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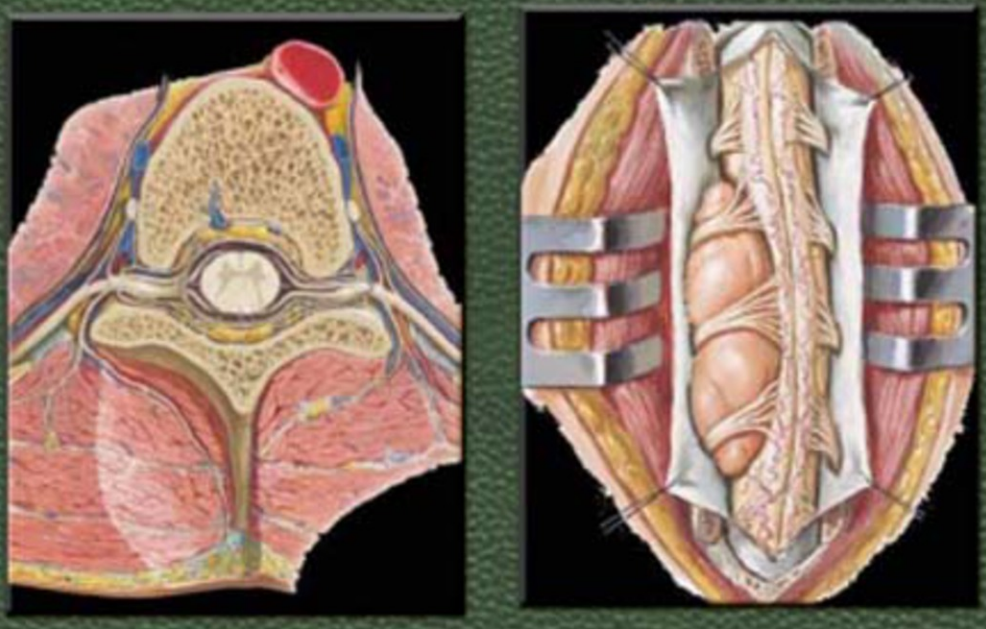
FRANK H. NETTER, MD 2nd Edition

VOLUME 7



Nervous System

PART II Spinal Cord and Peripheral Motor and Sensory Systems

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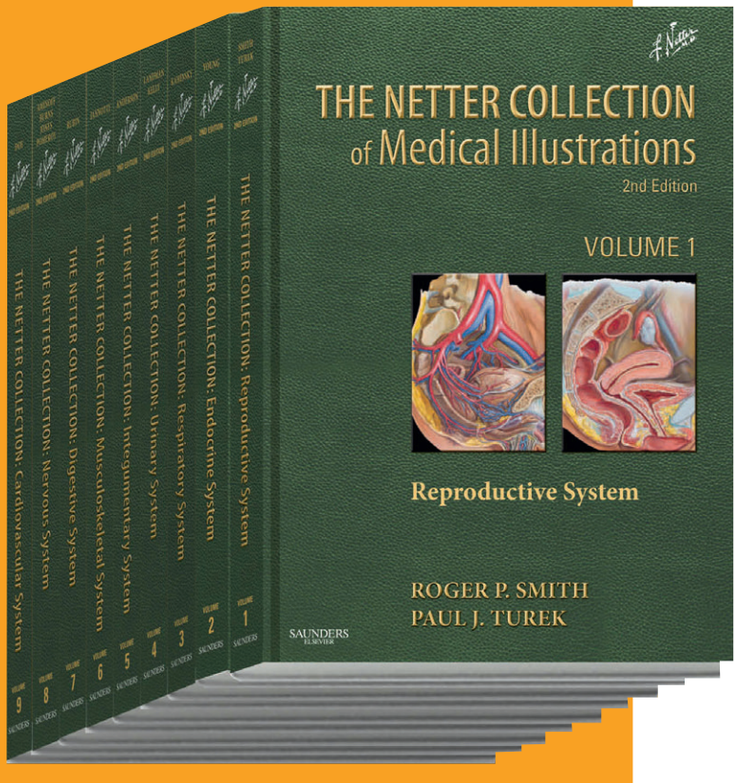

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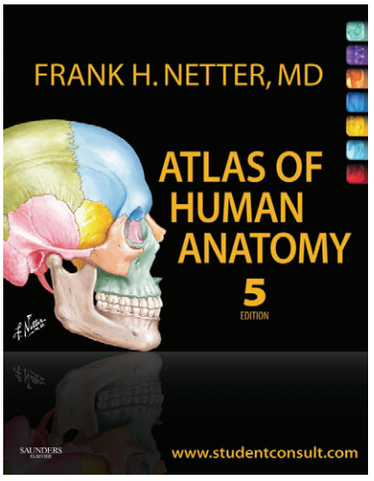

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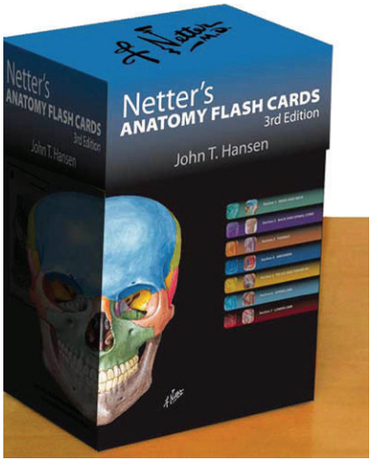

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VOLUME 7

The Netter Collection OF MEDICAL ILLUSTRATIONS

Nervous System

Part II—Spinal Cord and Peripheral Motor and Sensory Systems

2nd Edition

A compilation of paintings prepared by
FRANK H. NETTER, MD

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THE NETTER COLLECTION OF MEDICAL ILLUSTRATIONS: NERVOUS SYSTEM: PART II—SPINAL CORD AND PERIPHERAL MOTOR AND SENSORY SYSTEMS, Volume 7, Second Edition

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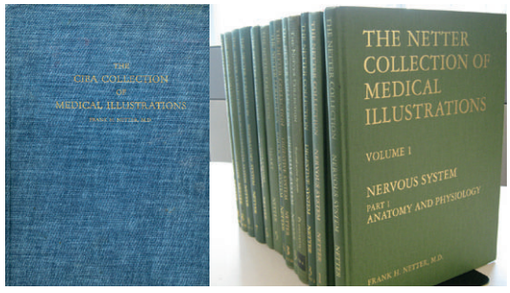
Dr. Frank Netter at work.



The single-volume "blue book" that paved the way for the multivolume *Netter Collection of Medical Illustrations* series aff ectionately known as the "green books."

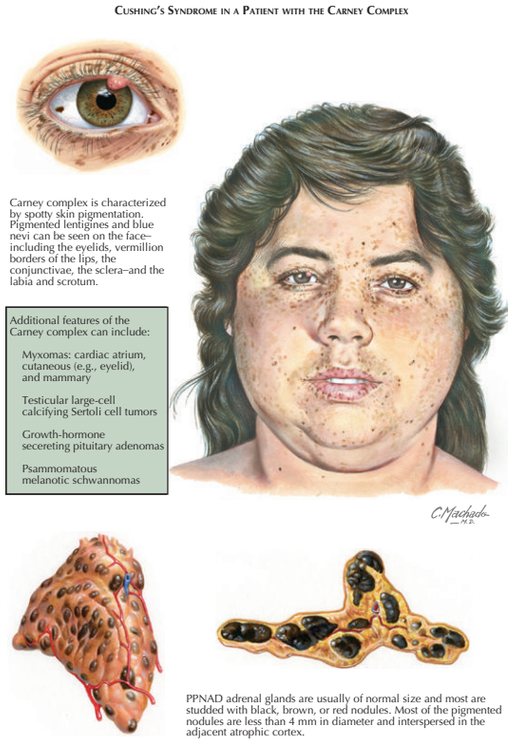
Dr. Frank H. Netter exemplified the distinct vocations of physician, artist, and teacher. Even more important—he unified them. Netter's illustrations always began with meticulous research into the detailed human clinical anatomy and pathology, a philosophy that steered his broad and deep medical understanding. He often said: "Clarification is the goal. No matter how beautifully painted, a medical illustration has little value if it does not make clear a medical point." His greatest challenge and greatest success was charting a middle course between artistic clarity and instructional complexity. That success is captured in this series, beginning in 1948, when the first comprehensive collection of Netter's work, a single volume, was published by CIBA Pharmaceuticals. It met with such success that over the following 40 years the collection was expanded into an 8-volume series—each devoted to a single body system.

In this second edition of the legendary series, we are delighted to offer Netter's timeless work, now arranged and informed by modern text and radiologic imaging contributed by highly respected neurologic authorities from world-renowned medical institutions, and supplemented with new illustrations created by artists working in the Netter tradition. Inside the classic green covers, students and practitioners will find hundreds of original works of art—the human body in pictures—paired with the latest in expert medical knowledge and innovation and anchored in the sublime style of Frank Netter.

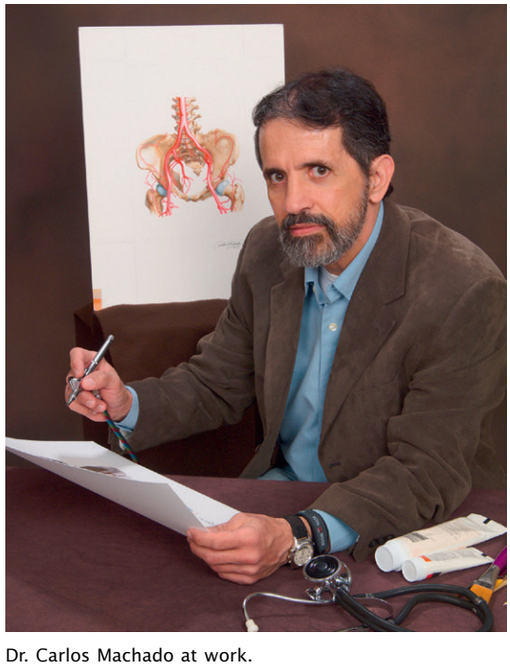
Noted artist-physician, Carlos Machado, MD, the primary successor responsible for continuing the Netter tradition, has particular appreciation for the Green Book series. "*The Reproductive System* is of special significance for those who, like me, deeply admire Dr. Netter's work. In this volume, he masters the representation of textures of different surfaces, which I like to call 'the rhythm of the brush,' since it is the dimension, the direction of the strokes, and the interval separating them that create the illusion of given textures: organs have their external surfaces, the surfaces of their cavities, and texture of their parenchymas realistically represented. It set the style for the subsequent volumes of Netter's Collection—each an amazing combination of painting masterpieces and precise scientific information."

Though the science and teaching of medicine endures changes in terminology, practice, and discovery, some things remain the same. A patient is a patient. A teacher is a teacher. And the pictures of Dr. Netter—he called them pictures, never paintings—remain the same blend of beautiful and instructional resources that have guided physicians' hands and nurtured their imaginations for more than half a century.

The original series could not exist without the dedication of all those who edited, authored, or in other ways contributed, nor, of course, without the excellence of Dr. Netter. For this exciting second edition, we also owe our gratitude to the Authors, Editors, Advisors, and Artists whose relentless efforts were instrumental in adapting these timeless works into reliable references for today's clinicians in training and in practice. From all of us with the Netter Publishing Team at Elsevier, we thank you.



A brand new illustrated plate painted by Carlos Machado, MD, for *The Endocrine System*, Volume 2, 2nd ed.



Dr. Carlos Machado at work.

ABOUT THE EDITORS

H. Royden Jones, MD, is Chair Emeritus of the department of neurology at Lahey Clinic in Burlington, Massachusetts, and Emeritus Director of the electromyography laboratory at Children's Hospital Boston. He is Clinical Professor of Neurology at Harvard Medical School and a lecturer in neurology at Tufts Medical School. At Lahey he holds the Jaime Ortiz-Patino Chair of Neurology. Dr. Jones graduated from Tufts College and Northwestern University Medical School. After interning at Philadelphia General Hospital, he became an internal medicine resident at Mayo, eventually specializing in neurology and clinical neurophysiology. Dr. Jones served over 3 years in the United States Army as Chief of Neurology at 5th General Hospital, Bad Cannstatt, Germany.

He joined Lahey Clinic in 1972, initially establishing their neurology residency affiliations with Boston City Hospital and later Tufts Medical Center. In 1984 he founded Lahey's clinical neurophysiology neuromuscular disorders fellowship and subsequently trained a number of future leaders in this field. At Lahey he has also served as Chairman of the Medical Personnel committee, Chair of Education, and Chair of the Division of Medicine and Medical Specialties and served on their Board of Governors for 19 years. He now enjoys patient care, clinical research, and teaching responsibilities full time.

In 1977 Dr. Jones joined the neurology department at Boston Children's Hospital, founding the electromyography laboratory in 1979. Noting that no clinical information was then available in pediatric EMG, this became a major clinical research interest of his, eventually leading to his co-editing three major textbooks on childhood clinical neurophysiology and neuromuscular disorders. Dr. Jones has edited three other Netter publications including the 1986 edition of this atlas and two editions of *Netter's Neurology*. He has been invited to speak worldwide on childhood neuromuscular disorders. Dr. Jones is a co-founder of the biennial International Paediatric EMG Conference based at Great Ormond Street Children's Hospital, London, England. He has broad adult clinical interests particularly neuroimmunologic and paraneoplastic neuromuscular disorders. Dr. Jones has contributed over 200 peer-reviewed papers and book chapters.

Dr. Jones served 8 years as a director of the American Board of Psychiatry and Neurology, becoming Chair of its Neurology Council in 2004. During this tenure he was a member of the Residency Review Council of the Accreditation Council for Graduate Medical Education. In 2007 he received the American Association of Neuromuscular and Electrodiagnostic Medicine's Distinguished Physician Award. Lahey Clinic's Medical Staff Association recognized Dr. Jones in 2010 with its highest honor—the Frank Lahey Award for "commitment to the values of Dr. Frank Lahey: respect, teamwork, excellence, commitment to personal best." In 2011 he received Lahey's Annual Research Award.

He and his wife have four children. Their daughter is a former New York City prosecutor, their oldest son is a professor at the University of Rochester Simon School of Business, and two other sons are physicians; one is an emergency medicine specialist in rural New Hampshire, and the other holds the Ackerman endowed chair of the Culture of Medicine at Harvard College and Medical School. Photography is Dr. Jones's major avocation.

Ted M. Burns, MD, is Professor of Neurology at the University of Virginia. He was born and raised in a suburb of Kansas City, Kansas. He received his undergraduate and medical degrees from the University of Kansas and then attended the University of Virginia for neurology residency and clinical neurophysiology fellowship. Dr. Burns completed a second fellowship in peripheral nerve disorders at Mayo Clinic in Rochester, Minnesota. He was on staff at Lahey Clinic in Burlington, Massachusetts, for 2 years before joining the neurology department at the University of Virginia in 2002. In 2008, he received a Harrison Distinguished Professor Chair at the University of Virginia. Dr. Burns is Vice Chair of the neurology department and Director of the Neurology Residency Program and the Clinical Neurophysiology Fellowship Program. He is also the Medical Director of the Neurology EMG Laboratory.

Dr Burns's clinical focus is on the care of patients with neuromuscular disease, including myasthenia gravis. He won the Myasthenia Gravis Foundation of America's "Doctor of the Year" award for 2010. His academic interests include the development and validation of user-friendly outcome measures for myasthenia gravis and other neuromuscular disorders. Dr. Burns is also interested in podcasting for the education of physicians, patients, and families. He is creator and editor of the *Neurology* journal's weekly podcast and the American Association of Neuromuscular and Electrodiagnostic Medicine's (AANEM) podcast. He is also the creator of the MGFA's podcast series designed to educate patients and families about practical aspects of MG.

Dr. Burns and his wife, Bonnie, have three wonderful children, Charlie, Elizabeth, and Sarah. He and his family live in Charlottesville, Virginia.

Michael J. Aminoff, MD, was born and educated in England, graduating from University College London in 1962 and from University College Hospital Medical School as a physician in 1965. He subsequently trained in neurology and clinical neurophysiology at The National Hospital for Neurology and Neurosurgery (Queen Square) in London and also undertook basic research on spinal physiology at its affiliated Institute of Neurology, which led to the award of an MD degree (which, in England, is an advanced medical degree based on research) on completion of his thesis. In 1974, he moved from England to the University of California San Francisco School of Medicine, where he has been Professor of Neurology since 1982 and now holds the title of Distinguished Professor. He was Director of the Clinical Neurophysiology Laboratories at UCSF until July 2004, when he stepped down to assume the role of Executive Vice Chair of the Department of Neurology. He is also director of the Parkinson's Disease Clinic and Research Center. He is currently involved in a number of clinical trials including one on gene therapy and also in physiological studies of patients with movement disorders.

Dr. Aminoff is the author of over 230 original medical and scientific articles, as well as the author or editor of numerous books, many of which have gone into several editions, and of a number of chapters on topics related to neurology. His published scientific contributions led to the award of a Doctorate in Science, an advanced doctorate in the Faculty of Science, by the University of London in 2000. He is the one of the two editors-in-chief of the four-volume *Encyclopedia of the Neurological Sciences* published by Academic Press in 2003 (a new edition is in press). He is also one of the series editors of the prestigious, multi-volume *Handbook of Clinical Neurology* (Elsevier). He was Editor-in Chief of the journal *Muscle and Nerve* from 1998 to 2007 and also serves on numerous other editorial boards. His other interests include medical history, and he has written two biographies on Brown-Séquard, one published by Raven Press in 1993, and the other by Oxford University Press in 2011.

Dr. Aminoff has received a number of awards over the years including the Lifetime Achievement Award of the American Association of Neuromuscular and Electrodiagnostic Medicine in 2006 and the A.B. Baker Award of the American Academy of Neurology in 2007 for lifetime achievements and contributions to medical education. He served for 8 years as a director of the American Board of Psychiatry and Neurology, serving as chairman of the board in 2011. He is married, lives in San Francisco, and has a daughter who is a pediatrician and two sons who are attorneys.

Scott L. Pomeroy, MD, PhD, graduated from Miami University and was the first graduate of the MD/PhD program of the University of Cincinnati. He trained in pediatrics at Boston Children's Hospital and in child neurology at St. Louis Children's Hospital. In 1989, he won the Child Neurology Society Young Investigator Award for work done as a postdoctoral fellow with Dale Purves at Washington University. He has won numerous awards for his research and clinical care of children with embryonal brain tumors including the Sidney Carter Award, the Daniel Drake Medal, and the Compassionate Caregiver Award of the Kenneth Schwartz Center.

Dr. Pomeroy currently is the Chair of the Department of Neurology and Neurologist-in-Chief of Boston Children's Hospital, the Bronson Crothers Professor of Neurology at Harvard Medical School, and the Director of the Eunice K. Shriver National Institutes of Child Health and Human Development–funded Intellectual and Developmental Disabilities Research Center of Boston Children's Hospital and Harvard Medical School. Dr. Pomeroy and his wife, Marie, live in Boston and have five grown children, Steve, Cole, Ann, Minna, and David.

FOREWORD

Combining Dr. Frank Netter's classic medical illustrations with a first-rate, current text is a brilliant idea. The choice of authors could not be better; as a group they are well-regarded clinicians whose experience as teachers, having national and sometimes international reputations, is well illustrated by the clarity of their writing. Very clearly there has been great attention to achieving a supple, readable style. The added images, such as the MRIs and other visual tools, are very well chosen. Their clarity for teaching purposes matches the text in quality, and these are nicely integrated with Netter's classic imagery. The most impressive thing about this effort is the marvelous embedding of Netter's illustrations into the text with preservation of coherence.

The original publication of these illustrations in the first Netter atlas was a regular, albeit unofficial, part of medical school neurologic learning early in my career during the 1960s. Concomitantly, Netter's corollary bi-monthly white-covered slim paperback Clinical Symposia was always welcome with the new mail … more than one issue were frequently strewn on my desk. These were essentially mini atlases always centered by a striking illustration immediately telling you what the dedicated subject would be. Each new edition was always accompanied by 15 to 20 new and now classic Netter illustrations. It was not clear how Ciba Pharmaceutical wanted to specifically influence us in trade for their marvelous free teaching aids. Now I wish I had saved many of them.

Dr. Netter's style is absolutely distinctive. It has the look of mid-20th century illustration art, somewhat like Norman Rockwell's. Not unlike a Rockwell, one can recognize a Netter illustration across the room. He is consistent no matter what his subject; his work, including its vivid coloration, is always particularly serious despite its sometimes cartoonish like appearance. Netter is distinctive the way all truly great artists' work invariably is, no matter what the level of sophistication. Think of Mondrian. Think of Francis Bacon. Totally different than Netter, they are good examples of great "high" art that are similarly distinctive and consistent. And such consistency, regardless of the subject, is surely part of what makes for genius with subsequent fame and greatness. Accompanied by their new text in two detailed parts covering the brain as well as the spinal cord and its related peripheral motor sensory units, Frank Netter's art has been beautifully resurrected once again. These will surely provide learning with pleasure to yet another generation of medical students during their neurologic studies.

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PREFACE, ACKNOWLEDGMENTS, AND DEDICATION

PREFACE

This new edition of *The Netter Collection of Medical Illustrations: Nervous System* recognizes the enduring nature of Dr. Frank Netter's incomparable artistic genius and his immense educational vision. Dr. Netter's initial atlas dedicated to neurology, first published in 1957, provided a very concise introduction to the nervous system for generations of students of medicine and the health sciences. His ability to simplify the essentials of very important components, namely the cerebral cortex and diencephalon, the complexities of the hypothalamus, fiber tracts within the brainstem and spinal cord, the cranial nerves, and the peripheral motor-sensory unit, was very remarkable. Furthermore, Dr. Netter's illustrations are absolutely outstanding in comparison to those available in other texts. His paintings are as vital today as at their artistic inception.

The initial single-part publication, providing an interaction between the basic neurologic sciences and clinical neurology, offered a stimulating introduction to many intriguing and important clinical aspects of neurologic medicine. Although the scope was somewhat limited in its clinical depth, its vivid and intriguing plates provided a unique catalyst for students, making the challenge of learning the neurosciences both exciting and rewarding. Indeed, Netter's initial volume was a major influence in leading some of us to consider a neurologic career.

Much of the anatomy of the peripheral nervous system and many central and peripheral clinical neurologic disorders were lacking in Netter's original *Nervous System*. To expand the scope of neuroanatomy and clinical disorders, a second volume was published in 1986. Although their publications were separated in time, these two parts are referred to as the "first edition." We now present a second edition, which is more comprehensive, carrying forward the vision that Frank Netter, MD, so brilliantly developed. Since the first editions, Elsevier purchased the publishing rights to the entire Netter art library, and it now has a dedicated division responsible for the publication of many Netter-illustrated medical texts and atlases that include some fine new artwork created by a superb group of medical artists carrying forward Frank Netter's tradition.

As editors of the current two-part volume, we have combined basic science information with clinical material, discussing the anatomy, physiology, pathology, and clinical presentation of many neurologic disorders, thus supplementing the system-based approach now used in many medical school curricula. We have been most privileged during our careers to participate in the exponential technologic advances leading to our very detailed understanding of the various neurologic disorders, particularly the rapid growth in diagnostic and management options now available. However, although these represent wonderful accomplishments not envisioned at the time of the last printing of this publication, such advances have created pleasant challenges for us both in organization and in definition of the scope of the topics discussed.

Each of us is ever mindful of the many unanswered questions, particularly regarding Alzheimer disease and other neurodegenerative disorders, various epilepsies, autism, schizophrenia, cerebral aneurysms, glioblastoma, multiple sclerosis, and amyotrophic lateral sclerosis, to name a few disorders that we hope will enjoy major advances during our lifetimes. We have confidence that our younger colleagues will shed further light on these very enigmatic clinical riddles and bring comfort and help to future generations of neurologic patients.

Each of us also hopes that today's medical students will find this new edition of the *Nervous System* an exciting introduction to the many challenges and rewards incumbent in a clinical neuroscience career.

ACKNOWLEDGMENTS

The editors thank their many neuroscience colleagues who contributed to this text, as listed on pp. xiv-xvi, as well as our many patients through whom we learned the art and science of neurology. We also express our admiration and thanks to our artist colleagues Carlos A. G. Machado, MD, John A. Craig, MD, James A. Perkins, MS, MFA, Anita Impagliazzo, MA, CMI, Tiffany S. DaVanzo, MA, CMI, and Kristen Wienandt Marzejon, MS, MFA, who have so carefully upheld Frank Netter's approach to medical illustration. These dedicated artists have expertly created a number of outstanding new plates for these volumes. Additionally, Barry Arnason, MD, the primary author of the multiple sclerosis section in Part 1, significantly contributed to the final artwork seen in Plates 10-6 through 10-12 and 10-14, providing his own detailed sketches, direction, and feedback to an artist. These unique drawings represent a very special artistic contribution by an author of this text. Most MRI and CT images for many previous plates used in this atlas were supplied by Richard A. Baker, MD, of the Lahey Clinic, who has expertly and tirelessly worked with Royden Jones on four Netter projects during the past 30 years. Finally, the entire Elsevier editorial team, particularly Marybeth Thiel and Elyse O'Grady, have been gracious and cooperative in supporting our goals. It has been a distinct pleasure having such professional and dedicated colleagues.

DEDICATION

These two volumes are dedicated to our wives, children, and grandchildren, whose love and support gave us the time to work on this project; to our students, residents, and fellows, who challenged us to be fine teachers; and to our many and dear patients for whom we have been honored and blessed to care.

H. Royden Jones
Ted Burns
Michael J. Aminoff
Scott Pomeroy
December 2012

FRANK NETTER, MD: A PERSONAL RECOLLECTION

While attending a major medical meeting more than two decades after using the first Netter *Nervous System*, published in 1957, I met a representative of the Ciba Pharmaceutical Medical Education division—the corporation that sponsored Dr. Frank Netter's medical artistic career for more than 40 years—and inquired about the possibility of having him create paintings relevant to the peripheral motor and sensory unit and, particularly, the major peripheral nerves. Within a few months, I was surprised to receive a handwritten letter from Dr. Netter, asking for more detailed suggestions. This led to an invitation to meet with him at his Florida beachfront home and to advise him in reference to his current orthopedic disorders project.

