24}–P_{40} interwave peak latency beyond the upper limit of normal (21.5 ms) indicates a lesion involving the spinal cord or higher levels.

Table 20–9 Four Channel Derivation for Tibial Somatosensory Evoked Potential

Stimulation of Left or Right Tibial Nerve	
Channel 1:	$C'_z(C'_1)$ to $F_z(F_{pz})$
Channel 2:	$C'_z(C'_1)$ to $A_1 + A_2$
Channel 3:	L1 (T12) spine to iliac crest
Channel 4:	Popliteal fossa (conventional bipolar recording)

C'_z is 2 cm posterior to C_z and C'_1 is 1 to 2 cm lateral to C'_z on the hemisphere ipsilateral to the side of stimulation.

Table 20–10 Upper Limit of Normal Values for Tibial Somatosensory Evoked Potentials, Mean + 2.5 SD

	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
Latency Differences		
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

radiculopathy,[375] lumbosacral radiculopathy,[110,120,368,379,458] and lumbosacral spinal stenosis.[402] Some advocate its clinical value,[240,333,380] whereas others refute such a contention.[7,10,11,110] Studies of longer pathways tend to mask latency changes across a short segment because normal conduction in the remaining region dilutes the focal delay (see Chapter 7–6). Thus, intertrial and side-to-side variation tends to mask any small change attributable to a focal lesion. The current data provide only insufficient evidence to support the use of dermatomal SEPs as a clinical diagnostic tool for radiculopathy, except perhaps in cases of spinal stenosis.[397,402] Surgical decompression of lumbar spinal stenosis may shorten the latency of tibial, peroneal, or sural SEPs.[89,166] Pudendal SEPs, together with the bulbocavernosus reflex, help evaluate sacral nerve

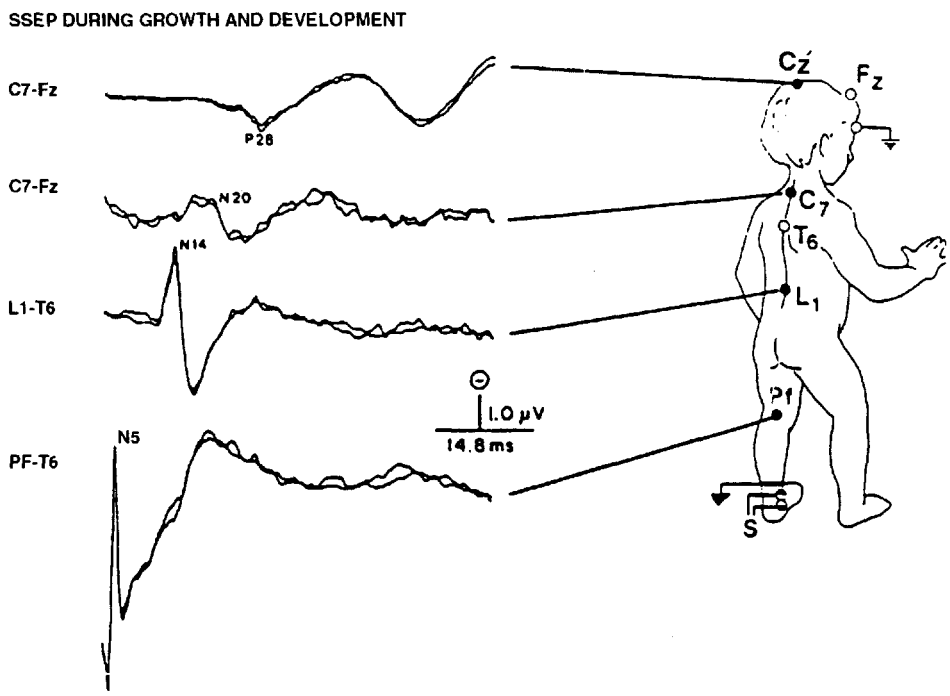


Figure 20–31. Tibial nerve SEP simultaneously recorded at various sites after stimulation at the ankle. The labels show the surface polarity and mean peak latencies observed in 32 normal young subjects (age = 1–8 years, height = 82–130 cm). Electrode placement included popliteal fossa (P_f), first lumbar (L_1) and seventh cervical (C_7) vertebral spinous processes, and C'_z (2 cm behind C_z) referenced to either F_z or the sixth thoracic vertebral spinous process (T_6). [From Gilmore, Bass and Wright,[163] with permission.]

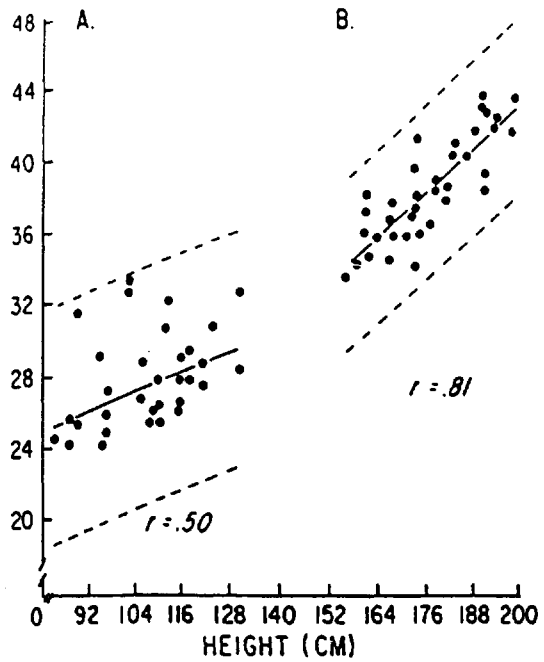


Figure 20–32. The correlation of height to cortical evoked potentials (P_{28} in children and P_{37} or P_{40} in adults). **A.** During growth and development (1–8 years old). **B.** During adulthood (18–40 years old). [From Gilmore et al,[163] with permission.]

root or plexus injuries and bowel, bladder, and sexual dysfunction.[177,313]

SEP measurement also provides sensory studies of the median, ulnar, radial, musculocutaneous, sural, superficial peroneal, and saphenous nerves.[129,419] Less commonly studied nerves include posterior femoral cutaneous nerve,[119] saphenous nerve,[436] and lateral femoral cutaneous nerve.[346] SEP studies help characterize peripheral sensory conduction, especially if peripheral neuropathies abolish sensory nerve action potentials.[361] In one series of eight patients with chronic acquired demyelinating neuropathy, however, 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.[337] In 27 patients with Guillain-Barré syndrome, 7 had normal SEPs despite an abnormal F wave from the same nerve, whereas none with normal late responses had abnormal SEPs.[358] Other conditions tested usefully include cisplatin-induced neuropathy,[261] retrograde effects of digital nerve severance,[60,61] and system disorders such as Machado-Joseph disease.[67]

Unfortunately, the test improves the accuracy of diagnosis less than one might expect on theoretic grounds in many instances. For example, in a combined study of SEPs and peripheral sensory nerve action potentials, preoperative findings correlated well with the discovered locus of brachial plexus lesions in only 8 of 16 patients.[216] In the remaining 8, 5 patients had only minor discrepancy between electrophysiologic and operative data, but the other 3 patients had unexpected root avulsions at surgery despite a prediction of a purely postganglionic lesion. The use of SEPs alone would have provided less help because abnormalities of peripheral sensory nerve action potentials 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.

Spinal Cord and Brainstem

Simultaneous recordings of a sensory nerve action potential and SEPs indicate central involvement in various neuropathies[364,385] and many systemic disorders, such as late-onset ataxia,[326] Kennedy's syndrome,[347] myoclonus,[386] HIV infection,[400] and myotonic dystrophy.[24] In Friedreich's ataxia, studies of the sural nerve show normal conduction velocity despite reduced amplitude. Similarly, the median sensory potentials recorded at the clavicular fossa show a marked attenuation but little evidence of delay. Studies of SEPs, however, reveal a dispersed and delayed cortical response, suggesting slowed conduction in central pathways.[210] Spinal SEPs also show frequent defects in spinal afferent transmission in diabetes,[73,496] Charcot-Marie-Tooth disease,[211] and other peripheral neuropathies.[401]

SEPs provide a unique means of assessing spinal cord injury,[33,498] spinal cord retethering,[272] spinal arteriovenous malformations,[274] subacute combined degeneration,[147,214,408,491,492] spondylotic mye-

lopathy,[86,340,354,355,454,483,487] hereditary spastic paraplegia,[429] HTLV-I associated myelopathy (HAM) or tropical spastic paraparesis,[230,286,312] Pott's paraplegia,[307] tabes dorsalis,[105] adrenomyeloneuropathy,[356] and metachromatic leukodystrophy.[464] Some of these patients also have slow peripheral sensory conduction. In syringomyelia (see Fig. 20–12), abnormalities of SEPs accompany clinical sensory loss despite normal sensory nerve conduction studies.[14,200] Patients with subacute myeloopticoneuropathy (SMON) also have marked attenuation of the cortical component and delayed central conduction of tibial SEPs with normal peripheral conduction.[384] Lumbosacral SEPs from tibial nerve stimulation may or may not show abnormalities in patients with neurogenic bladder resulting from suprasacral cord injuries.[280]

A focal compression of the spinal cord causing little symptoms generally results in few SEP abnormalities.[425] In contrast, diffuse or multifocal lesions of the spinal cord often lead to the absence of scalp response or slowing of spine-to spine and spine-to-scalp propagation velocities.[374] Cervical cord lesions attenuate or abolish cervical responses if evoked by stimulation of an appropriate nerve, for example, the musculocutaneous nerve for C5 or C6, the radial nerve for C6 or C7, the median nerve for C7 or C8, and the ulnar nerve for C8 or T1. High cervical lesions that spare early cervical potentials may abolish or delay the later components.[376] Finally, the electrophysiological characteristics of lumbosacral evoked potentials suggest a degree of spinal cord dysfunction caudal to the area of injury in a substantial number of patients with established spinal cord injury.[270]

SEPs also provide useful data about patients with lesions of the brainstem[78,145] and infratentorial space-occupying lesions.[459] Motor neuron disease may exhibit various SEP abnormalities, despite sparing of the sensory system clinically.[36,69,170,349]

Diencephalon and Cerebrum

In patients with localized cerebral lesions, SEP abnormalities vary considerably, depending on the site of involvement. The pattern of SEP changes, therefore, help localize lesions within the cerebral hemispheres.[414]

Capsular lesions tend to spare P_{14} and N_{18} 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.[472] A variety of SEP abnormalities observed in restricted nonhemorrhagic thalamic lesions reflect the presumed vascular territories.[467] 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 P_{14}[57,180] and N_{18}.[298] 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.[298,471]

Clinical application of SEP studies includes their use to localize subcortical infarction[263] and cortical infarction[258,259,486] and to establish functional prognosis in stroke.[241,289] In general, the degree of initial SEP abnormalities shows a good correlation with eventual clinical outcome.[493] In some cases, the corresponding peaks at the central and parietal electrodes may show independent abnormalities after stroke[469] or resuscitation from cardiac arrest.[40] Similarly, frontoparietal tumors may result in complete absence of N_{70} of the tibial SEP, whereas a frontal meningioma leads only to a slight alteration.[123] In patients with occlusive cerebral vascular disease, SEP studies may reveal increased amplitude on the affected side, perhaps reflecting a disturbance of the suppressor cortex.[412]

Patients with cortical myoclonus characteristically have grossly enlarged responses[196,226,227,306,330,365,383,386,428] that persist after administration of clonazepam or lisuride, known to reduce myoclonus.[366] Measurements of SEPs using

paired stimulation reveal hyperexcitability of the central nervous system in myoclonic patients.[446] Some patients with adult ceroid lipofuscinosis have nearly monophasic, very high-amplitude SEPs totally unlike those found in normal control subjects.[455] Interestingly, etomidate, an ultra-short-acting nonbarbiturate hypnotic, also produces a marked increase in the parietal P_{25} and frontal N_{30}.[122] 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.[442] Similarly, giant SEPs seen in children without clinical myoclonus may also represent a form of hyperexcitability of the central nervous system.[304,370,481,485]

In contrast to myoclonus, Huntington's disease shows a drastic diminution in amplitude of early cortical potentials in general and the N_{20}–P_{25} component of median SEPs and the N_{33}–P_{40} component of tibial SEPs in particular.[34,125,325,477] In Wilson's disease, most patients with neurologic manifestations have some abnormalities of median or tibial SEPs, as expected from widespread degeneration of the brain.[58] Other disorders showing abnormal cortical potentials include portal-systemic encephalopathy,[62] developing brain death,[42,457] head injury,[194,201] coma,[26,290] and locked-in syndrome.[176]

Cortical SEPs recorded with the use of subdural electrodes show a latency (mean ± SD) of 22.3 ± 1.6 ms for a postrolandic potential with initial positivity and 24.1 ± 2.7 ms for a prerolandic potential of opposite polarity, thus allowing clear localization of the central sulcus.[104] Other possible applications include various intraoperative monitoring,[276,329,396] and studies of the effect of sleep on SEPs.[1] Change in median SEP noted while monitoring carotid endarterectomy usually signals cerebral ischemia and the need for a shunt during the surgery.[142,161,164,174,294]

Multiple Sclerosis

Symptoms and signs of multiple sclerosis result from abnormal conduction of central nerve fibers across areas of demyelination. Delayed median SEPs in patients with impairment of position or vibration sense indicate conduction abnormalities of the posterior column (see Figs. 20–22 to 20–25). Studies of SEPs can also uncover clinically silent lesions and document dissemination of disease in patients with clinical signs confined to a single site.[54,66,97,478] Such studies also help quantitate any known abnormalities and localize the level of the sensory disturbance in patients with paraparesis.[107]

Scalp-recorded SEPs show an overall incidence of abnormality ranging from 50 to 86 percent in patients with an established diagnosis[25,54,296] and subclinical abnormalities in 20–40 percent of suspected or possible cases,[54,66,478] with greater sensitivity after stimulation of the lower limb.[9,395,474] A substantial number of patients have major asymmetries in the medium-latency and long-latency components (after NI) elicited by bilateral stimulation of the median nerve, despite normal short latency components (up to NI).[478] Rising body temperature causes conduction block in demyelinated axons in the sensory pathway, thereby distorting the cervical and scalp SEPs.[343]

Recording a short-latency median SEP (N_{13}) from the neck or FFP (P_{14}) from the scalp revealed abnormalities in 69–94 percent of those with a definite diagnosis and in 44–58 percent of patients with a possible diagnosis.[136,156] The latency difference between cervical and scalp-recorded negative peaks showed an 83 percent incidence of abnormality in the definitive group and 68 percent overall.[132] Stimulation of the tibial nerve commonly fails to elicit cervical potentials in definite multiple sclerosis, even with minimal clinical signs.[398]

The incidence of evoked potential abnormalities generally increases in proportion to the duration of clinical illness,[37] although it correlates more strongly with neurologic status of the functional subsystems.[372] Unfortunately, intertrial variability sometimes exceeds the expected changes brought about by disease processes, leading to a tenuous temporal correlation between clinical and electrical changes.[12,66,70,305] Indeed, evoked potential studies may not provide information

for monitoring progression of disease, with frequent disparity between the clinical and electrophysiologic courses.[12,83,87] Furthermore, some SEP abnormalities may not directly correlate with the presence or degree of clinical sensory impairment.[19]

As a diagnostic study of multiple sclerosis, SEPs and visual evoked potentials (VEPs) contribute more than brainstem auditory evoked potentials (BAEPs) or electrically elicited blink reflexes. Waveform analyses may yield a higher incidence of abnormality than latency measurement alone.[135] Serial studies of multimodality evoked potentials, if properly selected on the basis of clinical findings, can establish temporal or anatomic dissemination, but not necessarily the specific diagnosis of multiple sclerosis. Morphologic lesions seen in magnetic resonance imaging (MRI) of the cervical cord usually render appropriate electrophysiologic deficits in SEP.[445] Combined evoked potential testing yields a higher sensitivity than MRI,[160] but MRI offers a better yield than any single evoked potential study alone.[413] In one series of 222 patients suspected of having multiple sclerosis, an abnormality demonstrating a clinically silent lesion in any modality of evoked potentials predicted a 71 percent chance of clinical deterioration compared to 16 percent in the remainder.[193] In contrast to a high incidence of SEP abnormalities in multiple sclerosis, patients with acute inflammatory transverse myelopathy tend to have entirely normal responses.[359]

Spinal Cord Monitoring

Another clinical application of SEP relates to its use as an intraoperative spinal cord monitor.[80,81,171,172,208,213,327,390,399] During scoliosis surgery or removal of a spinal cord tumor, general or local anesthesia precludes clinical examination of spinal cord function. Tibial or peroneal SEPs persist under halogenated inhalational anesthesia, albeit with a slight reduction in amplitude.[371] Other factors of importance dictating latency and amplitude of SEP include blood pressure, body temperature, and administration of various medications. In one patient developing hemorrhagic hypotension, SEPs deteriorated only with systolic pressures in the low 40s.[461] Hypothermia induced for surgical repair of the aorta abolished cortical SEPs at about 20° C and subcortical components at lower temperatures.[173] Intravenous loading of diphenylhydantoin at serum levels below 30 μg/ml induces a reversible delay of synaptic transmission in spinal and central somatosensory structures.[301]

A normal SEP offers no guarantee for the integrity of the entire pathway of the spinal cord, whereas a markedly distorted or delayed response usually signals a warning and an impending risk. In patients with preoperative evidence of cord damage, the cortical response tends to fluctuate as a function of patient diagnosis, neuromuscular status, age, and procedural factors.[279] In fact, it could abate entirely without a major change in the concentration of the anesthetic agent or surgical manipulation of the cervical cord.[454]

Most initial studies dealt with cortical potentials evoked by peripheral nerve stimulation. This type of recording shows inherent variability in amplitude as a major disadvantage[16] dependent on fluctuating levels of consciousness during anesthesia.[323,338] Spinal cord potentials show less variability when recorded either from Kirshner wire electrodes inserted in the spinous processes[324] or from needles in the interspinous ligament.[283] A pair of surface electrodes placed over the neck and scalp register P_{14} and P_{31} after stimulation of the median and tibial nerve. These FFPs generated at the foramen magnum also serve as a useful measure showing less effect of anesthesia compared with cortical potentials.[283] If peripheral nerve stimulation fails to elicit a spinal cord potential or FFPs of adequate amplitude, cauda equina stimulation produces considerably higher evoked potentials, permitting reliable monitoring of spinal cord function.[103]

Stainless-steel wire electrodes inserted into the epidural space register two to three negative potentials after stimulation of the peripheral nerve in humans (Fig.

20–33).[212,391] Estimated conduction velocity ranges between 65 and 80 m/s for the fastest activity and 30 and 50 m/s for the slower waves.[212,291] In animals, spinal evoked potentials also consist of two negative peaks after direct cord stimulation.[422,444] Transection of the lateral column attenuates the first peak; 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. 20–34).[291] The same spinal stimulation also elicits a compound muscle action potential 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. Individual variabilities in the waveform and amplitude of the spinal potential reflect inconsistency in the placement of the stimulating or recording electrodes.[423] Precise positioning of electrodes at optimal locations would minimize this difficulty by selective stimulation of, or recording from, the spinal pathway in question (see Chapter 7–5). The facilitatory or inhibitory effect on the spinal motor neurons, however, may spread many segments below the level of the cathode.[175] Direct stimulation of the spinal cord also allows recording of peripheral nerve action potentials at the popliteal

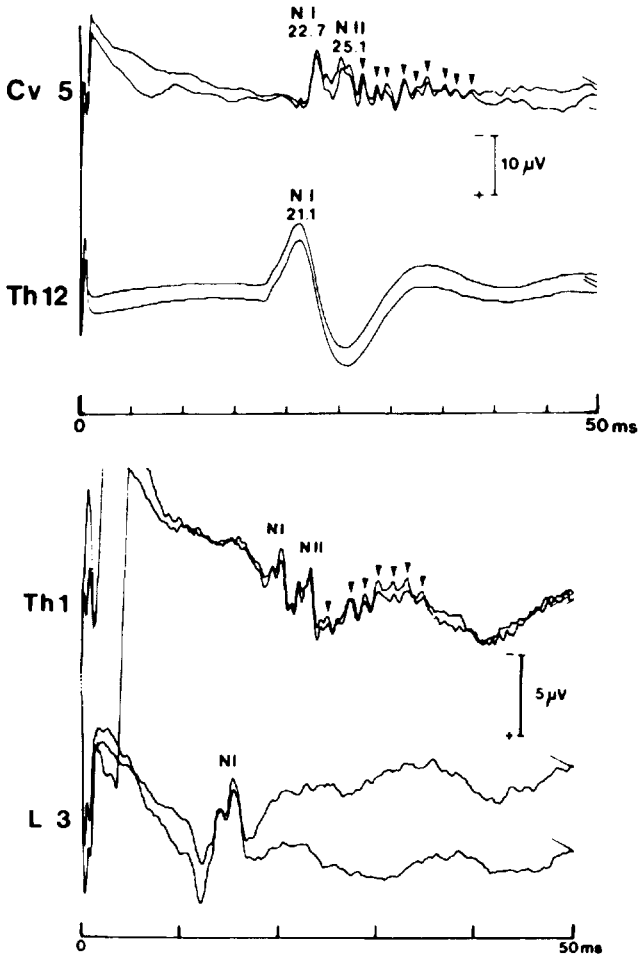


Figure 20–33. Spinal evoked potentials recorded from an epidural electrode placed at the rostral and caudal spine after stimulation of the tibial nerve in two subjects. The response recorded at the T12 spine level consisted of a single diphasic potential with the initial negativity. The waveform varied considerably when recorded at the L3 spine level or further caudally. Polyphasic waves followed the major negative peaks, NI and NII, at the rostral spine. [From Machida, Weinstein, Yamada et al,[291] with permission.]

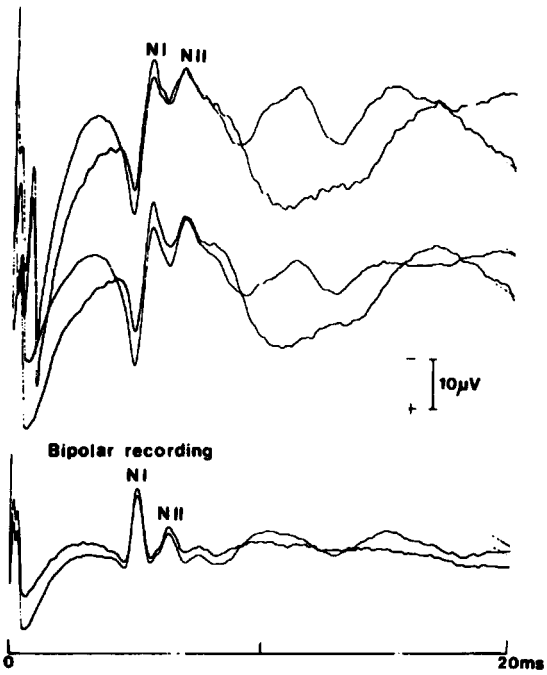


Figure 20–34. Comparison of monopolar and bipolar recording of spinal evoked potentials. Two top tracings show monopolar recordings from G_1 and G_2 placed 1 cm apart at the level of the T5 spinal process referenced to G_2 at the paraspinal muscle. The *bottom tracing* represents a bipolar derivation connecting G_1 and G_2 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. [From Machida, Weinstein, Yamada, et al,[291] with permission.]

spaces under maximum neuromuscular blockade.[344]

The various recording techniques described here complement one another in the assessment of spinal cord function in the operating room. Postoperative neurologic deficits, however, may ensue despite unchanged intraoperative SEPs,[271] or conversely, intraoperative SEP may abate without any consequent postoperative motor deficits.[51] A large multicenter study has shown that SEP monitoring reduces postoperative paraplegia by more than 50–60 percent.[328]

Clinical Value and Limitations

Although a number of neurologic conditions accompany abnormal SEPs, the value of the technique as a clinical test in some of these entities awaits confirmation.[56,244] This category includes head trauma,[46,382,392] brain death,[27,49,155,165,456] cerebral aneurysm,[149] cerebrovascular ischemic disease,[235,352] sleep,[1,468] cord injury,[108] idiopathic scoliosis,[38] cervical spondylosis,[393] neurogenic bladder,[177,280] spasticity,[91] degenerative diseases in children,[72] Down syndrome,[228] adrenoleukodystrophy,[157] xeroderma pigmentosa,[198] maturational changes,[22,124,159,221,236,237,266,292,427] trigeminal neuralgia,[416] olivopontocerebellar atrophy,[179] Parkinson's disease,[318] motor neuron disease,[490] progressive muscular dystrophy,[417] myotonic dystrophy,[23,168] achondroplasia,[320] and hypoglycemia.[100]

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, common with any new diagnostic procedure, poses a particular problem in SEP studies, which have become routine before their time, while the technique still continues to evolve rapidly.[128,243] Despite widely publicized clinical applications, in many instances, these investigative procedures can provide only limited information useful for the diagnostic work-up of individual patients.

Conservative and selective use of the test in proper clinical contexts would maximize its impact in electrodiagnostic medicine. Only with such a precaution will SEP studies play a meaningful role as a diagnostic procedure. SEPs can directly assess the transmission of the 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 cen-

tral nervous system in humans. Such clinical and experimental data will help define precisely its diagnostic value and limitations. With a 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.

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Chapter 21

MOTOR EVOKED POTENTIALS

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.[127,167,249] A modern electrical stimulation can excite the motor cortex transcutaneously using shocks of a high voltage.[199] Similar stimuli applied over the cervical spine activate C8 and T1 motor roots in the region of the intervertebral foramina.[200] Stronger stimuli excite the descending tracts directly at the level of the spinal cord[194,216,304] and the pyramidal decussation.[324,326,331] Transcutaneous electrical stimulation has provided important insight into motor physiology and pathophysiology,[85,264] and has revealed a high incidence of abnormality in patients with multiple sclerosis.[59,214,266] Discomfort associated with shocks applied at the scalp, however, limits its practical application.[268]

Painless transcranial magnetic stimulation has generally replaced electric shock, gaining wide acceptance in the clinical study of motor evoked potentials (MEPs).[12] In addition to the motor cortex, magnetic stimulation can also excite the motor roots in the region of the intervertebral foramina, as well as deep-seated nerves and plexuses, without causing pain.[46,93,303] A specially constructed coil can also activate the pyramidal decussation,[327,333,334,336,350] but not descending motor tracts within the spinal cord.[330] At present, this technique has little use in the assessment of the peripheral nerve for two reasons: uncertainty about the exact activation site and difficulty in achieving supramaximal stimulation without exciting neighboring structures.[33,94,240] Advances in coil design will further improve technical precision and, thus, the clinical utility of transcranial magnetic stimulation.

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 axons of pyramidal tract neurons in the region of the axon hillock. This results in a single descending volley,[4,60,133] or direct wave (D wave), so termed because of its short latency, with no interposing synapse.[248] Stimulation at higher intensities induces a series of descending volleys, or indirect waves (I waves), after the D wave at intervals of about 2 ms. They represent trans-synaptic activation of the same corticospinal neurons through interneurons.[147] Removal of the cortex abolishes the I waves but not the D wave. The twitch force produced in the first dorsal interosseous muscle by a single high-intensity anodal shock to the contralateral scalp can greatly exceed the force produced by supramaximal stimulation of the peripheral nerves.[69] This indicates that a single cortical shock can cause repetitive firing of motor neurons, which summate to produce a very large force.

D Wave and I Waves

In stimulating the motor cortex from the surface, anodal current, which hyperpolarizes dendrites, depolarizes the axon and cell body more effectively than cathodal current does.[118] With surface positivity, current flows out of the dendrites (source) of the pyramidal tract cells and enters the axon hillock (sink), depolarizing the first internode and producing a D wave. Stimulation with higher intensities activates interneurons and afferents to the cortex, resulting in trans-synaptic 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 trans-synaptic excitation of I waves.[69,273]

Human studies have confirmed this finding,[24] by altering firing probability of a voluntarily activated motor unit by randomly timed cortical stimulation. Low-intensity shocks elicit a single peak in the peristimulus time histogram corresponding to the excitatory postsynaptic potential 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 la-

tency of about 2 ms, followed, with increasing intensity, by a series of I waves.

Technical Considerations

Bipolar stimulation involves placing of an anode over the motor cortex and a cathode at the vertex.[58,214,215] With a specially made stimulator capable of delivering a high-voltage (2000 V) pulse of short duration (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.

A modified technique utilizes monopolar stimulation capable of exciting the motor cortex with a fraction of the shock intensities employed previously (Fig. 21–1).[111,268] A flat anode (4.8 cm^2) is placed on the scalp over the motor cortex, and a flexible stainless-steel belt cathode is wrapped around the head 2–3 cm above the nasion–inion plane (see Chapter 20–2). A unifocal stimulation tends to concentrate the electrical field from anode to cathode on the motor cortex, whereas a bifocal stimulation orients the field tangentially along the surface. A pair of surface electrodes placed conventionally over the target muscle suffices for recording the evoked potential.

High-voltage electrical stimulation at the base of the skull may also activate the descending motor tracts at a point midway between the cortex and the cervical enlargement.[331] The posterior aspects of the mastoid processes are used as anode and cathode. A small voluntary contraction of the target muscle tends to facilitate an evoked muscle response with no change in latency. One study[331] yielded a 1.5 ms latency difference 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 stimulate the pyramidal decussation at the level of the cervicomedullary junction. Unlike cortical stimulation, which elicits multiple descending volleys, brainstem stimulation probably evokes a single impulse.

Stimulation of the pyramidal tract at two levels along the spinal column allows the examiner to calculate conduction velocity in the same way as in the study of the peripheral nerve. The very large electrical stimuli (1500 V) necessary for transcutaneous stimulation of the spinal cord,[194,304] however, make it unsuitable for routine clinical studies. An alternative method to approximate spinal cord conduction velocity involves monopolar needle stimulation of the spinal cord at the C5 level, and recording of the muscle response from the ipsilateral tibialis anterior muscle.[19]

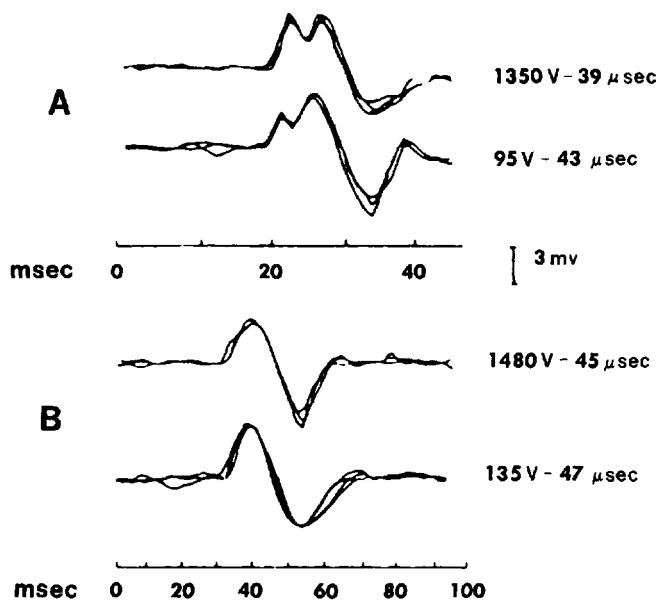

Figure 21–1. Compound muscle action potentials evoked by electrically stimulating hand (**A**) and leg (**B**) motor areas over the scalp in the same subject. Comparison between bipolar (*first and third tracings*) and unipolar (*second and fourth tracings*) stimulation show a substantial difference in stimulus voltage (*V*) and duration (*μs*) required to elicit similar muscle action potential waveform, amplitude, and latency in the two conditions. [From Rossini,[263] with permission.]

Clinical Studies and Limitations

Transcranial cortical stimulation is used for spinal cord monitoring of the motor tracts during surgery.[82,164,165,359] If muscle relaxants completely block neuromuscular transmission, some investigators[243,252] propose recording peripheral nerve potential from the popliteal fossa after stimulation of the spinal cord with needle electrodes inserted into spinous processes (see Chapter 20–6). Spinal evoked potentials recorded by epidural electrodes also serve as a means of monitoring spinal cord surgery.[150,299] Nitrous oxide suppresses the muscle response evoked by electrical stimulation of the motor cortex, inhibiting corticospinal pathways, presumably at the level of the spinal neuronal or interneuronal system.[361] Anesthesia, with inhalational agents such as halothane, enflurane, and isoflurane, also suppresses the descending impulse at the level of the spinal interneuronal or motor neuronal systems.[360] Ischemia associated with profound systemic hypotension can alter or obliterate evoked responses.[107] For this purpose, an electrical shock has an advantage over magnetic stimulation; use of smaller electrodes induces focal activation, overcoming the effect of anesthetic agents. In addition, the lack of pain with magnetic stimulation provides no benefit for intervention under anesthesia. Patients undergoing surgery may show an abnormal motor potential recorded directly from the spinal cord despite normal somatosensory evoked potentials (SEPs).[24,166]

Despite the advent of magnetic stimulation, certain physiologic studies still require an apparatus that delivers single electrical stimuli of up to 700 V with a half-decay time for discharge of 50 or 100 μs.[14,259,273] High-intensity stimulation of the scalp causes discomfort associated with contraction of the scalp and facial muscles. It also poses considerable concern regarding electrical hazards. The unifocal method requires relatively low-voltage stimuli, which can be delivered from an ordinary stimulator built according to established safety standards. Electrical 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 (50 μs) on several occasions will probably produce few side effects, if any. Nevertheless, one must seek unequivocal evidence from an animal model that no permanent adverse changes result from the specific modes of cortical stimulation under consideration.

3 TRANSCRANIAL MAGNETIC STIMULATION

Design of the Magnetic Coil

In conscious, alert subjects, magnetic coil stimuli applied to the human brain through the intact scalp and skull can elicit a motor evoked potential (MEP).[11,67,121,122] Up to 10 percent of normal subjects may have no lower limb responses with a circular coil. The figure-of-eight coil has a better yield with very precise placement that takes advantage of focal excitation under the site of intersection.[86,139] This type of coil can activate the bulbocavernosus, sphincter, and pelvic floor muscles.[91,241] Magnetic stimulation also induces a sensation described as tingling descending along the leg, usually accompanied by responses evoked in the leg muscles.[57] The coil can activate the peripheral nerves and roots in addition to cortex but, for some unknown reason, not the spinal cord.[330]

Magnetic stimulation relies on Faraday's principle;[106] 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. This technique, first applied in peripheral nerve stimulation, was soon used in studies of the motor cortex.[10,20,80] 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.[211] Analysis of the electric field orientation localizes the site of maximal intensity to the level of the gray–white junction, supporting activation of layer VI of the cerebral cortex.[90]

A magnetic coil generates a brief but intense magnetic field of up to 2 tesla when a capacitor charged to 4 kV is discharged, passing a current of about 5 kA. The magnetic field induced by the coil placed over the scalp penetrates unattenuated through the skull.[256] This in turn induces electrical currents inside the skull to a level that excites the motor cortex, even though the low current density at the surface causes no pain. In addition to the figure-of-eight or "butterfly" configuration,[36] other variations of coil shapes tested favorably include the "four-leaf," "slinky,"[367] and "double cone."[334,336]

Discharge Pattern of Motor Neurons

The factors that dictate the size of the MEP include the intensity of stimuli, location and orientation of the stimulating coil, and intrinsic excitability of neural elements.[121,217,229] Responses elicited on the contralateral side of the body have a latency consistent with conduction in fast central pathways (Fig. 21–2). A stimulus intensity set approximately 20 percent 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 a longer onset latency usually by about 2 ms than those elicited electrically.[123] This difference equals the time interval between the D wave and the first I wave, suggesting preferential excitation of interneurons rather than motor neurons by magnetic stimulation.[70,190,192] The D wave response generated only with stimuli of very high intensity has a shorter latency and resists anesthesia.[100] The direction of current flow in the magnetic coil also dictates the efficacy of cortical current for the interneurons or motor neurons.[68,352] To activate the left hemisphere and the right small hand muscles, a circular coil is centered at the vertex directing the inducing current anticlockwise as viewed from above (Fig. 21–3). Reversing the direction of the current by turning the coil over stimulates the opposite side. In one study, the threshold to activate the contralateral abductor digiti minimi was less for the left hemisphere than for the right.[183]

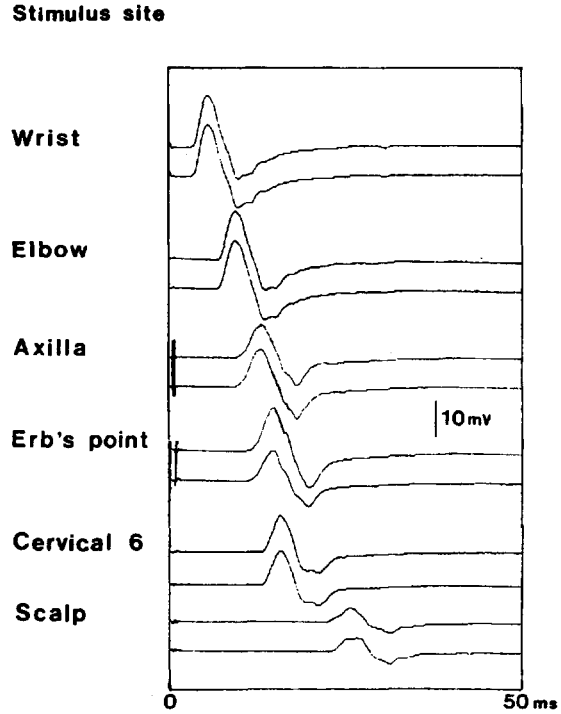

Figure 21–2. Compound muscle action potentials recorded from abductor pollicis brevis after magnetic coil stimulation at various points along the motor pathways. Scalp stimulation characteristically evokes less than maximal response despite the use of an optimal stimulus.

According to the size principle,[17] small cortical motor neurons with slowly conducting axons fire first during voluntary effort, followed by recruitment of larger, faster conducting neurons (Fig. 21–4). Magnetic stimulation also activates the cortical motor neurons in the same order, with the first motor units showing a relatively long latency.[123] 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. Stronger stimuli cause the same motor units to discharge with less latency and recruit other motor units.

Single electrical or magnetic stimuli may cause multiple firing at the level of

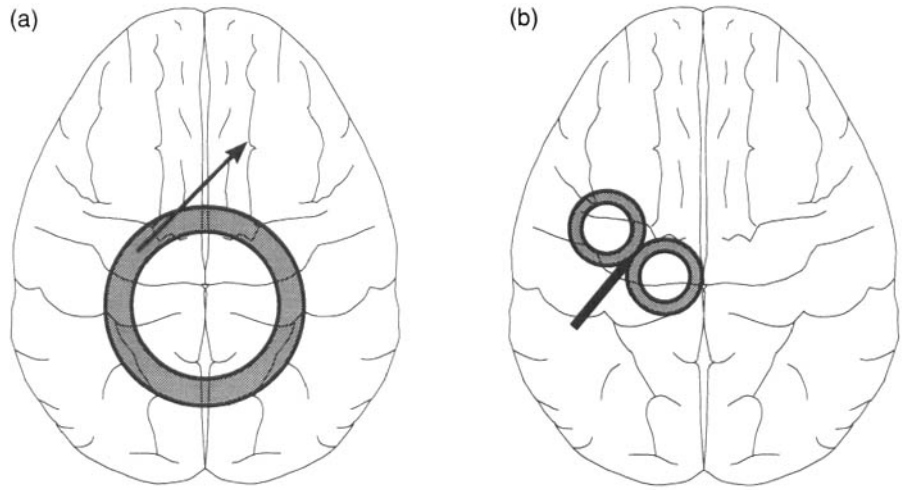

Figure 21–3. With a circular coil of diameter 10 to 12 cm centered at the vertex, the circumference of the coil overlies the hand area of the motor cortex. The tangent at the optimal site is approximately 45° to the parasagittal plane (**a**). A figure-eight coil with its central segment overlying the hand area is most effective when angled to lie along the same tangent (**b**). [From Mills,[208] with permission.]

the anterior horn cell. Thus, the duration and complexity of the evoked muscle response continues 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 motor neurons in response to a descending volley.[69,123,273] Hence, a maximal antidromic volley set up by stimulation at the wrist fails to eliminate entirely the orthodromic volley of the peripheral nerve induced by electric[69] or magnetic brain stimulation. Here, the remaining response corresponds to the spinal motor neurons firing more than once. These findings suggest that the enhancement of responses by voluntary background contraction depends not only on the additional recruitment of higher threshold motor units in the motor neuron pool but also on multiple firing of the same motor units (Fig. 21–5).

Magnetic stimuli applied transcranially can modulate the firing of tonically active hand muscle motor units. This technique involves constructing a peristimulus time histogram, building up a picture of motor-unit firing probability over many trials.[23,102,119,205–209,213] In normal subjects, firing probability increases approximately 20 ms post-stimulus, constituting the primary peak, which reflects the excitatory postsynaptic potentials (EPSPs) induced in motor neurons. This type of assessment has revealed abnormal excitability of the corticospinal pathway in patients with amyotrophic lateral sclerosis,[84,89,153,154,218] but not in Kennedy's disease, which selectively affects lower motor neurons.[349] The same technique has also elucidated the influence of the corticobulbar system on the orbicularis oris, providing evidence for a short-latency activation of EPSPs consistent only with a direct monosynaptic projection.[172]

Facilitation and Inhibition

Repeated trials of transcranial magnetic stimulation show a high degree of variability in the amplitude of evoked response.[148,235] This instability probably results from spontaneous fluctuations in corticospinal excitability.[87] Paired cortical stimuli reveal a series of excitability changes, including initial facilitation at intervals of 1–2.5 ms, followed by a period of suppression of up to 20 ms and gradual recovery thereafter.[134,269,281] Record-

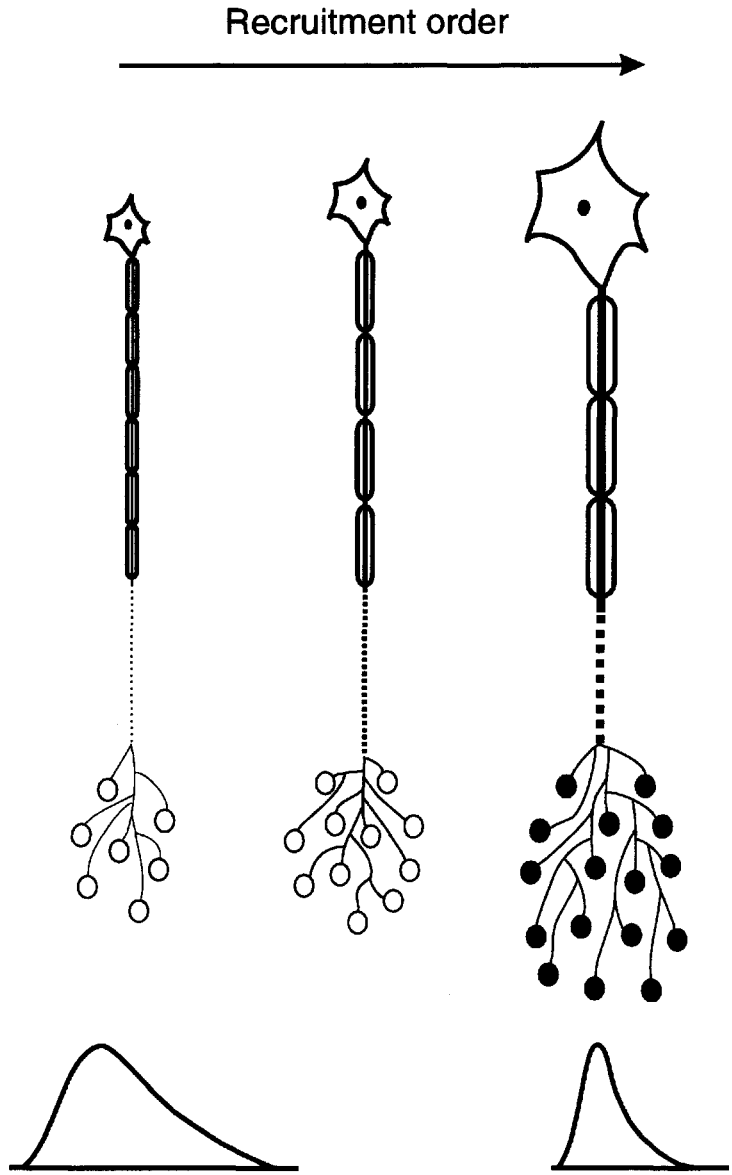

Figure 21–4. The recruitment order of spinal motoneurons under increasing voluntary or reflex drive is related to their physical size (Henneman's size principle). Small motoneurons have thin axons and connect with muscle fibers with slow twitch characteristics. Large motor neurons have thicker axons and produce fast twitches. [From Mills[208] with permission.]

ing the evoked corticospinal volleys also shows triphasic changes of motor cortex excitability, inhibition at 2.5 ms, facilitation at 25 ms, and a second inhibition at 100 to 200 ms after a conditioning stimulus.[144,145,228]

A voluntary effort to contract the muscle, or even having the thought without actually making the movement,[149] facilitates the responses evoked in that muscle by cortical stimulation.[121,122] This type of facilitation depends primarily on lowering the motor neuron threshold at the level of the motor cortex and spinal cord, with[181,289] or without[290] an additional peripheral mechanism. When using electric stimulation, voluntary contraction causes the otherwise insufficient D wave to discharge the motor neuron by summation, reducing the onset latency by 2–4 ms and increasing the amplitude approximately linearly with the degree of effort. With magnetic stimulation, a small contraction reaching only 5 percent of maximum has a marked effect on amplitude,[116] probably as the result of spinal

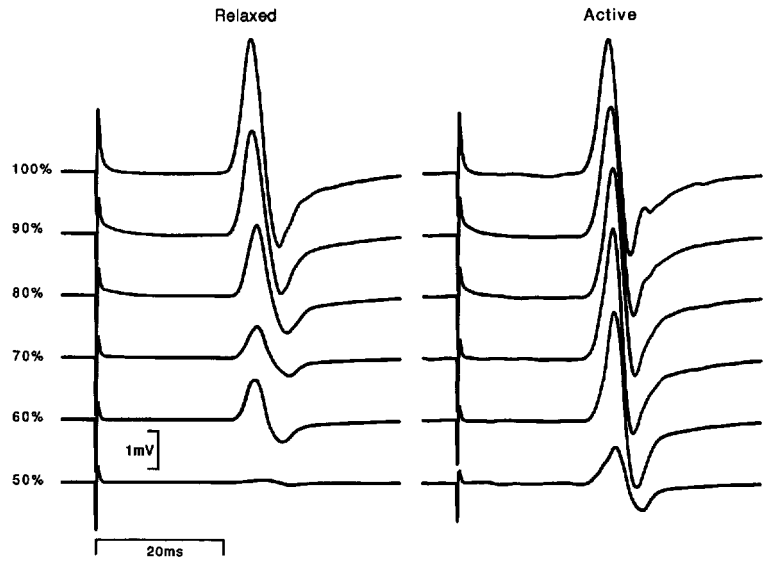

Figure 21–5. Voluntary activation facilitates the muscle response to brain stimulation. Compound muscle action potentials recorded from the FDI muscle at stimulus intensities from 50% to 100% of maximal stimulator output. At each intensity, five trials have been averaged. On the left the muscle was resting and on the right maintaining a 10% maximum voluntary isometric contraction. At all intensities below 100%, the response in the relaxed muscle is smaller than in the active muscle. The latency at 100% intensity in the resting state is 24.2 ms and in the active state is 22.8 ms. [From Mills,[208] with permission.]

summation,[144,145] shortening the onset latency of the compound muscle action potential by about 3 ms without further change when the background contraction increases (Fig. 21–6).

Mild non-fatiguing exercise causes postexercise facilitation with a decay to baseline over 2 to 4 minutes, whereas fatiguing exercise leads to postexercise depression, which returns to baseline after about 12 minutes.[26,29,280] In another study, however, voluntary contraction of the contralateral counterparts produced neither postexercise facilitation nor depression.[278] In one study[306] voluntary contraction of the dominant hand facilitated MEP elicited in the contralateral non-dominant hand, suggesting a transcallosal modulation of excitability. Similarly, postexercise facilitation elicited by ipsilateral simple finger movement suggests transcallosal transfer of excitability from the dominant to non-dominant cerebral hemisphere.[25] In experiments using ballistic contractions of the target muscle, spinal facilitation predominated at a low force level, whereas increased cortical excitability contributed equally at forces greater than 10 percent

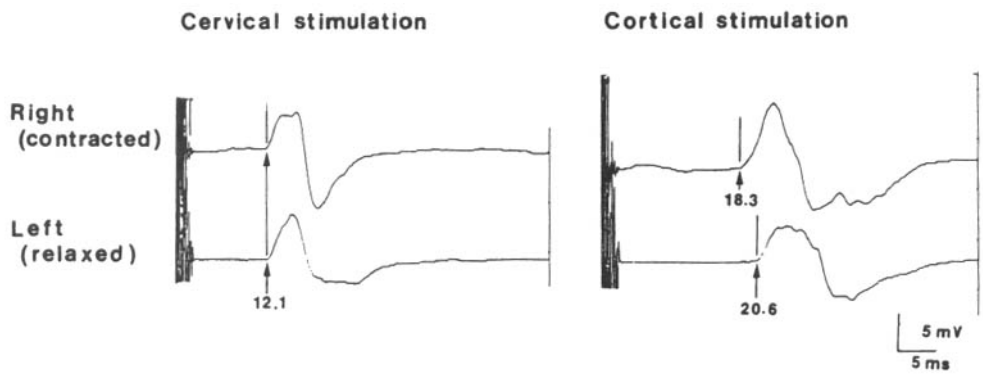

Figure 21–6. Compound muscle action potentials recorded from abductor digiti minimi after magnetic stimulation over the neck and scalp (C_z). Responses in each column represent simultaneous recording from the minimally contracted muscle on the right and the relaxed muscle on the left. Note the effect of voluntary facilitation with cortical stimulation, but not with cervical stimulation.

of the maximum.[212] Step as compared to ramp abduction of the index finger induced a longer facilitation.[146] Dynamic rather than static contraction gave rise to a greater facilitation of the target muscle.[6] Facial or eye movements induce nonspecific facilitation of the abductor pollicis brevis response.[5] A Jendrassik maneuver 200–400 ms preceding the magnetic stimulation also enhanced the response.[251]

Motor evoked potential is sustained during the silent period induced by stimulation of a mixed nerve[357] because activation of muscle afferents increases cortical motor excitability. Vibration of the target muscle enhances a cortically activated response by altering the excitability of alpha motor neurons.[52,158,301] Conditioning by motor threshold stimulation of the median nerve at the wrist enhances the MEP, probably on the basis of muscle afferent input.[156] Cortical excitability also reflects cutaneous afferent activities[73,271] and other inputs such as speech.[316]

A magnetic stimulus over the cerebellum reduces the size of responses evoked by magnetic cortical stimulation given 5–7 ms later.[332] Transcranial magnetic stimulation induces a silent period of the voluntarily contracted target muscle (see Chapter 19–5),[64,162,197,236,276] probably on the basis of intracortical inhibition.[99,337,338,340,353] Transcranial magnetic stimulation also induces inhibition of brainstem motor neurons at a cortical level.[64,163] Focal transcranial magnetic stimulation on one hemisphere suppresses ongoing voluntary muscle contraction in ipsilateral distal muscles.[66,203] This transcallosal inhibition, mediated by the anterior half of the trunk of the corpus callosum, develops after the age of 5 years.[114] Voluntary contraction reduces ipsilateral corticocortical inhibition induced by a conditioning subthreshold transcranial magnetic stimulation at short interstimuli of up to 6 ms.[258] Thus, voluntary drive seems to reduce the excitability at inhibitory circuits in cortical areas that project to active muscle. Intrathecal baclofen infusions induced a marked increase of the transcranially evoked silent period in a patient with dystonia.[300] Adolescents with diplegic cerebral palsy showed no transcallosal inhibition.[115]

Practice and Safety Considerations

A pair of surface electrodes placed conventionally over the target muscle suffice for recording the evoked potential.[79] Transcranial magnetic stimulation elicits the best response when the muscle is modestly facilitated in the range of 10–20 percent of maximal contraction. 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.[123] 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.[121] We choose the shortest onset latency and largest response from a series of four or five consecutive responses, expressing the amplitude as a percentage of the maximal muscle response evoked by peripheral nerve stimulation.[123] The size difference between peripherally and transcranially induced responses, at least in part, results from physiologic temporal dispersion and phase cancellation (see Chapter 7–5). Assessments should include waveform complexity, trial-to-trial variability[31,32] and corticomotor threshold.[210,217,218] Late muscle responses sometimes recorded after the cortically evoked short-latency primary potential probably reflect startle effect from the scalp stimulus.[125]

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 motor neurons. Reduced amplitude may also result from depressed excitability of spinal motor neurons 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, de-

spite some findings considered more typical of one than another. The technique may occasionally demonstrate subclinical motor abnormalities, although more often it confirms known deficits of the motor system, detected by clinical examination. The numerous physiologic variables affecting the descending volley in the corticospinal tract alter the central conduction time by a few milliseconds. Thus, the role of magnetic brain stimulation for quantification of abnormalities and for follow-up purposes remains undefined.

Magnetic stimulation capable of painless excitation of the motor system has an obvious advantage over electrical stimulation if it proves safe in the clinical domain.[58,120,214] In one series of 30 healthy subjects, EEG and cognitive and motor tests remained unchanged before and after transcranial magnetic stimulation. Except for a slight decline in serum prolactin level, biochemical studies showed no correlation between the test results and the extent of stimulation.[30] 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, and heart rate.[95] Although the heating of metal electrodes during rapid rate magnetic stimulation constitutes a possible safety hazard, temperature does not increase to the degree high enough to induce a skin burn.[3,272] 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.[138] Although many thousands of patients have undergone cortical stimulation, only isolated reports of focal seizures during or after the procedure have appeared.[126,142] The possibility of adverse effects, nonetheless, must be borne in mind with the clinical application of newer techniques. Theoretically, magnetic stimulation could dislodge intracranial metallic objects such as aneurysm clips and shunts, although this is highly unlikely. For now, we exclude patients with a history of epilepsy, those with a cardiac pacemaker, and those who have undergone neurosurgery. A published guideline describes the use and safety of a repetitive transcranial magnetic stimulator.[43,346,347]

4 STUDIES OF THE PERIPHERAL NERVE

Attempts to magnetically stimulate the peripheral nervous system date back to 1959, first in a frog nerve-muscle preparation[155] and later in a mixed human nerve[20] producing visible muscle contractions. A single pulsed magnetic field can elicit compound muscle action potentials,[10] with its clinical utility to activate the proximal nerve segments not easily accessible to electrical stimulation.[94,175,176]

Stimulator Characteristics

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 would depolarize the axons more effectively, although transverse fields also contribute.[274] Results may vary depending on soft tissue heterogeneity, which dictates current flow.[151] Lifting part of the stimulator head from the skin makes stimuli markedly less effective. A clockwise or counterclockwise current flow in the stimulator coil causes no major differences in effect. Submaximal nerve activation renders the estimation of the point of nerve stimulation less accurate.

Some investigators experienced failure of one type of round coil to selectively excite the peripheral nerves. For example, supramaximal stimulation of the median nerve at the wrist tended to concomitantly activate the ulnar nerve.[94] Using a different type of round coil, others reported success in focally exciting some peripheral nerves.[176,240] In one study, round coils delivered supramaximal stimulation in a tangential-edge orientation, but only at some selective sites. Currently available

round coils, in general, fail to fulfill the stimulation requirements for the peripheral nerve. In contrast, butterfly coils, although less precise than electrical stimulators, can provide selective supramaximal stimulation at all sites, presumably because of improved focus rather than increased strength of the magnetic field.

The differences in conduction velocities derived by means of round coils used on two separate occasions ranged from 5 to 11 m/s for motor studies[108] and up to 14 m/s for antidromic sensory conduction velocities.[240] The use of a butterfly coil showed differences of less than 7 m/s for sensory and motor conduction velocities in most segments. Calculated conduction velocities varied more with magnetic stimulation than with electrical stimulation, especially for the short segment of the ulnar nerve across the elbow, where differences reached 18 m/s.[240] Although electrical stimulation preferentially activates sensory axons over motor axons, magnetic stimuli show no such tendency, activating both fiber populations equally. Thus, electrical stimulation is better for detecting focal changes at common entrapment sites and eliciting H reflexes by selective submaximal activation of the sensory axons.[240] Magnetic stimulation applied directly over skeletal muscle elicits contraction indirectly through nerve activation at the motor point.[88,184] Such stimulation also evokes cerebral potentials[320] by activating terminal afferents in the muscle independent of muscle contraction.[363] Magnetic stimulation shows a greater longitudinal dispersion than electric shocks, as evidenced by collision experiments.[62] Muscle activation and stimulus artifact with magnetic stimulation preclude reliable recording of distal sensory nerve action potentials.[173]

Available data do not seem to 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.[94] 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.[94,176,240,303] Smaller stimulator heads with higher power output and improved coil configuration may perform more acceptably.[21]

Stimulation of Deep Structures

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, however, attenuate very little through tissues such as bone, providing a useful addition when studying deeply located proximal nerve segments.[63] High-voltage electrical stimulation given over the spinal column evokes supramaximal motor responses from the arm or leg.[187,194,216] Paravertebral magnetic stimulation can also elicit potentials in limb muscles with relatively little pain, although 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.[33] Modified designs may improve the capacity of a coil for focal supramaximal stimulation.

Magnetic as well as electrical stimulation applied over the cervical spinal cord near the C6 spinous process elicits muscle action potentials in the upper limbs. Voluntary contraction does not appreciably facilitate the effect of spinal, as opposed to cortical, stimulation. Onset latencies fall short of peripheral conduction times estimated from the F wave. In the cervical excitation of the roots, the site of stimulation using either the electric or magnetic method occurs 2–4 cm distal to the motor neuron.[216,283] In addition to the degree of nerve excitability, the electric field dictates the site of activation in heterogenous volume conductors.[179] In clinical practice, a slight shift in position of the magnetic coil induces no notice-

able change in latency of the evoked response.[178] Thus, depolarization must originate distal to the anterior horn cell, probably in the axon hillock, known to have the lowest threshold for excitation. 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.[283] 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.[368] Similarly, magnetic stimulation at the T10, T12, and L5 vertebral levels elicits cortical somatosensory evoked potentials showing correlation between body height and N2, but not other components.[319]

Similar strategies apply to the lumbosacral region to evoke muscle action potentials in the lower limbs.[193] Stimuli delivered over the cauda equina elicit a response less effectively than those delivered at the T12 spinous process over the conus medullaris.[329] 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 motor neuron for the motor axons with a conduction velocity of 50 m/s.[33] Consequently, the peripheral conduction time estimated by this means excludes the radicular part of the nerves. With progressively higher levels of supramaximal stimuli, latency often decreases further, reflecting the spread of effective current distally.[253] Configurations of the M responses elicited by proximal magnetic stimuli vary from one trial to the next partly because of intermittently generated F waves. We take advantage of this variability of successive response in indirectly recording proximally activated F waves by consecutive subtraction of sequentially elicited M responses. Collision studies also reveal the presence of F waves by eliminating orthodromic impulses, and consequently the overlapping M response, by the antidromic impulses produced by the concomitantly applied distal stimulation. Such an F wave starts 6–8 ms after the M response evoked by the same paravertebral stimulation alone. The onset latencies of the proximally evoked F waves, using the collision method or subtraction technique, provide a measure of the most proximal parts of the motor axons.

With the use of a figure-of-eight coil, a horizontally oriented junction over the distal cauda equina optimally excites the lumbar roots, whereas the vertically oriented junction tends to activate the sacral roots.[180,185] Using a vertically oriented junction of a figure-of-eight coil, and a cranially oriented induced current, magnetic stimuli can also excite the cauda equina proximally near or at the root exit zone.[180] 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 and H waves reveals a short interval corresponding to the latency of the central loop (see Chapter 19–2, Fig. 19–5).[318,362] Magnetic coil stimulation also has an advantage over electrical shocks when studying an otherwise inaccessible deep nerve, for example, the intracranial portion of the cranial nerves,[103,282] phrenic nerve,[101,366] femoral nerve,[254] and thoracic spinal nerve.[44]

Intracranial stimulation of the facial nerve generates an impulse approximately 6.5 cm proximal to the usual site for electric stimulation near the stylomastoid foramen.[177] The actual site of stimulation lies in the proximal part of the facial canal, with a transosseal conduction time of 1.2 ms.[261] In our series,[288] we used tangential placement of a magnetic coil over the scalp T5 or T6 based on the International 10-20 EEG Electrode Placement system (see Chapter 20–2) combined with electrical stimulation applied 1 cm below the anterior tragus. Compound muscle action potentials recorded from the ipsilateral nasalis muscle showed onset latencies of 4.5 ± 0.5 ms (mean $\pm$ SD) with magnetic stimulation and 3.2 ± 0.4 ms with 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 79.0 ± 8.6 mm proximal to the point of electrical stimula-

tion at the root exit zone of the facial nerve. In fact, direct electrical stimulation at this site intraoperatively elicits a response with the same latency as transcranial magnetic stimulation.[317] This technique helps evaluate Bell's palsy[177,261,262,317] and facial myokymia and other disorders of the facial nerve.[104,105,238] Similarly, stimulation of the trigeminal nerve below the zygomatic arch elicits a masseter response recorded with an electrode inserted into the pterygomandibular plica over the belly of the muscle.[323]

5 CENTRAL CONDUCTION TIME

Method and Normal Values

Table 21–1 summarizes the onset latencies of the compound muscle action potentials elicited by magnetic stimulation. The total conduction time comprises activation of the cortical structures, conduction down the corticospinal pathway, activation of spinal motor neurons, 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.[216] The conduction time, calculated as the difference in latency between scalp- and root-evoked compound muscle action potentials, 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 central motor conduction time of 5.5 ms. The use of F waves[268,279] and magnetic coil stimulation over Erb's point[8] has yielded a similar peripheral latency and calculated central conduction time.

Use of Root Stimulation

High-voltage electrical or magnetic stimulation over the spinal column excites the C8 and T1 roots in the region of the intervertebral foramina, providing a means of assessing peripheral conduction time.[216] 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.[283] 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. 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.[215] Percutaneous electrical stimuli on the order of 300 or 400 V causes moderate local discomfort in conjunction with a sudden twitch of the arm. Nonetheless, electrical stimulation elicits a larger amplitude and provides a more reliable means of studying the waveforms (see Chapter 6–3).

The calculated central conduction time using root stimulation for peripheral latency consists of the time for excitation of the cortical motor neuron, transmission along the corticospinal tracts, a 0.5–1 ms synaptic delay at the anterior horn cells,

Table 21–1 Normative Data (n = 36 SIDES)

Measurement	Mean	SD	Range	Mean + 2.5 SD
Conduction time C7/T1 to ADM (ms)	13.60	1.35	10.9–16.9	16.3
Conduction time C7/T1 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,[204] with permission.

and 0.4 ms conduction time across the cervical roots. Of these, 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.[53] Increasing the stimulus intensity in an attempt to obtain larger amplitude will move the site of activation distally along the motor root, decreasing the onset latency and increasing calculated central conduction time.

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.[187,330] The cathode or coil placed more caudally can stimulate the motor roots in the region of the intervertebral foramina. The central conduction time determined by these techniques also includes short radicular latency.

Calculation Based on the 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 by definition 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 18–5). Thus, the value calculated by the following formula equals the conduction time along the entire length of the peripheral motor pathway and 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 represents the 1 ms 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 central conduction time.

6 JERK-LOCKED AVERAGING

Technical Principles

Jerk-locked backward averaging of the scalp electroencephalogram (EEG) helps identify cerebral events time locked to a voluntary or involuntary muscle contraction. With this technique, rectified electromyographic signals serve as the trigger for averaging the cerebral activity, preceding the movement by means of a delay line (Fig. 21–7).[157] A number of investigators have used the method to assess movement related cortical potentials,[13,161,291,293] mechanisms of synkinesis,[293] the pathophys-

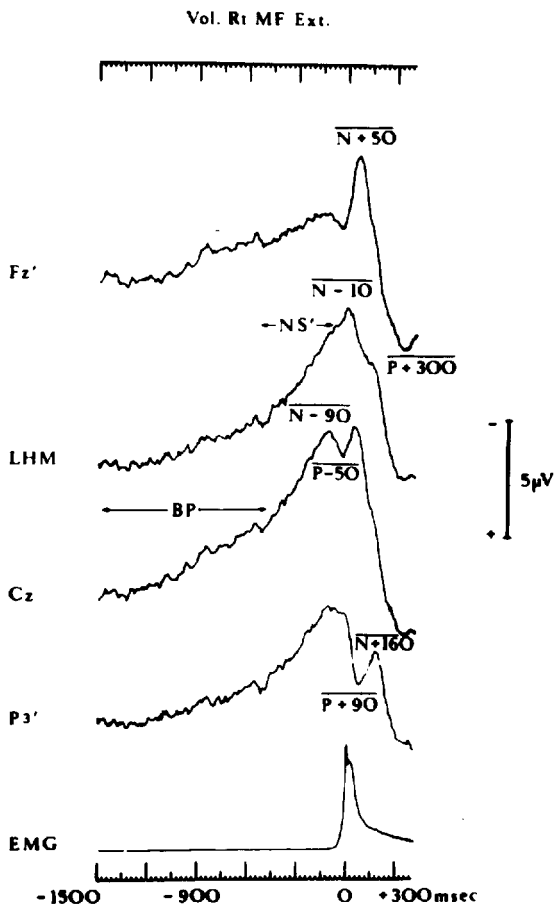

Figure 21–7. Terminology of each component of cortical potentials associated with voluntary, self-paced middle finger extension. The record shows a grand average in 14 healthy subjects, 200 trials for each subject. See text for details. [From Shibasaki, Barrett, Halliday et al.[292]].

iology of myoclonus,[110,297,305] parkinsonism,[77] and other involuntary movements.[295]

Movement-related cortical potentials consist of at least eight separate components.[230,231,291,292,308] Those preceding the onset of movement include a symmetric early negative shift called *Bereitschaftspotential* (BP); an intermediate shift (IS); a negative slow wave maximal over the contralateral precentral region (NS); 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 (see Fig. 21–7). 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.[72,296] 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 reflecting the dysfunction of the cerebellofugal or dentatothalamic pathways.[296]

Myoclonic Discharges

Averaging the EEG time locked to a myoclonic discharge helps in identifying the responsible cortical spike and determining cortical excitability after myoclonus.[132,221,222,298] The EEG correlates of myoclonus established by this means resemble the giant early cortical component of the somatosensory evoked potentials in waveform, topography, and time relationship to spontaneous myoclonus.[297] Cortical reflex myoclonus shows relatively enhanced cortical excitability for 20 ms just after the myoclonus, followed by a suppressed postmyoclonus period thereafter.[294] 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 demonstrate a focal, negative cerebral potential over the contralateral central region antecedent to the myoclonic jerks.[351]

Other Disorders

Cortical slow negativity similar to the BP/NS' precedes choreic movement in patients with chorea-acanthocytosis but not in those with Huntington's disease.[295] In patients with Gilles de la Tourette syndrome, spontaneous tics do not accompany any slow negativity, although a premotion negativity precedes voluntary jerks, mimicking their tics. Patients with mirror movement may show an abnormal topography of NS' that appears bilaterally, indicating unintended participation of the opposite motor cortex.[293]

7 CLINICAL APPLICATIONS

Normal Values

Magnetic stimulation is widely used in the evaluation of not only the motor system but also higher brain functions in healthy and diseased states.[60,270] Evaluation of the motor system complements somatosensory evoked potential studies assessing a lesion of the spinal cord or monitoring an operative procedure.[267]

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. Percutaneous stimulation of the motor roots yields a shorter peripheral conduction time than a calculation 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 motor neurons, this discrepancy will erroneously increase

the calculated value of central conduction.[314] In one study of 40 normal subjects, body height showed a linear correlation to cortical and spinal latencies by electrical stimulation, but not to central conduction time calculated as the difference between the two.[325] Magnetic stimulation shows a markedly increased threshold in infancy, decreasing to the adult level at about age 8 years.[152] The onset latency reaches adult values at about 11 years of age, and then increases linearly with age from the second to the ninth decade, with slowing occurring in both the central and peripheral motor pathways.[85] The amplitude also declines gradually with increasing years.

In normal subjects maintaining a small voluntary contraction, magnetic stimulation, with an intensity 20 percent above threshold for relaxed muscles, evokes compound muscle action potentials of at least 18 percent of the maximal response elicited by electrical stimulation of the nerve (see Fig. 21–2). Therefore, any response reduced to a level below 15 percent of the maximum compound muscle action potential suggests conduction block along the central or peripheral pathways.[204] In one study,[194] 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 exposed human cortex during neurosurgical procedures.[220] Table 21–2 shows normative data for conduction to abductor digiti minimi using magnetic cortical stimulation, electrical stimulation of the cervical roots, and a facilitatory background contraction.[226] The normal central motor conduction time to the voluntarily contracted tibialis anterior averages 12.5 ms after magnetic stimulation of the motor cortex.[50]

Prolonged central motor conduction usually implies demyelination, or degeneration of fast-conducting corticospinal fibers, with transmission via small myelinated fibers or by some other oligosynaptic pathways. Any reduction in the descending volley through loss of fibers or conduction block will diminish temporal and spatial summation at the alpha motor neurons, or the final common path, delaying their excitation. The correlation of central motor conduction time with voluntary phasic force and twitch force most likely reflects the degree of conduction block and temporal dispersion rather than the delay in conduction per se.[342]

Multiple Sclerosis

In early studies, electrical stimulation of the brain and the spinal cord revealed markedly prolonged central conduction in patients with multiple sclerosis.[16,59,214,215,266] Later reports confirmed these findings, with magnetic stimulation showing a much lower incidence of absent responses than did electrical stimulation.[9,15,31,32,124,137,265,341] Paired transcranial magnetic stimuli may reveal a substantial delay of the conditioned response, probably reflecting cortical abnormalities.[235] Upper limb MEP detects conduction abnormalities of multiple sclerosis as well as visual evoked potentials (VEPs) and better than upper-limb somatosensory evoked potentials (SEPs) or brainstem auditory evoked potentials (BAEPs). MEP studies, however, uncover

Table 21–2 Magnetic Brain Stimulation: Normative Data for Conduction to Abductor Digiti Minimi Muscle (n = 36 SIDES)

	Mean	SD	Range	Mean + 2.5 SD
Conduction time from C7–T1 (ms)	13.60	1.35	10.9–16.0	16.3
Conduction time from scalp (ms)	19.73	1.25	17.5–23.1	22.23
Central motor conduction time (ms)	6.13	0.89	4.7–7.7	8.35
Amplitude as % of amplitude from wrist	—	—	18.6–96.6	—

From Murray,[226] with permission.

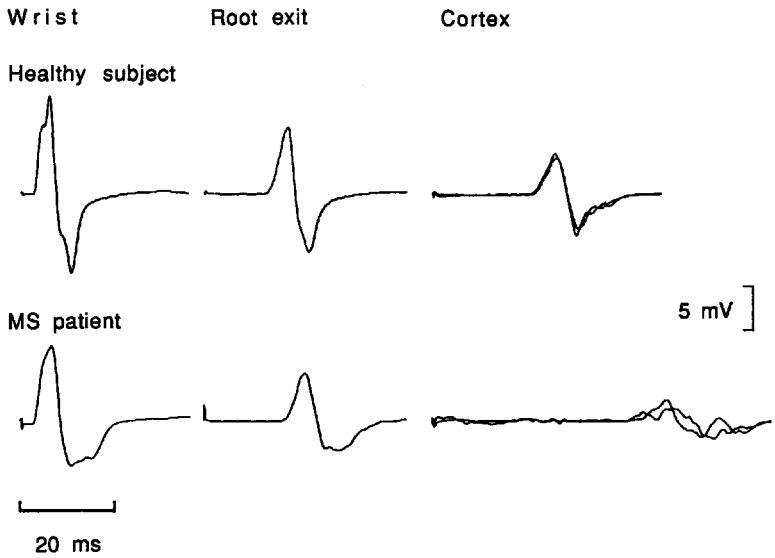

Figure 21–8. Central motor conduction is a healthy subject (above) and a patient with clinically definite multiple sclerosis (below). Recordings were made from the right abductor digiti minimi muscle. The ulnar nerve was supramaximally stimulated at the wrist (left traces); the C7/T1 roots were stimulated electrically by a high-voltage stimulator over the cervical spine (middle traces), and the cortex was stimulated with a circular coil centered at the vertex. In the normal subject, central motor conduction time is 5.8 ms and the compound muscle action potential amplitude is about 50% of the amplitude from ulnar nerve stimulation. In the patient, responses from cortical stimulation are delayed (central motor conduction time is 35 ms) and are also small and dispersed. [From Mills,[208] with permission.]

subclinical lesions less often than VEP or SEP studies. A number of other motor system diseases, such as Balo's concentric sclerosis,[174] motor neuron disease,[136] and radiation myelopathy,[304] show similar conduction abnormalities along the central motor system. Therefore, these findings by no means offer a specific diagnosis, although other conditions rarely cause the extreme prolongation of central motor conduction time characteristic of demyelination.[204]

Clinical signs showing a good correlation with conduction abnormalities[9] include weakness of the target muscle, pyramidal signs in the limb, brisk finger flexor reflexes,[124] and Babinski sign.[137] One study showed a delay in small hand muscles on one or both sides in 72 percent of 83 patients.[124] Most of the patients with a prolonged conduction time showed reduced amplitude and variability of the recorded response (Figs. 21–8 and 21–9). Brain stimulation commonly fails to evoke muscle action potentials especially in the lower limb. The onset latency variability may occasionally constitute the only abnormality.[31,32] Studies reveal subclinical deficits in 20–24 percent of neurologically normal limbs.[85,124] Serial MEP studies may uncover changes in central motor conduction consistent with clinical remission and relapse[141] or with the therapeutic effect of corticosteroid administration.[277] This technique, therefore, serves as a useful measure to quantify motor disability when monitoring the course of the disease.

Motor Neuron Disease

Patients with motor neuron disease have a high incidence of abnormality,[9,86,285] which typically consists of small amplitude and slight delays in latency. Some patients have subclinical deficits[131] whereas others have normal findings despite clinical evidence of central motor involvement.[285] Other studies of interest include mapping of cortical muscle representation.[71] In general, central motor con-

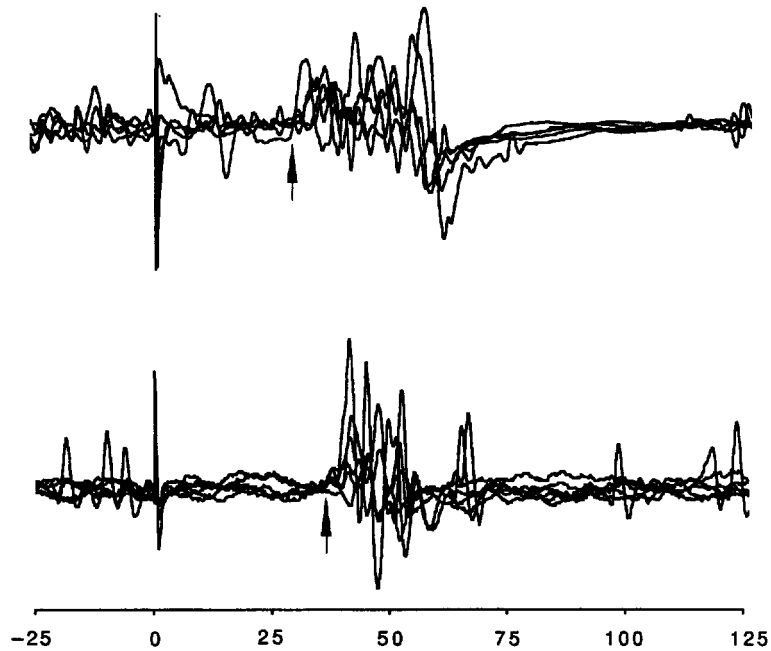

Figure 21–9. Central motor conduction in two patients with clinically definite multiple sclerosis. The central motor conduction time (CMCT) is prolonged in each case. The upper traces show a cortex to muscle latency of 28 ms, giving a CMCT of 14.2 ms. The lower traces show a cortex to muscle latency of 38 ms, giving a CMCT of 22.7 ms. Five traces are superimposed in each example to illustrate the marked variability and dispersion of compound muscle action potential configurations. [From Mills,[208] with permission.]

duction abnormalities do not appear to correlate with physical signs.[219] In one study,[86] almost all of the 40 patients had abnormalities in at least one recording from three upper limb muscles, and 75 percent showed abnormalities 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 another study of primary lateral sclerosis,[35] four of seven cases had no response in either upper or lower limb muscles. The remaining three had a gross prolongation of central conduction time.

In early stages of sporadic amyotrophic lateral sclerosis, patients have a reduced threshold for transcranial magnetic activation of the motor cortex,[217,218] a shorter cortical silent period,[255] and reduced intracortical inhibition,[356,365] all possibly reflecting cortical hyperexcitability. A study using a peristimulus time histogram showed dysfunction of the cortical motor neuronal projection system.[153,154,227,349]

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 commonly employed low rates of train. Magnetic stimulation has occasionally induced focal seizures in patients with ischemic lesions of the cortex and in those with multiple sclerosis.[126,142] A study of patients with partial or generalized epilepsy found no change in seizure pattern or in the EEG following magnetic stimulation.[310] Rapid magnetic stimulation to the cortex could induce a motor seizure, although it may[129] or may not[74] specifically activate the preexisting epi-leptic focus. Anticonvulsant medication probably raises cortical threshold intensity.[38,130,196]

In a patient with focal epilepsy and myoclonus, stimulation on the affected side induced a shorter silent period and reduced corticocortical inhibition, indicating asymmetry in cortical excitability.[135] In patients with myoclonic epilepsy, but not in healthy subjects, magnetic stimulation at the foramen magnum elicited long-loop reflex (see Chapter 19–5) via the ascending tracts in addition to direct response via the descending tracts.[335] 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.[17,39,78,126,141] The paretic muscle often shows no response to brain stimulation or increased threshold intensities.[2] Motor responses rarely detect subclinical deficits, but they may predict functional outcome better than clinical assessment, especially when combined with SEP studies.[182] Other aspects of the MEP reported in stroke include changes in the silent period,[40,339] and post-stroke reorganization of brain motor output.[49]

Movement Disorders

In Parkinson's disease, magnetic stimulation may show abnormally large MEPs[85,143] with normal central conduction time.[9,15] In one study,[37] 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 magnetic stimuli delivered after the end of the silent period.[18] Some but not all patients with progressive supranuclear palsy had abnormalities of central motor conduction suggesting functional damage to the corticospinal tracts.[3] In healthy subjects, a single dose of dopaminergic drugs enhanced inhibition, whereas antidopaminergic counterparts reduced it as tested by transcranial magnetic stimulation.[364] Thus, these two agents seem to serve as inverse modulators of motor cortex excitability.

MEP studies have found no abnormalities in Huntington's chorea or dystonia.[83,97] Patients with Wilson's disease may[301] or may not[47] have prolonged central conduction. The shortening of central motor conduction time seen in patients with Rett syndrome implies unique cortical hyperexcitability corresponding to the characteristic overactivity of motor function.[233] In some patients with congenital mirror movement, a reversed relationship between the direction of current flow and hemisphere activation suggests ipsilateral projections,[32,33] although in others unilateral stimulation elicited bilateral small hand muscle responses.[343] Patients with essential tremor have normal cortical excitability of the motor area.[260]

Ataxia

Patients with a cerebellar or cerebellothalamocortical lesion have an abnormal reduction in the physiologic suppression of cortically elicited MEP by preceding magnetic stimulation over the cerebellum.[327,350] In contrast, this suppression remains normal in those with Fisher's syndrome or with lesions in the afferent pathway to the cerebellum.[332] MEP studies may provide useful information in the differentiation of spinocerebellar atrophy (SCA) subtypes. In one study,[284] central motor conduction time exceeded 10 ms in all cases of SCA type I compared with an upper limit of normal at 8.5 ms. In contrast, SCA type III patients often had a normal value. MEP studies reveal 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.[51,65]

Myelopathies

A few studies have revealed a slowing or block of corticospinal conduction in patients with radiation myelopathy[304] or cervical cord trauma.[315] Patients with hereditary spastic paraplegia have 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.[53] These findings suggest length-dependent degeneration of the corticospinal tracts. Several studies have shown prolonged central conduction in patients with cervical spondylotic myelopathy[1,15,41,81,140,186,287,311,312] and after spinal cord injury.[42] In these patients, reinforcement of the subliminal flexion reflexes by transcranial magnetic stimulation can provide evidence of preserved corticospinal innervation to the segmental motor neuron or interneuron pools.[113] Additional slowing of the peripheral motor

pathway probably indicates radiculopathy associated with myelopathy.

Other disorders showing central conduction abnormalities include adrenoleukomyeloneuropathy,[160] cerebrotendinous xanthomatosis, HTLV-1–associated myelopathy, and tabes dorsalis.[328] and Pelizaeus-Merzbacher disease.[232] Additionally, cortical somatosensory potentials evoked by magnetic stimulation of the thoracic and lumbar roots also help evaluate the posterior column function.[319,321]

Neuropathies and Radiculopathies

In patients with Charcot-Marie-Tooth disease (CMT) types 1 and 2, MEP studies in the upper limb show normal central conduction if corrected for slowing of the proximal motor roots. Abnormalities of central motor conduction abound, however, in those with CMT type 5, showing pyramidal features such as extensor plantar responses.[53] Some patients with acute or chronic inflammatory demyelinating polyneuropathy may have similar abnormalities unilaterally or bilaterally.[242,355] Patients with multifocal motor neuropathy have normal central motor conduction time.[224] Some investigators advocate the use of magnetic stimulation in the diagnosis of lumbosacral radiculopathy.[22,45,92,170] The technique has, however, inherent limitation because of its uncertainty regarding the site of stimulation. Transcutaneous stimulation of the cauda equina at the L1 spine elicits a compound muscle action potential in the external anal sphincter.[307] Patients with idiopathic neurogenic fecal incontinence showed a greater pudendal nerve latency (7.3 ± 0.7 ms [mean ± SD] than 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.[8,307] These observations demonstrate the clinical utility of evaluating not only the afferent but also the efferent system.

Cortical Mapping

MEP studies have provided the means for noninvasively mapping the human motor cortex.[109,159,202,302,313] Areas so identified are small and are clearly separate from each other and from corresponding somatosensory areas.[28,48,55,96,185,223,225,245,354] Repetitive execution of identical movements in learning motor skills enhances MEP elicited by transcortical magnetic stimulation.[112] Reading activity also modulates motor cortical outputs to the reading hand in Braille readers.[244,247]

In one study of motor reorganization after upper limb amputation in humans,[54] magnetic scalp stimulation induced a sensation of movement in the missing hand or fingers in the patients with acquired amputation but failed to do so in the patient with congenital absence of a limb. Magnetic stimulation evoked a larger MEP at lower intensities of stimulation and recruited a larger percentage of the motor neuron pool in proximal muscles ipsilateral to the stump than those contralateral to the stump. Thus, cortical reorganization in adult human motor pathways seems to target the muscles proximal to the stump after amputations and the reinnervated muscles after anastomosis.[189,191]

Another human study[27] using anesthetic block revealed rapid, reversible modulation of human motor outputs after transient deafferentation of the forearm. Similar evaluation of patients with congenital mirror movements, amputations, spinal cord injuries, and hemispherectomy revealed the potential for reorganization of the motor system following lesions in the peripheral nervous system as well as the central nervous system.[56,348] Input–output curves obtained with a range of stimulus intensities at a single scalp site provide information similar to cortical mapping produced by stimulating different sites at the same intensity.[257]

Other Applications

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.[286] Patients with chronic "postviral" fatigue syndrome have normal central

motor conduction studies both at rest and after a prolonged muscle contraction.[344]

Other areas of interest studied by transcranial magnetic stimulation include reciprocal inhibition,[198] motor control,[128,309] tremor resetting,[246] eye movement,[168] symbolic visual information,[61] linguistic processing,[98] the effect of limb immobilization,[358] effects of digital nerve stimulation,[188] central fatigue,[26,169,276] chronic fatigue syndrome,[34,275] sympathetic skin responses (see Chapter 5–7),[171,195,234,322] spinal cord monitoring (see Chapter 20–6),[250] migraine,[7] brachial plexus injury,[237] mitochondrial disorders,[76] myotonic dystrophy,[239] and Duchenne muscular dystrophy.[75]

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Chapter 22

ELECTRODIAGNOSIS IN THE PEDIATRIC POPULATION

1 INTRODUCTION

An experienced physician may find electrodiagnostic examination of a distressed child challenging yet must perform the evaluation with confidence to minimize the anxiety of the family. Using a clinical diagnosis of the neuromuscular disease in question as a basis for a carefully planned approach facilitates the process of assessment. The wide range of normal values reflecting the differing rates of maturation of the neuromuscular system among children poses unique problems and limitations for pediatric studies.[5,25,26,35,46] Thorough knowledge of pediatric neurology greatly improves the clinical practice of pediatric electrodiagnosis.[9,16]

2 PRACTICAL APPROACH

Helpful additions to adult instrumentation include pediatric-sized surface discs, finger clips, and ring electrodes for recording. The use of a pediatric-sized bipolar probe improves the quality of stimulation in small children. An excessive application of conduction cream increases shock artifacts. For needle study, a standard 1 inch, 28 gauge monopolar or concentric electrode generally provides adequate information. The use of an intramuscular reference electrode may reduce interference during monopolar needle electromyography. Studies performed in an electrically noisy location, such as in intensive care units, call for excellent grounding. An incubator, if required to

maintain appropriate body temperature of an infant, may cause major electrical interference unless it is properly grounded.

The examination should be thoroughly explained to the parents to maximize their cooperation and reduce 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 the procedure in some detail. Demonstrating a conduction study on a parent may help relieve anxieties. Parents who understand the usefulness of the study are more likely to assist in the procedure by controlling the child. Some choose to stay and may even hold the infant on their lap during the examination. Parents should understand in advance that they may be asked to leave, depending on the progress of the examination and the degree of their tolerance.

If the procedure is explained with 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 study by listening to the loudspeaker and observing the response build on the oscilloscope. Thus they may be cajoled to participate in 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 stimulation studies.