Frank was a humble and engaging person entirely dedicated to his goal of illustrating all human anatomy and related clinical disorders. A day in his studio might be dedicated to interviewing physicians to discuss their area of expertise, who would provide him with a full appreciation of the subject before he started on his drawings. Sometimes after lunch he took a break from his ever-present cigars and his studio to play two or three holes of golf before returning to his various challenges. Most other days were dedicated to conceptualization, drawing, or painting sessions. Dr. Netter had an unbridled passion for his work. His artistic abilities were truly amazing—he was under contract to provide 93 new illustrations annually, which amounts to one every four days. He worked with vigor every day of the week until his death at age 85.

Unknown to me when we initially met, Frank previously had commenced his work on a new edition of his *Neuroscience Atlas*, having recognized the relatively limited scope of his initial volume. After we worked together for a while, he showed this project to me, noting that it had remained dormant for a few years; subsequently he asked me to become its clinical editor. There were to be two parts. *Part I*, dedicated to traditional basic neuroanatomy and neurophysiology, was essentially completed. The clinical portion of his revised atlas, *Part II Neurologic and Neuromuscular Disorders*, required extensive new artwork and text and was first published in 1986. However production costs and time restraints limited its clinical breadth and depth. Therefore , Frank and I envisioned production of a more complete set of texts within 5 to 10 years to add further to these volumes. Although long overdue, thanks to the foresight of Elsevier, these volumes are now completed. There is no doubt that Dr. Netter would be extremely pleased with these results subsequent to the dedication of so many expert neurologic physicians. The new two-part volume supports his dream of very comprehensive, relevant, and totally up-to-date neuroscience atlases.

H. Royden Jones, MD

INTRODUCTION TO THE FIRST EDITION

INTRODUCTION TO PART I

The Ciba Collection of Medical Illustrations was originally conceived as a series of atlases picturing the anatomy, embryology, physiology, pathology, and diseases of mankind, system by system. The creation of these atlases has been for me a labor of love to which I have devoted most of my working career. The first volume of this series was *Nervous System*. That volume was very well received and acclaimed by students, physicians, and members of allied professions throughout the world. It has been reprinted many times and published in a number of languages. The multitude of letters of appreciation I have received in the more than 30 years since its first publication have been a great source of satisfaction to me, even as I progressed with other volumes in the series.

From the beginning, however, certain deficiencies in the *Nervous System* volume became evident. It contained, for example, practically no coverage of the peripheral nervous system, of embryology, of basic neurophysiology, i.e., nerve impulse transmissions and synapse; and the presentation of the neurologic and neuromuscular diseases was far too skimpy and incomplete. Furthermore, as time progressed and our knowledge advanced, the deficiencies became more significant. Advances in neuroradiology and neurosurgery made it important to update the illustrations of the blood vessels of the brain and spinal cord. The advent of the CT scan as a valuable diagnostic tool necessitated its inclusion as a specific procedure. Our improved understanding of the neuromuscular diseases and increased application of electromyography, electroencephalography, and nerve conduction studies called for a better presentation of basic neurophysiology and nerve-muscle relationships. The great progress in the study of neurologic disorders such as poliomyelitis, Parkinsonism, myasthenia gravis, stroke, trauma, Alzheimer's disease, and many others demanded amplification of the section on specific diseases of the nervous system. Finally, the better definition of the congenital and developmental disorders not only prompted presentation of those disorders but emphasized the importance of including a section on neuroembryology.

Accordingly, it has for many years been my desire to revise and expand this atlas in a new edition. I was, however, so busy with preparing other volumes of the *Ciba Collection* that it took me a long time to accomplish it. This was, to a certain extent, fortuitous, for it allowed me to include newer material that would not have been available for an earlier revision. But the volume of illustrations and accompanying texts grew to such an extent that they could not all be included in a single book. It was therefore decided to issue the atlas in two parts; Part I to include anatomy, embryology, physiology, and functional neuroanatomy; and Part II, shortly forthcoming, to include all neurologic and neuromuscular diseases.

At the same time that I was working on this revision I was also occupied with preparing an atlas on the musculoskeletal system, and the great overlap between the fields of orthopedics, i.e., musculoskeletal disorders and neurologic or neurosurgical disorders, became apparent. Indeed, many of the disorders to be covered lay in the realm of both specialties. Thus, the two-part presentation of this atlas is advantageous, since Part II bridges the gap between the two fields, and I believe this will be pertinent to both neurology-neurosurgery and orthopedics, as well as to the fields of general practice and internal medicine. Part I, on the other hand, will serves as a reference for basic understanding of much of the material in Part II, and will be very useful for the student and for those in allied professions such as physical therapy, speech therapy, and psychology. All in all, I believe that in this revised edition of *Nervous System* I have corrected the deficiencies referred to above, as well as many others, and I hope it will prove as useful and helpful to all those who refer to it as the original edition apparently was in its day.

I take this opportunity to express my appreciation to all the collaborators and consultants who helped me with preparing this volume. They are all credited separately herein. I admire their erudition and I thank them for the time they gave me and the knowledge they imparted to me. It was a great pleasure for me to learn from them, and I cherish the friendships we established during our collaboration. The creation of this volume would have been impossible without their help. I also thank the CIBA-GEIGY Corporation and its executives for the free hand they have given me in this project, and the members of the editorial staff for their very helpful and dedicated cooperation.

Since the foundation for this volume was laid in its earlier edition, I reiterate here, with much nostalgia, my appreciation for the great men who guided me through that original endeavor. They were: Dr. Abraham Kaplan, neurosurgeon and gifted student of Dr. Harvey Cushing; Dr. Albert Kuntz, pioneer in unraveling the mysteries of the autonomic nervous system; Dr. Gerhardt von Bonin, brilliant neurophysiologist; and Dr. W.R. Ingram, professor of anatomy at the University of Iowa, who devoted much of his career to study the hypothalamus. In regard to the editor of that original edition, I quote herewith the last paragraph from my introduction to that volume. "Every artist thrives on appreciation, understanding, and encouragement. In this respect I have been double fortunate. First, the warm reception which the medical profession as accorded my pictures has been a wonderful source of satisfaction to me. Second, more person and close at hand, has been the inspiring personality of Dr. Ernst Oppenheimer. His understanding of the things I was trying to do, his appreciation of what I had done, and his encouragement to do more were a constant assurance that I was not alone. In addition, his vision of the scope and value of this atlas and his many co-ordinating activities in its behalf have been vital factors in the project.

Frank H. Netter, 1983

INTRODUCTION TO PART II

In the introduction to Part I of this volume on the nervous system, I wrote of why, after almost 35 years of widespread acceptance, it was necessary to revise and update the original atlas, Volume 1 of *The Ciba Collection of Medical Illustrations*. I also told there of how, as I progressed with the revision, the amount of material to be included grew to such a magnitude that it was decided to publish it in two parts. Part I, published in 1983, contained a depiction of what may be called the "basic science" of the nervous system, that is, the bony encasements, the gross anatomy, and the vasculature of the brain and spinal cord, the autonomic nervous system, the cranial nerves, the nerve plexuses and peripheral nerves, the embryology, and the physiology and functional neuroanatomy of the nervous system. Part II, presented herewith, is devoted to portraying the disorders and diseases of the nervous system. But once again, to my dismay, as I progressed with picturing the pathology and clinical aspects of those multitudinous ailments, the volume of material grew to such an extent that I was hard put to confine it to the limits of one book. Furthermore, the fantastic progress that was being made in the field even as I worked added to the difficulty of space limitation. Accordingly, I tried to place emphasis on those disorders most threatening to mankind because of incidence or severity, with due consideration for timeliness, diagnostic difficulty, and potential for beneficial management.

I believe that, in studying many of the conditions portrayed in this book, the reader will find it most helpful to refer repeatedly to Part I of this volume for an understanding of the basic science aspects underlying the disorder. For example, study of stroke in this book may be enhanced by reference to the arterial supply and functional subdivisions of the brain, as covered in Part I. Likewise, study of the peripheral neuropathies may call for a review of nerve conduction as well as of the course and distribution of the peripheral nerves.

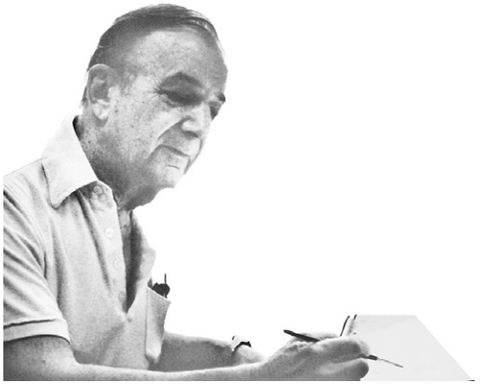
But the nervous system is not an isolated entity. It is intimately involved with the function of every other system of the body as portrayed in other volumes of the *Ciba Collection*. The association is, however, most marked with the musculoskeletal system. Indeed, there is great overlap between the fields of neurology and neurosurgery with the field of orthopedics, both diagnostically and therapeutically. Cerebral palsy and poliomyelitis are, of course, basically neurologic diseases, and they are so presented in this volume. But the aftercare, corrective surgery, and rehabilitation of such patients are usually in the hands of the orthopedists. Accordingly, those aspects of these diseases will be covered in the forthcoming atlases on the musculoskeletal system, on which I am now at work. Intervertebral disc herniation and spinal stenosis likewise fall into both fields of practice, and thus, while presented herein, their management will be amplified in the musculoskeletal volume. The neuromuscular diseases are among many other examples of overlap between the two disciplines.

The trials and tribulations of the production of this atlas were far outweighed by the pleasure and stimulation I received from working on it. This was largely due to those wonderful people, my consultants and collaborators, who helped me, taught me, advised me, and supplied me with the pertinent reference material as a basis for many of my illustrations. They are all listed separately herein and I thank them, each and every one, for the knowledge they imparted to me and for the time they so graciously gave me.

I was especially fortunate to have had the guidance and counsel of that delightful personality, Dr. H. Royden Jones, Jr. ("Roy" to me), of the Lahey Clinic. The many long hours we spent together planning and organizing the material to be included were not only informative and productive but exceedingly pleasurable as well. I was constantly impressed by his broad knowledge, his unique ability to define the essence of each subject we dealt with, and his ability to call upon knowledgeable consultants for special topics, yet maintaining an overall perspective of the project in relation to the total field of medical practice and neurology in particular. Our collaboration thus developed into a lasting friendship that I cherish highly.

I express here also my appreciation for the help and encouragement which I received from Dr. William (Bill) Fields, professor and chairman of the department of neuro-oncology at the MDAnderson Hospital and Tumor Institute, Houston. He was not only a definitive collaborator for some specific subjects, but readily gave me much practical advice and counsel throughout the undertaking. I thank Mr. Philip Flagler, director of Medical Education for the CIBA Company, and Dr. Milton Donin, a relative newcomer to our team, for their continuous efforts in coordinating the varied aspects of the undertaking, to keep it moving along, and to ensure that each person involved understood and felt happy in their contribution to it. My accolades go also to Ms. Gina Dingle for her diverse editorial activities, for her untiring and patient attention to frustrating details, for her great organizing accomplishments, and especially for her ever-present personality. Finally, I express once more my appreciation of the CIBA Pharmaceutical Company and its executives for their understanding of the significance of this project and for the free hand they have given me in its creation.

Frank H. Netter, 1986



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CONTENTS OF COMPLETE VOLUME 7—NERVOUS SYSTEM: TWO-PART SET

PART I Brain

ISBN: 978-1-4160-6387-2

PART II Spinal Cord and Peripheral Motor and Sensory Systems

ISBN: 978-1-4160-6386-5

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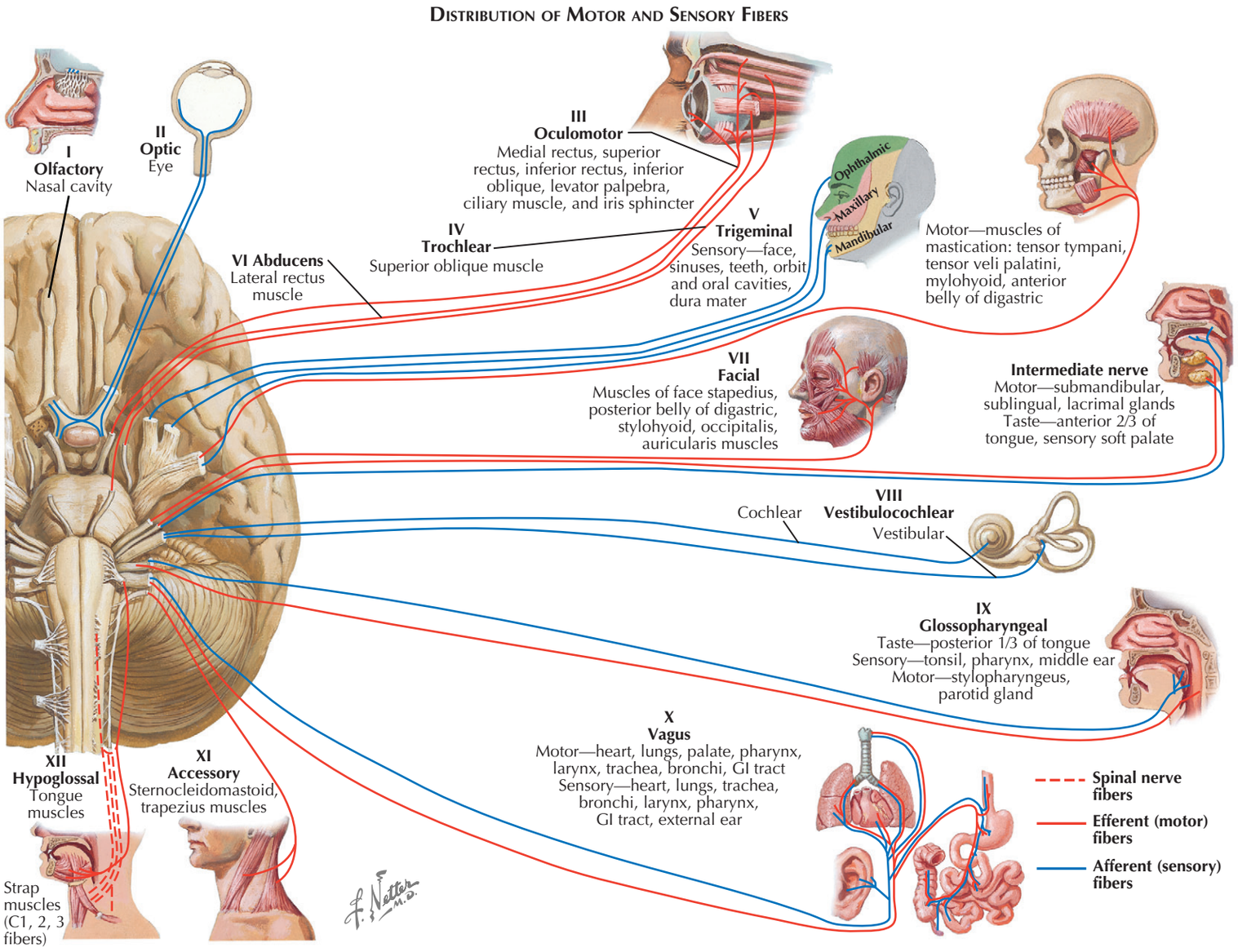
CRANIAL NERVE AND NEURO-OPHTHALMOLOGIC DISORDERS



Overview of Cranial Nerves

The brainstem is the source of all the cranial nerves and provides sensory, motor, and, through the vagus nerve, parasympathetic preganglionic innervation to the face, head, thorax, and most of the abdominal viscera. Distinct motor and sensory nuclei within the brainstem project to the various structures of the head to provide (1) general sensory information from the face, ears, and oropharynx and (2) motor innervations for facial movement and expression, mastication, extraocular eye movements, and complex functions such as speech and swallowing. The specialized olfactory, visual, auditory, and gustatory senses are provided by highly specialized receptor cells and end organs, with ultimately wide cortical projections.

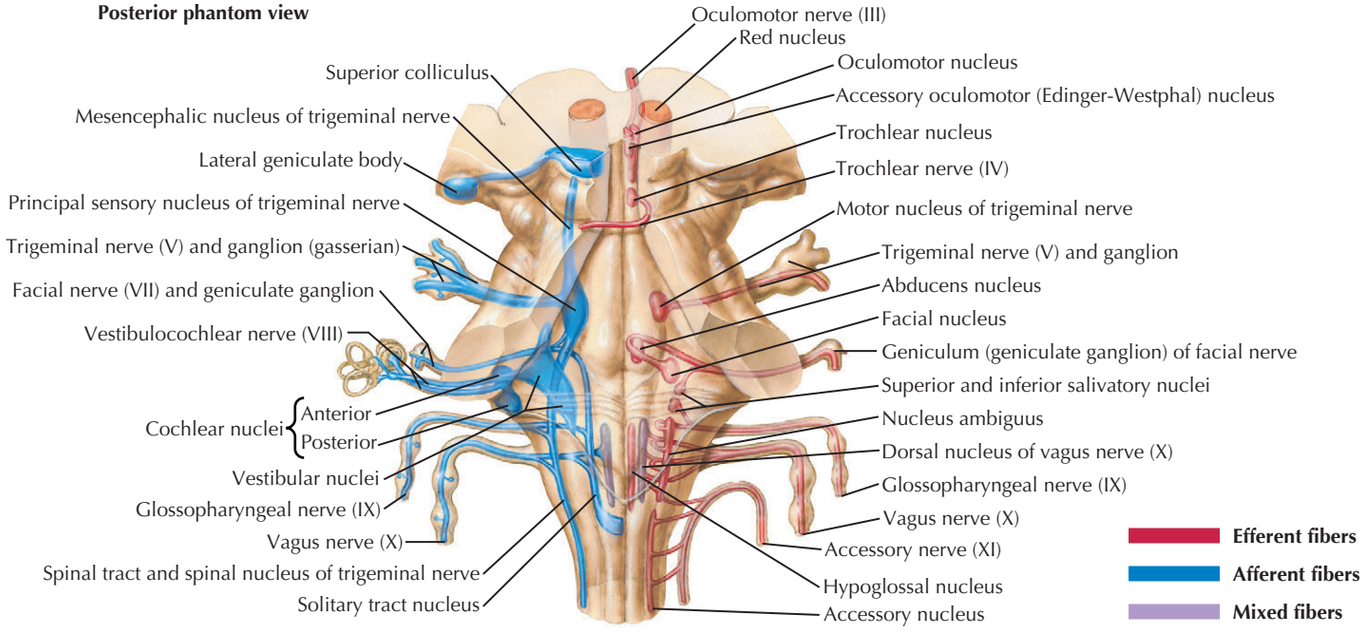
Cranial nerve motor nuclei are located medially, whereas the sensory nuclei are found generally more lateral. Three types of motor nuclei are present innervating voluntary striated muscles (somatic), muscles of facial expressions and mastication (special motor derived from embryonic branchial arch structures), and autonomic smooth muscles (visceral). Each cranial nerve serves a regional skull area and may provide more than one function to that area and therefore is not restricted to a single nucleus or nerve type. For example, the facial nerve provides voluntary motor innervations to the face as well as taste special sensation to the anterior tongue. The pure motor nerves (except for perhaps some proprioceptive function) are the oculomotor III, trochlear IV, abducens VI, spinal accessory nerve XI, and hypoglossal XI. The special sensory nerves are the olfactory, optic, and vestibulocochlear. Mixed cranial nerves are the trigeminal V, facial VII, glossopharyngeal IX, and vagus X. A summary of the origin, course, and distribution of each cranial nerve is outlined on the next plates.

Cranial neuropathies may manifest as a single cranial neuropathy or, less commonly, as multiple cranial neuropathies. Single cranial neuropathies are discussed in their respective sections. For example, Bell palsy is reviewed in the cranial nerve VII (facial nerve) section. Multiple cranial neuropathies involve any combination of cranial nerves, although cranial nerves III, V, VI, and VII are the most commonly affected in most clinical series. The manifestations of multiple cranial neuropathies reflect the sites of injury and function of the cranial nerves affected. The many different causes of multiple cranial neuropathies include infectious, neoplastic, autoimmune disease, trauma, and vascular disease. Infections associated with multiple cranial neuropathies include Lyme disease, tuberculous meningitis, cryptococcus, histoplasmosis, botulism, mucormycosis, certain viruses (e.g., herpes simplex virus, varicella-zoster virus) and bacterial meningitis. Guillain-Barré syndrome (GBS) and the Miller Fisher variant of GBS are monophasic, autoimmune polyradiculoneuropathies that can frequently involve multiple cranial nerves. Neoplasms cause multiple cranial neuropathies either by direct compression and local extension, such as with meningiomas, schwannomas, and nasopharyngeal tumors, or by diffuse dissemination and meningeal infiltration, such as with lymphoma and various carcinomas. Myasthenia gravis (MG) mimics multiple cranial neuropathies but the site of autoimmune attack in MG is directed against the postsynaptic muscle end rather than the nerve.

Name and number: Type of fibers	Origin, course, and distribution	Chief functions
Olfactory (I): ***Special sensory***	Olfactory cells in nasal mucosa aggregate into olfactory nerves that penetrate the cribriform plate and join to form the olfactory bulb. The bulb's posteriorly extending tract divides into a medial branch, which fans into the parolfactory and subcallosal areas, and a lateral branch, which ends in the uncus and the parahippocampal gyrus.	***Smell***
Optic (II): ***Special sensory***	Axons of the inner retinal *ganglion cell layer* form the retina's *nerve fiber layer* and gather at the optic disk (optic nervehead) before turning 90° and penetrating the scleral canal to exit the globe, now myelinated, as the *optic nerve*. The *optic chiasm* is the intersection of the optic nerve from each eye coming through the optic canal and is located above the pituitary body within the sella turcica. Axons from the temporal retina (nasal field) remain ipsilateral as they pass through the chiasm to the optic tract. In contrast, the nasal retinal fibers decussate, carrying temporal visual field information to the contralateral side. Inferior nasal fibers decussate within the chiasm more anteriorly than superior ones. As the inferior nasal retinal fibers approach the posterior aspect of the chiasm, the fibers shift to occupy the lateral aspect of the contralateral optic tract. The optic tract leads to the lateral geniculate bodies. The lateral geniculate nucleus (LGN) is a thalamic nucleus that serves as the synapse point as the retinal ganglion cells and relays visual information through the optic radiations to the striate and occipital cortex.	***Vision***
Oculomotor (III): ***Motor*** ***Visceral motor***	This nerve emerges as a collection of nine rostral midbrain subnuclei located ventral to the aqueduct at the level of the superior colliculus and includes the *accessory autonomic* (*Edinger-Westphal*) nucleus. Axons from the CNIII subnuclei gather into a fascicle that arcs through the red nucleus and emerges at the medial surface of the cerebral peduncle. In the interpeduncular cistern, the nerve passes beneath the posterior cerebral artery, then pierces the dura crossing next to the internal carotid artery en route to the cavernous sinus. From the lateral wall of the cavernous sinus, it enters the orbit through the superior orbital fissure to supply the superior rectus, medial rectus, inferior rectus, and inferior oblique. The fibers subserving pupillary constriction are located superficially and are susceptible to compression but are less prone to microvascular or ischemic changes than the deeper fibers are. These parasympathetic fibers split off the oculomotor nerve in the orbit and synapse in the ciliary ganglion from which postganglionic *short ciliary nerves* supply the pupillary sphincter and ciliary muscles.	***Somatic motor:*** Upper lid elevation (levator palpebrae superioris) and extraocular movements upward, medially, and downward ***Visceral motor:*** Parasympathetically mediated pupillary constriction and accommodation reflex
Trochlear (IV): ***Motor***	The CNIV nuclei are located in the midbrain at the level of the inferior colliculi off midline at the anterior edge of the periaqueductal gray. Axons from the trochlear nucleus arc posteriorally around the periaqueductal gray and cross the midline to emerge laterally beneath the inferior colliculus and wrap forward around the medial border of the brachium conjuctivum. CNIV completely decussates, a unique feature among the cranial nerves, and exits the brainstem from its posterior aspect. It passes the ambient cistern and through the lateral wall of the cavernous sinus to then enter the orbit via the superior orbital fissure. The trochlear nerve innervates a single extraocular muscle, the superior oblique.	***Somatic Motor:*** Superior oblique muscle, extraocular eye movement downward and intorsion
Trigeminal (V): ***Somatic sensory and special motor***	The *trigeminal somatic sensory column* is a posterolateral series of nuclei extending from the mid pons to the upper cervical cord and receive general sensory input from the eye, orbit, face, forehead, upper and lower jaws, sinuses, teeth, and nasopharynx. Proprioceptive receptors in the extraocular and masticatory muscles end in the *mesencephalic nucleus*. Pain, touch, and temperature fibers end in the *principal (pontine) sensory nucleus* and *spinal nucleus of trigeminal nerve. Trigeminal motor nucleus* in the upper part of the pons is the origin of special branchiomotor fibers to the muscles of mastication. Large sensory and smaller motor roots enter and emerge laterally at the midpons level. As the trigeminal nerve exits the posterior fossa, it expands over the apex of the petrous temporal bone into the *trigeminal (semilunar) ganglion* made of sensory nuclei from the *ophthalmic, maxillary,* and *mandibular* nerves that pass through the superior orbital fissure, foramen rotundum, and foramen ovale, respectively. The *ophthalmic nerve* divides into lacrimal, frontal, and nasociliary branches, which participate in innervating eye, nose, and scalp. The *maxillary nerve* traverses the pterygopalatine fossa, enters the infraorbital groove (canal), and emerges as the *infraorbital nerve* through infraorbital foramen; supplies meningeal, zygomatic, superior alveolar, inferio-palpebral, nasal, and superior labial branches, and is connected with pterygopalatine ganglion through which it supplies orbital, nasal, palatine, and pharyngeal branches. The *mandibular nerve* is joined by entire motor root of trigeminal nerve in the foramen ovale and gives off meningeal, buccal, auriculotemporal, lingual, and inferior alveolar branches, as well as motor nerves supplying mastricatory muscles, the tensors of the soft palate, and the tympanic membrane.	***Somatic sensory (touch, pain and temperature):*** Eyes, face, anterior scalp, sinuses, teeth, oral and nasal cavities as well as the dura mater ***Proprioceptive sensory (deep pressure, position, and movement):*** Teeth, temporomandibular joint, hard palate, and muscles of mastication ***Special motor:*** Branchiomotor fibers to the muscles of mastication, anterior belly of the digastrics, tensor tympani, and tensor veli palatini mylohyoid
Abducens (VI): ***Motor***	The abducens CNVI nucleus is in the floor of the fourth ventricle just lateral to the median eminence of the pons. It is enveloped by looping CNVII fibers (genu) that form the facial colliculus. The CNVI nucleus contains two physiologically distinct groups of neurons: one innervating the ipsilateral lateral rectus muscles and the other projecting across the midline up the contralateral medial longitudinal fasciculus (MLF) to the ventral nucleus of the contralateral CNIII nuclear complex. These internuclear connections produce the simultaneous activation of the contralateral medial rectus muscle and the ipsilateral lateral rectus that ensures conjugate lateral horizontal gaze. The CNVI fasciculus projects anteriorly and caudally to exit the inferior edge of the pons just medial to the corticospinal tracts. The nerve ascends between the pons and the clivus within the pontine cistern. It pierces the dura and then enters the lateral cavernous sinus below the trochlear nerve. It reaches the orbit through the superior-orbital fissure.	***Somatic motor:*** Lateral rectus muscle extraocular eye movement, eye abduction