A physical examination before the study will establish developmental reflexes of an infant or functional skills in an older child. Examiners rarely regain cooperation once it is lost during the needle exploration. Thus, a routine examination should begin with more easily tolerated nerve conduction studies, which provide important maturational information.[3,38,44] Minimal stimuli suffice to excite the superficially located peripheral nerves in children. Sensory nerve conduction studies that cause the least pain should be done first.

For the more threatening needle studies, the child should receive honest forewarning about pain to avoid any surprises. 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, and often encourages their participation in the evaluation. For a comprehensive study, the needle examination must survey multiple proximal and distal muscles in addition to the segment of concern. For children under the age of 7 who cannot provide optimal voluntary contraction, single-fiber studies are done by stimulation techniques (see Chapter 16–3).

A short well-executed evaluation usually eliminates the need for premedication, which may preclude 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 or in those with previous negative medical experience. A survey of pediatric electrodiagnosticians noted the most behavioral distress in 2 to 6 year olds,[21] who may benefit from sedation. Premedication also has its place for repetitive stimulation or for extended 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 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 nerve conduction studies without rendering the child too sleepy to recruit motor units during needle electromyography. Demerol, another commonly prescribed drug, tends to oversedate children.

Pain from procedures looms large for children, although examiners often underestimate it. The distress caused by pain could leave a persisting fear of future medical interventions. Making the study as comfortable as possible and helping the child anticipate the worst moments helps reduce the negative experience, rendering the investigation less stressful to the child (and examiner).

3 MATURATIONAL PROCESS

Peripheral nerve myelination, which begins at about the 15th week of gestation,[17] continues throughout the first 3–5 years after birth. Myelinated nerve fibers mature at the same rate whether in utero or ex utero,[38] exhibiting no accelerated myelination just after birth.[51] The axons also mature during the prenatal and postnatal periods, beginning at 20 weeks' gestation and reaching a maximum between ages 2 and 5 years.[51] The thickness of the myelin sheath directly correlates with the diameter of the axon. Thus, conduction velocities increase in proportion to the diameter of the axon. In the phrenic nerve, the number of myelinated axons doubles from birth to 1 year of age,[50] showing no further increase thereafter. The nodes of Ranvier also undergo remodeling, with a gradual lengthening of the internodal distances that peak at about 5 years of age.[20]

Conduction velocities calculated from the onset latency increase in proportion to the diameter of the largest axon, maintaining a ratio of 6:1.[4] Thus, infants of different weights but the same gestational age have a similar conduction velocity. Therefore, nerve conduction studies help distinguish premature babies from full-term infants with a small birth weight.[14] Premature infants of 23–27 weeks' gestation may have a motor conduction velocity as low as 9–11 m/s,[10,45] which gradually approaches the normal neonatal values toward the conceptional age of 40 weeks. In the newborn, distal motor latencies decrease with increasing gestational age.[52] At birth, the median, ulnar, and peroneal nerves conduct at approximately half the speed of normal adult values, with an average of 27 m/s. Conduction velocities then increase rapidly during the first year of life, and more slowly thereafter, plateauing by 5 years of age.[33,38,51,52]

The nerves conduct 7–10 m/s faster in the arms than in the legs in older children and adults,[24] but not in newborns, who show average velocities of 20–30 m/s in both the upper and the lower limbs. The ulnar and peroneal nerves mature most during the first 6 months of life, whereas the median nerve lags in development until the age of 1–3 years.[2] 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 values reach the lower adult range.[51] Table 22–1 summarizes a set of normal values for motor and sensory studies in children up to 2 years of age.

Earlier maturation proximally rather than distally tends to shorten the H-reflex and F-wave latencies more quickly than the distal latencies. The peripheral somatosensory pathways mature at a faster rate than the central pathways measured by somatosensory evoked potential (SEP).[54] Cortical SEP matures, reflecting conceptional age, primarily during the first 3 weeks of life, although the trend continues throughout the first 2 years of life.[15,18,37] This process of maturation also involves the compound muscle action potential, which triples in size as compared to nerve conduction, which doubles in velocity.[51] Orthodromic compound sensory nerve action potentials recorded proximally may comprise two distinct peaks in infants, representing two groups of maturationally different sensory fibers.[52]

Maturational factors also influence the interpretation of electromyography in newborns and infants. Careful quantification of the electrical characteristics of the motor units constitutes one of the most useful aspects of the needle examination. It often serves as the only 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 developmental derangement of the neuromuscular system. Proper assessment of motor unit potentials in health and disease, therefore, requires the knowledge of the maturational sequence of the nerve and muscle.

Nerve fibers reach the elongated myoblasts at 6 weeks of gestation and form the neuromuscular junction at 10 weeks, determining muscle fiber properties. Initially, 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

Table 22–1 Motor and Sensory Nerve Conduction Studies in Infants: Range of Normal Values

	Number	CMAP/SNAP* Amplitude (mV/μV)	Conduction Velocity (m/s)	Distal Latency (ms)	Distance (cm)
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
	1	8–17 (O)	—	—	—
Sural		8	—	3.3	5.5
Medial plantar	3	10–40	—	2.1–3.3	4.4–5.8
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) 9–26 (O)	36.3–41.9	1.5–2.3	4.3–6.3
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
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	1.4–3.2	2.2–5.5
Sensory					
Median	15	14–64 (A) 11–36 (O)	39.1–60	1.6–2.4	5.5–6.8
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
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) 7–36 (O)	46.5–57.9	1.7–3	5.7–9.1
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 sensory potential; CMAP = compound muscle action potential; O = orthodromic sensory potential; SNAP = sensory nerve action potential.

From Miller & Kurtz,[38] with permission.

during the first 10–15 weeks of gestation. By 15 to 20 weeks, type I fibers, larger in diameter, match the type II fibers in number.[16] Muscle fibers mature not only during intrauterine life but also after birth.[36] The increased proportion of type II fibers in adults may result from a transformation of type I to type II fibers.[36]

4 NERVE CONDUCTION STUDIES

The same anatomic landmarks used in adults apply when placing stimulating and recording electrodes in children. Active and reference leads placed 2 cm apart suffice when recording from the small hands of the

newborn. For motor conduction studies, a disc electrode placed on the thenar or hypothenar eminence serves as G_1, and a ring electrode wrapped around the third or fifth digit serves as G_2. For technical reasons, most electromyographers test the median and ulnar nerves in the upper limb and the peroneal nerve in the lower limb.

Studies should include at least one sensory nerve, especially in the assessment of a diffuse process. The median, ulnar, and sural sensory potentials are easily elicited in newborns.[38] In the upper limb, orthodromic studies consist of stimulating the digits and recording from the median or ulnar nerve at the wrist or elbow. Because of its length, the third digit is best suited for recording from the median nerve. Antidromic recording of digital potentials elicited by proximal stimulation generally provides more stable results for radial, ulnar, and musculocutaneous nerves in the upper limb and for the sural nerve in the lower limb. In cooperative children, quantitative thermal perception testing may uncover small nerve fiber dysfunction.[22]

Stimulation with a needle electrode lowers the shock intensity, substantially 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 reduce shock artifact include lowering the impedance by cleansing the skin, decreasing the surface spread of current by minimizing the amount of conduction cream applied, 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, but the movement usually habituates with repeated trials.

In infants with such short limbs, movements hinder measurement, especially if fat hides bony landmarks. With nerve segments under study extending only several centimeters in length, an error of only 1 cm will result in a 20–25 percent velocity change. Immobilizing the limb properly throughout the study improves accuracy. Despite the inherent difficulty in nerve length estimation, a conduction study serves its purpose. For example, the presence of a normal sensory nerve action potential excludes a lesion distal to the dorsal root ganglion. Here, studies add important information even without calculation of the forearm sensory conduction velocity. Neonates with poor temperature homeostasis should remain in an incubator during the study. Older children may sweat profusely with anxiety and crying, making the limb unexpectedly cool with evaporation.

5 LATE RESPONSES

Late responses elicited by distal stimulation add useful information in evaluating the peripheral nerves of infants. The unique advantages include a higher rate of abnormalities accumulated over the longer conduction distance and a greater reproducibility reflecting smaller measurement error. Submaximal stimulation gives rise to a constant H reflex, whereas supramaximal shocks evoke F waves with variable waveforms and latencies.[40]

The H reflex, although elicitable from most muscles in infancy, undergoes progressive central inhibition toward the end of the first year, when it is consistently recorded only from the calf muscle. For example, stimulation of the ulnar nerve elicits the H reflex in most fullterm infants, but not after 1 year of age. When tested using the H reflex latency, the sensory fibers of the ulnar nerves conduct approximately 10 percent faster than the motor fibers between the wrist and elbow in the newborn.[58]

Supramaximal stimulation of any peripheral motor nerve evokes the F wave. In one series of 20 fullterm newborns, median nerve stimulation elicited F waves of the abductor pollicis brevis in 100 percent of trials, showing a higher F wave/M response amplitude ratio and more uniform waveforms than in adults.[41] The latencies of late responses recorded by the standard technique change with both age and limb length.[3,38,44] In one study, F wave latencies of the median nerve were 16.0 ± 1.5 ms (mean $\pm$ SD) for infants less than 3 months of age and 14.4 ± 1.6 ms for youngsters between 4 months and 2 years

Table 22–2 F Wave Latencies in Infants: Range of Normal Values

Months	Nerve	Number	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

From Miller & Kuntz,[39] with permission.

of age. Table 22–2 summarizes normal F-wave latencies for infants up to 2 years of age.

6 BLINK REFLEX

Despite extensive studies in adults, only a few reports have dealt with the maturational pattern of blink reflexes in infants and children.[6,23] We have reported our experience with newborn infants less than 3 days of age to establish normal ranges of the blink reflex in the neonatal period.[30] As in adults,[31] the blink reflex elicited by unilateral electrical stimulation consisted of an early ipsilateral component, R_1 (see Fig. 17–7), and a late bilateral component, R_2 (see Fig. 17–8), in about two thirds of neonates. The remaining one third had ipsilateral R_1 and R_2 but absent R_2 contralaterally. The presence or absence of R_2 and its amplitude depended to a considerable degree on the intensity of stimulation, that is, the stronger the shock, the larger the size of R_2. Table 22–3 summarizes various aspects of direct response and of R_1 and R_2 components of the blink reflex in 30 neonates compared with those established in 30 older subjects aged 7–67 years (average age, 31 years).

Before initiating the study, we had anticipated various technical problems that might make testing difficult in small neonates, but these concerns were mostly unverified. In fact, optimally applied low-intensity stimuli elicited R_1 without even awakening the infant in light sleep. Recording R_2, however, posed a greater challenge because of the need to apply shocks of the higher intensity required for this nociceptive response while keeping the infants fully awake so that sleep would not suppress the reflex excitability. In many subjects, eliciting a direct response by stimulation of the facial nerve caused more technical difficulties than evoking the reflex response by stimulation of the trigeminal nerve.

The presence of R_1 in most newborn infants provides evidence of maturation of its pontine pathway at birth. Similarly, R_2 elicited on the side of stimulus in two thirds of neonates indicates at least partial establishment of its central connection. A comparatively greater latency of the direct response and of R_1 in infants suggests incomplete myelination of the trigeminal and facial nerves. Conduction velocities in fullterm infants average roughly half of those of adults. Thus, despite considerably shorter reflex pathways in infants, the latency of R_1 exceeds the adult value by approximately 1.5 ms (see Table 22–3). By about 6 years of age, the R_2 components in children parallel those in adults in consistency and excitability.[6,23] This corresponds with the time of completion of brainstem myelination in children.

Determination of various aspects of R_1 can aid in assessing the brainstem and the trigeminal and facial nerves in infants.[29,47–49] In contrast, R_2 varies so much in infants that its absence or asymmetry at this age has little clinical value. Of the two components of the electrically elicited blink reflex, the bilateral R_2 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 the same criteria apply to pediatric and adult populations except for infancy. In younger children, sedation facilitates limb

Table 22–3 Direct Response and R_1 and R_2 of the Blink Reflex (Mean ± SD) in 30 Neonates Compared with 30 Adults

	Direct Response		R_1 Component		R_2 Component Ipsilateral to Stimulus	
	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
Latency difference between two sides in the same subject (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
Amplitude ratio between two sides in the same subject, 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

*$p < 0.05$.
†$p < 0.01$.
Modified from Kimura, Bodensteiner and Yamada (1997).[30]

immobilization with restraining straps or tapes. For stimulation, the use of a needle minimizes movement-related intensity variability. For recording, a subcutaneously placed needle or wire may suffice, despite its restricted recording radius, although a pair of surface electrode is better for the evaluation of full responses. As in adults, the proximal limb muscles and facial muscles usually provide the highest yield. Repeat studies and testing multiple nerves help to confirm an abnormality by establishing reproducibility.

Studies performed with the infant's arm immobilized on a pediatric arm board serve as the primary electrodiagnostic method to quantitate clinical findings.[7,8] A warm blanket may help to maintain surface temperature, which can be monitored with a thermister. It takes less intensity to achieve supramaximal stimulation in children than in adults. With mild sedation, it is thus possible to do the test without awakening 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 s under adequate sedation. Single-fiber electromyography also depends on stimulation technique and not on voluntary contraction.

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,[32] continuous stimulation for 15 s at a rate of 1–2 Hz induced no change in amplitude. With an increased stimulus rate, 5 of 8 infants had at least a 10 percent facilitation at 5–10 Hz, and 12 of 17 infants had a decremental change averaging 24 percent at 20 Hz. Premature infants showed facilitation and exhaustion at rates greater than 20 Hz, possibly because of inadequate neuromuscular reserves. Although greatest in the premature infants, all 17 had a reduction, averaging 51 percent 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. These include myasthenia gravis, botulism, Lambert-Eaton myasthenic syndrome, and drug-induced conditions. Infants may also have congenital myasthenia or infantile botulism. Rare forms of congenital myasthenia characteristically show a series of two or more repetitive responses to a single stimulus (see Figure 10–8). This finding should prompt the electromyographer to perform further studies with repetitive stimulation.

8 ELECTROMYOGRAPHY

The examination of infants must often deviate from the routine order of steps followed in studying cooperating patients. If the child tolerates testing well, insertional and spontaneous activities should be studied first. If the infant resists, motor unit potentials can be observed. 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.

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 for the assessment of spontaneous discharges. Passive shortening of the muscle can also achieve enough relaxation for this part of the examination. Studies of the less active intrinsic foot and hand muscles suffice for the evaluation of resting states in a diffuse or generalized disease. The distal muscles, with a large motor point zone, tend to show frequent end-plate spikes. Their irregular high-frequency pattern of discharges stands in contrast to fibrillation potentials, which fire regularly at a slower rate.

The initial insertion, which usually induces a maximal volitional contraction, allows the evaluation of the recruitment

pattern of motor units in infants. Flexor muscles are reflexively activated as part of a withdrawal response. Studies of motor units should, therefore, center on the flexor muscles, which tend to show strong functional activation. The most active are the tibialis anterior and biceps brachii. If necessary, the use of primitive reflexes helps activate flexor responses.

Compared with adults, infants and young children have smaller muscle fibers and less fiber density, rendering motor unit potentials of lower amplitude and shorter duration. This makes a subtle myopathic change difficult to detect. With a 5- to 8-fold increase in fiber diameter during life, motor unit potentials also increase in size 2- to 5-fold.[43] In infants 3 years old or younger, the amplitude ranges from 200 to 700 μV, usually not exceeding 1 mV.[13,43]

In general, electrodiagnostic studies in infants detect neurogenic patterns of weakness more accurately than myogenic features.[11,42] In one series, electromyography and biopsy results showed 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.[12] A definite dropout in the number of motor units, as might be seen in patients with infantile spinal muscular atrophy, causes a rapid firing of large motor unit potentials, constituting a readily recognizable late recruitment. In fact, a needle study shortly after birth may document intrauterine onset of a neuropathic process.[27] In contrast, recognition of an early recruitment poses considerable difficulty because of irregular contraction.

Thus, in the study of a floppy infant (see this chapter, part 10), except for severe cases with unequivocal abnormalities, myopathic disorders tax the electromyographer more than neurogenic conditions.[11] Subtle changes call for careful follow-up studies rather than invasive procedures. Cases with suggestive but inconclusive evidence should be followed with a muscle biopsy for confirmation. Electromyographers should err on the side of under interpretation, working from the principle that patients have normal results unless proven otherwise.

9 SOMATOSENSORY EVOKED POTENTIALS

The same technical principles apply for infants as for adults (see Chapter 20) in eliciting somatosensory evoked potentials for study of the peripheral nerve, spinal cord, brainstem, and cerebral cortex.[53] In neonates, lower stimulation rates of 1–2 Hz are combined with a higher stimulus intensity.[15,18] Median nerve studies show a maturational variability in waveform during the first few years of life,[18,28,34,54] and stimulation of the lower limb nerves elicits spinal evoked potentials more easily in infants than in adults.[19,34]

10 THE FLOPPY INFANT

Despite some overlap, pediatric and adult neuromuscular diseases vary considerably. Most infants referred for evaluation have a floppy syndrome rather than the radiculopathies or mononeuropathies that abound in adult practice.[12]

Up to 80 percent of floppy infants have a primary central nervous system cause, showing hypotonia but not weakness per se. Experienced pediatricians can clinically differentiate central hypotonia from neuromuscular dysfunction. 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 the child is lifted from the prone position and supported 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.

Electrodiagnostic evaluation distinguishes neurogenic abnormalities from myogenic abnormalities of the motor unit. In a retrospective review of 51 hypotonic infants younger than 1 year old,[42] final

diagnoses included spinal muscular atrophy or Werdnig Hoffman disease,[43] myopathy,[20] infantile botulism,[52] benign congenital hypotonia,[4] and some types of central nervous system disorders.[51] Studies revealed appropriate neuropathic or myopathic findings except for the last two categories, which yielded normal findings. In another series of 41 infants who had muscle or nerve biopsy or both,[11] 23 had spinal muscular atrophy, which was accurately defined by electromyography. Some patients with myopathy had classical features, whereas others had either normal or nonspecific changes. The abnormalities of sensory conduction led to diagnoses of hypomyelinating neuropathies in five infants.

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Part VI

DISORDERS OF THE SPINAL CORD AND PERIPHERAL NERVOUS SYSTEM

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Chapter 23

MOTOR NEURON DISEASES AND MYELOPATHIES

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 laboratory. Of various classifications proposed, those based on clinical and genetic features have proved most satisfactory, pending the elucidation of the basic biochemical defects. Classic motor neuron disease characteristically shows combined involvement of the upper and lower motor neurons. This group of diseases comprises progressive bulbar palsy, progressive muscular atrophy, and amyotrophic lateral sclerosis and its variant, primary lateral sclerosis. In contrast, patients with the spinal muscular atrophies have ge-

netically determined degeneration of the anterior horn cells without corticospinal tract involvement.

A number of other conditions, infectious and toxic in nature, affect the motor neurons 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. Syringomyelia, another classical neurologic disorder, also involves the spinal cord. The disease often mimics motor neuron disease because cutaneous touch sensation may remain 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 motor neuron disease and familial spastic paraplegia. Some subtypes of spinocerebellar atrophy such as olivopontocerebellar atrophy, glutamate dehydogenase deficiency, and Joseph disease also have clinical and electromyographic evidence of lower motor neuron disease as a major finding. Other systemic disorders associated with amyotrophy and denervation include Parkinson's disease, Huntington's chorea, Pick's disease, and xeroderma pigmentosum. Juvenile spinal muscular atrophy with hexosaminidase deficiency resembles the Kugelberg-Welander phenotype.

Electromyography and nerve stimulation techniques help establish the differential diagnosis of these disease entities. Reduced recruitment suggests loss of motor neurons during early stages. Fibrillation potentials appear at least 2–3 weeks after the onset of illness. Large-amplitude, long-duration motor unit potentials develop later as the consequence of reinnervation. The clinical severity of the disease correlates approximately with the degree of reduction in amplitude of the compound muscle action potentials, 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 electromyography and nerve conduction studies. Readers interested in more comprehensive clinical reviews should consult other texts.[172,189,211,272–274]

2 MOTOR NEURON DISEASE

Etiology and Pathogenesis

Motor neuron disease together with parkinsonian syndrome and Alzheimer's disease constitute a triad of degenerative disorders of the aging nervous system.[271] In these disorders, selective vulnerability of a special set of cells leads primarily to degeneration of the upper and lower motor neurons. This group of disorders consists of common sporadic cases and 5–10 percent of familial incidence with an autosomal dominant pattern of inheritance. Patients with progressive muscular atrophy develop only lower motor neuron impairment, whereas those with amyotrophic lateral sclerosis have features of upper motor neuron lesions as well. In contrast, prominent corticospinal tract signs without lower motor neuron involvement characterize primary lateral sclerosis. Progressive bulbar palsy shows the combined features of brainstem dysfunction and spasticity. The various syndromes, although described as separate nosologic entities, may represent a disease spectrum according to the sites of maximal neuronal involvement.

Attempts to isolate a virus or other causative elements have consistently failed,[278] despite clinical resemblance to transmissible Creutzfeldt-Jakob disease and immunologic reactivity against certain infectious agents.[125] An unidentified virus might have caused a motor neuron disease with the clinical and pathologic appearance of amyotrophic lateral sclerosis in a woman severely bitten by a cat.[145] One study reports 17 patients in perfect health who developed a progressive motor neuron disease after an electrical injury.[110] In another case, the onset of the

disease occurred in the limb through which the shock entered.[290] Another clue to the pathogenesis may lie in the lack of hexosaminidase in some members of families with recessively inherited motor neuron disease.[16,80,212,269,305] Interestingly, their enzyme may fall to a very low level, as seen in their relatives with Tay-Sachs disease.[156] Another study implicates reduced levels of glutamate and aspartate, as well as increased glutamate dehydrogenase activity in the spinal cord as causally related to the neurodegeneration.[199,303] Dextromethorphan, an *N*-Methyl-D-aspartate (NMDA) antagonist, however, showed no favorable effect in a pilot trial.[14]

A monoclonal protein that usually produces a sensory motor peripheral neuropathy sometimes induces a motor system disorder resembling motor neuron disease. This observation suggests that the antibodies may impair the function of the cell body itself or the axons that extend from the cell body.[88,270,275] Immunocytochemistry with antibodies against cytoskeletal proteins has failed to show specific changes in this disorder.[188] The search for an immunologic abnormality has led to the demonstration of serum antibodies against a growth factor in some patients.[123] If confirmed, this finding implies that motor neuron disease results from a deficiency of nerve growth factor.[9] In still other uncontrolled trials, in some patients, thyrotropin-releasing hormone (TRH) has improved motor function clinically[87,215] and electrophysiologically.[121] In vitro application of TRH to rat muscles increases the frequency of fibrillation potentials and miniature end-plate potentials, possibly accounting for its effect on muscle strength.[317] In rats depleted of TRH, however, motor performance remained normal by clinical and electrophysiologic assessments.[319]

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 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 population.[8,99,122,210] Familial cases, accounting for 10 percent of patients with amyotrophic lateral sclerosis (ALS),[63] usually show a dominant pattern. Of these, one-fourth have a missense mutation in the antioxidant enzyme copper/zinc (Cu/Zn) superoxide dismutase (SOD1) gene on chromosome 21.[17,32,268] Linkage studies have also located the rare autosomal recessive form of ALS to the long arm of chromosome 2.[137] Etiologic possibilities include genetic,[38,219] toxic,[67,91,289] immunologic,[89] environmental,[13,47,56,62,138,191,201] and viral causes, although none has been proven.

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,[141,169] typically, although not entirely sparing Onuf's nucleus.[42,120] 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.[130] In the brainstem, histologic changes predominate in the motor nuclei of the tenth, eleventh, and twelfth cranial nerves and, less frequently, in those of the fifth and seventh nerves. Rarely, the pathologic changes involve the nuclei of the third, fourth, and sixth cranial nerves and frontal lobe motor neurons.[98] 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 motor neuron lesions in life. Disputes continue regarding the primary neuron involved in ALS. Some postulate primary involvement of the cortical motor neuron or the local circuit interneurons that inhibit its activity,[79,83,84] but there is no subsequent confirmation.[234] Others hypothesize retrograde transport of pathogens from neuromuscular junctions with the spread of the disease process monosynaptically from the lower to the upper motor neuron.[51] Although the anterior horn cells and the

corticospinal tracts undergo the 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 motor neurons then reinnervate the affected motor units. Reinnervation, as a relatively active process, sufficiently makes up for the progressive loss of motor neurons until more than 50 percent of the motor neurons have died.[34] Histochemical studies of fresh frozen specimens thus show characteristic denervation atrophy with fiber grouping that represents a compensatory mechanism.[75] Myopathic changes also appear, presumably as part of the denervation process, although most biopsies show a 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.[241] 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.[307] Motor nerve biopsy also shows less density of regenerative clusters of small myelinated fibers than in motor neuropathy.[54]

CLINICAL FEATURES

Symptoms usually begin in the fifth to seventh decades, affecting men two to four times as frequently as women.[220] Distal weakness commonly develops as an early symptom. 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. Bulbar signs tend to appear late in the course, but dysarthria, dysphagia and, rarely, respiratory failure[50] may constitute the initial symptoms. Although patients commonly complain of aching and other vague sensory complaints, they usually have no clear objective loss of sensation. In one series, however, 80 percent of the patients with motor neuron disease had abnormal thermal threshold tests.[152] Pathologic examination of the peripheral nerves also showed some involvement of sensory axons,[127] but not as an essential part of the disease.[77] Spasms and cramps of the leg muscles occur early, often occurring at night or after exercise. A neurogenic bladder, although rare at the onset, may develop terminally. Pathologic laughing and crying spells signal pseudobulbar manifestations at some stage of the illness. Infrequent and mild pleocytosis and oligoclonal bands seem to have no clinical importance in well-established cases of ALS.[228]

Clinical signs include widespread atrophy[162] affecting the limb and facial muscles, usually in proportion to the degree of weakness that primarily results from lower as opposed to upper motor neuron loss.[167] The sparing of the extraocular muscles stands 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 twitchings.[82] A paucity of fasciculations may suggest slow progression of the illness,[227] 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 motor neuron disease, neither muscle weakness nor atrophy develops, and electromyography provides no denervation.[27]

The signs and symptoms may wax and wane, with an apparent improvement presumably after reinnervation and collateral sprouting. In one study, 32 of 74 patients showed a fluctuating course.[315] Despite this pattern, the disease usually progresses without remission, leading to death in 2–4 years, most often as the result of respiratory difficulties.[119,261] Longer survival in younger patients probably reflects their greater neuronal reserve.[81] Perhaps as many as 20 percent of all patients have a more favorable course, with survival in excess of 5 years.[37] 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 (Cl^-) level reflecting degree of respiratory acidosis, a shorter interval from symptom onset to diagnosis of ALS, and greater weight loss.[297] In one series,[229] about 4 percent, mainly younger men, experienced unusually long courses with milder paralysis. Although very rare, some patients with a clinical syndrome closely resembling ALS recovered completely, without treatment, 5 months to 1.5 years after onset.[313,314]

Clinical diagnosis depends on the combined features of widespread muscular atrophy, weakness, fasciculations and evidence of damage to corticospinal and bulbar tracts.[192] Differential diagnoses include any condition associated with diffuse muscle atrophy. A syndrome clinically resembling ALS may appear in association with organochlorine insecticides,[104] lead intoxication,[29] chronic mercurialism,[161] multifocal motor neuropathy,[15,216,230,239,248,322] and proximal motor neuropathy.[45] 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 extremities and evidence of spasticity in the lower extremities. When motor neuron disease and cervical or lumbar spondylosis coexist, sensory symptoms of radiculopathy alter the picture of pure motor dysfunction. A myelogram helps distinguish these diagnostic possibilities. Elevated muscle enzyme levels do not exclude the diagnosis because the serum level reaches two or three times the normal value in about half of the patients with motor neuron disease.[326]

Therapeutic regimen include, in addition to supportive care,[208] administration of riluzole which may prolong life by a few months without tracheostomy.[197] A high dose of methylcobalamine may slightly retard muscle wasting in some patients.[158]

PHYSIOLOGIC CHARACTERISTICS

Electromyographic abnormalities found during various stages of the illness reflect the sequence of pathologic changes in the muscle.[83,84,303] Diffuse denervation gives rise to widespread fibrillation potentials and positive sharp waves (see Fig. 14–8B). Fasciculation potentials, as a nonspecific but characteristic feature of ALS, imply motor neuron irritability in an appropriate clinical context.[65,120] 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. Many motor unit potentials have large-amplitude and polyphasic waveforms, some with late components.[240] The motor unit potentials, reduced in number, recruit poorly and discharge rapidly, producing a less than full interference pattern (see Figs. 13–8B, and 13–9B). In one estimate, the motor unit population decreased by half in each 6 month period of the first year and then diminished more slowly thereafter.[60] Surviving enlarged motor units contribute less twitch force[323] and fatigue more easily[282] than normal units because of mechanical inefficiency. Motor unit number estimate (see Chapter 8–1) may predict disease progression and the length of patients survival.[11]

Additional physiologic findings include increased fiber density and jitter values as well as intermittent blocking determined by single-fiber electromyography.[296] These abnormalities, seen consistently in fasciculating motor units, reflect the degree and the recency of collateral reinnervation.[153] 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, progessive denervation produces a deteriorating clinical course. A computer-assisted quantitative measure of motor unit function showed that reinnervation only compensated for up to 50 percent loss of the motor neuron pool.[34,129]

Studies of the motor nerve reveal a reduced number of motor units showing higher average amplitude than normal (see Chapter 8–1) and slight slowing in association with the reduced amplitude of the muscle action potential.[179,223] The values rarely fall below 70–80 percent of the normal lower limits,[55,95] and some studies have found little or no change in maximal

conduction velocity[129,148] despite abnormal excitability of motor axons (see Chapter 8–3). These findings suggest at least partial preservation of the fastest fibers for a long time with no evidence to indicate their preferential loss. Pathologic slowing of normally slow fibers may increase the scatter of velocities. Near-nerve recording may detect subtle abnormalities in the sensory action potential in some patients.[285] One study also revealed a slight but significant reduction in sensory action potentials in 22 percent of 64 patients.[217] In most cases, however, sensory action potentials remain normal in amplitude and onset latency. Thus, any substantial abnormalities in sensory conduction studies suggest another disorder. Spectral analysis of heart rate variability may reveal subclinical involvement of the autonomic nervous system.[250]

The common complaint of easy fatigability suggests impairment of neuromuscular transmission that may result from decreased trophic function of the neuron. In these cases, needle examination reveals small unstable motor unit potentials with temporal amplitude variability (see Fig. 14–13). Discharging units usually show more stability in the relatively chronic forms. Many patients with a rapidly progressive form of the disease show abnormalities of the compound muscle action potentials elicited by slow repetitive nerve stimulation.[25,171] In one series,[69] 67 percent of 55 patients showed a decremental response, especially in the muscles showing atrophy or frequent fasciculations. As in myasthenia gravis, local cooling or administration of edrophonium (Tensilon) normalizes the findings, and exercise induces posttetanic exhaustion.

Cortical stimulation reveals a number of abnormalities including the absence of responses, increased central delay,[209] initially reduced and later raised thresholds for cortical excitation of single motor units and changes in cortical muscle representation (see Chapter 21–7).[64] Multimodality studies of evoked potentials often uncover evidence of mild sensory system involvement.[300] Increased excitability of the spinal motor neuron pool results in a higher amplitude of the H reflex in the soleus muscle after stimulation of the tibial nerve.[203] 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.[227] Although patients may experience few or no paresthesias during ischemia of the arm and after its release, the changes in axonal properties are not analogous to those in diabetes mellitus.[214]

DIAGNOSTIC CRITERIA

A variety of focal or diffuse neuropathic disorders may mimic ALS.[186] A set of electrophysiologic criteria has gained general acceptance to avoid falsely diagnosing this fatal disease[183]: (*1*) fibrillation and fasciculation 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 amplitude and duration of motor unit action potentials; (*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 percent 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.

More recent studies, however, have raised some concern that the classical diagnostic criteria may preclude earlier acceptance of many ALS patients into therapeutic trials.[21] To accommodate this need, El Escorial criteria[49] (World Federation of Neurology Research Group on Neuromuscular Diseases)[333] led to a 1998 revision of diagnostic criteria approved by the World Federation of Neurology. According to this proposal, electrophysiologic tests should confirm a combination of active and chronic denervation in at least two of four parts of the body divided into bulbar/cranial, cervical, thoracic, and lumbosacral regions. The criteria call for the evidence of denervation of one muscle in the bulbar region, paraspinal muscles at or below T6 or abdominal muscles in the thoracic region, and at least

two muscles innervated by different roots and peripheral nerves in the cervical and lumbosacral regions. The presence of fasciculations helps, especially if found in denervated muscles, showing long-duration, polyphasic potentials. Their absence should raise doubts, although it does not rule out the diagnosis.

Typical cases show asymmetric and multifocal abnormalities. The involvement of upper and lower limbs serves to differentiate this entity from a syrinx or spondylosis with segmental abnormalities. Optimal selection of the muscles for examination can minimize the ambiguity regarding cranial involvement.[252] 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 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 also serves to distinguish this entity from other disorders such as combined cervical and lumbar spondylosis.[181] Studies should include, in addition to the assessment of muscle strength using a standard tool,[18] electromyography, sensory as well as motor conduction measurements and, when appropriate, tests of neuromuscular transmission to exclude other disorders of the peripheral nerve. Sparing of sensory nerves provides an important clue, especially if demonstrated in one of the weaker extremities. Evidence of defective neuromuscular transmission with either repetitive stimulation or single-fiber electromyography suggests active disease with recent reinnervation and immature end plates and, hence, a poor prognosis.

Progressive Muscular Atrophy

In the rare syndrome of Aran-Duchenne or *progressive muscular atrophy*, clinical signs and symptoms suggest a selective disorder of the anterior horn cells, although pathologic studies may show some changes in the corticospinal tract as well. Most cases 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 motor neuron involvement. The patients initially have asymmetric wasting and weakness of the intrinsic hand muscles. They then develop atrophy of the shoulder girdle and the bulbar and lower limb muscles. Less commonly, the clinical signs may resemble Charcot-Marie-Tooth 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.[238] Despite generalized wasting and weakness, the stretch reflexes usually remain normal or only slightly decreased. The disease runs a slower course than classic ALS. Nonetheless, the symptoms and signs are unremitting, steadily progressing to death, often from aspiration pneumonia.

Progressive Bulbar Palsy

Signs and symptoms that predominantly involve the bulbar muscles justify the name *progressive bulbar palsy*.[5] The presence of disease in siblings suggests an autosomal recessive form of inheritance.[22] 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 the often localized initial symptoms, widespread involvement of motor neurons ensues in the terminal stage. Thus, the diagnosis usually denotes merely the bulbar onset of ALS in many instances.[229]

Primary Lateral Sclerosis

Pathologic studies in typical cases of primary lateral sclerosis show selective loss

of the corticospinal and corticobulbar tracts with sparing of the anterior horn cells.[253] The clinical signs include spasticity, diffuse hyperreflexia, Babinski signs, and pseudobulbar palsy. In the conspicuous absence of atrophy and weakness of distal musculature, the disease may simulate cord compression with a spastic paraparesis. Neither electromyography nor motor and sensory nerve conduction studies disclose abnormalities.[276] These negative findings distinguish this disorder from other motor neuron diseases as a distinct entity. Magnetic brain stimulation may reveal a markedly prolonged central motor conduction time.[253]

Familial Disorders with Geographic Predilection

Geographic foci of motor neuron disease described in the literature include the island of Guam,[35,284] and the Ryukyu Islands, south of Japan.[178] Epidemiologic studies have revealed a number of other smaller clusters.[288] The Guamanian motor neuron disease in the Chamorro population[112] shows a high familial incidence. Nearly 10 percent of the adult population on the island die of the disease. The parkinsonian–dementia complex affects the same population, but the two entities have no etiologic relationship. Some patients with motor neuron disease in Japan also suffer from presenile dementia.[213] Other reported associations with familial motor neuron disease include colonic neoplasia.[283]

Early studies may have underestimated the incidence of familial cases of juvenile and adult onset motor neuron disease with variation of penetrance.[331] Some of these kindreds have a mixed pattern of amyotrophy: for example, motor neuron involvement with pyramidal signs, and motor neuropathy[66] or upper limb amyotrophy, spastic paraplegia, and pseudobulbar palsy.[126] In contrast to the age-dependent incidence of sporadic ALS, familial ALS,[48] has an age of onset distributed about a mean of 45.7 years.[299]

Familial spastic paraplegia (FSP) comprises a heterogeneous group of neurodegenerative disorders characterized by slowly progressive weakness and spasticity of the lower limbs. Three genetic loci have been mapped: FSP1 to chromosome 14q, FSP2 to chromosome 2P, and FSP3 to chromosome 15q.[175,176]

3 SPINAL MUSCULAR ATROPHY

Spinal muscular atrophy (SMA), characterized by degeneration of anterior horn cells, has one of the most devastating outcomes of all the genetically determined neurologic disorders of childhood.[147] In a series of 108 patients seen in the Mayo Clinic between 1955 and 1975, the mortality rate reached 31 percent with a mean age of 65 months at the time of death.[182] Furthermore, only 35 percent of these patients could walk without assistance. The current classification of childhood SMAs into types I, II, and III has gained wide acceptance[222]: SMA I characterized by onset in the first month of life, SMA II occurring by age 18 months, and SMA III, with onset of illness thereafter. The disease is an autosomal recessive trait with deletion of the survival motor neuron (SMN) gene on chromosome 5q13 in more than 90 percent of infantile cases.[187,263] At least some adult-onset cases have the same deletion, but no consensus has emerged whether various subdivisions represent independent entities or a spectrum of the same disorder. In addition to SMN, other genes may cause or influence the SMA phenotype.[40,335]

Types I and III have clinically distinct features: the rapidly progressive infantile form (Werdnig-Hoffmann disease), with death before 3 years of age, and the late childhood or juvenile form (Kugelberg-Welander syndrome). Type II constitutes an intermediate form between types I and III. Despite an overlap in onset, the infantile, juvenile, and intermediate forms have different time courses of the disease and age of death. Table 23–1 summarizes these and other features useful in separating the three types of SMA.[174] Other clinically identifiable syndromes include juvenile progressive bulbar palsy (Fazio-Londe disease), scapuloperoneal SMA, facioscapulohumeral SMA, arthrogryposis

Table 23–1 Distinguishing Features of the Various Forms of Proximal Spinal Muscular Atrophy

Type	Age (Usual)		Ability to Sit Without Support*	Fasciculations of Skeletal Muscles	Serum Creatine Kinase Level
	Onset	Survival			
Infantile	<9 months	<4 years	Never	+/−	Normal
Intermediate	3–18 months	>4 years	Usually	+/−	Usually normal
Juvenile	>2 years	Adulthood	Always	++	Often raised
Adult	>30 years	50 years +	Always	++	Often raised

*At some time during the course of the illness.
From Kloepfer and Emery,[174] with permission.

multiplex with anterior horn cell disease, and distal SMA. Another form with adult onset,[149] once reported as a variant of the late juvenile type, may constitute a separate entity according to one survey over a 10 year period in northeast England.[245] The distribution of affected muscles distinguishes ALS with distal weakness from the adult form of SMA, which is characterized by more proximal involvement.

Morphometric analysis of intramuscular nerves showed less marked loss of myelinated nerve fibers with more effective reinnervation compared with ALS.[267] Various types of SMA share the same or similar electromyographic findings consisting of fibrillation potentials, positive sharp waves, fasciculation potentials, large motor unit potentials, and a reduced interference pattern. In a rapidly progressing infantile SMA electromyography suggests a mixture of denervation and regeneration with small motor unit potentials that vary temporally in configuration.

Infantile Spinal Muscular Atrophy

Infantile SMA, first described by Werdnig[327] and Hoffmann,[142] is 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 1 in 25,000 live births in Britian.[243] One third of the affected children have the disease already manifest at birth with decreased fetal movements or congenital arthrogryposis.[246] In the remainder, the onset of illness is usually by 3 months, and certainly before 6 months after birth with delayed developmental milestones. 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.[85,86,244]

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 are unable to hold their head up or sit and have 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, affected mildly, if at all, 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. Ultrastructural findings include massive muscle cell elimination by apoptosis and numerous immature muscle fibers, raising the possibility that muscle cell damage results in secondary death of motor neurons that no longer have the peripheral target.[101]

The incidence of fibrillation potentials and positive sharp waves depends on stage, progression, and severity of the disease. It reached 100 percent in one study,[135] but considerably less in another.[182] Fasciculation potentials occur infrequently if at all. One report[39] described unique potentials regularly discharging at a rate of 5–15 impulses per second in 75 percent of 30 patients, but without subsequent confirmation. A late recruitment of motor unit potentials reflects the loss of anterior horn cells. 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 impulses per second. As expected from collateral sprouting and a high fiber density, a quantitative survey shows high-amplitude, long-duration motor unit potentials. Regenerating axons, however, may also give rise to low-amplitude, short-duration potentials. In advanced stages, the motor unit potentials are either abnormally large or small, with no normal units between the two extremes.[135] The temporal variability of their waveform suggests instability of neuromuscular transmission.

Nerve conduction studies show normal or nearly normal velocities with a reduced amplitude of compound muscle action potentials. In one study,[182] 94 percent of the patients showed reduction of amplitude to less than 50 percent of the normal means. Mild slowing of conduction velocity results from the loss of fast-conducting axons. Repetitive stimulation of the nerve at either slow or fast rates causes a decreasing muscle response during ongoing reinnervation, suggesting defective neuromuscular transmission. In contrast to the motor responses, sensory nerve studies usually reveal normal amplitudes and velocities, although occasional patients may have minor electrophysiologic[256] or histologic abnormalities.[41] Rare cases of infantile neuronal degeneration clinically resemble infantile SMA. Nerve conduction studies showing marked slowing help distinguish this entity characterized by a demyelinative neuropathy as part of the widespread extensive neuronal degeneration.[298]

Juvenile Spinal Muscular Atrophy

The juvenile form of SMA,[180] 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 predilection 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.

The patient has a characteristic lordotic posture with protuberant abdomen, hyperextended knees, and hypertrophic calves with rare involvement of the cranial musculature such as ptosis. 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 survival into adulthood, albeit with confinement to a wheelchair by the mid thirties. Some patients develop chronic neurogenic quadriceps amyotrophy as a forme fruste of Kugelberg-Welander disease.[28,107] The differential diagnoses otherwise include polymyositis and muscular dystrophy.

A modest elevation of serum enzymes such as creatine kinase remains nearly constant as the disease progresses. In Duchenne muscular dystrophy, an initially very high level of creatine kinase 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 help classify chronic SMA, identifying the maturational stage of the muscle at the age of disease onset.[128]

An overall incidence of fibrillation potentials ranged from 20 to 40 percent in one series[136] and 64 percent in another.[182] More severely affected patients have an even higher percentage,[224] although it does not match the level seen in Werdnig-Hoffmann disease. Fasciculation potentials may[111] or may not[182] abound. Complex repetitive discharges, if present, suggest a late stage. Spontaneous activities involve the lower limbs more than the upper limbs and proximal muscles more than distal muscles.[136]

Voluntary contraction gives rise to high-amplitude, long-duration motor unit potentials that recruit poorly even at maximal effort.[39] Late components indicate the presence of slow-conducting regenerating axons. The percentage of large motor unit potentials increases with duration of the disease.[136] In advanced cases, small polyphasic potentials also appear, suggesting secondary myopathic changes of atrophic muscles. These potentials show a constant configuration, unlike the varying waveforms seen in the more rapidly progressive infantile cases.[182]

Motor and sensory nerve conduction studies, although usually normal,[218,280] may reveal a moderate reduction in amplitude of the compound muscle action potential. As in Werdnig-Hoffmann disease, this abnormality shows a strong correlation with the patient's functional capacity. In one series, 54 percent were bedridden when the amplitude fell below half of normal, compared to only 7 percent in the remainder.

Juvenile Progressive Bulbar Palsy

Slowly progressive bulbar palsy characterizes this very rare disorder of Fazio-Londe inherited as an autosomal recessive trait.[5] The diagnostic criteria based on a review of 24 children[204] include clinical features of a pure motor neuronopathy affecting the bulbar nuclei, exclusion of other causes of progressive bulbar paralysis, and positive support from electromyography or a pathology study. The clinical features consist of ophthalmoplegia, facial diplegia, laryngeal palsy, and other cranial nerve paralysis with onset in early childhood. Facial diplegia, if present at birth, suggests other entities such as infantile myotonic dystrophy, infantile facio-scapulohumeral dystrophy, and Möbius syndrome.[37] Progressive ophthalmoplegia and dysphagia may also develop as late manifestations in some cases of juvenile SMA, but they are not the presenting features. Electromyographic abnormalities, prominent in bulbar and pontine musculature, consist of fibrillation potentials, positive sharp waves, and impaired recruitment of motor unit potentials.

Scapuloperoneal Spinal Muscular Atrophy

As indicated by the name, a unique pattern of muscular weakness distinguishes scapuloperoneal SMA from the other types.[68,93] A form of muscular dystrophy also exhibits the same distribution of weakness with features often indistinguishable from those of muscular atrophy. Because of this, some prefer the term *scapuloperoneal syndrome* to include both neurogenic and myogenic forms.

In addition, Charcot-Marie-Tooth disease type 1 (CMT 1) may present as scapuloperoneal atrophy associated with distal sensory loss.[146,265] This variety of muscular atrophy slowly progresses after its usual onset in early adulthood. 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.[33] 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.[68] Muscle biopsies show a mixed neuropathic and myopathic pattern in most cases. Electromyographic studies demonstrate low-amplitude, short-duration motor unit potentials, fibrillation potentials, and positive sharp waves. Nerve

conduction studies reveal normal motor and sensory responses.

Facioscapulohumeral Spinal Muscular Atrophy

Like scapuloperoneal SMA, facioscapulohumoral SMA has a unique distribution of weakness and a similar counterpart among the muscular dystrophies.[96] 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 and takes a slowly progressive course. Clinical features resemble those of facioscapulohumeral muscular dystrophy. A descriptive term, *facioscapulohumeral syndrome*, used in some cases, suggests an inability to distinguish between the neurogenic and myogenic forms.

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.[102] 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.[105] One study describes a dominantly inherited lower motor neuron disorder as the cause of arthrogryposis present at birth.[103] Disorders of the motor neuron probably predominate, although different investigators postulate myogenic or neurogenic origins.[52] Electromyography may show spontaneous discharges such as fibrillation potentials or complex repetitive discharges. Motor unit potentials show reduction in number and poor recruitment. The nerve conduction studies reported in a few cases have shown no abnormalities.

Focal Amyotrophy

Distal amyotrophy of the upper limb develops in a heterogenous group of disorders.[72,207,235,320] Those reported from Japan and to a lesser extent elsewhere[140,232,247] have distal and segmental muscular atrophy of juvenile onset.[293] The clinical features include male preponderance, localized atrophy uniquely affecting the hand and the forearm, sparing of the lower limbs and cranial nerves, and initial rapid progression followed by slower change. The age of onset, distribution of atrophy, and benign course distinguish it from motor neuron disease.[134] Electromyography shows motor unit potentials of large amplitude and long duration, with impaired recruitment. Abnormal single-fiber electromyography results, if found over both arms and legs, suggest a more generalized disturbance than would appear clinically.[46] Nerve conduction studies reveal reduced amplitude of compound muscle potentials but normal velocities. Atrophy involving part of the body may not necessarily justify the diagnosis of focal motor neuron disease without first excluding other possibilities with extreme caution. Rare, monomelic amyotrophy with similar clinical features may follow trauma and immobilization in children.[236] Alternative diagnoses include spinal cord tumors, radiculopathy, plexopathy, and mononeuropathy. Sensory abnormalities, if present, help differentiate these conditions from motor neuron disease either clinically or by means of electrophysiologic studies.

Kennedy Disease

In patients with X-linked recessive bulbospinal atrophy or neuronopathy,[165] disease severity correlates with the size of the tandem CAG repeat in the androgen receptor gene.[73,190,286] Clinical features consist of mild facial weakness, facial fasciculations, severe atrophy of the tongue without prominent bulbar symptoms, postural hand tremor, hyporeflexia, testicular atrophy, gynecomastia, and a high serum creatine kinase level. Some patients have hyperlipoproteinemia, hypobetalipoproteinemia,[325] and hyperestrogenemia.[318] Autopsy studies show marked depletion of the spinal and brainstem motor neurons, with the exception of the third, fourth, and sixth cranial nerves.[292]

Electromyography typically shows fibrillation potentials, complex repetitive discharges, and large motor unit potentials. Nerve conduction studies usually reveal absent or low amplitude sensory nerve action potentials despite clinically normal sensation.[206] These abnormalities indicate very slowly progressive anterior horn cell disorder with a sensory neuronopathy that mimics an acquired process.[97] Despite the clinical resemblance, this entity carries a much better prognosis than motor neuron disease.[133] In one series, 2 percent of patients clinically diagnosed as having ALS showed the CAG repeat expansion, underscoring the importance of genetic screening.[237] Differential diagnoses also include Sandhoff disease, or hexosaminidase A and B deficiency,[308] and various motor neuronopathies.[4]

Other Disorders

Distal SMA resembles CMT 1 and 2 except for preservation of stretch reflexes, relative sparing of the upper limb, and a normal sensory examination. Some of these patients have evidence of peroneal muscular atrophy, whereas others suffer from cramps and fasciculations of the calves, showing true neurogenic hypertrophy.[118] In one study of 34 patients,[132] motor and sensory conduction studies revealed no abnormality.

One study reports three patients from a large family who had an autosomal dominant scapulohumeral form of SMA.[154] The disease progressed rapidly, without evidence of corticospinal tract dysfunction, and the patients died from respiratory failure.

Chronic asymmetric SMA typically shows asymmetric neurogenic atrophy involving one or more limbs without evidence of pyramidal tract dysfunction or bulbar signs.[131] Patients with this disease have no evidence of generalized neuropathy, although the motor nerve conduction velocities may show slight slowing because of muscle wasting.

Other entities include chronic segmental SMA of upper limbs, either as a familial or a sporadic form,[196,304] and a predominantly cervical form of SMA.[116]

4 CREUTZFELDT-JAKOB DISEASE

Despite the very early recognition of Creutzfeldt-Jakob disease,[57,151] only more recent studies have proven its transmissibility both in humans and the chimpanzee.[114] Accidental inoculation occurred after a corneal transplant in one patient[76] and after a surgical procedure with contaminated stereotactic electrodes in two others.[24] Although the organism has not been isolated, brain tissue from dying patients causes scrapie-like encephalopathy in goats.[124] The pathologic features resemble those of kuru, a transmissible disease seen in New Guinea,[113] 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. It affects both sexes equally, with onset in middle age or later. Following vague prodromal symptoms, mental deterioration, anxiety, depression, memory loss, and confusion develop. A variety of neurologic disturbances indicate cortical degeneration and upper and lower motor neuron involvement. The most commonly encountered symptoms include weakness, rigidity, spasticity with hyperreflexia, muscular atrophy, incoordination, tremor, and visual loss. Wasting of the muscles with fasciculations during late stages of illness mimics the typical appearance of motor neuron disease. The patient usually has spontaneous myoclonus, which may become less prominent in the advanced stages. The disease follows a rapidly progressive course, leading to severe dementia, blindness, lethargy, and eventual coma and death within a year after onset.

A characteristic electroencephalographic abnormality seen in 90 percent of cases consists of localized or diffuse bursts of high-voltage sharp or slow waves. The electromyographic evidence of denervation indicates muscular atrophy with involvement of motor cells in the medulla or spinal cord. Motor and sensory nerve conduction studies reveal no abnormality 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 Creutzfeldt-Jakob disease. With this disease, in contrast to the acquired immunodeficiency syndrome (AIDS), exposure to saliva, nasopharyngeal secretions, urine, or feces should cause no special alarm.[109] After such contact, recommended procedures consist of through washing of hands and other exposed parts with hospital detergent or ordinary soap and discarding the needle electrodes used for electromyography after incineration (see Chapter 3–2).

5 POLIOMYELITIS

Poliomyelitis no longer prevails as summer epidemics in the United States, but sporadic, mostly vaccine-associated cases still occur throughout the year.[61,255,291] Most clinical illness develops after infection by type I virus, but at times by type II or 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 percent of patients with paralytic illness.

The clinical features of systemic infection are flu-like symptoms such as fever, general malaise, diarrhea, and loss of appetite. Only a small percentage of patients in whom meningeal irritation develops 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. The spinal fluid examination reveals mild pleocytosis. Some studies[163,251] but not others[301] suggest a statistically significant association between poliomyelitis and motor neuron disease. Histopathologic and virologic studies in one patient with ALS and antecedent poliomyelitis provided no evidence of the continuing presence of poliovirus.[266]

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.[30] Increased jitter and fiber density, as well as large macromotor unit potentials, indicate pronounced, and often unstable, reinnervation as compensation for the loss of motor neurons, even in clinically unaffected muscles.[78,198,202] A supervised resistance training program can lead to improved dynamic strength of both symptomatic and asymptomatic muscles.[294] Reinnervation adequately compensates for the ongoing loss of neurons particularly in patients whose condition has stabilized.[150,295]

Late deterioration of function in some survivors suggested the possibility of late virus infection[7,221] but without subsequent confirmation.[205] Autopsy studies of the spinal cord revealed no difference between patients with stable postpoliomyelitis deficits and those with postpoliomyelitis progressive muscular atrophy.[249] Electromyographic studies show similar abnormalities in progressive and stable postpoliomyelitis patients,[258,332] although those with a more severe illness tend to develop postpolio weakness.[1]

If poliomyelitis has already depleted motor neurons, minor additional damage to the surviving anterior horn cells during advanced age might result in exaggerated clinical signs. In addition, the diseased neurons may have a certain predisposition to senile degeneration, or some surviving motor neurons may have incorporated too many muscle fibers from the denervated units beyond the metabolic capability.[19,90,173] A long-term follow-up study of poliomyelitis patients with apparent late progression has shown a relatively benign course, with the development of fasciculations but few upper motor neuron signs.[100,221] The incidence of an elevated creatine kinase level may[242,332] or

may not[225] differentiate those with delayed weakness and those without.

Electromyography initially shows only a reduced recruitment pattern during the acute phase of poliomyelitis. Fibrillation potentials develop as the motor axons degenerate. Reinnervation results in diminution of spontaneous discharges and the appearance of motor unit potentials of large amplitude and long duration. Weak muscles may have only a few extremely large motor unit potentials. Patients with a history of paralytic poliomyelitis usually reveal evidence of widespread chronic partial denervation despite restricted clinical weakness.[36,330] Clinically involved spinal segments may show a substantially increased mean interference amplitude not only in weak muscles but also in apparently unaffected contralateral muscles. Nerve conduction studies reveal normal velocities with reduced amplitude of the compound muscle action potentials, approximately in proportion to the degree of muscle atrophy.[155] Transcranial magnetic stimulation shows normal postexercise facilitation and depression, indicating no abnormality in the intracortical component of fatigue.[279]

In the absence of adequate reinnervation, fibrillation potentials may persist many years after the acute episode.[43] In these cases, the spontaneous discharges of very low amplitude indicate small atrophic muscle fibers. Even after reinnervation, diseased anterior horn cells may degenerate prematurely and cause the reappearance of spontaneous discharges.[94,277] Alternatively, muscle fibers may drop out of a motor neuron that can no longer meet the increased metabolic demand of an enlarged motor unit. Single-fiber electromyography in survivors of poliomyelitis has shown a significant increase in jitter and fiber density without neurogenic blocking.[311,329] These findings of defective neuromuscular transmission may also represent disintegration with aging of the reinnervated motor units. Routine electrophysiologic or morphologic techniques usually fail to differentiate weakening muscles in this syndrome from previously affected but stable muscles.[185] An increase in jitter with high-frequency stimulation implies ineffective conduction along immature nerve sprouts as the cause of the instability similar to ALS.[312] A sequential study using macro electromyography showed evidence of reinnervation until motor unit potential became around 20 times the normal size followed by failing capacity to maintain large motor units.[117]

A poliomyelitis-like disorder, Hopkin's syndrome, may develop in association with asthma.[143,193,328] The disease predominantly affects boys 10 years old or younger. The patient develops acute flaccid monoplegia involving a single upper or lower limb without sensory deficits. Marked atrophy in the involved limb 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[74] or anterior horns[328] as the locus of the disease. Despite clinical similarities to poliomyelitis, the disease can affect previously vaccinated children. Electromyographic features also resemble those seen in poliomyelitis. In one patient,[328] C5 root synkinesis developed between biceps and inspiratory muscles from aberrant regeneration.[168]

Patients with acute hemorrhagic conjunctivitis caused by enterovirus 70 may have polio-like paralysis of the limb and cranial muscles.[324] Early complaints include root pain and weakness. Electromyography of affected and some unaffected muscles shows fibrillation potentials early and large polyphasic motor unit potentials later. Nerve conduction studies reveal no specific abnormalities.

6 SYRINGOMYELIA

Signs and symptoms of syringomyelia result from cavitation and gliosis of unknown pathogensis affecting the spinal cord and medulla. The disease may begin at any age, but most often occurs in the third or fourth decade. It may occur sporadically or familially, affecting both sexes equally. The patient frequently has other congenital defects, such as spina bifida or Arnold-Chiari

malformation. Other associated features consist of 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 motor neuron disease, multiple sclerosis, spinal cord tumor, anomalies of the cervical spine, and posterior fossa lesions.[3]

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 various fiber tracts in any combination. Damage to the anterior commissure of the spinal cord causes the characteristic disassociation 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 and 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 affect the vibratory sense. Other signs include spasticity, hyperreflexia, Babinski signs, ataxia of the lower limbs, and a neurogenic bladder. A syrinx may affect the lumbosacral region alone or in association with lesions at the cervical level. The clinical features, then, include muscular atrophy and 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 fifth 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. In addition, spastic paraparesis results from interruption of the upper motor neuron tracts.

Electromyography reveals fibrillation potentials and positive sharp waves in the atrophic muscle. Sparing of the lower limbs serves to distinguish syrinx from motor neuron disease. Other abnormalities include continuous motor unit activity, synchronous motor unit potentials, respiratory synkinesis and myokymic discharges.[226] Motor nerve conduction studies show normal velocities but reduced amplitude of the compound muscle action potentials in the affected limb.[321] Motor evoked potentials using magnetic brain stimulation also uncover spinal cord dysfunction, as shown in a patient with posttraumatic syringomyelia.[195,262] The finding of normal sensory nerve potentials despite clinical sensory loss confirms a preganglionic involvement of the sensory pathway. In these instances, somatosensory evoked potentials (SEPs) may reveal central conduction block (see Fig. 20–12). One study showed absent or reduced N_{13} recorded by posterior-anterior cervical montage in 83 percent of median nerve SEPs despite normal P_{14} and N_{20} recorded using a noncephalic reference.[259] Pain-related SEPs following CO_2 laser stimulation also show clear abnormalities in most cases, thus providing a useful measure in the evaluation of dissociated sensory loss.[160] A lesion of the spinal tract or nucleus of the trigeminal nerve causes an afferent abnormality of the blink reflex with the absence of R_2 bilaterally after stimulation on the affected side of the face (see Fig. 17–16).

7 MULTIPLE SCLEROSIS

In multiple sclerosis, a demyelinating lesion with relative preservation of axis cylinders primarily affects upper motor neurons. Clinical presentations vary, al-

though the classical triad consists of nystagmus, scanning speech, and intention tremor. Patients also have symptomatic fatigue and muscle weakness.[166,281] The lesion may also involve the autonomic nervous system, causing incontinence as a characteristic feature of the disease. In one series, 3.9 percent of 282 newly diagnosed cases of multiple sclerosis developed acute radicular pain as a presenting symptom.[257] Demyelination in the ventral root exit zone probably accounts for lower motor neuron dysfunction and electromyographic evidence of denervation.[284] 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 17–4), somatosensory evoked potentials (see Chapter 20–6), motor evoked potentials (see Chapter 21–7), and autonomic evaluation (see Chapter 5–7). Conventional and some specialized nerve conduction studies have revealed subclinical peripheral nerve involvement in about 10 percent of patients.[334] The use of an abnormality scale may increase the robustness of changes in multimodal and longitudinal studies of sensory and motor evoked potential in multiple sclerosis.[20,194]

8 OTHER MYELOPATHIES

Subacute combined degeneration, usually associated with a low serum vitamin B_{12} level, may result from abnormal vitamin B_{12} binding protein despite its high serum level.[260] SEP studies show prolonged central conduction time[71] with improvement after cyanocobalamin therapy, which contributes little to the recovery of peripheral nerve function.[309] These findings suggest demyelination in the posterior column and axonal degeneration in the peripheral nerve. Longitudinal neurophysiologic studies may help evaluate progression of myelopathy and therapeutic effect following bone marrow transplantation in metachromatic leukodystrophy.[70]

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 abnormalities of tibial SEP in 7 of 8, nerve conduction abnormalities in 10 of 23, and evidence of denervation in 17 of 22. The anterior spinal artery syndrome results from ischemic cord infarction, which, during the acute stage, abolishes the F wave on the affected side.[6] Isolated paraplegia may develop from a remote stab wound probably as the result of radicular artery interruption in combination with systemic hypotension.[164] Infarction of the conus medullaris results in the absence of lower limb F waves as an early electrophysiologic finding.[53] A high cervical cord infarction may reduce or abolish R_2 of the blink reflex, indicating dysfunction of the spinal tract of the trigeminal nerve.[231]

Some patients with human T lymphotropic virus I (HTLV-I) infection develop chronic progressive myelopathy,[194] called *HTLV-I–associated myelopathy* (HAM) in Japan and *tropical spastic paraparesis* (TSP) in South America.[233,264] 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, therefore, may result from a concomitant myopathy (see Chapter 28–7).[108] Although rare, the same disorder has been reported in the United States[92] and elsewhere. Electrophysiologic abnormalities in HAM include segmental denervation of paraspinal muscles.[10] SEP changes were reported in 86 percent of patients in one study,[44] and peripheral nerve dysfunction was seen in 43 percent in another series.[26] Pain-related SEPs following CO_2 laser stimulation also show subclinical abnormalities of the spinothalamic tract in most patients.[159]

An epidemic of spastic paraparesis called *konzo* developed in a drought-affected rural area of Northern Tanzania. Konzo constitutes a distinct upper motor neuron disease probably caused by a toxic effect of insufficiently processed cassava ingested under adverse dietary circumstances.[144] Magnetic brain stimulation may fail to elicit motor evoked potentials

(MEPs) but other neurophysiologic studies remain largely normal.[316]

Monomelic amyotrophy may develop after irradiation of the lumbosacral spinal cord for malignancy, as the result of selective injury to the lower motor neuron.[184] Selective calf weakness usually suggests intraspinal pathology rather than peripheral neuropathy, which characteristically involves muscles innervated by the peroneal nerve.[31]

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.[23] Persisting abnormalities of serial single-fiber electromyography well beyond resolution of spinal shock suggest anterior horn cell dropout during the first year after acute spinal cord injury.[2] These findings provide supportive evidence for transsynaptic neuronal degeneration as the result of a rostral lesion, which effectively blocks descending impluses. In four patients with long-standing complete spinal cord injury, however, pathologic investigation failed to substantiate the loss of anterior horn cells below the lesion site.[157] Peripheral sprouting instead of root sparing may serve as a mechanism for recovery in the zone of injury in acute quadriplegia.[200]

Intervertebral recording of spinal somatosensory evoked potentials (see Chapter 7-5 and Chapter 20-6) help exclude clinically silent cord compression, directing surgical intervention to the appropriate level of concern. A high incidence of focal conduction block at C3, 4 or C4, 5 with normal conduction at C5, 6 and C6, 7 characterizes cervical spondylotic myelopathy.[305] Patients with acute cervical spinal cord injury[59] or transverse myelitis[302] may show a complete loss of F waves during initial examination, and subsequent gradual recovery. Spinal shock in part accounts for reduced F-wave excitability. One study also showed decreased sural sensory amplitude in addition to decreased muscle response after stimulation of the tibial nerve in patients with spinal cord injury.[115] In another series, however, sensory action potential amplitudes remained normal after clinical evidence of injury to the spinal cord.[254]

Electrical injury may cause myelopathy associated with delayed conduction of central motor and sensory pathways as tested by SEP and transcortical MEP.[310] Other rare cases of transverse myelitis include infectious agents such as Lyme borreliosis[177] and toxoplasmosis in patients with AIDS,[139] and odontoid fractures that may account for delayed progressive myelopathy years after a forgotten injury.[58]

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Chapter 24

RADICULOPATHIES AND PLEXOPATHIES

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. Peripheral lesions such as carpal tunnel syndrome can mimic proximal abnormalities of the root or plexus. Selective damage to these anatomic regions usually results from trauma, mechanical compression, and, less frequently, neoplastic and inflammatory processes. Thus, a relatively short list comprises the differential diagnoses of a proximal lesion compared with the much wider range of possibilities encountered in neuropathies and other distal involvement (see Chapter 25–1).

In the evaluation of radicular or plexus injuries, electrophysiologic studies help delineate the distribution of the affected muscles, localize the level, and elucidate the extent and chronicity (see Chapter 1–4).[213] A combination of clinical, laboratory, and electrodiagnostic features determine the level of a radicular lesion.[139]

Some studies report a high correlation among electromyographic evidence of denervation, myelographic abnormalities, and surgical findings.[123] In one series,[144] however, electromyography and magnetic resonance imaging agreed in 60 percent of patients, but only one study showed abnormality in the remaining 40 percent, suggesting that they provide complementary diagnostic information. Some advocate application of a computer-aided expert system to brachial plexus injuries.[70] Broad and frequently anomalous segmental innervations challenge the clinician in attributing any pattern of clinical or electromyographic findings to a specific spinal level.[160]

In the affected muscle, needle examination initially reveals poor recruitment of motor unit potentials indicating structural or functional loss of axons. Subsequent appearance of fibrillation potentials and positive sharp waves in 2–3 weeks suggests axonal degeneration. Low-amplitude, polyphasic motor unit potentials have temporal instability during active regeneration of motor axons. In contrast, high-amplitude, long-duration motor unit potentials with stable configuration appear later after completion of reinnervation. Nerve conduction studies reveal reduced amplitude of the muscle or sensory action potentials in appropriate distribution depending on the site of involvement.

2 CERVICAL AND THORACIC ROOTS

Anatomic peculiarity stems from a mismatch in number between eight cervical roots and seven cervical vertebrae. The C1 through C7 roots emerge above their respective vertebrae, whereas the C8 root exits between the C7 and T1 vertebrae. Common causes of cervical radiculopathy include spondylosis, herniated disc, and traumatic avulsion.

In compression of the C5 root, pain in the interscapular region radiates along the lateral aspect of the arm to the elbow. With involvement of the C6 root, pain extends over the shoulder to the lateral aspect of the arm and forearm and thumb. Pain induced by irritation of the C7 root typically involves the entire arm and forearm with radiation into the third digit and, to a lesser extent, the second and fourth digits. Less commonly encountered C8 root pain radiates to the fourth and fifth digits 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 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 almost exclusive control by single roots. Recommended maneuvers include shoulder abduction to 180 degrees (C5), elbow flexion in full and half supination (C6), and adduction of the shoulder, extension of the elbow, and extension and flexion of the wrist (C7).[155] A C8 root lesion affects the long extensors and flexors of the fingers and, to a lesser degree, the intrinsic hand muscles, which receive substantial supply from the T1 root. An ulnar nerve lesion spares the median-innervated thenar muscles, whereas a T1 root lesion affects all the small hand muscles. A 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), supinator (C6), triceps (C7), and finger flexors (C8).

Electromyographic studies provide an objective means to corroborate clinical diagnosis of a radicular lesion (Table 24–1; also see Table 1–2). Studies of paraspinal muscles help document the involvement of the posterior rami, thus confirming a radicular as opposed to a plexus lesion. The length-dependent delay of nerve degeneration[141] predicts the appearance of denervation potentials first in the paraspinal muscle. In one study,[158] however, multivariate estimates showed no correlation between paraspinal muscle spontaneous

Table 24–1 Innervation Patterns of the Cranial, Shoulder Girdle, and Upper Limb Muscles

NERVES	MUSCLES	C2	C3	C4	C5	C6	C7	C8	T1
Anterior Primary Rami									
Cervical Plexus									
Spinal Accessory Nerve	Sternocleidomastoid								
	Trapezius, upper, middle, lower								
Phrenic Nerve	Diaphragm								
Brachial Plexus									
Dorsal Scapular Nerve	Rhomboid								
Suprascapular Nerve	Supraspinatus								
	Infraspinatus								
Axillary Nerve	Teres Minor								
	Deltoid, anterior, middle, posterior								
Subscapular Nerve	Teres Major								
Musculocutaneous Nerve	Brachialis								
	Biceps Brachi								
	Coracobrachialis								
Long Thoracic Nerve	Serratus Anterior								
Lateral Pectoral Nerve	Pectoralis Major (clavicular part)								
Medial Pectoral Nerve	Pectoralis Minor								
Radial Nerve	Brachioradialis								
	Extensor Carpi Radialis								
	Triceps, long, lateral, middle heads								
	Anconeus								
Posterior Interosseous Nerve	Supinator								
	Extensor Carpi Ulnaris								
	Extensor Digitorum								
	Extensor Pollicis Brevis								
	Extensor Indicis								
Median Nerve	Pronator Teres								
	Flexor Carpi Radialis								
	Abductor Pollicis Brevis								
Anterior Interosseous Nerve	Flexor Digitorum Pronfundus (I & II)								
	Pronator Quadratus								
	Flexor Pollicis Longus								
Ulnar Nerve	Flexor Digitorum Profundus (III & IV)								
	Flexor Carpi Ulnaris								
	Adductor Pollicis								
	Abductor Digiti Minimi								
	Interossei, volar (I-III), dorsal (I-IV)								
Posterior Primary Rami	Cervical Erector Spinae								

activity and symptom duration. In practice, therefore, this time relationship may not necessarily hold.[49] Clinical findings should dictate which muscles to examine for the optimal identification of the involved root.[114] Affected muscles show reduced recruitment and incomplete interference pattern at the beginning and

fibrillation potentials, positive sharp waves, and high-amplitude, long-duration motor unit potentials later in the course of the disease. Although some advocate the use of cervical root stimulation,[15] late response, or somatosensory evoked potentials, these long-latency responses generally fail to conclusively document a very focal abnormality (see Chapter 7–6). Segmental stimulation in short increments would help if technically feasible during surgery. Preganglionic involvement spares the sensory nerve action potentials despite the degeneration of motor axons, which leads to muscle atrophy and reduction in amplitude of compound muscle potentials. Affected muscles may show a decremental response to repetitive stimulation of the nerve.[75] Thermography, although abnormal in some patients, provides no additional information in the diagnosis of cervical radiculopathy when compared with electromyography.[184]

The differential diagnosis of cervical radiculopathy should include lymphomatous meningitis,[75] a rare anomalous ectatic vertebral artery,[180] Pancoast's tumor with apical lung tumor eroding through the C7 and T1 pedicles,[201] and meningeal melanocytoma.[192] Misdiagnosis may lead to progression of neurologic signs and symptoms and improper mode of therapy. Spinal manipulation therapy performed in the presence of an organic lesion, for example, may carry the risk of spinal cord injuries.[164]

Cervical Spondylosis

Cervical spondylosis results from bony overgrowth of the vertebrae following degeneration of the intervertebral disc. A spondylotic bar, protruding posteriorly, most commonly impinges on the C5 and C6 roots and, less frequently, on the C7 root. Other cervical and thoracic roots are rarely affected. 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 root 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 the C7 root may enhance the triceps response and suppress the biceps and supinator reflexes.

Herniated Cervical Disc

The discs herniate less frequently in the cervical region than in the lumbar region. Cervical disc lesions usually affect patients having a history of neck trauma unilaterally. 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 the C6 root and those between C6 and C7 vertebrae, C7 root. Movement of the neck or the arm aggravates the initial symptom of pain over a typical root distribution. Compression of the ventral root causes weakness in the muscles innervated by the affected root.

Root Avulsion

The Erb-Duchenne palsy results from avulsion of C5 and C6 roots. This type of injury occurs with downward traction on the plexus, which increases the angle between the head and shoulder, for example, following a forceps delivery with the shoulder fixed in position. 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. The muscles innervated by C5 and C6 roots atrophy, but the sensory examination, although often limited in infants, usually reveals only mild changes.

The Klumpke palsy with avulsion of C8 and T1 roots occurs much less frequently from forced upward traction on the plexus. An attempt to grasp an overhead support during a fall increases the angle between the arm and thorax beyond the ordinary limit. This type of injury degenerates the ulnar nerve, the inner head of

the median nerve, and a portion of the radial nerve. The intrinsic hand muscles and long flexors and extensors of the fingers atrophy, producing a partial claw hand. The patient also has numbness along the inner aspect of the hand, forearm, and arm. Horner's syndrome indicates damage of the cervical sympathetic fibers.

Traumatic injury may cause preganglionic avulsion of cervical roots from the spinal cord, or postganglionic damage to the plexus, or both. This distinction has practical operative implications, as nerve grafting onto avulsed root results in no return of function. Myelography usually delineates the extent of root injury, but structural abnormalities do not necessarily coincide with functional deficits uncovered by electrophysiologic studies.[196] Pseudomeningoceles may accompany intact roots on the one hand, and root avulsion may fail to produce detectable meningoceles on the other. To exclude root avulsion definitively, direct stimulation of the individual surgically exposed cervical nerve root must elicit reproducible somatosensory evoked potential.[91] 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 reflex skin reaction, and nerve stimulation elicits a normal sensory action potential despite sensory loss. These findings stand in sharp contrast to the loss of chemical or electrical reactivity along the distal nerve segments in patients with plexus lesions. Earlier pessimism notwithstanding, recent studies show some functional recovery in primates after spinal cord implantation of avulsed roots.[31]

The deep cervical muscles receive innervation from the posterior as opposed to the anterior rami of the spinal nerves. 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 proximaly 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 muscles also serves to distinguish between root and plexus lesions.

Thoracic Radiculopathy

Isolated involvement of lower thoracic or upper lumbar roots, although rare, may result from collapsed vertebral bodies.[128] With lesions at this level, proximal weakness of the legs may lead to an erroneous diagnosis of myopathy. Electromyography shows spontaneous discharges localized to the affected myotomes in the limb and paraspinal muscles. This should provide an important criterion especially because myelography fails to differentiate symptomatic and asymptomatic thoracic herniated discs.[10]

3 BRACHIAL PLEXUS

During times of peace, brachial plexus lesions usually result from civilian gunshot wounds. Penetrating injuries from bullet wounds often involve the upper and lower trunks and the posterior cord. A difficult birth or sudden traction applied to the arm or neck can also damage the plexus. Although some affected infants have a favorable prognosis,[95] most show no recovery.[29] Some physicians recommend early surgical reconstruction in those having no improvement by the age of 4 months.[107,115] 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 dislocation of the shoulder.[48] 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,[61,217] axillary arteriography,[131] median sternotomy,[84,93,124] surgery for thoracic outlet syndrome,[211] liver transplantation not necessarily correlated with the side of the axillary venovenous shunt,[101] jugular vein cannulation for coronary

artery bypass graft surgery,[86,116,191] and constraints from a tight vest.[178] Appropriate radiologic and electrophysiologic studies help determine the indications for surgical intervention, which benefits only well-selected patients.[53,100,106,107]

Idiopathic plexopathy ranks the first in incidence among nontraumatic conditions affecting the brachial plexus.[13] The differential diagnoses include Hodgkin's disease,[157] desensitizing injections,[215] Ehlers-Danlos syndrome,[103] systemic lupus erythematosus,[20] an uncommon side effect of interferon therapy,[17] localized chronic inflammation with fusiform segmental enlargement,[40] subclavian–axillary artery aneurysm,[118,203] and familial pressure-sensitive neuropathy.[22] Chronic compressive lesions of the brachial plexus range from primary nerve tumors[8] to metastatic breast cancer and lymphoma. Cervical cord compression may mimic the neuralgia.[174] Patients with neoplastic invasion tend to have pain and Horner's syndrome.[117] Radiation therapy of the axillary region also causes plexopathy, mimicking tumor recurrence. Intermittent compression seen in some cases of thoracic outlet syndrome produces less well-defined neurologic syndromes with little or no objective abnormalities. One study reports reduced sensory nerve action potentials in asymptomatic professional baseball pitchers probably as an example of a repetitive use syndrome affecting the brachial plexus.[130]

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,[208] a heavy backpack,[44] or the common football injury called a "stinger."[48] 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, internally or externally rotate the shoulder, flex the elbow, or extend the wrist radially. Other clinical features include sparing of the rhomboid and serratus anterior innervated by more proximal branches, 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 and medial cord 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. Lesions affecting the C8 and T1 roots impair hand function and cause Horner syndrome. These clinical features bear a resemblence to those of Klumpke's palsy. In addition to the intrinsic hand muscles, finger flexors and extensors are weak. Sensory changes involve the medial aspect of the arm, forearm, and hand, including the fourth and fifth digits.

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, including the first two digits. Compressive lesions in the thoracic outlet tend to affect the medial cord. Motor and sensory deficits develop in the median- and ulnar-innervated region that receives supplies from the C8 root. Although rare, local trauma can selectively damage the lateral cord, causing weakness in musculocutaneous and median-innervated muscles that receive axons from the C6 and C7 roots.

The nerve conduction abnormalities commonly seen in demyelinative lesions include (*1*) severe amplitude attenuation of muscle and antidromic sensory nerve action potentials evoked with stimulation proximal to the site of nerve injury compared with those evoked at a more distal site and (*2*) slowing of conduction across the site of injury. These findings suggest that the palsies result from a local conduction block with or without axonal

loss.[195] Magnetic nerve root stimulation may help demonstrate segmental demyelination.[150] The pattern of sensory potential abnormality from each digit may help localize axonal injury.[37,38,145,171] In one series,[68] upper trunk lesions showed consistent sensory abnormalities of the lateral antebrachial cutaneous nerve and the median nerve recorded from digit 1 rather than digit 2. Lower trunk lesions regularly diminished sensory potentials of the ulnar nerve recorded from digit 5 and the dorsal ulnar cutaneous nerve. These findings suggest the importance of studying uncommonly tested sensory fibers in the localization of brachial plexus lesions.

Electrophysiolgic studies in radiation plexopathy often reveal abnormal sensory conduction, normal motor conduction, and myokymic discharges.[117] In traumatic plexopathies electromyography renders more information than nerve conduction studies in delineating the degree, distribution, and time course of the disease.[5] Motor unit number estimation (see Chapter 8–1) may help elucidate pattern of reinnervation in serial studies of congenital brachial palsy.[175] Abberant regeneration of phrenic motor neurons may induce arm–diaphragm synkinesis after injury to the proximal portion of the brachial plexus or cervical nerve roots.[189] Synkinetic movements and A waves may involve different, sometimes antagonistic, muscles in patients with brachial plexus injury at birth.[46] Simultaneous needle studies from multiple muscles help document such misdirected reinnervation.

Idiopathic Brachial Neuropathy

Idiopathic brachial neuritis, also known as *neuralgic amyotrophy*[154] or *brachial neuralgia*, probably originates in the roots, although the exact site of lesion remains unknown. 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,[166] or following a surgical procedure as recognized in Parsonage and Turner's original description[134] or various vaccinations, especially with injection into the deltoid. Trauma, infection, or serum sickness may precede acute onset of pain and other symptoms of neuralgia. Complement dependent, antibody-mediated demyelination may precipitate peripheral nerve damage,[205] suggesting an inflammatory-immune pathogenesis.[186] 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, be a few years before maximal recovery is achieved 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 (see Chapter 25–3).[3]

The disease typically begins with pain localized in the distribution of C5 and C6 dermatomes.[127,154,199] The clinical picture varies considerably, with some patients showing a chronic and painless form[177] and others evidencing progressive monomelic sensory neuropathy.[220] 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 the spinal accessory nerve and the C7 root. 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 sometimes leads to a frozen shoulder syndrome. Some patients develop involvement of multiple cranial nerves associated with otherwise typical neuralgic amyotrophy.[162] Conversely, structural lesions involving the skull base may cause spinal accessory mononeuropathy with ipsilateral cranial nerve involvement mimicking brachial neuropathy.[112]

The disease may cause selective paralysis in the distribution of a single root, trunk, cord, or peripheral nerve.[60] Such

mononeuropathies tend to involve the radial, long thoracic, phrenic, suprascapular, or accessory nerve.[19,111,207] Occasionally the initial presenting symptoms mimic an anterior interosseous nerve palsy.[199] Concurrent involvement of the shoulder muscles in neuralgic amyotrophy suggests two possibilities[168]: (*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.[187]

Electromyography usually shows evidence of denervation on the affected side and may also reveal subtle changes on the clinically asymptomatic side. Typical findings seen in the involved muscles include fibrillation potentials, positive sharp waves, high-amplitude polyphasic motor unit potentials, and reduced interference pattern. This together with the course of clinical recovery suggests axonal interruption and wallerian degeneration. Conduction studies reveal slightly to moderately increased latencies from Erb's point to severely affected muscles. The loss of fast-conducting fibers accounts for this change accompanied by reduced amplitude of the compound muscle potentials. Mild injury leading to pure demyelination improves rapidly without loss of axons.[168] A selective latency increase from Erb's point to individual muscles of the shoulder girdle suggests multiple mononeuropathies.[136] Conduction abnormalities may become more conspicuous after reinnervation has begun. The nerves in clinically unaffected extremities sometimes show widespread changes.[209] F wave studies may show increased latency and slow conduction velocity in the segment above the axilla, but not consistently, especially in the early stages of illness.[105]

The diagnosis often depends on the combination of amplitude abnormalities of median or ulnar sensory studies, slowed conduction of musculocutaneous motor fibers, and lack of paraspinal fibrillation potentials on needle examination.[71] The loss or diminution of the sensory action potentials localizes the lesion distal to the dorsal root ganglion. Normal paraspinal examination favors plexopathy but does not rule out radiculopathy.

Familial Brachial Plexopathy

Nontraumatic brachial plexus neuropathy may develop on a familial basis in association with lesions outside the plexus.[22,23,55] Acute episodes have features indistinguishable from sporadic idiopathic neuralgic amyotrophy, but patients with the familial variety have less pain. Inherited as an autosomal dominant trait, the disease tends to affect a younger age group with no preference for either sex, although pregnancy may herald its onset. The symptoms recurr more frequently in the familial than in the sporadic variety. The lesions outside the plexus cause additional signs, such as Horner's syndrome and dysphonia.[74] The disease can also involve the lumbosacral plexus, cranial nerves, individual peripheral nerves such as long thoracic nerve,[159] and autonomic nervous system.[7] Nerve conduction studies show normal or reduced amplitude of the recorded response. Electromyography reveals fibrillation potentials, positive sharp waves, and reduced recruitment, suggesting axonal damage.[55]

Some patients with familial pressure-sensitive neuropathy may also present with acute attacks of brachial plexopathy (see Chapter 25–5). This condition affects the peripheral nerves diffusely,[22] showing a predilection for the common sites of compression.[23] Sural nerve biopsies reveal bizarre focal swelling of the nerve fiber, mild reduction in the total myelinated fiber count, and an abnormal fiber diameter spectrum with loss of the normal bimodal distribution. The term *tomaculous neuropathy*, used to describe this pathologic condition, implies sausage-shaped thickenings of the myelin sheaths.

Plexopathy Secondary to Radiation

In one series of 79 breast cancer patients, 35 percent had radiation-induced plexopathy, most developing symptoms during or immediately after the exposure.[142] Plexopathy, however, may develop months to years after radiation treatment and take a progressive course.[65] Nerve conduction

studies reveal a mildly increased latency in proportion to a reduced amplitude of the evoked potentials. Electromyography shows fibrillation potentials, positive sharp waves, and large, polyphasic motor unit potentials. The presence of myokymic discharges favors the diagnosis of radiation plexopathies.[2,88]

In patients with cancer and brachial plexus signs, radiation injury may mimic tumor infiltration. According to 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.[108] Neoplastic infiltration may cause considerable slowing of conduction across the plexus, but not universally. The characteristic features emphasized in another study for this distinction[88] include absence of pain as the presenting symptom, no sign of discrete mass with computed tomography, detection of myokymic discharges, and temporal relationship to therapy, rather than the distribution of weakness or the results of nerve conduction studies.