Nerves and Nuclei Viewed in Phantom from Behind

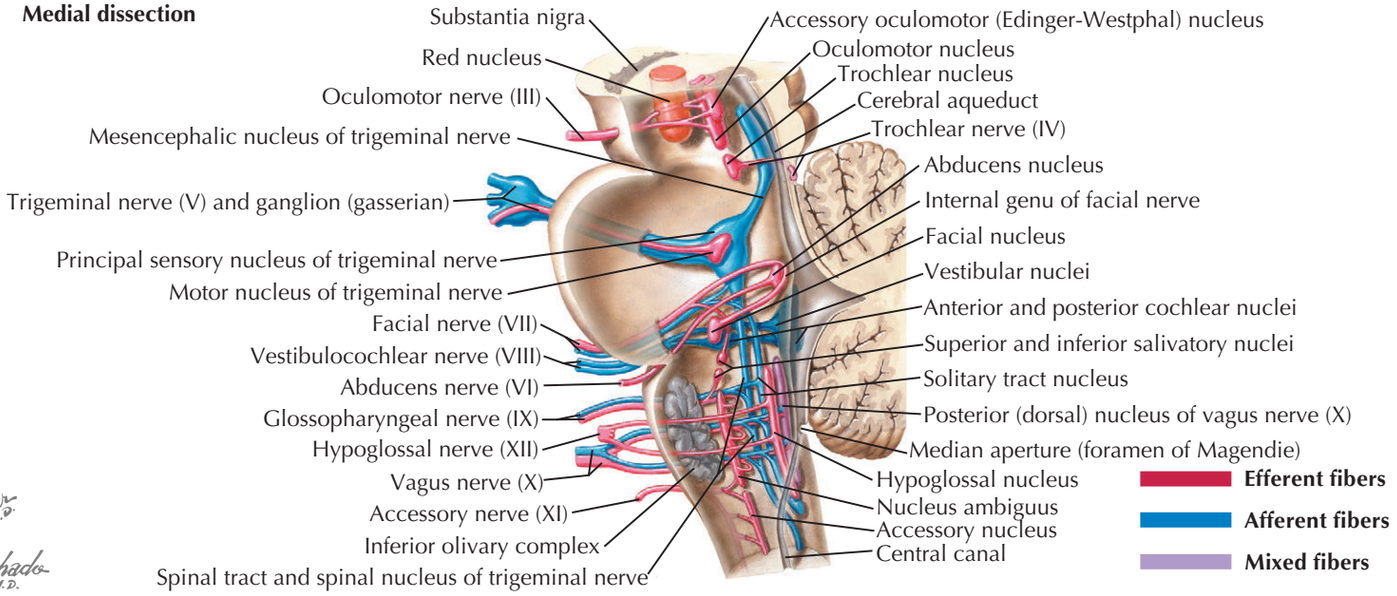
Posterior phantom view



Name and number: Type of fibers	Origin, course, and distribution	Chief functions
Facial (VII): ***Special motor*** ***General visceral motor*** ***Somatic sensory*** ***Special sensory***	Branchiomotor fibers arise from the *facial nucleus* in the lower pons and ascend to loop around the abducens nucleus and then descend anterolaterally between the spinal trigeminal complex and the VII nerve motor nucleus. The nerve emerges as two divisions through the recess between the inferior cerebellar peduncle and the medulla; a larger *motor root* and smaller *nervus intermedius* containing mainly afferent special sensory fibers for taste and secretomotor fibers to the *pterygopalantine ganglion* (lacrimation and mucous membrane secretory function in the mouth and nose). Both divisions of the facial nerve, along with CN VIII, then pass through the internal acoustic meatus. At the level of the geniculate ganglion secretomotor fibers (originating from the *superior lacrimal/salivatory nucleus*), separate and proceed superiorly to the pterygopalatine ganglion. The chorda tympani (carrying secretomotor fibers to the submandibular ganglion and special sensory taste fibers from the anterior two thirds of tongue and soft palate) separates distal to the geniculate nucleus and joins the lingual nerve to the tongue. The branchiomotor fibers proceed through the boney facial canal and emerge in the face anterior to the mastoid process from the stylomastoid foramen. It enters the parotid gland to divide into diverging branches toward the facial muscles and the platysma (Plate 1-24).	***Special motor:*** Muscles of facial expression, stapedius, stylohoid, and posterior belly of the digastrics muscle ***General visceral motor:*** Parasympathetic innervations of the submandibular, sublingual, lacrimal, and nasal/oral mucous membrane glands ***Somatic sensor:*** External auditory meatus and skin over mastoid ***Special sensory:*** Taste anterior 2/3rds of the tongue
Vestibulocochlear (VIII): ***Special sensory***	The vestibulocochlear nerve emerges through the internal acoustic meatus at the pontomedullary angle posterolateral to the facial nerve. The primary neurons are bipolar cells located in the vestibular and multiple spiral ganglia. Peripheral processes pass from special auditory (cochlea) and vestibular (ampullae, utriculus, and sacculus) receptors, while the central processes project to two cochlear, and four vestibular brainstem nuclei, respectively. The ventral and dorsal cochlear nuclei are located at the level of the inferior cerebellar peduncle in the superior medulla. Most cochlear nuclear fibers decussate through the trapezoid body, after which third- and fourth-order neurons then ascend the lateral lemniscus to the inferior colliculus with projections ultimately to the auditory cortex. The superior, inferior, medial, and lateral vestibular nuclei lie in the anterolateral floor of the fourth ventricle and connect with the cerebellum, the nuclei of CNs III, IV, and VI (through the medial longitudinal fasciculus) and to anterior horn cells controlling muscles of head and neck (vestibulospinal tract).	***Hearing*** ***Equilibrium and balance*** ***Reflexive eye movements***
Glossopharyngeal (IX): ***Special motor*** ***General visceral motor*** ***Visceral sensory*** ***Somatic sensory***	Special branchiomotor fibers arise from cranial end of nucleus ambiguous and supply the stylopharyngeus muscle. Secretomotor fibers arise from inferior salivatory nucleus and proceed as parasympathetic fibers through the tympanic nerve to the otic ganglion; postganglion fibers (lesser petrosal nerve) innervate the parotid gland. Special sensory taste fibers from the posterior third of tongue have their cell bodies in the petrosal ganglion and then project centrally to the solitary tract nucleus. "Visceral" sensory fibers from the posterior tongue, fauces, tonsil, tympanic cavity, eustachian tube, and mastoid cells end in a combined dorsal glossopharyngeal vagal nucleus but with ordinary sensory fibers probably ending in the spinal tract and nucleus of trigeminal nerve. Special visceral afferents from pressure receptors in the carotid sinus mediate decreased heart rate and blood pressure through vagus nerve connections. The nerve emerges from the medulla above the vagus nerve and leaves the skull through the jugular foramen. It runs forward between the internal carotid artery and internal jugular vein and curves over the stylopharyngeus muscle, to end in branches for the tonsils, and mucous membrane and glands of pharynx and pharyngeal part of tongue. The tympanic branch forms the main part of the tympanic plexus, which supplies the tympanic cavity and the lesser petrosal nerve carrying secretomotor fibers for the parotid gland.	***Special motor:*** Stylopharyngeus; elevation of pharynx ***General visceral motor:*** Parotid and mucous glands secretion ***Special sensory:*** Taste posterior third of tongue, and numerous taste buds in vallate papillae ***General visceral sensory:*** General sensation from posterior tongue, fauces, tonsil, tympanic cavity, eustachian tube, and mastoid cells. Carotid body and sinus ***Somatic sensory:*** Outer ear sensation

Nerves and Nuclei in Lateral Dissection

Medial dissection



F. Netter M.D.
C. Machado M.D.

Name and number: Type of fibers	Origin, course, and distribution	Chief functions
Vagus (X): ***Special motor*** ***General visceral motor*** ***Somatic sensory*** ***Visceral sensory*** ***Special sensory***	The dorsal vagal nucleus is a mixture of visceral efferent and afferent cells forming elongated column on each side of midline and extending through the length of the medulla, lateral to the hypoglossal nuclei. From here, preganglionic parasympathetic fibers go to parasympathetic ganglia innervating cardiac and unstriated muscles in the thoracic and abdominal viscera. Motor fibers for striated muscles of larynx and pharynx originate in the midportion of the nucleus ambiguous (ill-defined column of large cells located in the reticular formation). Afferent fibers from visceral receptors have their cell bodies in the inferior vagal (nodose) ganglion and end in the mixed dorsal vagal nucleus. They convey sensation from the pharynx, larynx, trachea, and viscera. However, a few special sensory taste fibers from the epiglottis and the adjacent tongue end in the solitary tract nucleus. General somatic afferents from auricular and meningeal branches with cell bodies in the jugular ganglion end in the spinal tract and nucleus of the trigeminal nerve. The nerve is attached by a series of medullary rootlets located laterally between the olive and inferior cerebellar peduncle. The vagus nerve leaves the skull through the jugular foramen and is soon joined by the cranial part of the accessory nerve to then descend in the neck within the carotid sheath. The vagus nerve continues through the thorax and contributes to cardiac, pulmonary, and esophageal plexuses. It enters the abdomen as the anterior and posterior vagal trunks.	***Special Motor:*** Intrinsic laryngeal muscles and contribute to pharyngeal constrictors ***General visceral motor:*** Parasympathetic supply (movement and secretion) to the heart, the great vessels, trachea, bronchi, and alimentary canal, and associated glands from pharynx almost to left colic (splenic) flexure ***Somatic sensory:*** Parts of auricle, external acoustic meatus, and tympanic membrane meninges of posterior cranial fossa ***General visceral sensory:*** Pharynx, larynx, trachea, and abdominal viscera ***Special sensory:*** Taste from epiglottis and valleculae
Accessory (XI): ***Special motor***	The accessory nerve consists of cranial and spinal roots. Cranial roots arises from cells within the lower end of the nucleus ambiguous and supply intrinsic laryngeal muscles. The spinal roots arise from a group of anterior horn cells in the upper five or six cervical segments (the spinal accessory nucleus) and supply the sternocleidomastoid and trapezius muscles. The cranial root fibers form the internal branch of the accessory nerve and arise as a series of rootlets on the surface of medulla oblongata below, and in line with the glossopharyngeal and vagal nerve rootlets. The spinal rootlets emerge through the lateral white column of the spinal cord and ascend behind the denticulate ligaments and unite to form the external branch of the accessory nerve entering the skull through the foramen magnum behind vertebral artery. Cranial and spinal roots unite for a short distance, before leaving the skull through the jugular foramen. The internal branch joins the vagus nerve. The external branch runs downward and backward through the sternocleidomastoid muscle, then crosses the posterior triangle of neck and ends in the trapezius muscle. It also communicates with branches of spinal nerves C2–C4.	***Special Motor*** ***Internal branch (vagus n.):*** Intrinsic muscles of the larynx via the recurrent laryngeal nerve (except cricothyroid-superior laryngeal nerve) and soft palate (except tensor veli palatine-mandibular division of the trigeminal nerve) ***External branch:*** Sternocleidomastoid and trapezius muscles
Hypoglossal (XII): ***Motor***	The hypoglossal nucleus is a medial column of cells situated in the lower floor of the fourth ventricle and extends the length of the medulla anterior to the central canal in the "closed" part of medulla oblongata. Axons from the nucleus course anteriorly and just lateral to the medial lemniscus and cross the most medial portion of the inferior olive to exit the brainstem in the anterolateral sulcus between the pyramidal tract and the prominence of the inferior olive. The fibers emerge as 10-15 rootlets and fuse to form two bundles that unite as they pass through the hypoglossal canal of the occipital bone. The hypoglossal nerve then runs forward between the internal carotid artery and internal jugular vein and inclines upward into tongue. It is joined by a filament from spinal nerve C1, but this soon leaves to form the superior root (descendens hypoglossi) of the ansa cervicalis.	***Somatic motor:*** Intrinsic and extrinsic muscles of the tongue

Cranial Nerve I: Olfactory Nerve

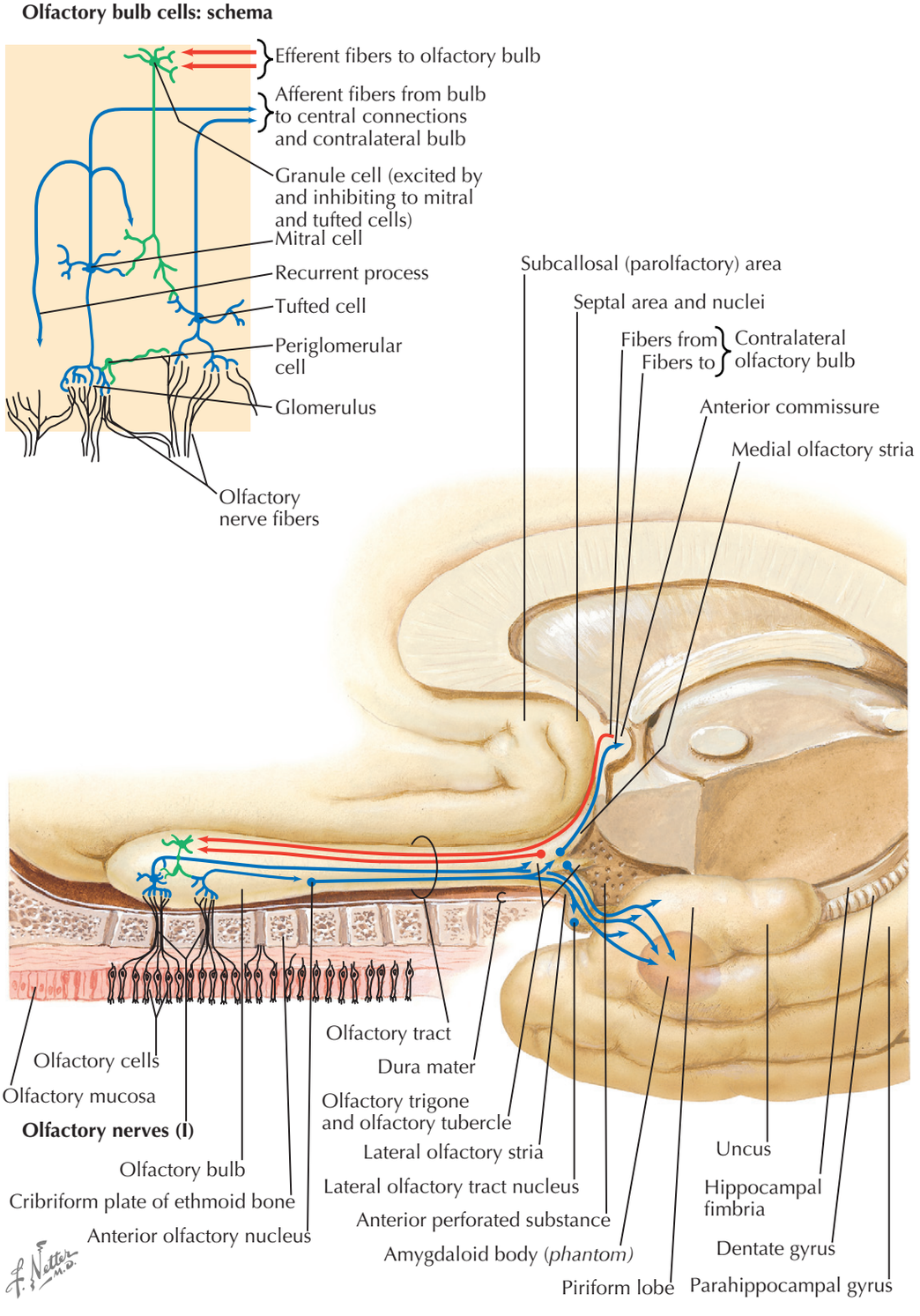
Anatomy

The olfactory nerves are concerned with the special sense of smell. The nerve fibers are the central processes of bipolar nerve cells located in the olfactory epithelium, which covers most of the superior-posterior nasal septum and the lateral wall of the nasal cavity. The unmyelinated peripheral olfactory fibers aggregate into approximately 20 slender olfactory bundles that make up the olfactory nerve. The nerve traverses the ethmoidal cribriform plate surrounded by finger-like extensions from the dura mater and arachnoid to end in the "glomeruli" of the homolateral olfactory bulb. Within the bulb, these fibers synapse with second-order neurons called mitral and tufted cells whose axons constitute the olfactory tract that courses along the frontal lobe base. It then divides into the medial and lateral olfactory striae on either side of the anterior perforated substance and projects directly into the primary olfactory cortex within the temporal lobe. This direct pathway without a central sensory relay site (such as in the thalamic nuclei) is unique among the cranial nerves. Although most of the olfactory tract fibers have ipsilateral central connections, some fibers decussate in the anterior commissure, making the cortical representation of smell bilateral. The human primary olfactory cortex includes the uncus, hippocampal gyrus, amygdaloid complex, and entorhinal cortex.

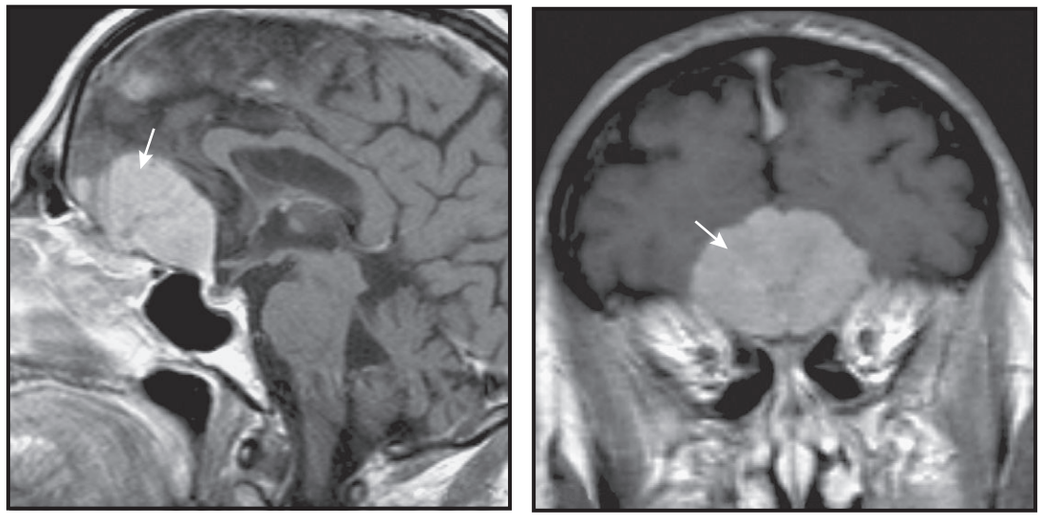
Olfactory Nerve Disorders

Anosmia is not always apparent to the patient, and due to the close association of flavor perception and olfaction, may be reported as altered taste rather than loss of smell. Bilateral anosmia is more common and usually of benign nature, whereas unilateral anosmia should raise suspicion for a more serious disorder, such as an olfactory groove meningioma or frontal basal tumor. The most common cause of anosmia is nasal and paranasal sinus infection with inflammation and is referred to as transport or conductive olfactory disorders. Post-traumatic olfactory dysfunction is the cause for 20% of patients with anosmia and is the result of olfactory nerve shearing as it passes through the cribriform plate. In more substantial damage, the olfactory nerve is torn by fractures involving the cribriform plate, with cerebrospinal fluid rhinorrhea and possible meningeal infection. Post-traumatic anosmia or hyposmia may be either unilateral or bilateral. Tumors of the olfactory groove affect the olfactory bulb and tract. The most common are olfactory groove meningiomas, which are usually histologically benign tumors causing mostly unilateral, and occasionally bilateral, gradual olfactory dysfunction. Other tumors include sphenoid and frontal osteomas, pituitary tumors, and nasopharyngeal carcinomas. Unless specifically tested, a presentation of anosmia is unusual because of generally unilateral involvement and slow tumor growth with slow decline in olfactory function. Once such tumors are large enough (>4 cm in diameter), they cause pressure on the frontal lobes and the optic tracts, with symptoms of headaches, visual disturbances, personality changes, and memory impairment. Very large olfactory groove tumors on rare occasion cause ipsilateral optic atrophy by exerting direct pressure on the optic nerve with

Olfactory Pathways



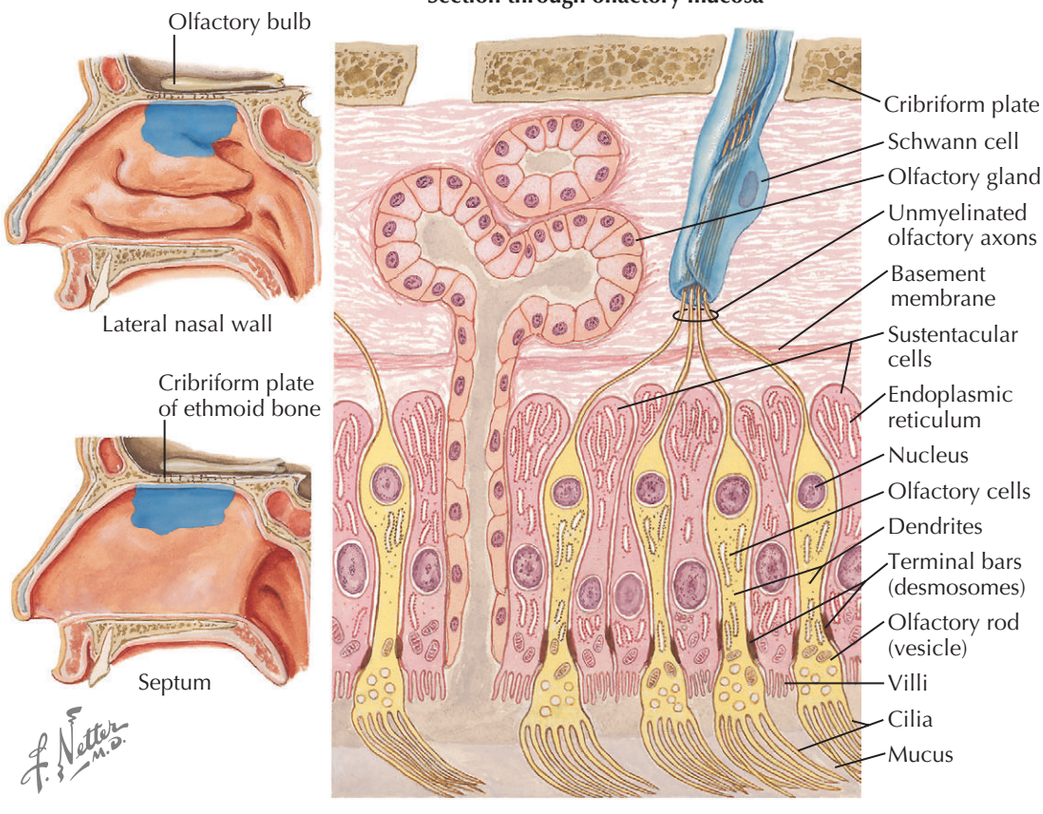
Olfactory Receptors



Subfrontal meningioma. T1-weighted, gadolinium-enhanced sagittal and coronal MR images show a large enhancing skull-based mass displacing and compressing the olfactory apparatus.

Cranial Nerve I: Olfactory Nerve *(Continued)*

contralateral papilledema from increased intracranial pressure. The finding of ipsilateral optic atrophy, contralateral papilledema, and ipsilateral anosmia is known as the Foster-Kennedy syndrome. Esthesioneuroblastomas arise from the upper nasal cavity and manifest with nasal obstruction and epistaxis. Rarely, they involve the orbit and cause diplopia, visual loss, proptosis, and periorbital swelling. Anosmia is an early sign of neurodegenerative processes, particularly Parkinson disease, Alzheimer disease, and Lewy body dementia. It frequently precedes other neurologic signs, such as motor findings or cognitive changes. Olfactory discrimination is affected by many medications thought to disrupt the physiologic turnover of receptor cell and includes opiates, anticonvulsants, and various immunosuppressive agents. Congenital or hereditary anosmia is rare. Kallmann syndrome consists of congenital hypoplasia or absence of the olfactory bulbs and hypogonatropic hypogonadism.