Cervical Rib and Thoracic Outlet Syndrome

A variety of anomalous structures in the neck may affect the roots or trunks of the brachial plexus causing a vascular or neurogenic syndrome.[126] The cervical rib may rarely compress the neurovascular structures, especially in women who tend to sag the shoulder girdle. A rudimentary cervical rib with a fibrous band causes symptoms more often than a fully formed cervical rib. A compression syndrome may also result from the first thoracic rib pressed upward by distortion of the thorax. In one study,[152] magnetic resonance imaging showed a bandlike 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 once widely publicized compression by the scalenus anticus muscle fell into disrepute because a true syndrome occurs only very rarely.[102] Patients with thoracic outlet syndrome often have low-set "droopy" shoulders and a long swanlike neck.[190] They usually complain of unilateral symptoms, even in the presence of bilateral cervical ribs. Some patients develop pain, numbness, and weakness principally over an ulnar distribution immediately after median sternotomy for coronary artery bypass graft. Despite a 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.[124]

Vascular featuress 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. Controversies continue whether the entity is underdiagnosed[170] or overdiagnosed.[212] Erroneous diagnosis may lead to inappropriate scalenotomies for the disputed scalenus anticus syndrome and removal of the first rib.[5,34,80,126,211] The procedure has limited indication for most patients with vascular symptoms.[76] If such intervention offers a beneficial effect in the management of arm pain, the initially normal electrophysiolgic studies usually fail to substantiate the subjective change.[113] Some investigators have reported consistent abnormalities of ulnar nerve studies with stimulation at Erb's point,[47,129,172,200] but without convincing data or subsequent confirmation.[39,45,149,210,214]

In contrast to the poorly defined condition described above, the classical thoracic outlet syndrome denotes a rare, but more clearly recognizable neurologic entity, usually affecting women with a rudimentary cervical rib.[77,78] 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.[165] Prominent atrophy of the abductor polli-

cis brevis may superficially suggest a diagnosis of carpal tunnel syndrome. 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 electrophysiologic studies demonstrate no abnormalities.[182,218]

Nerve conduction studies in patients with a clear neurologic deficit show reduced or absent sensory action potentials of the ulnar and medial antebrachial cutaneous nerves[109,124] normal sensory action potential of the median nerve, reduced amplitude of ulnar and median compound muscle action potential,[119] and an increase in latency of the F wave of the ulnar nerve on the affected side when compared with the normal side.[52,116] Cervical root stimulation may help localize the site of conduction abnormalities.[67] Reduced amplitude of the sensory action potential confirms a postganglionic involvement,[78,146,183] whereas normal conduction velocities help exclude the possibility of more distal entrapment. Electromyography shows 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.[45,105] Some investigators advocate the use of dermatomal, median, or ulnar somatosensory evoked potential studies, but their clinical usefulness is limited.[26,97]

4 LUMBOSACRAL ROOTS

Injury at the lumbosacral level most commonly occurs at the point where the root exits through its foramen. Preganglionic damage, however, can 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.[161] 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 are a more reliable localizing sign than are sensory impairments. The reverse seems to hold in the lower limbs. Patients with familial predisposition may develop lumbar disc herniation at a young age.[202] Lumbar radiculopathy may develop following spinal fusion for scoliosis.[87]

Radiculopathies rarely involve the first three lumbar roots that supply the skin of the anterior thigh. With compression of the L4 root, pain radiates from the knee to the medial malleolus along the medial aspect. With L5 root 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 the S1 root causes pain to radiate down the back of the thigh, leg, and lateral aspect of the foot. Irritation of the S2 through S5 roots 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. 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.[155] Lesions of a single root affect dorsiflexion of the foot to a lesser extent because of the dual control by the L4 and L5 roots. Similarly, plantar flexion is subserved by the S1 and S2 roots. 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. One series that tested the extensor digitorum brevis reflex for localization of L5 root lesions provided disappointing results.[135]

When radiologic and clinical findings conflict, electrodiagnosis plays a particularly important role in justifying surgical exploration.[198] For example, extraforaminal compression of the L5 root by lum-

bosacral ligaments may cause denervation despite a normal myelogram and other imaging studies.[151] Conversely, asymptomatic subjects may have abnormal magnetic resonance scans of the lumbar spine, making it imperative to seek a physiologic and clinical correlation.[21] To supplement electrophysiologic evaluations of functional deficits, T_2-weighted and short time to inversion recovery (STIR) magnetic resonance imaging sequences can be used to detect denervated skeletal muscle, which shows increased signal intensity. In one study,[32] this abnormality corresponded closely with spontaneous activities on electromyographic examination.

Conus Lesion

Tumors known to involve the conus medullaris, which comprises the S2 to S5 segments, include ependymoma,[143] dermoid cyst, lipoma, arteriovenous malformation,[122] and, less frequently, metastasis.[24] They typically invade the sacral roots from below, beginning with the S5 root. 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 the S1 root. The lesion typically spares the knee reflex. Initial unilateral weakness soon spreads to the other limb, leading to relatively symmetric involvement.

Electromyographic abnormalities often indicate a bilateral involvement of multiple roots despite asymmetric clinical signs. The anal sphincter also shows evidence of denervation and loss of tonus. Nerve conduction studies may reveal reduced muscle action potentials but normal sensory nerve potentials, as predicted from the preganglionic site of involvement. Some ascending spinal fibers undergo degeneration, as evidenced by abnormal somatosensory evoked potentials recorded over the scalp after intrathecal stimulation of the lumbosacral cord.[62] Electrophysiologic studies should reveal no abnormalities in the upper limbs.

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.[176] Such a mass lesion in the spinal canal below the T12 vertebrae can affect any 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.[94] With a laterally located lesion at the level of the L1, L2, and L3 vertebrae, pain typically radiates over the anterior thigh. Involvement of the L4 root 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 motor neuron signs. This rare, confusing presentation may lead to an erroneous diagnosis of amyotrophic lateral sclerosis.

A lipoma may involve a few cauda fibers, producing a distension in the region of the conus medullaris with only sexual and voiding dysfunction.[73] Midline or diffuse involvement of the cauda equina suggests metastasis from prostate cancer, direct spread of tumors in the pelvic floor, or chrondromas 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 motor neuron syndromes may also follow radiation therapy,[92] redundant nerve root syndrome,[167,188] spinal arachnoiditis,[153] or ankylosing spondylitis.[12]

Except for asymmetric distribution and severe pain, signs and symptoms of a cauda equina lesion resemble those of a conus medullaris lesion.[163] 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. Electromyographic studies show fibrillation potentials and large motor unit potentials in the distribution of several lumbosacral roots, including paraspinal muscles[12] and urethral sphincter.[72] Again, the findings mimic those of an intrinsic cord involvement except for an asymmetric distribution of the abnormalities with spread above the sacral myotomes. Unlike in axonal polyneuropathy motor conduction studies tend to show normal amplitude and distal latency in lumbosacral radiculopathy.[16] Nonetheless, a substantial side-to-side difference in amplitude of the compound muscle action potentials favors the diagnosis of cauda equina rather than conus medullaris lesions. Simultaneous recording of somatosensory evoked potentials from the lumbar area and the scalp permit evaluation of cauda equina lesions based on the relative effectiveness of the peripheral stimulation in eliciting these two responses.[120]

Herniated Lumbar Disc

Disc protrusion involves the L4 to L5 and L5 to S1 interspaces in most 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. 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 the L5 root, which emerges under the L5 vertebrae. Similarly, a disc protrusion between the L5 and S1 vertebrae damages the S1 root exiting the interspace below. As mentioned earlier, cervical disc herniation at the C6 to C7 space compresses the C7 root, 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.

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[140,169] and of the anterior tibial muscle with an L4 radicular lesion.[137] Neurogenic muscle hypertrophy may also result from a passive stretch mechanism, a tethered spinal cord,[18] and excessive spontaneous muscle activities.[137]

Needle studies help confirm the diagnosis and identify the damaged root (Table 24–2, also see Table 1–3 and Fig. 14–9). Denervation of the paraspinal muscles (see Fig. 14–8C) implies a lesion located proximal to the origin of the posterior ramus. The absence of denervation here, however, does not necessarily exclude the possibility of root compression. In addition to the diagnostic use, series of studies can guide the management by substantiating clinical progression or improvement.[99] The course of radiculopathy can be gauged better by studies of electrical abnormalities than by computed tomography results.[104]

Paraspinal studies help differentiate radiculopathy from diseases of the plexus or peripheral nerve. The multifidus muscles are innervated by a single root in contrast to the polysegmental innervation of the rest of the paraspinal muscle mass.[29] Nonetheless, paraspinal abnormalities usually fail to provide the exact location of the involved segment.[85] Determination of the precise level of lesion, therefore, depends on careful exploration of the affected muscles in the lower limbs. Because of anatomic peculiarities, lesions located much higher than the ordinary disc protrusion may compress the L5 or S1 roots within the cauda equina. For example, a tumor of a high lumbar root may produce this type of confusing clinical features and myelographic abnormalities.

The assessment of radiculopathy should include nerve conduction studies to exclude a neuropathy. Amplitude asymmetry of compound nerve and muscle action potentials also assists in detection of modest nerve damage. Despite the commonly

Table 24–2 Innervation Patterns of the Pelvic Girdle and Lower Limb Muscles

NERVES	MUSCLES	L2	L3	L4	L5	S1	S2
Anterior Primary Rami							
Lumbosacral Plexus							
Femoral Nerve	Iliopsoas	■	■				
	Sartorius	■	■	■			
	Rectus Femoris		■	■			
	Vastus Lateralis, Medialis		■	■			
Obturator Nerve	Gracilis	■	■	▒			
	Adductor Longus, Brevis, Magnus	■	■	■			
Superior Gluteal Nerve	Gluteus Medius			■	■	■	
	Gluteus Minimus			▒	■	▒	
	Tensor Facie Latae			▒	■	■	
Inferior Gluteal Nerve	Gluteus Maximus				▒	■	■
Sciatic Nerve							
Tibial Division	Semitendinosus, Semimembranosus				■	■	■
	Biceps Femoris, long head				▒	■	▒
Peroneal Division	Biceps Femoris, short head				▒	■	■
Common Peroneal Nerve							
Deep Peroneal Nerve	Tibialis Anterior			■	■		
	Extensor Digitorum Longus				■	■	
	Extensor Digitorum Brevis				■	■	
	Extensor Hallucis Longus				▒	■	
Superficial Peroneal Nerve	Peroneus Longus				■	■	
	Peroneus Brevis				■	■	
Tibial Nerve	Tibialis Posterior			■	■		
	Flexor Digitorum Longus				■	■	▒
	Flexor Hallucis Longus				■	■	■
	Gastrocnemius, medial head					■	▒
	Gastrocnemius, lateral head					▒	■
	Soleus				▒	■	■
Medial Plantar Nerve	Abductor Hallucis					■	■
Lateral Plantar Nerve	Abductor Digiti Minimi					■	■
	Interossei					■	■
Posterior Primary Rami	Lumbosacral Erector Spinae	■	■	■	■	■	■

held belief that root lesions spare sensory amplitude, L5 radiculopathy often causes a reduction in superficial peroneal nerve sensory action potentials.[121] In such cases, structural abnormalities compress the dorsal root ganglion located at the intraspinal canal, thus causing postganglionic rather than preganglionic damage. H reflex studies reveal abnormalities in an S1 radiculopathy, especially with the use of more sensitive spinal nerve stimulation[43,133,156] or magnetic activation of the root[132,197,221] to isolate the proximal radicular segment (see Chapter 21–4). These studies help differentiate S1 from L5 involvement. The measures of F-wave latencies, dermatomal somatosensory evoked potentials (SEPs), or motor evoked potentials may reflect delayed conduction, but usually not well enough to detect an early or mild radiculopathy.[4,54,56,57,105,125] Conduction studies over long distances gener-

ally provide an insensitive measure in evaluating focal nerve lesions (see Chapter 7–6), although some investigators advocate the use of dermatomal SEPs as a screen for radiculopathy.[206]

Stereotactic devices now allow percutaneous lumbar discectomy.[110,138] The introduction of microdiscectomy to lumbar spine surgery, together with the combination of long-acting anesthetic agents and corticosteroids, has led to a substantial decrease in postoperative discomfort and shorten the hospital stay.[79] These advances notwithstanding, and even with strict criteria for indication of surgery, patients may develop failed back syndrome at a rate eventually reaching 50 percent in some series.[30] Spinal cord stimulator implantation, then, seems preferable to repeated operation or dorsal root ganglionectomies.[147,148] A relatively normal electromyographic finding promises a good outcome, whereas neurogenic abnormalities generally imply a poor prognosis.[64] Overall outcome, however, seems to depend more on psychosocial aspects than on physiologic findings.

Following laminectomy, spontaneous activity may persist indefinitely, although it usually diminishes substantially by 3–6 months.[51] In one study, focal abnormalities found at least 3 cm lateral to the incision and 4 to 5 cm deep suggested a new lesion.[98] Other findings suggestive of an active radiculopathy in postlaminectomy patients include (*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 activity 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. Nerve root hypertrophy may cause lumbar stenosis in chronic inflammatory demyelinating polyradiculoneuropathy.[82] In a review of 37 patients, stenosis most commonly affected the L4 or L5 level or both.[179] In 36 patients, electromyography revealed fibrillation potentials and poorly recruiting, polyphasic long-duration motor unit potentials in several leg muscles and, to a lesser extent, in the paraspinal muscles bilaterally. Retrospective analysis of 244 patients with spinal stenosis has shown high medium- to long-term success with lumbar laminectomy and rare lumbar instability following surgery, requiring lumbar fusion only infrequently.[181]

Root Avulsion

Intradural avulsion does not involve the lumbosacral roots as often as the cervical roots,[69] although this condition is frequently overlooked in patients with pelvic fractures or sacroiliac dislocation.[89] In these instances, tension in the lumbar and sacral plexuses stretches the root intradurally.[11] Electromyography reveals 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 delineate clinical problems that tend to affect each portion independently.[50] 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 the 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. Traumatic injuries result from fractures of the pelvis

or inappropriate traction during orthopedic or other operative manipulations,[11,36] including hip arthroplasty.[81]

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 hot and dry foot.[41] In one series of 85 cases of documented pelvic tumors, plexopathy involved the upper portion (L1 to L4) in 31 percent, the lower portion (L4 to S3) in 51 percent, and both in 18 percent.[96] Clinical features comprised the 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, radiation plexopathy caused indolent painless leg weakness early, often bilaterally. In contrast, patients with tumors typically had painful unilateral weakness. Electromyography revealed partial denervation and chronic reinnervation in both entities. Myokymic discharges were found in more than half the cases of radiation plexopathy but rarely if at all in patients with tumors.[193]

Immune or vascular etiologies probably play an important role in the idiopathic type, similar to the better-described and more frequently occurring brachial plexopathies.[186] Acute pain in one or both legs usually precedes the onset of weakness and areflexia, followed by atrophy of affected muscles.[173] In 10 cases of idiopathic lumbosacral plexopathy with an average of 6 years of follow-up, the patients recovered slowly and often incompletely.[63] Some patients relapsed,[9] and persistent pain was the most prominent and debilitating symptom in others.[90] Some responded to corticosteroids or intravenous immunoglobulin.[194,204] Patients with diabetes[27] or those with amyloid polyneuropathy[6] may also develop features of lumbar plexopathy, femoral neuropathy, or radiculopathy.

Compression plexopathy may result from hematomas in patients with hemophilia or other coagulopathies or in those receiving anticoagulation therapy,[185] occurring as one of two anatomically distinct syndromes[35,83]: (*1*) involvement of the lumbar plexus by hematoma within the psoas muscle[58] and (*2*) selective compression of the femoral nerve.[219] In plexus lesions, 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.[58]

Other etiologies include aortoiliac vascular disease, which may cause a 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.[42] Pregnant women may be at risk of lumbosacral plexus injury resulting from small maternal size, a large fetus, midforceps rotation, or fetal malposition. Electrophysiologic studies often localize the site of obstetric paralysis to the L4 to L5 lumbosacral trunk and S1 root, where they join and pass over the pelvic rim.[66] Regional nerve injury may develop after internal or external iliac artery catheterization for intraarterial chemotherapy for localized pelvic or lower limb tumors. In one series of 11 patients, 9 developed lumbosacral plexopathies and 2 developed mononeuropathies within 48 hours of an intraarterial infusion.[33]

Electromyography plays a major role in distinguishing a plexopathy from a radiculopathy by examining the proximal muscles innervated rostral to the plexus. These include, in addition to the paraspinal muscles, the gluteus maximus, medius and minimus, and iliopsoas. Typical findings of plexopathy include poor recruitment of motor unit potentials and fibrillation potentials at rest in the myotomes supplied by the anterior rami of multiple spinal nerves. Distal nerve stimulation elicits a lower amplitude of the compound muscle or nerve action potentials on the affected side than on the normal side.[1,25] Root stimulation may reveal increased latency across the plexus in the appropriate dis-

tribution.[133] F waves may or may not have a prolonged latency (see Fig. 18–12). Involvement of the S1 root diminishes the amplitude of the H reflex and increases its latency (see Chapter 19–2).

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Chapter 25

POLYNEUROPATHIES

1. INTRODUCTION
2. NEUROPATHIES ASSOCIATED WITH GENERAL MEDICAL CONDITIONS
    - Diabetic Neuropathy
    - Alcoholic Neuropathy
    - Uremic Neuropathy
    - Neuropathies in Malignant Conditions
    - Neuropathies Associated with Paraproteinemia
    - Necrotizing Angiopathy
    - Sarcoid Neuropathy
    - Sjögren's Syndrome
    - Other Neuropathies
3. INFLAMMATORY, INFECTIVE, AND AUTOIMMUNE NEUROPATHIES
    - Guillain-Barré Syndrome
    - Miller Fisher Syndrome
    - Chronic Inflammatory Demyelinating Polyneuropathy
    - Multifocal Motor Neuropathy with Conduction Block
    - Acute Motor Axonal Neuropathy in China
    - Diphtheritic Neuropathy
    - Leprosy
    - Acquired Immunodeficiency Syndrome
    - Other Neuropathies
4. METABOLIC AND TOXIC NEUROPATHIES
    - Nutritional Neuropathies
    - Toxic Neuropathies
5. INHERITED NEUROPATHIES
    - Genetic Classification of Hereditary Motor and Sensory Neuropathies
    - Charcot-Marie-Tooth Disease Type 1 (HMSN Type I)
    - Charcot-Marie-Tooth Disease Type 2 (HMSN Type II)
    - Charcot-Marie-Tooth Disease X-linked Dominant Type I
    - Hypertrophic Polyneuropathy of Dejerine-Sotas (HMSN Type III)
    - Hereditary Ataxic Neuropathy of Refsum (HMSN Type IV)
    - Autosomal Dominant Cerebellar Ataxia
    - Hereditary Neuropathy with Liability to Pressure Palsies
    - Friedreich's Ataxia
    - Porphyria

Cerebral Lipidosis
Hereditary Sensory and Autonomic Neuropathy
Lipoprotein Neuropathies
Giant Axonal Neuropathy
Fabry's Disease
Familial Amyloid Neuropathy
Other Neuropathies

1 INTRODUCTION

Polyneuropathy consists of the triad of sensory changes in a glove and stocking distribution, distal weakness, and hyporeflexia. Certain types of neuropathy may show widespread sensory symptoms, and others may begin with more prominent proximal weakness. Positive sensory symptoms result from ectopic impulse generation and autoexcitation of myelinated afferent fibers.[106] In general, but not always, normal muscle stretch reflexes speak against peripheral neuropathy. Acute pandysautonomic neuropathy characteristically shows severe postganglionic sympathetic and parasympathetic dysfunction, with relative or complete sparing of motor and sensory function.[251] Milder autonomic dysfunction also accompanies most peripheral neuropathies, but manifests clinically detectable symptoms only in a few conditions, such as diabetes, amyloidosis, Guillain-Barré syndrome, porphyria, and familial dysautonomia. Such autonomic disturbances usually result from acute demyelination or damage to small myelinated and unmyelinated fibers.[560]

A detailed history often reveals general medical conditions such as diabetes, alcoholism, renal disease, malignancies, sarcoidosis, periarteritis nodosa, amyloidosis, and infectious processes such as diphtheria and leprosy. Inflammatory neuropathies include Guillain-Barré syndrome and chronic inflammatory demyelinative neuropathy. Metabolic neuropathies result from nutritional deficiencies or the toxic effects of drugs or chemicals. The family history is essential in establishing the type of inherited conditions associated with polyneuropathy. Sometimes a patient's own account may not provide sufficient information, necessitating independent examination of family members. For some patients with an unequivocal diagnosis of polyneuropathy, extensive studies may fail to uncover the exact etiology.[564,616] Hereditary and immune-mediated polyneuropathy account for most cryptogenic cases.[313] In one study, intensive evaluation permitted classification of 76 pecent of 205 patients with initially undiagnosed neuropathy; the final diagnoses included inherited disorders in 42 percent, inflammatory-demyelinating polyradiculoneuropathy in 21 percent, and neuropathies associated with systemic disorders in 13 percent.[229]

Anatomic diagnosis depends on clinical and electrodiagnostic evaluation, but few specific patterns of peripheral nerve involvement characterize a given disorder. Nerve conduction and electromyographic studies 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.[91,204] An index based on multiple electrophysiologic measures against standard norms may provide a better overall estimation,[789] as reported in the assessment of diabetic polyneuropathy.[706] Electrical studies alone rarely distinguish clinical types of neuropathies or establish the exact etiology in a given case. Arriving at a specific diagnosis and establishing a course of therapy depend heavily on clinical, electrophysiologic, and histologic assessments.[11,514,618]

This chapter reviews the essential characteristics of peripheral neuropathies as they relate to electrophysiologic abnormalities.[204] Interested readers should con-

sult other comprehensive reviews available elsewhere.[36,37,231]

2 NEUROPATHIES ASSOCIATED WITH GENERAL MEDICAL CONDITIONS

Neuropathies associated with general medical conditions include some of the most commonly encountered polyneuropathies. Despite a clear association with a general medical condition, the exact cause of the neuropathies remains uncertain.

Diabetic Neuropathy

Diabetes often causes a symmetric polyneuropathy that likely has a metabolic basis.[232] 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. In one study, the ulnar motor conduction velocity and F-wave latency improved slightly but significantly after treatment with an aldose reductance inhibitor. This finding would support the sorbitol pathway hypothesis.[245] Other factors considered important in the pathogenesis include insulin deficiency and altered myoinositol metabolism.

An equally attractive alternative theory suggests that small vessel disease leads to infarcts within the nerve,[688] resulting in asymmetric types of diabetic neuropathy and diabetic cranial mononeuropathies. In some of the affected patients, neuropathy is caused by an inflammatory vasculopathy.[463,730,929] Microvasculitis with infiltrative T cells may contribute to the pathogenesis.[929] The spatial distribution of fiber loss also suggests ischemia and hypoxia similar to those found in experimental embolization of nerve capillaries.[213,404] In fact, vascular insufficiency quantitatively aggravates diabetic neuropathy.[689] In animal studies, reduced endoneurial blood flow, insufficient to cause infarction, may result in measurable functional and morphologic abnormalities in peripheral nerves.[782] Ischemic changes in the nerve presumably result from proliferation of the endothelium in blood vessels and abnormalities of the capillaries.[531]

Overall, two thirds of diabetic patients have objective evidence for some variety of neuropathy, but only about 20 percent have symptoms.[220] A wide spectrum of neuropathic processes develop.[912] The most commonly used clinical classification[36] consists of (*1*) distal symmetric, primarily sensory, neuropathy; (*2*) autonomic neuropathy; (*3*) proximal asymmetric painful motor neuropathy; and (*4*) cranial mononeuropathies. Pathologic classification separates diabetic neuropathies into two groups: predominantly large fiber or small fiber disease. In the larger fiber type, segmental demyelination and remyelination predominate, perhaps as a secondary change to diffuse or multifocal axonal loss, which seems to constitute the primary pathology.[222] This process would distort the normally linear relationship between internodal length and fiber diameter. In the small fiber type, the primary impact of the disease is on the axons with secondary demyelination. In some patients, abnormalities in the autonomic nervous system closely parallel those in the peripheral nervous system.[2] In these cases, prominent histologic changes include active axonal degeneration, affecting mainly unmyelinated and small myelinated fibers. Distal axonopathy in experimental diabetes mellitus of the rat first affects the terminal portions of the susceptible nerves.[95]

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 dysesthe-

sias, 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.[489] Quantitative measures of impaired sudomotor function correlate well with the severity of polyneuropathy.[431,433] Acute painful neuropathy may follow precipitous weight loss, but severe symptoms subside within 10 months. Histologic studies show degeneration of both myelinated and unmyelinated axons.[117] Spontaneous axonal regeneration abounds even in advanced cases.[731]

Mononeuropathies most often involve the femoral nerve and lumbosacral plexus and, to a lesser extent, the sciatic, common peroneal, median, ulnar, and cranial nerves.[7,830] 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. Unlike the distal symptoms of diffuse polyneuropathy, the proximal weakness tends to improve with adequate control of the diabetes. This condition, although usually distinguished as *diabetic amyotrophy*, probably represents a form of diabetic mononeuropathy rather than a separate entity.[31,145] The sudden onset of pain may herald involvement of a major proximal nerve trunk, including the lateral cutaneous nerve of the calf.[258] Patients may have a rapidly evolving course or continued progression for many months. The rapidly evolving form, considered ischemic in nature, and the more slowly progressive condition, regarded as metabolic in origin, may overlap, causing confusion.[45]

Diabetic thoracic radiculopathy produces a distinct syndrome characterized by radicular involvement, abdominal or chest pain, and weight loss; it has a relatively good prognosis[434] and sometimes mimicks a myelopathy.[895] Polyradiculoneuropathy and truncal mononeuropathy may accompany advanced distal polyneuropathy.[813] The episodes of diabetic truncal neuropathy may selectively involve the distribution of the ventral or dorsal rami of the spinal nerves, or branches of these rami, or varying combinations of these distributions.[805] Focal, unilateral protrusion of the abdominal wall on this basis may mimic abdominal hernia.[658]

Electrophysiologic studies have revealed a number of abnormalities in diabetic neuropathies.[150,218,524] Patients with signs of neuropathy have slower nerve conduction velocities and smaller amplitudes than those without symptoms,[495] showing a close correlation between clinical findings and the degree of conduction changes.[330,387] In juvenile patients, those with the longest duration of disease have the highest incidence of abnormalities.[239] Patients with diabetes have abnormal persistence of sensory evoked potentials during induced ischemia, which may herald other electrophysiologic abnormalities.[370] The degree of resistance shows a correlation with hemoglobin A1c and therefore metabolic control, but not with the state of neuropathy.[683] Studies of spinal somatosensory evoked potentials suggest impairment of peripheral as well as central afferent transmission.[168,325] Increased interpeak latencies of the brainstem auditory evoked responses also suggest the presence of a central neuropathy in some cases,[203] but not in others.[880]

Conduction abnormalities develop diffusely along the entire length of the nerve, but more so in distal segments than in proximal segments (see Fig. 18–11).[158,444] Axon loss alone cannot explain the degree of slowing conduction velocity.[909] Abnormalities predominate at the common sites of compression, for example, across the carpal tunnel for the median nerve,[12,402] showing a delay with no major conduction block.[3] Studies reveal length-dependent changes involving the tibial and peroneal nerves more than the median and ulnar nerves,[444] with preferential involvement of the fastest conducting large myelinated fibers.[209] Some advocate the amplitude ratio between sural and radial sensory potential as a sensitive measure of neuropathy.[659,723] The disease can affect any part of the body, including the phrenic nerve.[917] Minimal F-wave latency is the most sensitive.[21,158,444] and repro-

ducible[453] measure in the assessment of conduction abnormalities of diabetic neuropathy. Motor unit number estimates reveal an axonal loss that parallels the severity of the demyelinative process.[339] Electromyography detects fibrillation potentials and positive sharp waves in patients with prominent axonal degeneration. Single-fiber studies provide a measure of reinnervation,[88] and reveals the degree of axonal loss as the eventual cause of weakness.[22]

Most patients with sensory motor peripheral neuropathy also show absence of sympathetic skin response and other abnormalities of sudomotor function.[605,806] Useful measures for detecting a subclinical neuropathy include nerve conduction abnormalities in two or more nerves and quantitative autonomic examination of heart beat during deep breathing or the Valsalva maneuver.[151,157,219,265,358] In one study,[598] combined cardiorespiratory and nerve conduction scores predicted survival better than separate scores.

Some studies emphasize other measures to characterize and quantitate the severity of a neuropathy.[221,833] Thermal threshold testing confirms length-dependent abnormalities of the small myelinated and unmyelinated nerve fibers, showing a good correlation with the severity of polyneuropathy.[340,597] Quantitative study of vibration perception threshold, in contrast, provides a useful measure in the assessment of the large diameter fibers.[449] These quantitative sensory tests complement nerve conduction studies, although sural sensory potentials serve as a better predictor of diabetic neuropathy.[692]

Many studies have dealt with improved clinical management of diabetic neuropathy.[912] A controlled double-blind study suggested the efficacy of uridine for modifying neurophysiologic measures of neuropathy.[281] Desipramine relieved pain caused by diabetic neuropathy with an efficacy similar to that of amitriptyline.[550] Some investigators have suggested the therapeautic effect of ganglioside in promoting the recovery of sensory and compound muscle action potentials presumably by fascilitating the process of reinnervation,[48] but without subsequent confirmation.[334] In one study, correction of hyperglycemia resulted in a slight increase in conduction velocity after 6 hours.[843] Another carefully controlled study, however, revealed little improvement in conduction at the end of 3 days.[755] In a further series, nerve conduction velocity improved by 2.5 m/s after 1 year of improved glucoregulation with continuous subcutaneous insulin infusion.[233] Attempts for better glycemic control, in general, show encouraging results.[200,894] Good glycemic control also plays an important role in the prevention of neuropathy in children and adolescents with diabetes mellitus.[280]

Alcoholic Neuropathy

In the United States, alcohol is a major cause of peripheral neuropathy. It primarily affects those who drink large quantities for a number of years and improves once a person abstains.[360] In addition to the possible toxic effect of the alcohol itself, dietary insufficiency and impaired absorption may play important roles. Indeed, many alcoholic patients have a vitamin B_1 or thiamine deficiency,[182] which alone can cause similar clinical findings. The pathologic changes include reduced density of large and small myelinated fibers, acute axonal degeneration and regeneration,[52] and secondary paranodal demyelination involving the most distal segment.

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 extremities resemble those in diabetic neuropathy. Trophic changes such as plantar ulcers develop when patients subject insensitive tissues to unusual amounts of trauma.[727] More advanced cases involve bilateral footdrop, associated with distal muscular atrophy involving the extensors more than the flexors. Neuropathic changes predominate in chronically weak and atrophic muscles. Sensory symptoms may respond to daily administration of vitamin B_1, but

muscular atrophy tends to persist despite therapy.

Electrophysiologic evaluations demonstrate impaired function 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 sensory nerve and compound muscle action potentials. Thus, nerve conduction studies initially reveal either normal or only slightly reduced velocities in most patients.[52,116] As in other axonal neuropathies, conduction velocity decreases in proportion to the loss of evoked sensory and motor responses.[40]

Conduction abnormalities may involve not only the distal but also the proximal segments of the nerve.[300] Assessments of sural nerve and late responses improve the diagnostic yield.[184] Electromyography 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,[599] as well as visual and brainstem auditory evoked potentials.[131]

Uremic Neuropathy

A variety of neuropathies result from the complex effect of renal failure on peripheral neurons, myelin, and Schwann cells.[729] Uremic neuropathy often develops in patients with severe chronic renal failure or in patients undergoing chronic hemodialysis. The use of neurotoxic drugs such as nitrofurantoin can contribute to the nerve damage. Histologic findings comprise axonal degeneration, secondary segmental demyelination, and, less frequently, segmental remyelination.[33,709,729,831]

Clinical symptoms of neuropathy usually develop 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.[831] After successful treatment with hemodialysis, vibratory perception returns to normal, followed by improvement in other clinical findings. A distal ischemic neuropathy has developed following the placement of bovine arteriovenous shunts for chronic hemodialysis.[73] Proximal muscle weakness may also appear in uremic patients receiving hemodialysis.[493] Patients may have paradoxical heat sensation in response to low temperature stimulation.[925] 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.[25]

Patients with severe renal insufficiency often have motor and sensory conduction abnormalities in all limbs, with greater deficits in the peroneal than the median nerve.[608] As a sensitive indicator of neuropathy, facial nerve latency may rival the conduction studies of the peroneal, median, and ulnar nerves.[580] Studies of late responses and sural nerve conduction also reveal a high degree of abnormality.[4] In acute renal failure, the muscle action potential may show a marked reversible reduction in amplitude, presumably as the result of conduction block.[99] The partly reversible acute uremic neuropathy may show some demyelinating features simulating Guillain-Barré syndrome.[709] In chronic renal failure, such diminution in size of the compound potentials signals axonal degeneration usually but not always associated with fibrillation potentials.[75] Most uremic patients have an abnormal pattern shift in visual evoked potentials and somatosensory potentials.[715] Electrophysiologic findings generally, but not exactly, correlate with the clinical signs, levels of serum creatinine, and pathologic changes of the peripheral nerve.[871,905] Mild electrical abnormalities sometimes herald clinical manifestations.[930] Conduction velocities decrease with the deterioration of signs and symptoms and increase with improvement after dialysis or kidney transplantation,[183,609,627,884] but the question still re-

mains whether nerve conduction studies can monitor the adequacy of renal dialysis.[675]

Neuropathies in Malignant Conditions

Malignant processes affect the peripheral nerve directly or indirectly.[169,680,811] Lymphomas and leukemias may invade or infiltrate through hematogenous spread,[464,892] whereas nonlymphomatous solid tumors may cause external compression. Occasionally a metastasis may involve the dorsal root ganglia.[403] Neuralgic amyotrophy may develop in association with radiation therapy for Hodgkin's disease.[533]

Paraneoplastic neuropathies, as an autoimmune disorder,[211] result from the distant effects of lymphoma,[166,407] bronchogenic carcinoma,[354] pancreatic carcinoma,[110] or, less commonly, tumors of the ovary, testes, penis, stomach, or oral cavity.[611] Approximately one third of patients with malignancies develop clinically latent neuropathies.[661] Patients with lung cancer have a slightly higher incidence. Remote malignancies usually affect the dorsal root ganglia, but also occasionally the anterior horn cells. Pathologic features include (*1*) neuronal degenerations with secondary peripheral or central axonal changes; (*2*) demyelination reminicent of acute or chronic idiopathic polyneuritis[511]; (*3*) microvasculitis with active wallerian degeneration, causing mononeuritis multiplex[630]; (*4*) perineuritis defined as perineurial thickening and inflammation[794]; and, possibly, (*5*) opportunistic neuropathic infection. Both cytotoxic T cell–mediated attack against neurons and humoral mechanisms play a role in paraneoplastic subacute sensory neuronopathy.[893]

Patients have clinical findings of sensory or motor deficits or, more commonly, mixed involvement. Sensory motor neuropathy represents a group of heterogenous conditions with overlapping clinical and histologic features.[27,125] Occasional patients develop a pure motor neuropathy mimicking myasthenic syndrome or polyradiculopathy seen in meningeal carcinomatosis. Systemic cancer may initially cause the symptom of mental neuropathy causing numb chin[545] or intestinal pseudo-obstruction.[504] Although results are generally disappointing, some patients with anti-Hu–associated paraneoplastic sensory neuropathy will respond to early aggressive immunotherapy.[628]

Distinguishing between paraneoplastic and nonparaneoplastic sensory neuronopathies can tax the clinician. Prominent neuropathic pain, neurologic dysfunction involving more than the peripheral sensory system, or an increased cerebrospinal fluid protein should prompt a careful search for a cancer.[125] Subacute sensory neuropathy of oat cell carcinoma may result in severe sensory loss secondary to dorsal root ganglionitis.[206] In one case, morphometric studies at autopsy showed preferential loss of large diameter sensory nerve cell bodies, marked loss of large myelinated fibers in the dorsal root and sural nerve, and almost total loss of myelinated fibers in the fasciculus gracilis.[632] Chronic idiopathic ataxic neuropathy[185] denotes the same type of progressive sensory neuropathy seen without evidence of cancer.[422]

Quantitative sensory testing may uncover subclinical abnormalities involving both large and small fibers.[510] The conduction studies reveal only mild slowing of sensory or motor fibers or both with substantial reduction in amplitude of sensory nerve,[681] or muscle action potentials, or both. Electromyography typically shows fibrillation potentials and high-amplitude, long-duration motor unit potentials in atrophic muscles.[661] Small, short-duration polyphasic motor unit potentials occasionally seen in wasted proximal muscles probably result from neuropathic abnormalities of the intramuscular axonal twigs.[47]

Neuropathies Associated with Paraproteinemia

A number of studies have demonstrated a clear association between IgM and IgG[812] and, to a lesser degree, IgA[772] monoclonal proteins and peripheral neuropathy.[311,565] Most affected patients have benign monoclonal gammopathy, sometimes with a genetic predisposition.[399] Other syndromes occasionally encountered include

primary systemic amyloidosis, osteosclerotic myeloma, and, less frequently, osteolytic multiple myeloma, Waldenstrom's macroglobulinemia, cryoglobulinemia, gamma heavy chain disease often associated with hepatitis C infection,[29,191] Castleman's disease, or angiofollicular lymph node hyperplasia with vasculopathy, papilledema, organomegaly, endocrinopathy, and paraproteinemia,[202] and the syndrome of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS).[575,732,776,847] Table 25–1 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.[817,857]

Benign monoclonal gammopathy occurs in 10 percent of all patients with idiopathic peripheral neuropathy.[207,426] Conversely, 30–70 percent of those with benign monoclonal gammopathy develop chronic sensory motor neuropathy. The clinical features closely mimic those of chronic inflammatory demyelinating poly-radiculoneuropathy (CIDP) with progressive sensorimotor loss[71,93,162,612,771] and occasional tremor.[665] The association with a central lesion,[499] although uncommon, includes cerebral lymphoma.[237] Plasma exchange rapidly lowers the level of monoclonal antibody, with some recovery of motor function.[634,760] Some patients also respond to high-dose intravenous immunoglobulin therapy[159,188,536] and immunosuppressive treatment.[241,615] The characteristic laboratory findings include IgM and IgG, and less commonly, IgA gammopathy and a high level of cerebrospinal fluid protein. Electrophysiologic and morphologic studies show evidence of demyelination, although axonal loss is a major finding in a few.[784]

This category also includes various polyneuropathy syndromes associated with antibodies either to peripheral nerve myelin or myelin-associated glycoprotein (MAG)[39,134,501,611,861,889] or to sulfated glucuronyl paragloboside (SGPG).[672,862] Slowly progressive sensory motor neuropathies of this type often show disproportionate prolongation of distal motor latency as evidenced by increased residual latency and decreased terminal latency indices (see Chapter 5–4),[414] showing a higher correlation with anti-MAG than anti-SGPG titers.[842] A combined syndrome of gait ataxia and polyneuropathy seen in some of these patients often improves after intravenous immunoglobulin or other immunosuppresive therapy.[670]

Primary systemic amyloidosis or the light-chain type of amyloidosis affects mul-

Table 25–1 Main Features of Monoclonal Protein-Peripheral Neuropathy Syndromes

Type of PN	Topography	Weakness	Sensory Loss	Autonomic Loss	Course	CSF Protein	MNCV	Pathology
Benign monoclonal (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)
Waldenströms macroglobulinemia	Distal, symmetric	++	++	0	Chronic progressive	++	Very slow	SD(occ'l AD)

MNCV = motor nerve conduction velocity; AD = axonal degeneration; SD = segmental demyelination; PN = peripheral neuropathy; CSF = cerebrospinal fluid.

From Kelly,[425] with permission.

tiple organ systems with symptoms similar to those of malignancy or collagen vascular disease. Patients with amyloidosis, however, have plasma cell dyscrasias and amyloidogenic immunoglobulins.[260,302,844] Amyloid accumulates in the flexor retinaculum, causing carpal tunnel syndrome. Diffuse peripheral neuropathy develops as the result of metabolic or ischemic changes or direct infiltration by amyloid.[152,425] The clinical features consist of a painful sensory and motor neuropathy, with prominent autonomic dysfunction affecting multiple systems. Axonal degeneration predominates in small myelinated and unmyelinated fibers,[835] usually sparing the large myelinated fibers. This accounts for the typical dissociated sensory loss with predilection for pain and temperature sense with relative sparing of vibratory and position sense, that is, the reverse of the findings in large fiber type diabetic neuropathy. Electrophysiologic abnormalities include slight slowing of the motor nerve conduction velocity with mild reduction in amplitude of the compound muscle action potential; absence of the sensory nerve action potentials with distal stimulation of the ulnar, median, or sural nerve; and evidence of superimposed compression of the median nerve at the wrist. Electromyography reveals evidence of denervation diffusely but more conspicuously in the distal muscles of the leg.[429] An in vitro study of sural nerve compound action potentials has shown a selective reduction in C and A delta potentials in familial amyloid neuropathy.[224] This supports the view that amyloid neuropathy predominantly causes distal axonal damage first in the sensory and then in the motor fibers.

Skeletal osteosclerotic lesions, although seen only in less than 3 percent of myeloma patients as a whole, develop in at least 50 percent of those with myeloma neuropathy.[428] This type of myeloma commonly affects younger patients and takes a benign clinical course although the patient often develops demyelinating neuropathy that resembles CIDP.[205] Neuropathy may improve following surgery, radiation, and chemotherapy.[716] Electrophysiologic and histologic evidence of prominent demyelination suggests an immunologic effect of the monoclonal protein on a myelin antigen as a precipitating cause.[427,546] Intraneural injection of patient serum into rat sciatic nerve, however, produces no demyelinative lesion.[428] Instead, the morphologic features suggest axonal attenuation or distal axonal degeneration with secondary demyelination.[631]

Patients with osteolytic multiple myeloma may have amyloid neuropathy much like the type seen in systemic amyloidosis without multiple myeloma. These cases show, in addition to prominent distal axonal loss and carpal tunnel syndrome, atypical features such as radiculopathy and mononeuritis multiplex. In this condition, a peripheral neuropathy also develops without amyloidosis in 30–40 percent of cases, based on electrophysiologic and histologic findings.[123,425] 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.[424] Those with primary motor abnormalities have features similar to CIDP, with prominent slowing of nerve conduction velocities.

Patients with Waldenstrom's macroglobulinemia may develop a primarily demyelinating sensory motor neuropathy of the type commonly associated with benign monoclonal gammopathy.[613] 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.[887]

In cryoglobulinemia,[123] two types of neuropathy develop: (*1*) a mild distal neuropathy probably the result of vasa nervorum microcirculation occlusion caused by intravascular deposits of cryoglobulins and (*2*) a severe distal symmetric sensory motor neuropathy with necrotizing vasculitis.[286] Hepatitis C virus may play a role in nonsystemic vasculitic mononeuropathy multiplex associated with cryoglobulinemia.[28,432,747] Electromyography

and sural nerve biopsy specimens show axonal degeneration with a preferential loss of large diameter fibers, confirming a major role of ischemia in the pathogenesis.[121,289,602] Treatment consists mainly of plasmapheresis.[826] A reversible sensory autonomic neuropathy seen in cold agglutinin disease may have a similar pathogenesis to those proposed for cryoglobulinemia.[839]

Necrotizing Angiopathy

In necrotizing angiopathy, which is probably related to autoimmune hypersensitivity, patients have systemic or nonsystemic vasculitic neuropathy.[215,636] The inflammatory process, possibly through endothelial cell activation,[647] involves the small- and medium-sized arteries in multiple organ systems, including the thoracic and abdominal viscera, the joints and 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 occurs in association with known or suspected connective tissue disease such as rheumatoid arthritis, systemic sclerosis, nonvasculitic, steroid-responsive mononeuritis muliplex,[515] and Sjögren's syndrome[352,636] or other multisystem diseases such as Wegener's granulomatosis[400,610] and cryoglobulinemia with an IgM kappa M protein.[829]

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 neuronal disturbances such as diffuse polyneuropathy and mononeuritis multiplex. Neuropathy 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, 10 of 16 patients had features of mononeuritis multiplex, and the remaining 6 had a distal symmetric sensory motor polyneuropathy.[448] In another study of 23 patients with giant cell arteritis, 11 had generalized neuropathy, 9 had mononeuritis multiplex, and 3 had a mononeuropathy.[114] Nerve conduction studies show slow velocity in proportion to reduced amplitude of the compound muscle and sensory potentials in the affected limbs. A conduction block may result from subinfarctive nerve ischemia affecting the segment outside the usual sites of compression mimicking a demyelinative neuropathy.[301,584,707] Serial studies, however, usually demonstrate conversion of the electrophysiologic findings to those most consistent with severe axonal loss.[551] Electromyography reveals spontaneous activities in atrophic muscles as expected in acute or subacute axonal neuropathy.[81,175]

Sarcoid Neuropathy

Patients with sarcoidosis develop distal sensory motor polyneuropathy as a rare complication.[603] Typical neuropathies associated with this disorder include Guillain-Barré syndrome, mononeuritis multiplex, lumbosacral plexopathy, and purely sensory neuropathy.[938] Histologic studies reveal granulomata or inflammatory changes in the epineural and perineural spaces that lead to periangitis, panangitis, and axonal degeneration.[625] Electrophysiologic abnormalities include reduced amplitude of the compound sensory and muscle action potentials and mild slowing in conduction studies,[126,625] and prominent fibrillation potentials and positive sharp waves in electromyography. In one case, morphologic studies confirmed the electrodiagnostic impression of an acute axonal and demyelinating neuropathy.[603] Differential diagnosis should include rare nerve root involvement causing polyradiculopathy.[452]

Sjögren's Syndrome

Patients with Sjögren's syndrome develop dryness of the eyes, mouth, and other mucous membranes. The disease involves various anatomic structures such as

joints, blood, internal organs, skin, muscle, and central and peripheral nervous systems. Subacute sensory neuropathy may develop as a presenting symptom,[315] sometimes primarily affecting the distribution of the trigeminal nerve.[532] Other forms include mononeuropathy multiplex, distal sensory neuropathy, distal sensory motor neuropathy, and pure sensory neuropathy.[419,420,890] Electrophysiologic and sural nerve biopsy studies reveal an axonal neuropathy in these cases.[673] In one series of 33 cases,[567] symmetric sensory motor polyneuropathy occurred most frequently, followed by symmetric sensory neuropathy. Approximately one fourth of patients had superimposed autonomic neuropathy, mononeuropathy, or cranial neuropathy. The symptoms, generally mild at the onset, slowly progress.[890] Nerve biopsy specimens may reveal evidence of necrotizing vasculitis, with axonal degeneration more than demyelination. Some of the clinical and neurophysiologic findings suggest the involvement of the spinal ganglion and postganglionic sympathetic ganglion cells.[469]

Other Neuropathies

Sensory-motor neuropathy may accompany some multisystem atrophy such as Shy-Drager syndrome,[279] and the syndrome of skin pigmentation, edema, and hepato-splenomegaly.[823,845] Patients with hypothyroidism or hyperthyroidism may have sensory and motor conduction abnormalities diffusely[50,455,676] or localized at the common sites of compression.[752] In systemic lupus erythematosus, patients may have a predominantly motor or sensory demyelinating polyneuropathy as the presenting feature.[553,639,640]

The neuropathy associated with the hypereosinophilic syndrome develops at the onset of marked eosinophilia.[295,430,899] It affects both the sensory and motor fibers with multifocal conduction abnormalities and evidence of severe axonal degeneration.[210] The eosinophilia myalgia syndrome[466] develops in some patients taking preparations containing L-tryptophan, causing sensory motor neuropathy characterized by segmental demyelination and distal axonal degeneration.[102,208,266,351] Migrant sensory neuritis of Wartenberg has a benign relapsing and remitting course. Movement of the limbs induces a stretch, leading to pain and subsequent loss of sensation in the distribution of individual cutaneous nerves. Stimulation of the affected nerves may elicit small or no sensory action potentials.[549] Patients with polymyalgia rheumatica with muscle aching, tenderness, and weakness may have not only steroid-responsive myositis[92] but also peripheral neuropathies.[728,751]

Meningococcal septicemia may cause a mixed sensory motor neuropathy with electrophysiologic findings consistent with axonal degeneration.[704] Critically ill patients may develop a severe motor and sensory polyneuropathy of unknown cause[74,937] and other neuromuscular diseases with prolonged ventilator dependency.[799] Some investigators advocate the term critical illness neuropathy as a useful clinical concept,[72] whereas others argue that the enormous complexity encountered in critical illness weakness makes the implication of a neuropathy as the cause of syndrome untenable.[87] 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 nerves and intramuscular nerve fibers.[916] 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.[764]

The neuropathy associated with polycythemia vera involves large and small myelinated fibers with mild slowing of motor and sensory conduction.[922] Distal axonal degeneration follows ischemia produced by thromboembolic occlusion of a major proximal limb artery,[902] especially in patients at risk with uremia, diabetes,[699] or peripheral arterial disease.[240] Multiple sclerosis occasionally accompanies hypertrophic demyelinating neuropathy with typical nerve conduction changes.[679,758] Denervation of the rectal sphincter characterizes multisystem atrophy, which resembles primary autonomic failure with an autonomic neuropathy as a common feature.[691] Burn patients may

have undiagnosed neuropathy.[540] Polyneuropathy may also result from lightning injury,[353] severe hypothermia,[6] and graft-versus-host disease.[18]

Other systemic disorders sometimes associated with mild polyneuropathy include Whipple's disease,[177] celiac sprue,[423] multiple symmetric lipomatosis,[596] acromegaly,[396] Crohn's disease,[375] Leigh's disease,[154,392] xeroderma pigmentosum,[359,417] cerebrotendinous xanthomatosis,[888] β-thalassemia,[648] hemophagocytosis syndrome,[367] sickle cell anemia,[763] juvenile Parkinson's disease,[820] tyrosinemia,[298] Machado-Joseph disease,[155] and multiple symmetric lipomatosis.[595]

3 INFLAMMATORY, INFECTIVE, AND AUTOIMMUNE NEUROPATHIES

Inflammatory, infective, and autoimmune neuropathies include a wide range of disorders, from Guillain-Barré syndrome and related disorders[365,369,708,802] to diphtheria and leprosy as well as acquired immunodeficiency syndrome (AIDS).

Guillain-Barré Syndrome

Although of unknown etiology, Guillain-Barré syndrome and related demyelinative neuropathies closely resemble experimental allergic neuritis,[749] either by active immunization with extracts of peripheral nerve[94,350] or by repeated transfer of P2 protein–reactive T cell lines.[490] Some patients with this syndrome have human immunodeficiency virus (HIV),[164] herpes zoster virus,[641] or hepatitis B virus infection. Other possibilities include *Campylobacter jejuni* enteritis,[238,320,349,474,759,934] *Mycoplasma* infection with anti-Gal-C antibody,[476] and *Cyclospora* infection.[697] In most, 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.[349]

Serum and cerebrospinal fluid (CSF) anti-GM_1 antibodies may play a key role in the pathogenesis of demyelination[686,777] as well as axonal degeneration.[393] The serotypic determinant of PEN 19 of *Campylobacter jejuni* may aide in the production of anti-GM_1 antibody by a GM_1-like lipopolysaccharide.[932] In vitro demyelination by serum antibody from patients with Guillain-Barré syndrome requires terminal complement complexes.[744] In one series,[49] the relative change in anti-GM_1 titers showed an inverse relationship with muscle performance. In another study,[757] circulating tumor necrosis factor-α correlated with electrophysiologic abnormalities of demyelination.

An inflammatory demyelinative neuritis affects all levels of the peripheral nervous system,[416] occasionally with retrograde degeneration in the motor cells of the spinal cord or brainstem. In mild cases, pathologic changes may consist of only slight edema of the nerves or roots with only minimal inflammatory infiltrates.[710,750] In contrast, the fulminant syndrome may show universal inexcitability of the peripheral nerves with axonal degeneration secondary to inflammation.[59,249] The segment of maximal involvement varies from one patient to the next. This helps explain the diversity of clinical findings and of conduction abnormalities in different cases. Guillain-Barré syndrome consists of a number of subtypes showing different clinical and pathologic features. These include, in addition to the common acute inflammatory demyelinating polyneuropathy (AIDP), Fisher syndrome, acute motor sensory axonal neuropathy (AMSAN), and acute motor axonal neuropathy (AMAN), or acute flaccid paralysis in China. A substantial proportion of the patients initially diagnosed with Guillain-Barré syndrome may turn out to have a neuropathy with another etiology, especially heavy metal intoxication.[250]

Although the clinical and pathologic findings vary even among patients with the classical syndrome, certain diagnostic criteria have emerged.[34,365] 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. Some patients seem to have other precipitating events such as polio,[447] rabies vaccine treatment,[105] and allogeneic bone

marrow transplantation.[897] The first symptoms of neuropathy usually appear in about 1–2 weeks, when the infection has resolved. Occasionally, the disease takes the form of encephalomyeloradiculoneuropathy with progressive central nervous system disease,[592] bilateral deafness,[601] or severe sensory motor neuropathy.[898] Rarely, seizures and other signs of cerebral involvement may signal the onset of illness in children.[906] 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 contrast with the distal weakness characteristic of other forms of neuropathy. Respiratory problems develop in approximately one half of the patients.[711] Occasional patients have an acute, severe, and progressive illness with quadriplegia in 2–5 days, requiring mechanical ventilation.[272,574] In addition to these features, unfavorable predictive factors include old age, preceding infection, bulbar paralysis, and onset of paralysis in proximal muscles.[297]

Other early signs include diminished or lost muscle stretch reflexes, miminum sensory loss despite painful distal paresthesias, and, occasionally, myokymia and even involuntary contraction resulting from continuous motor unit discharges.[682] 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[563] involving both sympathetic and parasympathetic fibers of the cardiovascular, sudomotor, gastrointestinal, and other systems.[936] Some patients have transient elevation or fluctuation of blood pressure and heart rate as the result of sympathetic hyperactivity.[261,712] The CSF typically contains high protein levels and no cells with the exception of some lymphocytes in occasional cases.

The disease follows an acute or subacute course with usual progression up to 6 weeks after onset.[374] The symptoms and signs then plateau for a variable period before gradually improving. Occasionally acute relapses occur after long asymptomatic intervals.[8,901] These patients have a high incidence of an antecedent illness, lack an apparent response to immunosuppressive therapy, and have a normal CSF protein level.[314] Although some patients improve dramatically following corticosteroid therapy,[624] prednisone may adversely affect the eventual outcome of the disease.[373] Plasma exchange[35,397] can be beneficial but not universally.[568] Some patients show antibody rebound after therapy, with deterioration of nerve conduction studies.[705,720] Treatment with intravenous immunoglobulin may[306,349,868,869] or may not be beneficial.[118]

The time course of recovery depends on the extent of demyelination and, more importantly, axonal degeneration. In one series, severe residual deficits developed in the patients with highly elevated anti-GM_1 activity[863] and in another in those with high IgG antibody titers against GD_{1a} ganglioside.[933,935] Some patients have severe axonal loss without inflammation or demyelination[246,247,694,866,931] or secondary to demyelination.[57,173,249] Such patients may not regain motor function for 1–2 years. Although specific treatment has shortened the duration of mechanical ventilation, elderly patients with pre-existing pulmonary disease tend to require tracheostomy.[491] In some patients, impaired joint mobility becomes a major disability despite an improving neurologic status.[795]

Electrodiagnosis plays a key role in the evaluation.[10,14,161,713] In advanced stages of disease, nerve conduction studies usually show velocities reduced by more than 30–40 percent from the normal mean value and abnormal temporal dispersion of the compound muscle action potential (see Figs. 5–8A,B). In milder forms, studies may reveal less dramatic changes because initial weakness commonly results from proximal conduction block without distal abnormalities.[98] Indeed, 15–20 percent of cases have entirely normal nerve conduction studies distally during the first 1–2 weeks.[236,443] Thus, normal conventional conduction studies by no means precludes the diagnosis.[483] In fact, the initial absence and later delay of the F-wave with normal distal conduction (see Figs. 18–6 and 18–10 and Table 18–4) charac-

terizes the typical pattern of abnormalities, indicating 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.[299,439,443,446,559] As in any neuropathy, the early changes may also selectively involve the common sites of nerve compression[98,480,483] and the most terminal segment, presumably reflecting the longest distance from the cell body. 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.[481] Early and severe demyelination with secondary axonal damage may mimic acute motor axonal variant clinically and electrophysiologically because of inexcitability of motor nerves.[411,544]

Despite the clinical pictures of predominantly motor involvement, sensory or mixed nerve conduction studies[520] 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.[590] Quantitative thermal threshold measurements may uncover early abnormalities at small nerve fibers.[827] Phrenic nerve conduction time may provide a sensitive measure in predicting impending ventilatory failure.[312] Studies of the blink reflex frequently reveal conduction abnormalities as expected from clinical facial palsy (see Figs. 17–4 and 17–12 and Tables 17–1 and 17–2). Although less sensitive than F-wave studies,[637] somatosensory evoked potentials to median nerve stimulation may demonstrate a proximal conduction delay between Erb's point and the cervical cord in patients with normal sensory conduction distal to Erb's point during the first few weeks of onset.[98,299]

Spontaneous activities include facial or limb myokymic discharges (see Fig. 14-12B), which may appear early, sometimes persisting during the course of illness,[547] and, rarely, continuous motor unit discharges, or neuromyotonia.[682] Otherwise, electromyography 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.[247,559]

Sequential conduction studies show great variability among different patients and even from one nerve to another in the same patient.[442] Relatively common patterns of conduction failure include a length-dependent and uniform reduction of compound muscle action potentials presumably based on a random distribution of lesions.[867] Reversible proximal conduction block often underlies rapid recovery.[62] In contrast, reduction in amplitude of compound muscle action potentials with distal stimulation generally suggests axonal degeneration, especially when accompanied by normal conduction velocities.[165,181,319,573] 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.[272,332] Thus, this finding does not necessarily imply a poor prognosis, especially in children.[927] After treatment, conduction studies may or may not revert toward normal values.[840] The nerve conduction velocity often becomes slower while the patient begins to improve, demonstrating again the lack of a strong correlation between clinical and electrophysiologic assessments.

Miller Fisher Syndrome

The Miller Fisher syndrome[259] consists of ataxic gait, absence of muscle stretch reflexes and ophthalmoplegia. Despite immunologic peculiarities of this subgroup,[534] as evidenced by its association with serum antibodies to GQ_{1b} ganglioside,[140,141,391,477,478,907] it probably constitutes a cluster within the overlapping spectrums of Guillain-Barré syndrome.[825] One atypical patient with this syndrome had abnormal pupils and normal eye movements;[904] another patient had a late central demyelination.[256] Patients with acute ataxic neuropathy, which resembles this syndrome, had severe sensory loss, no motor deficits, and a poor prognosis.[821]

Antibody against GD_{1b} may play a role in the pathogenesis of sensory ataxic neuropathy.[479,578,620]

Electrophysiologic studies usually show characteristics of an axonal neuropathy or neuronopathy with prominent sensory nerve changes in the limbs and motor damage in the cranial nerves.[269] The findings in one series included normal distal motor nerve conduction velocities, F-wave latencies, and blink reflex and abnormal sensory action potentials.[743] Serial studies in such a case, however, may show a time course of conduction changes similar to those in Guillain-Barré syndrome.[395,852] Electromyography usually reveals only slight abnormalities in the limbs and evidence of facial denervation. Immunoabsorption plasmapheresis, while improving ophthalmoplegia, may not prevent facial palsy, possibly because it fails to remove responsible antibodies.[142]

Chronic Inflammatory Demyelinating Polyneuropathy

Apart from its chronicity following axonal changes, the disease may continue to worsen with persistent evidence of ongoing demyelination.[44,555] This variety, referred to as *chronic inflammatory demyelinative polyradiculopathy* (CIDP), has progressive or relapsing, usually motor and sensory, but rarely only motor or sensory, dysfunction of a peripheral nature involving more than one limb, developing over at least 2 months.[20] Other clinical features include hyporeflexia or areflexia, usually involving all four limbs. The disease may follow a progressive course over several years with severe generalized disability,[214,684] or affect only upper limb.[310,834] Although rare, focal neuropathy may precede the onset by several years or asymmetrical polyneuropathy may show a stepwise progressive course.[881,886] A chronic demyelinating neuropathy may accompany a relapsing multifocal central nervous system disorder whose clinical features resemble multiple sclerosis.[569,593,838] In these cases, electrophysiologic studies reveal a slowing of peripheral conduction velocity as well as an increased central conduction time. The occurrence of both peripheral and central demyelination resembles chronic relapsing experimental allergic encephalomyelitis and neuritis. Chronic motor axonal polyneuropathy (CMAN) may constitutes a variant of CIDP.[148,308,411,853]

Other possible features include subclinical central nervous system involvement,[633,642] dropped head syndrome,[364] dysautonomia,[380] and pure sensory presentation[629,773] labeled chronic sensory demyelinating neuropathy.[61] The risk of relapse increases during pregnancy.[554] Familial occurrence may indicate a genetic predisposition.[274,378] Steroid–responsive hereditary sensory neuropathies may imply superimposed acquired demyelination.[67,230] The clinical features in children may mimic a genetically determined disorder.[781] Compared with adults, children tend to have a more precipitous onset, a higher incidence of gait abnormalities, and greater neurologic deficits.[774,775]

Nerve conduction studies reveal evidence of diffuse demyelination with characteristics quite similar to those of Gullain-Barré syndrome, except for chronicity.[441] Other electrophysiologic abnormalities include an increase in fiber density[283] and macromotor unit potential, and myokymic and continuous motor unit discharge.[475,570] The CSF cell count is less than $10/mm^3$ unless the patient is HIV seropositive. Magnetic resonance imaging may show abnormal enhancement reflecting inflammation.[172] Nerve root hypertrophy[194,548,581] may cause lumbar stenosis.[305] Nerve biopsy reveals unequivocal pathologic evidence of demyelination and remyelination by either electron microscopy or teased fiber studies.

Prednisone causes a small but statistically significant improvement over no treatment.[228,246] Plasma exchange is a useful therapy, especially in cases with features of demyelination rather than axonal degeneration.[267,307,677,891] Additional modes of therapy include cyclosporin,[42,363] immunoglobulin,[227,361,822,870,872,882] and interferon-α_{2a}.[309,724]

Successful treatment with plasma exchange suggests a role for pathogenic humoral factors.[328] Systemic passive transfer of immunoglobulin is known to cause demyelinative disease in monkeys with substantial reduction of conduction ve-

locity.[357] Antimyelin-associated glycoprotein antibodies may develop later during the course of the disease.[859] The GM_1 and GM_3 autoantibodies may play a role in the pathogenesis of CIDP in systemic lupus erythematosus.[778] Patients may have immunoglobulin and complement deposits in the nerve.[187]

Multifocal Motor Neuropathy with Conduction Block

As a unique variant of CIDP, multifocal motor neuropathy (MMN),[654,656,671] is a potentially treatable condition that needs to be distinguished from amyotrophic lateral sclerosis (ALS) and other motor neuron syndromes. Affected patients develop chronic asymmetric predominantly motor neuropthy with multifocal conduction delay and persistent conduction block.[461,809,814,864] 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.[635] Similar to earlier reported cases with sensory and motor involvements,[296,503,739] the long-lasting conduction block suggests chronic demyelination as the pathologic basis. Patients often have normal or occasionally even increased stretch reflexes[409] with a normal or only slightly elevated CSF protein (Table 25–2). Some patients develop cranial nerve involvement[413,685] others, central demyelination.[506,667] These features make it difficult to diagnose the condition solely on the basis of clinical examination.[440]

Conduction blocks typically involve unusual sites such as the median nerve in the forearm or brachial plexus[412] rather than the common sites of compression seen in multiple entrapment neuropathies.[65] Most patients have selective involvement of motor fibers with normal sensory conduction through the sites of motor conduction block. Both motor conduction block and abnormally increased threshold probably reflect a chronic focal demyelinating lesion that for yet undetermined reasons becomes persistent without repair.[408,441,923] Some patients with features indistinguishable from ALS have multifocal motor nerve conduction abnormalities.[5,914] In one series, 17 of 169 patients clinically diagnosed as having motor neuron disease had some abnormalities in motor nerve studies, including 10 with conduction block.[488] Demonstration of motor conduction block at multiple sites differentiates this potentially treatable clinical entity from the small subgroup of ALS patients with only lower motor neuron involvement.[485]

Electrophysiologic studies must confirm the diagnosis before therapeutic trials are initiated with, for example, immunosuppressants such as cyclophosphamide.[136] Several authors have documented successful treatment with intravenous immunoglobulin.[413,461,653,656,657,671,864] Outcomes of therapy with either immunosuppressants or immunoglobulin, however, vary considerably among different reported cases.[186] Some patients im-

Table 25–2 Characteristics of MMN and CIDP

	MMN	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-GM1 antibody	Frequent	Rare
Choice of therapy	Immunosuppressants, immunoglobulin	Steroids, plasma exchange

CIDP = chronic inflammatory demyelinating polyneuropathy; CSF = cerebrospinal fluid; MMN = multifocal motor neuropathy.

prove but do not return to normal, others stabilize, some require long-term therapy, and still others become refractory to any from of treatment. Most studies suggest better results with cyclophosphamide or human immunoglobulin therapy[135,614] than with prednisone or plasmapheresis.

In our series,[412,413] two patients with MMN had focal conduction block involving motor but not sensory fibers at the site of nerve swelling (see Fig. 7–16A,B). A nerve biopsy taken adjacent to the enlargement in one patient revealed subperineurial edema and slight thickening of the perineurium under low-power light micrographs.[412] 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-GM_1 antibodies found in a wide variety of neuromuscular conditions,[482] but more commonly in some lower motor neuron disorders and in MMN.[456,669] Antibodies may have a predilection for the GM_1 component of motor fibers, which have a longer carbon chain than sensory fibers.[622] Autoantibodies may exert their effect, in part, by binding to GM_1 on the surface of motor neurons.[160] Anti-GM_1 antibodies may[738] or may not[351,362,411,649] cause motor dysfunction by binding to the nodal and paranodal regions. Sera of patients with MMN but not with progressive spinal muscular atrophy induced conduction block in rat tibial nerves despite a similar elevation of anti-GM_1 titers in both categories.[854] These antibodies however, may not have a causal relationship with MMN, as evidenced by many patients without raised levels.[487,652] Surface-bound antibodies directed against a major axoplasmic antigen may be interfering with remyelination rather than causing demyelination.[408,411] In some cases, nerve ischemia may play a role in the pathogenesis.[619]

In an extraordinary case,[738] a patient had received a duck embryo rabies vaccine 3 months before the onset of her motor neuron disorder. She had multifocal conduction block, elevated levels of anti-GM_1 IgM antibodies, and deposits of IgM at nodes of Ranvier. Aside from attacking motor neurons guided by the abundant GM_1 on the cell surface, anti-GM_1 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.[883] It is necessary to clarify the exact pathogenesis underlying these findings to properly classify the motor neuron disease and MMN.

Acute Motor Axonal Neuropathy in China

Annual summer epidemics of acute onset flaccid paralysis occur in northern China. Based on a historical analysis of more than 3200 patients, distinctive features include a high incidence in children and young adults residing in rural areas. Patients develop rapidly progressive ascending tetraparesis often with respiratory failure without fever, systemic illness, or sensory involvement followed usually by a satisfactory recovery.[284,317,318,557,918] The CSF shows no cells with an elevated protein content in the second or third week of illness. Electrodiagnostic studies show reduced compound muscle action potential amplitudes, normal motor distal latencies and limb conduction velocities, and normal sensory nerve action potentials. When elicitable, F waves also fall within the normal range in latency. Autopsy studies have shown wallerian-like degeneration of motor fibers. Thus, despite its inclusion as a variant of Gullain-Barré syndrome, this acute motor axonal neuropathy (AMAN), mostly seen in China but

possibly elsewhere, probably constitutes a distinctive entity.[389] A similar relationship exists between CIDP and its presumed variant steroid-sensitive chronic motor axonal neuropathy (CMAN).[853]

Diphtheritic 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 percent of patients. 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. Neuropathy may also develop in adults after contracting cutaneous diphtheria, which still prevails in the tropics.

The clinical signs resemble those of Guillian-Barré syndrome.[170] 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 pharyngo-laryngo-esophageal weakness. Blurring of vision results from paralysis of accommodation. Other autonomic abnormalities include cardiac vagal dysfunction.[376] 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.[791] Conduction abnormalities usually begin a few weeks after the onset of neurologic symptoms and peak after clinical recovery has already begun.[472] F-wave studies also help establish serial changes in motor conduction.[291]

Leprosy

An acid-fast bacillus, *Mycobacterium leprae*, transmits leprosy, a chronic infectious disease, by close and prolonged contact. Although rare in the United States, the disease still prevails in Africa, India, and South and Central America. The organism seems to have a predilection for great auricular, ulnar, radial, peroneal, facial, and trigeminal nerves. Of the two clinical forms, the lepromatous, or neural, type 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. The thickened perineurium by an overgrowth of connective tissue compresses the myelin sheath and the axons. In the other type, the tuberculoid form, 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. The two types of clinical presentation commonly overlap without clear separation, giving rise to an intermediate or mixed form. Nerve biopsy material taken from sites remote from skin lesions reveals subperineurial edema and various amounts of loss 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.[762] Teased fiber studies in each leprosy type also reveal paranodal demyelination affecting successive internodes.[394]

Clinical features suggest mononeuritis multiplex or slowly progressive diffuse polyneuropathy. 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. Electrophysiologic abnormalities consist of moderately to markedly slowed motor and sensory conduction, not only across enlarged segments[527,818] but also along the unpalpable portions.[562] In one series, radial nerve sensory abnormalities correlated best with the clinical findings,[753] whereas in another ulnar sensory studies revealed more prominent changes.[97] Electromyog-

raphy reveals denervation in the atrophic muscles. The denervated muscle shows histopathologic changes of fascicular atrophy and inflammatory nodules.

Acquired Immunodeficiency Syndrome

Patients with acquired immunodeficiency syndrome (AIDS) develop various types of neuropathy[43,293,304,324,331,372,913] as evidenced by nerve conduction studies.[180,271,484,785] In this entity, cell-mediated tissue destruction results from human immunodeficiency virus (HIV) infection and serves as the pathogenetic mechanism of AIDS neuropathy.[193] Peripheral neuropathy may complicate all stages of HIV infection.[137,163,486,500,572] Acute inflammatory demyelinating polyneuropathy,[687] sensory and sympathetic ganglia neuritis,[242] and acute cranial nerve palsy all 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.[85,588] Neuropathy is also one of the most common neurologic manifestations in AIDS-related complex, affecting as many as 20 percent of patients.

In contrast to the autoimmune basis of demyelinative neuropathy,[810] less clearly established pathogenetic mechanisms of distal symmetric polyneuropathy include infections, toxins, and nutritional causes. Polyradiculopathy most likely results from infections with such agents as cytomegalovirus and herpes simplex virus. These cause a severe selective destruction of the motor neurons of ventral spinal roots and motor cranial nerves.[51,234] Zidovudine may induce mitochondrical myopathy but causes no clear neurotoxicity.[497] Electromyography reveals severe diffuse denervation distally, 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.[508,543] These patients may have reduced sural nerve action potentials as the sole electrophysiologic abnormality.[787]

Other Neuropathies

Subacute sensory neuropathy is a rare complication of Epstein-Bar virus infection.[719] Herpes zoster may cause a painful neuropathy in addition to the more common postherpetic neuralgia.[586,587] Hepatitis B viral infection, albeit rarely, may cause mononeuritis multiplex during acute stages.[153,381] In paralytic rabies, vascular and inflammatory changes predominate in the central nervous system but peripheral nerves may show segmental demyelination, remyelination, and wallerian degeneration with variable axonal loss.[146] Electrophysiologic abnormalities include slowing of motor and, to a lesser extent, sensory conduction velocities, and reduced numbers of motor unit potentials and fibrillation potentials.[816] Demyelinating neuropathy may occur as a rare manifestation of Creutzfeldt-Jakob disease.[604]

A tick (Ixodes) bite may result in meningoradiculoneuritis with electromyographic evidence of denervation, prolongation of distal motor latency, and low sensory amplitude, suggesting axonal degeneration.[858] Lyme borreliosis causes a severe, predominantly axonal polyradiculoneuropathy typically with cranial neuropathy and lymphocytic meningitis.[335,516,528,746] The syndrome of acute sensory and autonomic neuropathy often show a focal onset, suggesting an immune-mediated or vascular process at the level of the posterior root or the dorsal root ganglion.[662,910] Other infective diseases occasionally associated with neuropathy include rickettsial disease,[336] Chagas' disease, trypanosomiasis,[767] and other types of insect and spider stings.[171]

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 calorie intake suffer from retarded myelination or segmental demyelination.[147] They have abnormalities of motor and sensory nerve conduction related to the severity of the malnutrition. Severe malabsorption from blind loop syndrome also causes vitamin E deficiency.[89,896] Alcoholic and paraneoplastic neuropathies result, at least in part, from inadequate food and vitamin intake, although some toxins may also interfere with the metabolism of the nerves.[182] In primary biliary cirrhosis, a sensory neuropathy develops from poor nutrition, xanthomatous infiltrates, or immunologic abnormalities.[133]

Diets deficient in vitamins and other nutritional factors play a major role in the polyneuropathy associated with beriberi, pellagra, pernicious anemia, dysentery, and cachexia.[190] Beriberi, or thiamine deficiency, causes signs and symptoms similar to those of alcoholic polyneuropathy.[366] They consist of pain, paresthesias, distal sensory loss and weakness, and absent stretch reflexes. A similar neuropathy may develop during intended weight reduction[796] or anorexia nervosa.[525] Histologic studies reveal conspicuous axonal degeneration and less prominent demyelination. Pellagra, another deficiency disease involving the vitamin B_1 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. Isolated vitamin E deficiency, in the absence of lipid malabsorption, may cause ataxia and peripheral neuropathy.[388] Peripheral neuropathy may also develop from a serum proteinase inhibitor deficiency[264] and hypophosphatemia as a rare postoperative complication.[768]

Pernicious anemia results from a deficiency of intrinsic factors in gastrointestinal secretions that mediate absorption of vitamin B_{12}. Pathologic changes primarily involve the dorsal and lateral funiculi of the spinal cord, thus the name *combined system disease*. The peripheral nerves also show fragmentation of myelin sheaths and degeneration of axons.[457] 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. Somatosensory evoked potentials show marked abnormalities in the peroneal nerve and milder changes in the median nerve, in addition to peripheral conduction changes consistent with sensory motor axonopathy,[257,695] or rarely demyelinating neuropathy.[9] Most untreated patients have reduced conduction velocity in part because of a thiamine deficiency.[167] Patients with prominent axonal degeneration have diffuse spontaneous discharges detected electromyographically but nearly normal motor nerve conduction velocities.[457] Appropriate treatment arrests the progression of neuropathy, but residual neurologic abnormalities persist.[552]

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*) myelinopathy or Schwannopathy with primary segmental demyelination; and (*3*) distal axonopathy causing dying-back axonal degeneration. Of these, the first two types include rare acute sensory neuronopathy following antibiotic treatment[804] and segmental demyelination by perhexiline maleate used for therapy of angina pectoris.[79] Administration of diphtheria toxin[556] or tetanus toxoid[693] or chronic exposure to lead may also cause

myelinopathy. Distal axonopathies, the most common form of toxic neuropathy, often involve not only peripheral but also central axons, causing central–peripheral distal axonopathy. In experimental acrylamide neuropathy, recovery begins in the largest peripheral axons perhaps at the expense of central axons.[410]

A variety of drugs and industrial chemicals cause distal axonopathy. Drugs with known neurotoxicity include allopurinol,[38] amiodarone,[132,263,390,666] chloramphenicol, cisplatin,[698,703] colchicine,[470,722,928] dapsone,[454] diphenylhydantoin,[690] 2′,3′-dideoxycytidines[60] disulfiram,[26,638] FK506,[908] gold,[421] isoniazid, lithium,[130,875] L-tryptophan,[295] melarsoprol,[294] metronidazole,[84] misonidazole,[56] nitrofurantoin, nitrous oxide,[492,725] penicillamine,[664] perhexiline maleate,[79,726] phenytoin,[766] pyridoxine,[63,655,911] taxol,[235,509,860] suramin,[792] thalidomide,[273] and vincristine.[86,115]

Some drugs show a characteristic pattern of neuropathic involvement. For example, vincristine causes primarily motor neuropathy, whereas pyridoxine abuse leads to a pure sensory central–peripheral distal axonopathy.[655] Studies in chick embryos show that exogenous administration of gangliosides may attenuate the neurotoxicity of vincristine in vitro.[371] Cisplatin used to treat maligant tumors induces an axonopathy that bears a great resemblance to sensory neuropathy sometimes associated with such a neoplasm.[460] This dose-dependent sensory neuropathy primarily causes a distal lesion, affecting large sensory neurons as well as the spinal cord and brainstem.[462] The adrenocorticotropic hormone analogue Org 2766 can prevent or attenuate cisplatin neuropathy.[865] Psychiatric patients treated with the phenothiazine derivative perazine may develop subacute axonal neuropathy after intense sun exposure.[702]

Industrial chemicals causing toxic axonal neuropathy include acrylamide,[410,600] carbon disulfide,[646] isofenphos,[120] inorganic mercury,[13,30,780] methyl *n*-butyl ketone,[16,798] *n*-hexane,[129,623,660,783] nitrous oxide,[885] organophosphate ester mecarbam,[800] organophosphate parathion,[517,877] polychlorinated biphenyl,[139] tellurium,[850] thallium,[192,924] triorthocresyl phosphate,[876] and vinyl chloride.[668] These toxic axonal 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 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.[494] A few specific toxins such as perhexiline maleate result in demyelination as evidenced by motor nerve conduction studies.[79] Toxic exposure to *n*-hexane causes a primarily axonal polyneuropathy with secondary demyelination[623,783] and pathologic features consistent with giant axonal neuropathy.[128] Most other toxins lead to axonal loss, showing reduced amplitude of the compound nerve and muscle action potentials. In these cases, substantial degeneration of large, fast-conducting fibers accounts for a slight increase in distal latency and a decrease in conduction velocity. Electromyography shows fibrillation potentials and positive sharp waves. Lead and arsenic, two specific agents responsible for distal axonal neuropathies, merit further 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 may also affect

children with known plumbism or pica.[252] Predominent involvement of motor fibers innervating the extensor muscles of the upper limbs produces bilateral radial nerve palsies without sensory loss. The removal of the toxin leads to 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.[591] This type of pathologic change does not necessarily characterize the neuropathy seen in human cases,[101] which show severe axonal loss.[919] A group of workers exposed to lead had temporally dispersed compound muscle action potentials but normal maximal conduction velocity.[119]

Arsenic poisoning usually results from accidental ingestion of rat poison or exposure to industrial sprays.[253] The administration of melarsoprol, an organoarsenic compound, may also cause toxic arsenic accummulation in the presence of renal and hepatic dysfunction.[294] Polyneuropathy develops several weeks after acute poisoning or more slowly with chronic low-level exposure. Pale transverse bands bearing the eponym Mee's lines appear parallel to the lunula in all fingernails and toenails about 4–6 weeks after arsenic ingestion. 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.[589] Arsenic is found in the urine during acute exposure and in the hair and nails later. These 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. Flaccid paralysis may develop later, beginning in the lower limbs and eventually affecting the upper limbs. Electrophysiologic studies show marked sensory abnormalities indicative of axonal degeneration,[626] progressive slowing of motor conduction velocity,[589] and evidence of denervation in electromyography. Timely removal of the toxin leads to nearly complete recovery of conduction abnormalities. An acute demyelinating polyneuropathy may develop following acute exposure in contrast to the distal axonal predominantly sensory involvement associated with chronic low-level toxicity.[316]

5 INHERITED NEUROPATHIES

Hereditary motor and sensory neuropathy (HMSN) comprises several types: hypertrophic and neuronal varieties of Charcot-Marie-Tooth disease (CMT), Dejerine-Sottas disease, Refsum disease, and those associated with spinocerebellar degeneration, optic atrophy, and retinitis pigmentosa. Patients with these familial demyelinative neuropathies characteristically have uniform conduction slowing of all nerves without signs of major conduction block. This stands in sharp contrast to the typical findings in an acquired demyelinative neuropathy with multifocal slowing and conduction block and differential involvement of various nerves and nerve segments.[502] Other inherited polyneuropathies include hereditary neuropathy with liability to pressure palsies, Friedreich's ataxia, acute intermittent porphyria, cerebral lipidosis, hereditary sensory neuropathy, lipoprotein neuropathy, giant axonal neuropathies, Fabry's disease, and familial amyloid neuropathy.

Genetic Classification of Hereditary Motor and Sensory Neuropathies

Charcot-Marie-Tooth disease (CMT), although long regarded as a single entity, consists of two major varieties, hypertrophic and neuronal.[100,124,346,382] Genetic linkage studies provide evidence for further heterogeneity.[68,323,650] The most common hypertrophic or demyelinative form (Table 25–3) usually has an autosomal dominant inheritance genetically localized on chromosome 17 (CMT1A) or chromosome 1 (CMT1B).[196,333,345] The most prevalent form, CMT1A, has a tandem duplication of chromosome 17p11.2–12 with trisomic expression of the peripheral myelin protein 22 (PMP-22) gene[521] or, less frequently, a missense mutation of PMP-22.[127,856] Men tend to have a more severe form of the disease

Table 25–3 Genetic Classification of Hereditary Motor and Sensory Neuropathy

	Locus	Gene	Mechanism
CMT1 (HMSN type I)			
CMT1A	17p11.2-12	PMP-22	Duplication/point mutation
CMT1B	1q21-23	P_0	Point mutation
CMT1C	Unknown	Unknown	Unknown
CMT2 (HMSN type II)			
CMT2A	1p35-36	Unknown	Unknown
CMT2B	3q13-22	Unknown	Unknown
CMT2C	Unknown	Unknown	Unknown
CMTX (X-linked HMSN)			
CMTX1	Xq13.1	CX32	Point mutation
CMTX2	Xp22.2	Unknown	Unknown
CMTX3	Xq26	Unknown	Unknown
Dejerine-Sottas disease (HMSN type III)			
DSD type A	17p11.2-12	PMP-22	Point mutation
DSD type B	1q22–23	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 = CMT, X-linked dominant or recessive; DSD = Dejerine-Sottas disease; HMSN = hereditary motor and sensory neuropathy; HNPP = hereditary neuropathy with pressure palsies.

than women, who may have formes frustes.[346] In contrast to CMT1A, the less common CMT1B has a linkage to chromosome 1q21-23, showing point mutations in myelin protein zero (P_0).[522,779] Another type, CMT1C, has no linkage to either chromosome 1 or chromosome 17.

Genetic linkage analysis has identified at least three different forms of the neuronal type (CMT2) mapping to chromosomes 1p,3q and 7p: CMT2A (1p35-36), CMT2B (3q13-22), CMT2C (unknown loci), and CMT2D (7p14).[522,733] Other reported sites of mutation include chromosome 1q21-23 (P_0).[541] A neuronal type with onset in early childhood shows none of the regenerative features considered characteristic of autosomal dominant CMT2.[276] Occasional patients have an autosomal recessive,[346] X-linked dominant pattern (CMTX1),[674] or a recessive (CMTX 2 and CMTX 3) pattern.[386] Clinical electrophysiologic and histologic findings also support primary axonal or demyelinating neuropathy in the X-linked disorder (CMTX), which includes X-linked dominant CMTX1(Xq13.1) with connexin 32(CX32) point mutations,[69,737,819] and X-linked recessive CMTX2(Xp22.2) and CMTX3(Xq26) without CX32 point mutations.[382]

Some families with autosomal dominant HMSN have calf enlargement caused by muscle fiber hypertrophy predominantly of type I fibers,[195,734] and others have neuropathy with optic atrophy.[793] In one family with HMSN, some members had features of myotonic dystrophy, and others had only its genetic markers on chromosome 19.[797] A large group of clinically unequivocal cases show a bimodal distribution of nerve conduction velocities.[346] Some kinships have both the neuronal and hypertrophic types and some investigators emphasize the existence of an intermediate variety.[80,292,674]

Linkage analyses in autosomal dominant cerebellar ataxia have demonstrated genetic heterogeneity and subclassification:[467] spinocerebellar ataxia type 1 to type 7 (SCA1 to SCA7) with five identified genes all showing expanded and unstable CAG repeat, SCA1 on 6p22-23, SCA2 on 12q23-24.1, SCA 3/Machado–Joseph disease (MJD) on 14q24.3, SCA6 on 19p13, and SCA7 on 3p11-13, and two unidentified genes, SCA4 and SCA5 on chromosomes 16 and 11.

In another disorder called *hereditary neuropathy with liability to pressure palsy* (HNPP) with autosomal dominant inheritance,[496] 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 megabase (Mb) deletion in a segment of chromosome 17p11.2-12 that contains the PMP-22 gene.[418,537,607,926] The duplication in CMT1A and deletion in HNPP in the same region are probably consequences of unequal crossing-over during germ cell meiosis.[127] Both neuropathies result from an imbalance in PMP-22 expression.[278] In one series of 51 patients with multifocal neuropathies, DNA analysis detected the deletion of 17p11.2 in 24, establishing the diagnosis of HNPP.[848] In another study, underexpresssion of PMP-22 mRNA correlated with disease severity and with mean axon diameter.[748] Reports of kinships without the typical 1.5 Mb deletion suggest genetic heterogeneity.[19]

Charcot-Marie-Tooth Disease Type 1 (HMSN Type I)

The hypertrophic variety of CMT1 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.[873] 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.[277] In a kindred displaying a dominant inheritance, marriage between two heterozygotes resulted in two homozygous offspring. The homozygotes had clinical features of the classic Dejerine-Sottas disease. Unusual and sometimes devastating clinical features may result from a rare chance association of CMT1A with such disorders as facioscapulohumeral muscular dystrophy,[103] myasthenia gravis,[138] Noonan syndrome,[769] and posterior interosseous nerve syndrome.[112]

The symptoms begin insidiously during the first two decades, sometimes with subtle clinical signs appearing even in children before 1 year of age. These include pes planus, distal foot wasting, weakness of ankle eversion, and dorsiflexion and areflexia.[248] Atrophy initially involves the peroneal musculature and then the thigh and the upper limbs, sparing the trunk and girdle musculature. Some patients develop diaphragmatic paralysis with respiratory or cardiac failure.[343] The classic stork leg configuration develops only rarely in the hypertrophic type. Bilateral footdrop causes a characteristic gait difficulty. The patient has paresthesias, dysethesias, and muscle pain associated with foot deformity. Typical findings include palpable nerves, loss of vibratory and position senses, reduced cutaneous sensations, and diminished stretch reflexes, first at the ankle and later diffusely. The disease progresses very slowly over many decades, at times showing spontaneous arrest. Muscle atrophy and weakness may incapacitate the patient, but not always. Many investigators consider Roussey-Levy syndrome with a static tremor of the hands as a variant of this type.[107] Patients may suffer from temporary worsening of otherwise stable symptoms during pregnancy.[721] Neurologic deficits may result from compression of the spinal cord, vertebral arteries, or neural foramina by the hypertrophic nerve roots.[714] Occasionally, a patient with CMT1 will develop superimposed chronic inflammatory demyelinating polyradiculoneuropathy, which may respond to immunosuppressive therapy[577] or corticosteroids.[67] Possible surgical therapies for upper limb neuropathy include standard tendon transfers, nerve compression release, soft tissue releases, and joint fusions.[96]

Nerve conduction studies show a marked, diffuse, and uniform slowing as a hallmark of CMT1.[156,347,851] The uncommon recessive forms have slower conduction than the dominant form.[347] 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.[225] 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.[606] Slowing of conduction is completely concordant with the presence of the segmental duplication in CMT1A.[415] 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.[326] The disease affects both peripheral and central sensory fibers, as evidenced by delay and reduction of sensory potentials as well as somatosensory evoked potentials.[405]

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.[405] Such uniformity helps differentiate this entity from acquired inflammatory polyneuropathy. Conduction abnormalities may herald clinical onset of neuropathy.[874] Motor nerve conduction velocities attain maximal slowing over the first 3–5 years of life[326] and remain relatively stable thereafter,[435] whereas compound muscle action potentials decline in amplitude, reflecting a progressive axonal loss.[717] Both measures, despite an inverse relationship to clinical severity, show no correlation with age,[368] probably because the primary pathologic process remains inactive after childhood.[244] Serial electrophysiologic studies can detect the CMT1A gene abnormalities in infancy and early childhood.[285] 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,[55] although the florid clinical picture may not occur until the second decade of life.[285]

Other electrophysiologic abnormalities include absent or delayed F waves, a finding[442] that matches the slowing of motor nerve conduction in the distal segment (see Figs. 18–7 and 18–10 and Table 18–3).[438] Studies of facial nerve;[303,437] and phrenic nerve[111] also show increased latencies despite relatively normal strength of the facial muscles and diaphragm (see Figs. 17–12A and 17–14 and Tables 17–2 and 17–4). Recording isometric force during fastest voluntary contraction shows a prolongation in contraction time and a reduction in maximal rate of rise of tension.[513] In many patients, studies of evoked potentials detect a minor degree of involvement of visual[108] and auditory[459,745] pathways. Some patients also have impaired central conduction[790] and autonomic dysfunction,[790] but not universally.[379]

Charcot-Marie-Tooth Disease Type 2 (HMSN 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.[645] Most consider a third type of CMT disease, designated as the spinal form, as a variant of the neuronal type or of distal spinal muscular atrophy.

The clinical features, although much less generalized, resemble those of CMT1 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 states. 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 CMT1. Plexiform neurofibroma of the cauda equina may mimic peroneal muscular atrophy.[58]

Electrophysiologic studies reveal mild slowing of nerve conduction velocities, consistent with a reduction in amplitude of the compound sensory nerve and muscle action potentials.[56,347] Electromyographic studies typically show large motor unit potentials, fasciculation potentials, fibrillation potentials, and positive sharp waves.[223]

Charcot-Marie-Tooth Disease X-linked Dominant Type 1

The genetically heterogeneous group of hereditary motor and sensory neuropathies includes a rare variant with X-linked dominant inheritance.[718] In a large Canadian kindred traced through six gen-

erations,[329] affected fathers had no male-to-male transmission, whereas all their daughters expressed the disease. The typical clinical features included onset in early childhood, pes cavus, distal muscular atrophy, and sensory abnormalities. Electrophysiologic observations indicated a substantial loss of distal motor and sensory nerve fibers with primary axonal degeneration, a non-uniform slowing of motor conduction velocities and dispersion of compound action potential reminiscent of acquired chronic demyelination.[819]

Hypertrophic Polyneuropathy of Dejerine-Sotas (HMSN Type III)

Dejerine (1890)[197] and Dejerine and Sottas (1893)[198] described a very severe, generalized form of demyelinating sensory motor neuropathy inherited as an autosomal recessive trait.[742] The disorder shows a considerable genetic heterogeneity[522] with a mutation in either PMP-22[383,385,539,701] or P_0[355] or linkage to chromosome 8.[384] 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 CMT1. Pathologic analysis reveals 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.[644] Nerve conduction studies reveal marked slowing of the 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.[54]

The differential diagnosis should include congenital demyelinating motor and sensory neuropathy with focally folded myelin sheaths.[275] 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.[786] This entity 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 of primary perineurial cell hyperplasia or perineurinoma.[579] Nerve conduction studies suggest severe motor and sensory axonal loss with no evidence of slowed conduction velocity. Electromyography also indicates focal axonal loss with evidence of severe denervation limited to the territory of the affected nerve.

Hereditary Ataxic Neuropathy of Refsum (HMSN Type IV)

Hereditary ataxic neuropathy of Refsum is a rare disorder transmitted by an autosomal or a recessive gene that has characteristic pathologic changes in the olivocerebellar tracts, anterior horn cells, and peripheral nerves.[736] The typical clinical features comprise deafness, anosmia, night blindness with retinitis pigmentosa, ichthyosis-like skin, cerebellar signs, and nystagmus. Involvement of the peripheral nerves 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 acids 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.[471,832] Electrophysiologic studies reveal decreased sensorimotor conduction velocities in all limbs.[204] Severe axonal involvement in the lower limb may characterize other cases.[288] Dietary restriction of phytol results in considerable improve-

ment of symptoms. Some patients with retinitis pigmentosa and ataxia have a syndrome that clinically resembles Refsum's disease without detectable biochemical abnormalities. In these cases, electrophysiologic studies reveal mildly delayed, low-amplitude sensory action potentials but no evidence of hypertrophic neuropathy.[846]

Autosomal Dominant Cerebellar Ataxia

Autosomal dominant cerebellar ataxia with neuropathy (ADCA) superficially resembles CMT with distal wasting and weakness involving the legs more than the arms.[740,807] Some patients show muscle wasting presumably reflecting the loss of motor neurons.[1] Most patients have an extensor plantar response with normal or increased stretch reflexes in the upper limbs and at the knee, but often absent ankle jerks. In one series,[467] sensory or sensory motor polyneuropathy was found in 42 percent of patients with SCA1, 80 percent of SCA2 and 54 percent of SCA3. Further, SCA1 patients with polyneuropathy had a significantly higher CAG repeats than those without polyneuropathy.

Electrophysiologic abnormalities include lower than normal mean motor and sensory nerve conduction velocities and reduced amplitude of sensory nerve action potentials.[348,561] Median nerve somatosensory evoked potentials reveal decreased amplitude of N_{13} and N_{20} with increased interpeak latencies, implicating central and peripheral sensory pathways.[585] Sural nerve biopsies show fewer myelinated fibers and normal unmyelinated fibers.[561] Peripheral neuropathy also develops in some patients with infantile onset[458] and late onset[243,612] spinocerebellar degeneration, sometimes associated with ceroid lipofuscinosis.[915]

A predominantly sensory axonal neuropathy, seen in olivopontocerebellar atrophy, affects those patients with glutamate dehydrogenase deficiency, but not those with normal enzymatic activities.[143] Such a 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 reduced myelinated fibers in the sural nerve.[144]

Hereditary Neuropathy with Liability to Pressure Palsies

Hereditary neuropathy with liability to pressure palsies (HNPP) is a familial disorder of autosomal dominant inheritance.[496] Histopathologic changes include focal, sausage-like, or tomaculous thickening of the myelin sheaths and noncompacted "loose" myelin lamellae together with segmental demyelination and remyelination.[53,526,841] The most prominent feature of the disease is pressure-induced, reversible motor weakness, although sensory symptoms may also appear.[212] Compression palsy commonly affects the ulnar, radial, and peroneal nerves, with recovery occurring slowly over weeks or months. Occasional patients may develop acute anterior interosseous neuropathy[254] or recurrent familial brachial plexus palsies or other acute painless mononeuropathies[651] as the only or predominant clinical manifestation.[542,808] Others may have acute recurrent polyneuropathy[406,498] or chronic sensory motor neuropathy as the presenting symptom.[255,530] Rare associated features include central nervous system demyelination,[17] and the syndrome of moving toes and myoclonus.[756]

Motor and sensory studies show focal conduction abnormalities at usual compression sites[851] in paretic limbs but also in some clinically unaffected nerves.[841] Evaluations of clinically normal nerves reveal electrophysiologic abnormalities in approximately one half of the patients and some asymptomatic relatives.[179] A pathologically thick myelin sheath probably causes long-lasting conduction block and the slowing of conduction velocities seen in some cases,[754] although segmental demyelination also plays a role.[76]

Friedreich's Ataxia

Friedreich's ataxia is an autosomal recessive disorder associated with a GAA tri-

nucleotide repeat expansion in the first intron of the X25 gene on chromosome 9q13–21.1. Patients who develop mild symptoms without cardiomyopathy later than the usual onset may have limited GAA expansions.[287,290,523] 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 severe loss of large myelinated fibers, well-preserved unmyelinated C fibers conduct normally.[226,643] The only consistent clinical findings within 5 years of presentation consist of limb and truncal ataxia and absent stretch reflexes in the legs.[344] 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 average, patients lose the ability to walk by the age of 25 years and become chair-bound by the age of 44 years.[344] Common variabilities include late onset, preservation of the lower limb tendon reflex, and slow progression.[174]

Electrophysiologic studies show absent or considerably reduced sensory nerve potentials[558,735] and essentially normal motor conduction studies except for a modest slowing in some patients.[643] Nerve biopsy reveals a severe loss of large myelinated fibers, but no demyelination.[113] Somatosensory evoked potentials may reveal abnormal peripheral as well as central conduction.[199,663] Transcortical magnetic stimulation indicates an abnormal central motor conduction time, which progressively worsens as the disease advances.[178] Patients rarely complain of visual impairment, but most have an increased latency or reduced amplitude of the visual evoked potential.[109,512,663]

Porphyria

An acute, primarily motor neuropathy characterizes several forms of porphyria, a rare hereditary disorder that belongs to the category of inborn errors of metabolism.[23] These include acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria.[46] A partial defect in hepatic heme synthesis results in overproduction of delta aminolevulinic acid and porphobilinogen. The disease has 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, sulfonamides, or certain other drugs.

Acute axonal neuropathy affects motor fibers regularly and sensory fibers in about 50 percent of patients. Weakness progresses rapidly, involving the axial muscles more than the distal muscles. The sensory loss, although relatively mild, may also predominate proximally. Nerve conduction studies show low-amplitude compound action potentials with normal conduction velocities. Electromyography reveals prominent fibrillation potentials and positive sharp waves in the proximal muscles 1–2 weeks after onset.[15,78]

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 helps establish the clinical diagnosis, although confirmation comes from a nerve or cerebral biopsy.[282,538]

Krabbe's disease, an autosomal recessive disorder, affects the white matter of the central and peripheral nervous systems. A galactocerebrosidase (GALS) deficiency causes accumulation of undegraded psychosine, leading to the pathologic hallmarks of globoid cell leukodystrophy. Identification of a homozygous point mutation in the GALS gene confirms the diagnosis.[741] 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 a late manifestation, is occasionally one of the presenting features.[176,505]

In metachromatic leukodystrophy,[268, 465,920] 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[149,337] or adults.[77] Electrophysiologic studies reveal substantially slowed nerve conduction as would be expected in a demyelinative neuropathy. Morphometric studies reveal a marked reduction in sheath thickness, particularly in the large myelinated fibers.[41]

Hereditary Sensory and Autonomic Neuropathy

Hereditary sensory neuropathy consists of four distinct entities. Type I has autosomal dominant inheritance with degeneration of the dorsal root ganglias, early loss of sensory nerve action potential, and preservation of the sympathetic skin responses.[765] In one family, sural nerve biopsies showed a marked loss of all myelinated fibers and a comparable loss of unmyelinated fibers.[189] Clinical findings include loss of pain and temperature sensation, areflexia, and development of ulcers in the lower limbs with almost 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.[122] Characteristic features include progressive sensory neuropathy, spastic paraplegia, and a mutilating lower limb acropathy.[824,837] Nerve conduction studies show absent sensory action potentials and borderline slow motor nerve conduction velocities.

Type III is the same as familial dysautonomia or Riley-Day syndrome,[700,830] and type IV is a rare congenital loss of C fibers with complete insensitivity to pain.[518] Other entities in this category include familial sensory autonomic neuropathy with arthropathy in Navajo children.[401]

Lipoprotein Neuropathies

Two types of lipoprotein disorders accompany neuropathies. Patients with Bassen-Kornzweig syndrome, mostly Jewish children, have malabsorption, cerebellar signs, retinitis pigmentosa, acanthocytosis, and virtual absense of betalipoprotein in the serum, or abetalipoproteinemia. Diminished stretch reflexes and the absence of position and vibratory senses suggest a peripheral neuropahy. Neurologic signs resemble those of Friedreich's ataxia and Refsum syndrome. In one histologic study, the sural nerve showed a decreased number of large fibers with diameters greater than 7 μm, regeneration, and paranodal demyelination.[900]

Electromyographic findings include signs of chronic denervation in distal limb muscles; myotonic discharges; large-amplitude, long-duration motor unit potentials; and poor recruitment. Sensory nerve conduction studies reveal reduced amplitude with a slight slowing in distal conduction velocity.[900] Motor conduction studies show normal or slightly reduced amplitude with normal conduction velocities.[519,571] Other electrophysiologic abnormalities may include a prolonged latency of visual and somatosensory evoked potentials.[90] The fiber diameter spectrum of the sural nerve indicates a loss in the 8–12 μm diameter range.

Patients with Tangier disease have a low level of high-density lipoprotein and cho-

lesterol in the serum. Their enlarged tonsils have a characteristic bright orange color from the deposition of cholesterol esters. Their skin and rectal mucosa display similar changes. Both myelinated and unmyelinated fibers show degeneration.[450] Dissociated losses of pain and temperature sensation, not unlike those seen in syringomyelia, suggest selective involvement of the small fibers.[217] Patients may have a relapsing and remitting mononeuropathy with prominent demyelination and remyelination or slowly progressive neuropathy with advanced axonal degeneration.[678] Conduction studies may reveal abnormal velocities in some patients but not in others.[282]

Giant Axonal Neuropathy

Children with progressive peripheral giant axonal neuropathy[32,201,828] usually have minor central nervous system involvement and intellectual dysfunction.[582] The disease shows an autosomal recessive inheritance trait with the responsible gene localized to chromosome 16q24.[262] The accumulation of neurofilamentous material leads to ballooning and degeneration of the axons,[322,468] affecting the motor fibers more than the sensory fibers. The clinical features in a large kindred included infantile onset, progressive distal amyotrophy of four limbs, brisk reflexes, diffuse fasciculations, bulbar signs, and deep sensory loss in both lower limbs.[338] 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 are insufficient to characterize the condition. Abnormalities demonstrated by evoked potential studies confirm clinical and pathologic findings of central nervous system dysfunction.[529]

Fabry's Disease

Fabry's disease is a multisystem X-linked recessive disorder. An inborn error involving glycosphingolipid metabolism causes the accumulation of ceramide trihexose in various tissues. The enzymatic defect of ceramide trihexosidase affects the skin, blood vessels, cornea, and the 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.[770] Axonal degeneration primarily involves small myelinated and unmyelinated fibers.[270,451] The presenting clinical features include severe burning sensations of the hands and feet. Nerve conduction studies, although ordinarily normal, may show some slowing in affected men and occasionally in female carriers.[761] Electromyographic studies reveal no abnormalities in most cases.

Familial Amyloid Neuropathy

Signs and symptoms of amyloidosis result from deposits of amyloid around blood vessels and connective tissues in multiple organ 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 carpal tunnel syndrome in about one fourth of the patients. Familial amyloid neuropathies, unlike primary or nonfamilial amyloid neuropathies associated with paraproteinemia (see this chapter, part 2), have relentless progression of neurologic and cardiac impairment, lending to death within 7–15 years after disease onset. Compared to hereditary sensory and autonomic neuropathy, familial amyloid neuropathy shows a greater motor and autonomic involvement with an early loss of sympathetic skin responses.[765] Liver transplantation may offer hope for arrest of progression and improvement of sensory motorneuropathy.[64] Neurologic symptoms rarely develop in secondary amyloidosis seen in chronic debilitating inflammatory processes.

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,[621] Japanese,[24,341,377,788] Northwest Ireland,[801] Taiwanese,[921] and English ancestries.[445] Transthyretin gene mutations, found in some of these hereditary cases,[849] have also affected British and French patients without a family history.[66] The most common familial amyloid polyneuropathy, type I, has a variant transtlyretin with a single amino acid substitution.[70] These include a most frequent methionine-for-valine substitution reported from Portugal, Italy, Sweden and Japan, and alanine-for-value substitution found in a family of German origin and a leucine-for-valine substitution seen in Japanese pedigrees.[855] The familial amyloid polyneuropathy type IV phenotype in Finnish as well as Japanese kinships[85] results from a single base substitution, guanine to adenine at nucleotide position 654 in the gelsolin gene located on chromosome 9q32–q34.

Other Neuropathies

Other rare inherited systemic disorders associated with peripheral neuropathy include sialidosis type I, or the cherry-red spot myoclonus syndrome,[803] cerebrotendinous xanthomatosis,[473] a variety of extrapyramidal syndromes,[104] multiple endocrine neoplasias,[216] neurofibroma-tosis,[436,836] Cockayne's syndrome,[321] congenital hypomyelination polyneuropathy,[82,327,342] chorea acanthocytosis,[507] adrenomyeloneuropathy (see Fig. 18–8),[696,879,903] infantile neuroaxonal dystrophy,[594] mitochondrial disorders,[583] hereditary tyrosinemia,[576] hereditary motor and sensory neuropathy with treatable extrapyramidal features,[398] and lethal neonatal autosomal recessive axonal sensory motor polyneuropathy.[878]

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Chapter 26

MONONEUROPATHIES AND ENTRAPMENT SYNDROMES

8. COMMON PERONEAL NERVE
9. TIBIAL NERVE
10. SURAL NERVE
11. OTHER MONONEUROPATHIES
    - Hypertrophic Mononeuropathy
    - Idiopathic Mononeuropathy
    - Postherpetic Neuralgia
    - Sports Injury
    - Musicians' Entrapment Neuropathy
    - Traumatic Mononeuropathy
    - Perioperative Mononeuropathy
    - Reflex Sympathetic Dystrophy

1 INTRODUCTION

Despite the unpredictable nature of traumatic injuries, certain individual nerves are predisposed to isolated damage.[100,493] These include the long thoracic, suprascapular, musculocutaneous, and axillary nerves in the shoulder girdle and the lateral femoral cutaneous, femoral, and sciatic nerves in the pelvic girdle. Injuries resulting from acute or chronic repetitive external pressure produce compressive neuropathy, whereas chronic distortion or angulation of the nerve from an internal source causes entrapment neuropathy.[289] Entrapment syndromes develop at the common sites of chronic or recurrent constriction of the radial, median, ulnar, common peroneal, and tibial nerves.[493] Certain types of peripheral nerve disorders may develop occupationally. For example, instrumentalists may suffer from symptoms of cervical radiculopathies, thoracic outlet syndrome, and median, ulnar, and digital neuropathies.[282] A number of different nerve lesions also result from stretch, ischemia, compression, or laceration during a surgical procedure.[101] Unusual sites of involvement may suggest rare anomalies such as congenital ring constrictions of peripheral nerves.[312]

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 that 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 conducted as an extension of a physical examination in a proper clinical context.[46] Electromyographic examination delineates the exact distribution of denervated muscles in localizing a focal nerve lesion. In demyelinative or other neurapraxic conditions, a reduced recruitment of motor units despite the preservation of the axons signals a conduction block. The pattern of distribution here also helps elucidate the zone of involvement.

Nerve conduction studies may provide evidence of conduction abnormalities, which usually precede axonal degeneration in a compression neuropathy. Such focal conduction slowing may not necessarily accompany the reduced margin of safety for the impulse propagation usually attributed to demyelination.[233,332] Thus, other factors such as ischemia may contribute to the reversible conduction block seen in some of these cases. Stimulation above and below the suspected site of lesion will document not only the slowing of conduction velocity but also changes in amplitude and area of the muscle or nerve action potential as indices of functional block. Such a pattern of abnormalities of-

ten 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 localized pathology at the common sites of compression.

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.[511] Cranial nerves most commonly assessed in an electromyographic laboratory include the facial and accessory nerves. They both travel superficially, which allows easy access to electrical stimulation from the surface. They also innervate the muscles readily approachable by needle or disc electrodes for recording.

Facial Nerve

Bell's palsy affects the facial nerve sporadically in an isolated incidence. Although the exact etiology remains unknown, accumulating evidence suggests that herpes simplex virus type I (HSV-1) reactivation causes Bell's palsy in some, but not all patients,[38,151,313] giving a rational for antiviral therapy with acyclovir.[6] 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 and hyperacusis on the affected side. At least 80 percent of patients improve quickly without specific therapy.[556] Complete recovery follows the demyelinative form, whereas functions return slowly and poorly after degeneration of the facial nerve. Synkinesis nearly always develops with regeneration (see Fig. 17–11).[245] Patients may complain of sensory signs in the trigeminal distribution in an otherwise typical case of Bell's palsy. Patients with a rare familial type may suffer from recurrent episodes, which tend to leave increasing residual weakness after each attack.[12] 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.[308]

The same principles apply to the electromyographic examination of facial and limb muscles. In the face, however, physiologically small motor unit potentials may mimic fibrillation potentials, and signs of denervation appear early in less than 3 weeks following injury presumably because of the short nerve length. Serial electrodiagnostic studies help delineate the course of the illness (see Fig. 17–3 and Tables 17–2 and 17–3). The amplitude of the direct response elicited by stimulation of the facial nerve provides the best means for prognosis after the fourth to fifth day of onset. An amplitude greater than one half of the control value on the normal side indicates a good prognosis, although late degeneration can still occur. Preservation or return of R_1 or R_2 of the blink reflex also serves as a reliable measure in predicting a satisfactory recovery (see Fig. 17–9), providing 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 R_1 reappeared by the latter half of the first week in 57 percent, by the second week in 67 percent, and by the third week in 89 percent.[245] Other signs for good outcomes include incomplete clinical paresis and the presence of voluntary motor unit potentials in electromyographic studies.[560]

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 the latency of R_1 of the blink reflex, if present, is relatively normal during the first days, is delayed during the latter half of the first week, and plateaus up to the fourth week, followed by a notable recovery during the second month and a return to the normal range during the third to fourth months (see Fig. 17–10). These findings suggest that most patients with

Bell's palsy who develop little axonal degeneration suffer from a focal demyelination of the facial nerve. If the facial nerve undergoes substantial degeneration, the ultimate recovery depends on the completeness of regeneration. This process generally[88,247] takes a few months to a few years, resulting almost always in an aberrant reinnervation, sometimes associated with hyperexcitability.

Peripheral facial paresis secondary to herpes zoster infection carries a less favorable prognosis, although early administration of acyclovir and prednisone may reduce the nerve degeneration.[342] Patients with Bannwarth's syndrome may develop unilateral or bilateral facial palsy as part of multiple mononeuritis associated with erythema, pain, elevated cerebrospinal fluid protein, and pleocytosis.[558] Peripheral facial palsies may also accompany a systemic infection such as Lyme borreliosis[162,186] and human immunodeficiency syndrome or complicate[537] an inferior dental and, less commonly, upper dental anesthetic block.[31]

Diabetic patients who develop a facial palsy also tend to have a more severe paresis and evidence of substantial denervation.[5] Patients with Guillain-Barré syndrome usually develop prominent facial paresis as a consequence of acute demyelinative conduction block (see Figs. 17–12A and 17–14).[237] In contrast, the chronic insidious progression in hereditary Charcot-Marie-Tooth disease type 1 allows compensation for motor function despite a marked delay in conduction, showing minimal weakness.

An acoustic neuroma strategically located at the cerebellopontine angle may compress not only the facial nerve but also the trigeminal nerve and the pons, i.e., the efferent, afferent and central arcs of the blink reflex.[246,248,300,433] Thus, the electrically elicited blink reflex reveals various degrees of abnormality in most patients (see Tables 17–3 and 17–4) showing a high correlation with the tumor size.[363] Hypoglossal–facial nerve anastomosis may partially restore function after sacrifice of the facial nerve for removal of cerebellopontine angle tumors.[401] Sarcoidosis may also involve the facial nerve probably at the cerebellopontine angle.[169]

Peripheral facial palsy may herald other symptoms of multiple sclerosis in young adults (see Fig. 17–13B). In these cases, blink reflex studies usually show an absent or delayed R_1, indicating demyelination of the central reflex arc, which includes the intrapontine portion of the facial nerve.[236,238,239] Myokymic discharges, although characteristic of this disorder, may also appear in other conditions such as pontine glioma[183] and subarachnoid hemorrhage.[37] Progressive hemifacial atrophy may develop in scleroderma with or without associated hemiatrophy the body.[50,277,306]

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 minimal R_1 latency will confirm a peripheral abnormality. Reduced excitability may cause an apparent delay in R_1 latency during an acute stage of contralateral hemispheric lesions, especially if elicited by the glabellar tap.[140] In doubtful cases, paired stimuli counter the effects of supranuclear hypoexcitability, giving rise to the shortest R_1 latency as the accurate measure of the conduction time along the reflex arc. The excitability of polysynaptic R_2 may change substantially with a hemispheric lesion, showing either an afferent or efferent pattern (see Chapter 17–6 and Fig. 17–19).

Trigeminal Nerve

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 systemic sclerosis or mixed connective tissue disease.[281] Patients with trigeminal neuralgia have altered cutaneous sensations in both the affected and unaffected adjacent divisions, suggesting combined peripheral and central pathology.[366] A mandibular fracture may result in an isolated lesion of the mandibular nerve.[121] Demyelinating lesions affecting pontine trigeminal pathways may cause trigeminal neuralgia in patients with multiple sclerosis.[155,239] Ex-

posure to trichloroethylene causes a cranial neuropathy with peculiar predilection for trigeminal root damage.[280] Facial numbness may herald other symptoms of an expanding tumor involving the trigeminal nerve.[265] Other causes of trigeminal nerve lesion include perineural spread of carcinoma.[466] The blink reflex helps establish abnormalities of the trigeminal nerve (see Chapter 17–4). Other techniques of interest include conduction studies of the trigeminal motor nerve[112] and of the mandibular nerve.[292]

Accessory Nerve

Pressure from a tumor or surgical procedures of the posterior triangle can damage the spinal accessory nerve.[116] Other causes include stretch-induced injury,[297] cargo loading,[92] coronary artery bypass,[311] carotid endarterectomy,[504,559] and ligature injury during surgical exploration.[25] 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. The paralysis of the sternocleidomastoid causes weakness when the face is rotated toward the opposite shoulder in proportion to the degree of muscle atrophy. Bilateral involvement of the muscles makes flexion of the neck difficult. In a sequential study of patients with trapezius palsy, nerve conduction changes revealed evidence of spontaneous regeneration after complete axonal degeneration.[394]

Other Cranial Nerves

Hypoglossal nerve palsy may result from compression by an aneurysm, or kinking of the vertebral artery,[167,426] or as a complication in approximately 5 percent of endarterectomies.[554]

3 PHRENIC NERVE AND NERVES IN THE SHOULDER GIRDLE

The phrenic nerve originating from the C3 to C5 roots and certain peripheral nerves derived directly from the brachial plexus have a predilection to isolated injury by compression or stab wound. The most commonly affected include the long thoracic, dorsal scapular, suprascapular, musculocutaneous, and axillary nerves.

Phrenic Nerve

A phrenic nerve palsy develops in about 10 percent of cases after open-heart surgery. Possible causes of this complication, although uncertain, include hypothermia and nerve stretch. Unilateral lesions result in no symptoms. Electrophysiologic studies may reveal subclinical involvement of the contralateral diaphragm and limb muscles, suggesting the possibility of neuralgic amyotrophy.[272] Patients require total ventilatory support after rare bilateral involvement.[542] Phrenic nerve conduction studies help identify the cause of respiratory failure (see Chapter 6–3).[77,107,441]

Long Thoracic Nerve

The long thoracic nerve lies superficially in the supraclavicular region, where it may sustain trauma. In addition to stab injury, direct pressure results from a heavy shoulder bag or shoulder braces during surgery. Radical mastectomy may also damage the nerve. Its straight course from origin to insertion also makes it vulnerable to stretch associated with vigorous athletic activity[454] or chiropractic manipulation.[382]

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 exaggerates with abduction of the arm laterally. Lesions of the long thoracic nerve give rise to isolated electromyographic abnormalities in the serratus anterior muscle. Conduction studies provide valuable information in distinguishing partial from complete degeneration and in assessing the degree of regeneration.[395]

Suprascapular Nerve

Injury may result from ganglionic cysts, pressure on the shoulder, stab wounds above the scapula,[159,319,478] improper usage of crutches,[462] and stretching of the nerve as may occur in volleyball players during serving.[138,338] The rupture of the rotator cuff[222] or downward displacement of the upper trunk may also stretch the nerve anchored at the notch,[55] a mechanism in part responsible for Erb's palsy. 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.[295] Isolated weakness and atrophy of the infraspinatus muscle may also result in a lesion at the spinoglenoid notch.[338,487] 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 suprascapular nerve latency to the involved supraspinatus or infraspinatus muscles.[222] Electromyographic studies show selective denervation in the supraspinatus or infraspinatus or both, sparing other muscles supplied by C5 and C6 roots.

Dorsal Scapular Nerve

With entrapment or injury of the dorsal scapular nerve, the scapula tends to wing on wide abduction of the arm.[347] The patient may complain of pain in C5 and C6 distribution. The diagnosis depends on electromyographic demonstration of abnormalities restricted to the rhomboid major and minor and levator scapulae.

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.[314] Weight lifting and concomitant pectoralis minor hypertrophy may produce intramuscular entrapment of the medial pectoral nerve.[436]

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.[294] A lesion after a blunt trauma to the shoulder has a less favorable prognosis.[32] Other causes include the pressure of crutches[500] 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 C5 root lesion weakens all 180 degrees with involvement of both muscles. Isolated lesions of the teres minor often es-

cape clinical detection, being compensated by the infraspinatus, which also rotates the arm outward. Electromyographic abnormalities confined to the teres minor and deltoid help establish the diagnosis of axillary nerve palsy.

Musculocutaneous Nerve

Injuries of the musculocutaneous nerve result from fractures or dislocations of the humerus, gunshot or stab wounds, compression of the arm, entrapment by the coracobrachialis muscle, heavy exercise,[41] or rare complications of surgery.[122] Sensory examination reveals numbness along the lateral aspect of the forearm. Paralysis of the biceps results in an absent stretch reflex and weakness of elbow flexion, compensated in part by the brachioradialis. Electromyography shows denervation in the biceps brachii, brachialis, and coracobrachialis. Nerve conduction studies may corroborate the diagnosis.[516]

Antebrachial Cutaneous Nerves

Vigorous arm exercise as in prolonged wind surfing may give rise to a compression syndrome of the lateral antebrachial cutaneous nerve, the distal sensory termination of the musculocutaneous nerve[206] (see Fig. 1–8). This nerve, located in the antecubital fossa, may also sustain isolated injury by mechanical pressure from a heavy object carried with the forearm flexed or by venipuncture.[564] 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.[137]

Less frequently described mononeuropathies include medial antebrachial cutaneous neuropathy after stretch and associated with an arterial graft[70] and posterior antebrachial cutaneous neuropathy after an intramuscular injection in the upper arm[68] (see Chapter 6–3). Low-amplitude sensory action potentials help document the pathology.

4 RADIAL NERVE

Proximal and Distal Sites of Compression

Nerve injury at the axilla from an incorrectly used crutch results in weakness of all the radial-innervated muscles and in loss of the triceps stretch reflex. Fractures of the head of the radius injure the nerve more distally. External trauma at the spiral groove commonly injures the nerve with or without a concomitant supracondylar fracture of the humerus.[94,144,315,539] A local compression at this level also results from improper use of walkers and wheelchairs.[22,48] The lateral head of the triceps muscle may entrap the radial nerve following continuous repetitive arm exercise,[498] in association with focal myositis[14] or spontaneously.[344] An individual, often intoxicated, may compress the nerve by falling asleep while leaning against a hard surface or with an arm draped over a bench as in the so-called Saturday night palsy. The lesion here usually spares the triceps but involves all the remaining long extensor muscles of the hand, wrist, and fingers as well as the brachioradialis. A radial nerve injury 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 first two digits. Rarely, children also suffer from traumatic or atraumatic mononeuropathy involving the proximal or distal main radial nerve or the posterior interosseous nerve.[132] In newborn infants, the umbilical cord may play a role in the entrapment.[434]

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. 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 or from repetitive pronation and supination at work.[105]

Superficial radial neuropathy may develop after wearing a tight watchband.[415] Handcuff-related compression injuries often involve the sensory fibers of the radial nerve with or without concomitant involvement of the median or ulnar nerves at the wrist.[115,290,317,497] Nerve conduction studies should include comparison with the ipsilateral lateral antebrachial cutaneous nerve and with the contralateral superficial radial nerve.[482] Surgical maneuver for trigger release may cause iatrogenic laceration of the radial digital nerve of the thumb.[64]

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. Most cases have prominent conduction block and a varying degree of axon loss.[48,535] Electromyographic exploration helps demonstrate the type and location of injury (see Figs. 14–14 and 14–17).[515] Pressure neuropathy of the radial nerve usually resolves in 6–8 weeks, but recovery takes considerably longer after loss of a substantial number of axons.

Posterior Interosseous Nerve 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.[406] The compression syndrome here may develop spontaneously or following closed injuries to the elbow.[221] Other conditions occasionally associated with this syndrome include rheumatoid arthritis with synovitis,[327] congenital hemihypertrophy of the arm,[120] therapeutic excision of the radial head for certain fractures,[90] lipoma, chondroma,[134] and ganglion cysts arising from the proximal radicular joint[320] and Charcot-Marie-Tooth disease type 1 (CMT1).[65] Violin players may develop transient symptoms as the result of prolonged pronation of the forearm.[305] The entrapment usually involves the nerve at the arcade of Frohse between the two heads of the supinator.[152,361,430]

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 abductor of the thumb and extensors of the thumb and index.[200] 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 third and fourth digits with the intact digits on both ends results in the so-called longhorn sign. Operative neurolysis usually, but not always, results in good recovery from posterior interosseous nerve palsy.[562]

In addition to electromyographic abnormalities of the affected muscles, conduction studies may reveal mild slowing across the entrapment, especially if tested with the arm supinated against resistance.[429] The differential diagnosis includes rupture of the extensor tendons, especially if paralysis affects only the last three digits, with preservation of the first two. In this case, weak muscles show no evidence of denervation, and passive palmar flexion of the wrist induces no extension of the metacarpophalangeal joints.

5 MEDIAN NERVE

The median nerve traverses three common sites of constriction along its course. At the elbow, entrapment may occur between the two heads of the pronator teres or more distally with selective involvement of the anterior interosseous branch. Carpal tunnel syndrome results from compression at the distal edge of the transverse carpal ligament or less commonly within the intermetacarpal tunnel.

Pronator Teres Syndrome and Proximal Sites of Compression

In 83 percent 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,[218] or an 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, which spares the sensory branch passing superficially to the flexor retinaculum. The conduction studies may reveal mild slowing in the proximal forearm in conjunction with a normal distal latency.[340] Test maneuvers such as elbow flexion, forearm pronation, and finger flexion generally fail to enhance conduction abnormalities across the entrapment site.[343] Injection of corticosteroids into the pronator teres may relieve the pain to aid in diagnosis, but definitive treatment requires a surgical decompression.[256]

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.[33] 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[42] or an accessory bicipital aponeurosis,[485] often involving the pronator teres and flexor carpi radialis in addition to the more distal muscles. Incremental short segmental stimulation near the proximal portion of the aponeurosis localizes the precise site of compression.[359] Weakness and electromyographic abnormalities of the pronator teres and flexor carpi radialis serve to differentiate these conditions from the classic pronator teres syndrome, which usually spares the proximal muscles.[8,181,503]

Anterior Interosseous Nerve Syndrome

Anterior interosseous nerve syndrome, also called the syndrome of Kiloh and Nevin,[234] results from selective injury of the anterior interosseous nerve that branches off the median nerve just distal to the pronator passage, unilaterally or bilaterally.[349,543] The palsy occurs either spontaneously or as a complication of an injury such as a forearm fracture.[158] 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,[19] 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 instead of a circle—the so-called pinch sign. Spontaneous recovery takes place from 6 weeks to 18 months.

Neuralgic amyotrophy caused by lesions in the brachial plexus (see Chapter 24–3) may manifest as an anterior interosseous nerve palsy[421] presumably because the responsible lesion selectively involves the nerve bundle already grouped to form the

terminal nerve branch at this level.[451] Similarly, the syndrome may appear acutely in a patient with hereditary neuropathy with liability to pressure palsies.[136] A partial median nerve lesion at an antecubital level can also involve the bundle destined to form the anterior interosseous nerve[544] or, even more selectively, only the branches innervating the flexor pollicis longus.[87] The anterior interosseous nerve syndrome may develop bilaterally as an idiopathic case[99] or in association with cytomegalovirus infection.[124]

Ordinary nerve conduction studies of the median nerve reveal no abnormalities. Stimulation of the anterior interosseous nerve at the elbow may demonstrate a delayed latency of the compound muscle action potential recorded from the pronator quadratus.[349] Comparison of the median motor latency to the pronatus quadratus and abductor pollicis brevis may prove useful.[432] Electromyographic explorations show the evidence of selective denervation in the flexor pollicis longus, flexor digitorum profundus I and II, and pronator quadratus.

Although the current recommendation for the treatment of spontaneous anterior interosseous nerve paralysis centers on surgical decompression, some of theses lesions may 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.[333]

Carpal Tunnel Syndrome

Of all the entrapment neuropathies, carpal tunnel syndrome is by far the most prevalent, showing the lifetime risk of approximately 10 percent.[207] The median nerve passes, with nine extrinsic digital flexors, through the tunnel bound by the carpal bones and transverse ligament, which is attached to the scaphoid, trapezoid, and hamate. 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 also peaks at this level in patients with carpal tunnel syndrome.[299] Pathologic studies show that a striking reduction in myelinated fiber size takes place under the carpal ligament at this point.[510] Interestingly, even in normal subjects the slowest nerve conduction occurs 2–4 cm distal to the origin of the ligament.[241] This finding suggests a mild compression of the median nerve at this particular level in some clinically asymptomatic hands. In fact, a histologic study[357] revealed focal abnormalities at this site in 5 of 12 median nerves at routine autopsy despite the absence of any symptoms suggestive of the carpal tunnel syndrome in life.[163]

Certain anatomical peculiarities may predispose some individuals to the entrapment neuropathy. These include limited longitudinal sliding of the median nerve under the ligament,[525] a smaller cross-sectional area of the tunnel,[36] greater anteroposterior diameter of the wrist,[175] obesity,[353,540] and small hand.[345] Any expanding lesion in the closed space of the carpal tunnel enhances compression. Wrist flexion and extension also substantially alter the cross-sectional areas of the carpal tunnel as estimated by magnetic resonance imaging[477] and the intracarpal tunnel pressure as measured by a catheter.[506] A measurement of cross-sectional areas of the carpal tunnel by computerized axial tomography, however, paradoxically revealed a significantly larger area in carpal tunnel patients than in controls.[555] A statistical analysis based on median and ulnar nerve comparisons of motor and sensory latencies may provide a useful risk prediction for the diagnosis of carpal tunnel syndrome.[130]

Carpal tunnel syndrome affects women more than men, most commonly in the fifth or sixth decade[491] showing a greater prevalence in older populations.[354,355] Age-related changes of median nerve conduction, however, also develop naturally, not necessarily leading to symptoms of compression.[199,353] The symptoms usually involve the dominant hand[352] or are contralateral to amputation[418] and show a higher incidence in those who use their hands occupationally[43,403] or for ambulation with a cane, crutch, or wheelchair.[518,541] Symptoms may appear during pregnancy and resolve after delivery. The

rare syndrome seen during the early ages[108] causes a characteristic feature of short-lasting but severe attacks of pain.[444] In contrast to the sporadic incidence in most adult cases,[192] rare familial occurrence prevails in children,[40,176,285,412] sometimes with anomalous thickening of the transverse carpal ligament.[326] Other associated abnormalities include insensitivity to pain in the mutilated hand.[23,505]

The syndrome also accompanies a variety of polyneuropathies and systemic illnesses.[10,188] Hereditary neuropathy with liability to pressure palsies should rank high in the differential diagnosis of familial carpal tunnel syndrome.[524,565] Patients with familial amyloidosis have a high incidence of carpal tunnel syndrome.[268,346,431] Certain secondary amyloidoses, especially those associated with multiple myeloma, may also give rise to neuropathy. Of the endocrine disorders, acromegaly[231,367] occurs most often, one study reporting 35 of 100 patients with evidence of the entrapment neuropathy.[367] Carpal tunnel syndrome occurs in a high proportion of patients with rheumatoid arthritis,[143] often as the initial manifestation of the tenosynovitis affecting the wrist flexor. Patients with rheumatoid arthritis may also develop thenar atrophy from disuse, cervical spine disease, or compression of the ulnar nerve at the elbow. Other conditions associated with a high incidence of carpal tunnel syndrome include eosinophilic fascitis,[215] myxedema,[450] lupus erythematosus,[469] hyperparathyroidism,[427] toxic shock syndrome,[443] Lyme borreliosis,[187] long-term renal hemodialysis,[161] fibrolipomatous hamartoma,[325] torsion dystonia,[118] and other conditions associated with prolonged wrist and finger hyperflexion.[111]

Symptoms may develop with extra tunnel pressure by an anomalous artery[546] or sudden growth of ganglion cysts.[230] A nonspecific tenosynovitis also gives rise to symptoms similar to those of idiopathic carpal tunnel syndrome.[229] 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[291] isolated fracture of capitatum[452] or hamate,[309] acute soft tissue swelling after crushing injury of the hand, and acute intraneural hemorrhage.[195] 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 carpal tunnel syndrome, with additional findings of local tenderness and firmness in the forearm.[154,456]

Differential diagnoses also include high median nerve compression at the elbow, a C6 radiculopathy, and traumatic injury at the wrist, including a handcuff neuropathy.[290] Carpal tunnel syndrome may accompany degenerative cervical spine diseases. This combination, called the "double-crush syndrome,"[523] probably represents a chance occurrence of two very common entities.[75,422] Nonetheless, an awareness of this possibility underscores the need of adequate electrophysiologic assessments because the presence of one condition does not preclude the other. Some series[67,458] but not others[52,192] report a high incidence of electrophysiologic evidence for median and ulnar nerve lesions at the wrist.

In typical cases of idiopathic carpal tunnel syndrome, paresthesias in the hand frequently awaken patients at night. 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.[78] The differential diagnosis rests in part on the symptoms of proximal lesions that are exacerbated 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 carpal tunnel syndrome. Compression can affect the peripheral autonomic fibers, causing defective vasomotor reflex. Thus, Raynaud's phenomenon may develop, especially in patients with systemic diseases such as rheumatoid arthritis. Sensory changes vary a great deal in early stages.[490] Hypesthesia involves the first three digits and the radial half of the fourth digit or, not uncommonly, only the

second or third digit. Patients may indeed complain of a sensory loss outside the median nerve distribution. In one large series, 83 percent of 384 patients had a sensory disturbance mostly consisting of hypesthesia often confined to the tip of the third digit.[397] Typically, 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.[468] Examination of the fourth digit usually reveals characteristic sensory splitting into median and ulnar halves, a pattern rarely seen in radiculopathies.

Because of early detection, patients now seldomly develop major wasting of thenar muscles, once considered a distinctive feature of the syndrome. Nonetheless, a comparison between the affected hand and the normal side often reveals a slight weakness. 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.

Passive flexion or hyperextension of the affected hand at the wrist for more than 1 minute may worsen the symptoms,[396] whereas a gentle squeeze of the hand may ease the pain.[307] Hyperextension of the index finger may exacerbate the symptom with volar forearm pain.[269] Percussion of the median nerve at the wrist causes paresthesia of the digits, although it has no localizing value in the carpal tunnel syndrome.[322,494] 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.[241] The phenomenon originally described by Tinel[513] relates to tapping the proximal stump of an injured nerve to elicit a paresthesia as an indication for axonal regeneration and not for entrapment neuropathy.[484] Symptoms of carpal tunnel syndrome worsen during ischemia of the arm. The factors that determine the degree of such susceptibility include the severity of pain and paresthesia but not the extent of muscle wasting or duration of symptoms.[149] These findings suggest rapidly reversible changes in the nerve fibers associated with ischemic attacks. Sharply focal structural changes seen in entrapment neuropathy, however, indicate that mechanical factors must play an important role in the pathogenesis.[150,371]

Simpson's original contribution[475] on carpal tunnel syndrome, demonstrating focal slowing at the wrist, paved the way for clinical conduction studies of this entity. Since then a number of investigators have published extensive studies.[51,164,166,207,219,274,323,396,509] Early work yielded a higher sensitivity of sensory conduction testing than studies of the motor axons.[52,323,509] In our series,[241] however, the sensory and motor axons showed a comparable incidence of abnormalities. In addition, we often encountered selective involvement of motor fibers, with normal sensory conductions or vice versa. Antidromic or orthodromic sensory conduction studies find more abnormalities when tested in all the median nerve innervated digits.[461] In one series,[302] digit 3 proved the most sensitive, whereas in other studies digit 1[259] and digit 4[507] provided a better yield than the others. Wrist flexion may delay motor or sensory conduction across the wrist,[310,455] but not to the extent of any diagnostic value.[123] Nerve conduction measures generally show a good relationship to the clinical symptom severity.[561] Electrophysiologic procedures have, however, become so sensitive that they cannot only confirm the clinical diagnosis in most patients but also detect an incidental finding in some asymptomatic subjects.[419] A sensible interpretation of the test results in the context of patients' symptoms and clinical findings avoids unnecessary or premature surgical intervention.[1]

Diagnostic studies should establish selective conduction abnormalities involving the wrist-to-palm segment of the median nerve for sensory or motor fibers.[49,52,97,109,240,241,288,384,391,435,489] In our series,[241] palmar stimulation elu-

cidated 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. Recording of the orthodromic sensory action potential also revealed more abnormalities with the addition of palmar stimulation.[103,334] Palmar stimulation is a simple means to differentiate compression by the transverse carpal ligament from diseases of the most terminal segment, as might be expected in a distal neuropathy. In advanced stages, however, the axons may degenerate distal to the entrapment. Conversely, retrograde changes may also occur in the forearm as a result of a severe compression at the wrist.[16,495,519] The loss of fast-conducting fibers also leads to slowed conduction velocity proximal to the site of the lesion if recorded from digits.[145] Mixed nerve conduction study in the forearm measures the segment of interest per se,[392,495] although a possible cutaneous palmar branch bypassing the carpal ligament confuses the issue.[190]

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. 6–7A,B). In about one half of the affected nerves, there is an abrupt latency increase across a 1 cm segment, most commonly 2–4 cm distal to the origin of the transverse carpal ligament.[241,351,354,355] 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. 6–7C,D). In the remaining hands, conduction delay affected more than one 1 cm segment across the carpal tunnel but was usually maximal at the site described above. Segmental studies of the motor axons in short increments are technically more demanding because of the recurrent course of the thenar nerve that varies anatomically from one subject to another.[214,241,545] Digital stimulation allows simultaneous multichannel recordings of the orthodromic sensory potential across the carpal tunnel for segmental latency studies.[201,242] The inability to compare the amplitudes and waveform of the responses recorded from different sites limits the clinical value of orthodromic incremental studies (see Chapter 7–6).

A number of other variations may improve the sensitivity of the motor and sensory conduction studies. The difference between the right and left sides, although useful with unilateral lesions, provides limited help in assessing a bilateral compression. With palmar stimulation, the simultaneous recording from the digit and the median nerve trunk at the wrist has the advantage of instantaneously assessing the latencies over the two segments.[301] Recording from two different sites, however, precludes an accurate amplitude comparison between the antidromic sensory potential and mixed nerve potential. Other measures include the relative latency change of the median sensory latency to radial, ulnar, or palmar cutaneous sensory latency for the same nerve length[63,69,390,521] and between median and ulnar motor latencies by lumbrical and interossei or thenar eminence recording.[407,408,446,517,531]

An interesting approach along the same line takes advantage of simultaneous stimulation of two nerves, for example, median and ulnar for recording of sensory potentials from the fourth digit or median and radial for recording sensory potentials from the first digit.[73,213,384,522] Recording from the fourth digit also allows comparison of median and ulnar nerve potentials elicited by palmar and wrist stimulation. The affected median nerve typically shows a distally elicited synchronized response and a proximally evoked temporally dispersed delayed potential, in sharp contrast to the nearly identical ulnar responses regardless of stimulus sites (see Chapter 6–2). These studies generally fail to serve as a useful test in patients with polyneuropathy.[83]

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,[260] and the terminal latency index decreases below the normal range[244,463,474] in patients with carpal tunnel syndrome. Even with complete denervation of the thenar muscles, the first and second lumbricals may main-

tain part of their innervation presumably because of a deeper location of their motor funiculi.[106,142] Recognition of lumbrical sparing thus helps establish the diagnosis especially in advanced cases with severe loss of axons supplying thenar muscles.[296] Conversely, lumbrical muscles may show a prolonged latency despite an otherwise normal motor study.[142] In advanced cases, electromyographic 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 carpal tunnel syndrome may aid in excluding other diagnostic possibilities.[86,170]

Other techniques of theoretical interest include quantitative studies of sensory thresholds[178,324] and strength-duration testing.[335] Quantitative somatosensory thermotesting may demonstrate impairment of thin nerve fiber function,[276] but the ulnar-innervated digit 5 may also show abnormal findings.[171] Some advocate the use of portable nerve conduction testing for screening, but its inability to measure the amplitude and waveforms poses a major limitation.[488]

Nonoperative measures sometimes suffice as the initial treatment[212] although some recommend early surgery.[553] Conservative therapy consists of patient education, wrist splinting, B vitamins, nonsteroidal anti-inflammatory medication, steroid injections, oral administration of steroid, and job change or modification.[72,194] Splinting works best if applied within 3 months of symptom onset.[264] Local steroid injections for symptomatic relief help confirm the diagnosis and treat the disorder. In one series, treatment with a single dose of 40 mg triamcinolone acetonide resulted in complete remission in 35 percent of patients and partial relief in 58 percent.[160] An inadvertent injection into the nerve can result in permanent damage.[293] Two practices can help avoid this complication: placing the needle carefully midway between the palmaris longus tendon and the flexor carpi ulnaris tendon at the proximal edge of the transverse carpal ligament in a line with the superficial tendon of the ring finger[146] and discontinuing injection and redirecting the needle if the patient experiences paresthesia of any kind. Some advocate noninvasive laser neurolysis as an alternative therapy, although its role in management awaits further study.[538]

If conservative therapy fails, division of the transverse carpal ligament is usually the standard operative procedure for unilateral and occasionally for bilateral release at one operation.[385] Carpal tunnel decompression also benefits patients with advanced thenar atrophy and sensory deficits[139,362] and those with underlying peripheral neuropathy.[339] Although surgery is usually successful, 7–30 percent of patients will have either residual or recurring symptoms.[93,381] Endoscopic release may shorten the convalescence time for return to work[7] provided the intraoperative safety and outcomes equal those of surgery.[45]

Digital Nerve Entrapment

The interdigital nerves supply the skin of the index and middle 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 is associated with trauma, tumor, phalangeal fracture or inflammation of the metacarpophalangeal joint or tendon.[256] 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 a steroid may relieve the symptoms and assist in diagnosis.[348] Abnormal median sensory potentials may result from unsuspected digital nerve lesions.[208]

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.[59] Ulnar neuropathy commonly results from a focal entrapment in the retroepicondylar groove or at the humeroulnar aponeurotic arcade joining the two heads of the flexor carpi ulnaris.[58] In one study of 130 cadavers, the humeroulnar arcade lay from 3–20 mm distal to the medial epicondyle, the intramuscular course ranged from 18–70 mm through the flexor carpi ulnaris, and the nerve exited the tunnel 28–69 mm distal to the medial epicondyle.[58]

Ulnar neuropathy at the elbow results from widely varying causes.[329] These include repeated trauma at the retrocondylar groove, pressure from immobilization of the upper limb during surgery,[536] entrapment by the accessory anconeus epitrochlearis muscle,[316] spontaneous intraneural hemorrhage,[405] and a gouty tophus.[9,533] Originally, *tardy ulnar palsy* implied antecedent traumatic joint deformity or recurrent subluxation. Many clinicians, however, now use the term for entrapment of the ulnar nerve at the elbow, even without a history of trauma. 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.[492] Classic clinical symptoms also appear with a more proximal involvement at Erb's point[225,261] or at the level of the upper arm after injections into the middle deltoid.[157] Ulnar nerve palsy at the elbow may also constitute part of diffuse neuropathy or develop concomitantly with lower cervical spine disease involving C8 and T1 roots or with the thoracic outlet syndrome.[347] In one study, ulnar sensory and motor nerve fibers showed similar conduction changes across the elbow in motor neuron disease. This finding casts doubt on double crush syndrome, which postulates the greater susceptibility of the proximally affected axons to a distal entrapment.[75]

Some reports emphasize the cubital tunnel syndrome as the most common discrete entity.[129,328,329] In this condition, nerve entrapment accompanies neither a joint deformity nor a history of major trauma.[128] A number of factors give rise to entrapment of the nerve under the aponeurosis connecting the two heads of the flexor carpi ulnaris.[330,502] Here, the nerve has the largest diameter,[71] may show palpable swelling in the ulnar groove, and appears hyperemic at surgery. Frequent hand use in the elbow flexed position narrows the cubital tunnel and exacerbates the symptoms.[328] In one study,[357] routine autopsy revealed focal pathologic changes at the aponeurosis in 5 of 12 presumably normal nerves. The appearance of bilateral ulnar neuropathy in a large number of patients suggests a congenital predisposition to this syndrome.[191,328,329] In fact, the asymptomatic contralateral nerve may show some involvement histologically in some cases of idiopathic ulnar neuropathy.[356]

The earliest clinical features include impairment of sensation over the fifth digit and the ulnar half of the fourth digit. 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 interosseous, causing an inability to adduct the fifth digit, or the Wartenberg sign. Electromyography further defines 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 supplied by a proximal branch. This distinction, however, does not necessarily hold as commonly believed, reflecting variable innervation patterns.[57]

Nerve conduction and electromyographic studies help localize the site of major pathology in these patients.[249,417] Some have localized slowing of motor or sensory conduction velocity across the elbow compared with the more proximal or distal segments.[475] Tests conducted with the elbow flexed rather than extended generally yield a more reliable result.[257] Test accuracy is improved by maintaining the identical limb position during recording and measuring the surface distance. Waveform changes provide a more sensitive measure than the generally accepted criteria for slowing of conduction exceeding 10 m/s.[373] The segment distal to the presumed compression may show mild

slowing[165] associated with a reduction in amplitude of the compound muscle action potential 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.[321]

Recording from the flexor carpi ulnaris supplements the conduction study in severe cases showing atrophy of the intrinsic hand muscles.[520] Recording a normal or nearly normal compound muscle action potential from a clinically weak muscle with distal stimulation indicates the presence of conduction block at a proximal site of compression. A drop in motor amplitude greater than 25 percent across the elbow usually localizes the lesion in this segment.[399] Stimulating the nerve at multiple sites across the cubital tunnel identifies the precise site of the lesion.[60,220,328] A nonlinear change in amplitude or latency or both serves as the most sensitive measure of a focal abnormality (see Chapter 7–5).[243] 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 some cases. Some electromyographers advocate near nerve recording for better localization.[372]

A strict nonoperative regimen should constitute the initial management of the cubital tunnel syndrome.[104] Surgical treatment consists of transposition,[193] simple decompression,[287,331] or interfascicular neurolysis.[358] Patients may have some functional recovery if operated on early.[273] Once a moderate degree of motor deficit has developed, symptoms persist after operative intervention in 30 percent or more of patients.[129] In selected cases, anterior transposition of the nerve results in good clinical and electrophysiologic improvement[148,253,409] even as a reoperation for failed decompression.[153]

Compression at Guyon's Canal

The ulnar nerve enters the hand through Guyon's canal at the wrist.[113] Nerve injury at this level, seen less commonly than at the elbow, has 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 Guyon's canal syndrome,[464] the responsible lesion may involve both deep and superficial branches of the ulnar nerve (type 1) or only the deep branch, thus producing the palmaris brevis sign or sparing of this muscle innervated by the superficial branch (type 2).[202,402] In either case, the other ulnar-innervated intrinsic hand muscles show weakness and atrophy as well as electromyographic evidence of denervation, whereas the flexor carpi ulnaris and flexor digitorum profundus III and IV function normally. 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 interosseous muscle most consistently. Predominant involvement of the superficial branch results in selective paralysis of the palmaris brevis and loss of sensation in the fifth digit and ulnar half of the fourth digit (type 3).

Entrapment in Guyon's canal most commonly results from a ganglion.[380] Less frequent causes include trauma, rheumatoid arthritis, tortuous arteries,[459] calcium deposits in Guyon's canal in scleroderma,[512] an accessory palmaris muscle that arises from the base of the fifth metacarpal,[420] and pisiform-hamate coalition.[30] Ganglions and fractures usually cause combined motor and sensory deficits or isolated motor weakness, whereas synovitis may cause isolated sensory loss.[267] The presence of a Martin-Gruber anastomosis may confuse the issue with an unusual presentation.[251] Handcuff neuropathy, which usually involves the superficial radial nerve, may also affect the ulnar nerve selectively or concomitantly.[449,457] Ulnar nerve compression in the distal forearm may result from the enlarged normally tendinous portion of the flexor carpi ulnaris.[56] A segment of the nerve may anomalously penetrate this tendon.[569] Surgical decompression generally improves the symptoms.[224,383]

In types 1 and 2, motor conduction studies reveal reduced amplitude and increased digital latency of the abductor dig-

iti quinti and first dorsal interosseous responses showing asymmetry between the affected and normal sides.[380] Other useful techniques include short incremental stimulation across the wrist[383] and comparison between ulnar and median motor latency by lumbrical and interossei recording.[258,465] Eliciting a normal sensory potential from the proximally branching dorsal ulnar cutaneous nerve usually localizes the lesion at the wrist,[209,235] although a lesion at the elbow could possibly spare this branch in partial involvement.[527] Reduced or absent ulnar sensory action potentials of the fourth and fifth digits indicate involvement of the superficial branch. The mixed nerve action potential between the wrist and elbow remains normal. Recording from the fourth digit provides a sensitive measure of comparison between median and ulnar nerve sensory amplitude and latency (see Chapters 6–2 and this chapter, part 5).

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[168,499] or by the arch of origin of the adductor pollicis muscles[439] or tumor.[413] 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.[127,189] Other entities reported include video-game palsy,[147] and pizza cutter's palsy.[437] 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 fourth and fifth digits.[364]

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 compound action potential recorded from the first dorsal interosseous, however, may show a prolonged latency and reduced amplitude compared with the unaffected side. Segmental stimulation of the motor branch in the palm can establish precise localization of the lesion along the course of the nerve (see Chapter 6–2). Electromyography shows selective abnormalities of the ulnar-innervated intrinsic hand muscles except for the abductor digiti minimi. These findings indicate slowing or block of nerve conduction distal to the origin of the hypothenar branch.[39,126]

7 NERVES OF THE PELVIC GIRDLE

Although traumatic injury rarely affects the lumbar plexus because of the protection afforded by the pelvic bones, individual nerves derived from the plexus may sustain isolated damage by either chronic compression or acute injury.

Ilioinguinal Nerve

The ilioinguinal nerve may be injured accidentally or during surgery. Patients with ilioinguinal neuropathy complain of pain in the groin region, especially when standing.[256] 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 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 lateral femoral cutaneous nerve, a purely sensory nerve,

causes a condition known as meralgia paresthetica. The damage usually occurs at the anterior superior iliac spine where the nerve emerges from the lateral border of the psoas major and sharply angulates over the inguinal ligament.[256] The precipitating factors include the compression of the nerve by tight belts, corsets, seatbelts, or prolonged postoperative hip flexion for relief of pain after abdominal incision,[205] although the symptoms may develop without obvious cause as the nerve penetrates the inguinal fascia. Pathologic changes consist of local demyelination and wallerian degeneration, particularly of the large diameter fibers.[210] Malignant tumor of the psoas and other lesions located above the inguinal ligament can mimic meralgia paresthetica and bear 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.[256] Patients with an L2 or L3 lesion may also have radiating pain along the lateral aspect of the thigh.[423] The absence of motor deficits clinically as well as electromyographically despite objective sensory loss tends to support the diagnosis of meralgia paresthetica. Electrophysiologic studies may reveal slowed sensory conduction across the compression site.[53,448,481] The use of dermatomal or cutaneous somatosensory evoked potentials advocated by some[271,547] provides only limited help because assessments over the long conduction pathway tend to dilute a focal delay (see Chapter 7–6). Conservative treatment suffices for most patients unless intractable symptoms call for neurolysis with transposition or, in some, sectioning of the nerve.[551]

Femoral artery reconstructive surgery may injure an anterior femoral cutaneous nerve.[28] Rarely a venous malformation surrounding the nerve compresses the posterior femoral cutaneous nerve.[81]

Femoral Nerve

An intrapelvic lesion of the femoral nerve may result from compression by tumors of the vertebrae, psoas abscesses, retroperitoneal lymphadenopathy, or hematoma.[89,232,563] Diabetes and vascular diseases also commonly cause femoral neuropathy. Fractures of the femur or cardiac catheterization may render direct nerve damage.[54,228,411,534] In hyperextension injury from the lithotomy position during surgery or gestational deliveries,[318] excessive hip abduction and external rotation stretches the nerve compressed at the inguinal ligament.[11] A complete lesion results in the inability to flex the thigh on the abdomen or to extend the leg at the knee, reduced or absent knee stretch reflex, and variable sensory loss. Partial femoral nerve lesions may selectively affect a single head of the quadriceps muscle.[66] Electrophysiologic studies show increased femoral nerve latency, reduced amplitude of the compound muscle action potential, and evidence of denervation in the appropriate muscles. In general, two thirds of patients show functional improvement in 2 years.[266] In individual cases, the estimated axonal loss based on compound muscle action potential amplitude is a good measure of prognosis.

Patients with diabetes may develop apparent mononeuropathy of the femoral nerve. The syndrome begins with pain in the anterior aspect of the thigh followed by weakness and atrophy of the quadriceps. In most patients, careful clinical and electromyographic examinations reveal more widespread involvement in the territory of the L2 through L4 roots, suggesting polyradiculopathy. Differential diagnoses should also include bilateral quadriceps tendon rupture usually associated with trauma,[428] or an underlying disease such as anabolic steroid abuse,[98] and renal failure.[223]

Saphenous Nerve

The saphenous nerve exits from Hunter's subsartorial canal, together with the femoral vessels.[256] 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[347] and worsens with any exercise such as climbing stairs.

Saphenous neuropathy, usually seen as a spontaneous entrapment syndrome, may also develop as a complication of orthopedic and vascular procedures performed on the medial area of the knee with the formation of a neuroma in the dissection site.[460] Further distally saphenous nerve lesions caused by bursitis as part of an athletic overuse injury may mimic stress fracture of the tibia.[198] Electrophysiologic studies reveal a slowed saphenous nerve conduction tested either orthodromically[496] or antidromically.[532]

Obturator Nerve

The obturator nerve may sustain selective damage during pregnancy or labor by pressure from a gravid uterus. Other causes of obturator nerve injury include pelvic fracture, surgical procedures for obturator hernia and pelvic cancer,[425] entrapment in the obturator canal by increased intra-abdominal pressure, and stretching at the bony obturator foramen during prolonged urologic surgery.[393] 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, as well as hypesthesia or dysesthesia over the medial aspect of the upper thigh. Electromyographic studies show evidence of denervation in the gracilis and adductor muscles.

Superior and Inferior Gluteal Nerves

The superior and inferior gluteal nerves, situated directly behind the hip joint, suffer damage from fractures of the upper femur, by misdirected intramuscular injection,[211,368] with compression from iliac artery aneurysms,[179] or following pelvic trauma.[508,552] 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.[416] Compromise of the inferior gluteal nerve documented electromyographically may herald clinical signs of recurrent colorectal carcinoma.[270] 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 compromises the gluteus maximus, which extends, abducts, and rotates the thigh externally.

Sciatic Nerve

Sciatic neuropathy[566,567] results 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, fractures of the pelvis, hip, or femur, or ischemia resulting from aortic occlusion.[278] Other uncommon compressive lesions include solitary primary lymphoma of the sciatic nerve,[400] popliteal artery aneurysm,[27] segmental neurofibromatosis,[470] unusually prominent lesser trochanter,[91] and acetabular fracture.[135] Sciatic endometriosis may cause cyclic sciatic pain and a sensory motor mononeuropathy.[445] Misdirected intragluteal injection may damage the sciatic nerve,[350] the inferior gluteal nerve, posterior femoral cutaneous nerve,[204] or pudendal nerve.[368] Penetrating wound, hip surgery, or insertion of a prosthesis may also traumatize the sciatic nerve. Baker's popliteal cyst, formed by an effusion into the semimembranous bursa, can compress the sciatic, peroneal, tibial, or sural nerve in any combination, especially with the knee extended.[348] Prolonged squatting compresses the sciatic nerve in the segment between the ischial tuberosity and trochanter major or between the adductor magnus and hamstring muscles.[476] A bilateral posterior compartment syndrome may cause sciatic neuropathy as a complication of a surgical procedure performed with the patient in the sitting position. Nerve conduction studies and electromyography help delineate the extent and distribution of the abnormality.

The possible causes of isolated sciatic neuropathy in childhood include, in addition to compressive lesions, stretch injury during operation, traction injuries during breech deliveries,[486] puncture wound, lymphoma, eosinophilic vasculitis,[216] entrap-

ment by a fibrovascular band,[528] complication of umbilical vessel catheterization,[441] gluteal intramuscular injection,[95] and compressive injury in utero.[467]

The pyriformis muscle may rarely entrap the nerve as it exits the pelvis through the greater sciatic notch.[125,256] The pyriformis syndrome may also result as a complication of an operation performed with the patient in the sitting position[44] and from neural compression by a pseudoaneurysm of the inferior gluteal artery[386,387] or arteriovenous malformation of the pyriformis muscle.[96] Unlike more proximal lesions, it selectively involves the gluteus maximus, sparing the gluteus medius, gluteus minimus, tensor fasciae latae, and paraspinal muscles clinically and electromyographically. For such a focal lesion not accessible to segmental stimulation, conventional nerve conduction studies provide little, if any, clinically pertinent information. Some authors reported the clinical value of the H reflex latency, which changes following forcible contraction of the pyriformis muscle as a provocative test.[141]

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.[341,501,526] 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. Proximal sciatic nerve injury may elicit distally projected sensory symptoms, mimicking tarsal tunnel syndrome.[173] Studies of the H reflex or F wave or direct needle stimulation of the nerve at the radicular level and sciatic notch[303] may reveal conduction abnormalities in these cases.

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.[480] 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 can selectively involve the superficial branch,[502] which may show a number of anatomical variations.[4] Other uncommon compressive lesions include intraneural synovial cyst[365] and intraneural ganglion,[286] identifiable only after the incision of epineurium.[404] Prolonged squatting or sitting down in a kneeling position (considered good manners in Japan) may compress the peroneal nerve against the biceps tendon, the lateral head of the gastrocnemius, or the head of the fibula.[21,255,502] Unilateral peroneal nerve paralysis has developed during intended weight reduction,[479] following the use of an exercise bicycle,[185] as a complication of proximal tibial osteotomy,[252] from the lithotomy position during gestational deliveries,[85] and perioperatively during liver transplantation.[548] Peroneal neuropathy in a newborn may have a prenatal onset.[217]

Injury to the deep branch weakens the toe and foot dorsiflexors with sensory changes over the web of skin between the first and second toes. Lesions of the superficial branch affect eversion and plantar flexion with sensory deficits over most of the dorsum of the foot. Preservation of the ankle reflex and the ability to invert the foot normally distinguishes a peroneal nerve palsy from a sciatic nerve lesion in patients with footdrop. The tibialis posterior receives L4 and L5 innervation via the tibial nerve. Thus, a needle study of this muscle helps differentiate between peroneal palsy and L5 radiculopathy.[197] Foot drop may also result from a lesion of the peroneal division at the level of the sciatic nerve. Differentiation depends on electromyographic exploration of the hamstring muscles, especially the short head of the biceps femoris innervated by the peroneal component of the sciatic nerve.

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 by more than 20 percent from distal to proximal stimulation usually indicates a localized lesion at the compression site.[398] In our experience, incremental segmental stimulation serves as the most sensitive measure by revealing a nonlinear change in latency, amplitude, or waveform at the site of focal lesion. In one series, contrary to common belief, one half of the patients showed axonal loss, one fourth showed conduction block, and the remaining one fourth had a mixed pattern.[226] In another study, the extensor digitorum brevis tended to show signs of axonal degeneration, and anterior lateral compartment muscles had evidence of conduction block.[47] A smaller response elicited by distal compared with proximal stimulation suggests the presence of an accessory deep peroneal nerve. In these cases, a proximal shock at the knee but not distal stimulus at the ankle excites the anomalous fibers,[275] giving rise to the amplitude discrepancy (see Chapter 7–4). 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.[226,549] 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.[262] Nerve conduction studies show increased distal motor latency with stimulation of the deep peroneal nerve proximal to the inferior extensor retinaculum.[440] Electromyography in anterior tarsal tunnel syndrome reveals evidence of denervation in the extensor digitorum brevis and other appropriate muscles. Spontaneous discharges in the intrinsic foot muscles, however, may simply reflect chronic nerve damage caused by wearing a tight shoe.[133] The presence of fibrillation potentials compared with insertional positive sharp waves provides a more reliable indicator of true pathology.[156] A fascial band may compress an accessory sensory branch of the superficial peroneal nerve, which traverses the lateral malleolus laterally.[438]

9 TIBIAL NERVE

The tibial nerve, because of its deep location, rarely sustains injury in the posterior compartment of the thigh or leg. Occasional compression by the flexor retinaculum as it passes behind the medial malleolus causes tarsal tunnel syndrome.[110,174,483] It may result from trauma, tenosynovitis, venous stasis of the posterior tibial vein, or a ganglion arising from the subtalar joint. In our experience, most, if not all, patients with idiopathic tarsal tunnel syndrome have an underlying neuropathic condition such as overt or subclinical diabetic polyneuropathy. A patient with a more proximal lesion such as a tumor of the tibial nerve may show signs and symptoms of the tarsal tunnel syndrome possibly because of venous thrombosis in the calf.[20,550] The clinical features consist of painful dysesthesia and sensory deficits in the toes and sole and weakness of the intrinsic foot muscles. Electromyography reveals evidence of denervation in the intrinsic foot muscles supplied by the tibial nerve.

In the tarsal tunnel syndrome, nerve conduction studies show increased motor latencies along the medial or lateral plantar nerve with stimulation of the tibial nerve slightly above the medial malleolus. Additional stimulation of the nerve slightly below the malleolus may document segmental slowing across the compression site. 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. Near-nerve sensory conduction of the medial and lateral plantar nerve elucidates slowed velocities and abnormal temporal dispersion in most cases.[375,377] These findings indicate a focal segmental demyelination as the primary pathologic process. The conduction studies on the clinically unaffected side serve as a control. Both motor and sensory conductions improve after surgical decompression.[374]

The nerve may undergo rare compression more proximally in the popliteal fossa or more distally as it enters the abductor hallucis muscle. A lesion distal to the flexor retinaculum results in a deficit of either the medial or lateral plantar branch of the tibial nerve.[376] The patient complains of pain and sensory changes in the plantar aspect of the foot but not in the heel. Anterior heel pain syndrome may result from isolated injury of the inferior calcaneal nerve, which innervates the abductor digit quinti as the first branch of the lateral plantar nerve.[26,388] The medial plantar proper digital nerve arises from the medial plantar nerve as a terminal sensory branch. Its selective injury or compression causes a focal neuropathy, Joplin's neuroma.[82] Useful diagnostic techniques include electromyography of the intrinsic foot muscles and conduction studies of the medial and lateral plantar nerves[182,378] and medial calcaneal nerve.[388]

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.[347] 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.[410] Baker's cyst,[348] use of a combat boot,[453] or stretch injury.[180] Its superficial location makes the sural nerve suitable for diagnostic biopsy. 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. Nerve conduction studies help delineate the lesion.[180] Some investigators advocate combination of neurophysiological and ultrasound findings in evaluating sural nerve lesions.[478]

11 OTHER MONONEUROPATHIES

Hypertrophic Mononeuropathy

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.[472] If this condition of unknown etiology affects the tibial nerve, the patient develops progressive wasting of the leg muscles.[203]

Idiopathic Mononeuropathy

An unusual clinical entity described in young patients shows insidiously progressive, painless weakness in the distribution of a single major lower limb nerve.[131] Electrophysiologic and histologic findings suggest a chronic axonal mononeuropathy without conduction block or focal slowing.

Postherpetic Neuralgia

Focal weakness of an arm may follow segmental herpes zoster affecting the same

limb. Neurophysiologic investigation has localized the lesion at the root, plexus, or peripheral nerve level.[84,442] In one series,[184] 21 of 40 patients had evidence of denervation, suggesting widespread subclinical motor involvement. Another study[337] found no correlation between the degree of postherpetic neuralgia and electrophysiologic abnormalities, with the inference that pain has little to do with damage to the large diameter sensory fibers in this condition. Topical application of aspirin dissolved in chloroform induces prompt relief of pain for 2–4 hours.[250]

Sports Injury

In one study[263] involving 169 athletes, 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, and peroneal mononeuropathies. Bodybuilders also develop rare mononeuropathies of the upper limb, most commonly involving thoracodorsal, dorsoscapular, suprascapular, and medial pectoral nerves.[336] Acute focal neuropathies also affect weight lifters, who develop usually sudden, painless weakness in a muscle supplied by a terminal motor nerve branch.[34]

Musicians' Entrapment Neuropathy

Many instrumental musicians suffer from entrapment neuropathies, most commonly carpal tunnel syndrome and ulnar neuropathy.[304] The available information regarding ulnar neuropathy suggests that violinists and violists tend to develop symptoms depending on their playing position.[282,283,284] Ulnar neuropathy may initiate or sustain a hand dystonia by inducing a central disorder of motor control.[74] Conservative treatment, which provides relief for a substantial percentage of patients,[29] consists of a modification in playing technique or time, splinting, and medication.[283] Surgical decompression is an effective alternative. The specific diagnoses most likely to require surgery include trigger digits, carpal tunnel syndrome, ulnar nerve entrapment, rheumatoid arthritis, and Dupuytren's contracture.[102] Nerve conduction and electromyographic studies help confirm the diagnosis, establish the extent and type of pathology, detect coexisting peripheral nerve disorders, and determine the efficacy of therapy.[304]

Traumatic Mononeuropathy

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 compound action potentials and days 5–7 for sensory nerve action potentials.[76,379] With complete axonal degeneration, conduction studies alone cannot provide 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.[254] In studies of finger amputation and toe-to-digit transplantation, early surgical intervention prevented retrograde degeneration, improving recovery of function.[79,80]

Perioperative Mononeuropathy

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.[548] In another study,[62] 10 percent 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 travelling in the vicinity for different reasons such as compression, traction, and ischemia.[172,360] These include the peroneal division of the sciatic nerve,[227] femoral nerve,[471] and gluteal nerve,[3] and superior gluteal nerve.[114]

Reflex Sympathetic Dystrophy

Patients with reflex sympathetic dystrophy, or causalgia, if it follows a definable nerve injury, suffer from sustained burning pain and local tissue changes. The skin manifestations usually involve the entire limb and in most instances consist of color and temperature changes, often associated with edema and bony atrophy. Changes in peripheral blood flow may result from supersensitivity to sympathetic neurotransmitters, which also contributes to spontaneous pain and allodynia by disrupting efferent sympathetic modulation of sensation. The impairment of high-energy phosphate metabolism suggests reduced oxygen extraction in the affected limb.[196] Sympathetic blocks lead to a temporary reduction of these symptoms. During the block, even vigorous mechanical and cold stimuli fail to rekindle hyperalgesia, which presumably results from sensitization of central pain-signaling neurons to mechanoreceptor input.[514]

A normally painless signal from the low threshold afferents could activate the abnormally hyperexcitable pain-transmitting dorsal horn neurons, thus explaining stimulus-induced hyperalgesia.[298] Normal spontaneous sympathetic input to tactile mechanoreceptors might drive such afferent activity to maintain the vicious circle. This interaction would not only explain sympathetic dependence of the spontaneous pain but also relief of the symptom by blocking the normal sympathetic efferent.[424] Thus, sympathetic efferents excite tactile afferents, which in turn drive chronically hyperexcitable central nociceptors.[61,177] This feed-forward loop concept, advocated by some,[61,414] is questioned by others,[370,529] for the reasons described below.

Although reflex sympathetic dystrophy 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.[24,117,369,389] Psychologically mediated symptoms further confound the evaluation of patients with chronic pseudoneuropathic pain.[530] 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.[119] 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 release of substance P, calcitonin gene-related peptide, and histamine at the injury site, causing ectopic firing of peptidergic fibers and vasodilation.[35,279,568] Substance P together with histamine released from mast cells also promotes plasma extravasation. A 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, or wind-up, of pain-signaling dorsal horn neurons in response to single or repeated stimuli.[18] The central effects of the nociceptive response occur at NMDA receptor sites and are mediated by excitatory amino acids such as glutamate and aspartate. Thus, NMDA antagonists can reduce central hyperexcitability, inhibiting hyperalgesia and neurogenic pain.[17,557]

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Part VII

DISORDERS OF MUSCLE AND THE NEUROMUSCULAR JUNCTION

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Chapter 27

MYASTHENIA GRAVIS AND OTHER DISORDERS OF NEUROMUSCULAR TRANSMISSION

1 INTRODUCTION

Despite the early clinical description of myasthenic syndromes,[135] only recent work has elucidated the pathophysiology underlying disorders of neuromuscular transmission, correlating morphologic abnormalities with physiologic alterations in the kinetics of acetylcholine (ACh) release (see Figs. 9–1 and 9–2). Current evidence clearly implicates the postsynaptic ACh receptor as the site of pathology in myasthenia gravis. In contrast, presynaptic defects of ACh release characterize the Lambert-Eaton myasthenic syndrome and botulism. Although such a dichotomy helps simplify the classification of pathogenesis, the exact physiologic or morphologic basis of various myasthenic syndromes re-

mains 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 acetylcholinesterase.[83]

Physicians must always consider defects of neuromuscular transmission in any patient with unexplained weakness[287] because many of these disorders are potentially treatable by immunosuppression.[73] Diagnostic possibilities include not only primary diseases of the neuromuscular junction but also abnormalities of the nerve terminals seen in motor neuron disease and certain types of neuropathy. Electrodiagnostic studies help confirm and categorize the abnormalities.[63,249,252]

2 MYASTHENIA GRAVIS

Myasthenia gravis has an incidence of approximately 1 per 20,000 in the United States,[211,218] primarily affecting young women in the third decade and middle-aged men in the fifth and sixth decades, although the age-specific incidences show a bimodal distribution for both genders.[278] Women have a slightly higher overall average incidence by a ratio of 3:2. Children account for 11 percent of all patients with myasthenia gravis.[218] The female predominance in children changes with the disease onset, increasing from prepubertal to postpubertal stages, suggesting a modulating role of sex hormones.[6] The disease usually occurs sporadically, although about 5 percent have a familial incidence. The symptoms and signs tend to appear between the second and fourth decades.

Etiologic Considerations

Findings in support of the autoimmune hypothesis[226–269] include the development of thymoma in 10 percent and thymic hyperplasia in 70 percent of patients with myasthenia gravis.[81] Patients may also have other potentially immunologic diseases such as thyroiditis, hyperthyroidism, hypothyroidism, polymyositis, systemic lupus erythematosus, Hodgkin's disease,[295] transverse myelitis,[160] multiple sclerosis,[276] stiffman syndrome,[193] chronic inflammatory demyelinating polyneuropathy,[122] human immunodeficiency virus type 1 (HIV-1) infection,[13,59,60,304] and rheumatoid arthritis.[279] These disorders accompany myasthenia gravis with an incidence clearly higher than might be expected for coincidental association as reported for some other systemic disease such as Charcot-Marie-Tooth disease[46] or a seizure tendency.[274] Furthermore, 20 percent of infants born of myasthenic mothers have transient myasthenia following transplacental transfer of antibody. In contrast, a patient with HIV-1 infection may show clinical improvement of myasthenia gravis as the disease progresses, with a decline in cellular immune responses and ACh receptor antibody titers.[13,188,244] Similarly, proteinuria may cause remission followed by exacerbation after treatment of the nephrotic syndrome.[4,127]

About 80 percent of patients with myasthenia gravis have antireceptor antibodies.[52,108] Cytokines produced by $CD4^+$ and $CD8^+$ T helper cells mediate their production.[325] In addition, patients with thymoma tend to have anti–striated muscle (STR) antibodies, which may cause a defective release of Ca^{2+} from the sarcoplasmic reticulum.[125,221,222] In paraneoplastic myasthenia gravis, detection of anti-MGT30 (titin) antibodies may predict thymic epithelial tumor better than immunofluorescence assay of anti-STR antibodies.[309] Children with transient neonatal myasthenia gravis also have elevated antireceptor antibodies, which is one of the best indicators of the disease.[180] In one series of 221 patients, 18.5 percent had no detectable antibodies. These included 7 of 14 patients with only ocular symptoms and 25 of 145 patients with generalized myasthenia.[275] Antireceptor antibody assays fail to adequately discriminate between congenital myasthenia gravis and prepubertal onset juvenile myasthenia gravis characterized by a high frequency of seronegativity.[6,323] Patients with seronegativity also have a favorable response to thymectomy or plasmapheresis, indicating the presence of nondetectable antibodies.[40] Seronegative cases may have atypical electrophysiologic findings.[199] False-positive results, although

rare, may occur in penicillamine-treated or thymoma patients without myasthenia gravis, bone marrow transplant recipients, patients with Down syndrome, tardive dyskinesia, primary biliary cirrhosis, or amyotrophic lateral sclerosis, and, in the presence of thyroid or mitochondrial antibodies.[277]

Animal studies also suggest the presence of a circulating immunoglobulin and altered cellular immunity.[72,102,156,265] Passive transfer of a certain serum fraction from patients causes myasthenic features in mice histologically as well as electrophysiologically.[169] Injection of the nicotinic ACh receptor protein from the electric eel into the rabbit or monkey with Freund's adjuvant sensitizes the animal. After a second injection, many animals develop myasthenic features that improve with the administration of an anticholinesterase.[291] Thus, an immunologic abnormality must play a role in the destruction of the membrane architecture. Experimental studies in mouse muscle further indicate that immunoglobulins play an important role[181] and that this process requires a heat-sensitive factor.[158] The ACh receptor subunits found in the thymus alone, however, are not sufficient to produce myasthenia gravis.[130] Immunization of rats with thymus extracts also failed to produce a myasthenia-like condition.[184]

Histometric studies of motor endplate ultrastructure[86] 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. A decreased number of functional ACh receptors is demonstrated by binding of alpha bungarotoxin.[93,124,298] Myasthenic muscles contain IgG and complement bound to the postsynaptic membranes. These observations clearly implicate the ACh receptor in the pathogenesis of myasthenia gravis. A human study of the biopsied intercostal muscles revealed not only the failure of neuromuscular transmission but also reduced excitation–contraction coupling and contractility as the cause of myasthenic weakness.[221]

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.[142,193] Symptoms initially appear toward the end of the day or after strenuous exercise. Patients usually have weakness confined to restricted groups of muscles.[229] 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.[66] Less frequently, isolated bulbar or respiratory muscle weakness constitutes the presenting symptom.[167,176] Paralysis of palatal and pharyngeal muscles, seen in about one third of the patients, results in nasal speech and difficulty in swallowing and chewing. Patients rarely complain of generalized weakness of the trunk and extremities or of urinary and fecal incontinence[23,286] as the initial symptom. Paralysis worsens with elevation of body temperature[31,110] or following administration of certain drugs such as magnesium,[19] chloroquine,[238] β-blockers,[55,129] calcium channel blockers,[285,320] imipenem,[213] cocaine,[22,62] and interferon-alfa.[20]

Characteristic physical signs include a wide spectrum of ocular disturbance, ranging from nystagmus to complete ophthalmoplegia. Pupillary dysfunction may develop[157] as an exception to the rule that the disease affects only the striated muscles. Ptosis, if present as an early sign, may alternate between the two sides. Disturbance of ocular muscles, not confined to the distribution of a single nerve, varies from one examination to the next. Weakness of the orbicularis oris and other muscles of the lower face produces a characteristic, expressionless myasthenic face. To compensate for the weakness of the neck extensors, patients support the chin

with the hand. This maneuver also facilitates chewing and swallowing at the end of a meal despite the weakened muscles of mastication. Speech may deteriorate with fatigue, showing a flaccid dysarthria. Involvement of the respiratory muscles, common in advanced cases, poses a major threat to life. Some patients develop generalized or focal muscular atrophy.[321] Others show a limb-girdle distribution of weakness, presenting a diagnostic challenge.[119,206] The sensory examination reveals no abnormality.

The clinical courses vary, often showing remissions and exacerbations. Approximately one third of the patients improve spontaneously, some nearly completely, requiring no further medication.[210] 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 importantly, overmedication. Some patients develop respiratory failure or pneumonia. Although unpredictable, the disease commonly worsens during early pregnancy, followed by improvement later on. In the mildest form of the disease, weakness is 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 percent of such patients will have no further progression of symptoms.[217,229]

Semiquantitative assessment is useful in clinical evaluation with serial measurements of sustained upward gaze, grip dynamometry, vital capacity, and arm abduction. 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.[312] 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, which binds with the lactate produced during ischemic exercise.[227] Similarly, citrate used for anticoagulation during plasmapheresis reduces serum ionized calcium levels, thus aggravating myasthenic weakness at the end of exchange sessions.[319] Myasthenic muscles have characteristic hypersensitivity to curare, although the finding is common to any disorder with defective neuromuscular transmission, such as motor neuron disease, ocular myopathy, and antibiotic toxicity.

In previously untreated cases, an intravenous administration of edrophonium (Tensilon) 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 5–10 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, administration of the longer acting neostigmine (Prostigmin) may improve the strength more appreciably. Administration of edrophonium may improve the clinical signs in some cases of Lambert-Eaton myasthenic syndrome, botulism, congenital myasthenic syndrome, drug-induced myasthenia, Guillain-Barré syndrome, and amyotrophic lateral sclerosis.[200]

Differential diagnoses comprise all diseases characterized by weakness of ocular, bulbar, or limb muscles.[131] These include muscular dystrophy, motor neuron disease, progressive bulbar palsy, multiple sclerosis, ophthalmoplegia, pseudobulbar palsy, and psychoneurosis. Patients with myasthenia gravis 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 of myasthenia gravis by lowering the margin of safety in neuromuscular transmission.[30,267] Here, distinction from multiple sclerosis may prove difficult, especially if the patient presents with pseudo internuclear ophthalmoplegia.[162] Routine muscle biopsy has limited diagnostic value. Type II fiber atrophy, although commonly seen in myasthenia gravis, can also result from disuse or corticosteroid treatment.