Olfactory Receptors

Receptors responsible for the sense of smell are found in the patch of olfactory epithelium that is located on the superior-posterior nasal septum and the lateral wall of the nasal cavity. In addition to the receptor cells, this epithelium contains olfactory (Bowman's) glands and sustentacular cells, both contribute to the mucous secretion that coats the epithelial surface and makes odorants soluble. The sustentacular cells also act as supporting cells for the slender olfactory receptors.

Olfactory receptor cells may be considered specialized, primitive-type, bipolar neurons. Their nuclei are located at the base of the epithelial layer. Basal stem cells located along the basement membrane differentiate into olfactory receptors or supporting cells, replenishing the olfactory epithelium about every 2 weeks. From the nuclear region of the olfactory receptor cell, a thin dendritic process extends toward the surface of the epithelium. At its apical end, this process widens into an olfactory rod, or vesicle, from which 10 to 15 motile cilia project into the mucous layer covering the epithelium. Desmosomes at the base of the olfactory vesicle provide a tight seal between the membranes of olfactory and sustentacular cells, thus preventing external substances from entering the intercellular spaces. At its base, the olfactory receptor cell narrows and gives rise to a fine (0.2 to 0.3 μm) unmyelinated axon. Large numbers of these axons converge to run together within a single Schwann cell sheath. The fibers then penetrate the cribriform plate to collectively form the olfactory nerve. In humans, this nerve contains on the order of 100 million axons.

Odorant Transduction. The cell membranes of the olfactory receptor cells are able to convert chemical odorants into an electrical signal by activation of a G-protein–coupled protein receptor cascade that activates the enzyme adenylate cyclase, which produces cyclic adenosine monophosphate (cAMP) as a second messenger. cAMP then changes the structure of the cell membrane channel proteins to an open state. The channel is permeable to cations that flow from the nasal mucosa into the cell. The negative resting membrane potential (−70 mV) is shifted to a more positive value. Once a certain threshold is reached, the analog sensor

Cranial Nerve I: Olfactory Nerve *(Continued)*

potential is converted to a digital action potential, which is conducted via the axon of the olfactory cell to the brain.

Sense of Smell. As with taste fibers, which may respond to a variety of taste stimuli, individual olfactory nerve fibers respond to a number of different odors. Humans differentiate the odors of thousands of chemicals; nevertheless, it has not been possible to identify a set of primary odor qualities analogous to the four primary tastes.

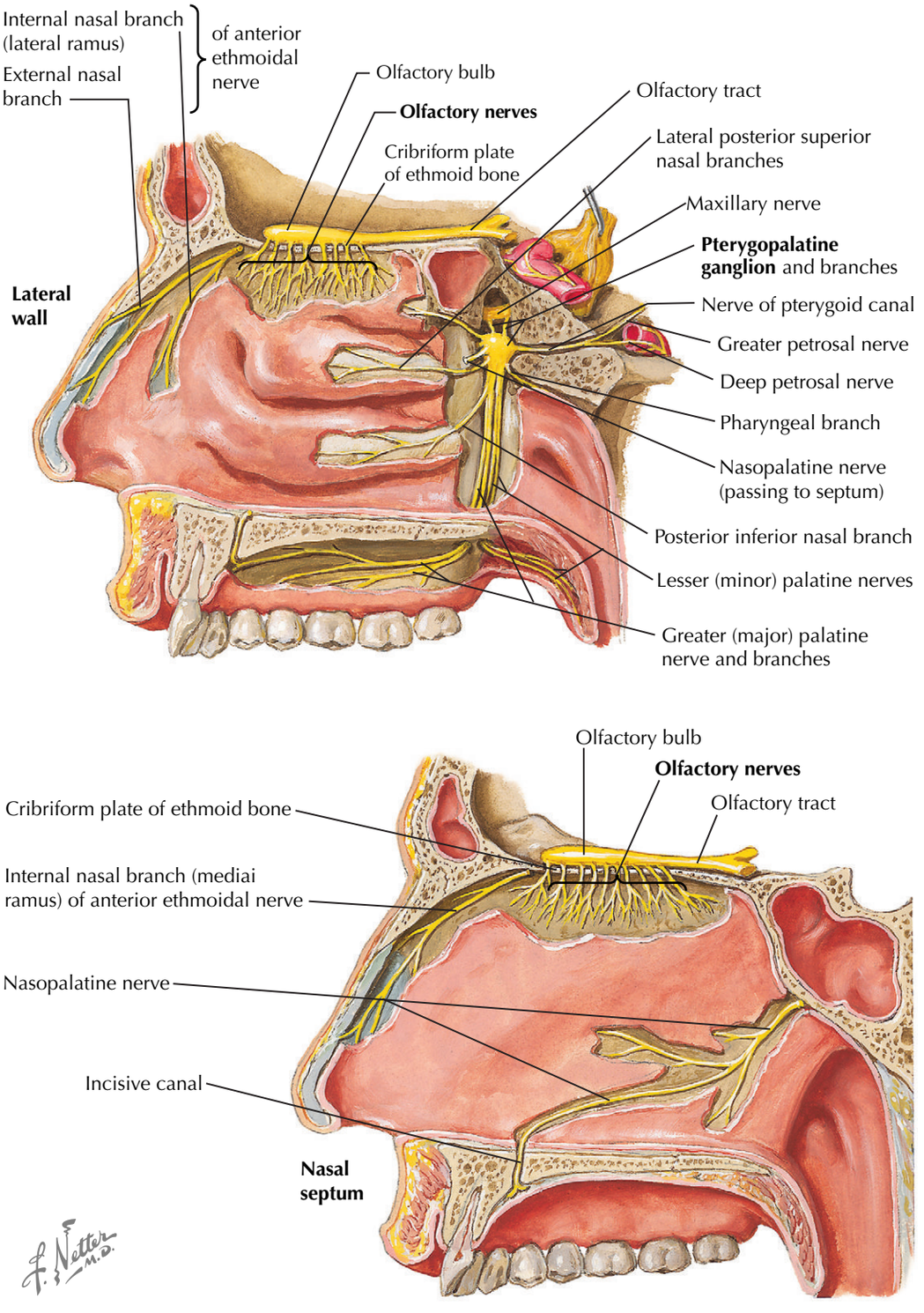
OLFACTORY PATHWAY

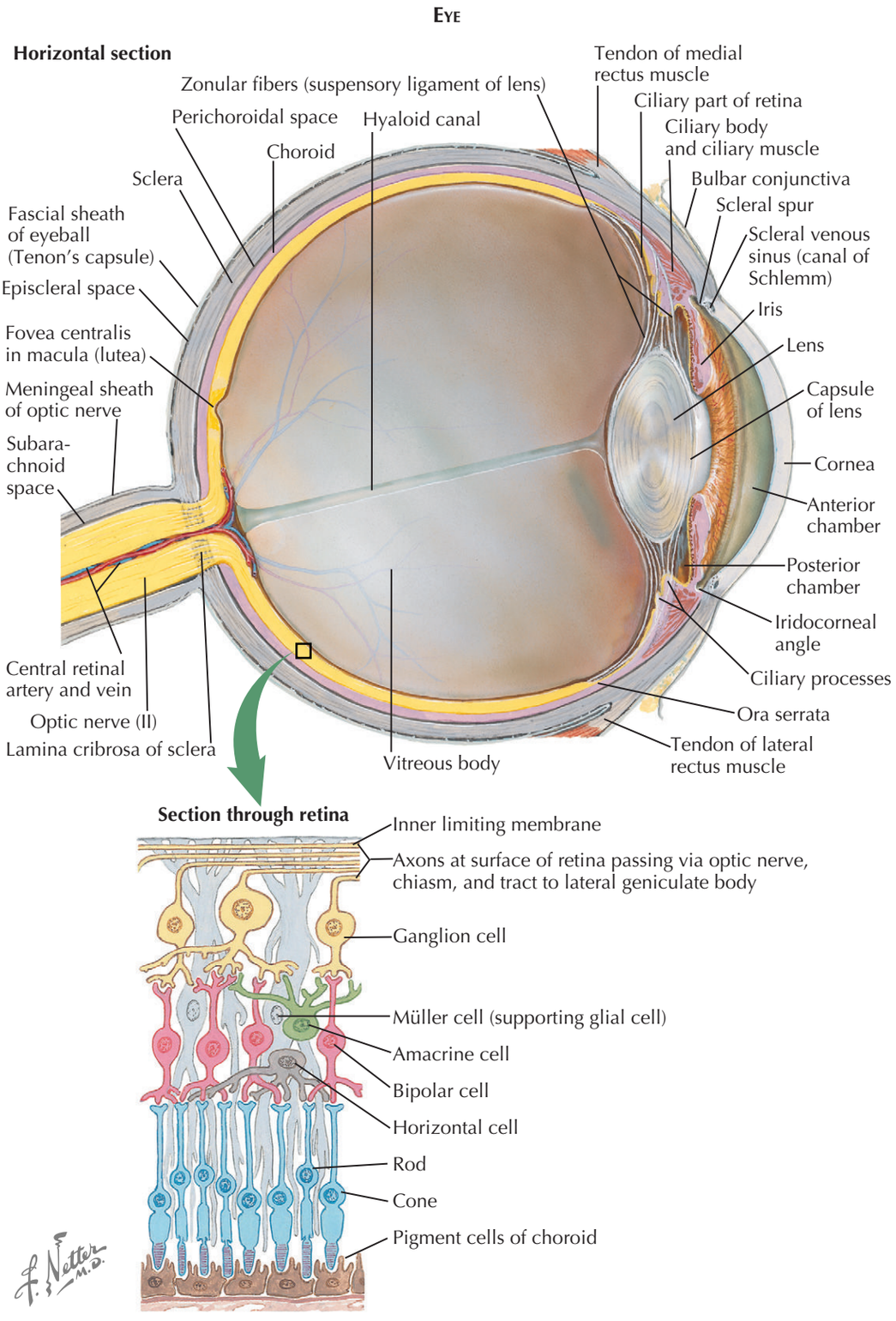
Olfactory Bulb. About 100 million olfactory afferent fibers enter the olfactory bulb, a flattened, oval mass lying near the lateral margin of the cribriform plate of the ethmoid bone. The incoming olfactory fibers coalesce in the outermost layer of the olfactory bulb to form presynaptic nests, or glomeruli. Each glomerulus is composed of about 25,000 receptor cell axon terminals. The terminals synapse and excite the dendrites of mitral and tufted cells, which are the second-order neurons in the olfactory bulb. Each mitral cell sends its dendrite to only a single glomerulus, while each tufted cell sends dendrites to several glomeruli. Olfactory afferents within the glomeruli also activate periglomerular cells, which then inhibit mitral and tufted cells. Further inhibition arises at the dendrodendritic contacts between mitral and tufted cells and the processes of granule cells, which lie deeper still within the olfactory bulb. These contacts are an example of two-way synaptic feedback connections: the granule cells are excited by mitral and tufted cells and, in turn, inhibit them. Integration of olfactory information occurs when excitation is spread throughout the multiple-branched granule cell processes, and also when granule cells are excited by the centrifugal efferent fibers that reach the olfactory bulb from higher centers. Another factor in this highly complex integrative process is the recurrent collaterals of mitral cells that appear to excite mitral, tufted, and granule cells.

There is a dramatic transformation in the response to odors between the glomeruli and the mitral cells. The glomeruli respond to different substances based on their physiochemical properties, whereas mitral cells respond to groups of substances that evoke subjective sensations.

Olfactory Tract and Central Connections. The axons of mitral and tufted cells form the olfactory tract, through which they project to the olfactory trigone and into the lateral and medial olfactory striae, establishing a complex pattern of central connections. Some mitral and tufted cell axons terminate in the anterior olfactory nucleus (a continuation of the granule cell layer throughout the olfactory tract) and olfactory tubercle, the sites of origin of the efferent fibers projecting to both the ipsilateral and contralateral olfactory bulbs. Other axons from the lateral stria reach the piriform lobe of the temporal cortex and terminate in the amygdala (amygdaloid body), the septal nuclei, and the hypothalamus.

Olfactory Bulb and Nerve





Cranial Nerve II: Optic Nerve

HUMAN EYE

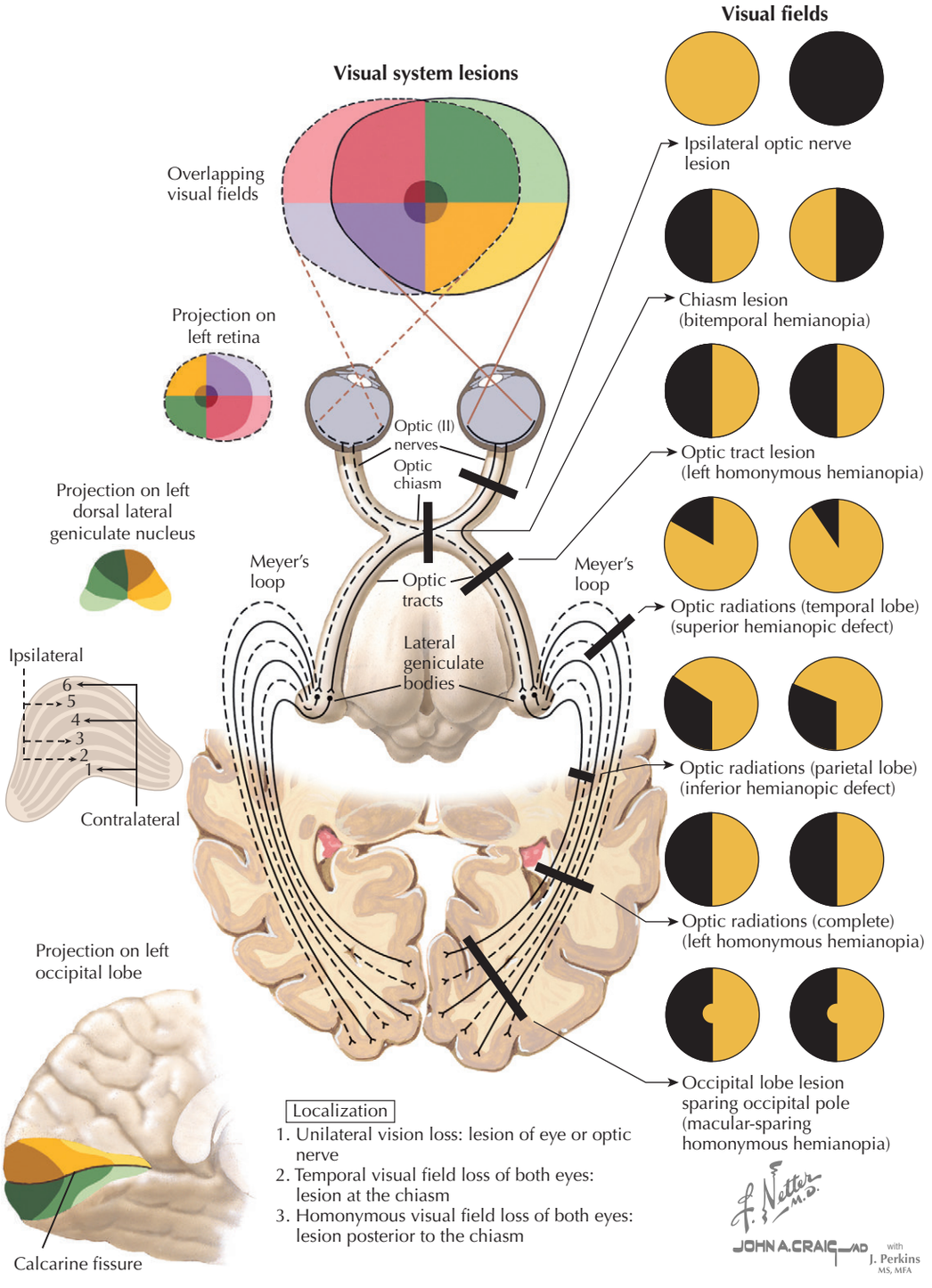
The human eye is a highly developed sense organ containing numerous accessory structures that modify visual stimuli before they reach the photoreceptors. The *extraocular muscles* move the eyeball, thus causing the image of the object viewed to fall on the *fovea*, the retinal area of highest visual acuity. The shape of the eyeball, its surfaces, and the refractive properties of the *tear film*, *cornea*, *lens*, and *aqueous* and *vitreous humors* assist in focusing the image on the retina. To allow viewing of near and far objects, this focus can be adjusted by the action of the *ciliary muscle*, which changes the shape of the lens. The intensity of the light reaching the retina is controlled by the muscles of the *iris*, which vary the size of the *pupillary aperture*. Incident light must traverse most of the retinal layers before it reaches the *photoreceptor cells* lying in the outer part of the retina. Beyond the photoreceptors is a layer of *pigment cells*, which eliminates back reflections by absorbing any light passing through the photoreceptor layer.

RETINA

The retina has several distinct layers. *Rods* and *cones* form synaptic connections with bipolar and horizontal cells. *Bipolar cells* are relay neurons that transmit visual signals from the inner to the outer plexiform layer of the retina; *horizontal cells* are interneurons activated by rods and cones and send their axons laterally to act on neighboring bipolar cells. As a result of the actions of horizontal cells, bipolar cells have concentric receptive fields; that is, their membrane potentials are shifted in one direction by light reaching the center of their receptive field, and in the opposite direction by light reaching the surrounding area. Neither bipolar nor horizontal cells generate action potentials; all information is transferred by changes in membrane potential, which spread passively through the cell bodies and axons.

The processes of bipolar cells that reach the outer plexiform layer form synapses with ganglion cells and amacrine cells. *Ganglion cells* are output neurons whose

Cranial Nerve II and Visual Pathways

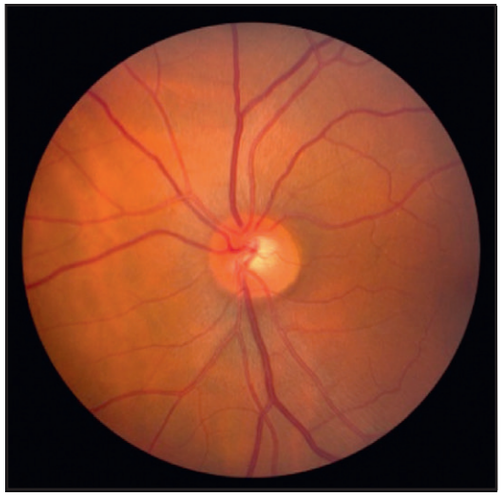


Cranial Nerve II: Optic Nerve *(Continued)*

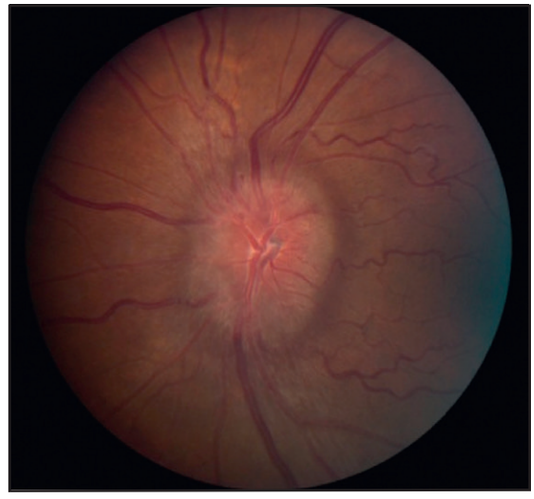
axons comprise the optic nerves and optic tracts; *amacrine cells* are interneurons. Unlike other retinal neurons, both amacrine and ganglion cells generate action potentials.

The photoreceptor cells are called rods and cones because of the shapes of their outer segments. *Rods* function as receptors in a highly sensitive, monochromatic visual system, whereas *cones* serve as receptors in the color vision system, which is less sensitive but more acute. Both receptors, however, are activated in a similar manner—they are hyperpolarized by photons of light falling directly upon them. For example, the detection of light in the rod begins with the absorption of photons by the visual pigment, *rhodopsin*. Rhodopsin is a combination of the protein, opsin and the *cis* isomer of retinine, a compound derived from vitamin A. It is located within the membranous lamellae of the rod's outer segment, a highly modified cilium associated with a typical basal body. Upon the absorption of a photon, rhodopsin is converted to *lumirhodopsin*, which is unstable and changes spontaneously to *metarhodopsin*, which is then degraded by a chemical reaction known as bleaching. Rhodopsin lost by this bleaching process is restored to its active form by enzymatic reactions that require metabolic energy and vitamin A. After a brief time lag, the absorption of a photon leads to changes in the ionic permeability of the membrane of the outer segment. The change in the receptor membrane triggered in the rod by light absorption is not the typical increase in ion permeability most sensory receptors undergo when activated; rather, there is a decrease in the permeability of the outer segment membrane to sodium ions (Na^+). In the absence of light, this permeability is relatively high, and there is a steady inward flow of Na^+ (the current flow resulting from this ionic movement, known as the "dark current," keeps the entire rod in a depolarized state). When light absorption provokes a decrease in Na^+ permeability, the dark current is cut off and the rod becomes more hyperpolarized. This hyperpolarization influences the synaptic action of the rod on horizontal and bipolar cells. Polarization changes in one rod may also spread to neighboring receptors via electrical synapses. Any photon that is successfully absorbed by photopigment produces the same electrochemical result, regardless of

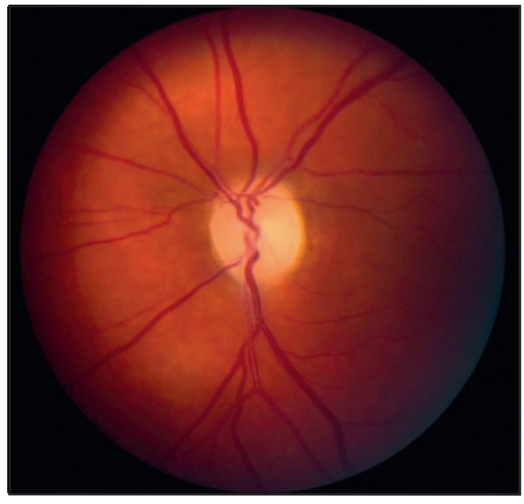
Optic Nerve Appearance



Normal optic nerve



Swollen optic nerve



Pale optic nerve

Cranial Nerve II: Optic Nerve *(Continued)*

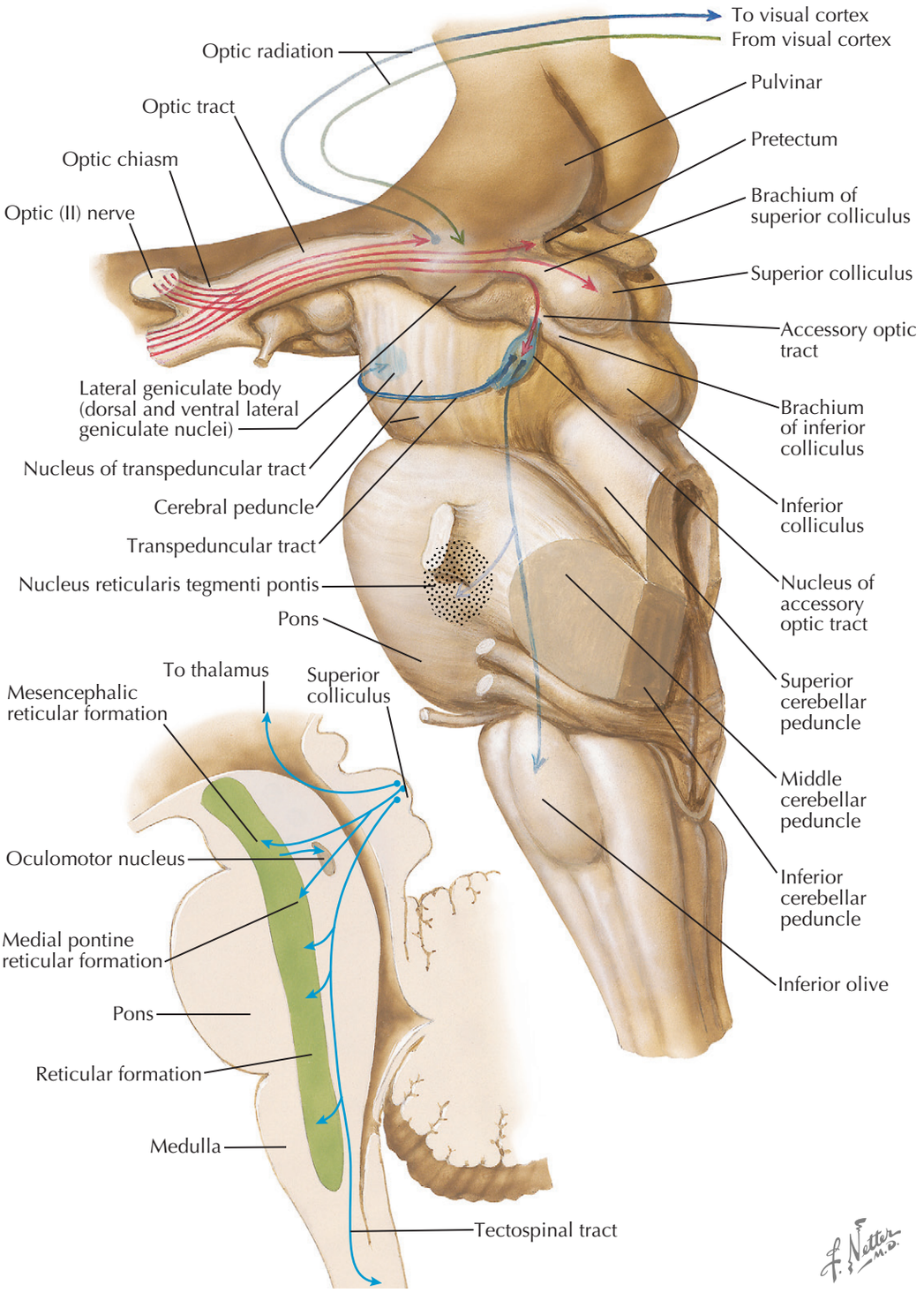
the wavelength of that photon. However, the probability that a photon will be absorbed by photopigment varies considerably with the wavelength of the incident light, and rhodopsin has a maximal absorbency for light with a wavelength of 500 nm. Cones may contain one of three different photopigments, with a maximum absorbency at 445 nm (blue), 535 nm (green), and 570 nm (red). Cone pigments all contain *cis* retinine but have different forms of opsin, which modify the light absorption pattern. By analyzing the relative activity produced by the three types of cones, the central nervous system (CNS) is able to determine the wavelength of the incident light, and a sensation of color vision results.