Effective therapeutic regimens include thymectomy, steroids, and immunosup-

pressive drugs.[186] In general, thymectomy is the treatment of choice for any symptomatic patients in the absence of surgical contraindications.[69,96,215,317] Some advocate thoracoscopic thymectomy.[245,284] For an invasive thymoma, treatment consists of total excision, if possible, and high doses of corticosteroids and combination chemotherapy for the remaining tumor.[311] In one series, the incidence of stable remission peaked at 2 years when treated with thymectomy alone and at 5 years with additional immunosuppressive therapy.[74] Administration of prednisone may cause acute inhibition of neuromuscular function. Patients then have increased decremental response to repetitive nerve stimulation, reduced twitch tension, and lowered force of maximum voluntary contraction.[177] As an alternative therapy, 3,4-diaminopyridine, which enhances ACh release, improves congenital or hereditary myasthenia, which comprises a heterogeneous group of disorders without immune abnormalities.[223] Plasma exchange induces a rapid improvement of neuromuscular transmission over 1–4 weeks in some patients.[195]

Neuromuscular functions improve in correlation with plasma drug levels of pyridostigmine.[35] Conversely, its overdose causes typical anticholinesterase toxicity with repetitive discharge and the maximal decrement in the second response followed by an increment.[224] Careful therapeutic management does not necessarily preclude the occurrence of myasthenic crisis, a potentially life-threatening complication that requires aggressive therapy.[214] Patients often improve after the initial treatment with intravenous immunoglobulin, which may rarely cause the complication of aseptic meningitis.[76] Those who fail with this regimen may respond to intensive plasma exchange.[282] Intranasal neostigmine also produces acute clinical and electrophysiologic improvement.[234]

Electrophysiologic Tests

Electrophysiologic studies play an important role in establishing the diagnosis of myasthenia gravis.[126] The incidence of a decremental response to repetitive nerve stimulation varies widely from 41 percent in one laboratory[253] to 95 percent in another.[219] In general, 65–85 percent of patients show a positive result, after a comprehensive survey from multiple recording sites.[202] Despite technical difficulties with movement artifacts, an adequate set of tests must include recordings from proximal muscles. Studies of distal muscles provide more consistent results but have less sensitivity. To compromise, one can proceed from the easily immobilizable intrinsic hand muscles to the anconeus, and then to the deltoid, trapezius, or other shoulder girdle muscles, and finally to the facial muscles. Warming the muscle increases the test yield (see Fig. 10–1). When conventional studies yield equivocal results, ischemic sensitization[305] or regional administration of curare may lower the margin of safety sufficiently to produce a clear abnormality,[38] but the technical complexity limits the clinical value of ischemic and curare tests in routine practice (see Chapter 11–2).

A single stimulus elicits a compound muscle action potential of a 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. 9–6 and 9–8). The amplitude drops maximally between the first and second responses of a train with less changes for the next few peaks and subsequent partial recovery or repair. According to generally accepted criteria, at least two muscles should show a reproducible reduction of more than 10 percent 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, intravenous administration of edrophonium will usually normalize the response partially or completely. A brief voluntary exercise for 15–30 seconds also repairs a bona fide tendency for decrement during subsequent trains, a phenomenon called *post-tetanic potentiation.* In contrast, amplitude diminution within a train exceeds the

preexercise value 2 to 4 minutes later during *posttetanic exhaustion.* Again, an additional 5 s of exercise will partially correct the change. Persisting changes may suggest technical factors rather than defective neuromuscular transmission. Thus, brief voluntary exercise helps differentiate an abnormal response from a movement artifact (see Fig. 10–4).

Electromyography shows varying amplitude and configurations of recurring motor unit potentials. Although unpredictable, the initial few discharges tend to decrease progressively in size and duration. Fibrillation potentials and positive sharp waves, if present, indicate the loss of innervation in severely affected muscles. Single-fiber electromyography (SFEMG) is one of the most sensitive measures of neuromuscular transmission abnormalities.[251,280] Clinically strong muscles that show no decrement to repetitive nerve stimulation may show increased jitter.[100] 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.[297] In most studies, the severity of disease correlated better with the degree of jitter than with the antibody titer to ACh receptor.[143,204] In one series of 43 patients with mild myasthenia gravis who showed normal repetitive stimulation tests, SFEMG detected abnormalities in 79 percent, anti-ACh receptor antibodies in 71 percent, and Lancaster red-green tests in 81 percent.[137] In another study, these three tests complemented each other in confirming the diagnosis.[126] SFEMG studies of the extraocular muscles[237] and, to a lesser extent, of the orbicularis oculi[199] and frontalis muscles[241] also serve as a good measure for ocular myasthenia. Normal SFEMG in the limb muscles tend to refute future development of generalized myasthenia gravis in patients with restricted ocular symptoms.[316]

Occasional patients with myasthenia gravis show the electrophysiologic features more typically associated with Lambert-Eaton myasthenic syndrome. Such cases suggested the existence of an intermediate disorder characterized by defective ACh release as well as diminished numbers of ACh receptors.[61,201] Although microelectrode studies have provided no convincing evidence to support such a contention in most such cases, immunologic evidence suggests the coexistence of the two entities in a few reported patients (see this chapter, part 3).[190] In general, Ach release progressively declines with low rates of stimulation and enhances with high rates of stimulation (see Chapter 9–5). These physiologic phenomena result in clinical and electrophysiologic abnormalities if the margin of safety diminishes in the presence of defective neuromuscular transmission (see Fig. 9–8). In the same patient, some muscles may demonstrate an abnormal pattern typical of myasthenia gravis, whereas others may show changes reminiscent of the myasthenic syndrome. The size of the first compound muscle potential often dictates the response pattern to repetitive stimulation. For example, an initially subnormal response tends to show an increment during a train of rapid stimulation even in patients with myasthenia gravis, whereas a full response has no room to enhance (see Fig. 9–7).

3 LAMBERT-EATON MYASTHENIC SYNDROME

The Lambert-Eaton myasthenic syndrome[75] affects men twice as commonly as women, with onset usually after age 40 years, although rare cases have involved children 4 and 9 years of age.[14,45] A clear association with malignancy is key to elucidating the mechanism that leads to a defective release of Ach. Recent accumulated evidence indicates the presence of autoantibodies that block ACh release by interfering with the voltage-gated influx of calcium at the nerve terminal.[54,150,159,189,209]

Etiologic Considerations

More than 50 percent of affected patients have small cell carcinoma of the bronchus, the most common tumor seen in conjunction with this syndrome.[283] A careful search reveals a malignant neoplasm in about 75 percent of men and 25 percent

of women, but not necessarily at the time of initial neuromuscular symptoms. In one series, a 62 percent risk of an underlying small cell lung cancer was estimated, which declined sharply after 2 years, becoming very low at 4–5 years.[209] Thus, the malignancy may escape detection for many months or, occasionally, for many years after the onset of the myasthenic syndrome. With adequate follow up, however, only 30 percent of the patients remain free of cancer.[149] The tumors include reticulum cell sarcoma,[240] rectal carcinoma,[41] renal carcinoma,[42] basal cell carcinoma of the skin,[289] leukemia,[263] malignant thymoma,[152] and lymphoproliferative disorders.[10] Systemic disorders associated with the syndrome include thyrotoxicosis,[196] Sjögren's syndrome,[39] rheumatoid arthritis,[289] systemic lupus erythematosus,[36] and other autoimmune disorders.[111]

Histometric studies of motor end-plate ultrastructure[90] have revealed overdevelopment and increased area of the postsynaptic membrane (see Fig. 9–2). The nerve terminal retains a normal mean synaptic vesicle diameter and mean synaptic vesicle 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 a low frequency of discharge of the miniature end-plate potential (MEPP) of normal amplitude.[77] The initially low mean quantum content of the end-plate potential (EPP) increases with repetitive nerve impulses.[147] 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 myasthenic syndrome must result from presynaptic abnormalities that lead to a reduced number of ACh quanta released per volley of nerve impulse. In an experimental setting, high magnesium or low calcium ion concentrations block neuromuscular transmission. Thus, a similar syndrome may also occur as an adverse effect of the calcium antagonist diltiazem.[301]

Immunoglobulin G (IgG) obtained from patients inhibits voltage-gated calcium flux in tumor cells, showing a good correlation with physiologic indexes of clinical severity.[150] IgG autoantibodies also inhibit calcium channels, diminishing transmitter release at the motor terminals.[109,148,155,232,273] When applied in vitro on a short-term basis, however, the autoantibodies do not consistently reproduce the physiologic abnormality.[141] In pharmacological experiments using antibody from patients, Q-type voltage-gated calcium channels were closely linked to the genesis of the parasympathetic response.[118,308,314,315] In one series of 36 patients,[159] 44 percent had a significant level of antibody. Antibody titers against voltage-gated calcium channel did not correlate with disease severity across individuals, but longitudinal studies showed a clear positive relationship between antibody titer and physiologic scores of clinical abnormalities.

The pathogenesis centers on the presence of autoantibodies to voltage-gated calcium channels and the related structures demonstrated in the patient's tumor.[54] Findings vary among 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 immunological evidence for the coexistence of the Lambert-Eaton syndrome and myasthenia gravis.[190] In these cases, radioimmunoassays detected serum antibodies to voltage-gated calcium channels, the antigenic target in the myasthenic syndrome, as well as to ACh receptors, the antigen in myasthenia gravis.

Clinical Signs and Symptoms

In striking contrast to the fatigue phenomena in myasthenia gravis, weakness in the myasthenic syndrome peaks after rest or immediately upon awakening in the morning. Strength tends to transiently improve with brief exercise, although it is not sustained during a prolonged effort. Weakness and fatigability primarily affect

the lower limbs, particularly the pelvic girdle and thigh muscles.[209] 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.[132] This distribution of weakness stands in sharp contrast to the typical patterns seen in myasthenia gravis with conspicuous bulbar symptoms such as ptosis, diplopia, dysphagia, and dysarthria. In the presence of ptosis, patients may have paradoxical improvement in lid elevation with sustained upgaze,[34] which is opposite the expected exacerbation of ptosis after exercise in myasthenia gravis. Some patients may remain asymptomatic until challenged by the administration of neuromuscular blocking agents, which may uncover the deficit by prolonged recovery.[163] Others may develop rapid respiratory failure as the first manifestation of disease.[18,28,194] Patients often complain of dryness of the mouth and, less frequently, impotence, paresthesias, and dysautonomia. These symptoms suggest that the defect of ACh release, not restricted to skeletal muscle, may affect the autonomic nervous system predominantly causing parasympathetic dysfunction.[51,116,140,216,242] Peripheral neuropathy and subacute cerebellar degeneration may develop probably as manifestations of a paraneoplastic syndrome.

Neurologic evaluation reveals marked weakness of the proximal muscles in the lower limbs, which appreciably improves after exercise. With each successive effort, the resistance needed to overcome the patient's strength increases, giving the examiner a sensation similar to drawing up water from a well with a hand pump.[37] Reduced muscle stretch reflexes may improve after brief exercise. Some patients have signs of polyneuropathy. The edrophonium (Tensilon) test is ordinarily negative equivocal, but a small dose of *d*-tubocurarine and decamethonium causes a depolarizing block at the neuromuscular junction.

Guanidine partially corrects defective calcium-dependent ACh release and results in dramatic improvement in strength, although hematologic and renal complications usually preclude a long-term use in high dosage.[203] The neuromuscular defect also improves partially after the administration of calcium, 4-aminopyridine, 3,4-diaminopyridine (DAP), aminophylline, or caffeine, which increase the cyclic adenosine monophosphate essential in calcium mobilization in cells.[254] Treatment with 3,4-DAP blocks voltage-sensitive potassium channels, prolonging the action potential duration, which in turn increases calcium influx and enhances transmitter release. Compound muscle action potentials augmented after voluntary contraction, however, decay faster after treatment with 3, 4-DAP, indicating that the rate of calcium (Ca^{2+}) efflux also accelerates.[164] Adverse side effects severely limit the use of 4-aminopyridine and related drugs.[185] Plasma exchange and immunosuppressive drugs may temporarily alleviate the symptoms.[191] Muscle strength may increase with simultaneous electrophysiologic improvement after long-term therapy with prednisone,[281] azathioprine,[250] or high-dose intravenous immunoglobulin.[15,29,182,235,290]

Electrophysiologic Tests

As the electrical hallmark of the syndrome, nerve stimulation typically elicits very small compound muscle action potentials (see Figs. 9–8 and 10–10) and, in striking contrast, entirely normal sensory responses.[209] Paired stimulation with interstimulus intervals of 5–10 ms causes the second response to increase rather than decrease as expected in normal muscles. Repetitive stimulation at low rates further diminishes muscle action potentials similar to the decrement seen in myasthenia gravis. Stimulation at high rates causes substantial increments, usually exceeding 50–200 percent of the baseline value in amplitude and area (see Figs. 10–6 and 10–7).[29] Brief voluntary contractions for up to 10 s, facilitate the subsequent responses elicited by nerve stimulation. A slower rate of stimulation also facilitates the response if combined with voluntary contraction.[161] Posttetanic facilitation, which decays exponentially within 20 s, lasts longer after cooling, reflecting the reduced rate of removal of calcium ions from the nerve terminal.[166] This prolongation of postexercise augmentation

underlies the patient's symptomatic improvement in cold weather. During posttetanic exhaustion, which peaks in 2–4 minutes, the muscle potential falls below the resting level (see Figs. 10–12 and 10–13). Electrophysiologic abnormalities may show various patterns, reflecting different degrees of blocking[198,205] and availability of releasable ACh from the terminal axon.[112]

Nerve stimulation may reveal marked abnormalities even in patients with mild clinical symptoms. Clinical remission after therapy usually accompanies a parallel improvement in serial electrophysiologic studies.[123] Interestingly, patients with a mild myasthenic syndrome complain of little motor dysfunction because posttetanic facilitation during voluntary contraction produces nearly normal strength. Rested muscles, however, have an unequivocal defect of neuromuscular transmission. Nearly all muscles show a mild decrement at low rates and a prominent increment at high rates of stimulation although abductor digiti minimi, abductor pollicis brevis, and anconeus serve best to detect the characteristic electrophysiologic findings.[165] In contrast to this uniformity in myasthenic syndrome, patients with myasthenia gravis have variable electrical abnormalities usually confined to clinically symptomatic muscles. In one reported case, electrophysiologic studies revealed a unique combination of marked depression to single-nerve stimulation and facilitation at all rates from 1–200/s.[145] This case may represent a separate entity or a variation of the myasthenic syndrome.

Needle studies show varying configurations of repetitive motor unit potentials with an incrementing tendency (see Chapter 14–5). As expected, increased jitter and blocking in single-fiber studies improve with high rates of stimulation and worsen following rest.[258] Treatment with 3,4-diaminopyridine may correct this feature.[247]

4 MYASTHENIA IN INFANCY

Transient Neonatal Myasthenia

Approximately 15 percent of infants born to myasthenic mothers have neonatal myasthenia gravis. This condition presumably results from transplacental transfer of anti-ACh receptor antibodies[208] or transient synthesis of receptor antibodies.[154] The onset of clinical weakness on the second or third day coincides with the release of antibodies from hemoglobins to which they are combined at birth.[136] A similar clinical syndrome develops in mice following injection of the IgG serum fraction from patients with myasthenia gravis.[294]

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.[117] The neonates usually respond to anticholinesterase medication. Symptoms generally disappear when the infant's own immune system becomes developed in a few weeks,[187] but they may occasionally persist beyond 2 months.[32] Electrophysiologic studies show characteristic abnormalities in distal muscles as late as 30 days after clinical recovery.[68] An elevated antibody titer against ACh receptors returns to the normal range over a 3 month period.[136]

Other Forms of Infantile Myasthenia

In the absence of maternal passive transfer, infantile myasthenia gravis may result from acquired autoimmune pathogenesis or nonautoimmune hereditary diseases. The term *congenital myasthenia gravis* or *familial infantile myasthenia* implies the absence of anti-ACh receptor antibodies in the serum.[307] These patients usually have a family history of similar disease but otherwise are clinically not readily distinguishable from the autoimmune type.[262] The congenital type accounts for about 1 percent of all cases of myasthenia gravis. Although the disease begins in infancy, it continues into childhood and adulthood, unlike transient neonatal myasthenia. 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.[57,95] They may[239] or may not[296] improve with anticholinesterase medication. This entity encompasses a va-

riety of specific defects at the neuromuscular junction, with no evidence of an immunologic attack against neuromuscular junctions. Thus, antibody determinations are useful in differentiating autoimmune and hereditary myasthenia in infancy. Rare varieties of congenital myasthenia gravis with onset at birth or in childhood and a persistent clinical course are reviewed here.

Detailed physiologic, chemical, and histologic studies have elucidated a number of types with specific presynaptic or postsynaptic abnormalities (Table 27–1). The newly recognized disorders have divergent features, such as absence of acetylcholinesterase from the neuromuscular junction,[79,83,120,121] failure of Ach synthesis or packaging,[82,179] an abnormality in the regulation of the density of Ach receptor molecules in the postsynaptic membrane,[78,153,271,300,306] slow channel abnormalities,[85,212] or other kinetic dysfunction of Ach receptors with[87] or without[91,300] Ach receptor deficiency, and familial limb-girdle myasthenia with tabular aggregates.[97]

These genetic defects either impair neuromuscular transmission directly or result in secondary derangements that eventually compromise its safety margin by one or more specific mechanisms, as described below.[21,80,88,105,106,131,266] For example, a kinetic abnormality of AChR stems from missense mutation in the α, β, or ϵ subunit of the receptor. In this type of abnormality, gain-of-function mutations cause the slow channel syndrome, whereas loss-of-function mutations usually involving the ϵ-subunit gene result in severe AChR deficiency.[207] These and other syndromes of congenital myasthenia probably represent separate pathologic, electrophysiologic, and clinical entities.[103,246,296,306] In vitro intracellular microelectrode studies have revealed a different mechanism of defective neuromuscular transmission in each of the following entities.

The first type, originally described in a 15-year-old boy who had intermittent ptosis, delayed motor development, and generalized weakness, showed three main features: acetylcholinesterase deficiency, small nerve terminals, and reduced ACh release.[79,83,120,121] The patient had a negative edrophonium (Tensilon) test, no serum antibodies to muscle ACh receptors, and absent acetylcholinesterase at the end plates. 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

Table 27–1 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	+	−	−	+	↓	−	−
LES	−	−	−	+	−	+	↓
Congenital							
A	−	+	↑	−	↓	−	↓
B	−	+	↑	+	↓	−	−
C	−	−	−	+	−	+	−
D	−	−	−	+	↓	−	−
Dog	−	−	−	+	↓	−	−

AChR = acetylcholine receptor; AP = Action Potential; MEPP = miniature endplate potential; EPP = endplate potential; MG = myasthenia gravis; LES = Lambert-Eaton syndrome; A = myasthenic syndrome with endplate acetylcholinesterase deficiency, small nerve terminals, and reduced acetylcholine release[83]; B = familial, congenital myasthenic syndrome possibly from an abnormal acetylcholine receptor with prolonged open time[84]; C = familial, congenital myasthenic syndrome possibly from deficient synthesis of acetylcholine[114]; D = familial, congenital myasthenic syndrome with a possible abnormality of acetylcholine receptor synthesis or incorporation in the postsynaptic membrane[146]; Dog = congenital myasthenia in dogs.

miniature end-plate potential (MEPP), a marked reduction in number of ACh quanta released per nerve stimulation, and prolonged duration of MEPP and end-plate 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.[303] Needle studies showed temporal variability of the motor unit potentials (see Fig. 10–8).

In an infant, a separate entity, probably caused by a deficient synthesis of ACh, caused intermittent ptosis, feeding difficulties, dyspnea or apnea, and vomiting.[14] Weakness worsened with febrile illness and during exercise, but gradually improved with age. Progressive weakness developed during prolonged nerve stimulation at 10 Hz. A brief repetitive nerve stimulation produced no decrement of the muscle action potential. In another term infant with similar clinical features, electrodiagnostic studies demonstrated defective neuromuscular transmission characterized by borderline low motor evoked amplitudes, profound decremental responses at all stimulus rates, and moderate facilitation ranging from 50–74 percent, 15 s after 5 s 50 Hz stimulation.[2] Although not proven, these findings suggest an abnormality in ACh resynthesis, mobilization, or storage rather than defective receptors.[82,179] Indeed, prolonged nerve stimulation induced a temporal decline in EPP and MEPP amplitudes in normal muscles after ACh synthesis was blocked with hemicholinium.[67] Despite abnormally small synaptic vesicles found in some patients with familial infantile myasthenia, vesicle size showed no reliable correlation with the MEPP amplitude.[179]

A case of congenital myasthenic syndrome with a possible abnormality of ACh receptor synthesis had clinical features consisting of ptosis, limb weakness, and easy fatigability since birth.[146] He had a similarly affected brother. Intracellular microelectrode studies revealed low-amplitude but normal duration and frequency MEPPs, a normal number of ACh quanta released by nerve stimulation, a normal store of readily releasable quanta in the nerve terminal, and abnormally low content of ACh receptor. In the absence of autoimmunity, the abnormality might result from a defect of the ACh receptor molecule or its synthesis. In still another type of ACh receptor 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.[271,272,300,322] Neurophysiologic studies demonstrated a 55 percent decremental response to stimulation at 3 Hz and a reversal of this abnormality by administration of edrophonium (Tensilon).

In another form, an abnormal ACh receptor caused a prolonged EPP despite normal muscle acetylcholinesterase.[84] The affected infants had ophthalmoparesis and weakness of neck muscles. Easy fatigability and weakness of shoulder girdle and forearm muscles developed later in the teens or adulthood. Single stimuli to motor nerves elicited repetitive muscle action potentials in proximal and distal muscles tested.[303] In view of normal muscle acetylcholinesterase, the prolonged EPP might result from abnormal transmitters resistant to muscle acetylcholinesterase[306] or an abnormal ACh receptor with a prolonged open time or slow channel.[85,242] The slow channel syndrome has an autosomal dominant inheritance pattern characterized by missense mutations in genes encoding subunits of the end-plate ACh receptor.[89,104] 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.[13] A similar immune-mediated disorder, called *acquired slow-channel syndrome*, results from an antibody that is specific to the adult form of the AChRs. In this variant of myasthenia gravis, alteration of the channel properties slows the closure of the channel and reduces the total current.[318]

Another type results from a kinetic abnormality of the ACh channel, which may stem from a point mutation in a receptor subunit.[91] The propositus had poor suck and cry after birth and intermittent ocular symptoms and abnormal fatigue later. A younger sister had elements of the same disease. Physiologic studies revealed a

normal quantal content of the EPP, but abnormally large miniature endplate currents and short decay time constant, considered characteristic of the high-conductance, fast channel syndrome.[87] Electromyography showed no decrement in limb muscles, but single-fiber examination of the facial muscles uncovered findings consistent with a neuromuscular transmission defect.

5 BOTULISM

Botulinum Toxin

The exotoxin of *Clostridium botulinum* has a generalized effect on the neuromuscular junction involving both striated and smooth muscles. Of the six immunologic types of *Bacillus botulinus*,[53] types A, B, and E account for most human cases. The most common infantile form develops after the consumption of food containing spores that germinate in the gut, producing 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.[115,178,293] An infected wound may occasionally harbor the toxins.[233] Bulbar weakness with visual symptoms in patients with subcutaneous heroin abuse strongly suggest the possibility of wound botulism.[171] Types A and B usually originate in contaminated canned vegetables and type E in fish products. Types A or E have higher mortality rates than type B.[175]

The incidence of botulism increases at high altitudes, probably because water boils at lower temperatures.[47,49] Botulism bears a great resemblance to the myasthenic syndrome, with marked impairment of ACh release from the nerve terminal.[133] In vitro studies of MEPPs 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 severe reduction of the EPP quantal content and a marked variability in their latencies.[170,171] 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.[299]

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 be the result of botulism, now recognized with increasing frequency in this age group.[128,230] In less severe cases, mild symptoms abate, and complete recovery usually ensues. Botulism in infants may relapse after apparent resolution of clinical symptoms.[101]

Symptoms appear within 1 to 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, or difficulty in mastication.[48] The involvement of the intestines 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 myasthenia gravis. Unlike the weakness seen in the myasthenic syndrome, 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.[264] Otherwise, patients should receive supportive therapy.[231] Administration of guanidine[134] or 3,4-diaminopyridine[65] fails to enhance recovery from botulism.

Electrophysiologic Tests

Nerve conduction studies show normal amplitude and latency of sensory action potentials. A small compound muscle action potential 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 two EPPs (see Fig. 10–3). This finding, also seen in myasthenic syndrome, stands in contrast to the normal pattern consisting of a full response followed by a smaller response during the refractory period. In botulism, as in the myasthenic syndrome, the refractory period plays a limited role because only a small number of muscle fibers discharge in response to the first stimulus. The remaining muscle fibers subliminally excited by the first shock tend to fire in response to the second shock.

Muscle response is facilitated with a fast train of stimuli or during posttetanic potentiation[302] but usually not to the same degree as in the myasthenic syndrome.[249] In severe cases, complete blocking of the neuromuscular junction may preclude any augmentation.[264] In infantile botulism, repetitive stimulation at 20–50 Hz is the most specific test, showing an incremental response in over 90 percent of patients (see Fig. 10–11).[58] Prolongation of posttetanic facilitation, at times for up to 4 minutes, also constitutes a unique feature of botulism.[92]

The presence of fibrillation potentials may indicate functional denervation caused by limited release of ACh.[98] Single-fiber EMG has shown increased jitter and blocking and some reduction in fiber density.[44,168,220,256] Local injection of botulinum toxin for blepharospasm causes abnormal jitters in arm muscles, indicating a remote spread of toxin from the site of injection.[8,16,151,255]

6 OTHER DISORDERS

A variety of natural toxins of animal, plant, and bacterial origin can cause disorders of neuromuscular transmission.[261] Animal toxins include those from venomous snakes[56,270,313] and arthropods, certain marine creatures, skin secretions of dart-poison frogs, and 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 the muscle action potential.

Tick Paralysis

Available data suggest that tick 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.[228] Most cases involve young children, especially girls with long hair, in spring or summer when ticks are active.[257] 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.

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. Occasionally 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 amplitude of the compound muscle action potential.[50,228,288] In one study,[288] muscle action potentials changed little on repetitive stimulation up to 50 Hz. Mildly increased distal motor and sensory latency during the paralytic phase returned to normal after clinical recovery. Persis-

tent weakness and the presence of fibrillation potentials in some cases after the removal of the tick suggest a structural lesion of distal motor axons.[71]

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 tetradotoxin and saxotoxin, 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,[50] but not with its synthesis or storage.[183] Intracellular studies of hamsters paralyzed by tick toxin, however, have shown normal size and frequency of MEPPs and normal quantal content of EPPs.[174]

Effects of Drug or Chemicals

The administration of some drugs, notably kanamycin and neomycin and all other polypeptide aminoglycoside antibiotics, may cause abnormalities of neuromuscular transmission.[9,11,138,139] At low rates of repetitive nerve stimulation, the muscle action potentials show a decremental response, although facilitation after exercise typically exceeds that seen in myasthenia gravis. In rats, small-amplitude MEPPs and an abnormally low mean quantum content of EPPs suggest combined pre- and postsynaptic effects.[64] Another type of abnormality produced experimentally with hemicholinium impairs ACh synthesis.[67] Myasthenia-like weakness may also develop during procainamide therapy.[192] Extended use of nondepolarizing neuromuscular blocking agents such as vecuronium, pancuronium, and atracurium can produce prolonged neuromuscular paralysis, imitating a myasthenia syndrome.[17,259] Hypermagnesemia may present as a spectrum of symptoms and signs, including neuromuscular junction defect and quadriparesis.[43] Repetitive stimulation studies suggest a presynaptic defect. Numerous drugs affect neuromuscular transmission, producing only subclinical effects because of a high margin of safety. These effects may become clinically evident in cases of drug overdoses, as reported in children with carbamazepine intoxication.[324]

The use of penicillamine may herald the clinical onset of myasthenia in rheumatoid arthritis,[12,70,94] and less commonly in Wilson's disease.[7] The clinical and electrophysiologic characteristics, although indistinguishable from those of idiopathic myasthenia gravis, improve after discontinuation of the drug.[3] The degree of jitter is positively correlated with the duration of administration but not the dosage of penicillamine.[1] This disorder and idiopathic autoimmune myasthenia gravis probably share the same pathophysiology that underlies the presence of ACh receptor antibody and resultant quantitative reduction in available junctional Ach receptors.[144] These data suggest that penicillamine produces myasthenia gravis by initiating a new autoimmune response rather than by enhancing ongoing autoimmunity.

Exposure to an organophosphate insecticide causes flaccid paralysis. Electrophysiologic studies demonstrate repetitive compound muscle action potentials in response to a single stimulus of the nerve.[25,243,303] Other findings include a decrement–increment response at higher rates of stimulation, a tendency accentuated by administration of edrophonium (Tensilon) (see Fig. 10–9), and normal nerve conduction studies during acute stages.[172,260,310] Intravenous pancuronium partially abolishes the decrement–increment phenomenon to repetitive stimulation, probably by blocking ACh receptors located on the terminal axon.[24,26]

Organophosphate poisoning can also produce a subacute postsynaptic neuromuscular syndrome without marked symptoms of acute toxicity.[107] In vitro microelectrode studies in rats showed no reduction in the amplitude of MEPPs or in the quantal content of EPPs, although their half-decay times were significantly prolonged. Trains of stimuli induced sustained end-plate depolarization via a staircase phenomenon of summation of prolonged EPPs, a phenomenon enhanced by edrophonium and abolished by *d*-tubocurarine. These results indicate that sustained end-plate depolarization can directly account for the decrement and weakness in acute

organophosphate intoxication.[173] In humans, electrophysiologic studies can rapidly determine the efficacy of oximes in reactivating ACh esterase.[27]

Lower Motor Neuron Disorders

Defects of neuromuscular transmission also accompany motor neuron disease 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 at low rates results in a progressive decrement of the muscle action potential. In contrast to the changes seen in myasthenia gravis, this decrement, minimal at low rates, becomes progressively more prominent at faster rates of stimulation.[99] Posttetanic potentiation and exhaustion may also occur.

Muscle Diseases

In myotonia[5] and periodic paralysis,[236] a decremental response on repetitive stimulation results from increasing muscle membrane refractoriness associated with recurring discharges (see Chapter 10–8). Unlike the pattern seen in myasthenia gravis, 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, the compound muscle action potential diminishes in proportion to the number of refractory muscle fibers. The amplitude returns to resting values in 15 to 30 seconds. Thus, exercise first induces a reduction in muscle excitability followed by recovery, as opposed to the initial posttetantic potentiation and subsequent exhaustion seen in myasthenia gravis. The decremental response in myotonia may erroneously suggest defective neuromuscular transmission. Improper interpretation of such findings may account for the alleged coexistence of both myotonic dystrophy and myasthenia gravis in a few reported cases.

Based on a small series, patients with proximal myotonic myopathy show no postexercise depression despite a clinical resemblance to myotonic dystrophy.[248] In McArdle's syndrome and other muscle glycogenoses, weakness increases with exertion, which induces electrically silent muscle contractures (see Fig. 12–3). The compound muscle action potential progressively decreases in amplitude as contractures develop in response to rapid repetitive stimulation.[33]

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Chapter 28

MYOPATHIES

1. INTRODUCTION
2. MUSCULAR DYSTROPHY
   - Duchenne Muscular Dystrophy
   - Becker-Type Muscular Dystrophy
   - Facioscapulohumeral Dystrophy
   - Limb-Girdle Dystrophy
   - Other Dystrophies
3. CONGENITAL MYOPATHY
   - Central Core Disease
   - Nemaline Myopathy
   - Myotubular or Centronuclear Myopathy
   - Congenital Fiber Type Disproportion
   - Other Congenital Myopathies
4. METABOLIC MYOPATHY
   - Acid Maltase Deficiency (Type II Glycogenosis)
   - Debrancher Deficiency (Type III Glycogenosis)
   - Muscle Phosphorylase Deficiency (Type V Glycogenosis)
   - Muscle Phosphofructokinase Deficiency (Type VII Glycogenosis)
   - Disorders of Lipid Metabolism
   - Mitochondrial Disease
   - Malignant Hyperthermia or Hyperpyrexia
   - Toxic Myopathies
5. ENDOCRINE MYOPATHY
   - Thyroid Myopathy
   - Parathyroid Disease
   - Adrenal and Pituitary Disease
6. MYOSITIS
   - Dermatomyositis
   - Polymyositis
   - Inclusion Body Myositis
   - Other Myositic Diseases
7. OTHER MYOPATHIES
   - Critical Illness Myopathy
   - Myopathies Associated with General Medical Conditions

1 INTRODUCTION

The myopathies include any disorder whose primary pathology involves muscle tissue. Primary diseases of muscle include genetically determined disorders and those of a toxic or inflammatory nature. Entities traditionally referred to as *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 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 polymyositis affect the muscle. Dysmaturation myopathy without specific histochemical or cytoarchitectural characteristics accounts for many cases of hypotonia in infancy.[515]

Although patients with a myogenic disorder develop hypotonia as one of the essential features, not all floppy infants have a primary muscle disease (see Chapter 22–10). Overall, disorders of the motor unit constitute less than 10 percent 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, poliomyelitis, inflammatory polyneuropathy, myasthenia gravis, and botulism. Central sleep apnea may complicate a variety of neuromuscular syndromes, sometimes appearing as isolated symptoms of excessive daytime sleepiness.[286] 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,[13] 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 defective 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.[238]

Useful screening tests include determination of creatine kinase level and erythrocyte sedimentation rate. Electromyographic studies and analysis of force help delineate the physiologic mechanism of weakness and fatigue.[160] Muscle biopsy specimens provide histologic and histochemical confirmation. Some advocate needle biopsies over the traditional surgical techniques.[318] In patients with clinical myopathic disorders, biopsy reveals prominent myopathic features regardless of the age of the patients, although myopathy in the elderly tends to accompany neurogenic changes.[291] Additional studies of interest include computer tomography[128,480] and magnetic resonance muscle imaging.[339,399]

Electromyographic studies contribute not only in differentiating myogenic from neurogenic paresis but also in delineating the distribution of abnormalities and categorizing dystrophies and myopathies.[123,259,527] 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 also mimic a neuropathic process of the motor axons with a reduction in amplitude of compound muscle action potentials and preservation of sensory nerve potentials. Neuromuscular transmission studies show no abnormality in primary disorders of muscles. This chapter provides a simplified overview of the major disorders commonly encountered in an electromyographic laboratory. Other texts provide further details for interested readers.[153,166,170,214,296,524]

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 in-

fancy. Most types result from a primary myogenic lesion in the form of muscle fiber degeneration. A currently accepted classification based on the mode of inheritance and distribution of muscle degeneration has four main categories of muscular dystrophy, which include most patients: Duchenne, Becker, facioscapulohumeral, and limb-girdle. Of these, Duchenne and Becker dystrophies collectively belong to the newly proposed entity termed *dystrophinopathy*. Other categories include oculopharyngeal dystrophy, hereditary distal myopathies, muscular dystrophy of the Emery-Dreifuss type, and myotonic dystrophy. 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.[316,426] Dystrophin is associated with a large oligomeric complex of sarcolemmal glycoproteins, including dystroglycan, which provides a linkage to the extracellular matrix component laminin.[329] 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. Conversely, any myopathy caused by a mutation at another location should affect some other gene product. Carriers with myopathy and a normal karyotype may have a dystrophin deficiency as evidenced by immunohistochemical studies showing a mosaic of fibers with and without dystrophin.[345] The proportion of dystrophin-deficient fibers, however, does not correlate directly with the degree of clinical weakness in manifesting carriers.[447]

The dystrophin gene has more than 70 exons containing 2.4 million bases, nearly 0.1 percent of the haploid genome. Two promoters are associated with alternative first exons, one for brain and the other for skeletal, cardiac, and smooth muscle. The 400 kD protein contains 24 repeats of a spectrin-like motif that forms an alpha helix. The amino-terminal end has homology to the actin binding domain of alpha-actinin and the carboxyterminal end has homology to the calcium-binding domain 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 (DAG). Components of DAG identified to date are: dystroglycans, sarcoglycans, sarcospan, syntrophins and dystrobrevins. Defects in these components associated with limb-girdle muscular dystrophies include mutations in the genes for sacroglycan.[334,386]

Another rare type of Duchenne-like muscular dystrophy has an autosomal recessive mode of inheritance and thus is named *severe childhood autosomal recessive muscular dystrophy*.[385] This entity results from a defect of any one of four genes encoding for the sarcoglycan complex, which forms one component of the dystrophin–glycoprotein complex. Pathogenic mutations in each gene determine a group of disorders now called *sarcoglycanopathies*.[11]

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy also known as the *pseudohypertrophic* variety of dystrophy, has X-linked recessive inheritance.[155] All mothers of affected sons carry the affected gene. These phenotypically normal females transmit the disease to 50 percent 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.[437] 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. Symptomatic young girls, if not carriers, have childhood muscular dystrophy of autosomal recessive inheritance.[229] Molecular biologic techniques identified the primary biochemical defect based solely on the chromosomal location.[237,238]

In Duchenne muscular dystrophy mutations of the dystrophin gene cause a

frameshift, early termination, or deletion of the carboxy-terminal or amino-terminal ends, resulting in a nonfunctional protein. Dystrophin is associated with a large oligomeric complex of sarcolemmal glycoproteins including the laminin-binding glycoprotein called *dystroglycan*, which provides a linkage to the extracellular matrix.[328] The absence of dystrophin leads to a drastic reduction in all of the dystrophin-associated proteins. In severe childhood autosomal recessive muscular dystrophy with a similar phenotype, a specific deficiency of the 50 kD dystrophin-associated glycoprotein called *sarcoglycan* causes disruption of the linkage between the subsarcolemmal cytoskeleton and the extracellular matrix, rendering muscle cells susceptible to necrosis.[11]

A number of investigators once advocated the neurogenic[333,388] or vascular[226,337] theories with vigor but without universal acceptance. The neurogenic hypothesis introduced the concept of sick motor neurons subserving the muscle. Others described defects of erythrocyte membranes[344] but without subsequent confirmation.[425,522] Some also suggested possible involvement of calcium (Ca^{2+}) metabolism in the dystrophic process.[330,351]

The main pathologic sequence of events in the early stages consists of repeated episodes of muscle fiber necrosis and regeneration.[86,423] Incomplete regeneration reduces the number of muscle cells, rendering some fibers hypertrophic and others atrophic.[441] Progressive accumulation of collagen finally replaces the muscle cells. Preservation of extraocular muscle function suggests protective properties of fast-twitch fibers against degeneration.[265] In the murine animal model of the disease, mdx mice, diaphragm muscles show greater contractile abnormalities than hindlimb muscles,[56,157] reflecting unfavorable factors such as a large proportion of fast oxidative fibers and sustained activity associated with forced lengthening during each eccentric contraction.[89,205] Some patients may develop hypermetabolism and rhabdomyolysis during anesthesia, but contracture testing with caffeine or halothane reveals no evidence of malignant hyperthermia.[217]

Proximal weakness of the leg begins during early childhood, although histologic evidence indicates that abnormalities already exist at birth. The child normally attains 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 or 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,[184] 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, leading 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.

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.[207] Severe spine deformities may cause upper motor neuron abnormalities, which in turn lead to urinary dysfunction.[84] The calf muscle, although initially strong, develops pseudohypertrophy, as do the deltoid, quadricep, and gluteal muscles. With a steady, downhill course, frequent falls force 90–95 percent 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. Other features include macroglossia, mild nonprogessive mental retardation seen at birth in 30–50 percent of children with IQs ranging from 50 to 90, pulmonary problems, and cardiac myopathy with congestive heart failure.

Prenatal studies of amniotic fluid usually show normal levels of creatine kinase (CK). The newborn may have abnormal

values, which implies 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 never return to normal. No other neuromuscular disease has such an extremely high CK value. Other enzymes such as pyruvate kinase, aldolase, lactate dehydrogenase (LDH), glutamic-oxaloacetic transaminase (GOT), and glutamic pyruvic transaminase (GPT) all show nonspecific elevation. Cardiac involvement results in typical electrocardiographic changes that consist of a tall, right precordial R wave and a deep limb and precordial Q wave[118] in conjunction with characteristic abnormalities seen by cardiac echo and positron emission tomography.[408] Muscle biopsy material usually reveal 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 is based on clinical presentation, a 100–700-fold elevation in CK, the 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. DNA-based diagnosis also serves as prenatal screening in many cases.[467] About 65 percent of dystrophin mutations result from deletions. Southern analysis and polymerase chain reactions detect nearly 98 percent of these deletions. Either RNA analysis or fetal protein analysis is used to assess point mutations. Laboratory diagnosis and prognosis are generally determined by DNA analysis of the dystrophin gene and immunoassay of muscle with antibodies directed against different regions of the protein product.[340,436] The clinical spectrum of the dystrophinopathies ranges from a severe form presenting at birth to an asymptomatic elevation of CK.[362] Females may present as a manifesting carrier or severe phenotype with expression of the abnormal gene as an X-autosome translocation or monosomy X.

Prednisone produces a rapid increase in muscle strength, with maximal effect at a dosage of 0.75 mg/kg or less.[215] 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.[188] In one study, dantrolene, which inhibits calcium release from the sarcoplasmic reticulum, reduced serum CK associated with a lessening trend in motor function deterioration.[48] In another study, long-term low-frequency electrical stimulation of affected muscles also improved strength compared with the nonstimulated control side.[537] Endurance training may or may not have a beneficial effect.[163] Surgical stabilization by spinal fusion prevents progressive deformity for relative ease and comfort of wheelchair seating, although the vital capacity primarily related to muscle weakness continues to decline.[450] Many patients do well on long-term ventilation, but some choose to discontinue this method of life prolongation.[235] Preliminary results suggest a possible role for human myoblast transplantation,[244] which, with improved efficacy, may deserve a therapeutic trial.[267,343]

Electromyographic evaluation reveals characteristic 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) but to a much lesser extent than in myositis or motor neuron disease. Low-amplitude, short-duration motor unit potentials result from random loss of muscle fibers. When recruited in abundance (see Figs. 14–16 and 14–19B), these potentials give rise to a characteristic noise resembling a shower of fibrillation potentials. In mildly affected muscles, limited in degree and distribution, the abnormalities could escape detection without careful exploration. Electromyography is generally of little value 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 age-matched control children (3.2 ± 0.5 m/s).[111] This abnormality may reflect an increased diameter variation which also causes complex and long-duration motor unit potentials.[112] Magnetic cortical stimulation in patients reveals a higher threshold of stimulation than in normal persons, perhaps reflecting a deficiency of brain synaptic dystrophin.[137]

Becker-Type Muscular Dystrophy

The Becker type of muscular dystrophy is a benign, X-linked recessive dystrophy that affects male offspring. It also results from a 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.[39,417] A common pathogenesis underlies both Becker and Duchenne variants. 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.[484]

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's difficulty involves climbing stairs and rising from the floor. Unlike Duchenne muscular dystrophy, patients with the Becker type usually walk for 25 to 30 years after onset, and many may reach an advanced age. Patients eventually develop contractures and skeletal deformities, but not as severely as in Duchenne dystrophy. Early myocardial disease and myalgia may develop as a primary feature, unrelated to the severity of skeletal muscle damage.[131,370] Patients may develop cardiac failure as a late complication but 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.

Electromyography shows nearly symmetric abnormalities in the proximal muscles. Fibrillation potentials and complex repetitive discharges abound in the paraspinal muscles. Small and polyphasic motor unit potentials show an early recruitment. Muscle biopsy specimens in an early stage look like those of Duchenne dystrophy with necrotic fibers, basophilic fibers, 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.[264] In another study, each of eight families reviewed had mixed features of myopathy and denervation.[63] Muscle biopsy material revealed fiber atrophy and hypertrophy with many split and angulated fibers and clumps of pyknotic nuclei.

Facioscapulohumeral Dystrophy

Facioscapulohumeral dystrophy, also known as Landouzy-Dejerine type, affects both genders equally,[273] with an incidence of approximately 1 per 100,000. The disorder has an autosomal dominant inheritance with complete penetrance and variable expression, and the responsible gene is localized to the telomeric region of chromosome 4q35.[216,519] Some authors prefer the term *facioscapulohumeral syndrome* with subdivisions into neurogenic, myopathic, and rare myositic entities.[154,358] Initial myositic features may lead to clinical patterns indistinguishable from the myopathic type after some months to years. 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.[222] Early signs often missed by patients or physicians include variable degrees of mimetic muscle weakness ac-

counting for myopathic faces. Patients usually have protruded lips, a transverse smile, weak eye closure, and an inability to wrinkle the forehead. The loss of the ability to use the arms, a common initially recognized symptom, results from weakness of the pectoralis major, latissimus dorsi, biceps, triceps, and brachioradialis muscles. Attempted abduction of the arm elevates the weak trapezius, giving rise to the typical appearance called *trapezius hump*. Weakness of the tibialis anterior may cause foot drop as an early sign, but otherwise the disease affects the lower limbs later than the upper limbs. Beevor's sign is a prelude to functional weakness of abdominal wall muscles.[26] The patient has bilateral foot-drop as the presenting sign in a variety known as *scapuloperoneal dystrophy*.[493]

The very slowly progressive deficit causes only minor disability and little alteration in life expectancy. 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.[73] 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 Charcot-Marie-Tooth disease resulted in severe generalized weakness and early death.[77]

Unlike in Duchenne or Becker dystrophy, CK levels in facioscapulohumeral dystrophy tend to remain normal. Measurement of pyruvate kinase is a more sensitive test. Biopsy material reveals variably sized fibers of both types, with many large fibers, groups of small angular fibers reminiscent of denervation atrophy, and inflammatory responses.[15] In the initial stages, electromyography may show only a limited abnormality, which may escape detection even in clinically weak muscles. The jitter studied by single-fiber electromyography in facial muscles also remains within normal limits.[500] Well-advanced cases show low-amplitude, short-duration, polyphasic motor unit potentials with early recruitment out of proportion 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 disorders include congential myopathies like myotubular myopathy, central core disease, and nemaline myopathy, as well as polymyositis, spinal muscular atrophy, and myasthenia gravis. Complete electrophysiologic testing should include studies of neuromuscular transmission and paraspinal electromyography to exclude myasthenia gravis and polymyositis with weakness in the facioscapulohumeral distribution. A pilot trial of albuterol, a β_2-adrenergic agonist, has shown some encouraging results, increasing certain measures of strength.[277] Thoracoscapular fusion may improve function and cosmesis.

Limb-Girdle Dystrophy

The designation limb-girdle dystrophy includes a heterogenous group of hereditary disorders involving at least six different genetic loci[76,148,271] progressive weakness mainly affects the proximal muscles of the shoulders, pelvic girdles, 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 recessive pattern of inheritence.[502] Both sporadic cases and a kindred with a rare autosomal dominant pattern[101,177,320,389] present similar clinical and histologic features.[510]

The illness often begins during the second or third decade of life, with involvement of the pelvis and a highly elevated serum CK level. Weakness soon spreads to the shoulder girdle, typically but not always sparing the facial muscles.[389] Symptoms, restricted to these areas for many years, show only mild progression.[476,477] Rarely, involvement of the diaphragm heralds the onset of a limb-girdle sydrome as the presenting symptom.[530] Some patients have weakness of only one limb without developing other characteristic features or only one muscle as in quadriceps myopathy.[481] The disease process usually runs a more rapid course in the

tibialis anterior than in the plantar flexor muscles.[41] Pseudohypertrophy may or may not occur in the calves and deltoid. Despite eventual confinement to a wheelchair, the patient usually has normal life span.

The name *limb-girdle syndrome* appropriately denotes the heterogeneity of this entity, with subdivision into myogenic and neurogenic types based on clinical, histologic, and electrophysiologic findings (see Fig. 13–8C). In addition, a clinical syndrome of progressive proximal limb-girdle distribution may appear as a secondary manifestation in other well-defined conditions. These include chronic polymyositis, myasthenia gravis, and various metabolic and congenital myopathies, such as late onset acid maltase deficiency and carnitine deficiency. Spinal muscular atrophy also has a similar distribution of weakness, making clinical differentiation difficult.

A review of 18 patients with proximal weakness in the limb-girdle distribution established a firm diagnosis only in four cases even after histologic evaluation—two with spinal muscular atrophy and two others with muscular dystrophy.[102] Motor innervation patterns suggested spinal muscular atrophy in 4 of the 18 and limb-girdle dystrophy in the others. Electromyographic features revealed myopathic changes in 11, denervation in 3, and inconclusive results in 4. In another series of 20 patients, single-fiber electromyography confirmed the original diagnosis of myopathic limb-girdle syndrome in 11 and chronic spinal muscular atrophy in 5 and helped differentiate the other four cases into myopathic and neuropathic varieties.[452]

Other Dystrophies

Oculopharyngeal dystrophy, a rare form of progressive ophthalmoplegia, affects French-Canadian families in an autosomal dominant fashion,[30,109,224] with the responsible gene localized to chromosome 14q11.2–q13.[65,471] Progressive ptosis and dysphagia develop late in life with or without extraocular muscle weakness, although a childhood myopathy occasionally affects the same muscle group.[9] 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.[154] Differentiation from myasthenia gravis poses a major problem clinically. Patients with oculopharyngeal dystrophy have absent titers for acetylcholine receptor antibody and a negative edrophonium (Tensilon) test. Progressive external ophthalmoplegia can also develop in a number of congenital myopathies such as centronuclear and myotubular myopathy and multicore disease.[260] This general category, classified as ocular myopathy, has either recessive or dominant inheritance.

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. Electromyographic studies usually reveal no spontaneous activity. Brief, low-amplitude, polyphasic motor unit potentials show an early recruitment in proximal muscles of the upper limbs.[60] A neurogenic pattern with large motor unit potentials may accompany the myopathic features.[442] Conduction studies reveal low-amplitude compound muscle action potentials in the weak muscles. Repetitive nerve stimulation shows no decrement of muscle response.

Primary muscle disease with a definite distal predilection includes large series of adult onset hereditary myopathy in Sweden and rare sporadic distal myopathy with early adult onset.[341] The differential diagnoses include myotonic dystrophy and inclusion body myositis, both of which characteristically cause atrophy of distal rather than proximal musculatures. Late onset distal myopathy, first described by Welander,[526] is a rare autosomal dominant disorder with onset in adulthood.[341] 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 or, less commonly, in the small muscles of the foot. As the disease slowly pro-

gresses, 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.[58] 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[159,321] and increased staining for spectrin, desmin, and Leu-19 as seen in denervated muscle fibers.[59] These findings may support a neurogenic component in this dystrophy, fulfilling the criteria for hereditary inclusion body myopathy.[5] Electromyography demonstrates an abundance of low-amplitude, short-duration motor unit potentials during mild voluntary contraction.

Another type of progressive distal myopathy described in Japan has an autosomal recessive inheritance[36,350] with linkage to chromosome 2p12–14.[40] The disease affects young adults with the initial features of impairment in standing on the tiptoes, followed by difficulty in climbing stairs and standing. Muscle atrophy involves the distal muscles in the legs and forearms, sparing the intrinsic hand muscles as detected clinically and computed tomography and magnetic resonance imaging.[339] Asymptomatic subjects may have an elevated serum CK value as a prelude of the disease.[199] Electromyography reveals abnormalities consistent with myopathy. Muscle biopsy specimens show severe segmental necrosis and regeneration of myofibers with little inflamatory responses.[173] Other hereditary distal myopathies include familial adult onset muscular dystrophy with leukoencephalopathy,[513] late adult onset tibial muscular dystrophy,[503] and autosomal recessive distal myopathy with rimmed vacuole formation,[479] which represents an inclusion body myositis (see this chapter, part 6).

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 early conduction defects.[165,427] This entity is also known as scapuloperoneal muscular dystrophy, scapulohumerodistal muscular atrophy, and humero peroneal neuromuscular disease. Some families have a wide phenotypic spectrum.[136] Most pedigrees show an X-linked inheritance, but rare kindreds have autosomal dominant transmission.[342] Mutation of the responsible gene results in loss or reduction of emerin, which serves as a membrane anchor.[189,352,376] 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, muscles of the arms, extensors of the hands, fingers, and feet, and ocasionally 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. Patients also develop cardiopathy with atrioventricular block, atrial fibrillation, decreased ventricular rate, and exertional dyspnea, often dying suddenly from cardiac arrest. Electrophysiologic studies usually reveal early recruitment of short, polyphasic, and relatively high-amplitude motor unit potentials;[424] nerve conduction studies are normal. Histologic studies of muscle show mixed patterns of neurogenic and myogenic changes with internal nuclei, necrotic fibers, round cell infiltrates, and occasionally type 1 fiber predominance. An autopsy of a typical case disclosed no abnormalities of the spinal cord or of the ventral spinal roots.[223]

A variant of this syndrome has an 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 death eventually by cardiac arrest. Other possibly related entities include scapuloperoneal myopathy inherited as an autosomal dominant or X-linked recessive disease and scapuloperoneal 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, oc-

curring 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.[176,314,410,494]

Other dystrophies include benign hereditary myopathy, an autosomal dominant disorder with an extremely slow progression and a normal life expectancy, and quadriceps myopathies, which may represent a generalized myopathy despite selective quadriceps muscle atrophy and absent knee jerks. Congenital muscular dystrophies comprise a heterogeneous group of autosomal recessive disorders of a slow evolution with multiple contractures and generalized weakness. The entity has two subgroups, one with a fairly homogeneous merosin deficiency[14,158,228,365] and another with heterogeneous merosin positivity.[182,371] A dominantly inherited multisystem disorder called *proximal myotonic distrophy*, although phenotypically similar to myotonic dystrophy, has no CTG repeat expansion (see Chapter 29–2).[292,415,473]

3 CONGENITAL MYOPATHY

A number of congenital conditions have nonprogressive or only slightly progressive muscular weakness.[52,169,181] Some have morphologically distinctive structual alterations in muscle biopsy material. These conditions include central core disease, nemaline myopathy, 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. In rare cases, two or more structual changes coexist in the same patient or in one family,[3,403] possibly indicating Z-band abnormalities.[492] The diagnosis of these rare conditions depends not on clinical or genetic findings but on histologic examination of the muscle, identifying distinctive pathologic features that may or may not represent the fundamental manifestations. 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, absent or decreased stretch reflexes, and slow or no progression. Other features include short-duration, small-amplitude polyphasic motor unit potentials, normal conduction studies, muscle biopsy abnormalities of type I fiber predominance or type II fiber paucity, and characteristic histopathologic or electromicroscopic changes, which virtually name the individual disorder. Concurrent structural cardiomyopathy may result in cardiac conduction abnormalities or contractile insufficiency.[127]

Central Core Disease

Central core disease is a heterogeneous myopathy with typical core features in nearly all fibers, irrespective of the mode of genetic transmission. Its pathogenesis, although unknown, is probably related to an abnormality of neural influence, which may affect 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 lordorsis, kyphoscoliosis, and abnormalities of the foot.[491] Malignant hyperthermia may complicate operative interventions in children with central core disease.[167,194] For high-risk patients who require surgery for musculoskeletal defects, preoperative evaluation should include in vitro tests for this devastating phenomenon, described later (see this chapter, part 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 because of the virtual absence of mitochondria.[154] 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, but their absence does not preclude the diagnosis.[355] The resemblance of the cores to target fibers, which usually indicates denervation and reinnervation, supports the disputed idea that the disease may be neurogenic in nature.[369] An increased terminal innervation ratio described in this entity also suggests a neurogenic process.[103,249] A rare variant of central core myopathy shows characteristic collections of abnormally stained myofibrils along the entire length of a muscle fiber.

Electrophysiologic findings vary but tend to suggest a mixed myopathic–neuropathic process. Electromyographic studies usually detect normal insertional activity, no spontaneous discharges at rest, and small motor unit potentials with early recruitment.[357] Other studies have revealed large and polyphasic potentials[249] with increased fiber density.[110] Nerve conduction studies show reduced amplitude of muscle potentials with either normal[249] or mildly slowed conduction velocity.[241]

Nemaline Myopathy

Nemaline myopathy can be sporadic or inherited as an autosomal dominant trait,[280] causing nonprogressive hypotonia that usually begins at a very early age. Although considered benign in older children and adults, it may be responsible for early death in neonates and young infants.[374] In the severe infantile form, increased axonal sprouting of the intramuscular nerve suggests maturational arrest of developing muscle or nerve fibers.[373] 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,[287] dropped head[312] and an occasional scapuloperoneal distribution of weakness. 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 and carriers both have a predominance of small type I fibers in muscle biopsy specimens.[42,114] 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. Nemaline myopathy[455] 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. They are seen not only in nemaline myopathy but also in other neuromuscular disorders and occasionally in normal muscles. The number of rods does not correlate with severity of disease. A repeated biopsy may find a dramatically decreased number of rods, implying a reversible anomaly of Z-discs.[227]

Electromyography may show low-amplitude, short-duration motor unit potentials with early recruitment or, conversely, fibrillation potentials and a decreased number of high-amplitude, long-duration motor unit potentials.[374] These changes probably result from degeneration and regeneration of muscle fibers secondary to myopathic involvement.[523]

Myotubular or Centronuclear Myopathy

In myotubular myopathy,[469] or centronuclear myopathy,[44,445] fetal myotubes persist into adult life. Central nuclei are the common feature of this rare heterogeneous condition, which otherwise has diverse clinical and genetic characteristics.[37] Three subgroups have been identified based on severity and mode of presentation together with genetic pattern: a severe neonatal X-linked recessive type,[311,465] a less severe infantile-juvenile autosomal recessive type, and a milder autosomal dominant type.[230] The autosomal dominant type progresses more slowly than the generally severe X-linked form, which may lead to death from respiratory insufficiency. The milder autosomal dominant type may show clinical features simulating facioscapulohumeral

syndrome.[185] 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. Patient 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 aggegates of mitchondria near the central nuclei. Myotubes resemble those in fetal muscle, thus the name *myotubular myopathy*. The fetus-like dystrophin expression further suggests maturational arrest,[247,353] although sequential muscle biopsy findings indicate a progressive nature of the disease in some cases.[121] 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.

Electromyographic abnormalities include an excessive number of polyphasic, low-amplitude motor unit potentials, fibrillation potentials, positive sharp waves, and complex repetitive discharges.[29,230] These findings distinguish this entity as the only congenital myopathy consistently associated with spontaneous activities in electromyographic studies.[162] Occasional myotonic discharges may lead to an erroneous diagnosis of myotonic dystrophy, especially in a patient with distal weakness and ptosis.[409] Two sisters with otherwise typical centronuclear myopathy had clinical myotonia.[206] Patients usually have normal motor and sensory nerve conduction studies.

Congenital Fiber Type Disproportion

In normal muscles, type II fibers comprise more than 60 percent of the fibers and type I, 30–40 percent. A reversed relationship characterizes the histologic findings in some children with congenital hypotonia.[71,113] Infants may have generalized weakness with dysmorphic features at birth.[478] 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.[496] Patients have short stature and fail to develop expected motor skills despite a normal or above-normal mental capacity. A family history, if present, shows a variable pattern of inheritance.

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. The presence of occasional rods suggests possible but unconfirmed relationships between this condition and nemaline myopathy.[275] Electromyography usually demonstrates low-amplitude, short-duration motor unit potentials with early recruitment. Some patients have fibrillation potentials, positive sharp waves, and large motor unit potentials.[478]

Other Congenital Myopathies

In cystoplasmic 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 nerve conduction and abnormal electromyographic findings consistent with myopathy sometimes showing myotonic discharge.[364,393] Other entities include multicore myopathy with multifocal degeneration of muscle fibers,[171,535] fingerprint body myopathy with typical electron

microscopic features showing inclusions of complex lamellae arranged in fingerprint patterns, zebra body myopathy with hypotonia and weakness clinically and distinct zebra bodies ultrastructurally,[412] 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,[372] and actin myopathy with intranuclear rods.[208]

4 METABOLIC MYOPATHY

A variety of myopathies result from inborn errors of metabolism.[61] These include certain types of glycogen storage disease and disorders of lipid metabolism. Of the 10 glycogen storage diseases identified to date, prominent muscle involvement occurs only in types II (Pompe's disease), III (Cori-Forbes), V (McArdle), and VII (Tarui) glycogenosis.[243] 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, the deficiency leads to accumulation of glycogen in tissue lysosomes,[16,234] causing a vacuolar myopathy.[517] 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.[57] 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.

In the more benign childhood and adult types, the symptoms limited to skeletal muscle mimic those of limb-girdle 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.[172,323] Acid maltase deficiency may have heterogeneous presentations within a family, and an adult onset case can present as a scapuloperoneal neuromuscular syndrome.[35] Increased net muscle protein catabolism is involved in the pathogenesis because the conditon improves with a high protein diet.[463] In the adult variant, symptoms begin with insidious limb-girdle weakness during the second or third decade and respiratory difficulty some years later, necessitating a tracheostomy.[146,482,498] Both types have elevated serum enzymes. Muscle biopsy specimens reveal a vacuolar myopathy affecting type I fibers more than type II fibers. Glycogen commonly deposits in the central nervous system, particularly in the infantile form. Tissue cultures have reproduced the enzymatic defect.[23]

Electromyographic studies of the infantile form find increased insertional activity, fibrillation potentials, positive sharp waves, and complex repetitive discharges, as expected from anterior horn cell involvement.[172] Severely affected muscles typically lack insertional activity. As one of the few exceptions to the rule (see Chapter 14–3) true myotonic discharges may occur in the absence of clinical myotonia. Mild voluntary contraction recruits polyphasic, low-amplitude, short-duration motor unit potentials 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 electromyographic findings of myopathy without fibrillation potentials.[498] Studies of motor and sensory nerve conduction and of neuromuscular transmission reveal no abnormalities, except for reduced amplitude of the compound muscle action potentials.

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. Despite the generalized enzymatic defect, the skeletal muscles do not necessarily show weakness on clinical examination.[74,360]

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. Patient may improve in adolescence despite the enzymatic defect. Distal weakness and wasting sometimes resemble those in patients with motor neuron disease.[145] Muscle biopsy specimens show subsarcolemmal periodic acid–Schiff-positive vacuoles in type II fibers, without histochemical signs of denervation.[145] Electromyography may reveal profuse fibrillation potentials, complex repetitive discharges, and small, short-duration motor unit potentials.[145]

Muscle Phosphorylase Deficiency (Type V Glycogenosis)

McArdle[331] first described muscle phosphorylase deficiency as a rare autosomal recessive condition, although others have subsequently reported families with an autosomal dominant pattern.[100] It affects men more frequently than women by a ratio of 4 to 1.[143] Myophosphorylase deficiency blocks the conversion of muscle glycogen to glucose during heavy exercise under ischemic conditions. Although the exercise intolerance mainly results from impaired adenosine triphosphate generation from anaerobic glycogenolysis,[301] defects of oxidative metabolism may also play a role.[27,130] The myophosphorylase gene has been sequenced and assigned to chromosome 11. Although genetically heterogeneous, thymine substitutes for cytosine at codon 49 is the most common mutation.[501] In about 90 percent of cases, analysis of the patient's leukocytes identifies the responsible mutations, confirming the diagnosis.[501]

The disease has a wide clinical spectrum.[93,257,406] In infants, generalized hypotonia may lead to respiratory insufficiency and early death.[144] Patients developing symptoms later in life have more variable clinical presentations[187] as late onset or childhood myopathies.[107] The abnormality, confined to skeletal muscles, initially causes only nonspecific complaints of mild weakness and fatigue. Sometime during adolescence patients begin to notice exercise intolerance.[435] Despite the onset of symptoms in childhood or adolescence, muscle cramps rarely develop before late adulthood.[1,282] Atypical clinical presentations in adult patients include progressive muscle weakness without exercise-induced contracture.[326] The differential diagnoses include muscle phosphofructokinase deficiency characterized by recurrent myoglobinuria and persistent weakness,[45] phosphoglycerate mutase deficiency,[497] lactase dehydrogenase-A deficiency,[349] and Brody's disease, or a deficiency of calcium (Ca^{2+})-adenosine triphosphatase in sarcoplasmic reticulum.[270]

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. 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. Muscle pain and fatigue may improve during continued exercise if the patient slows down and sustains nonstrenuous activity. This second wind phenomenon presumably results from increased mobilization of serum free fatty acids as an alternative source of energy. Exposure to cold during exercise may also delay the development of contracture.

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 glycoly-

sis 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. The ischemic exercise test can identify patients with absence of myophosphorylase but fails to detect partial expression of McArdle's disease.[490]

The pathogenesis of the contracture initially centers around the depletion of high energy phosphates in the absence of glycogen metabolism. This might prevent the energy-dependent reuptake of calcium (Ca^{2+}) by the sarcoplasmic reticulum, but no studies have confirmed such an abnormality.[70] Membrane excitability also appears unimpaired during ischemic exercise as tested by muscle fiber conduction velocity and surface analysis of the frequency spectrum.[310] Muscle fatigue may result from failure of energy-dependent excitation–contraction coupling, but magnetic resonance imaging studies have shown no depletion of adenosine triphosphate.[17] Contractures probably develop following the disruption of the complex interplay among the contractile proteins, calcium release, and the calcium sequestration mechanism.[429] In addition, a reduced density of sodium (Na^+)-potassium (K^+) pumps on skeletal muscle fibers will reduce muscle fiber membrane excitability,[220] which in turn decreases exercise capacity.[430]

Between attacks, electromyographic studies may find no abnormalities or may reveal fibrillation potentials and polyphasic motor unit potentials[144] or spontaneous activity and myopathic features as seen in inflammatory muscle disease.[404] Myotonic or complex repetitive discharges may appear predominantly in paraspinal muscles.[395] In one study, quantitative analysis of the motor unit potential in the biceps showed a mean duration of 7.1 ms compared with 9.4 ms in the controls, suggesting myopathic changes.[66] Others have proposed a reduction in the number of motor units[506] but without subsequent confirmation. Nerve stimulation techniques reveal normal motor and sensory nerve conduction studies. During regional ischemia, a prolonged low rate of repetitive nerve stimulation causes a progressive decrease in the evoked muscle action potentials.[313] During contracture (see Chapter 29–12), electromyographic studies of the cramped muscle reveal no electrical activity despite muscle shortening (see Fig. 12–3). In contrast, the ordinary muscle cramp or spasm shows abundant discharges of motor unit potentials. In one patient, the posttetanic mechanical tension of the contracture reached only 17 percent of the peak tetanic tension, and twitches superimposed on the contracture fell by one half, as did the amplitude of the action potentials.[66]

Muscle Phosphofructokinase Deficiency (Type VII Glycogenosis)

Muscle phosphofructokinase deficiency, first described by Tarui and associates,[489] results from a defect in muscle phosphofructokinase that precludes the conversion of fructose-6-phosphate to fructose 1–6 diphosphate.[488] The clinical features include painful muscle contracture and myoglobinuria much like those of McArdle's disease.[4] An infant with this syndrome may have, in addition to limb weakness, seizures, cortical blindness, and corneal opacifications.[446] Distinguishing this entity from McArdle's disease depends on biochemical or histochemical determination of phosphofructokinase activity in the muscle biopsy specimen. Electromyography reveals no abnormalities between attacks. Studies have shown reduced phosphofructokinase activity not only in the muscle but also in the heart and liver.[10]

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 palmitoyl transferase catalyzes the reversible binding of carnitine to plasma fatty acids; once bound, carnitine can transport fatty acids across the mitochondrial membrane for oxida-

tion. Disorders of lipid metabolism include carnitine palmitoyltransferase deficiency, carnitine deficiency,[147] and other rare conditions such as lipid myoneuropathy with normal carnitine.[24]

Carnitine palmitoyltransferase deficiency, a rare disorder inherited as an autosomal recessive trait, results most commonly from a missense mutation that replaces a leucine for a serine residue at amino acid position 113 of the CPT II protein.[324,332] The patient develops painful muscle cramps and, on prolonged exercise or fasting, recurrent episodes of myoglobinuria.[28,87,141,302] Long-chain fatty acids not coupled to carnitine cannot shuttle across the inner mitochondrial membrane, leading to impaired oxidation of lipid substrates.[303] 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.[200] Muscle biopsy specimens may show no abnormalities or only a slight excess of intrafiber lipid droplets next to the mitochondria in type I fibers. Electrophysiologic studies, reported in only a few patients, have revealed normal electromyographic findings and normal motor and sensory nerve conduction velocities.[28,174]

Carnitine deficiency, probably inherited as an autosomal recessive disorder, is the first biochemical defect to be identified in muscle lipid metabolism.[12,168] Of the two forms of this condition, the restricted type develops lipid storage predominantly or exclusively in the muscle, causing 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 the systemic type, insufficient synthesis lowers the carnitine levels in the serum, liver, and muscle. Carnitine deficiency causes a congenital and slowly progressive myopathy of the limb-girdle type and episodic hepatic insufficiency.[62,268] Severe defects from bulbar and respiratory involvement may lead to death at an early age.[62,108,225] Some patients show features of both systemic and muscle carnitine deficiency.[88] Muscle biopsy specimens reveal an excess of lipid droplets mostly in the type I fibers, which depend on oxidation of long-chain fatty acids to a greater extent than do type II fibers.

Electromyographic studies reveal mild voluntary contractions that recruit small-amplitude, short-duration, polyphasic motor unit potentials in abundance. Slightly over half of patients have fibrillation potentials and other forms of spontaneous activity such as complex repetitive discharges. Neuropathy may develop in some,[322] but motor and sensory nerve conduction studies and tests of neuromuscular transmission usually reveal no abnormalities.

Most infants with a lipid metabolism disorder benefit from long-term therapy with L-carnitine.[449] Lipid utilization takes place in the mitochondria. This link may explain some overlap between lipid storage myopathies and mitochondrial myopathies.[64] In one series, 21 of 48 patients with mitochondrial myopathy had a plasma carnitine deficiency. Most responded favorably to L-carnitine therapy.[81] Treatment with riboflavin and carnitine had a favorable effect on pure myopathy associated with complex 1 deficiency.[46]

Mitochondrial Disease

Many proteins in the mitochondria are coded for not only in the nuclear DNA of the cell but also in their own DNA. Mitochondrial DNA codes for 13 proteins that are subunits of the respiratory chain complexes, two ribosomal RNAs and 22 transfer RNAs. Thus, defects in aerobic oxidation result from deletions and point mutations of the mitochondrial DNA. 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. Mitochondria, with their own genome predominantly inherited from cytoplasm of the oocyte, follow maternal transmission rather than mendelian ge-

netics, 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 fibers*. Abnormal fibers, often restricted to type I, show high activity when stained for oxidative enyzme. Heat shock proteins localized in ragged red fibers using monoclonal antibodies may act as a protein repair enzyme, catalyzing the refolding of misfolded proteins in the matrix of mitochondria.[466] Ragged red fibers are only a nonspecific abnormality, appearing also in polymyositis, hypothyroiditis, thyrotoxic myopathy, and spinal muscular atrophy. 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.[392,456] Patients with mitochondrial cytopathy have abnormalities of muscle energy metabolism, which can be tested by venous lactate response to subanaerobic exercise.[232,366,457]

Structural changes of the mitochondria cause progressive muscle weakness as a part of complex neurologic manifestations.[240,397,421,438] These entities comprise three subgroups: chronic progressive external ophthalmoplegia (CPEO), including Kearns-Sayre syndrome; mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS); and myoclonic epilepsy with ragged red fibers (MERRF). Mitochondrial gene studies[94,175,272,299,384,453] 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. Some reports indicate phenotypic heterogeneity,[458,505] for example, absence of ophthalmoplegia in CPEO,[485] chronic progressive external ophthalmoplegia in otherwise typical MELAS syndrome,[179] association with MERRF and Ekbom's syndrome consisting of lipomas, ataxia, and neuropathy,[78] and MERRF/MELAS overlap syndrome.[82]

In Kearns-Sayre syndrome, or ophthalmoplegia plus, a deletion of the mitochondrial DNA lead to progressive external ophthalmoplegia, retinitis pigmentosa, heart block, cerebellar syndrome, and a cerebrospinal fluid protein level above 100 mg/dl. Ophthalmoplegia occurs sporadically, with the clinical signs of ptosis and extraocular palsy appearing during childhood or adolescence.[43,269,443] As indicated by its alternative name, oculocraniosomatic neuromuscular disease with ragged red fibers,[380] characteristic features include ragged red fibers in muscle biopsy material, indicating a mitochondrial abnormality. Progressive weakness and fatigue may accompany a wide variety of neurologic deficits such as sensorineural deafness, cerebellar degeneration, endocrine abnormalities, sensory motor neuropathy, demyelinating radiculopathy, and myasthenic symptoms.[191,218,335,396] Laboratory studies reveal a moderate increase in cerebrospinal protein level and a mild elevation of serum CK.

Electromyographic results are normal or mildly abnormal, with early recruitment of low-amplitude, short-duration motor unit potentials. Clinically asymptomatic members of the family may have subtle changes consistent with subclinical myopathy as detected by conventional or single-fiber recordings.[183] In the more advanced stages, electrophysiologic studies may uncover neuropathic changes of the axonal type but no abnormalities of neuromuscular transmission.[495] Other neuropathic abnormalities include absent or reduced ankle jerk, impared distal vibration sense, and reduced sural nerve potentials.[336] In one series, 10 of 20 patients had abnormalities of nerve conduction, although only 5 had clinical features of a mild sensory motor neuropathy. In these patients, sural nerve biopsy material revealed a reduced density of myelinated fibers and axonal degeneration affecting myelinated and unmyelinated fibers.[533]

In another study,[132] brief periods of low-intensity exercise produced a decrease in twitch tension with only a very slight change in the amplitude of the compound action potential. Progressive dissociation between the electrical and mechanical responses suggests a failure of contraction rather than a disorder of the neuromuscular apparatus.[356] Abnormalities of multimodal evoked potentials often reveal

subclinical impairment of central sensory and motor pathways.[138,516] Blink reflex studies showed increased latencies and decreased amplitudes of R_1 and R_2 and greater habituation, perhaps indicating reduced excitability of brainstem pathways.[283]

The syndrome of MELAS results from multiple sites of point mutations that may give rise to the same or similar clinical features.[281,482] 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.[354] Some families with mitochondrial myopathy have deficiency of nicotinamide adenine dinucleotide–ubiquinone oxidoreductase, or complex I,[212] whereas others show decreased activity of complex I as well as cytochrome c oxidase, or complex IV, resulting in a fatal infantile mitochondrial disease.[363,420] Still others suffer from a marked deficit in the activity of complex IV.[392] Other genetic abnormalities found in association with a mitochondrial encephalopathy include deficiencies of two respiratory chain polypeptides and a circulating autoantibody to a mitochondrial matrix protein.[440] A deficiency of the mitochondrial enzyme lipoamide dehydrogenase may give rise to recurrent myoglobinuria and lactic acidemia.[164]

MERRF, or Ramsay-Hunt syndrome, results from a point mutation in a mitochondrial gene coding for a transfer RNA at various loci.[92,197,252] The syndrome may accompany celiac disease with or without overt gluten intolerance.[49,95,178,453] Clinical manifestations include myoclonus, rare generalized seizures, mitochondrial myopathy, cerebellar ataxia dementia, short stature, and sensorineural hearing loss.

Malignant Hyperthermia or Hyperpyrexia

Malignant hyperthermia, or hyperpyrexia, is a rare entity with autosomal dominant inheritance. Affected individuals have unusual susceptibility to anesthetics in general and to halothane and succinylcholine in particular.[69,387] After the induction of general anesthesia, affected individuals develop fasciculations and increased muscle tone. An explosive rise in temperature coincides with the development of muscular rigidity and necrosis. The remarkable hyperpyrexia, metabolic in nature, may result from abnormal depolarization of skeletal muscle by halothane.[201] Patients with malignant hyperthermia characteristically show reduced reuptake of calcium (Ca^{2+}) by the sarcoplasmic reticulum.[248] 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 patients have a more severe form, resulting in clinical symptoms in the absence of triggering agents and showing marked muscular weakness and elevated serum CK levels between attacks.[134]

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. The abnormal muscle shows hypersensitivity to caffeine, which normally causes muscle contracture by increasing the concentration of calcium in the sarcoplasm. 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.[68] As mentioned before, malignant hyperthermia may develop in association with central core disease.[194]

Toxic Myopathies

Some toxic myopathies have distinct clinical, morphologic, biochemical, or molecular characteristics. These myopathies are caused by ingestion of a toxic substance or are the side effects of drugs such as zidovudine, azidothymidine, cholesterol-lowering agents, and the combination of blocking agents with corticosteroids.[116]

Eosinophilia-myalgia syndrome, characterized by generalized muscle pain and eosinophilia, presumably results from ingestion of contaminated L-tryptophan. Most

studies emphasize neuropathy, but pure or combined myopathy also occurs as evidenced by electrophysiologic studies.[486] Pentazocine abuse masquerades as a myopathy, with proximal weakness and electromyographic findings of low-amplitude, short-duration polyphasic motor unit potentials.[99] Chronic alcoholism may cause myopathy not associated with a deficiency in mitochondrial energy supply.[83] Acute myopathy and myoglobinuria with a markedly elevated CK level may develop after gasoline sniffing, presumably as the result of lead toxcity.[284] Other infrequent causes of myopathy include mushroom poisoning from ingestion of *Amanita phalloides*, which also causes fulminant hepatic failure.[209]

Zidovudine induces a mitochondrial myopathy with ragged red fibers. Partial cytochrome c oxidase deficiency is a marker in this condition.[91] The symptoms ameliorate with discontinuation of the drug, or administration of prednisone or nonsteroidal anti-inflammatory drugs.[117] 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.[289] The accompanying signs of axonal neuropathy persist longer with little functional consequence.[288]

Therapeutic administration of chloroquine may cause a vacuolar myopathy.[448] Other drugs known to induce myopathy include bezafibrate,[518] ipecac,[151] finasteride used for prostatic hyperplasia,[219] and colchicine.[432,534] Focal myopathy with fibrosis also resuts from chronic intramuscular administration of analgesics such as heroin,[315] pentazocine,[129] pethidine,[307] and piritramide.[508] Deficiency of vitamin D may cause osteomalacic myopathy,[431] and selenium-deficient myopathy[382] may complicate human immunodeficiency virus infection.[90]

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 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 electromyographic features of myopathy.[258] Myopathy affects men more frequently than women, although women 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, similar to those in experimental mice.[274] Quantitative electromyographic studies have shown low-amplitude, short-duration motor unit potentials, even in the absence of clinically evident muscle weakness.[407] Other neuromuscular conditions commonly associated with thyrotoxicosis include exophthalmic ophthalmoplegia, myasthenia gravis, and hypokalemic periodic paralysis.

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 muscle contractibility—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*, is electrically silent.

Electromyography may show increased insertional positive waves with some transient myotonic discharges without evidence of clinical myotonia (see Fig. 14–6).

Elevations of serum CK levels, commonly a result of deranged creatine metabolism, do not necessarily imply the presence of myopathy.

Parathyroid Disease

The influx of calcium (Ca^{2+}) into axon terminals facilitates the release of acetylcholine at the neuromuscular junction, leading to excitation–contraction coupling. Calcium apparently plays an opposite role at the central junction of axons: A reduction in calcium here results in increased conductance for sodium (Na^+) and potassium (K^+), causing instability and hyperexcitability of the cell membrane. Thus, in hypoparathyroidism, chronic hypocalcemia gives rise to tetany, the most dramatic neuromuscular complication. Less frequently, neuromuscular symptoms in hypercalcemia may also result from osteolytic metastases, multiple myeloma, or chronic renal disease.

Varying degrees of proximal muscle weakness develop in patients with hyperparathyroidism,[394,464] usually affecting the pelvic girdle more than the shoulder girdle. Brisk stretch reflexes and occasional extensor plantar responses, combined with axial muscle wasting, raise the diagnostic possibility of motor neuron disease.

Electromyographic changes in tetany include the presence of motor unit potentials in doublets and triplets. Weak muscles show early recruitment of low-amplitude, short-duration motor unit potentials but no spontaneous activities. Nerve conduction studies reveal reduced amplitude of the compound muscle action potentials and normal motor and sensory nerve conduction velocities.

Adrenal and Pituitary Disease

Diseases of the adrenal and pituitary glands may give rise to nonspecific muscle weakness, as in Cushing's syndrome, acromegaly, or Addison's disease. Similar weakness also appears after systemic administration of corticosteroids or adrenocorticotropic hormone. 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, as might be expected from the degree of muscle wasting observed clinically.[401]

The compound muscle action potentials may show a reduced amplitude especially in proximal muscles. Endocrine or steroid myopathy with type II fiber atrophy usually reveals no specific abnormality in electromyography, which only assesses the initially recruited type I fibers. Patients with 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 recuitment of low-amplitude, short-duration motor unit potentials, but such mild abnormalities generally reverse with withdrawal of steroids. Patients with endogenous Cushing's syndrome may, however, have electromyographic abnormalities in keeping with an inflammatory myopathy.[378] Thus, such findings should not preclude the appropriate biochemical and imaging studies to exclude this treatable entity.

6 MYOSITIS

A variety of inflammatory processes affect the muscle, including the most frequently encountered polymyositis.[55,115] Although macrophages play an important role in mediating muscle fiber injury,[152] no studies have shown a persistent enterovirus as the cause of inflammatory myopathies.[261,306] Patients with dermatomyositis have skin

rash in conjunction with the signs and symptoms of muscle involvement. Despite the usually typical characteristic of myositis, its protean clinical presentation poses a considerable diagnostic challenge in some cases. Complicated schemes of classifying inflammmatory myositis reflect the uncertainty whether different clinical forms represent separate entities or a spectrum of the same illness. Subtypes based on the patient's age and underlying disorder include[54] (*1*) primary idiopathic polymyositis, (*2*) primary idiopathic dermatomyositis, (*3*) dermatomyositis (or polymyositis) associated with neoplasia, (*4*) childhood dermatomyositis (or polymyositis) associated with vasculitis, and (*5*) polymyositis or dermatomyositis associated with collagen vascular disease. 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.

Dermatomyositis

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 disease but rarely malignancy. Other common associations include Raynaud's phenomenon, lupus erythematosus, polyarteritis nodosa, Sjögren's syndrome, and pneumonitis. Accumulating evidence indicates that a complement-mediated microvasculopathy may play a pathogenic role. In one study of 39 dermatomyositis biopsy specimens,[276] fascicular comparison showed a significant correlation between focal myofibrillar loss considered ischemic in origin and capillarly deposits of membrane attack complex. Conversely, fascicles with perifascicular atrophy tended to show less membrane attack complex deposits. A perifascicular distribution of muscle fiber atrophy presumably implies the interruption of blood supply to the peripherally located fibers.[2,54] The expression of the 65 kD heat shock protein may also serve as an auto antigen recognized by an autoreactive T cell.[239]

The initial presentation comprises such nonspecific systemic symptoms as malaise, fever, anorexia, weight loss, and features of respiratory infection. Rare systemic manifestations include acute abdominal pain as a result of spontaneous hemorrhage.[381] Despite the traditional emphasis, pain and tenderness of affected muscles, if present, constitute neither a presenting nor a primary symptom in most patients. Some patients have demonstrable tenderness restricted to the muscles of the shoulder. Vague pains and muscle aches have no specific diagnostic value in this context. The skin lesions that may precede or follow the onset of weakness consist of a heliotrope or purple-colored rash over the cheeks and eyelids, often resembling the shape of a butterfly. Particularly prominent discoloration over the upper eyelids usually accompanies periorbital edema. An erythematous rash may also appear in exposed body parts such as the neck, 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 has had a favorable effect in some patients.[511]

Polymyositis

Except for the absence of skin lesions, the signs and symptoms of polymyositis closely resemble those of dermatomyositis. Initial systemic manifestations also bear close resemblence in the two varieties. Polymyositis primarily affects adults with possible underlying conditions such as collagen vascular disease or malignancy.[38] Conversely, children usually develop dermatomyositis with skin rashes and only rarely polymyositis as a paraneoplastic phenomenon.[451] Men have a higher incidence of neoplasms that in-

volve bowel, stomach, lung, or breast. Muscle-specific autoantibodies may play a role in the pathogenesis of paraneoplastic myositis.[190,504] Polymyositis has also accompanied billiary cirrhosis[532] and essential cryoglobulinemia.[520]

In human immunodeficiency virus (HIV)–associated polymyositis, patients may develop subacute structural myopathy characterized by selective loss of thick filaments and widespread formation of rod bodies.[210,472] Typical features consist of progressive proximal weakness, elevated serum CK level, and electromyographic changes consistent with myopathy with spontaneous activity.[459] Some patients with acquired immunodeficiency syndrome develop myopathies with unusual segmental vesicular changes of myofibers while receiving zidovudine therapy.[116,390] Thus, both infection with HIV type I and ingestion of zidovudine cause myopathy,[117,298] although HIV rather than the drug seems to play a more prominent role.[460,461] The muscle fibers or the cultured myotubes contain neither HIV sequences nor transcriptional products.[306] Therefore, HIV-associated polymyositis does not seem to result from a persistent infection of muscle fiber by the virus.

Human T-cell lymphotrophic virus (HTLV) type 1 infection causes various systemic conditions.[383] These include HTLV-1–associated myelopathy, or tropical spastic paraparesis (HAM/TSP), and polymyositis.[19] The myopathies associated with this condition have clinical and pathological features similar to those of a dystrophy, with a predominantly proximal weakness of the lower limbs.[140,198] Patients with cryptogenic adult myopathies, therefore, should have serological screening for HTLV-1 antibody. Retrovirus can trigger polymyositis not only in HIV-infected patients but also HTLV-1–infected patients,[529] even in the absence of detectable viral genome within the muscle fibers.[116]

Weakness, as the usual presenting symptom, 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. The initial involvement of pelvic girdle muscles causes difficulty in climbing stairs or rising from a chair. Subsequent paresis of the shoulder girdle renders patients incapable of lifting objects or combing their hair. In most patients, weakness soon spreads to involve the distal limb muscles. The disease may begin as a focal process that mimics a localized inflammatory reaction[231] or as paralysis and wasting of only one limb.[304] Weakness of the neck musculature shows predilection for the anterior rather than the 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.[51] The patient has normal muscle stretch reflexes until very late in the course of the disease. Atrophy may escape detection in the deep muscles of the pelvic or shoulder girdle but not in the orbicularis oculi or other superficial muscles. Conversely, focal lipoatrophy caused by loss of subcutaneous tissue may produce an appearance of focal muscle atrophy as might be seen in polymyositis.[251]

The serum CK level is usually a helpful indicator in determining the diagnosis and clinical course of myositis. Approximately 10 percent of patients with proven diagnoses, however, have no elevation even during acute stages. A normal enzymatic level despite active myositis suggests extensive muscle atrophy in longstanding disease.[54] Enzymes may leak from defects in the muscle plasma membrane as postulated in Duchenne dystrophy.[359] Alternatively, anastomosis of transverse tubules with terminal cisternae may cause the leakage.[98] Other inconsistent laboratory findings include elevated erythrocyte sedimentation rate and gammaglobulin. Magnetic resonance imaging show high intensity on T_2-weighted and normal intensity on T_1-weighted images in the active stage.[195,196,411] This abnormality, probably representing edema and inflammation, usually reverts to normal after corticosteroid therapy.

A triad of electromyographic abnormalities nearly always appear in untreated myositis, especially in the clinically weak muscles. They consist of (*1*) fibrillation potentials and positive sharp waves (see Fig. 14–8D), (*2*) complex repetitive discharges, and (*3*) polyphasic low-ampli-

tude, short-duration motor unit potentials with early recruitment (see Chapter 14–6 and Fig. 14–19A). Certain muscles, however, may remain electrically normal, even in patients with moderately advanced disease. For adequate assessment, therefore, examination should include a number of proximal and distal muscles with emphasis on those exhibiting moderate weakness clinically. Muscle biopsy findings include necrosis, phagocytosis, atrophy, degeneration and regeneration of both type I and type II fibers, internal nuclei, vacuolization, random variation of fiber size, mononuclear inflammatory infiltrates, and endomysial or perimysial fibrosis.[54] Single-fiber electromyography and histochemical investigations have revealed changes of the terminal innervation pattern consistent with reinnervation.[233] Denervation could result either from segmental necrosis of muscle fibers separated from the end-plate region[133] or from involvement of the terminal nerve endings. Electromyographic and histologic abnormalities often involve the paraspinal muscles predominantly or selectively.[348,475]

A retrospective study of 153 patients with polymyositis or dermatomyositis revealed the following electromyographic abnormalities:[55] (*1*) small-amplitude, short-duration, polyphasic motor unit potentials (90%); (*2*) fibrillation potentials, positive sharp waves, and insertional irritability (74%); (*3*) complex repetitive discharges (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,[135] electromyographic findings consisted of (*1*) fibrillation potentials, positive sharp waves, and polyphasic, low-amplitude, short-duration motor unit potentials with early recruitment (45%); (*2*) the above changes of motor unit potentials but without spontaneous activity (44%); and (*3*) no abnormalities (11%). No correlation emerged between the grade of clinical impairment at the onset of illness and the electromyographic findings. Contrary to the common description of low-amplitude potentials based on manual analysis, a quantitative study[499] revealed no amplitude differences between patients and normal subjects. The patients had three to four times more short-duration motor unit potentials than the controls. The average incidence of polyphasic potentials was four times higher in patients than in controls. Electromyographic findings change in the chronic stage, showing motor unit potentials with increased duration and amplitude, and late components of the type seen in satellite potentials.[483] Quantitative studies have revealed a minimal, if at all, increase in amplitude of macromotor unit action potentials, with a slight increase in fiber density.[31] Thus, reinnervation does not seem to play an important role in motor unit remodeling.

Compound muscle action potentials may show a decrement or, less frequently, an increment upon repetitive stimulation of the nerve.[242,245,514] Such electrophysiologic abnormalities often accompany clinical features of myasthenia. These patients probably have myasthenia gravis with concomitant inflammatory changes of polymyositis and represent an overlap of these two entities. Indeed, the electrophysiologic and histologic features characteristic of polymyositis commonly occur in patients with severe myasthenia gravis.

High-dose steroid therapy retards the progression in most patients, but the remission may not last long,[416] showing frequent clinical relapses.[305] In one series,[398] 30 of the 50 patients experienced relapses during a follow-up period of up to 13 years. Unlike in wallerian degeneration, spontaneous activity in polymyositis diminishes or disappears within a few weeks of successful steroid therapy.[419] Because the time course of this change correlates well with clinical improvement, serial electromyographic evaluation can objectively assess patient response to various therapies. It also helps distinguish a recurrence of myositis from the emergence of steroid myopathy. Patients refractory to conventional steroid and immunosuppressive treatment may respond to cyclosporin A[317] or high-dose intravenous immunoglobulin.[253] Clinical recovery generally parallels serial improvement in electromyographic findings. Motor unit potentials show progressive increases in

amplitude and duration initially some weeks or months after therapy, followed by diminution of the number of polyphasic units in a year or two.

Inclusion Body Myositis

In inclusion body myositis, a distinct but infrequently recognized inflammatory disease of skeletal muscle,[22,25,33,85,213,266,462] the pathologic characteristics consist of rimmed vacuole[256] containing osmophilic membranous whorls and intracytoplasmic or intranuclear filamentous inclusions. These filaments share properties with intracellularly formed amyloid proteins.[338] In fact, muscle fibers in both sporadic and hereditary inclusion body myositis contain β-amyloid protein, two other epitopes of the β-amyloid precursor protein,[21] and apolipoprotein E as intracellular deposits within rimmed vacuoles.[203,347] This phenomenon, therefore, stands in contrast to the extracellular deposits of amyloid in Alzheimer's disease. Some investigators stress the mixed myopathic and neurogenic aspects[161] and the difficulty of identifying rimmed vacuoles.[512] Unlike dermatomyositis, the disease lacks the features of collagen vascular involvement, but some patients have evidence of associated autoimmune disease.[278,297] Immunoreactivity with mumps virus antibodies has led to a postulate of a "slow" mumps infection[96] but without subsequent confirmation.[192,193] Mitochondrial DNA deletions may play a role in the pathogenesis, causing respiratory chain dysfunction in muscle fiber segments.[379]

The disease frequently affects distal muscles in men with early weakness of forearm flexors, knee extensors, and foot dorsiflexors.[8,186,309,444] It progresses slowly, taking a benign clinical course. The familial form usually[433] but not always[368] spares the quadriceps muscles, which the sporadic form severely affects. A small proportion of patients respond to corticosteroid or immunosuppressive therapy.[308] In refractory cases, other options include intravenous immunoglobulin and low-dose whole-body or lymphoid radiation.[7,47,327] A supervised progressive resistance training program may lead to gains in dynamic strength of the least weak muscles.[468]

Related disorders include distal vaculolar myopathy with complete heart block and no filamentous inclusions.[285] Familial inclusion body myositis among Kurdish-Iranian Jews shows slowly progressive limb-girdle muscle weakness with a remarkable sparing of the quadriceps muscles.[325] Frequent consanguinity and the familial incidence indicate a genetic cause with autosomal recessive inheritance[433] and various types of hereditary inclusion body myopathies map to chromosome 9p1–q1.[18,246] Autosomal dominant myopathy with congenital joint contractures, ophthalmoplegia and rimmed vacuoles constitutes another variant of hereditary inclusion body myopathies.[122]

Electromyographic abnormalities, as in other myositic conditions, comprises fibrillation potentials, positive sharp waves, complex repetitive discharges, and low-amplitude, short-duration motor unit potentials with early recruitment. Most patients have changes suggestive of a mixed neurogenic and myopathic pattern with or without myotonic discharges.[263,297] In one series, quantitative studies of interference pattern showed changes consistent with myopathy in all 13 patients tested.[32] About one third of cases have a pattern of large and small motor unit potentials, considered highly suggestive of inclusion body myositis to some.[262]

Other Myositic Diseases

Bacterial and viral infections of muscle occur less commonly than dermatomyositis and polymyositis.[106,142,254] Parasitic infection, however, prevails in tropical countries. In cysticercosis, *Taenia solium* mostly affects the trunk muscles,[439] whereas in trichinosis, *Trichinella spiralis* preferentially invades the extraocular muscles.[126] HIV-infected patients with fever, encephalitis, multiorgan dysfunction and elevated serum CK level of obscure origin may have skeletal muscle toxoplasmosis.[204] Patients with idiopathic inflammatory myopathy may also have increased anti-toxoplasma antibodies prob-

ably as the result of concurrent rather than causal infection.[67]

Inflammation of muscles may follow the use of an antigenic agent, concomitant with a variety of other allergic reactions.[139] A myopathy may develop in conjunction with L-tryptophan-induced eospinophilia myalgia syndrome usually associated with axonal neuropathy.[75,434]

Myositic conditions may also accompany systemic disorders such as histoplasmosis,[521] scleroderma,[156] Behçet's disease,[531] tuberculosis,[125] and sarcoidosis,[150,202,405] sometimes accompanied by a rash typical of dermatomyositis.[250] Neuromuscular involvement in patients with Legionnaires' disease include myosites, with elevations of serum CK level. The organisms may invade the muscle directly in some patients.[525] Biopsy-proven polymyositis may complicate severe poisoning by ciguatera fish toxin, which apparently predisposes the muscle to inflammation.[474] Myositis may also develop in association with giant cell arteritis.[72]

Focal myositis, a benign inflammatory pseudotumor of skeletal muscle, may cause a localized painful swelling within the soft tissue, sometimes as a treatable cause of compression neuropathy[6] or dropped head syndrome.[50] The disease may involve any muscle of the limb, neck, abdomen, and face as an indolent lump.[79,104,367] Histologic examination reveals lymphocytic infiltration, scattered muscle fiber necrosis and regeneration, and interstitial fibrosis. Complete recovery follows surgical removal of the lesion. Soft tissue sarcoma may mimic the condition, presenting as atypical limb pain.[124] Diabetic muscle infarction also begins with the acute onset of focal pain and swelling in the thigh as an unusual neuromusular complication of diabetes.[34,53,300] Magnetic resonance imaging reveals the focal region of muscle damage, which shows confluent areas of necrosis and edema in muscle biopsy material. A lesion of the anterior compartment involves the quadriceps, posterior compartment, and hamstring muscle group.[34] In progressive unilateral hypertrophic myopathy, the affected muscles show complex repetitive discharges, necrosis, and variations in fiber size.[400]

7 OTHER MYOPATHIES

Critical Illness Myopathy

Acute quadriplegic myopathy may develop after large parenteral doses of corticosteroid in myasthenia gravis,[391] following liver transplantation,[80,528] or as a complication of treatment with steroids, nondepolarizing blocking agents, or both in patients with severe systemic illness such as renal failure, sepsis, or status asthmaticus.[236,295] Neuromuscular disorders play an important role in prolonged ventilator dependency.[470] Acute myopathy predominates over acute axonal polyneuropathy as the cause of generalized weakness in intensive care units.[294] A muscle biopsy specimen shows prominent necrotizing fibers with an extensive loss of thick myosin filaments and relative preservation of thin actin filaments.[120,221,293] Immunocytochemical analysis reveals depletion of either fast or slow myosin[346] with some evidence of calpain-mediated proteolysis.[454]

Electromyographic studies of critical illness myopathy generally show a mixture of neurogenic and myopathic changes suggestive of a necrotizing myopathy.[180,211,418,536] Some of these patients may have the characteristic pattern of evolution with early evidence of denervation followed by changes consistent with myopathy later during recovery phase.[414,418] Nerve stimulation elicits small compound muscle action potentials, with evidence of defective neuromuscular transmission in some. In one study, direct muscle stimulation revealed muscle membrane inexcitability in severe quadriplegic myopathy in contrast to retained excitability in polyneuropathy.[413] Steroids may have suppressive effects on membrane excitability, as suggested by a decline in muscle fiber conduction velocity during short-term, high-dose methylprednisolone therapy.[509]

Myopathies Associated with General Medical Conditions

Amyloidosis may cause myopathy, although less commonly than neuropathy.

In the typical form, findings include macroglossia from pseudohypertrophy and hoarseness of voice, although amyloid myopathy may develop in the absence of these features. In contrast, systemic amyloidosis may accompany severe, debilitating myopathy.[255] Progressive amyloid myopathy has electron microscopic features distinct from the intracellular amyloid deposits characteristic of sporadic or inherited inclusion body myositis[361] (see this chapter, part 6). Respiratory failure may develop as a presenting feature with amyloid infiltration of the diaphragm.[20] In one series of 17 patients, electromyography showed fibrillation potentials in 69 percent of muscles, most frequently in the gluteus medius and paraspinals, and motor unit potentials consistent with myopathy in 72 percent of muscles.[428]

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 electromyographic findings consistent with myopathy, slightly elevated CK level, and myopathic changes with type I fiber predominance in muscle biopsy.[279]

Although rare, proximal weakness, accompanied by electromyographic abnormalities, may result from extensive leukemic cell infiltration or discrete carcinomatous metastatic desposits in the affected muscle.[149,377] In paraspinal muscle metastasis, electromyographic examination demonstrates marked segmental involvement of the posterior primary ramus with relative sparing of the anterior ramus.[290]

Rare familial myopathies showing changes resembling inclusion body myositis may accompany periventricular leukoencephalopathy[105] or thrombocyopenia.[319] Another rare familial myopathy has an unusual distribution of desmin intermediate filament proteins in skeletal and probably also cardiac muscle.[507]

Sarcoplasmic reticulum adenosine triphosphatase deficiency, inherited as either autosomal recessive or dominant, causes a distinct myopathy with impaired muscle relaxation aggravated by exercise.[119,402] Dantrolene sodium therapy may improve exertional rhabdomyolysis, elevated serum CK level, and abnormal ischemic exercise test showing excessive potassium afflux.

A primary tardive myopathic condition predominantly affecting the entire axial musculature may cause dropped head syndrome and bent spine syndrome mostly in elderly patients.[375] Some patients may respond to prolonged immunosuppressant treatment.[422]

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Chapter 29

DISEASES CHARACTERIZED BY ABNORMAL MUSCLE ACTIVITY

1 INTRODUCTION

Muscles may stiffen pathologically because of lesions involving the central nervous system, peripheral nerve trunk, axon terminal, or muscle membrane. Myotonia, or delayed relaxation of voluntarily or reflexively contracted muscle, occurs in several myogenic syndromes, including myotonic dystrophy, myotonia congenita, paramyotonia congenita, and a form of periodic paralysis. Advances in molecular biology have resolved some of the issues re-

garding classification of these entities. Two groups of disorders have now been defined: (*1*) muscle sodium channel–associated diseases, which include hyperkalemic periodic paralysis and its clinical variants as well as paramyotonia congenita; and (*2*) muscle chloride channel–associated disorders, which comprise both the dominant and recessive forms of myotonia congenita.[150,170,251,298,349,352,353] Involuntary muscle contraction also results from disorders of the peripheral nerve as in myokymia, Schwartz-Jampel syndrome, and neuromyotonia or continuous muscle fiber discharge. In still other sustained muscle contractions, spontaneous discharges originate centrally, as in the stiffman syndrome. Other conditions with abnormal muscle activity include the common cramp, contracture, tetanus, tetany, and hemifacial spasm. Muscle percussion may induce myoedema or stationary, electrically silent muscle mounding, considered physiologic with no implication of a neuromuscular disorder[197] despite its traditional link to hypothyroidism (see Chapter 28–5).

Several electrophysiologic techniques help characterize involuntary movement and determine the site of abnormal discharges.[129] 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. In contrast, curarization does not affect abnormal discharges originating from intrinsic muscle fibers. Some cramp syndromes display a distinctive pattern of abnormalities on electromyography. Others produce a normal interference pattern, although the subject has no voluntary control over the number and frequency of discharging motor units. In contracture, unlike true cramps, the contracted muscle is electrically silent.

2 MYOTONIA

In myotonia, the muscle membrane, once activated, tends to fire repetitively, inducing delayed muscle relaxation. Unlike cramp or spontaneous spasm, this type of prolonged muscle contraction causes no pain. Myotonic discharges, provoked by voluntary contraction, muscle percussion, or needle insertion, characteristically wax and wane at varying frequencies up to 150 Hz.[415] Amplitude decrements often accompany shortening of the interspike interval, giving the impression that motor unit potentials cannot keep up with the increasingly higher firing rate. Conversely, increments tend to occur in association with a declining rate of discharges. These relationships, however, sometimes reverse, suggesting that different ionic mechanisms may dictate changes in 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 postactivation and percussion myotonia. Myotonic muscles typically have reduced torques during maximal voluntary contraction and decreased mean amplitude of the compound muscle action potentials.[36] Muscle action potentials decline further with repetitive nerve stimulation (see Chapter 10–8) or after isometric exercise.[428,431]

Myotonic discharge with or without clinical myotonia develops in a number of metabolic muscle diseases such as hyperkalemic periodic paralysis, acid maltase deficiency,[134] hyperthyroidism,[329] hypothyroidism, familial granulovacuolar lobular myopathy,[221] and malignant hyperpyrexia (see Chapter 28–4). Myotonia and myositis may also constitute part of the symptom complex seen in multicentric reticulohistiocytosis[7] and possibly paraneoplastic syndrome.[335] Myotonic and repetitive discharges also appear in hypokalemic myopathy associated with glycyrrhizin-induced hypochloremia.[188] Other medications known to induce a myopathy with occasional myotonia include the hypocholesterolemic agent, diazocholesterol,[419] and colchicine.[390] In all these entities, myotonia plays neither a predominant nor an essential role as in myotonic dystrophy, myotonia congenita, and paramyotonia.

The specific defect in myotonia causing membrane hyperexcitability remains unknown. Potassium ions (K^+) accumulate in the transverse tubular system during activation of the muscle membrane, giving rise to a negative after-potential (see Chapter 2–3, Fig. 2–3). This degree of depolarization, although normally not large enough to generate an action potential, could initiate repetitive discharges in the myotonic muscle. Such membrane instability may result from an abnormally low chloride (Cl^-) conductance in the myotonia of goats or those induced experimentally with drugs.[71,154,421] In humans, only myotonia congenita shows a low chloride permeability.[368] In myotonic dystrophy, a combination of an incomplete sodium (Na^+) channel inactivation and potassium ion accumulation in the T-tubule compartment may lead to myotonia and paralysis.[82] As part of multiorgan involvement, erythrocytes may[308,340] or may not demonstrate biochemical and biophysical abnormalities.[155]

Myotonic Dystrophy

Myotonic dystrophy is one of the most common dominantly inherited muscular dystrophies, with an incidence of 1/8000. The mechanisms underlying the myotonic phenomenon, although not clearly established, may involve the sodium channel,[388] the apamin-sensitive potassium channel,[35] or calcium metabolism.[231] The responsible gene, which maps to serine/threonine protein kinase on 19q13.3, normally has a run of 5–30 copies of the trinucleotide sequence CTG in the 3′-untranslated region of the mRNA.[10] In myotonic dystrophy, this repeat expands to more than 50 copies,[63,217,232] showing a positive correlation between repeat size and clinical severity.[343,453] 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 or, less frequently, contract during oogenesis, possibly accounting for genetic anticipation or earlier onset of disease in subsequent generations, largely confined to the offspring of affected mothers. In addition, mitochondrial inheritance of modifying genes or imprinting may play a role in materal inheritance of congenital myotonic dystrophy. Rare chromosomal aneuploidies associated with this disorder include Klinefelter and Down syndromes.[45] In one family, 8 of 13 members with hereditary motor and sensory neuropathy also had signs of myotonic dystrophy. The syndrome could result from an allelic form of the myotonic dystrophy gene or two closely linked genes on chromosone 19.[422]

Typically, the illness begins in adolescence or early adult life. Neuromuscular symptoms consist 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 eventually spreads to involve all the muscles, including the flexors of the neck. In atypical cases with onset in late adulthood, the initial weakness may predominantly involve proximal rather than distal limb muscles.[239] The disease affects numerous other systems as evidenced by cardiac abnormalities,[306] and disturbances of ocular motility,[6] bowel symptoms,[198] respiratory infections, polyneuropathy,[68,474] personality disturbances,[113] and low intelligence. Cognitive abnormalities, associated with relatively mild brain pathology,[332] remain relatively stable despite progressive motor deficits.[269] Unusual response to certain medications such as barbiturates increases the risks of general anesthesia.[360] Symptomatic patients have greater susceptibility to anesthetic and surgical complications.[277] 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.

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 pa-

tient 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. Usually, however, grip or percussion myotonia 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.[101] Additional features include early frontal baldness, cataracts, gynecomastia, testicular or ovarian atrophy, and cardiac conduction defects. Neurogenic features also occur as part of the generalized membrane abnormality. These include occasional hypertrophy of peripheral nerves[52] and eye movement abnormalities.[472]

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*, neuromuscular and systemic manifestations develop during the neonatal period in offspring of mildly affected mothers.[184,185,220,437] 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.[180] 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.[53,95] Infants frequently die of respiratory infections. Curiously, congenital myotonia rarely shows a paternal inheritance, appearing nearly always in children born to myotonic mothers. Approximately 10 percent of all the offspring and 20 percent of affected offspring from women with myotonic dystrophy develop a congenital expression. If a mother has previously given birth to a child with congenital myotonic dystrophy, a subsequent child has an 80 percent risk of having the same.

Electromyography shows myotonic discharges giving rise to "motorcycle" sounds (see Fig. 14–7) in all affected adults and approximately one half of the relatives at risk for myotonic dystrophy.[344] In 25 patients from 15 different families,[430] electrical myotonia occurred most frequently in the intrinsic hand muscles and orbicularis oculi, less commonly in the tibialis anterior and extensor digitorum muscles, 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 myotonic dystrophy.[428] Patients with partial syndrome, however, lack clinical or electrical evidence of myotonia.[348] During infancy and early childhood, patients may have neither characteristic clinical myotonia nor myotonic discharge.[125] Needle studies may show a myopathic process with low-amplitude, short-duration, polyphasic motor unit potentials.[72] Surface recording reveals abnormal decrements in the first seconds of sustained contraction.[92]

Other electrophysiologic abnormalities include mildly slowed motor as well as sensory nerve conduction velocities,[25,211,257,274,303,377,383] a striking reduction in the number of functioning motor units,[211,280] and decreased velocity of the visually guided saccades correlated with the prolonged visual evoked potential latencies.[445] The decreased smooth pursuit seen in some patients may result from periventricular white matter abnormalities rather than extraocular myopathy.[51] Patients may also have a reduction in heart rate response to standing and in blood pressure response to sustained handgrip, as well as prolonged latency to reach peak velocity of pupillary light reflex. All these may reflect dysfunction of skeletal and smooth muscles rather than the autonomic nervous system.[114] The severity of the neuropathic changes does not correlate with the degree of muscular atrophy and weakness.[334] Despite slowing of peripheral motor conduction, central motor conduction time may remain within the normal range[105] or show only

a slight delay associated with increased threshold[331] when tested by transcranial magnetic stimulation.

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 to estimate the size of the CTG repeat discloses asymptomatic gene carriers, who may escape detection by neurologic examination, slit-lamp test, or electromyography.[67] A normal gene contains less than 30 repeats, whereas a myotonic dystrophy allele has more than 50 repeats. Additional confirmatory features include electrical pattern of repetitive discharges, demonstration of lens opacities, and a degenerative pattern in muscle biopsy. which reveals type I fiber atrophy and long chains of internal nuclei. Some biopsy specimens have shown a severe deficiency of type IIB fibers,[13] which may develop consequent to lasting myotonic activity rather than genetic factors.[189] In one study, the severity of muscular weakness correlated with the predominance of type I fibers and the reduced number of hypertrophic type II fibers.[452] Peripheral nerve morphometry has shown no significant abnormality in the cutaneous branches of the common peroneal nerve.[345] Therapeutic trials have generally failed to induce remarkable clinical improvement, although amitriptyline combined with exercise may provide some benefit.[293]

Myotonia Congenita

Patients with myotonia congenita characteristically show stiffening and at times paralysis of the skeletal muscles during voluntary contraction after a period of rest. Genetic studies have revealed about 30 point mutations and 3 deletions in CLCN-1, the gene encoding the skeletal muscle chloride channel, ClC-1 on chromosome 7.[29,30,234,475] Genetic and clinical features distinguish three different varieties of myotonia congenita. The first type originally described by Thomsen[450] in four generations of his own family shows an autosomal dominant trait. The disease affects both genders equally, showing characteristic features of myotonia and calf hypertrophy with little or no loss of strength. Muscle biopsy material show few or no degenerative changes. Myotonia appears in infancy or early childhood, but remains mild throughout life. Occasional asymptomatic patients with electromyographic evidence of myotonic discharge may represent sporadic cases of Thomsen's disease. The second, more common type, as described by Becker,[34] appears in an autosomal recessive fashion but affects men more frequently than women. More severe myotonia develops in the recessive type, although the two varieties otherwise share similar clinical features.[435,492] Electrical after-activity results in slowed relaxation of the muscle.[202] In a third, rare type of myotonia congenita, the patient may have, in addition to myotonia, painful muscle cramps induced by exercise.[33] A mutation in the skeletal muscle voltage-gated sodium channel α-subunit gene may cause painful congenital myotonia.[379]

In myotonia congenita, 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. Their Herculean appearance, when present, stands in striking contrast with 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 is a useful provocative test. Muscle biopsy material reveals the absence of type IIB fibers and the presence of internal nuclei, al-

though to a lesser extent than in myotonic dystrophy.[104] Painful muscle stiffness provoked by fasting or oral potassium (K^+) 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.[399,425] In some patients, acetazolamide alleviates myotonia dramatically.[459] Some patients with a resistance to one type of antimyotonic agent such as mexiletine or focainide may respond well to another type of sodium channel blocking agent, for example, flecainide.[379]

Electromyography plays an important role in establishing the diagnosis of myotonia. In one study, 67% of the heterozygous carriers of recessive myotonia congenita had electrical myotonia, making distinction difficult from very mildly affected parents with dominant myotonia congenita.[121] Repetitive nerve stimulation may cause a progressive decline in successively evoked muscle action potentials as a result of increased muscle fiber refractoriness (see Chapter 10–8). Unlike in myasthenia gravis, the decremental tendency continues toward the end of a train, with a faster rate of stimulation producing a greater change. This phenomenon occurs in any type of myotonic disorder, but particularly in the Becker variety[5] showing a close association to the transient muscle weakness considered characteristic of this entity.[119] Single-fiber studies show a progressive decline, sometimes leading to complete disappearance at 10 or 20 Hz direct stimulation of muscle fibers.[240,290] A small percentage of muscle fibers in normal human limb muscle may show similarly profound decrements in amplitude but progressive waveform changes and conduction block characterize myotonic fibers.[458]

Proximal Myotonic Myopathy

The characteristic features of proximal myotonic myopathy, a hereditary disorder, include cataracts, myotonia, and predominantly proximal weakness without muscle pain or atrophy. Unlike myotonic dystrophy, patients have no weakness of the facial muscles, no signs of mental disturbance, and no striking muscular atrophy.[239,275,366,367,426] Despite the clinical similarities, genetic testing differentiates it from myotonic dystrophy based on the absence of the chromosome 19 CTG repeat.[366,367,397,398,451] The exercise test also distinguishes the two entities.[398] On needle examination, myotonic discharges worsen with heat and abate with cold, perhaps indicating another physiologic basis different from that in traditional myotonic syndromes.[397]

Paramyotonia Congenita

Paramyotonia congenita of Eulenburg,[137] transmitted by a single autosomal dominant gene, affects both sexes equally.[32,34] Like hyperkalemic periodic paralysis, the responsible mutations involve the adult skeletal muscle sodium channel gene on chromosome 17, although the abnormality is not identical.[350,351] The symptoms begin at birth or in early childhood, showing no improvement with age. Paradoxically the myotonia intensifies rather than remits with exercise,[179] thus the name *paramyotonia*. When exposed to cold, the patient may develop stiffness of the tongue, eyelids, face, and limb muscles. Electrical discharges disappear with cooling, despite increasing muscular stiffness.[315,486] Thus, the cold-induced rigidity may not represent true myotonia. The disorder closely resembles hyperkalemic periodic paralysis. Attacks of flaccid weakness accompanied by 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 effectively,[38] although its administration may conversely trigger severe weakness in some patients. The lidocaine derivative tocainide can also effectively suppress myotonia, but it may cause reversible agranulocytosis.[418,428] Mexiletine, another class 1b lidocaine derivative, also demonstrated clinical efficacy in several myotonic syndromes.[85,208]

Electromyography shows evidence of myotonia and, in some, fibrillation potentials on cooling.[179] The compound muscle action potential steadily declines on repetitive nerve stimulation.[75,76] Cold induces a substantial fall in amplitude of the evoked response, worsens the decremental tendency, and virtually abolishes myotonic discharges as well as voluntary recruitment of motor unit potentials.[208,431,433] Stimulation of the nerve shows normal conduction between attacks but fails to elicit muscle action potentials during episodes of paralysis.

3 PERIODIC PARALYSIS

Periodic paralysis results from reversible inexcitability of muscle membranes. The traditional classification distinguishes hypokalemic, hyperkalemic, normokalemic types based on the serum level of potassium (K^+) during a paralytic attack. All three categories share a number of clinical features, and changes in serum potassium level show no direct cause and effect relationship with paralytic events. Indeed, episodes of weakness associated with either hypokalemia or hyperkalmia can occur in a given individual.[90] Of these, primary hereditary types consist of hypokalemic periodic paralysis and potassium-sensitive hyperkalemic or normokalemic periodic paralysis. The secondary acquired types include thyrotoxic hypokalemic periodic paralysis, acute or chronic potassium depletion and retention, hypokalemia caused by renal tubular acidosis[37] and chronic hypernatremia.[267] In typical cases of periodic paralysis, nerve stimulation demonstrates a decrease in compound muscle action potential amplitude after several minutes of exercise. In patients with thyrotoxic hypokalemic periodic paralysis, this abnormality may show a dramatic improvement after treatment when they attain a euthyroid state.[207]

In hyperkalemic periodic paralysis, periodic weakness typically follows a low carbohydrate intake or exercise. An elevated serum potassium level and frequent myotonia characterize the episode of weakness. Studies have identified some 20 different point mutations in the gene coding for the α-subunit of the adult skeletal muscle sodium (Na^+) channel on chromosome 17q23–25.[81,193,387,476] Hyperkalemic or normokalemic type, when accompanied by myotonia, bears great resemblance to paramyotonia congenita. Corticotropin-induced potassium changes precipitate weakness in both hypo- and hyperkalemic periodic paralysis, making it feasible to use adrenocorticotropic hormone gel administration as a provocative test.[427]

During an attack of periodic paralysis direct or indirect stimulation fails to excite the muscle membrane.[194] An end plate potential persists during the paralytic episodes, but action potentials cease to propagate along the muscle fibers (see Chapter 13–4).[172] In the hypokalemic types, application of calcium (Ca^{2+}) induces normal contraction in the muscle fibers stripped of their outer membranes.[135] Thus, inexcitability must result from dysfunction of muscle membrane rather than the contractile elements. An important finding common to hypokalemic[194,372] and hyperkalemic periodic paralysis[64] includes substantial depolarization of the resting membrane potential, presumably reflecting increased sodium conductance together with normal potassium and chloride (Cl^-) conductance.[194] These observations suggest that persistent inactivation of sodium channels leads to muscle fiber inexcitability at least in hypokalemic periodic paralysis. Interestingly, tetrodotoxin, a sodium channel blocker, cannot reverse the depolarization block.

Hypokalemic Periodic Paralysis

Thyrotoxic periodic paralysis typically occurs between 20 and 40 years of age, in contrast to the primary form in which the onset of attack usually begins before age 20 and almost invariably before age 30.[169] Otherwise, the two entities have indistinguishable clinical and biochemical findings. Predominance in Oriental males suggests some genetic factors predisposing the muscle membrane for easy induction of paralytic attack under a slightly low potas-

sium condition.[250] Genetic abnormalities may affect calcium conductance in skeletal muscle, although how calcium channelopathies lead to paroxismal weakness remains unknown.[167] A thyrotoxic variety can occur as an isolated manifestation of incipient thyrotoxicosis.[483] 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, and weight loss.[169] The diagnosis then depends on a depression of thyroid stimulating hormone level; T_3 and T_4 levels may remain normal or only slightly elevated. Patients may respond to a β-blocker but not to acetazolamide, the usual treatment for hypokalemic periodic paralysis.

Autosomal dominant and sporadic hypokalemic periodic paralysis can result from mutations of the dihydropyridine receptor,[354] affecting men more than women.[136,156] Although variable in onset, episodes of paralysis typically begin in the second decade. During an attack, weakness starts in the legs and gradually spreads to involve all the muscles of the body, with the exception of the ocular muscles, diaphragm, and other respiratory muscles. 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 complete recovery. These attacks vary in frequency and severity but tend to remit after age 35 years. Eyelid myotonia, originally described in the hyperkalemic type of periodic paralysis, may also appear in the hypokalemic variety.[363]

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.[456,471] Although this and other carbonic anhydrase inhibitors can cause nephrolithiasis, successful lithotripsy or surgical removal of renal calculus permits continued treatment.[443] Between attacks, the patient has neither clinical nor electrophysiologic abnormalities, except for the development of progressive myopathy.[136,338] The myopathy shows a strong correlation to age but not to the history of paralytic attacks, when judged by mean computed tomographic grading.[254] Hypokalemic myopathy may also result from other conditions associated with potassium loss.[389] The light microscope reveals few structural abnormalities. Electron microscopic studies, however, show vacuoles arising from local dilation of the transverse tubules and sarcoplasmic reticulum.[133]

Electrophysiologic studies during severe paralytic episodes show a reduction in the number of voluntarily recruited motor unit potentials and decreased muscle excitability with preservation or enhancement of end-plate noise (see Chapter 13–4). Thus, electrical stimulation of the nerve elicits no muscle action potentials. Less severe cases show decreased amplitude of the compound muscle action potentials in proportion to the degree of weakness. Repetitive nerve stimulation at a rate of 10–25/s may produce an incremental response in mildly affected muscles[172] but no change in very weak muscles.[80] Analogous to electrical recovery with repetitive stimulation, muscle strength improves temporarily after gentle exercise, followed by severe rebound weakness. A prolonged exercise test reveals the gradual decline of the elicited muscle response, serving as a measure of muscle membrane excitability.[14,282] In one study of a large kinship, surface studies revealed decreased muscle fiber conduction velocity and lowered power spectra in the affected members compared with asymptomatic offspring.[493]

Hyperkalemic Periodic Paralysis (Adynamia Episodica Hereditaria)

In hyperkalemic periodic paralysis, an autosomal dominant disorder that affects the two genders equally, episodes of flaccid weakness accompany an elevated serum potassium level.[54,156] The disease begins in infancy or early childhood with spells of generalized hypotonia. 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 some linkage between hyperkalemic periodic paralysis and paramyotonia congenita. Both entities may appear in a single family, suggesting that they represent part of the spectrum of a single or closely related genetic disorder.[109] Evoked response testing, with exercise and cold provocation, may help determine the physiologic pattern that predominates in any individual case.

Between attacks, electromyography may reveal only increased insertional activity or show myotonic potentials and complex repetitive discharges. During a paralytic episode, muscle irritability and myotonic discharges increase, although electrical or mechanical stimulation fails to excite the muscle. In the presence of prominent myotonia, repetitive nerve stimulation may cause a decrement of the evoked muscle action potentials,[263] a tendency accentuated by cooling.[371] An abundance of low-amplitude, short-duration motor unit potentials and early recruitment suggest progressive myopathy, which tends to develop at a time when attacks of paralysis decline in frequency. Muscle biopsy specimens show variability in fiber size, internal nuclei, and fibers with vacuoles.[55]

Possible physiologic mechanisms underlying episodic paralysis[252] include reduced muscle membrane potentials at rest,[103] reversible depolarization during the attacks,[54,64,73] and neural hyperexcitability.[406] Sustained immobility reduces the amplitude and area of electrically elicited compound muscle action potentials, 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. 10–15).[434]

Normokalemic Periodic Paralysis

Normokalemic periodic paralysis is a very rare condition that also seems to have an enigmatic relationship to potassium. Only a few reports have appeared since the original account[346] describing attacks of flaccid quadriplegia in infancy with normal serum levels of potassium. The clinical features closely resemble those of hyperkalemic periodic paralysis[289] of which the normokalemic type may be a variant.

4 NEUROMYOTONIA

Isaacs[205,206] originally described two patients with progressive painless stiffness and rigidity of the trunk and extremities. Subsequent authors referred to this entity either as the Isaacs syndrome or, more descriptively, as *continuous muscle fiber activity*,[206,260,264,394,463] *neuromyotonia*,[288] *neurotonia*,[479] or *generalized myokymia*.[212] 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.[441] Symptoms begin at any age, although rarely in the neonatal period.[46] Similar sustained muscle contractions may develop focally in the trigeminal nerve distribution following radiation of its motor branch.[123]

Some reports describe hereditary forms of sustained muscle activity,[16,20] at times in association with a neuronal type of Charcot-Marie-Tooth disease[469] and other forms of sensory motor or motor neuropathy.[159,181,222] Continuous muscle activity has also appeared in association with distal spinal muscular atrophy,[84] central pontine myelinolysis,[9] chronic inflammatory demyelinative polyneuropathy,[324] multifocal motor neuropathy,[473] and myasthenia gravis.[191,272]

Clinical evidence for a possible autoimmune etiology include the presence of oligoclonal bands in the spinal fluid, improvement following plasma exchange, as-

sociation with thymoma and myasthenia gravis, raised antiacetylcholine receptor antibody titers, and induction by penicillamine. These clinical data, taken together with physiological changes observed in mice injected with patients' immunoglobulin G suggest antibody-mediated autoimmune mechanisms, possibly directed to peripheral nerve potassium (K^+) channels.[15,187,309,310,414,420,484] In a patient with acquired neuromyotonia, a spinal epidural abscess may have triggered the production of the autoantibodies detected during his acute illness.[265]

In milder forms of the syndrome, the abnormal activity appears restricted in degree and distribution, inducing focal muscle twitching, especially in the legs. Asynchronous contraction of single or multiple motor units may produce generalized myokymia.[16] In a severe form, continuous and excessive muscle contraction may give rise to abnormal posture, hyporeflexia, and the 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. Laryngeal spasm may develop.[209,253] Enlarged muscles likely reflect pseudohypertrophy. A marked type I myofiber predominance probably represents conversion of type II fibers to type I fibers from continuous neuromyotonic stimulation.[177] The patient may have an increased level of gamma-aminobutyric acid in the cerebrospinal fluid.[394]

In myotonia abnormal muscle activity occurs only after voluntary or induced muscle contraction. In contrast, as one of several causes of visible myokymia, 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.[46,205,206] Local administration of curare eliminates the activity. Intramuscular injection of the botulinum toxin can also eliminate or greatly diminish the discharges.[120] Diphenylhydantoin and carbamazepine render beneficial effects in most patients[16,20,205,206] but not all. Intravenous administration of methylprednisolone may also reduce the spasm.[210]

Electromyographic abnormalities consist of fibrillation and fasciculation potentials and doublet, triplet, or multiple single-unit discharges that have a high intraburst frequency, the frequency of the bursts themselves being irregular.[310] In advanced stages, studies reveal characteristic spontaneous discharges firing rhythmically and continuously in all involved muscle groups. Waveforms of varying configuration usually appear at high frequencies up to 300 Hz, representing either motor unit or single-fiber discharges. A marked decrement in successive amplitude results from an inability of the motor unit to follow rapidly recurring nerve impulses. This high-frequency, decrementing discharge produces a unique musical sound, "pings," that differs from other spontaneous potentials, including myotonic discharge.[242] 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.

Microelectrode studies of end-plate potentials in an intercostal muscle biopsy have demonstrated normal miniature end-plate potentials and no evidence of quantal squander.[242] Electrophysiologic abnormalities include hyperexcitability of motor and sensory neurons seen in some members of a patient's family,[244] repetitive after-discharges following each stimulation of motor axons,[19,20,466] and conduction abnormalities of the peripheral nerve,[46,463,487] together with the morphologic changes of intraterminal and ultraterminal sprouting.[323] These findings suggest that the high-frequency discharge originates at various sites along the motor axon and intramuscular nerve twigs.[454,466] Increased strength-duration time constant found by threshold tracking technique may contribute to the axonal hyperexcitability responsible for the ectopic activity.[74,266]

5 SCHWARTZ-JAMPEL SYNDROME

Continuous muscle fiber activity occurs in osteochondromuscular dystrophy of autosomal recessive inheritance, originally described by Schwartz and Jampel.[405] The characteristic clinical features include short stature, muscular hypertrophy, diffuse bone disease, ocular and facial anomalies, and severe voluntary and percussion myotonia.[152,233,337] The muscle biopsy may reveal myopathic and neurogenic features.[141] The defect responsible for the continuous muscle contraction presumably lies in the terminal axons, although it may also involve a muscle component of the neuromuscular junction.[405,444]

Electromyographic findings resemble neuromyotonia or complex repetitive discharges. 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[444] or succinylcholine.[77] Other features reported include increased insertional activity and absence of the silent period following muscle contraction.

6 MYOKYMIA

The term *myokymia*, first introduced to describe a patient with leg cramps,[404] 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[157] or, more broadly, manifestation of benign neuromuscular irritability.[160] 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 microtremor of the globe, causing oscillopsia.[58,436] Generalized myokymia with impaired muscle relaxation may develop in association with the syndromes of continuous muscle fiber activity,[209] restless leg syndrome,[199] muscular pain–fasciculation syndrome (see this chapter, part 11),[417] and peripheral neuropathy.[487] In autosomal dominant familial paroxysmal kinesigenic ataxia and continuous myokymia, patients have attacks of loss of coordination and balance lasting a few minutes.[69] Associated features include a postural tremor of the head and hands and fine rippling myokymia detected in about half of the cases. In one study, carbamazepine led to nearly total symptomatic relief.

According to current usage, myokymia has a distinctive clinical appearance and is associated with certain neurologic disorders.[175] In this entity, spontaneous repetitive contraction 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." Whereas electromyographic abnormalities vary slightly from one patient to another, the prolonged undulating movements of myokymia all seem to result from brief tetanic contractions of repetitively discharging single or multiple motor units.[319] Most likely, these ectopic discharges arise from terminal branches of the nerve fibers showing prolonged conduction block.[384] Thus, myokymic discharges originating in motor axons usually occur alone without concomitant fibrillation potentials, positive sharp waves, or spontaneous single muscle fiber discharges. In most limb myokymia, discharges arise focally at the site of a chronic peripheral nerve lesion.[2,3] Less commonly, myokymia results from biochemical, rather than structural, alterations, as the one seen in association with clozapine therapy[108] or timber rattle snake envenomation.[59]

Two electromyographic patterns characterize myokymic discharges.[358] In the continuous type, rhythmic single or paired discharges of one or a few motor units recur with striking regularity at intervals of 100–200 ms. In the discontinuous type, bursts of a single motor unit ac-

tivity at 30–40 Hz last for 100–900 ms and repeat in semiregular intervals of 100 ms to 10 s (see Chapter 14–4). They do not typically wax or wane despite occasional association with myotonia.[462] 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 (Ca^{2+}) enhances myokymic discharges.[175,176] 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.

Myokymia occurs in a heterogenous group of disorders including, most notably, Guillain-Barré syndrome[60,276] and radiation plexopathy,[186,446] probably representing a nonspecific neuronal response to injury. Other conditions associated with limb myokymia include spinal stenosis,[99] nerve root compression,[78] cardiopulmonary arrest,[307] subarachnoid hemorrhage,[49] and neurocysticercosis.[42] Metastatic tumor that interrupts the supra-nuclear pathways descending on the facial nucleus may also give rise to myokymia.[407,485] Facial myokymia usually suggests segmental demyelination,[325] as may be seen in multiple sclerosis[192] (see Fig. 14–12A) or pontine glioma,[89,178,238] but also commonly appears in association with Bell's palsy,[41] syringobulbia,[365] meningoradiculitis,[164] and polyradiculoneuropathy (see Fig. 14–12B).[107,468]

7 HEMIFACIAL AND HEMIMASTICATORY SPASM

Idiopathic hemifacial spasms typically occur in middle age, affecting women more often than men. Vascular compression of the facial nerve may play an important role.[128,138,216,342] In one study,[1] magnetic resonance imaging and tomographic angiography revealed findings consistent with vascular compression in 65 percent of the patients compared with 6 percent in the controls. Familial hemifacial spasm may involve anatomic variants or anomalies of the posterior circulation.[97] Hemifacial spasm also develops as a late complication of Bell's palsy or other disorders of the facial nerve, including compression of the brainstem by posterior fossa tumors[44,318] and facial nerve injury.[271]

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 spasms of several muscles on the affected side of the face. Volitional activation of one muscle results in synchronous involuntary contraction of other muscles. Unlike focal convulsive twitches of the face, the spasmodic contractions that often follow blinking consist of simultaneous rapid twitching in several facial muscles. Less commonly, one side of the face may show prolonged contraction with irregular, fluctuating movements. Although spontaneous discharges of this type nearly exclusively involve the facial muscles, hemimasticatory spasm, a rare disorder of the trigeminal nerve, may develop alone or in association with facial hemiatrophy,[228,447] producing paroxysmal involuntary contraction of the jaw-closing muscles unilaterally. Needle electromyography demonstrates irregular bursts of motor unit potentials 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 hemifacial spasm.[21]

The diagnosis of hemifacial spasm depends on visual inspection or electromyographic recording of abnormal movements. In clinically equivocal cases the electrically elicited blink reflex[18,230,312] can document synkinesis by demonstrating the presence of R_1 and R_2 components not only in the orbicularis oculi but also in the orbicularis oris, platysma, or other muscles innervated by the facial nerve (see Chapter 17–4, Fig. 17–11). Synkinesis found in hemifacial spasm and in some patients after Bell's palsy serves to differentiate these entities from other motor disorders, such as essential blepharospasm, facial dystonia, focal seizures, and focal myokymia. In none of these conditions does stimulation of the supraorbital nerve elicit a blink reflex in facial muscles other than

orbicularis oculi. A temporal variability of responses characterizes hemifacial spasm in contrast to the highly reproducible results seen in postparalytic synkinesis after regeneration of the degenerated facial nerve in Bell's palsy.[18]

Spontaneous bursts of discharges may result from either hyperexcitability of the facial nucleus after axonal injury[102,144] or ectopic excitation at the site of injury.[312,313,317,392] The frequency of repetitive motor unit discharges typically varies between 200 and 400 Hz, although some patients have a slower irregular pattern in the range of 20–40 Hz.[192] Polygraphic studies reveal progressive diminution of spasmatic movements with deepening sleep stages, revealing lowest values in REM sleep.[304] Central inhibitory processes may account for this partial decline. Inhalation anesthesia, which normally abolishes R_1 and R_2 of the blink reflex, however, fails to suppress the spasm.[302]

A number of investigators have suggested various pathophysiologies underlying the hemifacial spasm. Although the published accounts lack complete accord, the evidence of ephaptic transmission (cross-talk) has gained popularity. Focal slowing secondary to demyelination constitutes an important prerequisite for ephapses in experiments with squid axons.[359] An increased latency of R_1 on the affected side of the face provides supportive evidence for this mechanism in some patients,[312] but not in others.[230] Regardless of the type of physiologic mechanisms responsible for synkinesis, the beneficial effects of surgical decompression suggest that the primary site of involvement in hemifacial spasm probably resides in the facial nerve and not in the nucleus.[22,316] This finding does not preclude hyperexcitability of the facial motor neurons, which could develop secondarily as the result of a peripheral lesion.

In the presence of ephaptic transmission, stimulation of the individual facial nerve branches may evoke a delayed muscle response.[183,400,442] Thus, stimulation of one branch of the facial nerve and recording from muscles innervated by another branch would allow clear separation between an ephaptically activated response and a direct response.[196] 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.[312,314] 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. When the response was recorded from the orbicularis oculi muscle after electrical stimulation of the marginal mandibular nerve, however, its latency exceeded the sum by a few milliseconds. This finding suggests the involvement of the facial nucleus rather than the motor fibers in the generation of the delayed response.[302] Intraoperative recordings also suggest backfiring of the facial motor neurons as the cause of the abnormal muscle response, which a properly timed blink reflex can eliminate at the facial nucleus.[301] 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.[385]

Stimulation of the supraorbital nerve normally activates only a fraction of the motor neuron pool destined to innervate the orbicularis oculi muscle. Thus, the size of the compound muscle action potential evoked by direct stimulation of the facial nerve far exceeds that of the reflexively activated R_1. The increased amplitude of R_1 found in hemifacial spasm suggests lateral spread of the impulse, activating more fibers contained in the zygomatic branch. Synkinetic responses of R_1 and R_2 in the mental muscle, not ordinarily involved in the blink reflex, further supports the theory of lateral spread of impulses to other fibers. Paired shock technique reveals an upward shift of the R_2 recovery curve not only on the side of spasm[127] but also on the unaffected side, suggesting enhanced excitability of the facial motor neurons and brainstem interneurons.[464] The presence of after-activity and late activity implies autoexcitation of the involved fibers.[313] Enhanced reflex responses on the affected side of the face also suggest hyperexcitability of the facial nucleus.[465] Unfortunately none of these findings conclusively distinguish ephaptic

or ectopic discharges along the motor fibers from excitation of the facial nucleus.[385]

A possible therapeutic regimen includes carbamazepine. Botulinum toxin injection induces muscle weakness, thereby diminishing or abolishing the spasm without demonstrable effect on ectopic or ephaptic transmission in the facial nerve.[163] Despite side effects that include, in order of frequency, facial weakness, facial bruising, diplopia, ptosis, and various other mild complaints,[491] this preferred treatment provided effective relief of spasm[477] for a mean duration of 18.9 weeks in one series.[148]

8 TETANUS

The toxin of *Clostridium tetani* travels from wound to central nervous system via blood or retrograde axonal transport. 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.[416] 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 tenatus still poses a health hazard in developing countries as an important, preventable cause of death.[112,229]

Tetanus toxin presumably blocks postsynaptic inhibition in the spinal cord and brainstem, thereby increasing the excitability of the alpha motor neurons.[65] The continuous motor unit discharges seen in electromyography resolves during sleep, with administration of general or spinal anesthesia, and after peripheral nerve block. The shortened or absent silent period probably results from failure of Renshaw inhibition. This characteristic electrodiagnostic feature of tetanus seldom occurs in other disorders with motor unit hyperactivity.[374,432] Reduction in the silent period induced by transcranial magnetic stimulation suggests impaired inhibitory mechanisms at multiple levels.[481] 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.

Some clinical and electrophysiologic findings suggest peripheral nerve involvement in severe tetanus.[408] Facial nerve conduction studies may[158] or may not[461] show abnormalities. Increased jitter and block in single-fiber electromyography suggest a presynaptic defect of neuromuscular transmission in human tetanus.[145] Electrophysiologic studies revealed evidence of mild subclinical axonal polyneuropathy in one series of 40 patients seen after recovery from tetanus.[262]

9 TETANY

The physiologic term *tetanus* is also used to describe tetany caused by hypocalcemia and alkalosis. Decreased extracellular calcium (Ca^{2+}) increases sodium (Na^{+}) 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. They include a gentle tap over the facial nerve (Chvostek's sign) or the lateral surface of the fibula (peroneal sign) and artificially induced ischemia of the forearm (Trousseau's sign).

Electromyography reveals grouped motor unit potentials firing asynchronously at a rate of 4–15 Hz, with periods of relative silence in between.

10 STIFFMAN SYNDROME

A number of authors have described the clinical and electrophysiologic features of the stiffman syndrome.[19,268,281] It usually occurs sporadically in adult men and women, but a congenital form also ex-

ists.[396] 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, in contrast to tetanus, usually spares 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 stiffman syndrome may mimic hysteria because of facial grimacing, unusual posture, and complaints of muscle cramps that superficially resemble 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.

Electromyography shows a sustained interference pattern consisting of normal motor unit potentials in agonistic as well as antagonistic muscles.[270,424] 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.[287] Increased central excitability leads to enhanced exteroceptive reflexes, including cutaneously elicited responses, such as the blink reflex, showing a contralateral in addition to the physiologic ipsilateral R_1 and, with higher intensity, R_3 components following the normal R_2 responses (see Chapter 17–1).[284]

The exact neurophysiologic mechanism underlying the abnormal discharge remains unknown. Clinical similarities with chronic tetanus suggested a possible relationship between these two entities. Tetanus toxin causes hyperexcitability of motor units by blocking spinal inhibitory postsynaptic potentials. Similarly, the motor neuron pool may become excessively excitable in the absence of the inhibitory spinal mechanisms in the stiffman syndrome.[330] Unlike those with tetanus, however, patients with the stiffman syndrome may have a normal silent period.[270,424] The rigidity and electrical discharges markedly improve with the administration of baclofen[291,423,488] or diazepam (Valium), which suppresses interneurons at spinal and supraspinal levels. In contrast, clomipramine injection severely aggravates the clinical symptoms.[284]

Some patients seem to have an autoimmune pathogenesis with circulating islet cell and anti-glutamic acid decarboxylase antibodies.[106,149,171] This autoantigen located in the β cells of the pancreas and in the GABA producing neurons may explain occasional association between this syndrome and diabetes mellitus[201] and neurological symptoms caused by inhibition of GABA synthesis.[124] Other patients with this syndrome have paraneoplastic syndrome[31,146,149,171,380,470] and still others, thymoma and myasthenia gravis.[311] Treatment with plasma exchange and immunosuppressants benefits some patients,[48,56,200] further strengthening the autoimmune hypothesis.[245]

Other conditions described in association with stiffman-like features include nocturnal myoclonus and epilepsy,[273] focal cortical atrophy with increased spinal fluid gammaglobulin,[268] diffuse stiffness following ingestion of alcohol,[47] and sudden death.[166,299] These symptoms probably represent a variant called progressive encephalomyelopathy with rigidity and myoclonus.[285]

11 CRAMPS

Cramps represent briefly sustained, painful or painless involuntary contractions lasting seconds to minutes.[246] This

definition excludes such sustained movements seen in tremor, chorea, hemiballisms or myoclonus, and isolated muscle twitches associated with fasciculation potentials or complex repetitive discharges. Painful cramps commonly involve the calf muscles and other flexors of the lower limbs in healthy subjects. Cramps start after maintaining a certain posture for a prolonged period of time and improve by rubbing or lengthening the muscle. Numerous predisposing factors include salt depletion, other causes of hyponatremia, hypocalcemia, and vitamin deficiency. Most cases of cramps in otherwise asymptomatic individuals have no detectable underlying cause.

Cramps occur in hereditary cases[223,248,369] and sporadic cases[115,199] of the muscular pain or cramp fasciculation syndrome. The familial variety with an autosomal dominant inheritance pattern affects both genders. The symptoms appear during the first or second decade. Exercise induces painful cramps predominantly in the hands and feet, sometimes leading to more generalized symptoms. Involvement of the esophagus may cause difficulty swallowing.[57] Nonfamilial types also 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. The tubular aggregates reported in biopsy specimens may have some relationship with muscle cramps.[247] Fasciculation potentials constitute the only abnormality found in routine electrodiagnostic studies. Supramaximal stimulation of the nerve may produce showers of electric potentials following the compound muscle action potential, which abate with application of curare but not by nerve block.[417,438]

The syndrome of progressive muscle spasm, alopecia, and diarrhea[401,402] affects women more frequently than men. Painful intermittent cramps involve the limb muscles initially and then the neck, trunk, and mastication muscles several years later. These painful muscle spasms originate centrally and, except for normal serum calcium (Ca^{2+}) levels, resemble tetani. 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 cramps constitute an early feature of motor neuron disease, sciatica, and peripheral neuropathies. Patients with certain inborn errors of metabolism may complain of exertional cramps, but not as an essential symptom. Other disorders associated with muscle cramping include the syndrome of insulin resistance, acanthosis nigricans, and acral hypertrophy.[296]

Electrically, muscle cramps consist of high-frequency irregular motor unit discharges at rates ranging from 40 to 60 Hz and occasionally reaching 200–300 Hz. They involve a large part of the muscle synchronously, as opposed to asynchronous activation 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.[40] These findings suggest a peripheral origin. In sporadic cases of muscular pain fasciculation syndrome, nerve conduction studies may show decreased conduction and increased distal latencies. Needle studies may reveal fibrillation potentials and positive sharp waves. In one study, patients with familial cramps had fasciculation potentials, high-amplitude long-duration polyphasic motor unit potentials, and low normal nerve conduction velocities.[248]

Carbamazepine therapy partially suppresses hyperexcitability of the peripheral nerve.[438] Tocainide also reduces disabling muscle spasms and cramps associated with conditions characterized by neuromuscular irritability.[355] Transcutaneous nerve stimulation may relieve severe muscle cramps as reported in a patient with muscle hypertrophy and fasciculation potentials.[292]

12 CONTRACTURE

The term *contracture* refers to intense mechanical muscle shortening in the absence of muscle action potentials. Thus, electromyography reveals no electrical activity

in the contracted muscle.[126] Ischemia induces contracture most commonly in patients with muscle phosphorylase or muscle phophofructokinase deficiencies (see Fig. 12–3) but also rarely in those with other conditions.[247] In these entities, failure to produce adenosine triphosphate possibly prohibits reaccumulation of calcium (Ca^{2+}) by the sarcoplasmic reticulum. The essential steps for muscle relaxation, however, need further clarification (see Chapter 12–2 and Chapter 28–4). Electromyography shows normal activity during voluntary muscle contraction. After strong effort, the muscle relaxes only slowly over a period of 10 s. During this period the stiff muscle is electrically silent.[241] Normal motor unit potentials reappear if the patient voluntarily contracts the stiff muscle. Needle insertion or voluntary contraction initiates no myotonic discharge.

Some patients without enzymatic deficiency may develop painless exertional contracture.[61] In an entity caused by a deficiency of calcium and adenosine triphosphatase, sarcoplasmic reticulum had a decreased capacity to accumulate calcium.[226] Painful contracture has accompanied a hereditary myopathy associated with electromyographic signs of generalized myotonia.[399,425] Muscle stiffness may also appear as an autosomal dominantly inherited condition.[222,370] In these cases, muscles display an unusual sensitivity to stretch, manifested by rippling waves of muscle contraction not accompanied by muscle fiber action potentials. Patients with certain myopathies may have slow muscle relaxation during repetitive nerve stimulation without accompanying electrical activity.[357]

13 MYOCLONUS

Cortical, subcortical, spinal, and, less frequently, peripheral lesions can induce myoclonus, defined as a sudden, brief, involuntary muscular contraction.[321,411] Myoclonus occurs in a group of heterogeneous disorders such as progressive myoclonus epilepsy of Unverricht-Lundborg, Lafora body disease, and myoclonus epilepsy with ragged red fibers.[91,153,297] Other entities associated with myoclonus include Rett syndrome,[174] akinetic-rigid syndrome,[81] corticobasal degeneration,[70,373,448] hereditary neuropathy with liability to pressure palsy,[409] and post-traumatic stimulus suppressible myoclonus of peripheral origin.[17] Detailed electrophysiologic analyses help elucidate the origin of the discharge to identify different forms of myoclonic jerks.[410,411] Treatment depends on the type and usually consists of valproic acid, clonazepam, and piracetam.[236]

Abnormal sensory motor cortical discharges can cause a wide range of clinical motor phenomena.[294,295,322] Brief muscle jerks probably involve cerebral cortical mechanisms, which also accounts for the abnormal enhancement of somatosensory evoked potential (SEPs) and premotor cortical potentials time locked to the preceding spontaneous or action-induced jerking.[410] The site of abnormality in the sensory motor cortex probably dictates the varied pattern of motor responses such as stimulus-sensitive myoclonus, spontaneous myoclonus, and focal motor epilepsy. Other related entities of interest include cortical tremor, which is defined as a type of reflex myoclonus associated with giant SEPs, enhanced long-loop reflex, and premyoclonus cortical spikes recorded by the jerk-locked averaging.[204,328,455]

Various SEP studies have revealed enhanced cortical excitability for 20 ms just after the myoclonus, followed by suppression throughout the postmyoclonus period.[413] These findings indicate a pathological enhanement of certain early cortical components seen normally.[412] Similar waveforms and scalp topography imply that the giant SEP and myoclonus-related cortical spikes may have a common,[413] if not identical,[116] physiologic mechanism. In reflex reticular myoclonus, the complete movement pattern may reside in the jerk-generating subcortical structure.[362] Post anoxic myoclonus also belongs in this category.[439] A single neural rhythm generator may produce both positive and negative myoclonus as documented in a patient with a pontine hemorrhage.[333]

Paroxysmal axial spasm arises in propriospinal systems intrinsic to the spinal

cord.[66] This type of spinal myoclonus may also present as thoracoabdominal muscle jerks showing rostral propagation.[93,94] Segmental myoclonus may arise 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.[235] Studies of lumbosacral SEPs by paired stimulation have revealed increased spinal cord excitability in a patient with rhythmic segmental myoclonus.[122]

14 TREMOR

Tremor can be divided clinically into three types: (1) the rest tremor seen in Parkinson's disease, (2) the intention or ataxic tremor representing dysmetria seen during voluntary movement, and (3) the postural tremor seen during a maintained limb position. Of these, both intention and postural tremor occur during voluntary muscle activation, thus the joint name *action tremor.* Postural tremor has three subdivisions based on the underlying mechanism: (*a*) physiologic tremor accentuated by stress, drugs, and toxins; (*b*) symptomatic tremor associated with various disorders such as hereditary motor and sensory neuropathy, dystonia, parkinsonism, myoclonus, vitamin E deficiency, and other metabolic conditions; 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 characteristics (see Chapter 13–8).[23,79,147,168]

Increasing evidence indicates the involvement of the cerebellum in the generation of parkinsonian rest tremor, which may depend on the interaction between nigrostriatal, pallidothalamic, and cerebellothalamic systems.[261] If so, degeneration of the substantia nigra would cause akinesia and rigidity, whereas involvement of the adjacent ventromedial tegmentum provokes tremor. In support of this view, positron emission tomography studies showed enhanced regional cerebral blood flow in the cerebellum ipsilaterally for unilateral parkinsonian tremor[111] and bilaterally for essential tremor.[218]

Mechanical factors such as changing hand position determine the peak frequency of physiologic tremor.[190,195] Motor unit synchronization provides the mechanical basis for higher amplitude physiologic tremor.[256] Topical anesthesia may suppress the tremor amplitude and the associated electric activity.[347] Tremor associated with some polyneurpathy results from minimal weakness and possibly impairment of the stretch reflex, both of which increase central drive and enhance physiologic temor.[393]

Symptomatic tremors have varied pathophysiologies. Patients with anti-myelin-associated glycoprotein peripheral neuropathy often develop a distinct form of neurogenic tremor.[339] Distal ulnar neuropathy at Guyon's canal may initiate finger tremor.[429] Delayed and enhanced long-latency reflexes may induce postural tremor in late cerebellar atrophy.[279] Rhythmic olivocerebellar discharges can cause tremorogenic excitation and inhibition of postural electromyographic activity in the upper limbs as reported in one patient with palatal myoclonus and progressive ataxia.[132]

Essential tremor is one of the most common adult neurologic disorders, although its estimated prevalence varies a great deal depending mostly on the choice of diagnostic criteria.[140,258,259] Early essential tremor qualitatively resembles the 8–12 Hz component of physiologic tremor, but advanced essential tremor has a frequency of 4–8 Hz.[131] Two subtypes of essential tremor have emerged based on pharmacological response to propranolol and electrophysiologic studies, including polygraphic recording and long-latency reflex.[117] The underlying mechanism of essential tremor, however, remains enigmatic with some conflicting reports, for example, abnormally reduced physiologic reciprocal inhibition of the forearm flexor muscles reported in one study[286] but not in another.[386] Despite its name, orthostatic tremor is not purely related to the upright posture.[449] This tremor shifts from low to high frequencies with forceful muscle contractions,[283] making it distinct from essential tremor clinically and electrophysiologically.

Transcranial magnetic stimulation resets both essential tremor and postural tremor in Parkinson's disease, implicating the role of the intracortical structure in their generation.[336] Patients with essential tremor have normal cortical excitability judged by the silent period that shows a similar duration as in control subjects.[376] Established treatments for essential tremor include propranolol and primidone,[24] and as an alternative to medication, streotactic surgery. Some advocate botulinum toxin injection to cervical and forearm muscle to control head and hand tremor.[214] This toxin may restore presynaptic inhibition of Group IA afferents in patients with essential tremor.[300]

15 MIRROR MOVEMENT

In congenital mirror movements, electromyographic studies show normal temporal characteristics, response latency, duration, and recruitment pattern on the normal and mirror sides. These findings suggest a similar motor command for both voluntary and mirror movements.[151] Neurophysiologic studies suggest as one of the possible mechanisms of mirror movements abnormally branched fast conducting corticospinal tract fibers that project to motor neuron pools on both sides of the spinal cord.[142,278] A shortened contralateral silent period seen in this condition may imply an abnormal bilateral activation of the hand motor cortex causing an early recovery of background activity via non-stimulated motor cortex.[96] In one case, a unilateral stretch of distal but not proximal arm muscles gave rise to bilateral long-latency reflex.[143] 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.

16 RESTLESS LEGS SYNDROME

Patients with restless legs syndrome have an uncontrollable urge to move the legs when lying in bed or during periods of prolonged rest.[130] Dysesthesias in the legs either closely precede or follow occurrences of irresistible leg movements.[341] Periodic movements may occur in sleep, although the frequency decreases from wakefulness to sleep stages 1 and 2.[305] The syndrome may precede clinical and electrophysiologic evidence of a peripheral neuropathy.[395] In one series,[203] eight consecutive patients seen with the primary complaint of leg movement had mild axonal neuropathy. In another study,[391] 5.2 percent of patients with polyneuropathy had prominent symptoms of restless legs. In most patients, muscle contractions show a constant order of propagation, descending or ascending the spinal segments.[457] This and other electrophysiologic patterns seem to indicate the spinal origin of the involuntary limb movements. Treatment with dopaminergic agonists may provide effective relief of the symptoms.

17 DYSTONIA

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, inducing abnormal posture, and the twisting nature of abnormality giving rise to torsional movement, as implied by the phrase *torsion dystonia.* The symptom may appear secondary to other neurologic conditions such as structural lesions of the basal ganglia, cerebral palsy, and exposure to toxins, but more commonly without an identifiable underlying cause showing an estimated overall prevalence of 329 per million, including 294 focal dystonia cases.[320,480] 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. Dystonia-plus syndromes comprise the phenotype of dystonia and additional neurologic features, for example, myoclonus for myoclonic dystonia, parkinsonism for dopa-

responsive dystonia, and rapid-onset dystonia-parkinsonism,[139] and two varieties of paroxysmal dystonia, paroxysmal kinesigenic dystonia and paroxysmal dystonic choreoathetosis. Advances in molecular technology have led to discoveries of the increasing number of genes causing dystonia with distinguishable clinical phenotypes.[4,8,26,440] Segregation analyses of adult-onset blepharospasm and cranial–cervical dystonia suggest an autosomal dominant transmission with reduced penetrance, or polygenic inheritance.[110]

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 would include pronator teres syndrome, radial nerve palsy, lower brachial plexus lesion, median nerve compression, and thoracic outlet syndrome.[356,403] Mechanical irritation of brachial plexus can precipitate rhythmic myoclonus in the arm.[27] Focal dystonia may follow soft tissue injury, suggesting a role of altered sensory information from a painful limb disturbing motor performance.[227] Spasmodic torticollis may develop in association with eighth nerve lesions.[62] 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.[43] Some believe that this distressing syndrome results from a true functional disorder of the central nervous system, whereas others stress a psychogenic origin.

In one series of 672 musical instrumentalists, 7 percent of patients with playing-related disorders had focal dystonia compared with 64 percent for musculoskeletal disorders and 22.5 percent for peripheral nerve problems.[249] Ulnar neuropathy, seen commonly in musicians, may predispose them to focal dystonia.[86,381] Task-specific hand cramps also develop during writing, typing, and piano and guitar playing. In these patients, electromyography shows generalized muscle spasms with co-contraction of agonist and antagonist muscles, the findings characteristic of a focal dystonia.[326] The use of the asymptomatic hand may provoke dystonic movements of the contralateral symptomatic hand. This phenomenon, termed *mirror-movement dystonia*, provides further evidence of the presumed central origin of the dystonic movements.[255] The inhibitory effects induced by transcranial magnetic stimulation are reduced in patients with writer's cramp during voluntary muscle activation.[88] The underlying abnormality in torticollis also involves central motor programing for head position rather than the activity of individual neck muscles.[162] Studies of movement-related potentials show an abnormal cortical processing of voluntary muscle relaxation in patients with focal hand dystonia.[118,490] Anomalous somatosensory homunculus seen in patients with hand dystonia suggests that abnormal plasticity may also play a role in the development of dystonia.[28]

Blink reflex recovery curves characteristically show increased excitability of R_2 in patients with blepharospasm and generalized dystonia.[127] The same abnormality, seen in spasmodic dysphonia, indicates that the dystonia involves not only the larynx but also other anatomic structures.[98] Surface electromyography of the orbicularis oculi helps classify the pattern of blepharospasm[327] to distinguish it from apraxia of lid opening or, according to some, focal eyelid dystonia.[12,219,237] Electromyographic studies also reveal a characteristic pattern of co-contraction of the agonist and antagonist muscles of the forearm and hand in writer's cramp.[364] Somatosensory evoked potential studies show increased amplitude of N_{30} in dystonia patients in contract to decreased amplitude in Parkinson's disease.[361]

Botulinum toxin injections effectively relieve symptoms of focal dystonias including blepharospasm, torticollis, writer's cramp[460] and other hand dystonia when other forms therapy have failed.[215,467] The primarily peripheral effect of botulinum toxin[182,478] may also have an indirect influence on the spinal cord through the action on the intrafusal pathway.[39,224] The possible central effect supports the hypothesis that idiopathic focal dystonia results from a disorder of muscle spindle afferents.[173,225,378] Patients with medically intractable cervical

dystonia also respond favorably to botulinum toxin therapy, most improving substantially within the first week after injection.[213] In one series of 32 patients, pain improved in 65 percent, posture in 65 percent, tremor in 50 percent, and range of motion in 46 percent.[50] Some patients develop hoarseness and dysphagia, although the frequencies of these complications show no clear correlation to the total dose or site of injection.[100] Diffusion of toxin to adjacent noninjected muscles contributes to suboptimal outcome.[375,387] Adductor spasmodic dysphonia is treated by injection of 3.00–3.75 units of botulinum toxin into the thyroarytenoid muscle bilaterally. In one series,[489] 96 percent of patients' diary reports showed an improvement with a median of 7 days to peak effect and a 5 weeks' duration thereafter.

Botulinum toxin injection to the neck muscle to treat torticollis results in increased jitter values[161,243] and histologic evidence of mild muscle atrophy[11] in distant limb muscles uncovering subclinical effects on uninjected sites. Distant effects of botulinum toxin also involve autonomic function, showing mild abnormalities of cardiovascular function.[165]

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APPENDICES

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Appendix 1

ETHICAL CONSIDERATIONS IN CLINICAL PRACTICE

Ethical principles in medical practice were established to 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.[13] To ensure high standards of medical practice and to enforce technical and ethical standards for practitioners, the American Association of Electrodiagnostic Medicine (AAEM) has also published a series of news and comments,[1] guidelines,[2,4–6,9,11,12] position statements,[3,7,10] and a summary of the current recommendations.[11,12] This appendix briefly reviews important aspects of these documents, whose general principles apply to any practice in electrodiagnostic medicine. Specific details may, however, differ from one place to another in such areas as consultant–patient relationships, conflicts of interest related to clinical research, compensation for electrodiagnostic services, and professional misconduct.[13,14]

A medical consultant must recognize a 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 their race, religion, nationality, or gender. A particular diagnosis, specifically one related to human immunodeficiency virus infection or another communicable disease, must not preclude electrodiagnostic evaluation if indicated for the care of the patient.

A clinical research project requires the 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 not bill for unnecessary services. As a guideline, a reasonable fee should reflect the difficulty of the technique, the skill and time required for the study, customary charges in the locality for similar services, the experience of the physician, and the 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[2,3,11,12] outline a maximum number of specific tests necessary for a physician to arrive at a diagnosis in at least 90 percent 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 poor medical judgments based on inadequate information. The AAEM[8] recommends the following minimum standards:

1. Electrodiagnostic testing must be medically necessary.
2. Testing must be performed with electrodiagnostic equipment that provides assessment of all aspects of the recorded signals. Studies performed with devices designed only for "screening purposes" rather than diagnosis are not acceptable under this policy.

3. The number of tests performed must be the minimum needed to establish an accurate diagnosis.

4. Nerve conduction studies must be either (*1*) performed directly by a physician or (*2*) 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 underway, is immediately available to provide the trained individual with assistance and direction, and is responsible for selecting the appropriate nerve conduction studies 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 AAEM guidelines[2] state that "consultants should not knowingly ignore a colleague's incompetence or professional misconduct" in order to protect the public from an impaired physician. The AAEM 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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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 for a more detailed discussion.[4–6,8,12]

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. Because 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 electrical potential energy (for a unit test charge) between two points in space is called the *voltage*, or 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:

$$\text{Resistance} = \frac{\text{Voltage}}{\text{Current}}$$

from which derives the more familiar form of OHM'S LAW:

$$\text{Voltage} = (\text{Resistance}) \times (\text{Current})$$

and also

$$\text{Current} = \frac{\text{Voltage}}{\text{Resistance}}$$

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

$$R = \frac{E}{I} \qquad E = I \times R \qquad I = \frac{E}{R}$$

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 is assumed to be constant, for simplicity. The units of resistance are called *ohms*:

$$1 \text{ Ohm} = \frac{1 \text{ Volt}}{1 \text{ Amp}}$$

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:

$$\text{Power} = \frac{\text{Energy}}{\text{Time}} \quad \text{or}$$
$$\text{Energy} = \text{Power} \times \text{Time}$$

The unit of power, a *watt*, equals 1 joule of energy per second. From the definition of voltage above, energy in a charge flow equals the voltage (difference) times the amount of charge. Because current is the time rate of charge flow, then

$$\text{Power} = \frac{\text{Energy}}{\text{Time}} = \text{Voltage} \times \left(\frac{\text{Charge}}{\text{Time}}\right)$$
$$= \text{Voltage} \times \text{Current}$$

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 LAWS

Circuits and Schematics

Car headlights are an example of an electric circuit, an interconnection of components such that currents flow in one or

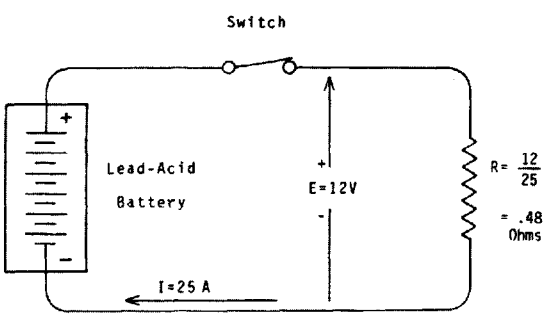
more closed loops. Electrical systems take the form of circuits so that charge does not accumulate at any one point. Appendix Figure 2–1 shows the headlight circuit schematically.

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.

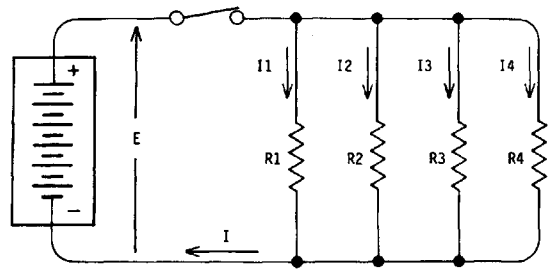
The solid lines represent ideal (zero-resistance) conductors, which interconnect the components. Ideal sources of energy are the constant-voltage source and the constant-current source. A battery is a fair approximation to an ideal voltage source. A fixed resistance models the load that the headlights represent.

Resistors in Parallel

Suppose more headlights were connected across the battery in the circuit in 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



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.



Appendix Figure 2–2. Resistances in paralell. A schematic of the headlight circuit with more lights.

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. Thus the current in each resistor can be calculated by Ohm's law, giving the total current from the battery as

$$I = \left(\frac{E}{R_1}\right) + \left(\frac{E}{R_2}\right)$$

which manipulates to

$$\frac{I}{E} = \left(\frac{1}{R_1}\right) + \left(\frac{1}{R_2}\right)$$

or

$$\frac{E}{I} = \frac{1}{(1/R_1) + (1/R_2)}$$

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

$$R_{eq} = \frac{1}{(1/R_1) + (1/R_2) + \ldots + (1/R_n)}$$

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.

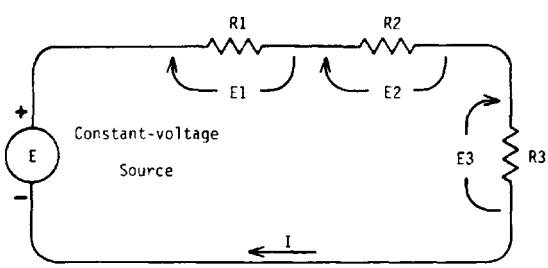
Resistors in Series

The circuit in Appendix Figure 2–3 shows several resistors connected to a battery in *series*. A series connection of two components means they have a node in common that does not connect anywhere else. By Kirchhoff's current law, above, 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 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, above, 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.



Appendix Figure 2–3. resistors in series. The direction of the current follows the ppositive-current convention, as it does in Appendix Figures 2–1 and 2–2.

To apply Kirchhoff's voltage law to the series circuit in 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

$$E = (I \times R_1) + (I \times R_2) = I \times (R_1 + R_2)$$

So for resistors in series:

$$R_{eq} = R_1 + R_2 + \ldots + R_n$$

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 R_3 is given by

$$V_{R3} = \frac{E \times R_3}{(R_1 + R_2 + R_3)} = E \times (\text{a constant} < 1)$$

A fraction of the voltage applied to the series circuit of resistors appears across R_3. This frequently used *voltage divider* arrangement provides a voltage output that is always a fixed fraction of the voltage input.

4 CAPACITANCE

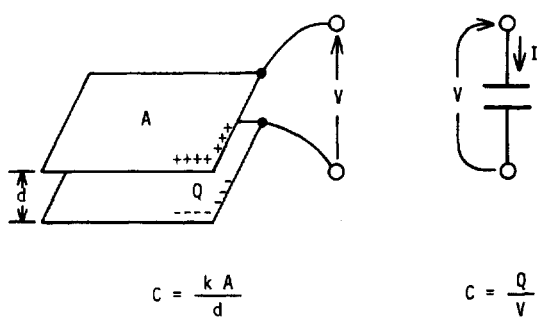
When a nonconducting region of space separates two conducting regions, charge cannot flow through the nonconducting medium. Within the conducting regions, charge can flow freely and distributes so there are no voltage gradients. If one conducting region has a charge different from the charge in the other, 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. Although 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 km square. More common units of capacitance are the microfarad ($\mu f = 10^{-6}$ 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.



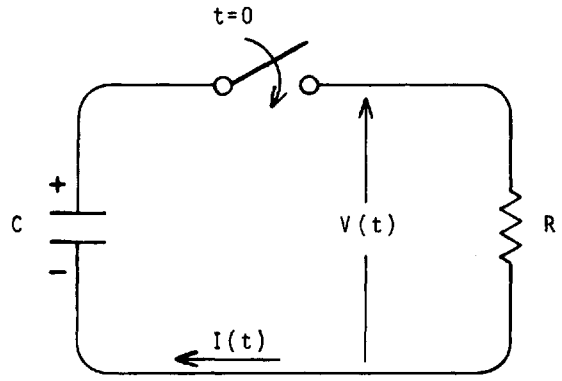
Appendix Figure 2–4. The paralell-plate capacitor and the schematic symbol for capacitance. Capacitance is proportional to the area of the plates and inversely proportional to the distance between them. The constant depends on the insulating material between the plates.

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. Because 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 potentials, forms a relatively large capacitance between the interior and the exterior of the cell: on the order of 1 $\mu f/cm^2$. 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 (App. 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. Thus, 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,

$$d[V(t)]/dt = \frac{I}{C} = \frac{[V(t)/R]}{C} = V(t)/RC$$

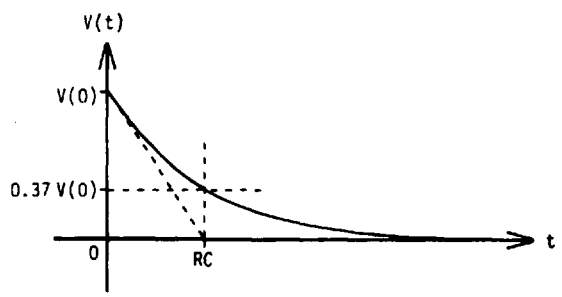
The solution of this differential equation for the voltage during discharge is an *exponential* function of time (shown in App. Fig. 2–6). Assuming the resistor is connected at t = 0,

$$V(t) = V(0)\, e^{-t/RC}$$

$$I(t) = V(t)/R$$

so,

$$I(t) = I(0)\, e^{-t/RC}$$



Appendix Figure 2–6. RC discharge voltage curve. After one time constant, the voltage is about 37 percent of its initial value.

where the constant "e" (~2.7183 . . .) is a special number such that:

$$d[e^t]/dt = e^t$$

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 percent of its value at the beginning. Therefore, after five time constants, the voltage will be less than 1 percent of its initial value.

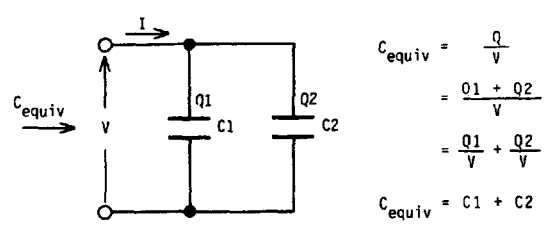
Capacitors in Parallel

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. Thus, the equivalent capacitance of *capacitors in parallel*, the total charge divided by the voltage, equals the sum of the individual capacitances:

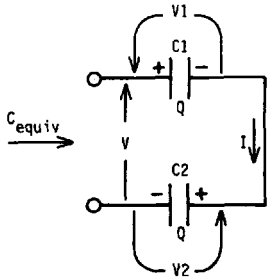
$$C_{eq} = C_1 + C_2 \quad \{+ \ldots + C_n\}$$

Capacitors in Series

Consider two capacitors connected in series, as in Appendix Figure 2–8. Any current in one capacitor must pass through



Appendix Figure 2–7. Capacitors in parallel. The equivalent capacitance is the sum of the individual capacitances.



$$C_{equiv} = \frac{\int I\,dt}{V} = \frac{Q}{V} = \frac{Q}{\frac{Q}{C1} + \frac{Q}{C2}}$$

$$C_{equiv} = \frac{C1\ C2}{C1 + C2}$$

Appendix Figure 2–8. Capacitance in series. The equivalent capacitance is less than the smallest, as is the case with resistances in parallel.

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 thus 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*:

$$C_{eq} = \frac{Q}{V} = \frac{Q}{(V_1 + V_2)} = \frac{1}{\left(\frac{V_1}{Q} + \frac{V_2}{Q}\right)} = \frac{1}{\left(\frac{1}{C_1}\right) + \left(\frac{1}{C_2}\right)}$$

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 electrical 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.

Thus a flowing current has a magnetic field. Also, when a moving charge encounters a magnetic 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. Establishing this field, however, 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 principle to induce excitation current within the body fluid.

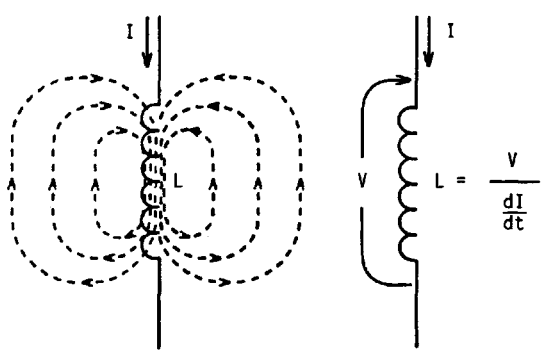
The increasing magnetic field of a coil

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). 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.

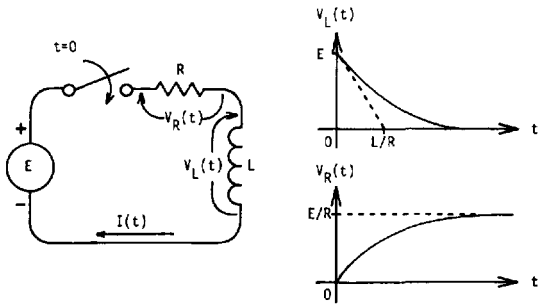
A coil in a vacuum has a certain intrinsic inductance for a given geometry. The same coil wound around various materials may have more or less inductance than in a vacuum, depending on how the atoms interact with a magnetic field and how well the material conducts induced currents. Like the dielectric 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. The magnetic permeability of materials varies greatly, however, 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.



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.

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 a voltage source (at t = 0). The sum of the resistor and inductor voltages equals the source, a constant. The inductor volt-



Appendix Figure 2–10. RL time-constant circuit. The current in the inductor rises exponentially to its final value.

age 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 (above), a differential equation describes the resulting current, an 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).

$$L_{eq} = V/(dI/dt) = (V_1 + V_2)/(dI/dt) = L_1 + L_2 \{+ \ldots + L_n\}$$

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

$$L_{eq} = \frac{1}{(1/L_1) + (1/L_2) \{+ \ldots + (1/L_n)\}}$$

which is the same relationship as for resistors in parallel.

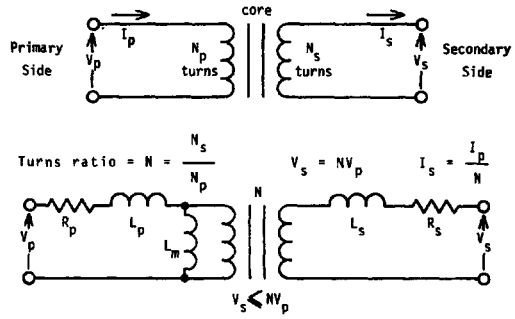
The magnetic field around an inductor carrying current represents some stored energy, equal to the work required to establish the field. In an lossless inductor, this same amount of energy is available for release to the rest of the electric circuit. It can be shown that the energy stored in inductance "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. Because 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 (App. Fig. 2–11).

Practical transformers have limitations of power loss, maximum power capability,



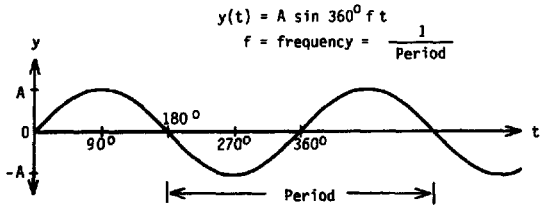
Appendix Figure 2–11. Transformer symbols. The ideal transformer and a simple linear model of a real transformer.

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 that 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 2–12, is completely characterized by a frequency, an 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 nonzero average value attributable to metal/electrolyte interfaces. Subtracting this average value leaves the *AC component*, a varying potential that includes biopotentials, noise, and interference.[3]



Appendix Figure 2–12. The sine function.