RETINOGENICULOSTRIATE VISUAL PATHWAY

In mammals, most retinal ganglion cells send excitatory or inhibitory impulses via the *optic nerves* and *tracts* to the *dorsal lateral geniculate nucleus* of the lateral geniculate body of the thalamus, from where retinal information is relayed to the primary visual cortex via the *geniculostriate projection*, or *optic radiations*. In man, this cortical area covers both walls of the posterior calcarine fissure and adjacent parts of the occipital pole (Brodmann's area 17). The transmission of information from retina to visual cortex is *topographically organized*. Stimuli in the right half of the visual field activate neurons in the left half of each retina. Ganglion cells from these areas project to the left lateral geniculate body, which then projects to the left visual cortex. Input from both eyes is relayed by neurons in different layers of the lateral geniculate body. Similarly, stimuli in the left half of the visual field are relayed to the right visual cortex.

The upper and lower visual fields are also topographically mapped onto the lateral geniculate body and visual cortex. The upper field is represented in the lateral parts of the lateral geniculate nuclei and the inferior portions of the visual cortex, and the lower visual field is represented in the corresponding medial and superior regions. The *macula* (central visual field) is represented in the central parts of the lateral geniculate nuclei and the posterior visual cortex, and in the *peripheral retina*, in the peripheral parts of the lateral geniculate nuclei, and the anterior visual cortex. The

Retinal Projections to Thalamus, Midbrain, and Brainstem



Cranial Nerve II: Optic Nerve *(Continued)*

fovea, the central spot of the macula, is represented by a proportionally larger cortical area than the periphery of the retina.

NEUROLOGIC DEFICITS OF THE RETINA AND OPTIC NERVE

Neurologic deficits in the visual system can be localized by determining the type and extent of the resultant visual field deficit. Retinal and optic nerve damage produces vision loss in the affected eye. Most retinal lesions will be visible on ophthalmoscopy of the ocular fundus. Optic nerve lesions will produce central scotomas and visual field defects that might respect the horizontal meridian. If the optic nerve is affected in its anterior portion (i.e., where it is visualized on ocular funduscopy), one may see swelling of the optic nerve head during the acute phase of injury. If the retrobulbar portion of the optic nerve is the site of injury, then the optic nerve head (so-called "optic disc") will look normal acutely. After several weeks, injury to the optic nerve anywhere along its course will manifest as relative pallor of the optic nerve head. Unilateral or asymmetric bilateral optic nerve damage will cause a relative afferent pupillary defect (less transmission of light along the more damaged optic nerve to the brain centers controlling pupillary constriction).

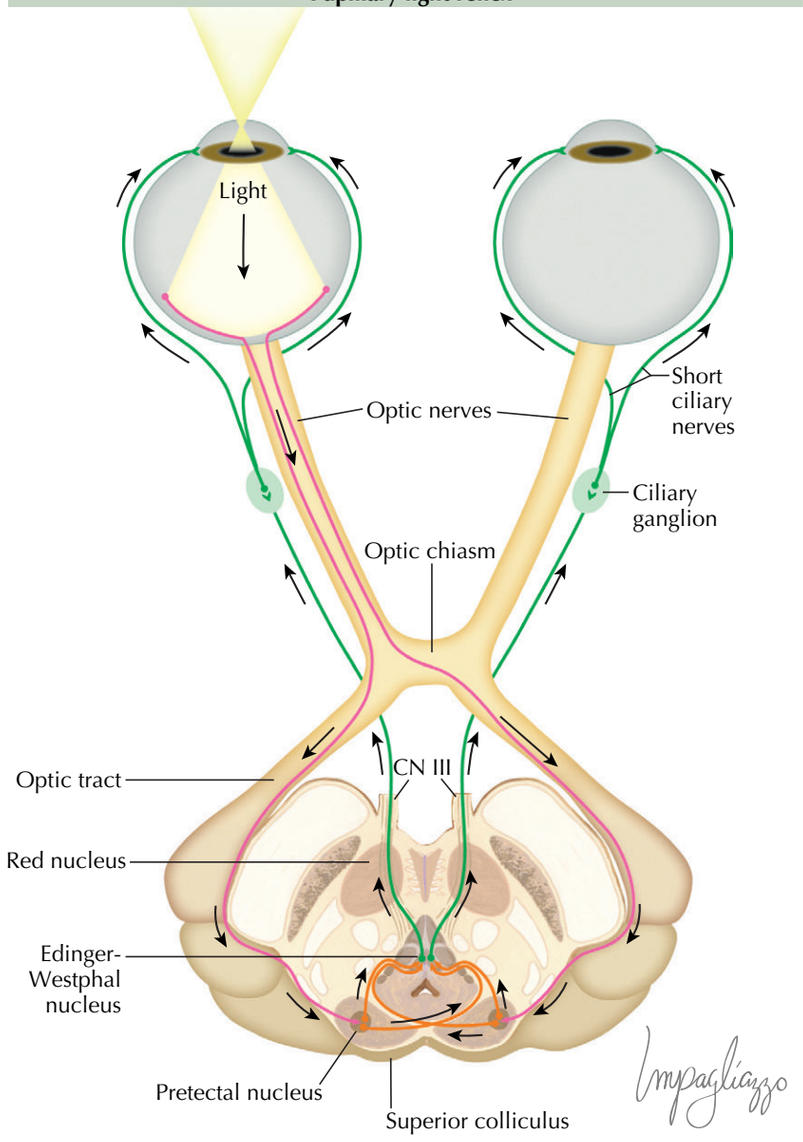
CHIASMAL AND POSTCHIASMAL NEUROLOGIC DEFICITS

Lesions at the optic chiasm will result in bitemporal hemianopsia, caused by damage to the fibers from the nasal segment of both retinas. Interruption of the optic tract (that portion of the visual pathways between the chiasm and lateral geniculate body) results in a contralateral homonymous hemianopsia. Similarly, lesions of the optic radiations or striate cortex will cause partial or complete contralateral homonymous hemianopic defects.

VISUAL SYSTEM: RETINAL PROJECTIONS

The main retinal projection is to the *dorsal lateral geniculate nucleus*, which then projects to the visual cortex. The retinogeniculostriate system thus formed is

Pupillary light reflex



Left relative afferent pupillary defect

No light; both pupils dilate

Light in right eye; both pupils constrict

Light in left eye; both pupils dilate

CRANIAL NERVE II: OPTIC NERVE *(Continued)*

the basis for essentially the entire visual consciousness in man.

Other optic nerve fibers terminate within the *superior colliculus*. This multilayered structure plays an important role in orienting the reactions that shift the head and eyes in order to bring an object of interest into the center of the visual field. In addition to direct optic nerve input, the superior colliculus receives indirect visual input via the visual cortex. As is the case throughout the visual system, this input is topographically organized so that each point within the colliculus corresponds to a particular region within the visual field. Collicular neurons tend to respond best to interesting or moving stimuli, and the discharge of neurons in the deeper layers of the colliculus is closely related to the orienting movements of the eyes evoked by such stimuli.

The deeper collicular layers are the source of several efferent projections. One group of fibers crosses the midline and runs caudally, sending terminals to the brainstem reticular formation and then continuing on to cervical and thoracic levels as the *tectospinal tract*; these fibers are probably involved in the orienting movements of the head and body. A second group of fibers projects to the posterior thalamus (pulvinar), which then projects to the cortical association areas. Fiber projections responsible for eye movements relay in the mesencephalic reticular formation below the superior colliculus (vertical eye movements), and in the paramedian pontine reticular formation (horizontal eye movements).

PUPILLARY LIGHT REFLEX AND THE ACCOMMODATION REFLEX

The *pretectum*, like the superior colliculus, receives visual information from optic nerve fibers not destined to synapse in the lateral geniculate bodies. This area is involved in the pupillary light reflex (which regulates the size of the pupil) and the accommodation reflex (which controls the degree of curvature of the lens). The former is a subcortical reflex and relays in the accessory oculomotor (Edinger-Westphal) nucleus, whereas the latter involves pathways through the cerebral cortex. In the pupillary light reflex, afferent pupillary fibers leave the optic tract before the lateral geniculate bodies, travel in the brachium of the superior colliculus, and synapse in the pretectal nuclei (explaining why lesions of the geniculate bodies, the optic radiations, or the visual cortex do not affect the pupillary reactivity, and why lesions of the brachium of the superior colliculus can cause a relative afferent pupillary defect without causing a visual field defect). Both pretectal nuclei receive input from both eyes, and each sends axons to both Edinger-Westphal nuclei. Parasympathetic fibers for pupillary constriction leave the Edinger-Westphal nucleus and travel along the ipsilateral third cranial nerve to the ipsilateral ciliary ganglion within the orbit. The postganglionic parasympathetic fibers innervate the pupillary constrictor muscle and the ciliary muscle for accommodation.

Oculomotor (III), Trochlear (IV), and Abducens Nerves (VI)

Cranial Nerves III, IV, and VI (Oculomotor, Trochlear, and Abducens)

Oculomotor Nerve

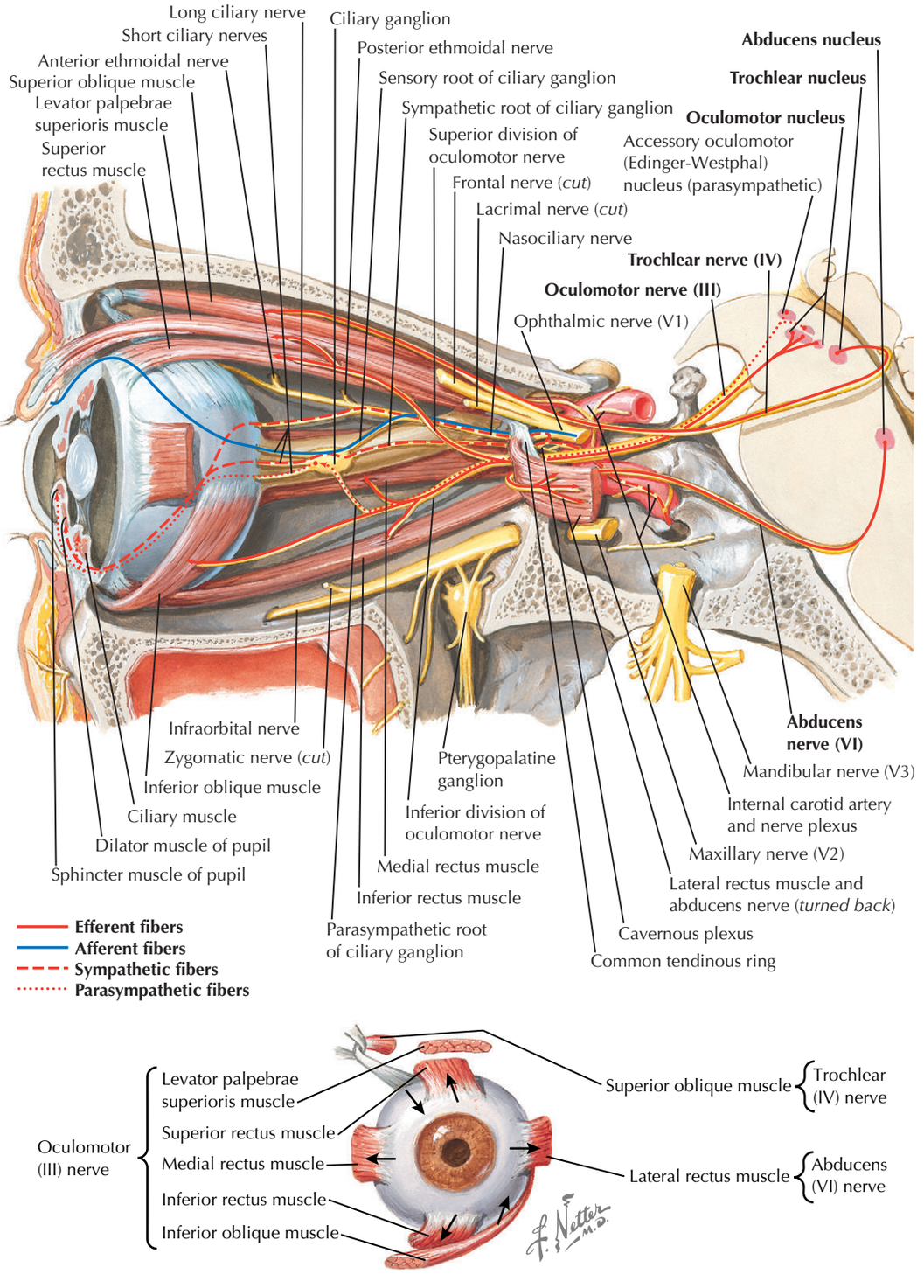
The oculomotor nerve carries somatic motor fibers to the levator palpebrae superioris muscle and to the medial, superior, and inferior rectae muscles, and to the inferior oblique muscle. It also conveys important parasympathetic fibers to intraocular structures, such as the sphincter pupillae and ciliary muscles, and is joined by sympathetic fibers from the internal carotid plexus, which are distributed with its branches. Some oculomotor proprioceptive fibers may reach the midbrain through the oculomotor nerve; most of them join the ophthalmic branch of the trigeminal nerve via its communications with the oculomotor nerve.

Oculomotor Nuclei. The somatic and parasympathetic efferent fibers in the oculomotor nerve are the axons of cells located in the complex oculomotor nuclei situated anterolateral to the upper end of the cerebral aqueduct. The nuclei are composed of groups of large and small multipolar cells. The main groups of large cells are arranged in two columns of *posterolateral*, *intermediate*, and *anteromedial nuclei*, one on each side of the midline, which control the rectus and oblique extraocular muscles. A single *median nucleus*, composed of similar cells and partly overlying the caudal and posterior aspects of the bilateral columns, controls the levator muscles of the upper eyelids. Cranial to the median nucleus, and also partially overlying the posterior aspects of the main bilateral columns, are two narrow, wing-shaped nuclei, which are interconnected across the midline at their cranial ends—the *accessory (autonomic) nuclei (Edinger-Westphal)*. They are the source of parasympathetic preganglionic fibers for the ciliary ganglion. The multiple subnuclei of the oculomotor nucleus each project ipsilaterally via the oculomotor nerve to the individual muscles that they innervate, with the exception of the superior rectus subnucleus, which projects contralaterally via the contralateral oculomotor nerve to the contralateral superior rectus muscle.

Oculomotor Nerve. The axons from the bilateral oculomotor nuclear cells form minute bundles, which run through the mesencephalic tegmentum, traversing the red nuclei to emerge from the mesencephalic oculomotor sulcus as the oculomotor nerve rootlets.

Each *oculomotor nerve* runs forward between the posterior cerebral and superior cerebellar arteries and lateral to the posterior communicating artery in the interpeduncular subarachnoid cistern. It pierces the arachnoid and dura mater in the angle between the free and attached margins of the tentorium cerebelli to enter first the roof of the cavernous sinus and then its lateral wall. Continuing forward above the trochlear nerve, the oculomotor nerve divides into superior and inferior rami as it enters the orbit through the superior orbital fissure.

The smaller *superior division* supplies the superior rectus muscle and the main superficial (voluntary, or striated, muscular) lamina of the levator palpebrae superioris. The deep lamina is a tenuous layer of involuntary, or unstriated, fibers—the superior tarsal muscle; a similar but even more tenuous inferior tarsal muscle is present in the lower eyelid, and both these tarsal muscles are innervated by sympathetic fibers. The larger *inferior division* supplies the medial and inferior recti and the inferior oblique muscles.



Ciliary Ganglion

The ciliary ganglion is tiny and lies in the posterior part of the orbit between the optic nerve and the lateral rectus muscle. Only the first of its three roots is constant because the sensory and/or sympathetic roots may bypass the ganglion.

Motor Root. The ciliary ganglion is the relay station for preganglionic *parasympathetic fibers*, which originate in the accessory (autonomic) oculomotor nucleus and reach the ganglion through a short offshoot from the oculomotor branch to the inferior oblique muscle. The postganglionic fibers form the 12 to 20 delicate *short*

Cranial Nerves III, IV, and VI (Oculomotor, Trochlear, and Abducens) *(Continued)*

ciliary nerves that penetrate the sclera around the optic nerve and continue forward in the perichoroidal space to supply the ciliaris and sphincter pupillae muscles and the intraocular vessels.

The sensory and sympathetic roots of the ciliary ganglion are derived from the nasociliary nerve and the internal carotid vascular nerve plexus, but they do not always join the ganglion. Instead, their fibers may reach the eye by joining the ciliary nerves directly, while the *sympathetic fibers* (already postganglionic after relaying in the superior cervical trunk ganglia) may follow the ophthalmic artery and its branches to their destinations. The *sensory fibers* convey impulses from the cornea, iris, and choroid and the intraocular muscles.

TROCHLEAR NERVE

The trochlear nerve is slender, and its nucleus of origin is located in the midbrain just caudal to the oculomotor nuclei. The trochlear fibers curve posterolaterally and slightly caudally around the cerebral aqueduct to reach the upper part of the superior medullary velum; here the nerve fibers from opposite sides decussate before emerging on either side of the frenulum veli, below the inferior colliculi. No other cranial nerves emerge from the dorsal aspect of the brainstem.

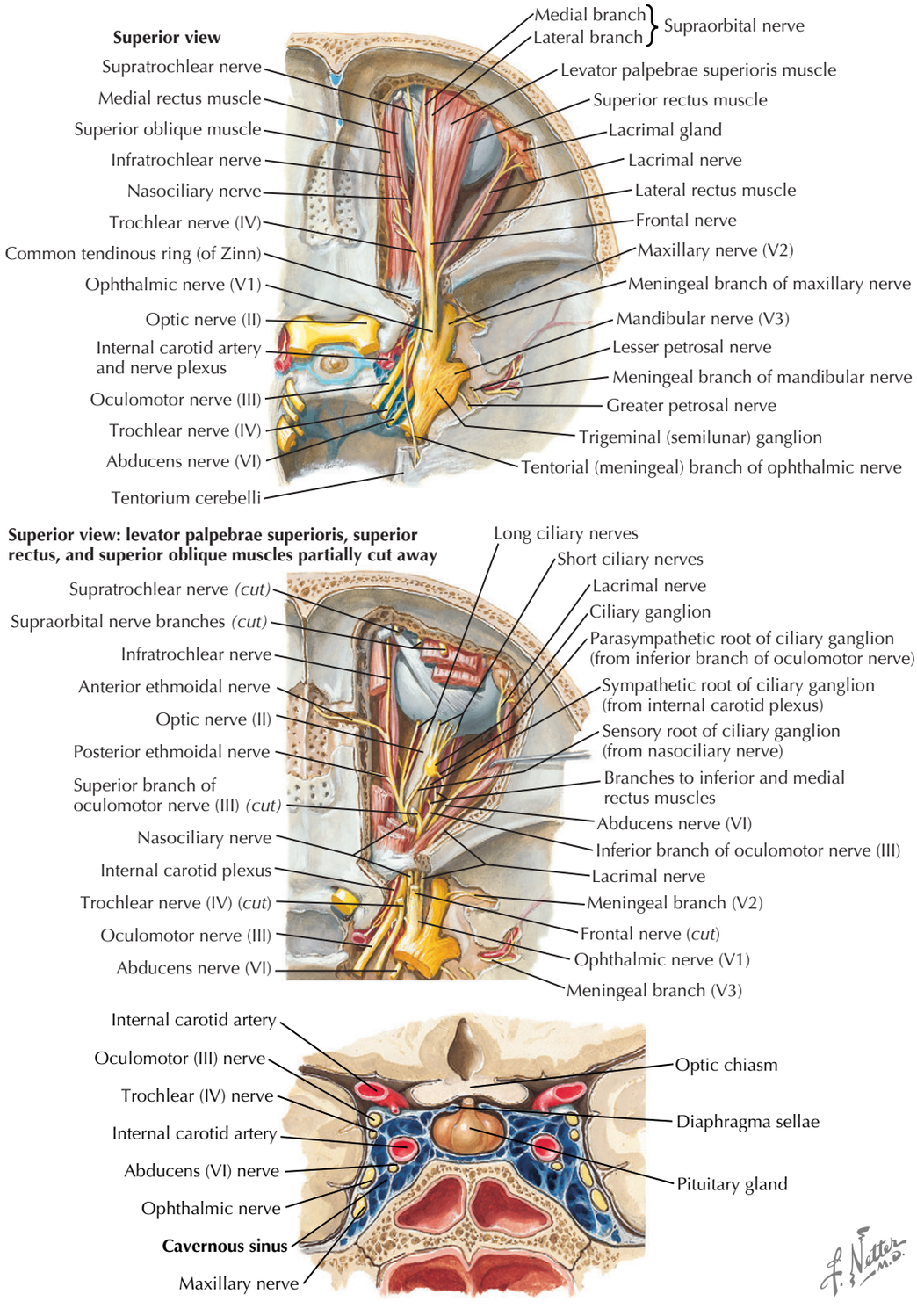
Each trochlear nerve winds forward around the midbrain below the free edge of the tentorium cerebelli, passes between the superior cerebellar and posterior cerebral arteries and above the trigeminal nerve, and pierces the inferior surface of the tentorium near its attachment to the posterior clinoid process to run forward in the lateral wall of the cavernous sinus between the oculomotor and ophthalmic nerves. The nerve enters the orbit through its superior fissure, immediately lateral to the common annular tendon, and passes medially between the orbital roof and the levator palpebrae superioris to supply the *superior oblique muscle*. Proprioceptive fibers are transferred through a communication with the ophthalmic nerve to the trigeminal nerve. The trochlear nerve usually receives sympathetic filaments from the internal carotid nerve plexus.

ABDUCENS NERVE

The abducens nerve arises from the abducens nucleus, which is located in the pons, subjacent to the facial colliculus in the upper half of the floor of the fourth ventricle. The nucleus is encircled by fibers of the homolateral facial nerve. The abducens nerve fibers pass forward to emerge near the midline through the groove between the pons and the pyramid of the medulla oblongata. Each abducens nerve then inclines upward in front of the pons, usually behind the inferior cerebellar artery. Near the apex of the petrous part of the temporal bone, the nerve bends sharply forward above the superior petrosal sinus to enter the cavernous sinus, where it lies adjacent to the internal carotid artery. There the abducens may transfer proprioceptive fibers to the ophthalmic branch of the trigeminal nerve and receive sympathetic filaments from the internal carotid nerve plexus. The abducens nerve enters the orbit through the superior orbital fissure, within the common annular tendon, and ends by supplying the *lateral rectus muscle*.

The abducens has a relatively long intracranial route in the posterior cranial fossa and cavernous sinus. Consequently, it is vulnerable to increases in intracranial pressure and to pathologic or traumatic lesions affecting nearby parts of the brain, skull, or sinus.