AC Circuit Laws

DC circuit theory, the circuit laws and calculations considered above, 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 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

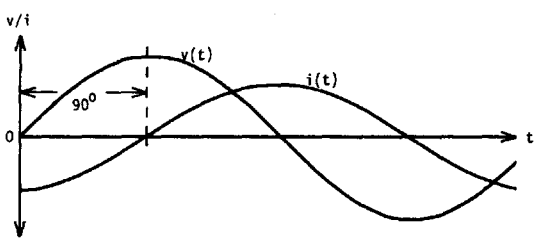
the current would be 25 amps AC (RMS), and the average power would still be 300 watts.

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.

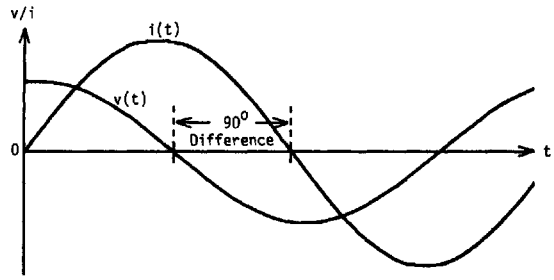
If a sinusoidal current passes through a capacitor, the AC voltage across the capacitor "lags" the current in phase by 90 degrees. When the current is crossing zero, reversing polarity, the voltage is at a peak, reversing slope. When the current is at a peak, the voltage is crossing zero, the point of 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 above. 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" equals $(2\pi fL)$.

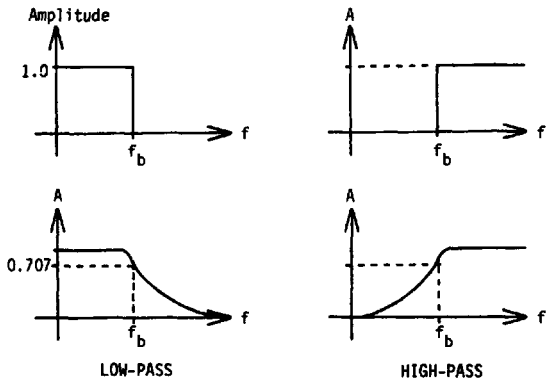
The magnitude of capacitive reactance decreases with increasing frequency while the phase remains −90 degrees. A more rapid voltage variation across a capacitor (at constant amplitude) requires greater current flow. The *capacitive reactance* of a capacitance value "C" equals $1/(2\pi fC)$.

AC Power

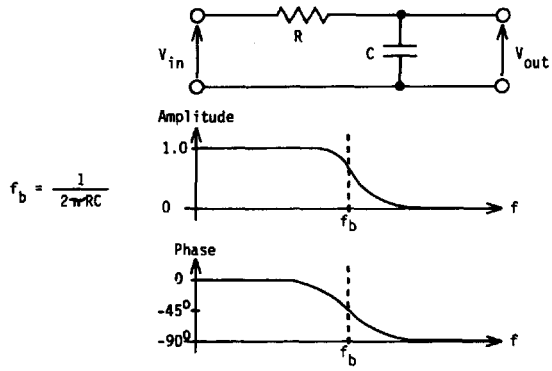
An ideal reactance does not dissipate any energy. Energy may be stored or released, but none is lost. The instantaneous power in a capacitor or inductor, the instantaneous voltage times current, can be positive or negative, but the average power equals zero. Distributed resistance accounts for the power loss in real reactances.

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



Appendix Figure 2–15. Ideal and practical filter response curves. **A.** Low-pass. **B.** High-pass.

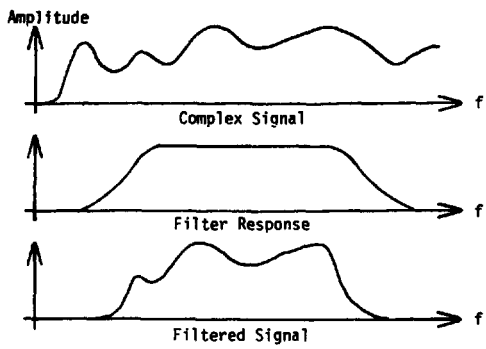


Appendix Figure 2–17. RC low-pass filter-network. **A.** Schematic. **B.** Attenuation curve. **C.** Phase curve.

bass and treble 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.

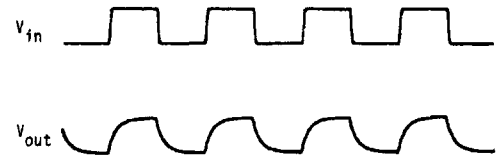
Complex signals composed of a spectrum of frequencies, such as a voice signal or a compound action potential, can often only be described as a graph of component magnitudes versus frequency. Multiplying such a graph times the attenuation curve of a filter, point by point in frequency, yields the frequency spectrum of the output signal passed through the filter, as shown in Appendix Figure 2–16.

The simple RC network in 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 of 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.



Appendix Figure 2–16. Frequency-domain effects of band-pass filtering.

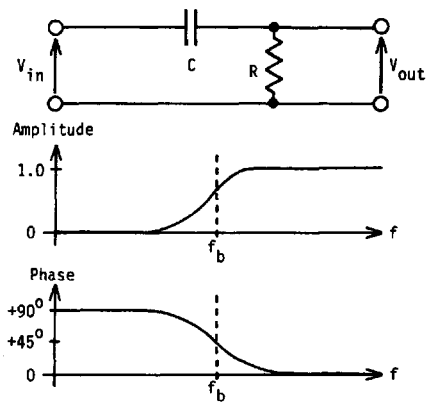
To specify a filter response curve completely, one must also specify the phase of the output relative to the sine wave input at each frequency. Appendix Figure 2–17C shows the phase response of the RC low-pass filter. Note that significant phase shift occurs at frequencies where the amplitude attenuation 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. Lowpass filters increase the latency of fast peaks and limit 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.



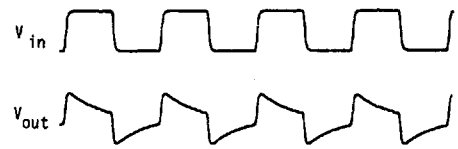
Appendix Figure 2–18. Time-domain effects of low-pass filtering. Note the slowing of abrupt transitions in the square-wave (calibrating) signal, creating a delay.

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 (above).

The phase response of this high-pass filter (App. Fig. 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 droop in the response to square-wave signals, such as the calibration signal in Appendix Figure 2–20.



Appendix Figure 2–19. RC high-pass filter network. **A.** Schematic. **B.** Attenuation curve. **C.** Phase curve.

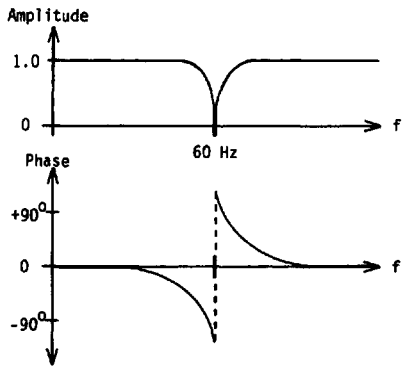


Appendix Figure 2–20. Effect of high-pass filter on square-wave (calibrating) signal.

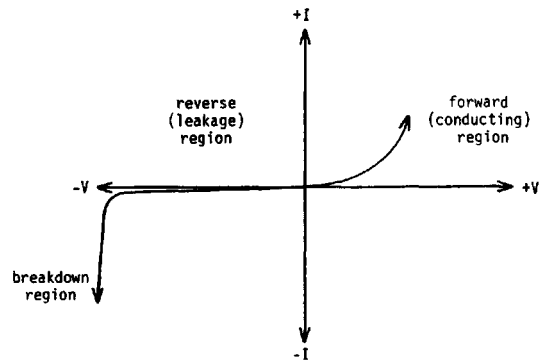
These simple RC high- and low-pass filters, called *first order*, have an attenuation slope in the stop band proportional to frequency; attenuation doubles at each octave of frequency. Higher order filters can have more abrupt descent into the stop band, but also have greater phase shift in the pass band and sharper phase transitions near the corner 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 electromyog-raphy and other electrophysiologic studies use wide band-pass filters, with adjustable low- and high-frequency cutoffs, to eliminate baseline shifts, undesirable components, and excessive noise.[7,9,11]

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. Although 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.[10]



Appendix Figure 2–21. Amplitude and phase curves for 60-Hz notch filter.



Appendix Figure 2–22. V/I curve of a semiconductor diode.

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, 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 that 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 electrical field, which modulates the transistor conductivity in the output circuit, allowing large output currents to be controlled with very little input current (or power). *CMOS* (complementary metal oxide silicon) transistors are a type of FET, with the input insulated by silicon dioxide (glass).

Transistors replaced vacuum tube amplifers 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 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 dis-

able 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 less 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."

Appendix Table 2–1 Powers of Two

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

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 (App. Table 2–1).

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 compact disk 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 approx-

imated 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.[2]

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

ELECTRICAL SAFETY

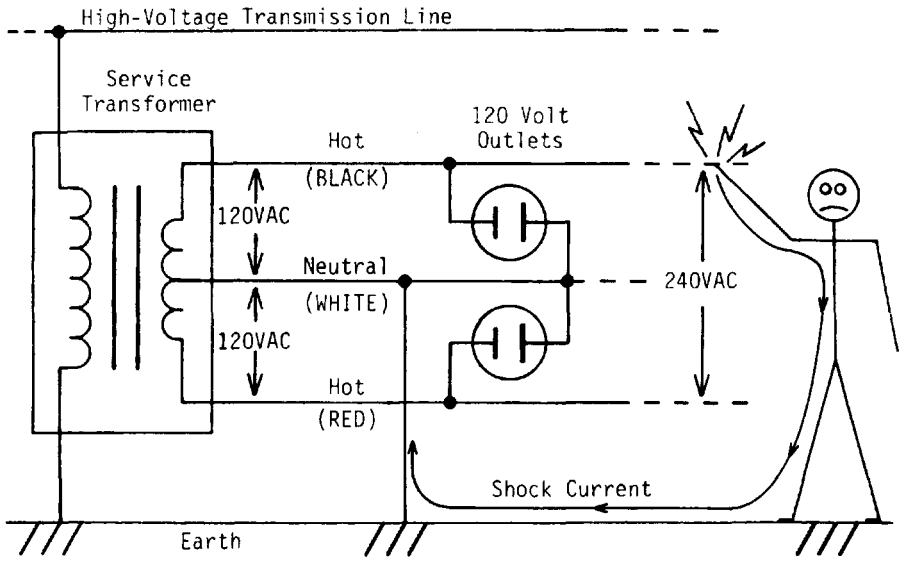
1 INTRODUCTION

All personnel involved in recording bioelectric potentials should be knowledgeable about electrical safety. Electrical safety recommendations are concerned with detecting or preventing dangerous situations. Violating safety standards or neglecting inspections could invalidate insurance coverage or accreditations. If an accident occurs, individuals or institutions could face charges of negligence or malpractice. In addition, some of the measures intended to ensure safety also reduce artifacts and interference in the recording.

The standards and recommendations for electrical safety have changed frequently. Electromyographers and staff should understand not only the most current regulation but also the theory of electrical safety.

2 THE ELECTRICAL HAZARD SITUATION

In the United States, the common electrical power is distributed from transformers as 120 VAC (volts alternating current) at 60 Hz frequency, as shown in Appendix Figure 3–1. The center wire of this transformer supply, called the *neutral* or *cold line*, connects to the earth (*ground*). The other wires from the transformer, called the *hot* lines, have 120 VAC with respect to the neutral, and thus to the earth (240 VAC is available between the two hot phases for high-power equipment). Touching any hot line while in contact with some conductive path to the earth would cause a shock. In healthy people, the sensation of shock from a steady application of 60 Hz AC occurs from about 1 mA of current and above. Thus, from a 120 VAC source, a conduc-



Appendix Figure 3–1. 120 VAC power distribution circuit. The hot lines will supply current through any path to ground.

tive path of 120 Kohms impedance or less could cause a shock. The impedance from one hand to the other in grasping wires is on the order of 50 Kohms, attributable almost entirely to the dry surface layer of the skin. The levels of current in this situation cause a sensation of shock and a jerk-back reflex. At somewhat higher currents, the shock itself may stimulate nerves or muscles. A still higher current may tetanize muscles so that the person cannot release the shock source. If enough current flows across the body, it will induce cardiac fibrillation.

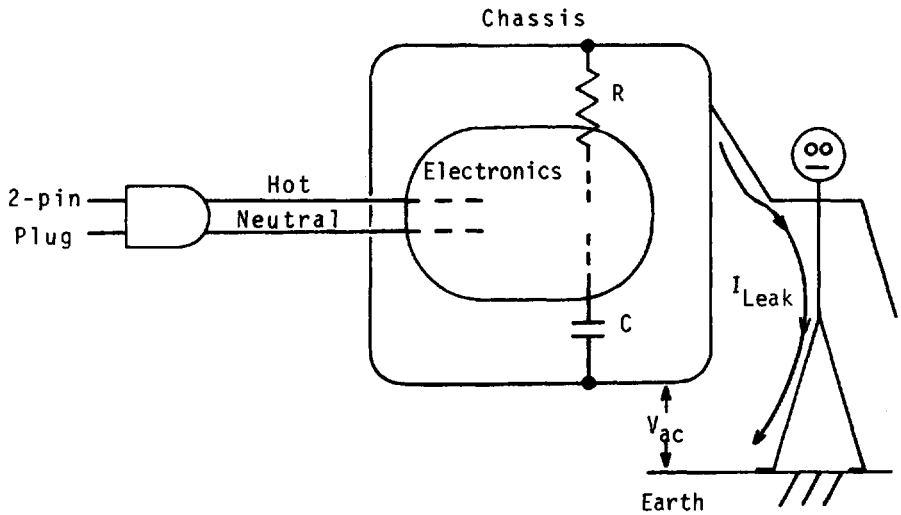
In debilitated patients or those with the surface layer of skin penetrated by a conductor, such as a needle, much less current causes a serious shock. In these "electrosensitive patients," as little as 50 microamps (μA) can cause cardiac fibrillation because of a direct path via a cardiac catheter, for example.[4] This has also been termed *microshock*.

Any line-powered equipment, and especially devices that have a metallic case, could be a safety hazard. Capacitance between the case and wiring, fluids spilled in the machine, or failed insulation could provide an accessible conductive path to the hot line. *Leakage current* will flow through such paths to any earth ground. The hazard is greater, therefore, in areas where earth grounds abound, such as bathrooms, kitchens, basements, outdoors, or other wet areas. Most metal plumbing pipes are good earth grounds.

Appendix Figure 3–2 shows equipment leakage paths to its chassis. With good insulation, the resistive path should conduct very little. The capacitive path is always present to some degree and accounts for most of the "normal" leakage current. A hazard occurs if these leakage paths become sufficient to conduct an unsafe level of current.

To reduce the hazard of leakage current, modern wiring systems incorporate a separate earth ground wire in the outlets and power cords, sometimes called the *third-wire ground*, or *safety ground*. These outlets and plugs have three pins: neutral, hot, and earth ground. The earth ground wire connects to the chassis of the equipment and any other exposed metal, conducting the leakage current to earth.[5] The chassis remains at ground potential, and no current flows to a grounded person, as in Appendix Figure 3–3.

The abundance of equipment and fluids in the hospital environment demands a three-wire grounded electrical system for safety. The patient may also have abnormal susceptibility to shock because of health conditions or invasive attachments.

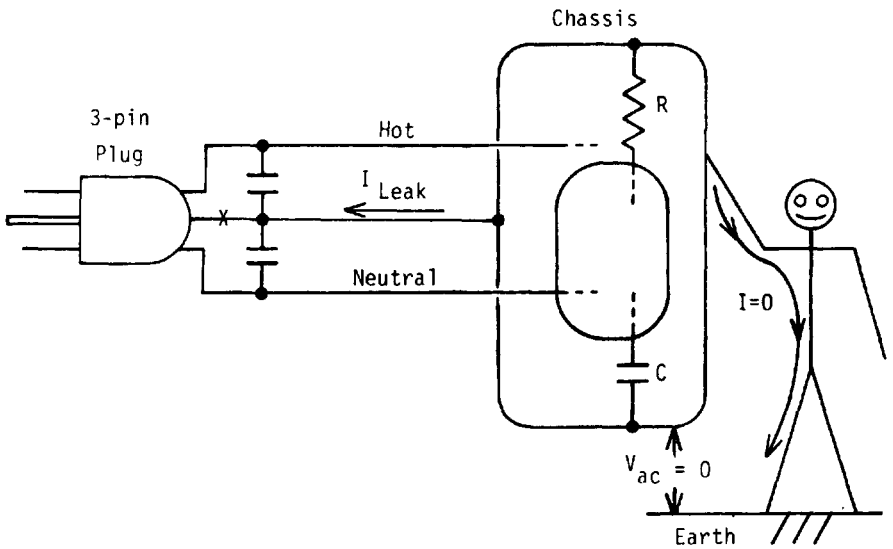


Appendix Figure 3–2. Equipment leakage paths between the hot line and the chassis. A grounded person touching this chassis would conduct the leakage current to earth.

Any equipment that is electrically connected to the body presents a much greater risk because the patient cannot quickly break the conductive path by reflex.

Several pieces of equipment in the same room with a patient increase the electrical hazard, especially if more than one is connected to the patient. This situation occurs commonly with multiple monitors in operating rooms or intensive care units. Such a situation may call for portable electromyography, or patients may come to the laboratory with ancillary equipment attached.

If any one machine has loss of ground, then patients touching it or connected to it would have their whole body at some AC potential above ground due to its leakage current. The proximity of other machines increases the likelihood that the patient



Appendix Figure 3–3. The safety ground wire conducts leakage current in a three-wire system. Notice that capacitance between the hot and ground wires in the power cord adds some leakage current. If the ground connection is broken at the plug ("X"), then this capacitance becomes an additional leakage path to the chassis.

could also touch a ground, becoming a path for that leakage current. If they are already connected to another machine, these connections may conduct to ground at that AC potential. In fact, some equipment may ground the patient directly.

Another hazardous situation could arise from multiple equipment if the earth grounds at their various outlets have some AC potential difference between them. As little as 50 mV difference between the grounds could cause a hazardous current to flow through a patient from one ground connection to the other. Voltage between different grounds could result from fault currents flowing in the ground, improper wiring, or magnetic induction from other wiring. The wiring in patient areas should use a concept known as the "equipotential ground bus." In this system, each of the receptacles in one room has a separate ground connection to a common point. That point ties to earth ground by a wire that does not connect anywhere else.

The above hazards are greatly reduced if all the patient connections from all the instruments are "isolated." An isolated connection will not conduct more than 20 μA even if its potential is 120 VAC to ground. Patient leads are isolated by using nonconductive coupling methods or current-limiting devices. Any isolation can fail if subjected to voltages above its rating, and any isolated circuit has some small leakage current to ground. Battery-powered devices have no connection to earth and no hot power wires to leak. However, battery devices are not necessarily completely safe. Under fault conditions they can supply enough current to endanger the patient, for example, when fluid is spilled in a battery-powered instrument. Hence, patient connections should still have current-limiting devices, especially with electrosensitive patients.

3 THE SAFETY PROBLEM—LEAKAGE CURRENT AND LOSS OF GROUND

The third-wire "safety" ground basically solves the problem of hazard from leakage current provided that no components of the system fail. If this connection opens somehow, then leakage current could flow through a patient or operator to some other ground. If, in addition, the leakage current of the equipment is above safe limits, then a hazardous situation exists. Safety standards and recommendations attempt to prevent or detect this possibility by testing the integrity of the ground system and the leakage current levels in the absence of a ground.

4 ADDITIONAL SAFETY CONCERNS

Appendix Tables 3–1 and 3–2 list some kinds of faults that can lead to electrical hazards.

Several pieces of equipment in the same room with a patient increase the likelihood of electrical hazard, especially if more than one is connected to the patient. This situation occurs commonly with multiple monitors in operating rooms or intensive care units. Such a situation may call for portable electromyography, or patients may come to the laboratory with ancillary equipment attached.

If any one machine has loss of ground, then a patient touching it or connected to it would have their whole body at some AC potential above ground, due to its leakage current. The proximity of other machines increases the likelihood that the patient could also touch a ground, becoming a path for that leakage current. If they are already connected to another machine, then these connections may conduct to ground at that AC potential. In fact, some equipment may ground the patient directly.

Another hazardous situation could arise from multiple equipment if the earth grounds at their various outlets have

Table 3–1 Common Faults That Could Result in Loss of Ground

Broken ground pin on equipment power cord
Broken ground wire in power cord
Poor ground connection inside equipment
Poor earth ground connection to outlet
Weak contact tension between outlet and plug
Corroded, bent, or broken pins on power cord or outlet
Ground system defeated with two-pin adaptors or extension cords
Use of equipment in old or faulty wiring systems

Table 3–2 Faults that Could Result in Excessive Leakage Current

Failed insulation in equipment or cord
Fluid spilled in or on equipment
Use of extension cords on equipment
Improperly wired outlets—reversed polarity or reversed neutral/ground
Electrical faults in equipment circuits
Unapproved equipment

some AC potential difference between them. As little as 50 mV difference between the grounds could cause a hazardous current to flow through a patient from one ground connection to the other. Voltage between different grounds could result from fault currents flowing in the ground, improper wiring, or magnetic induction from other wiring. The wiring in patient areas should use a concept known as the "equipotential ground bus." In this system, each of the receptacles in one room has a separate ground connection to a common point. That point ties to earth ground by a wire that does not connect anywhere else.[7]

The above hazards are greatly reduced if all the patient connections from all the instruments are "isolated." An isolated connection will not conduct more than 20 μA even if its potential is 120 VAC to ground. Patient leads are isolated by using nonconductive coupling methods or current-limiting devices. Any isolation can fail if subjected to voltages above its rating, and any isolated circuit has some small leakage current to ground.

Battery-powered devices have no connection to earth and no hot power wires to leak. However, battery devices are not necessarily completely safe. Under fault conditions they can supply enough current to endanger the patient, for example, when fluid is spilled in a battery-powered instrument. Hence, patient connections should still have current-limiting devices, especially with electrosensitive patients.[9]

5 SAFETY REGULATION DOCUMENTS

The following are examples of agencies that regulate the manufacture and maintenance of equipment as well as the wiring of hospitals, homes, and private offices. These agencies provide publications of the regulations:

National Fire Protection Association (NFPA), 1981
Underwriters Laboratories (UL), Inc., 1980
Joint Commission on Accreditation of Hospitals (JCAH), 1982
Veterans Administration (VA), 1978[12]

The section entitled Electricity in Health Care Facilities of the *National Electrical Code of the NFPA* (1981) specifies standards for the wiring of examination or care areas. It requires that all patient areas have three-pin grounded outlets, where the earth grounds are connected with a separate third wire. The use of metal conduits, raceways, or junction boxes to supply the earth ground connections is not adequate. Some older wiring systems may not comply with this specification even though they have three-pin outlets.[8]

UL's *Standard for Medical and Dental Equipment*, UL544, contains specifications for the performance of equipment. These include a variety of electrical and mechanical safety standards, as well as labeling and documentation requirements. To be listed as UL544 compliant, equipment must be submitted to UL for testing. The use of equipment without a UL rating may invalidate accreditations or insurance coverage. Equipment that is UL rated will bear appropriate stickers or insignia, usually on a rear panel where electrical ratings are listed.[11]

The JCAH's *Functional Safety and Sanitation* (1982) and the *Veterans Administration Circular 10-77-111* (1982) specify the requirements for safety inspections. These are summarized in the *Hospital Electrical Standards Symposium* of the American Society of Hospital Engineering (1981). These documents require records of periodic safety inspections.[6]

6 PROTOCOL FOR LABORATORY SAFETY

Safe laboratory protocol involves understanding, prevention, inspection, and record keeping. The laboratory director

has the ultimate responsibility for the establishment and execution of safety protocols. Personnel should have some formal training in electrical safety theory and practices and should receive annual reviews. Ideally, staff should understand the basis of electrical safety so that they can react to unfamiliar situations.

Routine practices of prevention can avoid or detect hazardous situations. All electrophysiologic examinations should follow such practices as part of a written protocol. This is especially important in portable recordings. Appendix Table 3–3 lists some common prevention measures.

Periodic electrical inspections of equipment and wiring are a required part of safety protocol. Standards and guidelines set by the JCAH, the NFPA, or the National Electrical Code may apply. If such inspection services are not available, laboratory personnel may have to perform these tests themselves. A good safety test meter may cost from $500 to $2000 and requires some training in its use.

Outlets and wiring in patient areas should be checked at least once a year. Checking every outlet for absence of ground connection or reversal of hot and neutral tests the wiring. The longer slot of the outlet should be neutral and the shorter slot hot. The ground pin of each outlet should be at neutral potential and have a resistance to a common ground point of not more than 0.1 ohms in sensitive patient areas and 0.2 ohms elsewhere. The voltage on outlet grounds, relative to a common ground point, should not exceed 20 mV RMS in sensitive patient areas and 50 mV elsewhere.[10]

Measuring the force required to extract a pin from each outlet contact tests the contact tension. This should be greater than 8 ounces. Hospital-grade outlets and plugs have greater initial retention and longer wear. Even these require periodic replacement.

Equipment must also be periodically tested for ground integrity and leakage current. The resistance between the instrument chassis and the ground pin on the power cord should not exceed 0.1 ohms while pulling and bending the cord in all directions for detection of intermittent or weak connections.

Instruments require testing for leakage current to the chassis and each of the patient leads, using a standard impedance to simulate the body in a leakage circuit. The standard impedance equals about

Table 3–3 Preventing Hazards

Remove any ungrounded devices (two-wire power cords) and nonessential battery-powered devices from patient areas: TV, radio, clock, lamp, tape player
Keep liquids away from equipment. Spills on or in instruments can increase leakage current, corrode ground connections, and cause equipment failures. Electrode creams contain conductive electrolytes that can destroy electronics and corrode metals
Inspect all plugs for tightness in outlets. All the plugs and outlets should be *hospital grade*, identified with a green dot. They have better retention, contact, and wear properties
Always pull plugs straight out of outlets when unplugging, not to the side or wiggling. Of course, never pull plugs out by the power cord
Unplug equipment before moving it. Jerking the power cord may break the wire or insulation and may damage the pins in the plug or outlet. Report any such accidents immediately, for proper testing and repair of the equipment and the outlet
Check daily for wear or damage to power cords and plugs
Never use extension cords on equipment, even three-wire extension cords. The added length of a power cord increases the capacitive leakage current between the hot wire and ground. The extra set of contacts increases the chances of the ground connection failing
In familiar and unfamiliar settings, verify that all equipment near a patient connects only to outlets in the same room
Never use two-pin outlets or two-pin adaptors
Never turn the main power to equipment on or off while it is connected to a patient. During these transitions the electronics may not function normally
Locate the ground electrode on the same side of the body as the recording and stimulating electrodes unless recording requirements absolutely dictate otherwise. This prevents leakage/fault currents from flowing across the body, where they might affect the heart. When multiple Instruments are directly connected to a patient, all the grounds should be on the same side of the body. This is especially important if any of the ground leads is not isolated

1000 ohms at 60 Hz. Leakage current to the chassis, the RMS value in microamperes at 60 Hz,[1] is measured with the ground to the instrument open and the standard impedance connected between the chassis and ground, under the conditions of equipment turned on and turned off, and with the hot/neutral supply normal and reversed. The worst-case leakage should not exceed 100 μA if the patient ground lead has an isolator or 50 μA if the patient ground lead connects directly to the chassis. For electrosensitive patients, the limit is 20 μA.[2]

The leakage current of the patient leads, including patient ground, is measured with the standard impedance between the lead connection and ground, under the conditions of equipment on and off, normal and reverse line, and with the instrument ground connected and open. Worst-case lead leakage should not exceed 20 μA for electrosensitive patients and 50 μA elsewhere.

Isolated inputs are also tested for leakage with their potential at 120 VAC by connecting the standard impedance between the hot line and the lead input connection. (Do not try this test with nonisolated inputs!) Under all of the above conditions, the worst-case leakage of isolated inputs should not exceed 20 μA. A good safety meter has provision for readily making all these types of measurements.

The JCAH Accreditation Manual for Hospitals requires that protocols and procedures be established for these inspections and that records of the periodic tests be kept. Inspected equipment should bear a dated safety sticker.

7 SPECIAL SAFETY DEVICES AND CIRCUITS

Isolated Power Systems

In isolated power systems, the transformer supplying the 120 VAC is not connected to earth. Then the power lines are no longer "hot" and "neutral," but "float" with respect to earth; that is, neither line has more than some small leakage conductance to earth. A grounded person could touch either one of the power lines directly and only conduct the leakage current of the system.

Isolated power systems are commonly found in operating rooms. They usually include some monitoring circuits that sound an alarm if leakage limits are exceeded. Isolation-monitoring circuits may cause interference on the power lines, which can cause artifacts in recording equipment. Leakages of large isolated power systems are typically on the order of 1 mA, which is excessive for patient protection. Patient-connected equipment must still have safe leakage limits when used on isolated power.[3]

Isolated power systems are also found on recording equipment that has several different line-powered devices, such as computers, printers, and monitors, often not designed for low leakage. The total leakage current of all these devices at the common power cord would exceed safe limits. An internal isolation transformer reduces the total power-cord leakage of the equipment to that of the transformer.

Ground Fault Interrupters

The ground fault interrupter (GFI), a device in the power wiring, senses the amount of line current flowing to earth and shuts off the power if this current to earth exceeds a trip level, usually about 4 mA. Ground fault interrupters are common, and generally required, for new wiring installations in bathrooms, kitchens, garages, and outdoors. For hospitals, however, their trip level is too high to be adequate for patient protection in all cases.

Redundant Grounding

For additional safety against loss of ground, some equipment has a redundant ground wire independent of the power cord. Intensive care units and operating rooms typically have redundant-ground panels for this connection. With a redundant ground connected, the instrument remains grounded, even if the power cord

ground fails. This is recommended on equipment for routine portable use.

Much of the material in this appendix reflects the work of Mr. Peter J. Seaba, MSEE, who co-authored this section in the first edition.

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Appendix 4

HISTORICAL REVIEW

1 INTRODUCTION

Electrophysiology was developed toward the end of the eighteenth 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 at about the mid-nineteenth century, the existence of bioelectricity was firmly established by Galvani and others. The basic concepts of electricity were also established 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 second half of the nineteenth 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 responses to electrical stimulation as a diagnostic test. The method gained popularity during the first half of the twentieth 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 seventeenth century that the world 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 eighteenth 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 in 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[74] in 1797 and Matteucci[102] in 1844. 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 Galvanti'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, Galvanis' 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 with 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,[118] in 1825, 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,[109] in 1830, 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] in 1883, 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 1819 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 1857, 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 end plates for the nerve endings of striated muscle.

Hammond[104] translated Meyer's comprehensive discussion on electrical stimulation of the muscle into English. 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. Baierlacher[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 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. In 1870, Engelman showed 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 nineteenth 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 texts 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. Lapicque[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 condensors (capacitors) for diagnostic purposes. Using this apparatus, Bourguignon[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[103] in 1934 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, Heofer 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 2 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 armamentation after standardization by Lambert[86] and Desmedt.[29]

Piper[110] and Münnich[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 man 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.[7,44,117] Harvey and Kuffler[60] and Harvey, Kuffler, and Tredway[61] studied peripheral neuritis in man, 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 above, 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]

The above outline includes most of the major events that have taken place in the history of clinical electrophysiology of muscle and nerve. Inclusion of further details, although tempting because of a number of intriguing anecdotes, falls 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 5

AAEE GLOSSARY OF TERMS IN CLINICAL ELECTROMYOGRAPHY*

FOREWORD

One of the objectives of the American Association of Electromyography and Electrodiagnosis (AAEE) is the publication of information to increase and to extend the knowledge of electromyographers. In 1974, the Board of Directors of the AAEE established a Nomenclature Committee with the task of compiling and defining a list of terms used in electromyography. The resultant Glossary was published by the AAEE in 1980. The Glossary was widely accepted and helped to standardize the terms used in clinical reports and in scientific publications. Subsequent advances in electromyography necessitated a review and revision of the 1980 Glossary. In 1983, a new Nomenclature Committee was created by the AAEE. Every term in the 1980 Glossary was reviewed; some old terms were redefined, a few were deleted, and some new terms were added. Also new to this 1987 Glossary are illustrations of selected waveforms and lists of terms grouped by subject.

AAEE Nomenclature Committee

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*Compiled by the Nomenclature Committee of the American Association of Electromyography and Electrodiagnosis. Second Edition published in *Muscle & Nerve*, Volume 10, Number 8S/Supplement, October 1987. Reproduced and modified in part by permission.

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INTRODUCTION

In all areas of science, terms should be precisely defined and standardized. Terms should be used consistently so that one scientist in a field can speak or write to another without ambiguity. The need for definitions exists in electromyography because there are numerous clinical investigators conducting studies. By agreeing upon terminology, investigators can understand and verify the findings of others. It is suggested that the terms in this glossary be used by authors of papers for publication in electromyography and by clinical electromyographers for patient reports.

The first edition of this Glossary was prepared and published by the American Association of Electromyography and Electrodiagnosis (AAEE) in 1980. In 1983, the International Federation of Societies for Electroencephalography and Clinical Neurophysiology (IFSECN) published an adaptation of that glossary for its members. This second edition of the AAEE Glossary was compiled after an extensive review of the first AAEE Glossary, of the changes made by the IFSCEN, of new terms suggested by AAEE members, and of the recent literature. The following definitions are the result of considerable deliberation. In some cases, the committee members compromised and retained terms which have been in use for such a long time that it was agreed that they should remain as they are, even though they are not ideal.

This glossary is presented in four sections. In Section I, all terms are listed in alphabetical order and are defined. The alphabetical presentation permits electromyographers to use the glossary efficiently to prepare and to review reports. An asterisk adjacent to a term indicates that an illustration of that waveform is contained in Section II. In Section III, terms are grouped by subject without definition to permit the systematic review of related terms.

SECTION I: ALPHABETICAL LIST OF TERMS WITH DEFINITIONS

***A wave** A compound action potential evoked consistently from a muscle by submaximal electric 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 may occur afterwards. The A wave is due to normal or pathologic axonal branching. Compare the *F wave.*

absolute refractory period See *refractory period.*

accommodation True accommodation in neuronal physiology is 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, accommodation described 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.*

action current The electric currents associated with an *action potential.*

action potential (AP) The brief regenerative electric potential that propagates along a single axon or muscle fiber membrane. The action potential is an all-or-none phenomenon; whenever the stimulus is at or above threshold, the action potential generated has a constant size and configura-

*Illustration in Section II.

tion. See also *compound action potential*, and *motor unit action potential*.

active electrode Synonymous with *exploring electrode*. See *recording electrode*.

adaptation A decline in the frequency of the spike discharge as typically recorded from sensory axons in response to a maintained stimulus.

AEPs See *auditory evoked potentials*.

afterdischarge The continuation of an impulse train in a neuron, axon or muscle fiber following the termination of an applied stimulus. The number of extra impulses and their periodicity in the train may vary depending on the circumstances.

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.

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 the *compound muscle action potential* is measured from the 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.

anodal block A local block of nerve conduction caused by *hyperpolarization* of the nerve cell membrane by an electric stimulus. See *stimulating electrode*.

anode The positive terminal of a source of electric current.

antidromic Propagation of an 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 See *action potential*.

artifact (also artefact) A voltage change generated by a biologic or nonbiologic source other than the ones of interest. The *stimulus artifact* is the potential recorded at the time the stimulus is applied and includes the *electric* or *shock artifact*, which represents cutaneous spread of stimulating current to the recording electrode. The stimulus and shock artifacts usually precede the activity of interest. A *movement artifact* refers to a change in the recorded activity caused by movement of the recording electrodes.

auditory evoked potentials (AEPs). Electric waveforms of biologic origin elicited in response to sound stimuli. AEPs are classified by their latency as short-latency brainstem AEPs (BAEPs) with a latency of up to 10 ms, middle-latency AEPs with a latency of 10–50 ms, and long-latency AEPs with a latency of over 50 ms. See *brainstem auditory evoked potentials*.

axon reflex Use of this term is discouraged as it is incorrect. No reflex is considered to be involved. See preferred term, *A wave*.

axon response See preferred term, *A wave*.

axon wave See *A wave*.

axonotmesis Nerve injury characterized by disruption of the axon and myelin sheath, but with preservation of the supporting connective tissue, resulting in axonal degeneration distal to the injury site.

backfiring Discharge of an antidromically activated motor neuron.

BAEPs See *brainstem auditory evoked potentials*.

BAERs Abbreviation for *brainstem auditory evoked responses*. See preferred term, *brainstem auditory evoked potentials*.

baseline The potential recorded from a biologic system while the system is at rest.

benign fasciculation Use of this term is discouraged to describe a firing pattern of fasciculation potentials. The term has been used to describe a clinical syndrome and/or the presence of fasciculations in nonprogressive neuromuscular disorders. See *fasciculation potential*.

BERs Abbreviation for *brainstem auditory evoked responses*. See preferred term, *brainstem auditory evoked potentials*.

bifilar needle recording electrode *Recording electrode* that measures variations in voltage between the bare tips of 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. The latter may be grounded.

biphasic action potential An *action potential* with two phases.

biphasic end-plate activity See *endplate activity (biphasic)*.

bipolar needle recording electrode See preferred term, *needle bifilar recording electrode*

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 response Strictly defined, one of the *blink responses.* See *blink responses.*

***blink responses** *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 probably oligosynaptic and polysynaptic brainstem reflexes, respectively, together called the *blink reflex,* with the afferent arc provided by the sensory branches of the trigeminal nerve and the efferent arc provided by the facial nerve motor fibers.

***brainstem auditory evoked potentials** (BAEPs) Electric waveforms of biologic origin elicited in response to sound stimuli. The normal BAEP consists of a sequence of up to seven waves, named 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 responses (BAERs, BERs) See preferred term, *brainstem auditory evoked potentials.*

BSAPs Abbreviation for brief, small, abundant potentials. Use of term is discouraged. It is used to describe a recruitment pattern of brief-duration, small-amplitude, overly abundant motor unit action potentials. Quantitative measurements of motor unit potential duration, amplitude, numbers of phases, and recruitment frequency are to be preferred to qualitative descriptions such as this. See *motor unit action potential.*

BSAPPs Abbreviation for brief, small abundant, polyphasic potentials. Use of term is discouraged. It is used to describe a recruitment pattern of brief-duration, small-amplitude, overly abundant, polyphasic motor unit action potentials. Quantitative measurements of motor unit potential duration, amplitude, numbers of phases, and recruitment frequency are to be preferred to qualitative descriptions such as this. See *motor unit action potential.*

cathode The negative terminal of a source of electric current.

central electromyography (central EMG) Use of electromyographic recording techniques to study reflexes and the control of movement by the spinal cord and brain.

chronaxie (also chronaxy) See *strength-duration curve.*

clinical electromyography Synonymous with *electroneuromyography.* Used to refer to all electrodiagnostic studies of human peripheral nerves and muscle. See also *electromyography* and *nerve conduction studies.*

coaxial needle electrode See synonym, *concentric needle electrode.*

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 action potential See preferred term, *serrated action potential.*

complex motor unit action potential A *motor unit action potential* that is polyphasic or serrated. See preferred terms, *polyphasic action potential* and *serrated action potential.*

***complex repetitive discharge** Polyphasic or serrated action potentials that may begin spontaneously or after a needle movement. They have a uniform fre-

*Illustration in Section II.

quency, shape, and amplitude, with abrupt onset, cessation, or change in configuration. Amplitude ranges from 100 μV to 1 mV and frequency of discharge from 5 to 100 Hz. This term is preferred to *bizarre high frequency discharge, bizarre repetitive discharge, bizarre repetitive potential, near constant frequency trains, pseudomyotonic discharge,* and *synchronized fibrillation.*

compound action potential 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 (compound mixed NAP) A compound nerve action potential is considered to have been evoked from afferent and efferent fibers if the recording electrodes detect activity on a mixed nerve with the electric stimulus 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 is considered to have been evoked from efferent fibers to a muscle if the recording electrodes detect activity only in a motor nerve or a motor branch of a mixed nerve, or if the electric stimulus is applied only to such a nerve or a ventral root. The amplitude, latency, duration, and phrases should be noted. See *compound nerve 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 wave* 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).

***compound sensory nerve action potential** (compound SNAP) 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, the latency 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 has been referred to as the *sensory response* or *sensory potential.*

concentric needle electrode *Recording electrode* that measures an electric potential difference between the bare tip of an insulated wire, usually stainless steel, silver or platinum, and the bare shaft of a steel cannula through which it is inserted. The bare tip of the central wire (exploring electrode) is flush with the level of the cannula (reference electrode).

conditioning stimulus See *paired stimuli.*

conduction block Failure of an action potential to be conducted past a particular point in the nervous system whereas conduction is possible below the point of the block. Conduction block is documented by demonstration of a reduction in the area of an evoked potential greater than that normally seen with electric 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 See *conduction velocity.*

*Illustration in Section II.

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) 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 velocity represents the conduction velocity of the fastest fibers and is expressed as meters per second (m/s). As commonly used, the term *conduction velocity* refers to the maximum conduction velocity. By specialized techniques, the conduction velocity of other fibers can be determined as well and should be specified, e.g., minimum conduction velocity.
contraction A voluntary or involuntary reversible muscle shortening that may or may not be accompanied by *action potentials* from muscle. This term is to be contrasted with the term *contracture*, which refers to a condition of fixed muscle shortening.
contraction fasciculation Rhythmic, visible twitching of a muscle with weak voluntary or postural contraction. The phenomenon occurs in neuromuscular disorders in which the motor unit territory is enlarged and the tissue covering the muscle is thin.
contracture The term is used to refer to immobility of a joint due to fixed muscle shortening. Contrast *contraction.* The term has also been used to refer to an electrically silent, involuntary state of maintained muscle contraction, as seen in phosphorylase deficiency, for which the preferred term is *muscle cramp.*
coupled discharge See preferred term, *satellite potential*
cps (also c/s) See *cycles per second.*
***cramp discharge** Involuntary repetitive firing of *motor unit action potentials* at a high frequency (up to 150 Hz) in a large area of muscles, 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.*
c/s (also cps) See *cycles per second.*
CV See *conduction velocity.*
cycles per second Unit of frequency. (cps or c/s). See also *hertz* (Hz).
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 (2–5 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. Contrast with *incrementing response.*
delay As originally used in clinical electromyography, delay referred to the time between the beginning of the horizontal sweep of the oscilloscope and the onset of an applied stimulus. The term is also used to refer to an information storage device (delay line) used to display events occurring before a trigger signal.
denervation potential This term has been used to describe a *fibrillation potential.* The use of this term is discouraged because fibrillation potentials may occur in settings where transient muscle membrane instability occurs in the absence of denervation, e.g., hyperkalemic periodic paralysis. See preferred term, *fibrillation potential.*
depolarization See *polarization.*
depolarization block Failure of an excitable cell to respond to a stimulus because of depolarization of the cell membrane.
discharge Refers to the firing of one or more excitable elements (neurons, axons,

*Illustration in Section II.

or muscle fibers) and as conventionally applied refers to the all-or-none potentials only. Synonymous with *action potential.*

discharge frequency The rate of repetition of potentials. When potentials occur in groups, the rate of recurrence of the group and the rate of repetition of the individual components in the groups should be specified. See also *firing rate.*

discrete activity See *interference pattern.*

distal latency See *motor latency* and *sensory latency.*

double discharge Two action potentials (*motor unit action potential, fibrillation 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. Contrast with *paired discharge.*

doublet Synonymous with *double discharge.*

duration The time during which something exists or acts. (1) The total duration of individual potential *waveforms* is defined as the interval from the beginning of the first deflection from the baseline to its final return to the baseline, unless otherwise specified. If only part of the waveform duration is measured, the points of measurement should be specified. For example, the duration of the *M wave* may refer to the interval from the deflection of the first negative phase from the baseline to its return to the baseline. (2) The duration of a single electric stimulus refers to the interval of the applied current or voltage. (3) The duration of recurring stimuli or action potentials refers to the interval from the beginning to the end of the series.

earth electrode Synonymous with *ground electrode.*

EDX See *electrodiagnosis.*

electric artifact See *artifact.*

electric inactivity Absence of identifiable electric activity in a structure or organ under investigation. 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.

electrode A conducting device used to record an electric potential (*recording electrode*) or to apply 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 apply an electric current. Depending on the relative size and location of the electrodes, however, the stimulating or recording condition may be referred to as *monopolar* or *unipolar.* 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 recording and analysis of responses of nerves and muscles to electric stimulation and the identification of patterns of insertion, spontaneous, involuntary and voluntary action potentials in muscle and nerve tissue. See also *electromyography, electroneurography, electroneuromyography,* and *evoked potential studies.*

electrodiagnostic medicine A specific area of medical practice in which a physician uses information from the clinical history, observations from the physical examination, and the techniques of *electrodiagnosis* to diagnose and treat neuromuscular disorders. See *electrodiagnosis.*

electromyelography The recording and study of electric activity from the spinal cord and/or from the cauda equina.

electromyogram The record obtained by *electromyography.*

electromyograph Equipment used to activate, record, process, and display nerve and muscle action potentials for the purpose of evaluating nerve and muscle function.

electromyography (EMG) Strictly defined, the recording and study of insertion, spontaneous, and voluntary electric activity of muscle. It is commonly used to refer to nerve conduction studies as well. See also *clinical electromyography* and *electroneuromyography.*

electroneurography (ENG) The recording and study of the action potentials of peripheral nerves. Synonymous with *clinical electromyography.*

EMG See *electromyography.*

***end-plate activity** Spontaneous electric

*Illustration in Section II.

activity recorded with a needle electrode close to muscle end-plates. May be either of two forms:

1. *Monophasic:* Low-amplitude (10–20 μV), short-duration (0.5–1 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:* Moderate-amplitude (100–300 μV), short-duration (2–4 ms), biphasic (negative-positive) spike potentials that occur irregularly in short bursts with a high frequency (50–100 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 *biphasic spike potentials*, *end-plate spikes*, and, *incorrectly*, *nerve potentials*.

end-plate noise See *end-plate activity* (*monophasic*).

end-plate potential (EPP) The graded nonpropagated membrane potential induced in the postsynaptic membrane of the muscle fiber by the action of acetylcholine released in response to an action potential in the presynaptic axon terminal.

end-plate spike See *end-plate activity* (*biphasic*).

end-plate zone The region in a muscle where the neuromuscular junctions of the skeletal muscle fibers are concentrated.

ENG See *electroneurography*.

ENMG See *electroneuromyography*.

EPP See *end-plate potential*.

EPSP See *excitatory postsynaptic potential*.

evoked compound muscle action potential See *compound muscle action potential*.

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 electric or physiologic stimuli. Generally used to refer to studies of waveforms generated in the peripheral and central nervous system, whereas *nerve conduction studies* refers to studies of waveforms generated in the peripheral nervous system. There are two systems for naming complex waveforms in which multiple components can be distinguished. In the first system, the different components are labeled PI or NI for the initial positive and negative potentials, respectively, and PII, NII, PIII, NIII, and so forth, for subsequent positive and negative potentials. In the second system, the components are specified by polarity and average peak latency in normal subjects to the nearest millisecond. The first nomenclature principle has been used in an abbreviated form to identify the seven positive components (I–VII) of the normal *brainstem/auditory evoked potential.* The second nomenclature principle has been used to identify the positive and negative components of *visual evoked potentials* (N_{75}, P_{100}) and *somatosensory evoked potentials* (P_9, P_{11}, P_{13}, P_{14}, N_{20}, P_{23}). Regardless of the nomenclature system, it is possible under standardized conditions to establish normal ranges of amplitude, duration, and latency of the individual components of these *evoked potentials.* The difficulty with the second system is that the latencies of components of evoked potentials depend upon the length of the pathways in the neural somatosensory evoked potential tissues. Thus the components of somatosensory evoked potential recorded in a child have different average latencies from the same components of somatosensory evoked potential recorded in an adult. Despite this problem, there is no better system available for naming these components at this time. See *auditory evoked potentials,*

brainstem auditory evoked potentials, visual evoked potentials, 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 or a synapse. Contrast with *inhibitory postsynaptic potential.*

exploring electrode Synonymous with *active electrode.* See *recording electrode.*

F reflex See preferred term, *F wave.*

F response Synonymous with *F wave.* See preferred term, *F wave.*

***F wave** A *compound action potential* evoked intermittently from a muscle by a supramaximal electric 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 the *H wave* and the *A wave.*

***facilitation** Improvement of neuromuscular transmission that results in the activation of previously inactive muscle fibers. Facilitation may be identified in several ways:

1. *Incrementing response:* A reproducible increase in the amplitude associated with an increase in the area of successive electric responses (*M waves*) during *repetitive nerve stimulation.*
2. *Postactivation* or *posttetanic facilitation:* Nerve stimulation studies performed within a few seconds after a brief period (2–15 s) of nerve stimulation producing *tetanus* or after a strong voluntary contraction may show changes in the configuration of the *M wave*(s) compared with the results of identical studies of the rested neuromuscular junction as follows:
   a. *Repair of the decrement:* A diminution of the decrementing response seen with slow rates (2–5 Hz) of *repetitive nerve stimulation.*
   b. *Increment after exercise:* An increase in the amplitude associated with an increase in the area of the M wave elicited by a single supramaximal stimulus.

Facilitation should be distinguished from pseudofacilitation. *Pseudofacilitation* occurs 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. *Pseudofacilitation* produces a response characterized by an increase in the amplitude of the successive M waves with a corresponding decrease in the duration of the M wave resulting in no change in the area of the negative phase of the successive M waves.

far-field potential Electric activity of biologic origin generated at a considerable distance from the recording electrodes. Use of the terms *near-field potential* and *far-field potential* is discouraged because all potentials in clinical neurophysiology are recorded at some distance from the generator and there is no consistent distinction between the two terms.

fasciculation The random, spontaneous twitching of a group of muscle fibers or a motor unit. This twitch may produce movement of the overlying skin (limb), mucous membrane (tongue), or digits. The electric activity associated with the spontaneous contraction is called the *fasciculation potential.* See also *myokymia.* Historically the term *fibrillation* has been used to describe fine twitching of muscle fibers visible through the skin or mucous membrane, but this usage is no longer acceptable.

***fasciculation potential** The electric potential often associated with a visible *fasciculation* which has the configuration of a *motor unit action potential* but which occurs spontaneously. Most commonly these po-

*Illustration in Section II.

tentials occur sporadically and are termed "single fasciculation potentials." Occasionally, the potentials occur as a grouped discharge and are termed a "brief repetitive discharge." The occurrence of 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 frequency of occurrence, should be specified.

fatigue Generally, a state of depressed responsiveness resulting from protracted activity and requiring an appreciable recovery time. Muscle fatigue is a reduction in the force of contraction of muscle fibers and follows repeated voluntary contraction or direct electric stimulation of the muscle.

fiber density (1) Anatomically, fiber density is a measure of the number of muscle or nerve fibers per unit area. (2) In *single fiber electromyography*, the fiber density is the mean number of *muscle fiber action potentials* fulfilling amplitude and rise time criteria belonging to one motor unit within the recording area of the *single fiber needle electrode* encountered during a systematic search in the weakly, voluntarily contracted 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*.

fibrillation potential 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. The potentials 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 (1–50 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 old 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 potential arises from an area immediately adjacent to the needle electrode.

firing pattern Qualitative and quantitative descriptions of the sequence of discharge of potential 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*.

frequency Number of complete cycles of a repetitive waveform in one second. Measured in *hertz* (Hz) or *cycles per second* (cps or c/s).

frequency analysis Determination of the range of frequencies composing a potential waveform, with a measurement of the absolute or relative amplitude of each component frequency.

full interference pattern See *interference pattern*.

functional refractory period See *refractory period*.

G1, G2 Synonymous with *Grid 1*, *Grid 2*, and newer terms, *Input Terminal 1*, and *Input Terminal 2*. See *recording electrode*.

"giant" motor unit action potential Use of term discouraged. It refers to a *motor unit action potential* with a peak-to-peak amplitude and duration much greater than the range recorded in corresponding muscles in normal subjects of similar age. Quantitative measurements of amplitude and duration are preferable.

Grid 1 Synonymous with G_1. *Input Terminal 1*, or *active* or *exploring electrode*. See *recording electrode*.

Grid 2 Synonymous with G_2. *Input Terminal 2*, or *reference electrode*. See *recording electrode*.

ground electrode An electrode connected to the patient and to a large conducting body (such as the earth) used as a com-

mon return for an electric circuit and as an arbitrary zero potential reference point.

grouped discharge The term has been 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*, and (3) general term to describe repeated firing of *motor unit action potentials*. See preferred term, *repetitive discharge*.

H reflex Abbreviation for Hoffmann reflex. See *H wave*.

H response See preferred term *H wave*.

***H wave** 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 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 through a monosynaptic connection in the spinal cord. The reflex and wave are named in honor of Hoffmann's description (1918). Compare the *F 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.

hertz (Hz) Unit of frequency equal to *cycles per second*.

Hoffmann reflex See *H wave*.

hyperpolarization See *polarization*.

Hz See *hertz*.

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 responses (M wave) 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 deceases, 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*.

indifferent electrode Synonymous with *reference electrode*. Use of term discouraged. See *recording electrode*.

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 The potential difference between a normal region of the surface of a nerve or muscle and a region that has been injured; also called a demarcation potential. The injury potential approximates the potential across the membrane because the injured surface is almost at the potential of the inside of the cell.

Input Terminal 1 The input terminal of the differential amplifier at which negativity, relative to the other input terminal, produces an upward deflection on the graphic display. Synonymous with *active* or *exploring electrode* (or older term, *Grid 1*). See *recording electrode*.

Input Terminal 2 The input terminal of the differential amplifier at which negativity, relative to the other input terminal, produces a downward deflection on the graphic display. Synonymous with *refer-*

*Illustration in Section II.

ence electrode (or older term, *Grid 2*). See *recording electrode.*

***insertion activity** Electric activity caused by insertion or movement of a needle electrode. The amount of the activity may be described as normal, reduced, increased (prolonged), with a description of the waveform and repetitive rate.

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 arising outside the system being studied.

***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* (*MUAP*) can be clearly identified. A *reduced interference pattern* (*intermediate pattern*) is one in which some of the individual MUAPs may be identified while other individual MUAPs cannot be identified because of overlap. The term *discrete activity* is used to describe the electric activity recorded when each of several different MUAPs can be identified. The term *single unit pattern* is used to describe a single MUAP, 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 *recruitment pattern.*

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 between the nasion and inion in the sagittal plane, and between 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 on each waveform.

involuntary activity *Motor unit potentials* that are not under voluntary control. The condition under which they occur should be described, e.g., spontaneous or reflex potentials and, if elicited by a stimulus, the nature of the stimulus. Contrast with *spontaneous activity.*

IPSP See *inhibitory postsynaptic potential.*

irregular potential See preferred term, *serrated action potential.*

iterative discharge See preferred term, *repetitive discharge.*

***jitter** Synonymous with single fiber electromyographic jitter. Jitter is the variability with consecutive discharges of the *interpotential interval* between two muscle fiber action potentials belonging to the same motor unit. 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).

Jolly test A technique described by Jolly (1895), who applied an electric current to excite a motor nerve while recording the force of muscle contraction. Harvey and Masland (1941) refined the technique by recording the M wave evoked by repetitive, supramaximal nerve stimulation to detect a defect of neuromuscular transmission. Use of the term is discouraged. See preferred term, *repetitive nerve stimulation.*

late component (of a motor unit action potential) See preferred term, *satellite potential.*

late response A general term used to describe an evoked potential having a longer latency than the *M wave.* See *A wave, F wave, H wave,* and *T wave.*

latency Interval between the onset of a stimulus and the onset of a response. Thus the term *onset latency* is a tautology and should not be used. 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 ini-

*Illustration in Section II.

tiate a regenerative action potential in the fiber(s). This time is usually on the order of 0.1 ms or less. An equivalent term now rarely used in the literature is the "utilization time."

latent period See synonym, *latency.*

linked potential See preferred term, *satellite potential.*

long-latency SEP That portion of a *somatosensory evoked potential* normally occurring at a time greater than 100 ms after stimulation of a nerve in the upper extremity at the wrist, or the lower extremity at the knee or ankle.

M response See synonym, *M wave.*

***M wave** A *compound action potential* evoked from a muscle by a single electric stimulus to its motor nerve. By convention, the M wave elicited by supramaximal stimulation is used for motor nerve conduction studies. Ideally, the recording electrodes should be placed so that the initial deflection of the evoked potential is negative. The *latency*, commonly called the *motor latency*, is the latency (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.*

macromotor unit action potential (macro MUAP) The average electric activity of that part of an anatomic motor unit that is within the recording range of a *macro-EMG electrode.* The potential is characterized by its consistent appearance when the small recording surface of the macro-EMG electrode is positioned to record action potentials from one muscle fiber. The following parameters can be specified quantitatively: (1) maximal peak-to-peak amplitude, (2) area contained under the waveform, (3) number of phases.

macro MUAP See *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.

macro-EMG See *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 Use of this term is discouraged to describe a firing pattern of fasciculation potentials. Historically, the term was 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. 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.*

membrane instability Tendency of a cell membrane to depolarize spontaneously, with mechanical irritation, or after voluntary activation.

MEPP Miniature end plate potential.

microneurography The technique of recording peripheral nerve action potentials in humans by means of intraneural electrodes.

midlatency SEP That portion of the waveforms of a *somatosensory evoked potential* normally occurring within 25–100 ms after stimulation of a nerve in the upper extremity at the wrist, within 40–100 ms after stimulation of a nerve in the lower extremity at the knee, and within 50–100 ms after stimulation of a nerve in the lower extremity at the ankle.

miniature end plate potential (MEPP) The postsynaptic muscle fiber potentials produced through the spontaneous release of individual quanta of acetylcholine from the presynaptic axon terminals. As recorded with conventional concentric needle electrodes inserted in the end plate zone, such potentials are characteristically monophasic, negative, of relatively short duration (less than 5 ms) and generally less than 20 μV in amplitude.

*Illustration in Section II.

MNCV Abbreviation for *motor nerve conduction velocity*. See *conduction velocity*.
monophasic action potential See *action potential* with one phase.
monophasic end-plate activity See end plate activity (*monophasic*).
monopolar needle recording electrode A solid wire, usually stainless steel, usually coated, except at its tip, with an insulating material. Variations in voltage between the tip of the needle (active or exploring electrode) positioned in a muscle and a conductive plate on the skin surface or a bare needle in subcutaneous tissue (reference electrode) are measured. By convention, this recording condition is referred to as a monopolar needle electrode recording. It should be emphasized, however, that potential differences are always recorded between two electrodes.
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 conduction velocity (MNCV) See *conduction velocity*.
motor point The point over a muscle where a contraction of a muscle may be elicited by a minimal-intensity, short-duration electric stimulus. The motor point corresponds anatomically to the location of the terminal portion of the motor nerve fibers (end-plate zone).
motor response (1) The compound muscle action potential (*M wave*) recorded over a muscle with stimulation of the nerve to the muscle, (2) the muscle twitch or contraction elicited by stimulation of the nerve to a muscle, and (3) the muscle twitch elicited by the muscle stretch reflex.
motor unit The anatomic unit 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) Action potential reflecting the electric activity of a single anatomic motor unit. It is the compound action potential of those muscle fibers within the recording range of an electrode. With voluntary muscle contraction, the action potential is characterized by its consistent appearance with, and relationship to, the force of contraction. The following parameters should be specified, quantitatively if possible, after the recording electrode is placed so as to minimize the *rise time* (which by convention should be less than 0.5 ms):

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, if any, with consecutive discharges.
   g. Presence of *satellite* (*linked*) *potentials*, if any.
2. *Recruitment* characteristics
   a. Threshold of activation (first recruited, low threshold, high threshold).
   b. *Onset frequency* (Hz).
   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*.
motor unit fraction See *scanning EMG*.
motor unit potential (MUP) See synonym, *motor unit action potential*.
motor unit territory The area in a muscle over which the muscle fibers belonging to an individual motor unit are distributed.
movement artifact See *artifact*.
MSD Abbreviation for mean sorted difference. See *jitter*.
MUAP See *motor unit action potential*.
multielectrode See *multilead electrode*.
multilead electrode Three or more insulated wires inserted through a common metal cannula with their bared tips at an aperture in the cannula and flush with the outer circumference of the cannula. The arrangement of the bare tips relative

*Illustration in Section II.

to the axis of the cannula and the distance between each tip should be specified.

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 or muscle fiber. See *double* and *triple discharge*.

multiplet See *multiple discharge*.

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 cramp Most commonly, an involuntary, painful muscle *contraction* associated with electric activity (see *cramp discharge*). Muscle cramps may be accompanied by other types of *repetitive discharges*, and in some metabolic myopathies (McArdle's disease) the painful, contracted muscles may show *electric silence*.

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. The muscle fiber conduction velocity is usually less than most nerve conduction velocities, varies with the rate of discharge of the muscle fiber, and requires special techniques for measurement.

muscle stretch reflex Activation of a muscle that follows stretch of the muscle, e.g., by percussion of a muscle tendon.

myoedema Focal muscle contraction produced by muscle percussion and 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 potentials*. See *myokymic discharge*, *fasciculation*, and *fasciculation potential*.

*Illustration in Section II.

***myokymic discharge** *Motor unit action potentials* that fire repetitively and may be associated with clinical myokymia. Two firing patterns have been described. Commonly, the discharge is a brief, repetitive firing of single units for a short period (up to a few seconds) at a uniform rate (2–60 Hz) followed by a short period (up to a few seconds) of silence, with repetition of the same sequence for a particular potential. Less commonly, the potential recurs continuously at a fairly uniform firing rate (1–5 Hz). Myokymic discharges are a subclass of *grouped discharges* and *repetitive discharges*.

myopathic motor unit potential Use of this term is discouraged. It has been used to refer to low-amplitude, short-duration, polyphasic *motor unit action potentials*. The term incorrectly implies specific diagnostic significance of a motor unit potential configuration. See *motor unit action potential*.

myopathic recruitment Use of this term is discouraged. It has been used to describe an increase in the number of and firing rate of *motor unit action potentials* compared with normal for the strength of muscle contraction.

myotonia The clinical observation of delayed relaxation of muscle after voluntary contraction or percussion. The delayed relaxation may be electrically silent, or accompanied by propagated electric activity, such as *myotonic discharge*, *complex repetitive discharge*, or *neuromyotonic discharge*.

***myotonic discharge** Repetitive discharge at rates of 20–80 Hz are of two types: (1) biphasic (positive-negative) spike potentials less than 5 ms in duration resembling *fibrillation potentials*, (2) positive waves of 5–20 ms in duration resembling *positive sharp waves*. Both potential forms are recorded after needle 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 to be identified as myotonic discharges. 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.*

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. Use of term is discouraged as it incorrectly implies diagnostic significance of a motor unit potential configuration. The term has been used to refer to very low-amplitude, long-duration, highly polyphasic motor unit potentials observed during early states of reinnervation of muscle. See *motor unit action potential.*

NCS See *nerve conduction studies.*

NCV Abbreviation for *nerve conduction velocity.* See *conduction velocity.*

near constant frequency trains See preferred term, *complex repetitive discharge.*

near-field potential Electric activity of biologic origin generated near the recording electrodes. Use of the terms *near-field potential* and *far-field potential* is discouraged because all potentials in clinical neurophysiology are recorded at some distance from the generator and there is no consistent distinction between the two terms.

needle electrode An electrode for recording or stimulating, shaped like a needle. 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 studies (NCS) Synonymous with *electroneurography.* Recording and analysis of electric *waveforms* of biologic origin elicited in response to electric or physiologic *stimuli.* Generally *nerve conduction studies* refer to studies of waveforms generated in the peripheral nervous system, whereas *evoked potential studies* refer to studies of waveforms generated in both the peripheral and central nervous system. The waveforms recorded in *nerve conduction studies* are *compound sensory nerve action potentials* and *compound muscle action potentials.* The *compound sensory nerve action potentials* are generally referred to as *sensory nerve action potentials.* The *compound muscle action potentials* are generally referred to by letters which have historical origins: *M wave, F wave, H wave, T wave, A wave,* R_1 *wave,* and R_2 *wave.* It is possible under standardized conditions to establish normal ranges of amplitude, duration, and latencies of these *evoked potentials* and to calculate the maximum conduction velocity of sensory and motor nerves.

nerve conduction velocity (NCV) Loosely used to refer to the maximum nerve conduction velocity. See *conduction velocity.*

nerve fiber action potential Action potential recorded from a single nerve fiber.

nerve potential Equivalent to *nerve action potential.* Also commonly, but inaccurately, used to refer to the biphasic form of *end-plate activity.* 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 Failure of nerve conduction, usually reversible, due to metabolic or microstructural abnormalities without disruption of the axon. See preferred electrodiagnostic term, *conduction block.*

neuromyotonia Clinical syndrome of continuous muscle fiber activity manifested as continuous muscle rippling and stiffness. The accompanying electric activity may be intermittent or continuous. Terms used to describe related clinical syndromes are continuous muscle fiber activity, Isaac syndrome, Isaac-Merton syndrome, quantal squander syndrome, generalized myokymia, pseudomyotonia, normocalcemic tetany and neurotonia.

***neuromyotonic discharge** Bursts of *motor unit action potentials* that originate in the motor axons firing at high rates (150–300 Hz) for a few seconds, and which often start and stop abruptly. The amplitude of the response typically wanes. Discharges may occur spontaneously or be

*Illustration in Section II.

initiated by needle movement, voluntary effort and ischemia or percussion of a nerve. These discharges should be distinguished from *myotonic discharges* and *complex repetitive discharges.*

neuropathic motor unit potential Use of this term is discouraged. It was used to refer to abnormally high-amplitude, long-duration, polyphasic *motor unit action potentials.* The term incorrectly implies a specific diagnostic significance of a motor unit potential configuration. See *motor unit action potential.*

neuropathic recruitment Use of this term is discouraged. It has been used to describe a recruitment pattern with a decreased number of *motor unit action potentials* firing at a rapid rate. See preferred terms, *reduced interference pattern, discrete activity,* and *single unit pattern.*

neurotmesis Partial or complete severance of a nerve, with disruption of the axons, their myelin sheaths and the supporting connective tissue, resulting in degeneration of the axons distal to the injury site.

noise Strictly defined, potentials produced by electrodes, cables, amplifier or storage media and unrelated to the potentials of biologic origin. The term has been used loosely to refer to one form of *end plate activity.*

onset frequency The lowest stable frequency of firing for a single *motor unit action potential* that can be voluntarily maintained by a subject.

onset latency Tautology. See *latency.*

order of activation The sequence of appearance of different *motor unit action potentials* with increasing strength of voluntary contraction. See *recruitment.*

orthodromic Propagation of an impulse in the direction the same 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 discharge Two action potentials occurring consistently in the same relationship with each other. Contrast with *double discharge.*

paired response Use of this term is discouraged. See preferred term, *paired discharge.*

paired stimuli Two consecutive stimuli. The time interval between the two stimuli and the intensity of each stimulus should be specified. The first stimulus is called the *conditioning stimulus* and the second stimulus is the *test stimulus.* The *conditioning stimulus* may modify the tissue excitability, which can then be 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 the evoked potential.

phase That portion of a *wave* between the departure from, and the return to, the *baseline.*

polarization As used in neurophysiology, the presence of an electric potential difference across an excitable cell membrane. The potential across the membrane of a cell when it is not excited by an input or spontaneously active is termed the *resting potential;* it is at a stationary nonequilibrium state with regard to the electric potential difference across the membrane. *Depolarization* describes a reduction in the magnitude of the polarization toward the zero potential while *hyperpolarization* refers to an increase in the magnitude of the polarization relative to the resting potential. *Repolarization* describes an increase in polarization from the depolarized state toward, but not above, the normal resting potential.

polyphasic action potential An *action potential* having five or more phases. See *phase.* Contrast with *serrated action potential.*

***positive sharp wave** A biphasic, positive-negative *action potential* initiated by needle movement and recurring in a uniform, regular pattern at a rate of 1–50 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, with a duration of 10–100 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. Its configuration may result from the position of

the needle electrode which is felt 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.

positive wave Loosely defined, the term refers to a positive sharp wave. See *positive sharp wave.*

***postactivation depression** A descriptive term indicating a reduction in the amplitude associated with a reduction in the area of the M wave(s) in response to a single *stimulus* or *train of stimuli* which occurs a few minutes after a brief (30–60 seconds), strong voluntary contraction or a period of *repetitive nerve stimulation* that produces *tetanus. Postactivation exhaustion* refers to the cellular mechanisms responsible for the observed phenomenon of *postactivation depression.*

postactivation exhaustion A reduction in the safety factor (margin) of neuromuscular transmission after sustained activity of 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 Refers to the increase in the force of contraction (mechanical response) after *tetanus* or strong voluntary contraction. Contrast *postactivation facilitation.*

posttetanic facilitation See *facilitation.*

posttetanic potentiation The incrementing mechanical response of muscle during and after *repetitive nerve stimulation* without a change in the amplitude of the action potential. In spinal cord physiology, the term has been used to describe enhancement of excitability or reflex outflow of the central nervous system following a long period of high-frequency stimulation. This phenomenon has been described in the mammalian spinal cord, where it lasts minutes or even hours.

potential A physical variable created by differences 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. See *polarization.*

potentiation Physiologically, the enhancement of a response. Some authors use the term *potentiation* to describe the incrementing mechanical response of muscle elicited by *repetitive nerve stimulation*, i.e., *posttetanic potentiation*, and the term *facilitation* to describe the incrementing electric response elicited by *repetitive nerve stimulation*, i.e., *postactivation facilitation.*

prolonged insertion activity See *insertion activity.*

propagation velocity of a muscle fiber The speed of transmission of a muscle fiber action potential.

proximal latency See *motor latency* and *sensory latency.*

***pseudofacilitation** See *facilitation.*

pseudomyotonic discharge Use of term discouraged. It has been used to refer to different phenomena, including (1) *complex repetitive discharges*, and (2) *repetitive discharges* that do not wax or wane in both frequency and amplitude, and end abruptly. These latter discharges may be seen in disorders such as polymyositis in addition to disorders with *myotonic discharges.* See preferred term, *waning discharge.*

pseudopolyphasic action potential Use of this term is discouraged. See preferred term, *serrated action potential*

R1, R2 waves See *blink responses.*

recording electrode Device used to record electric potential difference. All electric recordings require two *electrodes.* The recording electrode close to the source of the activity to be recorded is called the *active* or *exploring electrode*, and the other recording electrode is called the *reference electrode.* Active electrode is synonymous with *Input Terminal 1* (or older terms *Grid 1*, and *G1*) and the reference electrode with *Input Terminal 2* (or older terms *Grid 2*, and G2).

In some recordings, it is not certain which electrode is closer to the source of the biologic activity, i.e., recording with a *bifilar* (*bipolar*) *needle electrode.* In this situation, it is convenient to refer to one electrode as Input Electrode 1 and the other electrode as Input Electrode 2.

*Illustration in Section II.

By present convention, a potential difference that is negative at the active electrode (Input Terminal 1) relative to the reference electrode (Input Terminal 2) causes an upward deflection on the oscilloscope screen. The term *monopolar recording* is not recommended, because all recording requires two electrodes; however, it is commonly used to describe the use of an intramuscular needle exploring electrode in combination with a surface disk or subcutaneous needle reference 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 with gradually increasing strength of 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 with gradually increasing strength of voluntary muscle contraction. The reciprocal of the recruitment interval is the *recruitment frequency.*

***recruitment pattern** A qualitative and/or quantitative description of the sequence of appearance of *motor unit action potentials* with increasing strength of voluntary muscle contraction. The *recruitment frequency* and *recruitment interval* are two quantitative measures commonly used. See *interference pattern* for qualitative terms commonly used.

reduced insertion activity See *insertion activity.*

reduced interference pattern See *interference pattern.*

reference electrode See *recording electrode.*

reflex A stereotyped *motor response* elicited by a *sensory stimulus.*

refractory period The *absolute refractory period* is the period following an *action potential* during which no stimulus, however strong, evokes a further response. The *relative refractory period* is the period following an *action potential* during which a stimulus must be abnormally large to evoke a second response. The *functional refractory period* is the period following an *action potential* during which a second *action potential* cannot yet excite the given region.

regeneration motor unit potential Use of this term is 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 the same form. The term may refer to recurring potentials recorded in muscle at rest, during voluntary contraction, or in response to single nerve stimulus. See *double discharge, triple discharge, multiple discharge, myokymic discharge, myotonic discharge, complex repetitive discharge.*

***repetitive nerve stimulation** The technique of repeated supramaximal stimulations of a nerve while recording M waves from muscles innervated by the nerve. 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 the activation procedure 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 the terms *incrementing response, decrementing response, facilitation* and *postactivation depression.*

repolarization See *polarization.*

residual latency Refers to the calculated time difference between the measured distal latency of a motor nerve and the expected distal latency, calculated by dividing the distance between the stimulus cathode and the active recording electrode by the maximum conduction velocity measured in a more proximal segment of a nerve. The residual latency is due in part

*Illustration in Section II.

to neuromuscular transmission time and to slowing of conduction in terminal axons due to decreasing diameter and the presence of unmyelinated segments.

response Used to describe an activity elicited by a *stimulus.*

resting membrane potential Voltage across the membrane of an excitable cell at rest. See *polarization.*

rheobase See *strength-duration curve.*

rise time The interval from the onset of a 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 and firing in a time-locked relationship to the main *action potential.* These potentials usually follow, but may *precede,* the main action potential. Also called *late component, parasite potential, linked potential,* and *coupled discharge* (less preferred terms).

scanning EMG A technique by which an electromyographic electrode is advanced in defined steps through muscle while a separate single-fiber electromyography electrode is used to trigger both the oscilloscope-sweep and the advancement devices. This recording technique 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 the 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,* and *monophasic.*

sensory delay See preferred terms, *sensory latency* and *sensory peak latency.*

sensory latency Interval between the onset of a stimulus and the onset of the *compound sensory nerve action potential.* This term has been loosely used to refer to the *sensory peak latency.* The term may be qualified as *proximal sensory latency* or *distal sensory latency,* depending on the relative position of the stimulus.

sensory nerve action potential (SNAP) See *compound sensory nerve action potential.*

sensory nerve conduction velocity See *conduction velocity.*

sensory peak latency Interval between the onset of a *stimulus* and the peak of the negative phase of the *compound sensory nerve action potential.* Note that the term *latency* refers to the interval between the onset of a stimulus and the onset of a response.

sensory potential Used to refer to the compound sensory nerve action potential. See *compound sensory nerve action potential.*

sensory response Used to refer to a sensory evoked potential, e.g., *compound sensory nerve action potential*

SEP See *somatosensory evoked potential.*

serrated action potential An action potential waveform with several changes in direction (*turns*) that do not cross the baseline. This term is preferred to the terms *complex action potential* and *pseudopolyphasic action potential.* See also *turn* and *polyphasic action potential.*

SFEMG See *single-fiber electromyography.*

shock artifact See *artifact.*

***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 in the lower extremity at the ankle.

1. *Median nerve SSEPs:* Normal short-latency response components to median nerve stimulation are designated P_9, P_{11}, P_{13}, P_{14}, N_{20}, and P_{23} in records taken between scalp and noncephalic reference electrodes, and N_9, N_{11}, N_{13}, and N_{14} 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.

2. *Common peroneal nerve SSEPs:* Normal short-latency response components, to common peroneal stimulation are designated P_{27} and N_{35} in records taken between scalp and noncephalic reference electrodes, and L3 and T12 potentials in bipolar derivation from respective spines.

*Illustration in Section II.

3. *Posterior tibial nerve SSEPs:* Normal short-latency response components to posterior tibial nerve stimulation are designated as the PF potential in the popliteal fossa, P_{37} and N_{45} waves in records taken between scalp and noncephalic reference electrode, and L3 and T12 potentials in bipolar derivation from respective spines.

silent period A pause in the electric activity of a muscle such as that seen after rapid unloading of a muscle.

***single fiber electromyography** (SFEMG) General term referring to the technique and conditions that permit recording of a single *muscle fiber action potential.* See *single-fiber needle electrode* 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) permitting the recording of single muscle fiber action potentials between the active recording surface and the cannula. See *single-fiber electromyography.*

single unit pattern See *interference pattern.*

SNAP Abbreviation for *sensory nerve action potential.* See *compound sensory nerve action potential.*

somatosensory evoked potentials (SEPs) Electric waveforms of biologic origin elicited by electric stimulation or physiologic activation of peripheral sensory fibers, for example, the median nerve, common peroneal nerve, or posterior tibial nerve. The normal SEP is a complex waveform with several components that are specified by polarity and average peak latency. The polarity and latency of individual components depend upon (1) subject variables, such as age, sex, (2) stimulus characteristics, such as intensity, rate of stimulation, and (3) recording parameters, such as amplifier time constants, electrode placement, and electrode combinations. See *short-latency SEPs.*

spike (1) In cellular neurophysiology, a short-lived (usually in the range of 1–3 ms), all-or-none change in membrane potential that arises when a graded response passes a threshold. (2) The electric record of a nerve impulse or similar event in muscle or elsewhere. (3) In clinical EEG recordings, a wave with duration less than 80 ms (usually 15–80 ms).

spinal evoked potential Electric waveforms of biologic origin recorded over the sacral, lumbar, thoracic or cervical 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 or nerve at rest after insertion activity has subsided and when there is no voluntary contraction or external stimulus. Compare with *involuntary activity.*

SSEP See *short-latency somatosensory evoked potential.*

staircase phenomenon The progressive increase in the force of a muscle contraction observed in response to continued low rates of direct or indirect muscle stimulation.

stigmatic electrode Of historic interest. Used by Sherrington for *active* or *exploring electrode.*

stimulating electrode Device used to apply electric current. All electric stimulation requires two electrodes; the negative terminal is termed the *cathode* and the positive terminal, the *anode.* By convention, the stimulating electrodes are called *bipolar* if they are encased or attached together. Stimulating electrodes are called *monopolar* if they are not encased or attached together. Electric stimulation for *nerve conduction studies* generally requires application of the cathode to produce depolarization of the nerve trunk fibers. If the anode is inadvertently placed between the cathode and the recording electrodes, a focal block of nerve conduction (*anodal block*) may occur and cause a technically unsatisfactory study.

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 generally applied to a nerve or muscle. The electric stimulus may be described in absolute terms or with respect to the evoked potential of the nerve or muscle. In absolute terms, the electric stimulus is defined by a duration (ms), a waveform (square, exponential, linear, etc.) and a strength or intensity measured in voltage

*Illustration in Section II.

(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 that stimulus 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 the stimulus 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 may be 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 for a muscle with the stimulating cathode positioned over the *motor point.* The *rheobase* is the intensity of an electric current of infinite duration necessary to produce a minimal visible twitch of a muscle when applied to the motor point. In clinical practice, a duration of 300 ms is used to determine the rheobase. The *chronaxie* is the time required for an electric current twice the *rheobase* to elicit the first visible muscle twitch.

submaximal stimulus. See *stimulus.*

subthreshold stimulus See *stimulus.*

supramaximal stimulus See *stimulus.*

surface electrode Conducting device for stimulating or recording placed on a skin surface. The material (metal, fabric), configuration (disk, ring), size, and separation should be specified. See *electrode (ground, recording, stimulating).*

synchronized fibrillation See preferred term, *complex repetitive discharge.*

***T wave** A compound action potential evoked from a muscle by rapid stretch of its tendon, as part of the muscle stretch reflex.

temporal dispersion Relative desynchronization of components of a compound action potential due to different rates of conduction of each synchronously evoked component from the stimulation point to the recording electrode.

terminal latency Synonymous with the preferred term, *distal latency.* See *motor latency* and *sensory latency.*

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 tensions all combine to produce a steady, smooth maximum contraction of the whole muscle.

tetanus The continuous contraction of muscle caused by repetitive stimulation or discharge of nerve or muscle. Contrast *tetany.*

tetany A clinical syndrome manifested by muscle twitching, cramps, and carpal and pedal spasms. 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* and are enhanced by systemic alkalosis or local ischemia.

tetraphasic action potential *Action potential* with four phases.

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 a group of axons. It is also operationally defined as the intensity that produces a response in about 50% of equivalent trials.

threshold stimulus See *stimulus.*

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

*Illustration in Section II.

stimuli and the frequency of the stimuli should be specified.

triphasic action potential *Action potential* with 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 or muscle fiber. The interval between the second and the third action potential often exceeds that between the first two, and both are usually in the range of 2–20 ms.

triplet See *triple discharge.*

turn Point of change in direction in the waveform and the magnitude of the voltage change following the turning point. It is not necessary that the voltage change passes through the baseline. The minimal excursion required to constitute a change should be specified.

unipolar needle electrode See synonym, *monopolar needle recording electrode.*

utilization time See preferred term, *latency of activation.*

VEPs See *visual evoked potentials.*

VERs Abbreviation for *visual evoked responses.* See *visual evoked potentials.*

***visual evoked potentials** (VEPs) Electric waveforms of biologic origin are recorded over the cerebrum and elicited by light stimuli. VEPs are classified by stimulus rate as transient or steady state VEPs, and can be further divided by presentation mode. The normal transient VEP to checkerboard pattern reversal or shift has a major positive occipital peak at about 100 ms (P_{100}), often preceded by a negative peak (N_{75}). The precise range of normal values for the latency and amplitude of P_{100} depends on several factors: (1) subject variables, such as age, sex, 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 responses (VERs) See *visual evoked potentials.*

volitional activity See *voluntary activity.*

voltage Potential difference between two recording sites.

volume conduction Spread of current from a potential source through a conducting medium, such as the body tissues.

voluntary activity In electromyography, the electric activity recorded from a muscle with consciously controlled muscle contraction. The effort made to contract the muscle should 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 of the muscle and artifacts have been excluded, it can be concluded that there is no voluntary activity.

waning discharge General term referring to a *repetitive discharge* that gradually decreases in frequency or amplitude before cessation. Contrast with *myotonic discharge.*

wave An undulating line constituting a graphic representation of a change, e.g., a changing electric potential difference. See *A wave, F wave, H wave,* and *M wave.*

waveform The shape of a *wave.* The term is often used synonymously with wave.

*Illustration in Section II.

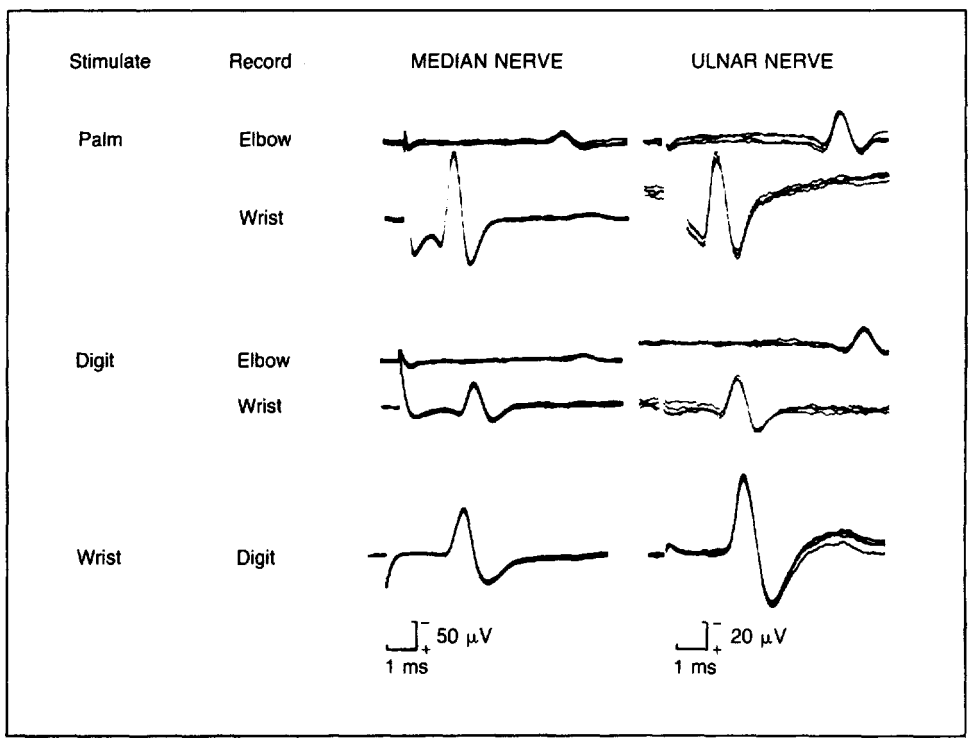
SECTION II:
ILLUSTRATIONS OF SELECTED WAVEFORMS

5–17. Repetitive nerve stimulation: pseudofacilitation
5–18. Insertion activity
5–19. End-plate activity
5–20. Fibrillation potential
5–21. Positive sharp wave
5–22. Myotonic discharge
5–23. Complex repetitive discharge
5–24. Fasciculation potential
5–25. Myokymic discharge
5–26. Neuromyotonic discharge
5–27. Cramp discharge
5–28. Motor unit action potentials
5–29. Satellite potential
5–30. Recruitment pattern
5–31. Single fiber electromyography
5–32. Macroelectromyography

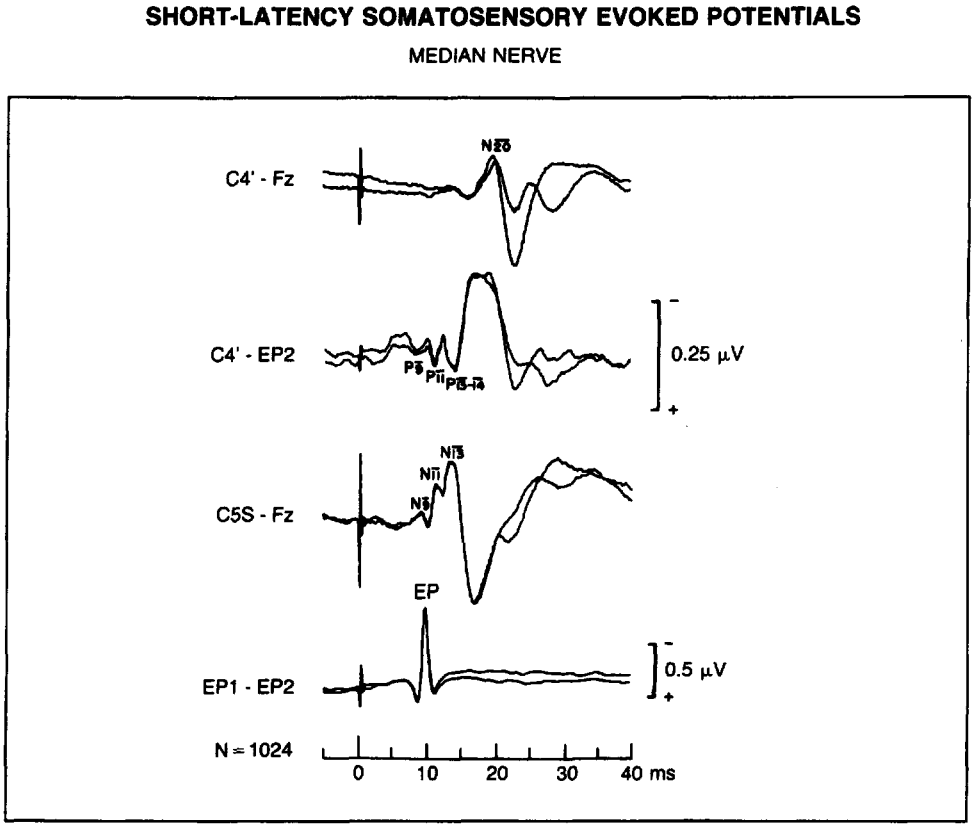
Each illustration is accompanied by a complete explanation, which is the same as that given in the glossary. The definitions have been repeated fully with the illustrations so that readers do not need to refer back and forth between the illustrations and definitions.