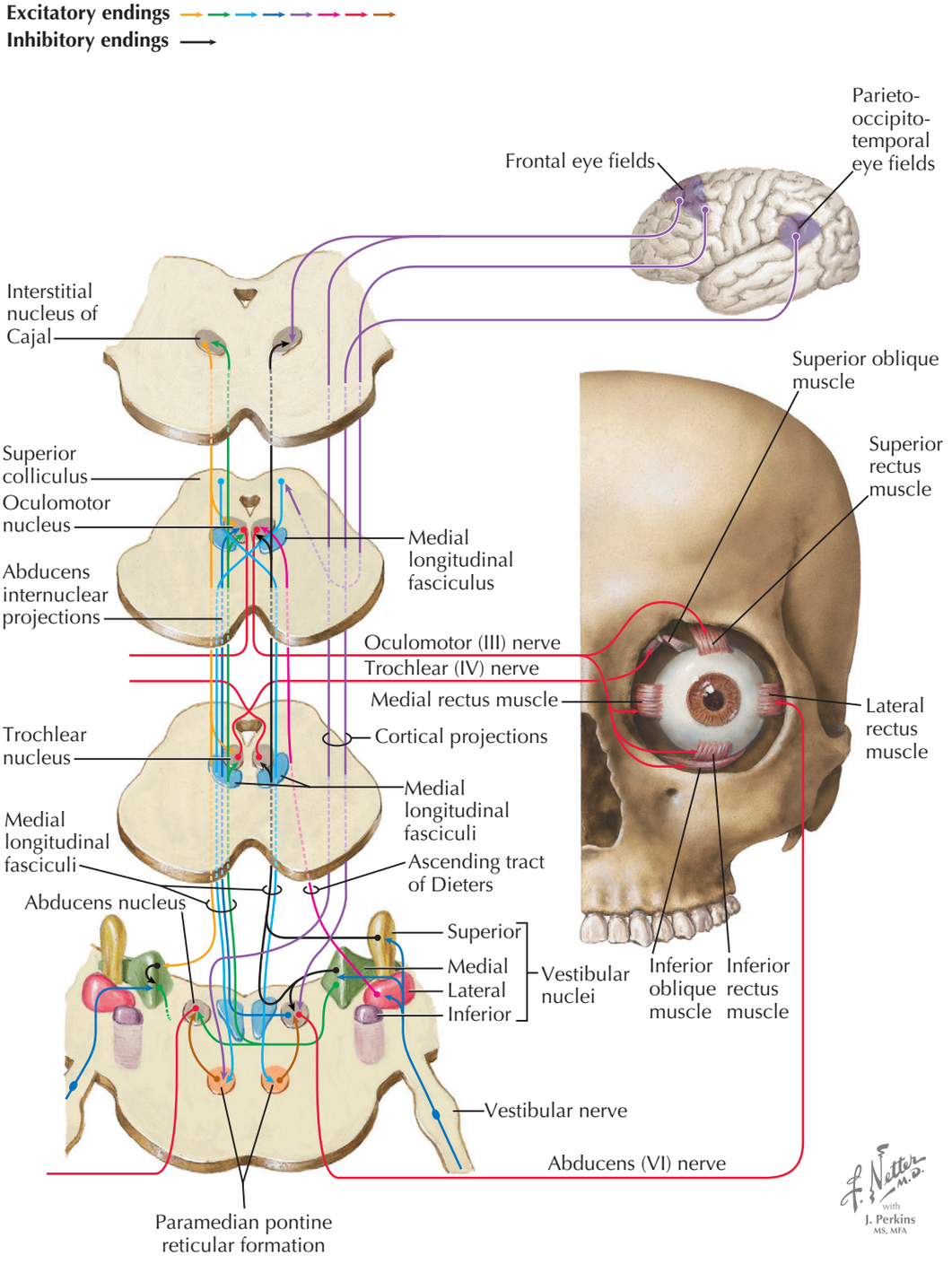
Nerves of Orbit and Cavernous Sinus



Control of Eye Movements

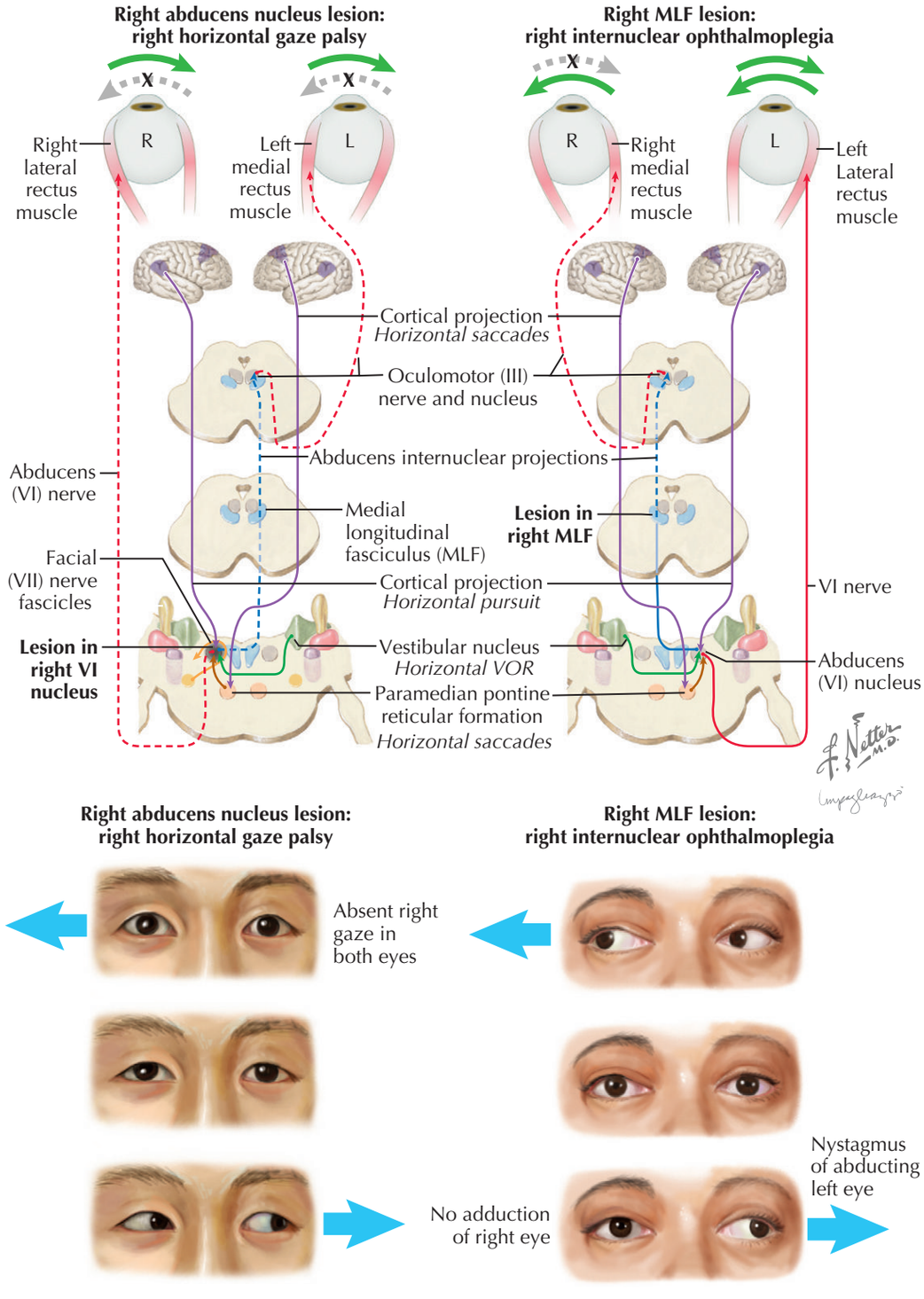
The extraocular muscles responsible for eye movements are controlled by motor neurons located in various nuclei. Thus the lateral rectus is controlled by the abducens nucleus, the superior oblique by the trochlear nucleus, and the superior, inferior, and medial recti and the inferior oblique muscles by the oculomotor nucleus. Both smooth (pursuit) and rapid (saccadic) eye movements depend on patterns of activity produced in these muscles by direct projections from the vestibular nuclei and the reticular formation, and by indirect activation from the superior colliculus and the cerebral cortex.

The *medial* and *lateral rectus muscles* move the eyeball horizontally, causing the cornea to look medially or laterally. The actions of the superior and inferior rectus muscles and those of the oblique muscles are more complicated. The *superior* and *inferior rectus muscles* move the eyeball upward and downward, respectively. Because they are disposed at an angle of about 20 degrees to the sagittal plane (due to the long axis of each orbit being directed slightly outward), they also impart a minor degree of rotation to the eyeball (intorsion for the superior rectus and extorsion for the inferior rectus). When the eyeball is abducted, the superior and inferior rectus muscles purely elevate and depress the eyeball. The *inferior oblique muscle* rotates the eyeball outward (excyclotorsion) and elevates the eyeball when it is adducted. However, an exact idea of the actions of the extrinsic eye muscles cannot be obtained by considering each muscle separately because, under normal circumstances, none of the six extraocular muscles acts alone. Consequently, all eye movements are the result of highly integrated and delicately controlled agonist and antagonist activities. The actions of individual muscles have been determined from studies of congenital defects or from functional disturbances caused by disease or injury to the nerve supply.



VESTIBULAR PROJECTIONS IMPORTANT FOR VISUAL FIXATION

The vestibular projection is important for the maintenance of visual fixation during head movements. To effect smooth movement, tracking, and proper visualization, the contraction of one eye muscle must be accompanied by the relaxation of its antagonist. The action of turning the head excites *vestibular afferent fibers* from semicircular canal receptors. Fibers from an individual semicircular canal excite two specific groups of relay neurons in the *vestibular nuclei*. One group excites the extraocular motor neurons that cause the eyes to move in the direction opposite to the head movement, and the other group inhibits motor neurons that activate movement of the eyes in the same direction as the

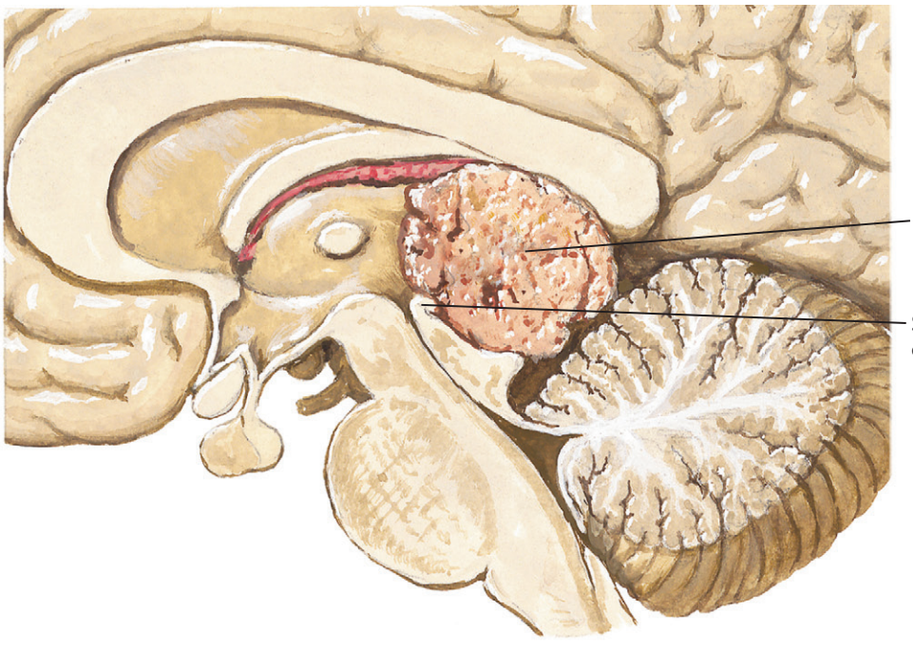


CONTROL OF EYE MOVEMENTS
(Continued)

head. For example, turning the head to the right will excite fibers from the right horizontal semicircular canal, which, in turn, will activate neurons in the right medial and lateral vestibular nuclei. Some of these vestibular neurons will then excite motor neurons controlling the right medial and left lateral rectus muscles. Other vestibular neurons will inhibit motor neurons controlling the right lateral rectus and internuclear neurons controlling the left medial rectus. The result will be a compensatory movement of both eyes to the left. The vestibulocerebellum modulates the vestibulo–extraocular reflex in such a way that the resulting eye movement precisely compensates for the head movement and thus keeps the gaze fixed on the same point.

The connections of the right vestibular nuclei to the *abducens*, *trochlear*, and *oculomotor nuclei* can be divided into two sections. The first section comprises vestibular projections to motor neurons supplying the superior and inferior rectus and superior and inferior oblique muscles. These motor neurons all receive excitatory input from the contralateral medial nucleus and inhibitory input from the ipsilateral superior nucleus. The innervation of medial and lateral rectus motor neurons, which mediate horizontal eye movements, is organized differently. The medial vestibular nucleus sends excitatory fibers to the contralateral abducens nucleus and inhibitory fibers to the ipsilateral abducens nucleus. These fibers excite or inhibit the lateral rectus motor neurons and another group of neurons within the abducens nucleus, the internuclear neurons, which project to the opposite oculomotor nucleus to excite the medial rectus motor neurons. The latter neurons are also excited by fibers that originate in the lateral vestibular nucleus and pass upward in the ascending tract of Deiters.

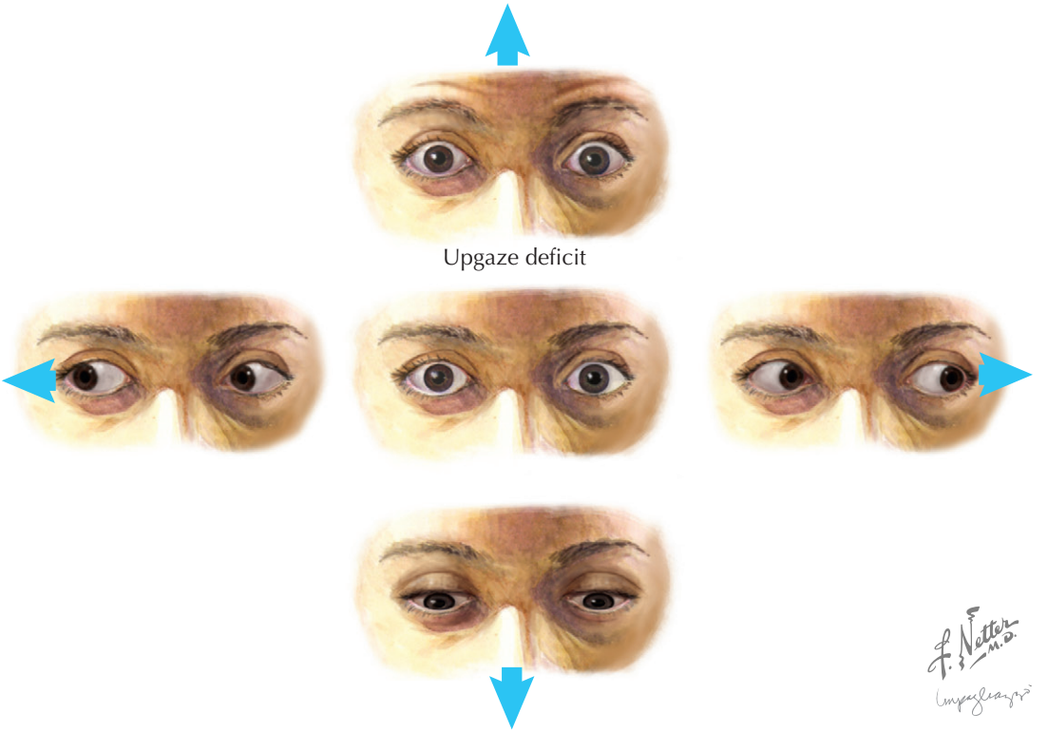
In addition to the pathways described above, each ocular motor nucleus also receives input for saccadic and pursuit eye movements that do not involve the vestibular nuclei. These pathways ultimately converge on the final common pathways for horizontal and vertical ocular motor control also used in the vestibulo-ocular system, but initially via different anatomic pathways. For example, saccadic eye movements (fast conjugate eye movements to a fixed target, either voluntary or reflex in origin) are initiated in the frontal and parietal lobes. The horizontal saccade pathway is a crossed pathway. Pathways from the frontal and parietal eye fields descend via the superior colliculus into the brainstem and cross at the level of the midbrain–pontine junction to synapse on the contralateral paramedian pontine reticular formation. The paramedian pontine reticular formation projects to the ipsilateral abducens nucleus, from which abducens neurons project to the ipsilateral lateral rectus muscle, whereas abducens interneurons project cross the midline to ascend in the



CONTROL OF EYE MOVEMENTS
(Continued)

contralateral medial longitudinal fasciculus and synapse on the medial rectus subnucleus of the contralateral oculomotor nucleus. The pathways for vertical saccades involve the rostral interstitial nucleus of the medial longitudinal fasciculus, the interstitial nucleus of Cajal, the posterior commissure, and the nucleus of the posterior commissure.

In contrast to the saccadic pathways, the pathways for horizontal smooth pursuit (conjugate maintenance of fixation of the eyes while following a moving target) descend ipsilaterally from cortical centers of eye movement control to synapse directly on the abducens nucleus, and from there to the ipsilateral abducens nerve and lateral rectus and the contralateral oculomotor nerve and medial rectus. This internuclear connection between the abducens nucleus and the contralateral oculomotor nucleus via the medial longitudinal fasciculus is the final common pathway responsible for conjugate horizontal gaze, whether initiated reflexively via the vestibulo-ocular system or voluntarily via the saccadic or pursuit systems.



Posterior midbrain syndrome (with upgaze palsy and lid retraction) secondary to a pineal mass

NEUROLOGIC DEFICITS

Eye movement disorders from brainstem involvement of the pathways subserving horizontal and vertical gaze are usually exquisitely localizing. For example, a lesion in the right abducens nucleus will cause a complete loss of gaze of either eye toward the right (usually with an associated ipsilateral lower motor neuron facial palsy because the fascicles of the facial nerve wrap around the abducens nucleus before exiting the brainstem), whereas a lesion of just to the right paramedian pontine reticular formation will cause an absence of voluntary and reflex saccades to the right, with relative preservation of the vestibulo-ocular reflex (VOR) and pursuit eye movements. A lesion of the right medial longitudinal fasciculus will disrupt only the abducens interneuron projections, and therefore the patient will have all eye movements intact except for poor adduction of the right eye (poor movement of the right eye toward the nose), a so-called internuclear ophthalmoplegia.

Vertical gaze may be selectively abnormal, with lesions in the midbrain and pretectal area, especially from compression from above, such as typically seen with pineal tumors. If the posterior commissure is primarily involved, these patients may have selective absence of upward eye movements with preservation of all other eye movements. Associated clinical abnormalities include upper lid retraction and nonreactive pupils to light with intact pupillary constriction when viewing a near target (all part of the so-called dorsal midbrain syndrome).

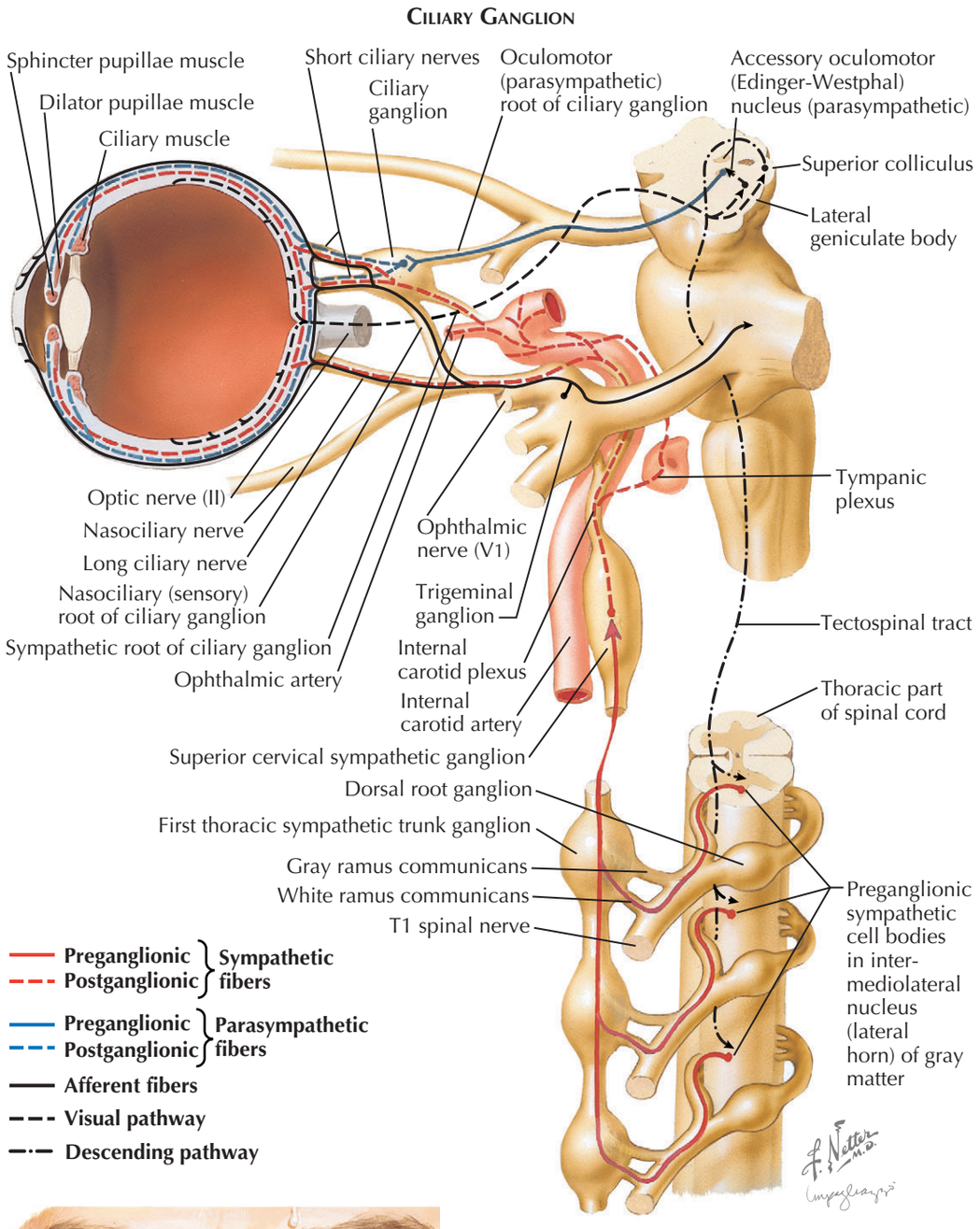
Autonomic Innervation of the Eye

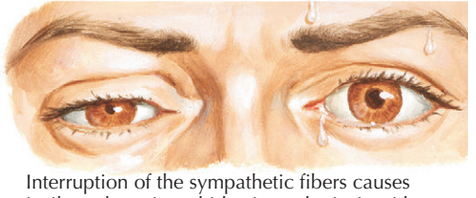
Sympathetic Fibers. The sympathetic *preganglionic fibers* for the eye emerge in the ipsilateral first and second, and occasionally in the third, thoracic spinal nerves. They pass through white or mixed rami communicantes to the sympathetic trunks in which the fibers ascend to the superior cervical ganglion, where they relay, although a proportion may form synapses higher up in the internal carotid ganglia. The *postganglionic fibers* run either in the internal carotid plexus and reach the eye in filaments that enter the orbit through its superior fissure, or else they run alongside the ophthalmic artery in its periarterial plexus.

Some of the filaments passing through the superior orbital fissure form the *sympathetic root of the ciliary ganglion*; their contained fibers pass through it without relaying to become incorporated in the 8 to 10 *short ciliary nerves*. Other filaments join the ophthalmic nerve or its nasociliary branch and reach the eye in the two to three *long ciliary nerves* that supply the radial musculature in the iris (dilator pupillae). Both long and short ciliary nerves also contain afferent fibers from the cornea, iris, and choroid. Fibers conveyed in the short ciliary nerves pass through a communicating ramus from the ciliary ganglion to the nasociliary nerve; this ramus is called the *sensory root of the ciliary ganglion*. The parent cells of these sensory fibers are located in the trigeminal (semilunar) ganglion, and their central processes end in the *sensory trigeminal nuclei* in the brainstem. The sensory trigeminal nuclei have multiple interconnections with other somatic and autonomic centers and thus influence many reflex reactions. Other sympathetic fibers from the internal carotid plexus reach the eye through the ophthalmic periarterial plexus and along its subsidiary plexuses around the central retinal, ciliary, scleral, and conjunctival arteries.

Parasympathetic Fibers. The parasympathetic preganglionic fibers for the eye are the axons of cells in the *accessory, or autonomic, (Edinger-Westphal) oculomotor nucleus*. They run in the third cranial nerve and exit in the *motor root of the ciliary ganglion*, where they relay. The axons of these ganglionic cells are postganglionic parasympathetic fibers, which reach the eye in the *short ciliary nerves* and are distributed to the constrictor fibers of the iris (sphincter pupillae), to the ciliary muscle, and to the blood vessels in the coats of the eyeball.

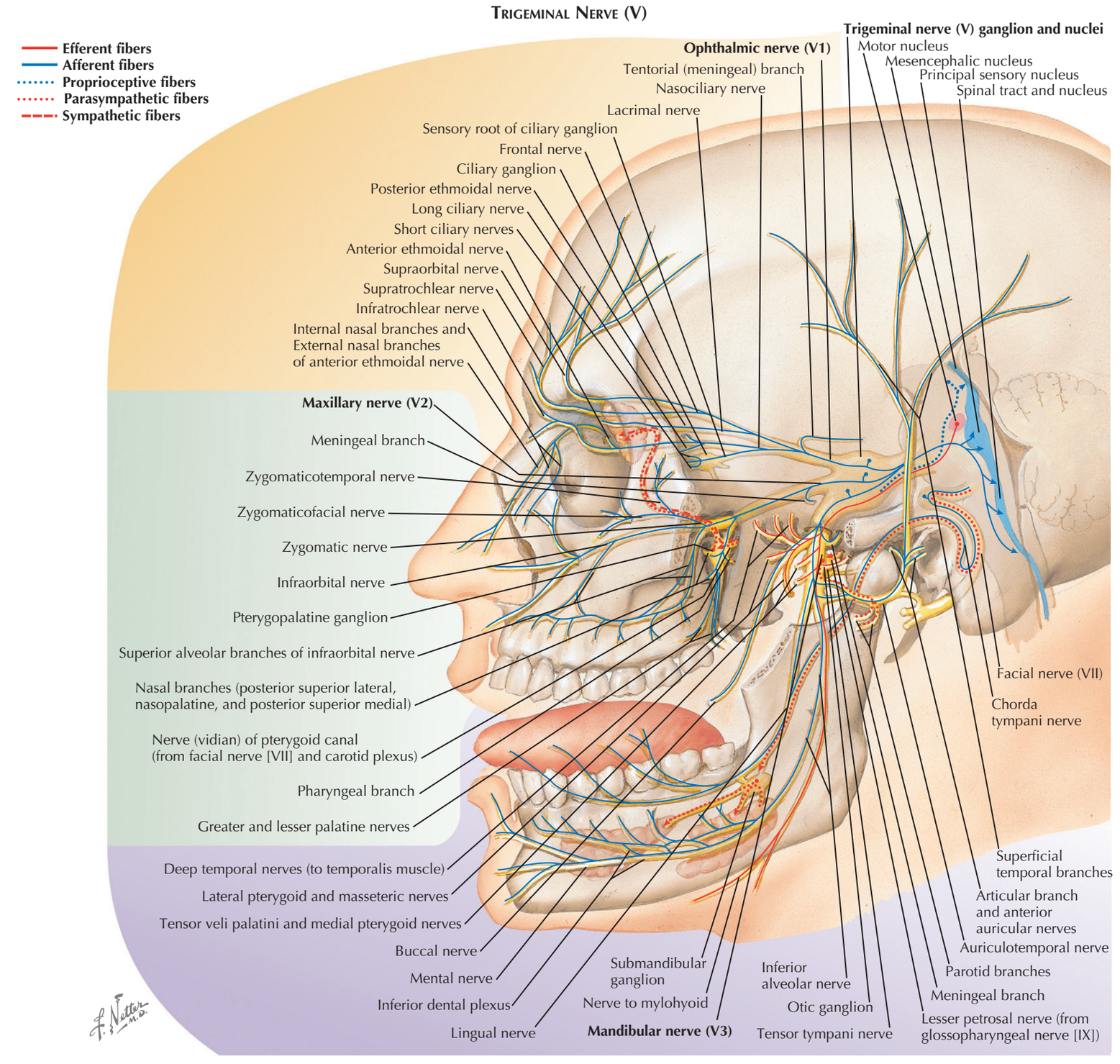
Neurologic Disorders. Disruption of the sympathetic innervation to the eye at any level along the sympathetic pathways will result in a Horner syndrome, in which the pupil on the involved side is smaller and dilates poorly, especially notable in the dark, and the upper lid droops slightly (ptosis). Depending on where the sympathetic chain is disrupted, there may also be loss of sweating on the ipsilateral face. A lesion of the ciliary ganglion will cause disruption of the parasympathetic fibers to the pupillary constrictor muscle, and there will be isolated enlargement of the ipsilateral pupil, especially notable in lighted conditions, but no findings such as ptosis or extraocular muscle weakness to suggest a lesion along the course of the oculomotor nerve.