The illustrations have been modified and adapted from material submitted by members of the AAEE. The illustrations of the short-latency somatosensory evoked potentials were reproduced from the *Journal of Clinical Neurophysiology* (1978; 1:41–53), with permission of the journal editor and the authors.

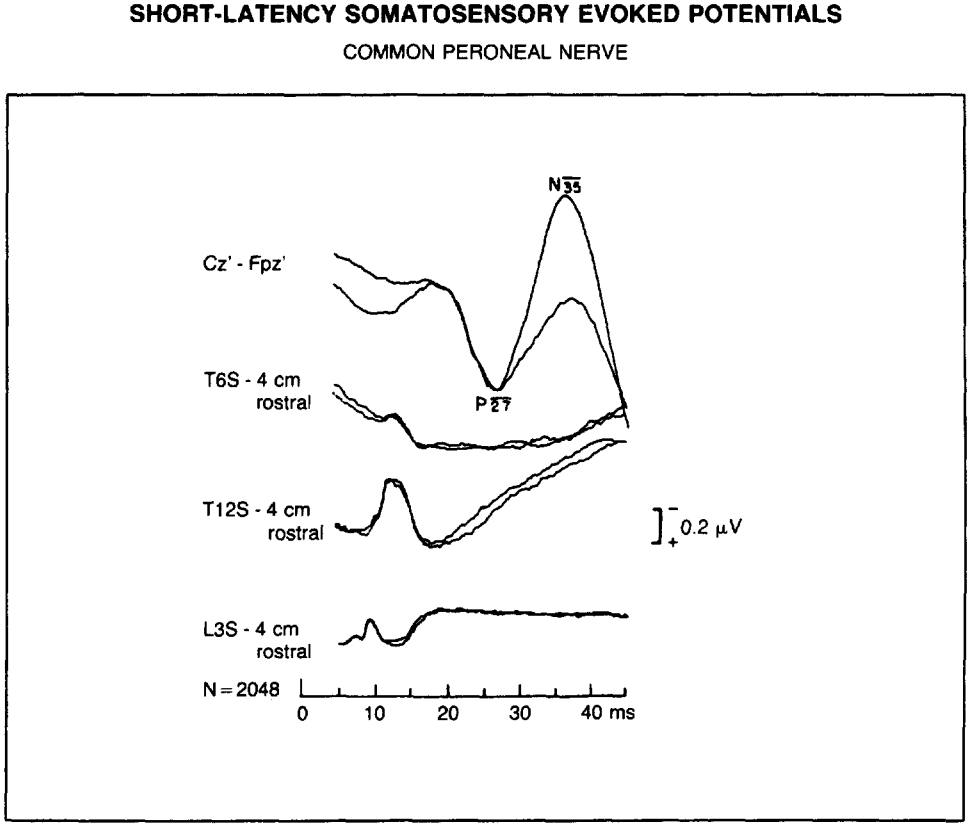
COMPOUND SENSORY NERVE ACTION POTENTIALS



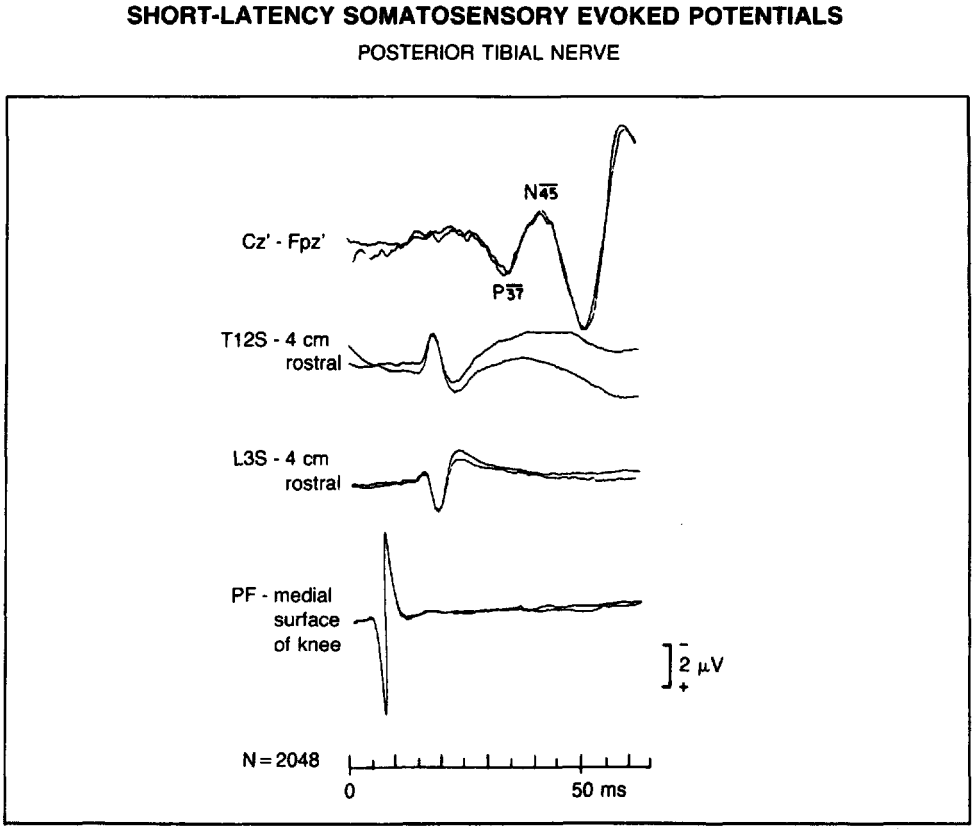
Appendix Figure 5–1. Compound sensory nerve action potentials recorded with surface electrodes in a normal subject. A compound nerve action potential is considered to have been evoked from afferent fibers if the recording electrodes detect activity only in a sensory nerve or in a sensory branch of a 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, the latency 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 has been referred to as the *sensory response* or *sensory potential*.



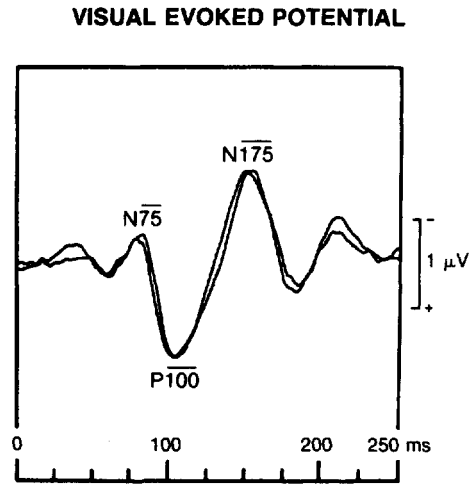
Appendix Figure 5–2. *Short-latency somatosensory evoked potentials* elicited by electric stimulation of the median nerve at the wrist (MN-SSEPs) occur within 25 ms of the stimulus in normal subjects. Normal short-latency response components to median nerve stimulation are designated P_9, P_{11}, P_{13}, P_{14}, N_{20}, and P_{23} in records taken between scalp and noncephalic reference electrodes, and N_9, N_{11}, N_{13}, and N_{14} 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 C_4' designation indicates that the recording scalp electrode was placed 2 cm posterior to the International 10–20 C_4 electrode location.



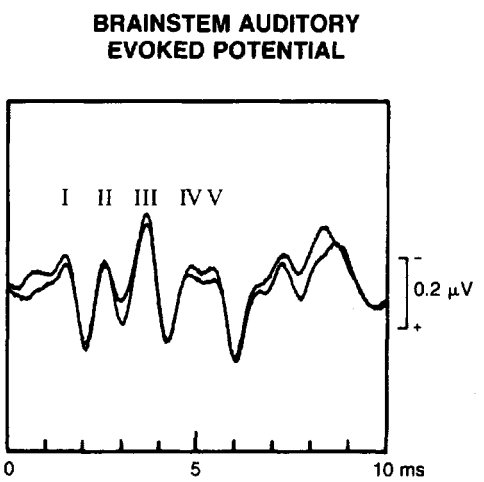
Appendix Figure 5–3. *Short-latency somatosensory evoked potentials* elicited by stimulation of the common peroneal nerve at the knee (CPN-SSEPs) occur within 40 ms of the stimulus in normal subjects. It is suggested that individual response components be designated as follows: (1) Spine components: L3 and T12 spine potentials. (2) Scalp components: P_{27} and N_{35}. The C_z' and F_{pz}' designations indicate that the recording scalp electrode was placed 2 cm posterior to the International 10–20 Cz and Fpz electrode locations.



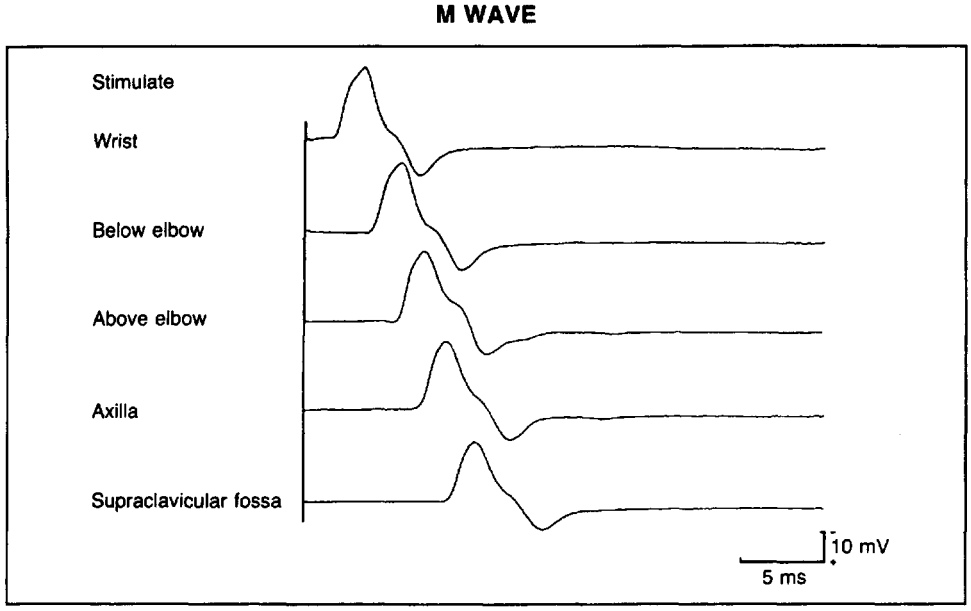
Appendix Figure 5–4. *Short-latency somatosensory evoked potentials* elicited by electrical stimulation of the posterior tibial nerve (PTN-SSEPs) at the ankle occur within 50 ms of the stimulus in normal subjects. It is suggested that individual response components be designated as follows: (1) Nerve trunk (tibial nerve) component in the popliteal fossa: PF potential. (2) Spine components: L3 and T12 potentials. (3) Scalp components: P_{37} and N_{45} waves. The C_z' and F_{pz}' designations indicate that the recording scalp electrode was placed 2 cm posterior to the International 10–20 C_z and F_{pz} electrode locations.



Appendix Figure 5–5. Visual evoked potential (VEP). Normal occipital VEP to checkerboard pattern reversal stimulation recorded between occipital (O1) and vertex (C_z) electrodes showing N_{75}, P_{100} and N_{175} peaks. Visual evoked potentials are electric waveforms of biologic origin recorded over the cerebrum and elicited by light stimuli. VEPs are classified by stimulus rate as transient or steady-state VEPs and can be further divided by presentation mode. The normal transient VEP to checkerboard pattern reversal or shift has a major positive occipital peak at about 100 ms (P_{100}), often preceded by a negative peak (N_{75}). The precise range of normal values for the latency and amplitude of P_{100} depends on several factors: (1) subject variables, such as age, sex, 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.

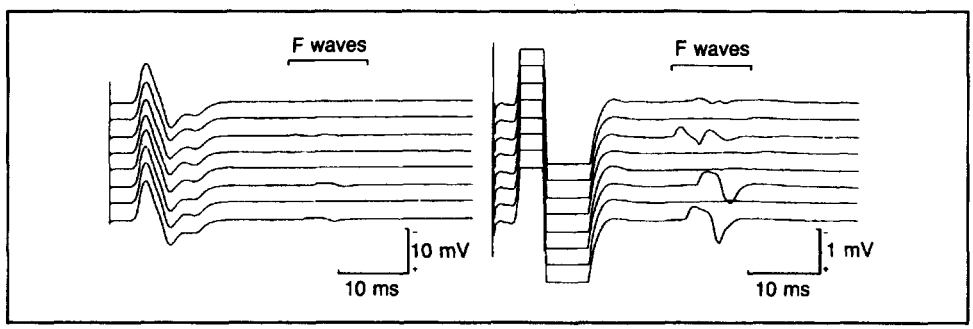


Appendix Figure 5–6. Brainstem auditory evoked potential (BAEP). Normal BAEP to stimulation of the left ear, recorded between left ear (A2) and vertex (C_z) electrodes. Brainstem auditory evoked potentials are electric waveforms of biologic origin elicited in response to sound stimuli. The normal BAEP consists of a sequence of up to seven waves, named 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.



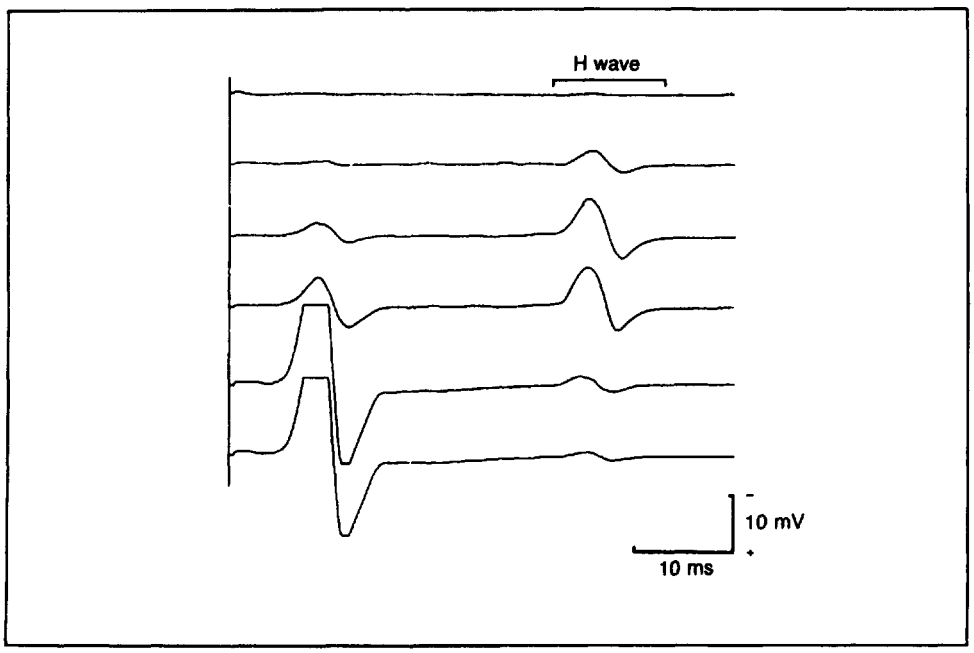
Appendix Figure 5–7. M waves recorded with surface electrodes over the abductor digiti quinti muscle elicited by electric stimulation of the ulnar nerve at several levels. The M wave is a *compound action potential* evoked from a muscle by a single electric stimulus to its motor nerve. By convention, the M wave elicited by supramaximal stimulation is used for motor nerve conduction studies. Ideally, the recording electrodes should be placed so that the initial deflection of the evoked potential is negative. The *latency*, commonly called the *motor latency*, is the latency (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

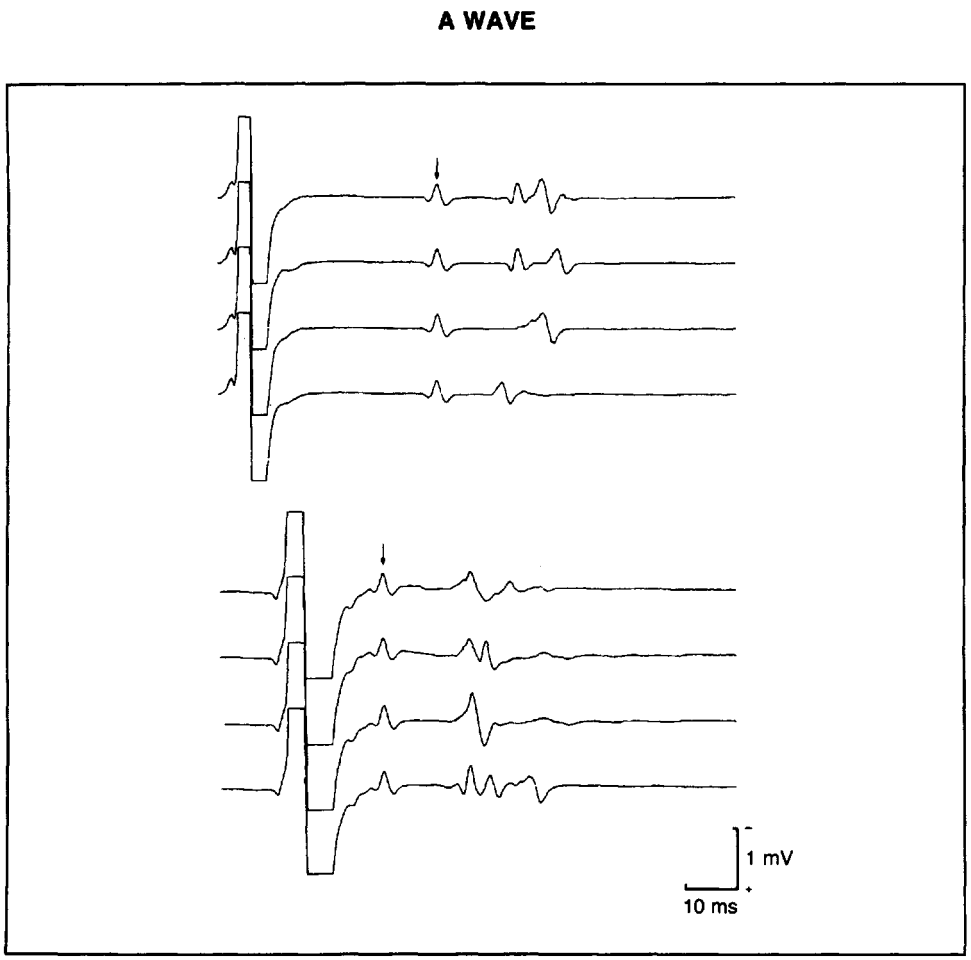


Appendix Figure 5–8. F waves recorded with surface electrodes over the abductor digiti quinti muscle elicited by electric stimulation of the ulnar nerve at the wrist with two different gain settings. The F wave is a compound action potential evoked intermittently from a muscle by a supramaximal electric 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 the *H wave* and the *A wave*.

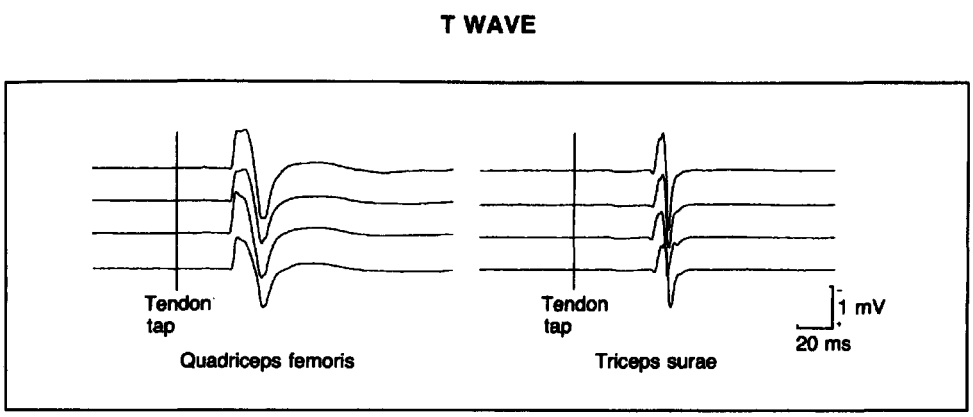
H WAVE



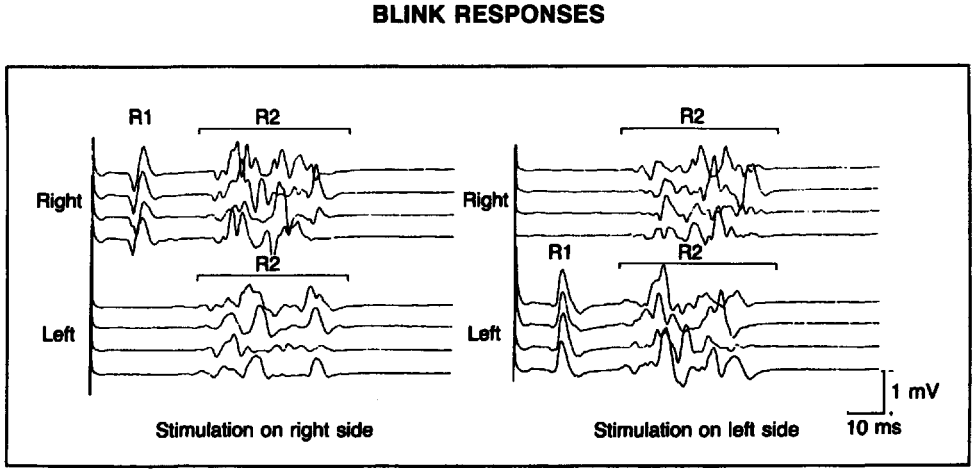
Appendix Figure 5–9. H waves recorded with surface electrodes over the soleus muscle elicited by electric stimulation of the posterior tibial nerve at the knee. The stimulus intensity was gradually increased (top tracing to bottom tracing). The H wave is a compound muscle action potential having a consistent latency evoked regularly, when present, from a muscle by an electric stimulus to the nerve. It is regularly found 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 through a monosynaptic connection in the spinal cord. The reflex and wave are named in honor of Hoffmann's description in 1918. Compare the *F wave*.



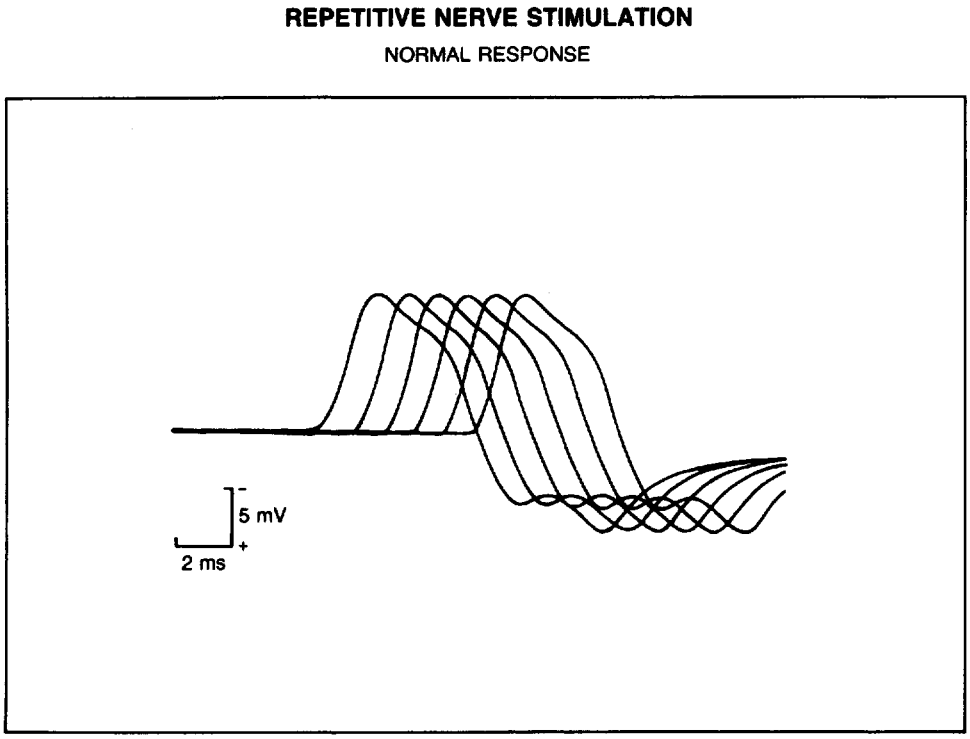
Appendix Figure 5–10. A waves (under arrows) recorded with surface electrodes over the abductor hallucis brevis elicited by electric stimulation of the posterior tibial nerve at the level of the ankle (top four traces) and at the level of the knee (bottom four traces). The A wave is a compound action potential evoked consistently from a muscle by submaximal electric 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 may occur afterward. The A wave is due to normal or pathologic axonal branching. Compare the *F wave*.



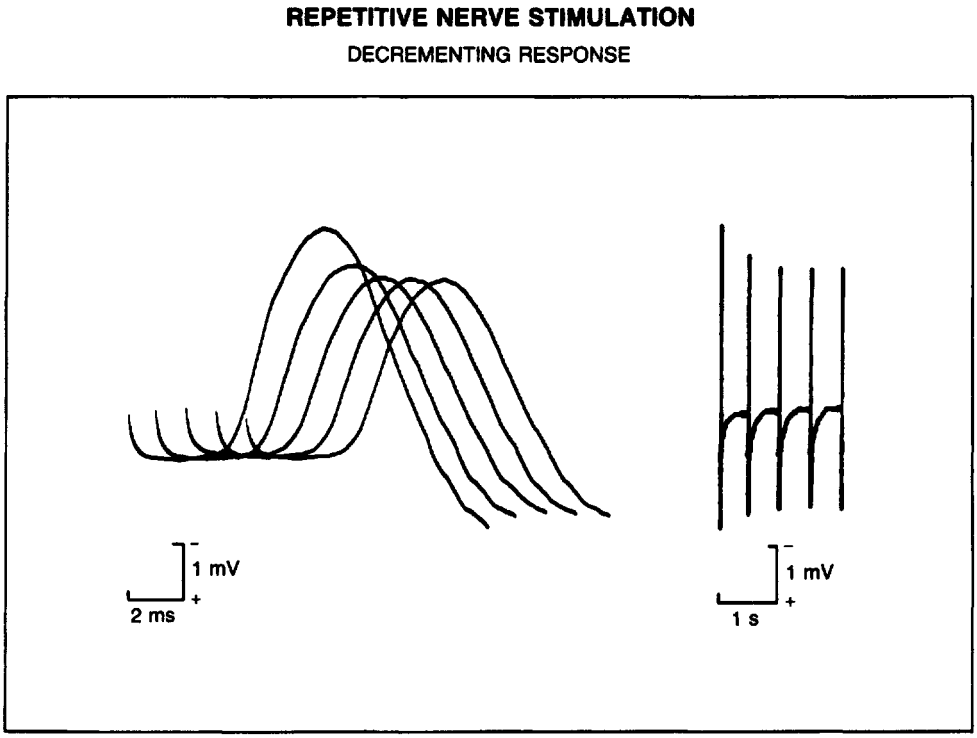
Appendix Figure 5–11. The T wave is a compound action potential evoked from a muscle by rapid stretch of its tendon, as part of the muscle stretch reflex. The T waves were recorded with surface electrodes over the quadriceps femoris (left tracings) and triceps surae (right tracings) and elicited by stretching the muscles by tapping the corresponding tendon.



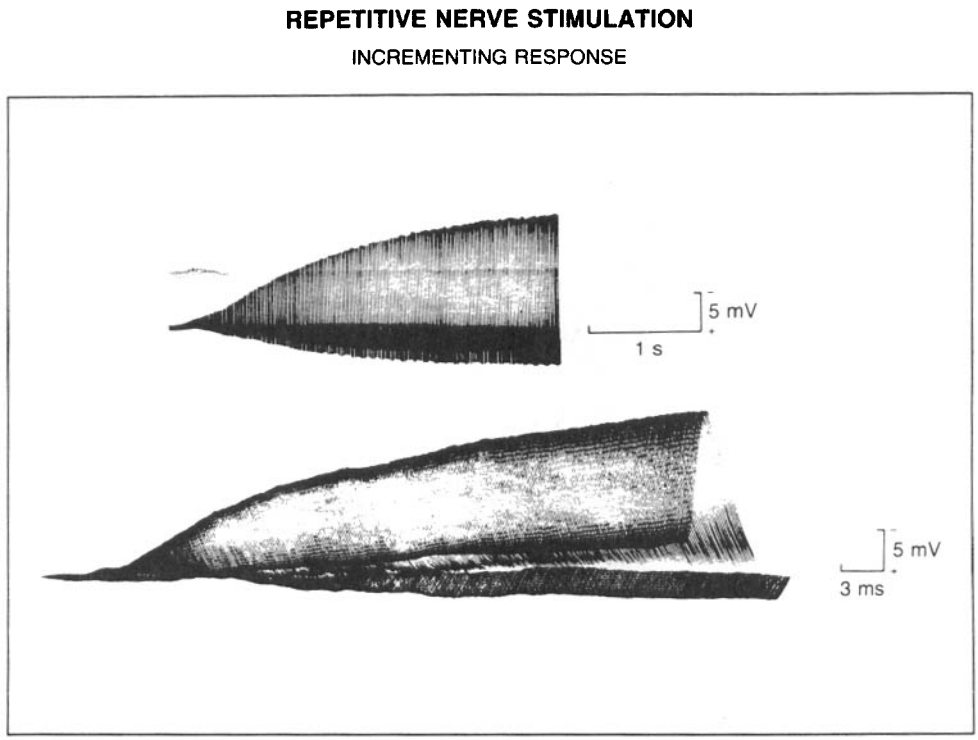
APPENDIX FIGURE 5–12. Blink responses recorded with surface electrodes over the right orbicularis oculi (upper tracings) and left orbicularis oculi (lower tracings) elicited by electric stimulation of the supraorbital nerve on the right (left tracings) and on the left (right tracings). The blink responses 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 (R_1 *wave*) ipsilateral to the stimulation site with a latency of about 10 ms and a bilateral late compound muscle action potential (R_2 *wave*) with a latency of approximately 30 ms. Generally, only the R_2 *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. R_1 and R_2 waves are probably oligosynaptic and polysynaptic brainstem reflexes, respectively, together called the *blink reflex*, with the afferent arc provided by the sensory branches of the trigeminal nerve and the efferent arc provided by the facial nerve motor fibers.



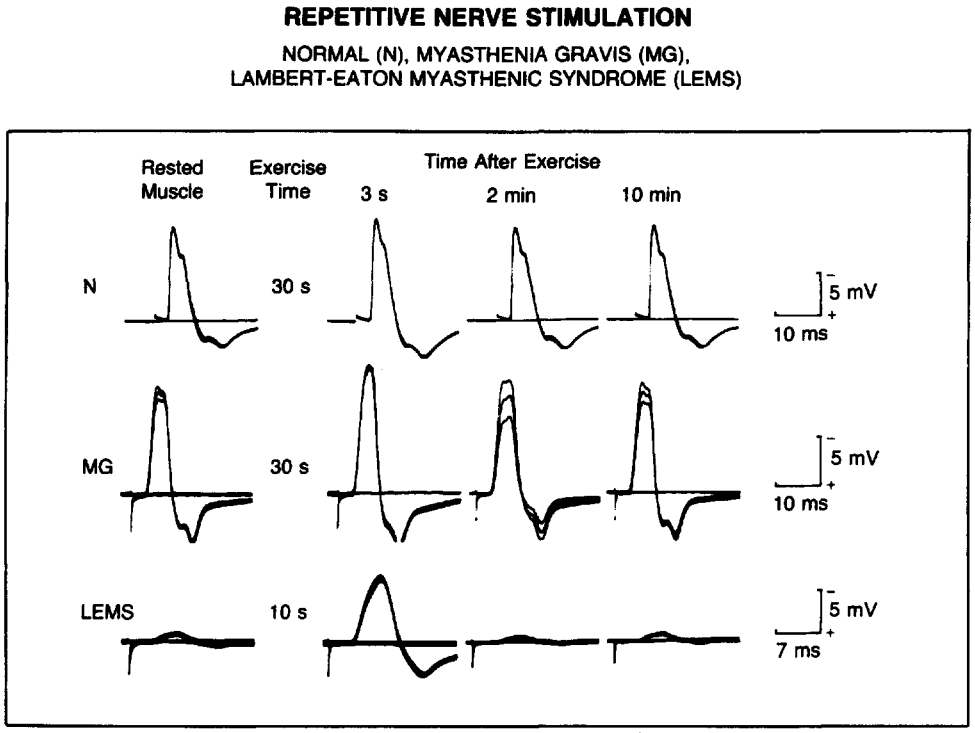
Appendix Figure 5–13. Study in a normal subject. The successive M waves are displayed to the right. The M waves were recorded with surface electrodes over the hypothenar eminence (abductor digiti quinti) during ulnar nerve stimulation at a rate of 3 Hz. Note the configuration of the successive M waves is unchanged. *Repetitive nerve stimulation* is a technique of repeated supramaximal stimulations of a nerve while recording M waves from muscles innervated by the nerve. 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 the activation procedure 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 the terms *incrementing response*, *decrementing response*, *facilitation*, and *postactivation depression*.



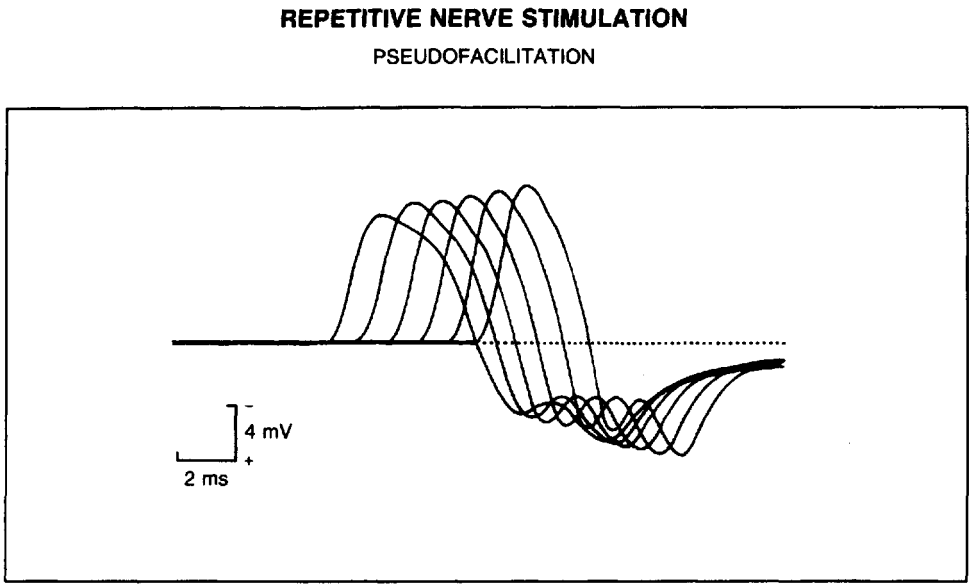
Appendix Figure 5–14. Repetitive nerve stimulation study in a patient with myasthenia gravis. Successive M waves were recorded with surface electrodes over the rested cheek (nasalis) muscle during repetitive facial nerve stimulation at a rate of 2 Hz, with a display to permit measurement of the amplitude 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 (2–5 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. Contrast with *incrementing response.*



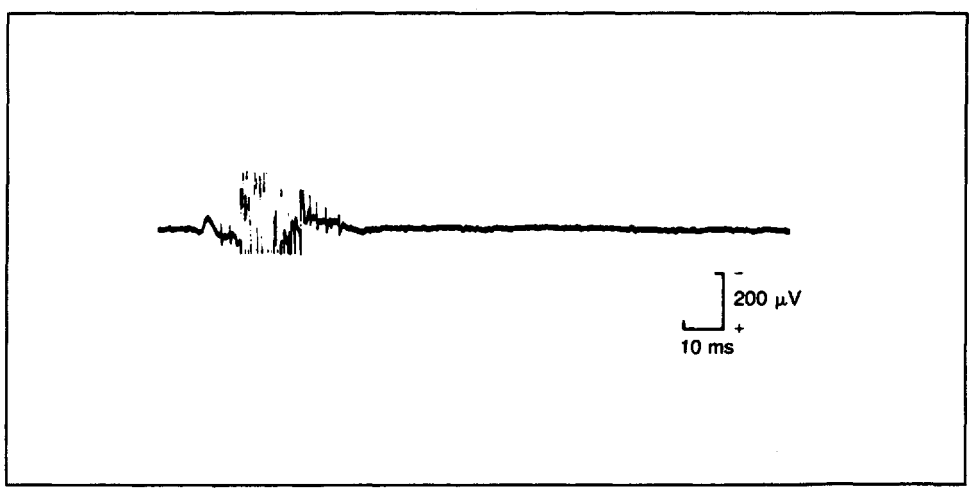
Appendix Figure 5–15. Repetitive nerve stimulation study in a patient with Lambert-Eaton myasthenic syndrome (LEMS). An incrementing response was recorded with surface electrodes over the hypothenar eminence (abductor digiti quinti) during repetitive ulnar nerve stimulation at a rate of 50 Hz with a 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 producible increase in amplitude and/or area of successive responses (M wave) 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.*



Appendix Figure 5–16. 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 the order of the responses. In each superimposed display of three responses where the configuration did change, the highest amplitude response was the first response, and the lowest amplitude response was the third response. After testing the rested muscle, the muscle was forcefully contracted for 10 to 30 seconds (exercise time). The repetitive nerve stimulation was carried out again 3 seconds, 2 minutes, and 10 minutes after the exercise ended. The results illustrate *facilitation* and *postactivation depression.*

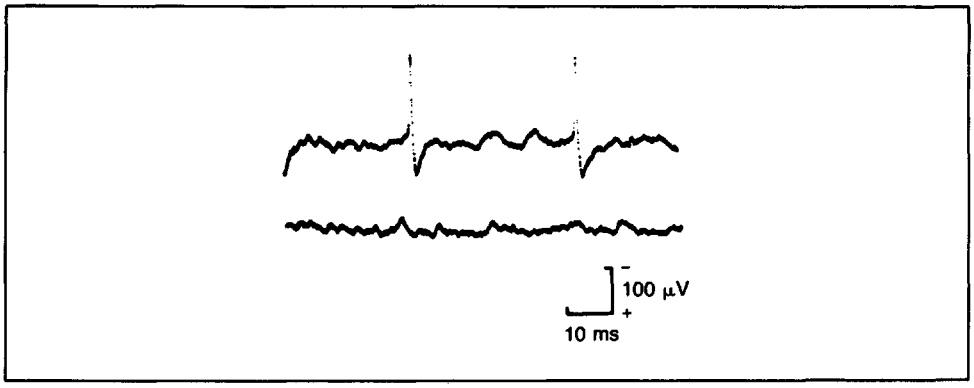


Appendix Figure 5–17. Repetitive nerve stimulation study in a normal subject. The successive M waves were recorded with surface electrodes over the hypothenar eminence (abductor digiti quinti) during ulnar nerve stimulation at a rate of 30 Hz. *Pseudofacilitation* may occur in normal subjects with *repetitive 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 action potentials of muscle cells 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 of the M wave resulting in no change in the area of the negative phase of the successive M waves.



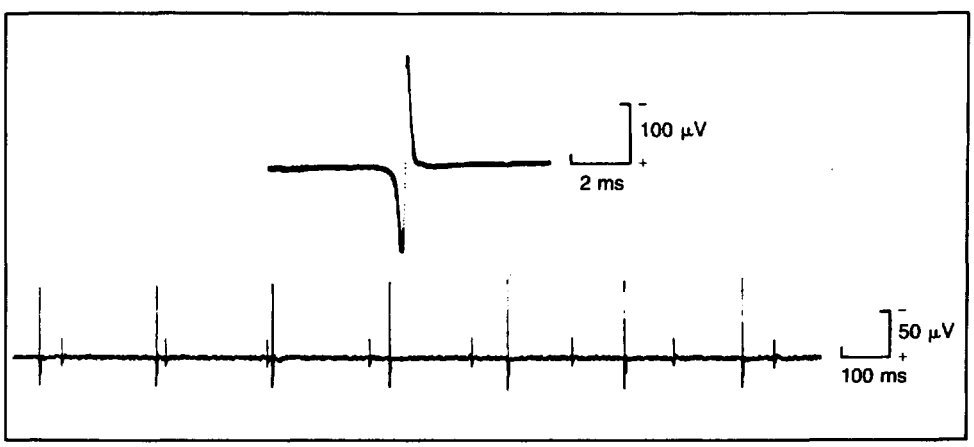
Appendix Figure 5–18. Insertion activity in a normal subject. *Insertion activity* is the electric activity caused by insertion or movement of a needle electrode. The amount of the activity may be described as normal, reduced, or increased (prolonged), with a description of the waveform and repetitive rate.

END-PLATE ACTIVITY

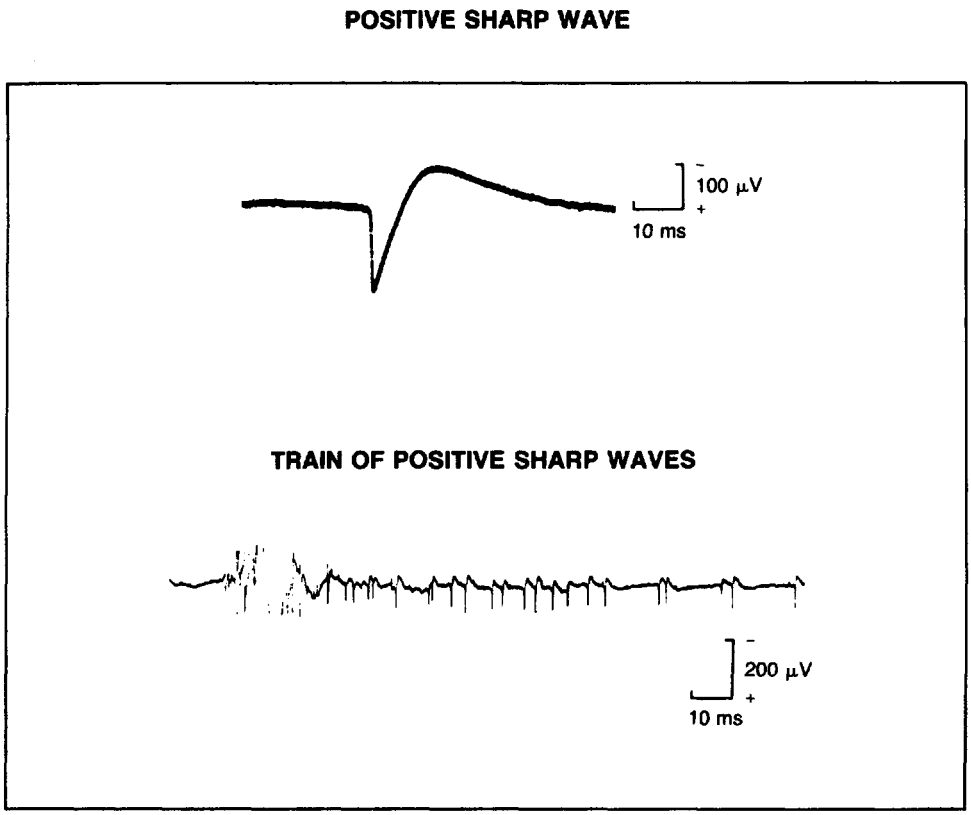


Appendix Figure 5–19. Spontaneous electric activity recorded with a needle electrode close to muscle end-plates. May be either of two forms: (1) *Monophasic* (upper and lower traces): Low-amplitude (10–20 μV), short-duration (0.5–1 ms), monophasic (negative) potentials that occur in a dense, steady pattern 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* (upper trace): Moderate-amplitude (100–300 μV), short-duration (2–4 ms), biphasic (negative–positive) spike potentials that occur irregularly in short bursts with a high frequency (50–100 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 *biphasic spike potentials*, *end-plate spikes*, and, incorrectly, *nerve potentials*.

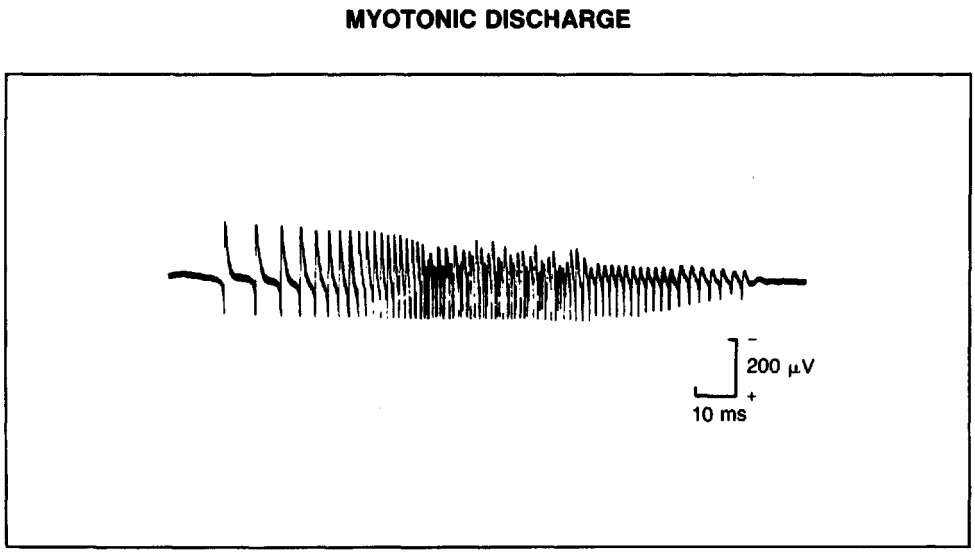
FIBRILLATION POTENTIAL



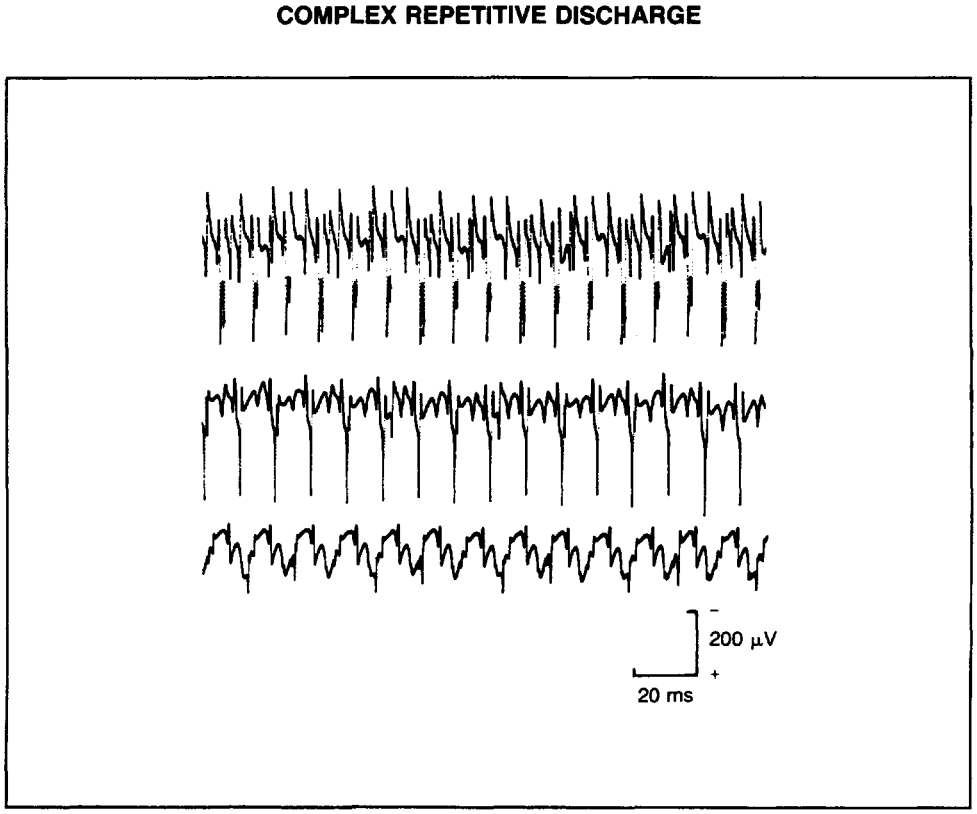
Appendix Figure 5–20. The top trace shows a single *fibrillation potential* waveform. The bottom trace shows the pattern of discharge of two other *fibrillation potentials*, which differ with respect to amplitude and discharge frequency. A *fibrillation potential* is the electric activity associated 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. The potentials 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 a concentric or monopolar needle electrode, the firing rate has a wide range (1–50 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 old 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 potential arises from an area immediately adjacent to the needle electrode.



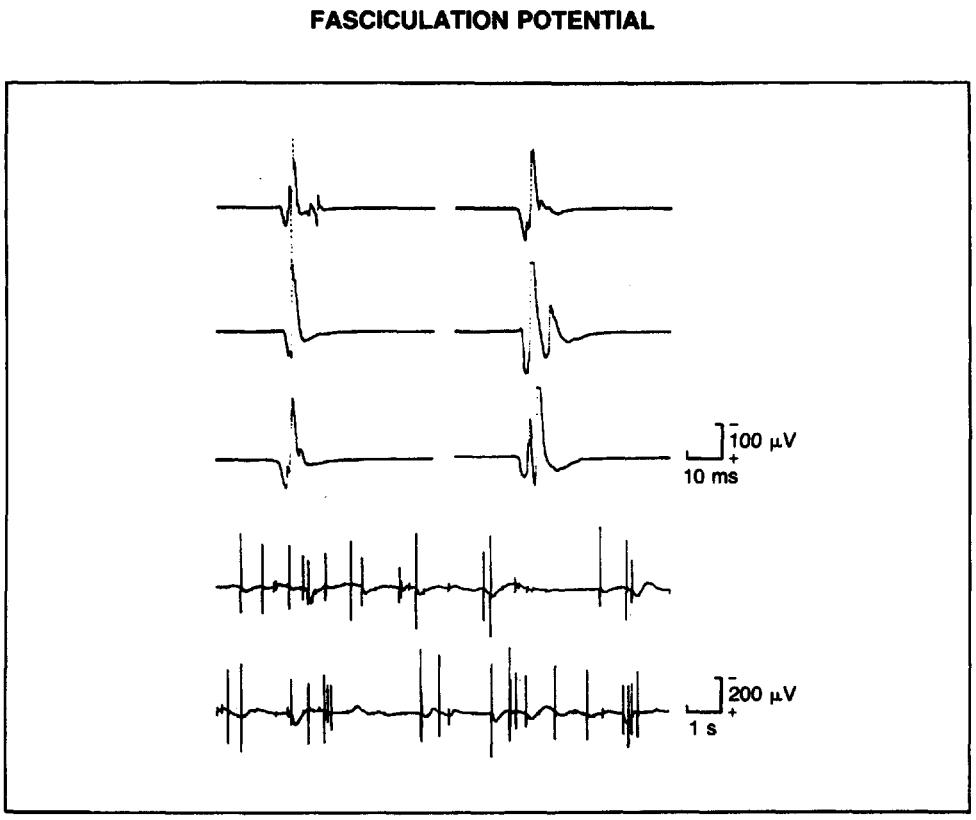
Appendix Figure 5–21. The top trace shows a single *positive sharp wave.* The bottom trace shows the pattern of initial discharge of a number of different *positive sharp waves* after movement of the recording needle electrode in denervated muscle. A *positive sharp wave* is a biphasic, positive-negative *action potential* initiated by needle movement and recurring in a uniform, regular pattern at a rate of 1–50 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, with a duration of 10–100 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. Its configuration may result from the position of the needle electrode which is thought 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.



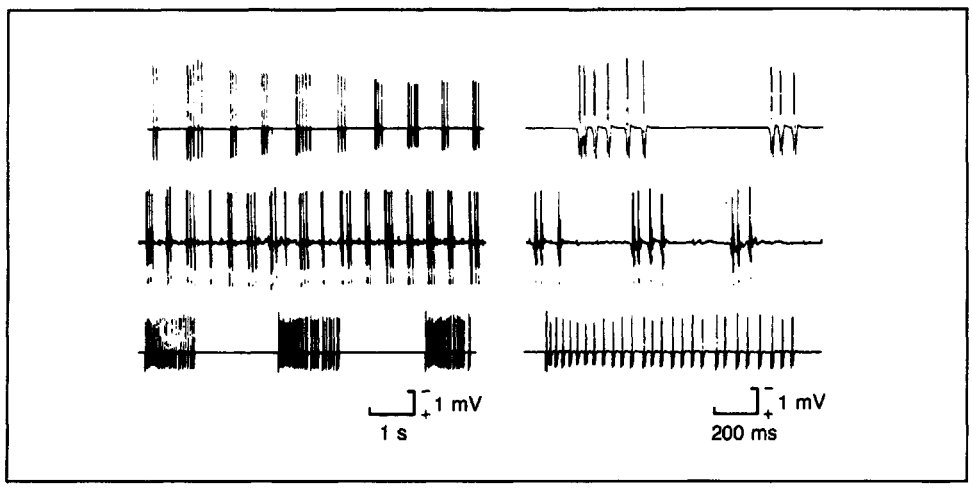
Appendix Figure 5–22. Repetitive discharge at rates of 20 to 80 Hz are of two types: (1) biphasic (positive–negative) spike potentials less than 5 ms in duration resembling *fibrillation potentials*, (2) positive waves of 5 to 20 ms in duration resembling *positive sharp waves*. Both potential forms are recorded after needle 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 to be identified as myotonic discharges. 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 "diver bomber." Contrast with *waning discharge.*



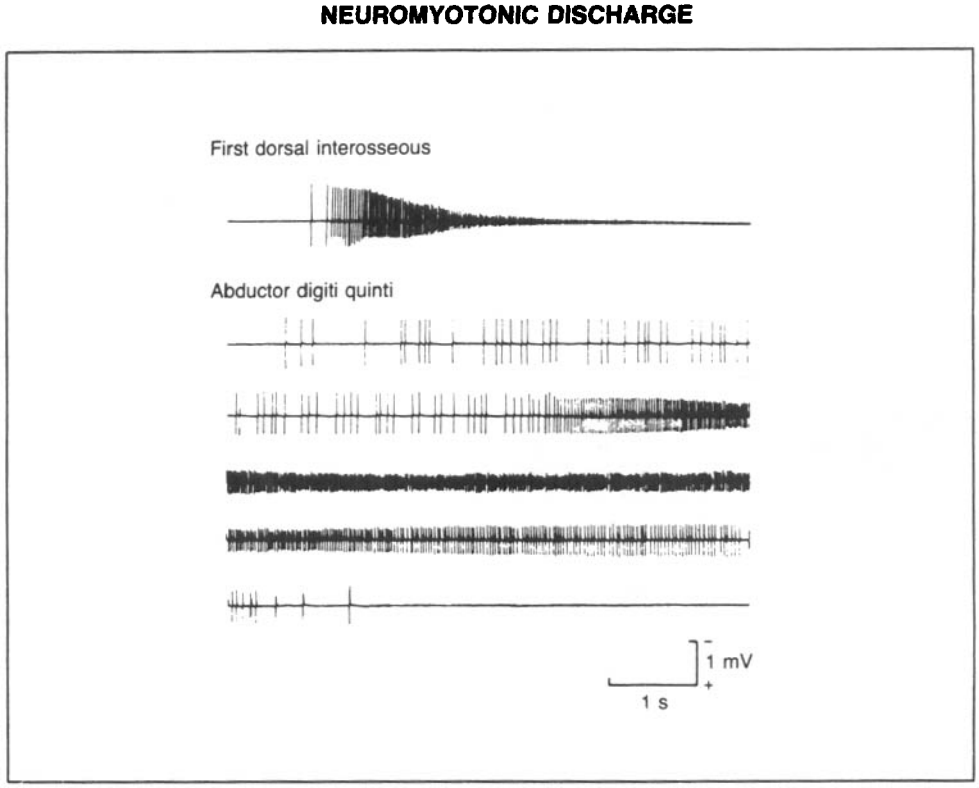
Appendix Figure 5–23. A *complex repetitive discharge* is a polyphasic or serrated action potential that may begin spontaneously or after a needle movement. They have a uniform frequency, shape, and amplitude, with abrupt onset, cessation, or change in configuration. Amplitude ranges from 100 μV to 1 mV and frequency of discharge from 5 to 100 Hz. This term is preferred to *bizarre high-frequency discharge, bizarre repetitive discharge, bizarre repetitive potential, near constant frequency trains, pseudomyotonic discharge,* and *synchronized fibrillation.*



Appendix Figure 5–24. Six different *fasciculation potentials* are displayed in the top traces with a time scale to permit characterization of the individual waveforms. The bottom two traces display *fasciculation potentials* with a time scale to demonstrate the random discharge pattern. A *fasciculation potential* is the electric potential often associated with a visible *fasciculation* that has the configuration of a *motor unit action potential* but that 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 occurrence of 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 frequency of occurrence, should be specified.

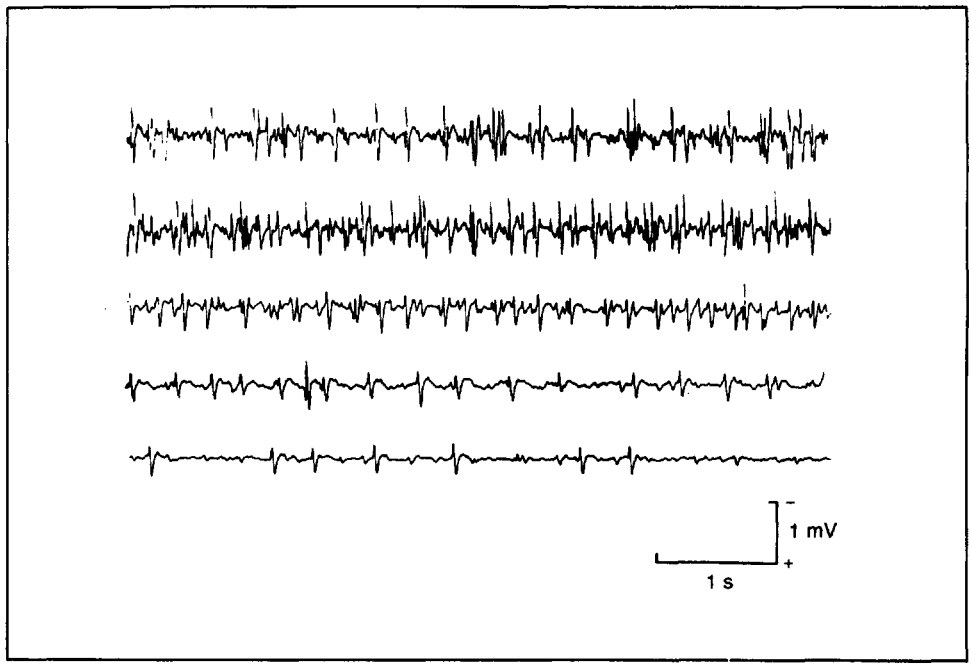


Appendix Figure 5–25. Tracings of three different *myokymic discharges* displayed with a time scale (left) to illustrate the firing pattern and with a different time scale (right) to illustrate that the individual potentials have the configuration of a *motor unit action potential.* A *myokymic discharge* is a group of *motor unit action potentials* that fire repetitively and may be associated with clinical myokymia. Two firing patterns have been described. Commonly, the discharge is a brief, repetitive firing of single units for a short period (up to a few seconds) at a uniform rate (2–60 Hz) followed by a short period (up to a few seconds) of silence, with repetition of the same sequence for a particular potential. Less commonly, the potential recurs continuously at a fairly uniform firing rate (1–5 Hz). Myokymic discharges are a subclass of *grouped discharges* and *repetitive discharges.*



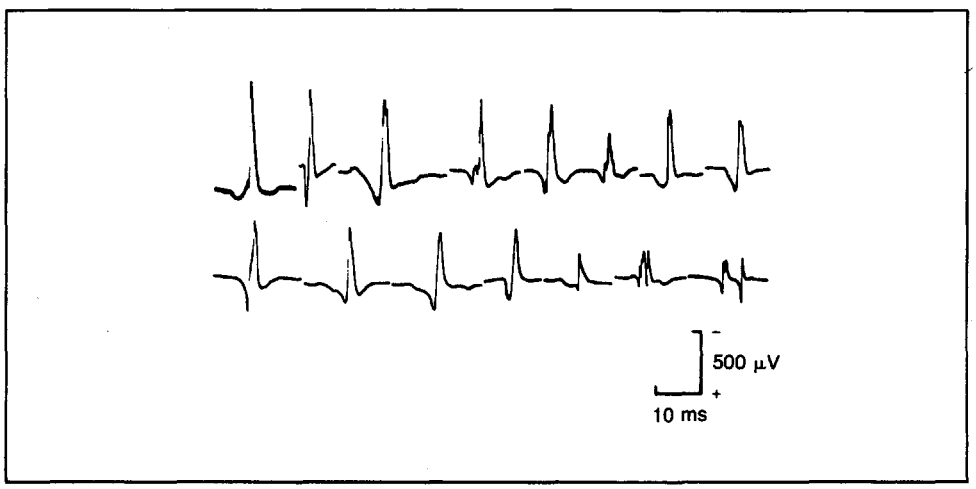
Appendix Figure 5–26. The time scale was chosen to illustrate the characteristic firing pattern. A *neuromyotonic discharge* is a burst of *motor unit action potentials* that originate in the motor axons firing at high rates (150–300 Hz) for a few seconds, and often start and stop abruptly. The amplitude of the response typically wanes. Discharges may occur spontaneously or be initiated by needle movement, voluntary effort, and ischemia or percussion of a nerve. These discharges should be distinguished from *myotonic discharges* and *complex repetitive discharges*.

CRAMP DISCHARGE

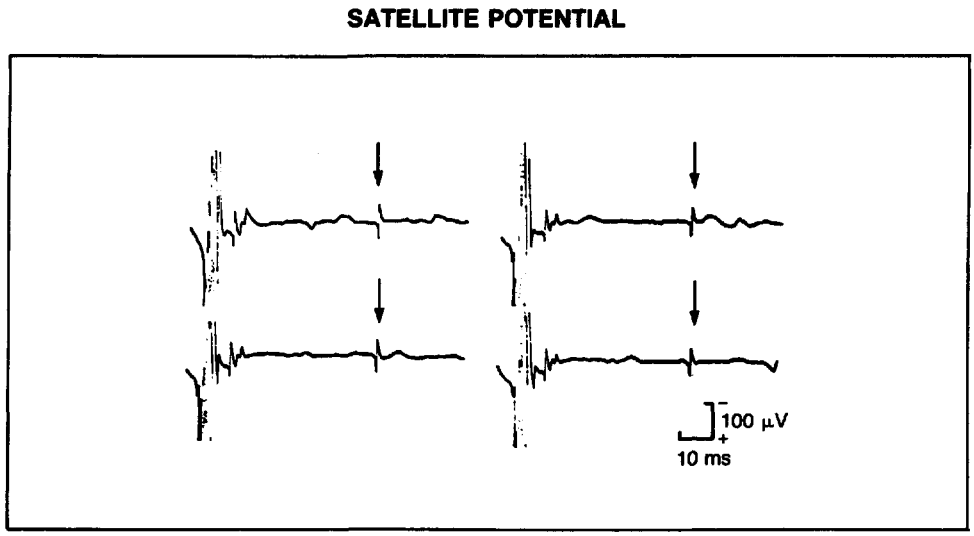


Appendix Figure 5–27. A *cramp discharge* arises from the involuntary repetitive firing of *motor unit action potentials* at a high frequency (up to 150 Hz) in a large area of muscle, usually associated with painful muscle contraction. Both the discharge frequency and the number of *motor action potentials* firing increase gradually during development, and both subside gradually with cessation. See *muscle cramp*.

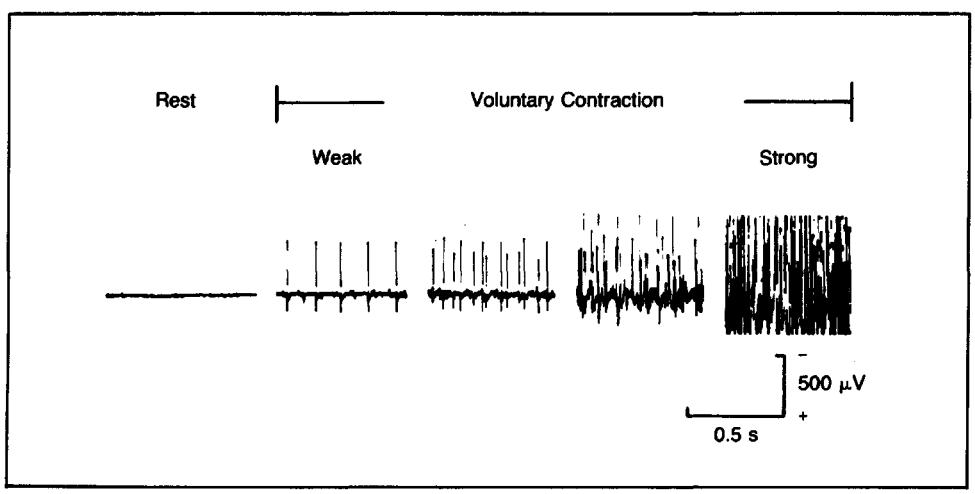
MOTOR UNIT ACTION POTENTIALS



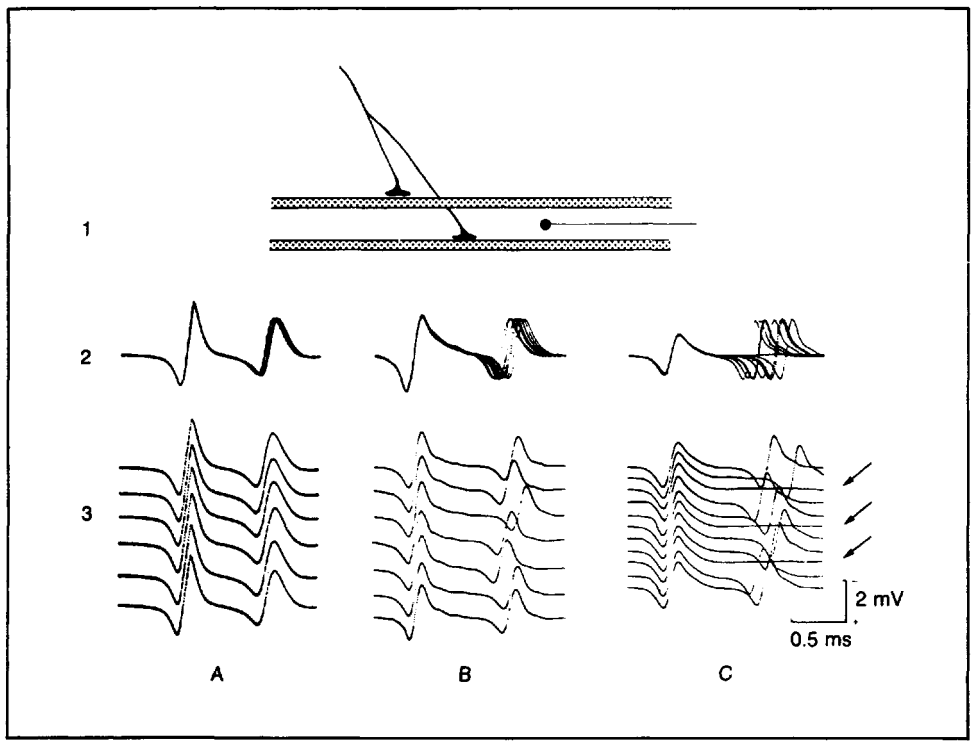
Appendix Figure 5–28. A *motor unit action potential* (MUAP) is the action potential reflecting the electric activity of a single anatomic motor unit. It is the compound action potential of those muscle fibers within the recording range of an electrode. With voluntary muscle contraction, the action potential is characterized by its consistent appearance with, and relationship to, the force of contraction. The following parameters should be specified, quantitatively if possible, after the recording electrode is placed so as to minimize the *rise time* (which by convention should be less than 0.5 ms).



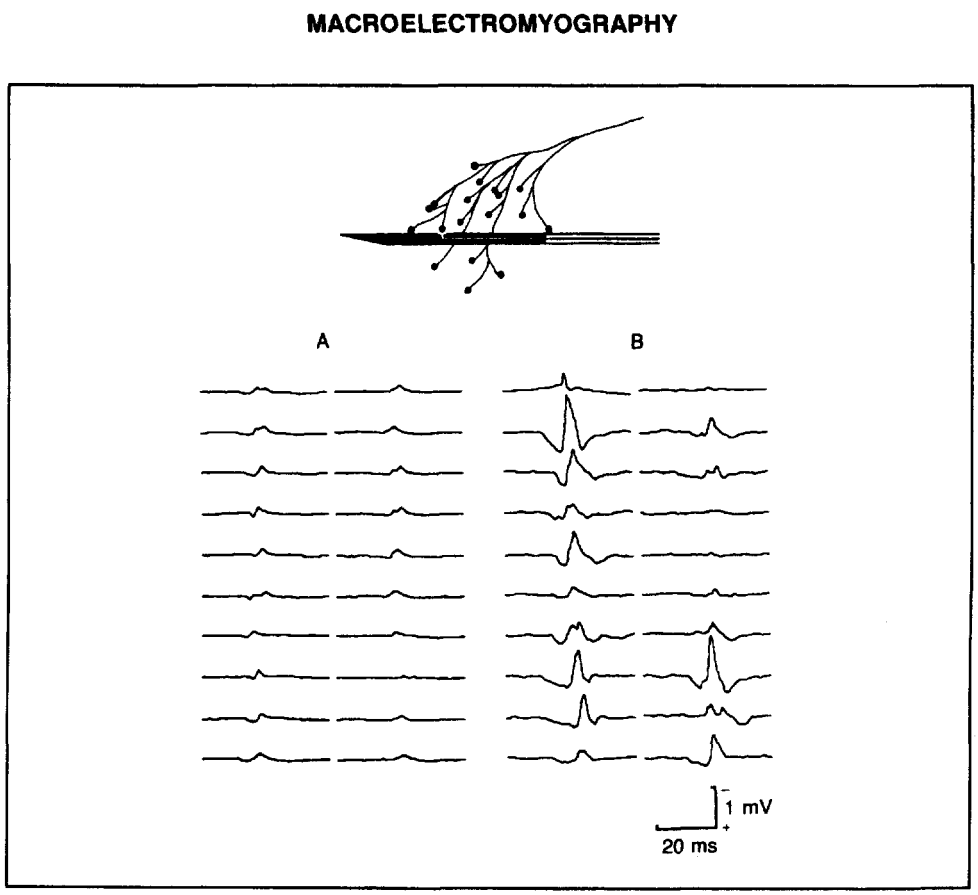
APPENDIX FIGURE 5–29. Four tracings of the same *motor unit action potential* (MUAP) indicated by the arrow. A *satellite potential* is a small action potential separated from the main MUAP by an isoelectric interval and firing in a time-locked relationship to the main action potential. These potentials usually follow, but may proceed, the main action potential. Also called *late component, parasite potential, linked potential,* and *coupled discharge* (*less preferred terms*).



Appendix Figure 5–30. Recruitment pattern and interference pattern. *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* with increasing strength of 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 potential* (MUAP) can be clearly identified (see tracing on far right). A *reduced interference pattern* (*intermediate pattern*) is one in which some of the individual MUAPs may be identified while other individual MUAPs cannot be identified because of overlap. The term *discrete activity* is used to describe the electric activity recorded when each of several different MUAPs can be identified. The term *single unit pattern* is used to describe a single MUAP, firing at rapid rate (should be specified) during maximum voluntary effort. The force of contraction associated with the interference pattern should be specified.



Appendix Figure 5–31. Single-fiber electromyography—jitter. Schematic representation of the location of the recording surface of 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 and 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." Jitter is the variability with consecutive discharges of the *interpotential interval* between two muscle fiber action potentials belonging to the same motor unit. 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).



Appendix Figure 5–32. Macroelectromyography (macro-EMG). Schematic representation of the location of the recording surface of the macroelectromyography electrode recording from all the muscle fibers innervated by the same motor neuron (upper diagram). Muscle fiber action 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.

SECTION III:
TERMS GROUPED BY SUBJECT WITHOUT DEFINITION

The AAEE Nomenclature Committee felt that electromyography terms should be presented in two ways as follows: the conventional alphabetical list (Section I) and a list of the same terms grouped by subject (Section III).

This listing of the terms of electromyography by subject should be particularly useful for students and physicians who are new to the discipline. It may also help more experienced electromyographers to understand the logic behind the choices of terms that were made by the Committee.

In several instances, one term has been chosen as the preferred expression to describe a phenomenon for which several terms appear in the literature. The glossary is inclusive and, in the following list of terms grouped by subject, the preferred terms are listed first in the small groupings of like terms.

Basic Neurophysiology Terminology

The definition of these terms is based on their usage in neurophysiology literature.

Action current
Action potential
Muscle fiber action potential
Nerve fiber action potential

Refractory period
Absolute refractory period
Relative refractory period
Functional refractory period

Voltage
Potential
Resting membrane potential
Threshold
Membrane instability
Polarization
Depolarization
Depolarization block
Hyperpolarization
Repolarization
Afterpotential
Injury potential

Baseline
Noise
Interference

Wave
Waveform
Spike

Near-field potential
Far-field potential

Discharge
Afterdischarge
Adaptation

Frequency
Cycles per second
Hertz
Frequency analysis

Anode
Cathode

Excitatory postsynaptic potential
Inhibitory postsynaptic potential

End-plate potential
Miniature end-plate potential
End-plate zone

Accommodation
Accommodation curve

Excitability
Reflex
Muscle stretch reflex
Habituation
Fatigue
Silent period
Backfiring

Volume conduction
Tetanic contraction
Staircase phenomenon

Latency of activation
Utilization of time

Motor unit
Motor unit territory

General Terminology

The Board of Directors of the AAEE selected the term "Electrodiagnostic Medicine" to describe the area of medical practice in which a physician uses information from the clinical history, observations from the physical examination, and the techniques of nerve conduction studies and electromyography to diagnose and treat neuromuscular disorders.

Electrodiagnosis
Electrodiagnostic medicine

Nerve conduction studies
Evoked potential studies

Electromyography
Electromyograph
Electromyogram
Electroneurography
Microneurography

Electroneuromyography

Clinical electromyography

Central electromyography

International 10–20 Electrode Placement system

Equipment Terminology

Some of the terminology related to equipment dates back to the early descriptions of amplifiers in which one input was re-

ferred to as "Grid 1" or "G_1" and the other input was called "Grid 2" or "G_2." In studies of activities generated by the central nervous system in response to peripheral nerve stimulation (e.g., somatosensory evoked potentials), this convention is preserved by the terms "Input Terminal 1" and "Input Terminal 2" because the exact site of the origin of the recorded activity is not known. In nerve conduction studies and electromyography, the electrodes that lead to the input terminals of the amplifier can be referred to as "Input Terminals 1 and 2," but more commonly they are referred to as the "active electrode" and the "reference electrode," respectively, because the source of the electric activity is better understood.

Electrode
Surface electrode
Needle electrode
Bifilar needle recording electrode
Coaxial needle electrode
Concentric needle recording electrode
Monopolar needle electrode
Unipolar needle electrode
Multilead electrode
Multielectrode

Stimulating electrode
Anodal block

Recording electrode
Active electrode
Exploring electrode
Stigmatic electrode
Reference electrode
Indifferent electrode
Input Terminal 1
Input Terminal 2
Grid 1, Grid 2
G_1, G_2

Ground electrode
Earth electrode

Single fiber needle electrode

Macro-EMG electrode

Stimulus Terminology

In performing nerve conduction studies, it is important to identify the direction of propagation of the stimulus (antidromic or orthodromic), the intensity of the stimulus relative to the response (subthreshold, submaximal, or supramaximal), and the number of stimuli. The terms related to strength-duration curves are included here solely for historic purposes because these tests are now rarely used.

Antidromic
Orthodromic

Stimulus
Threshold stimulus
Maximal stimulus
Subthreshold stimulus
Submaximal stimulus
Supramaximal stimulus

Paired stimuli
Conditioning stimulus
Test stimulus

Strength-duration curve
Chronaxie
Rheobase

Artifact
Stimulus artifact
Electric artifact
Shock artifact
Movement artifact

Response Terminology

The terms in this section refer to the electric activity recorded from peripheral nerve and muscle and from the central nervous system in response to physiologic, mechanical, or electric stimuli. Historically, the terms chosen to describe these responses often implied physiologic mechanisms that, in some cases, subsequent investigations have disproved. In other cases, the term chosen has also been used to describe more than one phenomenon. To solve these problems, the Nomenclature Committee recommends that some waveforms be referred to by terms (letters) that are specific and unbiased. For example, the term *M wave* specifically refers to the compound muscle action potential recorded over a muscle directly in response to electric nerve stimulation. This term is preferred to the term *motor response* which may mean ei-

ther an M wave or the contractile movement of the muscle. For similar reasons, the terms *F wave* and *H wave* were chosen to refer to the late responses elicited indirectly from a muscle by electric stimulation of the nerve. The terms *A wave* and *T wave* are introduced to replace the terms *axon reflex* and *tendon reflex.*

The terminology to describe short-latency somatosensory evoked potentials is based on the recommendation in the American EEG Society's Clinical Evoked Potentials Guideline (*J Clin Neurophysiol* 1:41–53, 1984).

Evoked potential

Motor point

Motor response

Compound muscle action potential
Evoked compound muscle action potential
Muscle action potential

*M wave
M response

Late response

*F wave
F response

*H wave
H response
H reflex
Hoffmann reflex

*A wave
Axon reflex

*T wave

*R1 wave
*R2 wave
Blink responses
Blink reflex

Compound nerve action potential
Nerve action potential
Nerve trunk action potential

Compound mixed nerve action potential
Compound motor nerve action potential

*Compound sensory nerve action potential
Sensory response
Sensory potential

Sensory nerve action potential
Compound action potential

Amplitude
Conduction block

Duration
Temporal dispersion

Latency
Distal latency
Proximal latency
Latent period
Peak latency

Latency of activation

Motor latency
Terminal latency

Residual latency

Sensory latency

Sensory peak latency
Sensory delay

Conduction velocity
Nerve conduction velocity
Motor nerve conduction velocity
Sensory nerve conduction velocity
Conduction time
Conduction distance
Maximum conduction velocity

Muscle fiber conduction velocity

Brainstem auditory evoked potential

Brainstem auditory evoked response

Spinal evoked potential

*Visual evoked potential
Visual evoked response

*Somatosensory evoked potential (SEP)
Short-latency SEP (SSEP)
*Median nerve SSEP
*Common peroneal nerve SSEP
*Posterior tibial nerve SSEP

Midlatency SEP
Long-latency SEP
Interpeak interval

Repetitive Nerve Stimulation Terminology

Repetitive nerve stimulation has gained widespread acceptance as a valid and reproducible clinical technique to assess the

*Illustration in Section II.

integrity of neuromuscular transmission. Abnormal results of repetitive nerve stimulation studies may also be seen in primary disorders of nerve and muscle, as well as in primary disorders of neuromuscular transmission. Therefore, it is important to be certain that the results of the studies are described completely so that the basis of the conclusion can be reviewed. Descriptive terms such as *decrementing response, incrementing response, repair of the decrement,* and *increment after exercise* should be used to describe the results. Quantitative values indicating the magnitude of the change, as well as the method of calculation, should be included in the report.

*Repetitive nerve stimulation
Jolly test

Train of stimuli

*Decrementing response
Decremental response

*Repair of the decrement

*Postactivation depression
Postactivation exhaustion

*Incrementing response
Incremental response

*Increment after exercise

*Facilitation
Postactivation facilitation
Posttetanic facilitation

Potentiation
Postactivation potentiation
Posttetanic potentiation

*Pseudofacilitation

Needle Examination Terminology

Needle examination terms comprise the largest "group" in the Glossary. They include the range of activities that are observed in muscle with a needle electrode. The activities can be subdivided into insertion activity, spontaneous activity, involuntary activity and voluntary activity. In several cases, different terms have been used in the literature to describe the same phenomena. The committee has made an effort to select the one term that is preferred for each phenomenon. For example, the term *complex repetitive discharge* was chosen to characterize the electric discharge that has two or more different components (complex) and repeats regularly (repetitive). Other terms that have been used to describe the same activity are *bizarre high-frequency discharge, bizarre repetitive discharge,* and *bizarre repetitive potential.* These latter terms were not chosen since the word *bizarre* is a relative one and it has a negative connotation. The term *pseudomyotonic discharge* has also been used to describe complex repetitive discharges but is to be avoided because there are other electric phenomena that resemble myotonia, for example, waning discharges. Two more terms that have been used to describe complex repetitive discharges are *near constant frequency train* and *synchronized fibrillation.*

Occasionally a term that describes a clinical phenomenon is used incorrectly to describe an electric phenomenon. In order to make clear the distinction between them, both terms have been included in this Glossary. Examples of these pairs would be

fasciculation-fasciculation potential
myokymia-myokymic discharge
neuromyotonia-neuromyotonic discharge
muscle cramp-cramp discharge
myotonia-myotonic discharge.

It is important for physicians to use each term in these sets correctly and specifically. For example, it would be incorrect to describe *myotonic discharge* as *myotonia* or vice versa. Not all delayed muscle relaxation (myotonia) is accompanied by *myotonic discharges,* and not all *myotonic discharges* are accompanied by visible, delayed muscle relaxation.

The term *motor unit action potential* is preferred to the term *motor unit potential* to described the synchronized muscle fiber action potentials belonging to one motor unit. This recommendation is in keeping with the origins of the term in the basic neurophysiology laboratory.

Attention is called to the terms *recruitment frequency* and *recruitment interval* which provide more quantitative descriptions of recruitment than the older terms

*Illustration in Section II.

single unit pattern, discrete activity, reduced interference pattern, and *full interference pattern.* Many electromyographers now assess the number of motor unit action potentials available in the muscle from the recruitment frequency or recruitment intervals, and report the results directly as a normal number of motor unit action potentials, or as a mild, moderate, moderately severe, or severe decrease in the number of motor unit action potentials.

*Insertion activity
Reduced insertion activity
Increased insertion activity
Prolonged insertion activity

Electric silence
Electric inactivity

Spontaneous activity
Involuntary activity

*End-plate activity
End-plate noise
End-plate spike
Nerve potential
Sea shell sound (sea shell roar or noise)

Fibrillation
*Fibrillation potential
Denervation potential

*Positive sharp wave
Positive wave
Trains of positive sharp waves

Motor unit
*Motor unit action potential
Motor unit potential
MUAP
MUP

Amplitude
Duration
Rise Time
Phase
Monophasic action potential
Biphasic action potential
Triphasic action potential
Tetraphasic action potential
Polyphasic action potential
Serrated action potential
Turn
Irregular potential
Complex motor unit action potential

*Satellite potential
Late component (of a motor unit action potential)
Coupled discharge
Linked potential
Parasite potential

Neuropathic motor unit potential
"Giant" motor unit action potential

Myopathic motor unit potential
BSAP
BSAPP

Nascent motor unit potential

Recruitment
*Recruitment pattern
Recruitment frequency
Recruitment interval
Firing rate
Firing pattern
Discharge frequency
Order of activation
Onset frequency
*Interference pattern
Full interference pattern
Reduced interference pattern
Intermediate interference pattern

*Complex repetitive discharge
Bizarre high-frequency discharge
Bizarre repetitive discharge
Bizarre repetitive potential
Pseudomyotonic discharge
Synchronized fibrillation
Near constant frequency trains

Fasciculation
*Fasciculation potential
Benign fasciculation
Malignant fasciculation
Contraction fasciculation

Repetitive discharge
Grouped discharge
Iterative discharge
Double discharge
Doublet
Triple discharge
Triplet
Multiple discharge
Multiplet

Tetanus
Tetany

Myokymia
*Myokymic discharge

Muscle cramp
*Cramp discharge

*Illustration in Section II.

Neuromyotonia
*Neuromyotonic discharge

Myotonia
*Myotonic discharge
Myotonic potential
Pseudomyotonic discharge

Waning discharge

Voluntary activity
Volitional activity

Contraction
Contracture
Myoedema

Discrete activity
Single unit pattern

Neuropathic recruitment
Myopathic recruitment

Single-Fiber Electromyography and Macroelectromyography Terminology

Recent modifications of recording electrodes have led to the development of single fiber electromyography (SFEMG), macroelectromyography (macro-EMG), and scanning electromyography. Because these techniques are used in clinical neurophysiology laboratories, terminology related to them is included in this Glossary.

*Single-fiber electromyography
Single-fiber EMG
SFEMG

*Jitter
MCD
MSD

Fiber density

Interpotential interval
Interdischarge interval

Propagation velocity of a muscle fiber

*Macroelectromyography
Macro-EMG

Macro motor unit action potential
Macro-MUAP
Macro-EMG needle electrode

Scanning EMG
Motor unit fraction

*Illustration in Section II.

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INDEX

Note: Page numbers followed by "f" indicate figures; numbers followed by "t" indicate tables; numbers followed by "g" indicate glossary terms in the *AAEE Glossary for Terms* [Appendix 5]