Interruption of the sympathetic fibers causes ipsilateral ptosis, anhidrosis, and miosis without abnormal ocular motility (Horner syndrome)

Left dilated pupil with no other sign



Cranial Nerve V: Trigeminal Nerve

ANATOMY

The trigeminal nerve is the largest cranial nerve and gives rise to three major branches: the ophthalmic, maxillary, and mandibular nerves. It is a mixed nerve that provides motor innervation to the muscles of mastication and sensory innervation to the face and mucous membranes of the nasal and oral cavities.

The trigeminal nerve emerges from the anterolateral aspect of the upper pons. The large sensory root conveys sensation from most of the face and scalp; parts of the auricle; and the external acoustic meatus, the nasal, and oral cavities; teeth; temporomandibular joint; nasopharynx; and most of the meninges in the anterior and middle cranial fossae. It carries proprioceptive impulses from masticatory and, likely, from extraocular and facial muscles. The smaller medial motor root supplies muscles derived from the first branchial arch: the masticatory muscles, the mylohyoid, the anterior belly of the digastric, the tensor veli palatine, and tensor tympani. Numerous parasympathetic and sympathetic fibers join branches of the trigeminal nerve through interconnections with the oculomotor (III), trochlear (IV), facial (VII), and glossopharyngeal (IX) nerves. The sensory and motor roots emerge from the pons and travel over the superior border of the petrous temporal

Cranial Nerve V: Trigeminal Nerve *(Continued)*

bone near its apex. The sensory root expands into the semilunar-shaped trigeminal ganglion (gasserian ganglion) and contains pseudounipolar cells with peripheral processes conveying sensory impulses from the face and head structures through the three major trigeminal divisions.

The central processes coalesce to form the sensory root, which enters the brainstem to end in one of three major nuclear complexes, the spinal (inferior) trigeminal nucleus, the principal sensory (pontine) nucleus, or the mesencephalic nucleus. The spinal tract of the trigeminal nucleus descends from the pons, through the medulla, and into the spinal cord, where it is contiguous with Lissauer's tract. The spinal tract gives off fibers to the medially located nucleus of the spinal tract of the trigeminal nerve. The spinal nucleus of the trigeminal nerve receives pain, temperature, and soft touch input from the face and mucous membranes. From the spinal nucleus, the ascending fibers travel ipsilaterally in the trigeminothalamic tract to the ventral posteromedial (VPM) and intralaminar nucleus of the thalamus. Projections ascend to the proximal sensory cortex for pain and temperature perception.

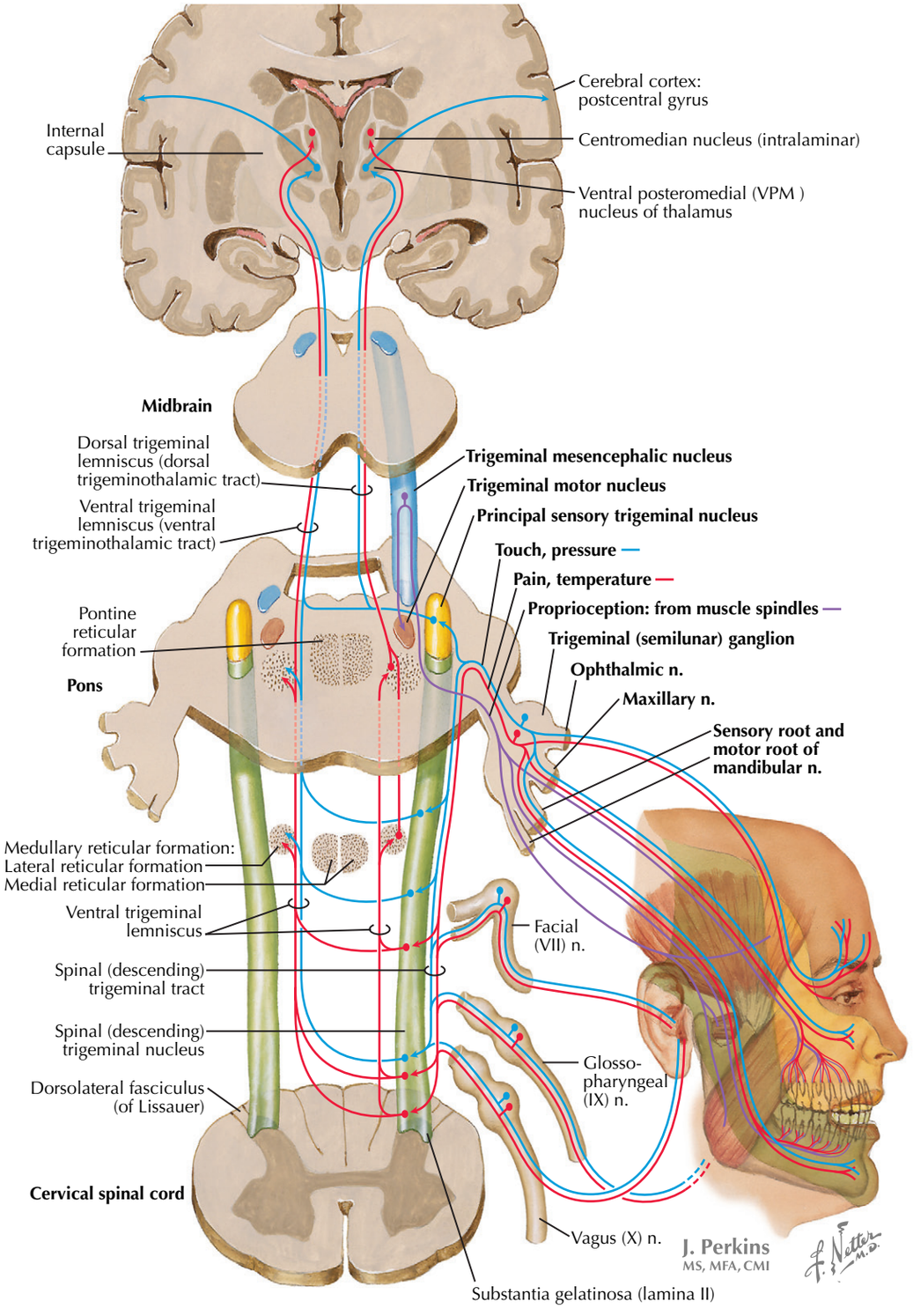
The principal sensory nucleus, which is located in the lateral pons, receives tactile and proprioceptive sensation. It gives off fibers that travel in the trigeminal lemniscus and the uncrossed dorsal trigeminothalamic tract, both of which terminate in the VPM nucleus of the thalamus. It is represented bilaterally in the cortex.

The mesencephalic nucleus contains cell bodies that carry proprioceptive input from masticatory and extraocular muscle spindles. It is the only place in the central nervous system (CNS) where cell bodies of primary sensory afferents are found in the CNS and not in sensory ganglia. The trigeminal mesencephalic nucleus extends from the main sensory nucleus to the superior colliculus of the mesencephalon.

The motor fibers originate in the trigeminal motor nucleus. The sensory and motor roots of the trigeminal nerve leave the pons and pass through Meckel's cave to form the trigeminal ganglion. This ganglion then divides into the three nerve trunks: the ophthalmic, maxillary, and mandibular nerves. The small motor root passes under the ganglion to join the mandibular nerve.

The ophthalmic nerve (V1) collects pain, temperature, touch, and proprioceptive information from the upper third of the face, top of the nose, scalp regions, and adjacent sinuses. It is joined by filaments from the internal carotid sympathetic plexus and communicates with the oculomotor, trochlear, and abducens nerves as it runs forward in the lateral wall of the cavernous sinus. Near its origin, it gives off a small recurrent tentorial (meningeal) branch to the tentorium cerebelli and then

Trigeminal Nuclei: Afferent and Central Connections

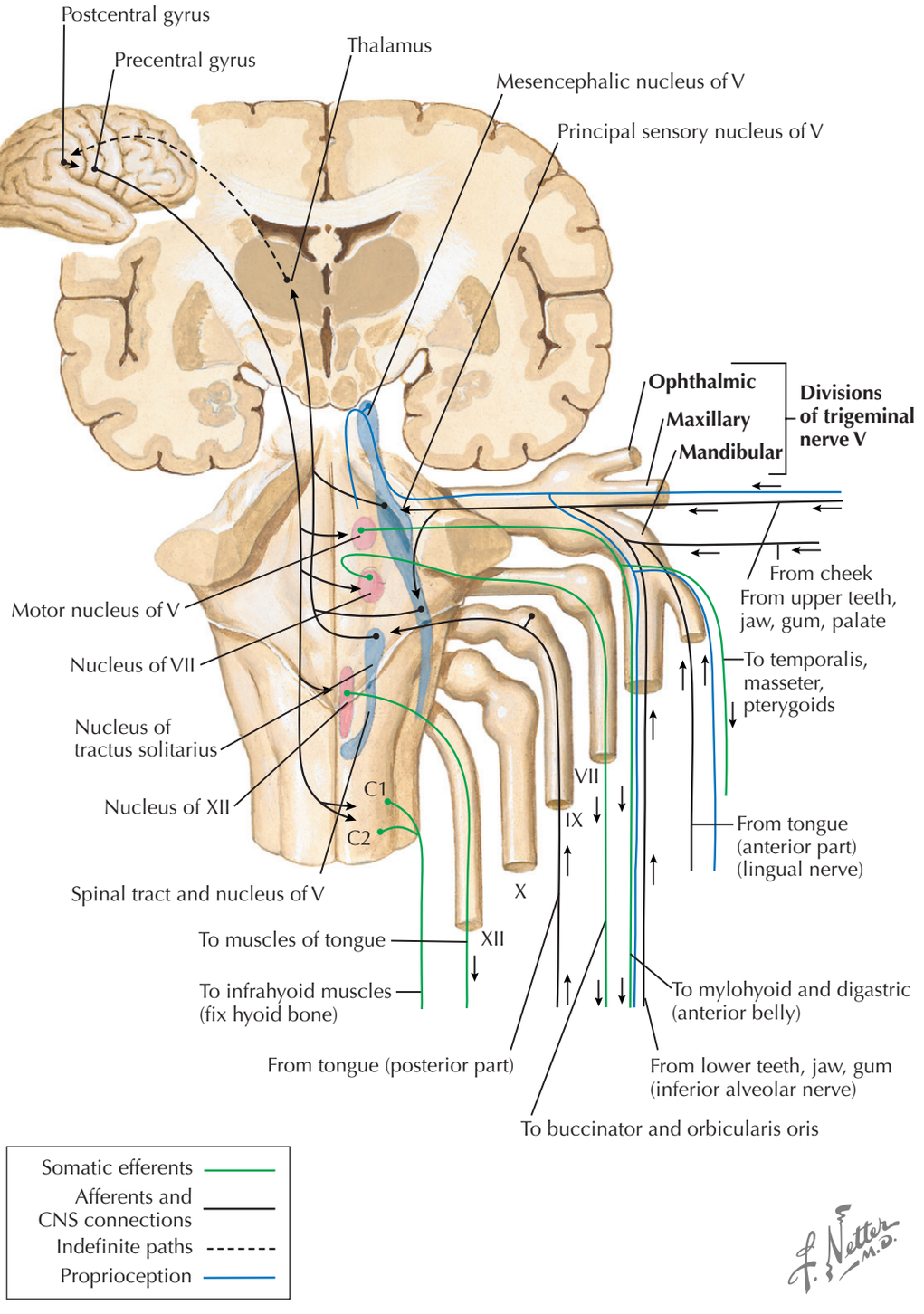


Cranial Nerve V: Trigeminal Nerve *(Continued)*

divides into the lacrimal, frontal, and nasociliary branches, which enter the orbit through the superior orbital fissure.

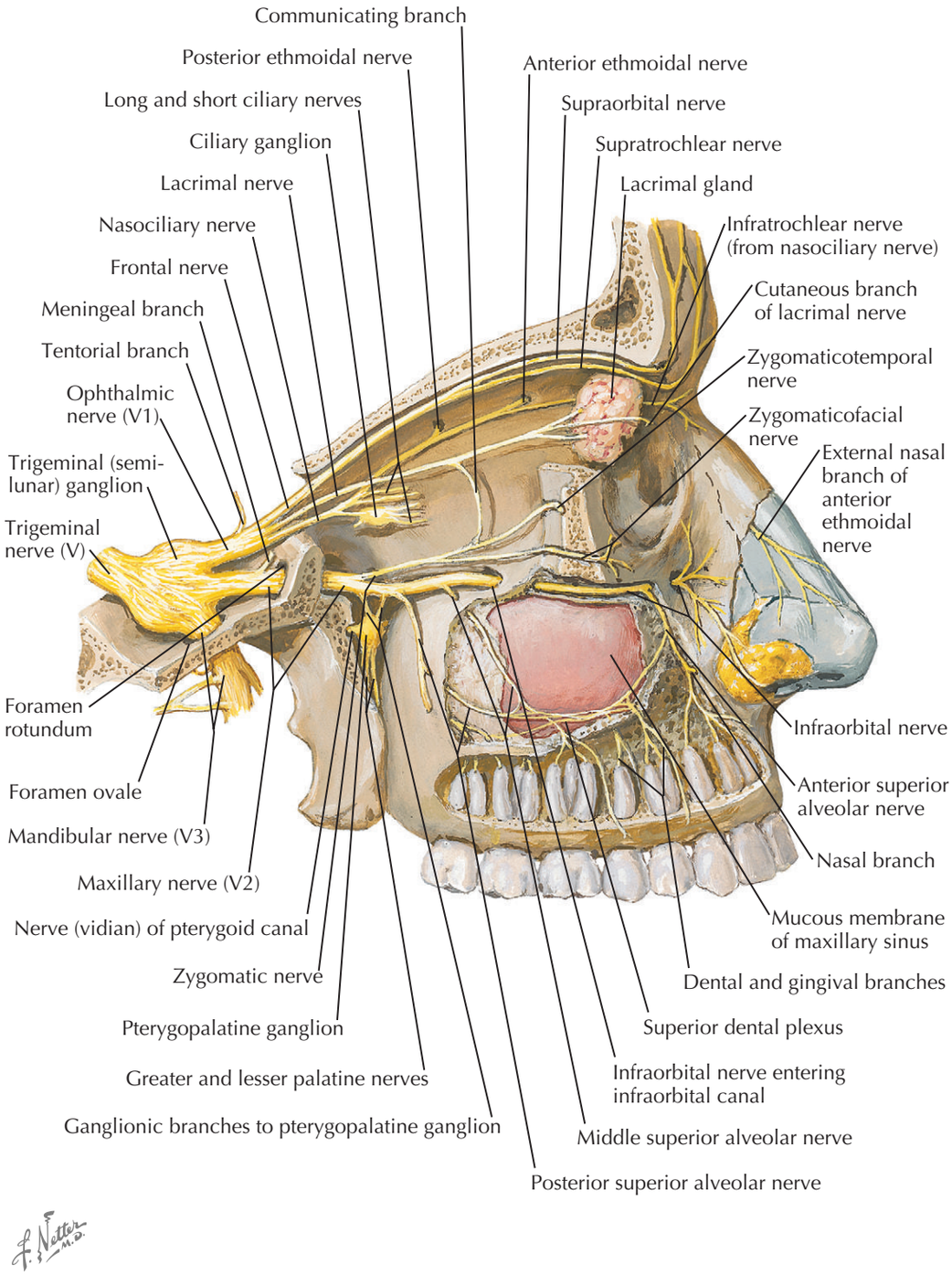
The maxillary nerve (V2) is larger than the ophthalmic nerve and is also sensory. It supplies the side of the forehead, medial cheek, side of the nose, upper lip, palate, upper teeth, nasopharynx, anterior and medial cranial fossae, meninges, and the skin overlying the maxilla. As with the other branches of the trigeminal nerve, it serves as a vehicle for the distribution of autonomic fibers to the skull structures. The maxillary nerve gives off a small meningeal branch to the meninges of the middle cranial fossa before passing through the lower part of the lateral wall of the cavernous sinus. It then leaves the skull through the foramen rotundum and enters the pterygopalatine fossa, where it communicates with the pterygopalatine ganglion before branching into different directions. In the pterygopalatine fossa, the maxillary nerve superiorly gives off the zygomatic nerve (with the zygomaticotemporal and zygomaticofacial branches), and inferiorly the superior posterior alveolar nerves. The superior middle and superior anterior alveolar nerves arise from the infraorbital part of the nerve that descend in the wall of the maxillary sinus between the bone and the mucous membrane, with dental and gingival rami uniting to form the superior dental plexus of the upper teeth and gums. The maxillary nerve ultimately moves anterolaterally across the upper part of the posterior surface of the maxilla to traverse the inferior orbital fissure on the way to the orbit. It then passes through the infraorbital groove as the infraorbital nerve, with the external and internal nasal, inferior palpebral, and superior labial branches, which supply the nasal alae, lower lid, upper lip skin, and mucous membranes, respectively.

Trigeminal Nuclei: Central and Peripheral Connections



The mandibular nerve (V3) is the largest branch of the trigeminal nerve and consists of a large sensory root and a small trigeminal motor root. The sensory portion innervates the cheeks, chin and lower lip, gums, inferior teeth, mucous membranes of the mouth, anterior two thirds of the tongue, side of the head, lower jaw, anterior wall of the external auditory meatus, external wall of the tympanic membrane, and the temporomandibular joint. The sensory and motor parts leave the skull through the foramen ovale and unite to form a short nerve that lies between the lateral pterygoid and tensor veli palatine muscles, anterior to the middle meningeal artery. The small otic ganglion closely adheres to the medial side of the nerve. Just below the foramen, the mandibular nerve gives off a meningeal branch (nervus spinosus). It supplies the meninges of the middle and anterior cranial fossae and calvaria, and the mucous membrane of the mastoid air cells. The nerve to the

Ophthalmic (V1) and Maxillary (V2) Nerves



Cranial Nerve V: Trigeminal Nerve *(Continued)*

medial pterygoid muscle sends fibers through the otic ganglia without relay to supply the tensor veli palatine and tensor tympani muscles. The main mandibular nerve divides into a small anterior and a larger posterior part. The anterior part contains primarily motor fibers through the nerve to the lateral pterygoid and two or three deep temporal nerves that innervate the temporalis muscle. The anterior portion has one sensory branch, the buccal nerve, which innervates the areas of skin overlying the buccinators muscle and the mucous membranes beneath. The posterior part of the mandibular nerve is primarily sensory and divides into the auriculotemporal, lingual, and inferior alveolar nerves. The mylohyoid muscle and the anterior belly of the digastrics are supplied by a few motor fibers that are distributed in the mylohyoid branch of the inferior alveolar nerve. At its origin, the auriculotemporal nerve divides in two around the middle meningeal artery. It ends in the superficial temporal branches that supply the skin and fascia of the temple and adjacent areas of the scalp. The auriculotemporal nerve also gives branches to the temporomandibular joint, the external acoustic meatus, and the tympanic membrane, and an anterior auricular branch to the skin of the tragus and part of the helix. It supplies filaments containing secretomotor and vasomotor fibers to the parotid gland, which reach the nerve through the otic ganglion. Sensation to the anterior two thirds of the tongue and floor of the mouth is carried by the lingual nerve. It is joined near its origin by the chorda tympani, a branch of the facial nerve, which conveys taste from the part of the tongue anterior to the V-shaped sulcus terminalis. The lingual nerve supplies the mucous membrane of the anterior two thirds of the tongue, lower part of the isthmus of the fauces, and the floor of the mouth, including the lingual surfaces of the lower gums. The branches communicate with the terminal branches of the glossopharyngeal and hypoglossal nerves. The inferior alveolar nerve descends behind the lingual nerve. It gives off its only motor branch, the mylohyoid nerve, before entering the canal. The mylohyoid nerve supplies the mylohyoid muscle and the anterior belly of the digastric. The other branches of the inferior alveolar nerve are the mental nerve and inferior dental and gingival rami, which arise from the nerve as it passes through the mandibular canal. The latter are delicate nerves that unite to form the inferior dental plexuses supplying the lower teeth and gums. They may be joined by branches of the buccal and lingual nerves or by filaments from nerves supplying the muscles attached to the mandible. These branches may carry sensory fibers, which explains why blocking the inferior alveolar nerve alone does not always anesthetize the lower teeth.

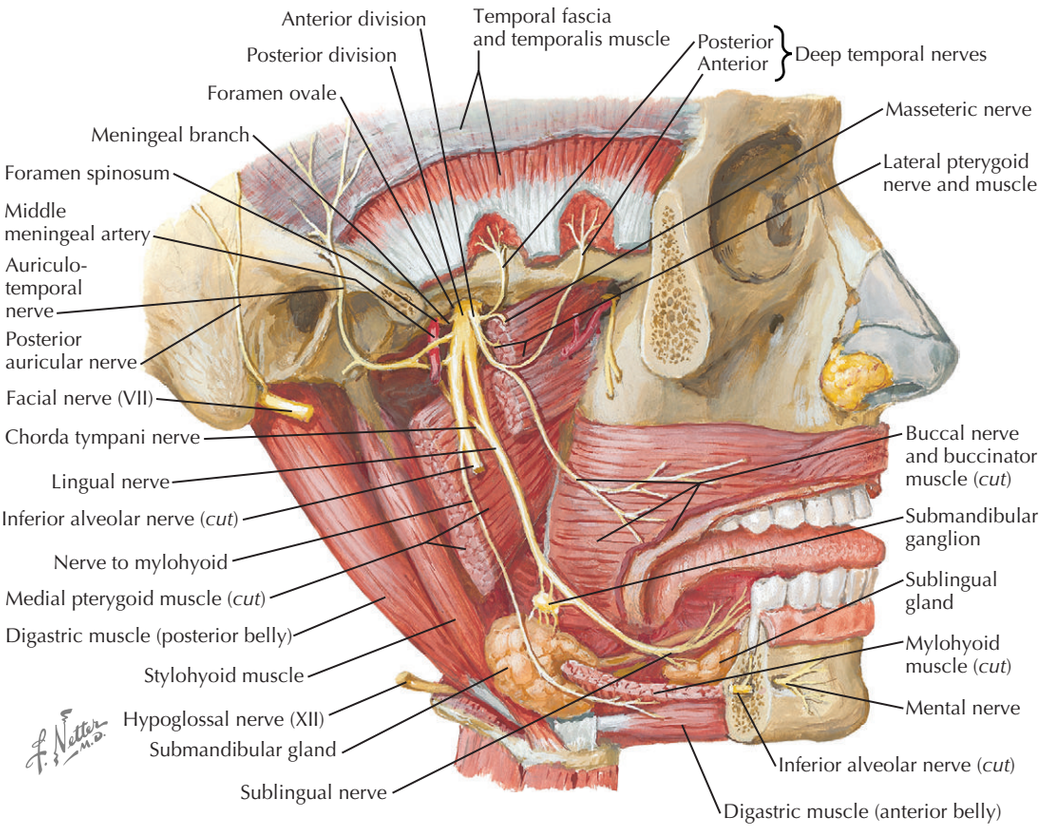
Cranial Nerve V: Trigeminal Nerve *(Continued)*

Trigeminal nerve disorders

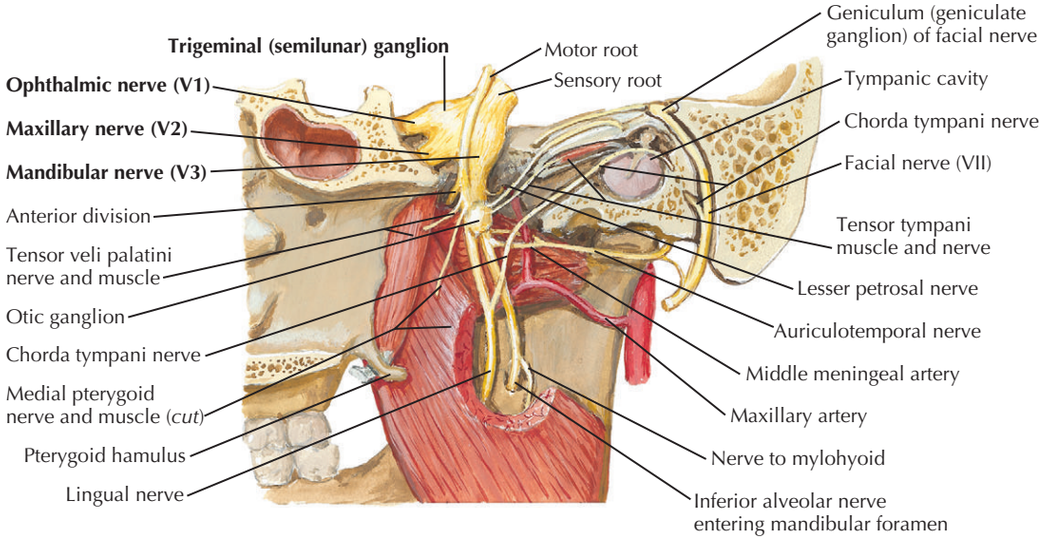
Patients with trigeminal neuropathy frequently have facial numbness. The examination of touch, pain, and temperature in the three divisions of the trigeminal nerve, as well as the blink reflex, is routinely checked. Although the muscles of mastication are frequently difficult to assess, jaw deviation toward the paretic anterior pterygoid muscle on forward protrusion may help to indicate trigeminal motor weakness or isolated V3 division involvement. Impairment of general sensation from the tongue and palate carried by the trigeminal nerve can, at times, result in mild taste disturbances, even though the special sensory fibers providing primary taste sensation, supplied by the facial and glossopharyngeal nerves, are not involved. Facial trauma or, rarely, invasive dental treatments account for the majority of trigeminal nerve injuries with sensory loss depending on the involved site. Herpes zoster is a common viral cause of a trigeminal neuropathy and occurs when latent varicella-zoster virus within the trigeminal ganglion becomes reactivated. A vesicular rash and neuralgic pain along the involved division are characteristic, with a chronic postherpetic neuralgia persisting for months to years. Herpes zoster ophthalmicus occurs when the ophthalmic division is involved. If not promptly addressed, corneal scarring and visual loss is the most serious potential complication. Rarely, ipsilateral carotid and middle cerebral artery granulomatous angiitis with infarctions may occur as the virus travels retrograde from the ganglion along the trigeminal nerve. Worldwide leprosy or Hansen disease is the most common cause of trigeminal neuropathy. It affects with coolest areas of the skin, and sensory loss confined to the pinna of the ear or tip of the nose raises Hansen disease as a consideration.

Mandibular Nerve (V3)

Lateral view



Medial view



Trigeminal ganglionopathy in association with connective tissue disease is likely caused by circulating autoantibodies to ganglion cell bodies. This is particularly seen in scleroderma or Sjögren syndrome. Numbness begins around the mouth and spreads slowly over months to involve all trigeminal divisions. Frequently, the ophthalmic division is less involved or spared. In Sjögren syndrome, trigeminal ganglionopathy is typically part of a more widespread sensory ganglionopathy.

Metastatic neoplasm or tumors involving the face, such as squamous cell carcinoma, microcystic adnexal carcinomas, and keratoacanthoma, may invade cutaneous nerve branches, especially at their exit point from the skull (mental and infraorbital neuropathies), and exhibit focal sensory loss. The numb chin syndrome (or

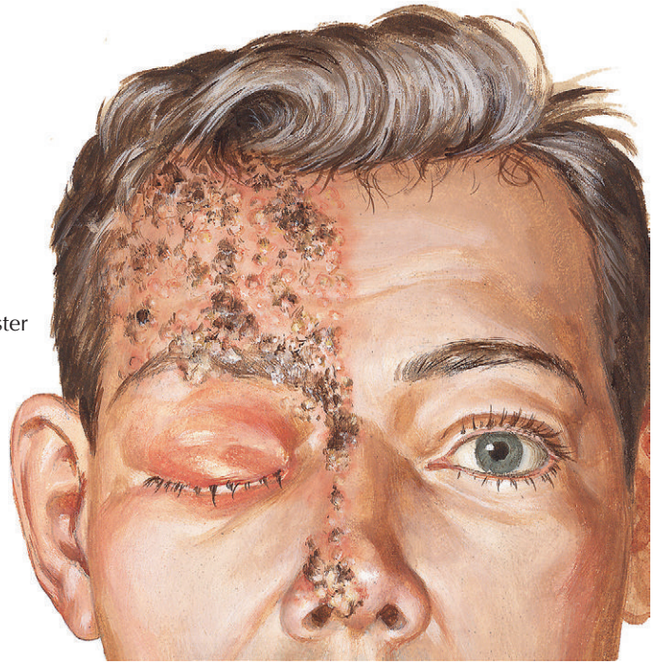
Cranial Nerve V: Trigeminal Nerve *(Continued)*

isolated mental neuropathy) consists of unilateral numbness of the chin and adjacent lower lip and may be an ominous sign of primary or metastatic cancer involving the mandible, skull base, or leptomeninges. The most common etiologies are metastatic breast cancer and lymphoproliferative malignancies.

Trigeminal neuralgia, also known as tic douloureux, is an often severe and disabling lancinating or electrical facial pain syndrome occurring in the trigeminal nerve distribution (typically maxillary or mandibular) without associated neurologic deficits. It characteristically affects middle-aged people, women more than men, and involves the right side more than the left. It is rare to have bilateral attacks of trigeminal neuralgia except in the setting of multiple sclerosis. The attacks are mostly unilateral and brief, lasting for seconds to several minutes, and rarely occur during sleep. Paroxysms of pain are frequently provoked by non-nociceptive triggers, including talking, chewing, shaving, drinking hot or cold liquids, or any form of sensory facial stimulation. Between paroxysms, a constant dull ache can persist, often leading patients to believe the problem is of dental origin. The frequency of attacks fluctuates markedly, disabling a patient for weeks and then remitting for months to years. The etiology is thought to involve loss of myelin insulation within the posterior root of the trigeminal nerve. It may be idiopathic or due to compression at the entry zone of the trigeminal nerve root by the ectatic artery, (branch of the superior cerebellar artery), multiple sclerosis plaque, infarction, vascular malformation, cerebellopontine angle tumor, or rarely, posterior communicating or distal anterior inferior cerebellar artery (AICA) aneurysm. Magnetic resonance imaging (MRI) scanning of the brain with gadolinium is indicated for all patients with trigeminal neuralgia. Bilateral symptoms, trigeminal sensory findings, and loss of corneal reflexes are strong indicators of secondary trigeminal neuropathy and should raise concern. Anticonvulsants are the primary medical therapy for trigeminal neuralgia, with most patients responding to carbamazepine and, more recently, oxcarbazepine. Baclofen, an antispasmodic, is advocated by some as an adjuvant treatment to carbamazepine if higher doses alone are inadequate or cause side effects. Tricyclic antidepressants and other anticonvulsants, such as phenytoin, gabapentin, lamotrigine, topiramate, and pregabalin, may also be useful as adjuvant drugs or monotherapy. Several surgical approaches are available for patients who do not respond to medical therapy. Trigeminal neuralgia can recur after any procedure at a lifetime rate of about 20%.

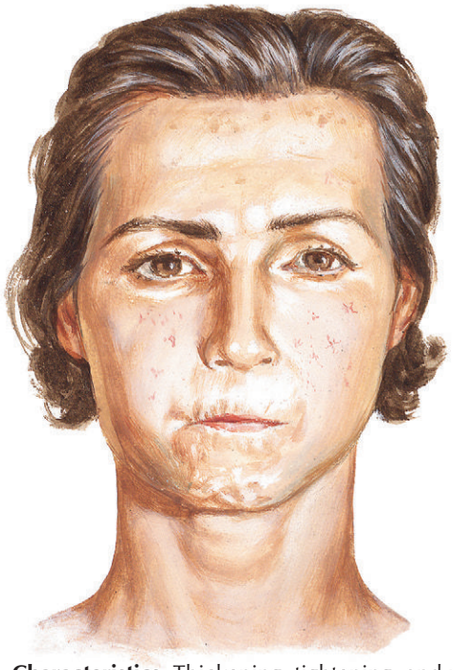
Trigeminal Nerve Disorders

Varicella-zoster with probable keratitis

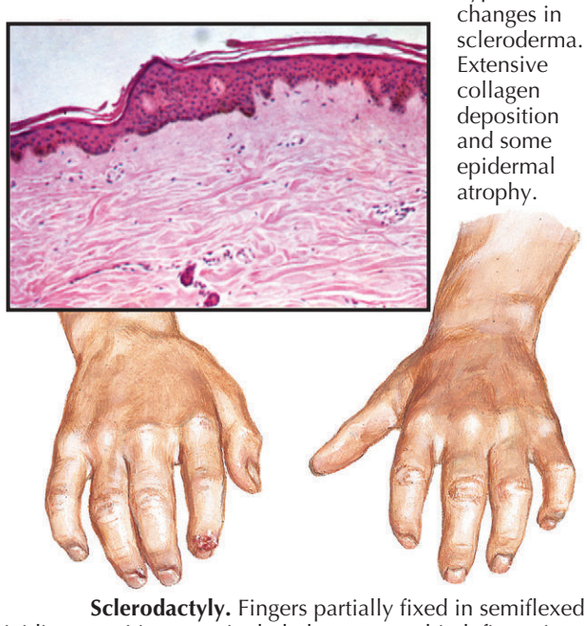


Herpes zoster

Progressive systemic sclerosis (scleroderma)



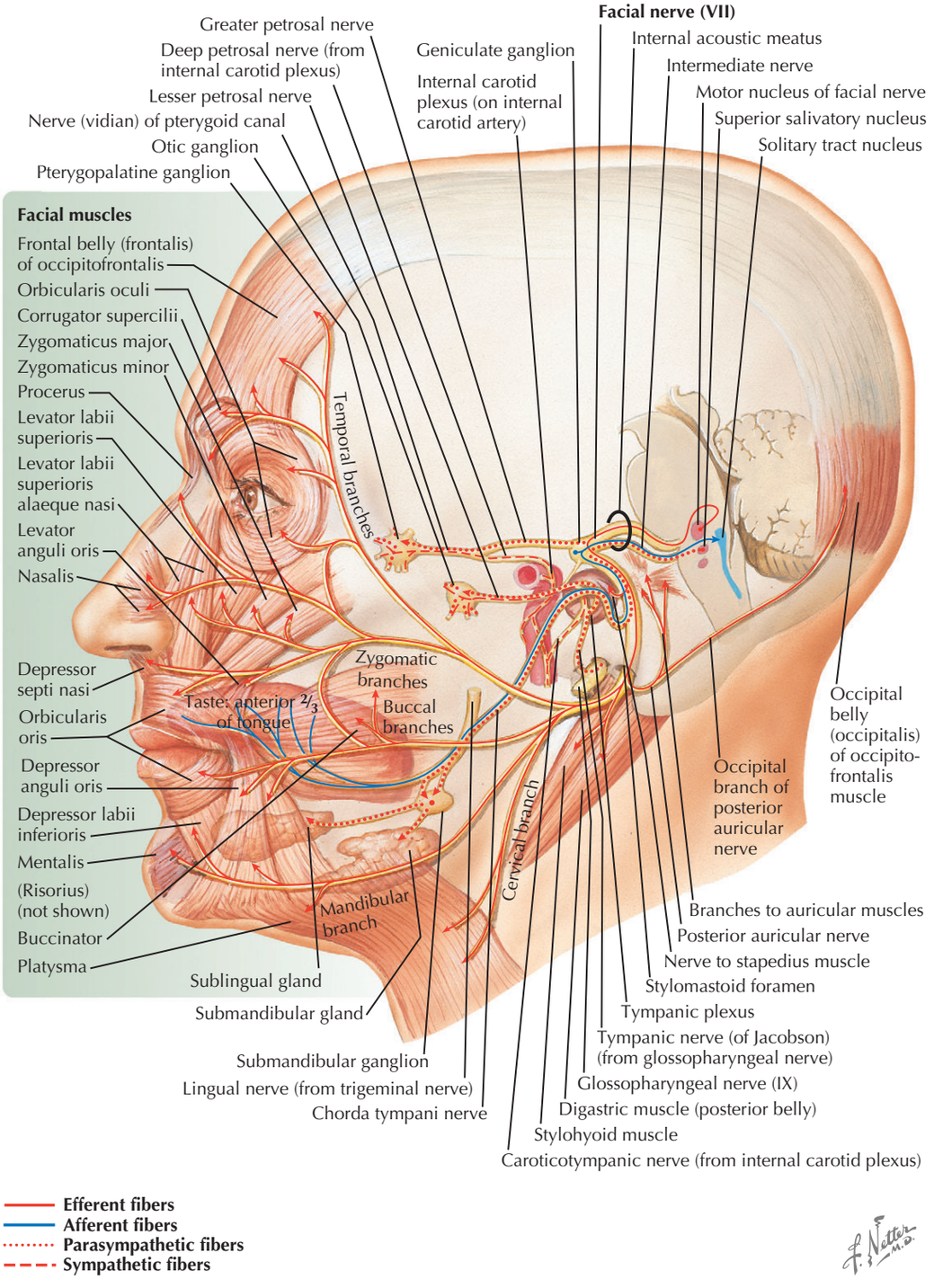
Characteristics. Thickening, tightening, and rigidity of facial skin, with small, constricted mouth and narrow lips, in atrophic phase of scleroderma



Typical skin changes in scleroderma. Extensive collagen deposition and some epidermal atrophy.

Sclerodactyly. Fingers partially fixed in semiflexed position; terminal phalanges atrophied; fingertips pointed and ulcerated

Facial Nerve (VII)



Cranial Nerve VII: Facial Nerve

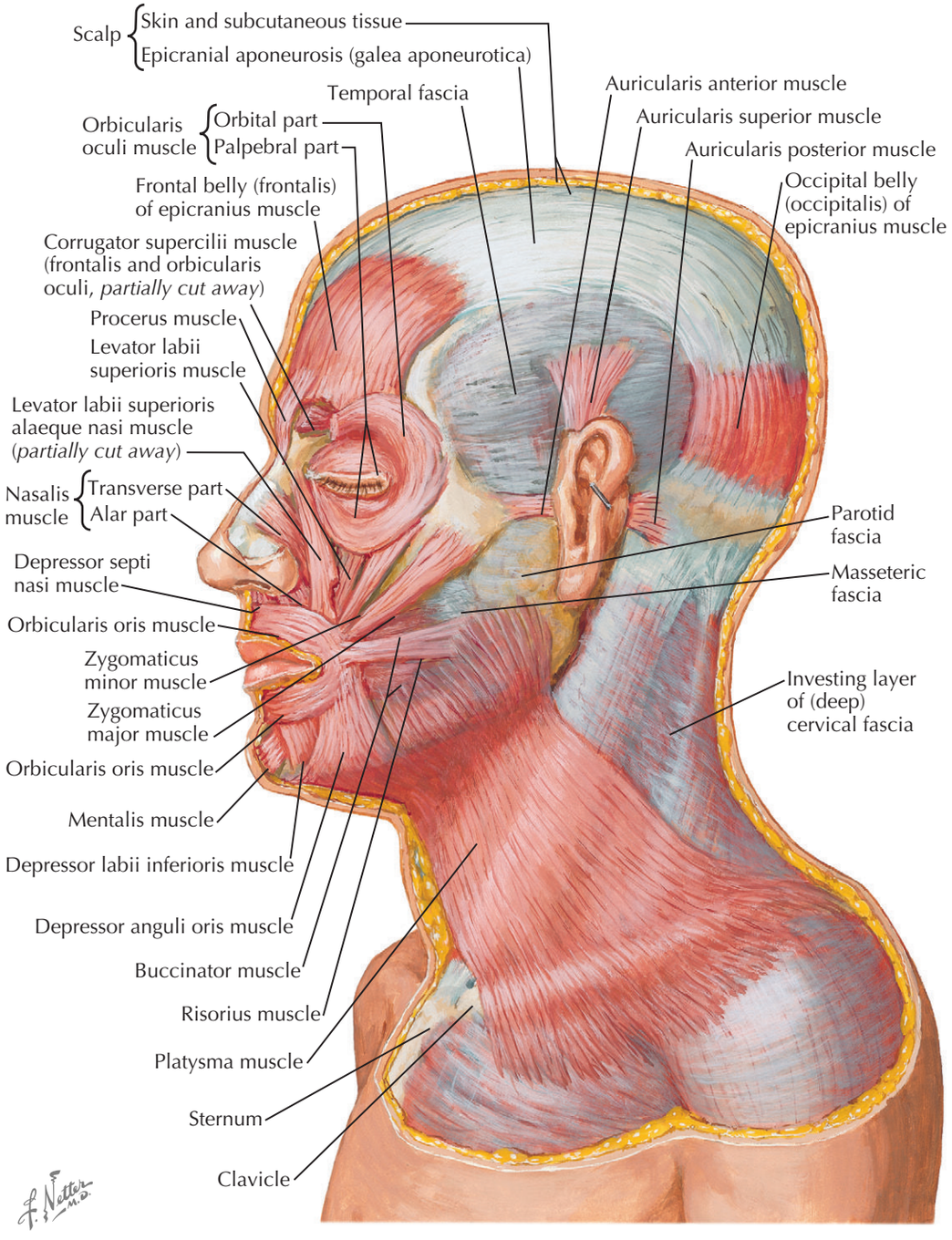
ANATOMY

The facial nerve is a mixed nerve containing special motor, special sensory, general sensory, and parasympathetic fibers. The facial nerve comprises two roots: a larger motor root, which supplies the facial mimetic musculature, the stapedius, the stylohyoid, and the posterior belly of the digastric, and a smaller sensory root called the nervus intermedius, which carries sensation and parasympathetic fibers.

THE MOTOR DIVISION

Fibers arise from the motor facial nucleus, located in the reticular formation of the lowest part of the pons. The nucleus is posterior to the superior olive, medial to the nucleus of the spinal tract of the trigeminal nerve, and anterolateral to the nucleus of the abducens nerve. The supranuclear control of facial movements occurs through the corticonuclear fibers originating in the precentral gyrus. These fibers course through the corona radiata, genu of the internal capsule, and the medial portion of the cerebral peduncle to the pons. The posterior portion of the facial nucleus controls the upper facial musculature and receives bilateral supranuclear input, while the anterior facial nucleus controls the lower facial muscles and receives predominantly contralateral input. Supranuclear lesions, such as with stroke, would therefore produce a pattern of contralateral predominantly lower facial weakness. The efferent fibers of the motor nucleus form a motor root and course around the abducens nucleus superiorly and exit the brainstem laterally in the cerebellopontine angle. The motor root travels with the nervus intermedius and CN VIII in the cerebellopontine angle and enters the internal auditory meatus of the temporal bone. Within the temporal bone, there are four portions of the facial nerve. (1) In the meatal (canal) segment, the motor division is on the superoanterior surface of CN VIII, and the nervus intermedius is in between them. (2) In the labyrinthine segment, the motor root, and nervus intermedius enter the facial canal in the petrous bone. The labyrinthine segment passes above the labyrinth and reaches the geniculate ganglion, which contains the sensory fibers of the nervus intermedius. Here the greater superficial petrosal nerve arises from the geniculate ganglion. This nerve is composed of preganglionic parasympathetic efferents that innervate the nasal, lacrimal, and palatal glands via the pterygopalatine ganglion. The greater superficial petrosal nerve also carries sensory fibers from the external auditory meatus, lateral pinna, and mastoid. (3) The horizontal (tympanic) segment contains the facial nerve as it runs horizontally backward

MUSCLES OF FACIAL EXPRESSION: LATERAL VIEW



CRANIAL NERVE VII: FACIAL NERVE *(Continued)*

below and medial to the horizontal semicircular canal. (4) In the mastoid (vertical) segment the facial nerve bends inferiorly. The nerve to the stapedius muscle branches off in this segment. The chorda tympani also branches off here and joins the lingual nerve. It contains the preganglionic parasympathetic fibers from the superior salivatory nucleus and innervates the submandibular and sublingual glands via the submaxillary ganglion. The chorda tympani also contains afferent taste fibers from the anterior two thirds of the tongue that then continue on to the nucleus of the solitary tract. CN VII exits the facial canal through the stylomastoid foramen and gives off the posterior auricular nerve (to the posterior auricular, transverse and oblique auricular muscles, and occipitalis) and digastric and stylohyoid branches. The facial nerve pierces the parotid gland and divides into temporofacial and cervicofacial branches, which further divide into temporofrontal, zygomatic, buccal, marginal mandibular, and cervical branches.

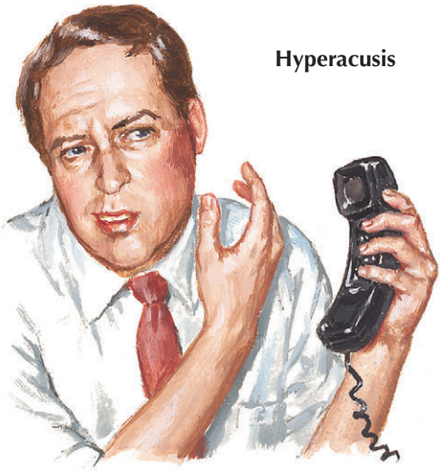
THE SENSORY AND PARASYMPATHETIC DIVISION (NERVUS INTERMEDIUS)

The nervus intermedius is the parasympathetic and sensory division of the facial nerve. It carries the preganglionic parasympathetic fibers to the submaxillary ganglion (and then postganglionic fibers travel to the submandibular and sublingual glands) and to the pterygopalatine ganglion (postganglionic fibers travel to the lacrimal, nasal, and palatal glands). The nervus intermedius receives sensory fibers from the geniculate ganglion. This ganglion receives afferents from the mucosa of the pharynx, nose, palate, and skin of the external auditory meatus, lateral pinna, and mastoid, and it carries taste sensation from the anterior two thirds of the tongue. The superior salivatory nucleus of the pontine tegmentum gives rise to the parasympathetic fibers. The lacrimal nucleus contains the fibers controlling lacrimation. The gustatory afferents end in the nucleus of the tractus solitarius in the medulla. Fibers conveying general sensations from the external auditory meatus, lateral pinna, and mastoid likely come through interconnections between the chorda tympani and the auricular branch of the vagus and terminate in the spinal nucleus of the trigeminal nerve. The afferents from the meninges and their arteries in the middle cranial fossa likely reach the facial nerve through the greater petrosal branch.

FACIAL NERVE DISORDERS

Facial weakness is caused by both central and peripheral lesions, and differentiating between the two frequently requires close examination. Peripheral facial weakness

Central Versus Peripheral Facial Paralysis

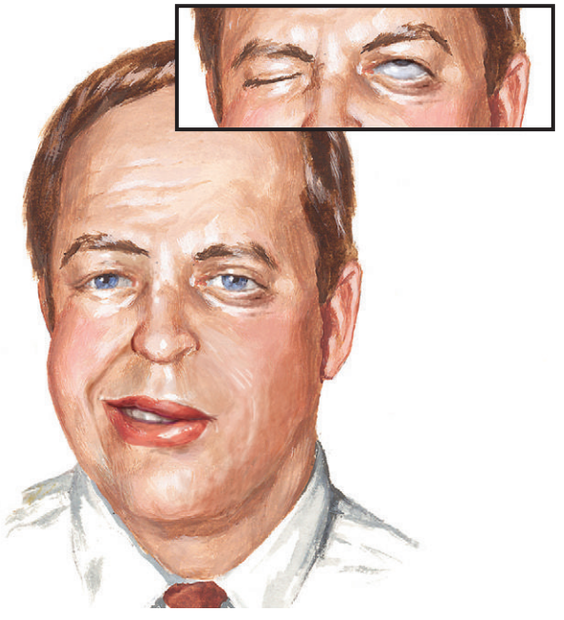


Hyperacusis

This may be an early or initial symptom of a peripheral VII nerve palsy: patient holds phone away from ear because of hyperacusis, an uncomfortable sensitivity to sound. Loss of taste also may occur on affected side.

Left peripheral VII facial weakness

Attempt to close eye results in eyeball rolling superiorly exposing sclera (Bell phenomenon) but no closure of the lid per se



Patient unable to wrinkle forehead; eyelid droops very slightly; cannot show teeth at all on affected side in attempt to smile; and lower lip droops slightly

Left central facial weakness

Incomplete smile with very subtle flattening of affected nasolabial fold; relative preservation of brow and forehead movement

Cranial Nerve VII: Facial Nerve *(Continued)*

involves both the upper and lower part of the face to the same degree, whereas upper motor neuron lesions typically manifest with a gradient of weakness, with relative preservation of movement in the brow and forehead (e.g., frontalis muscles). Supranuclear lesions, such as in suprabulbar palsies, may result in an absence of voluntary facial movements but retention of reflexive movements (e.g., smiling) in response to emotional stimuli.

Intrapontine lesions that affect the facial motor nucleus or its exiting fibers will often involve neighboring brainstem structures; for instance, a paramedian pontine reticular formation lesion causing ipsilateral conjugate gaze palsy, an associated sixth cranial nerve tract lesion with limited ipsilateral lateral rectus palsy, or contralateral hemiparesis of the arm and leg.

The facial nerve can be damaged at any level along its course (Plate 1-27). Facial musculature paralysis is the hallmark of seventh cranial nerve lesions. The presence or absence of symptoms related to the various other components of the facial nerve are important for further localization. The patient with a *peripheral facial nerve* palsy, with the exception of an early very distal branch lesion within the parotid gland, has weakness of the entire ipsilateral side of their face, with asymmetric smile, inability to close the eye (orbicularis oculi), or wrinkle the forehead (frontalis). *Intracranial, extramedullary lesions* affecting the seventh nerve typically occur within the cerebellopontine (CP) angle, most commonly caused by large acoustic neuromas, and often involve the vestibulocochlear nerve. In these cases, diminished hearing, at times initially presenting with tinnitus, usually precede the onset of peripheral facial paresis. Rarely, very large tumors may also involve the ipsilateral trigeminal cranial nerve with accompanying unilateral facial anesthesia and loss of corneal reflex. A *proximal pregeniculate, intracanicular facial nerve* lesion characteristically also causes diminished lacrimation from greater petrosal nerve involvement, as well as hyperacusis (i.e., increased sensitivity to sound) due to associated stapedius muscle paresis. These lesions also lead to diminished salivation, absent or altered taste for the anterior two thirds of the tongue, and affected somatic sensation for the external auditory canal and mastoid area. Lesions *between the geniculate ganglion and the stapedius nerve* spare lacrimation, because the greater petrosal nerve has already exited. Damage *between the branch points of the stapedius nerve and the chorda tympani* results in hyperacusis and impaired salivation and taste,

Cranial Nerve VII: Facial Nerve *(Continued)*

but not change in lacrimation. Lesions distal to the chorda tympani branch point result in pure ipsilateral facial weakness. Distal lesions that affect individual motor branches result in weakness that may be restricted to individual facial muscles.

BELL PALSY ("IDIOPATHIC" FACIAL PALSY)

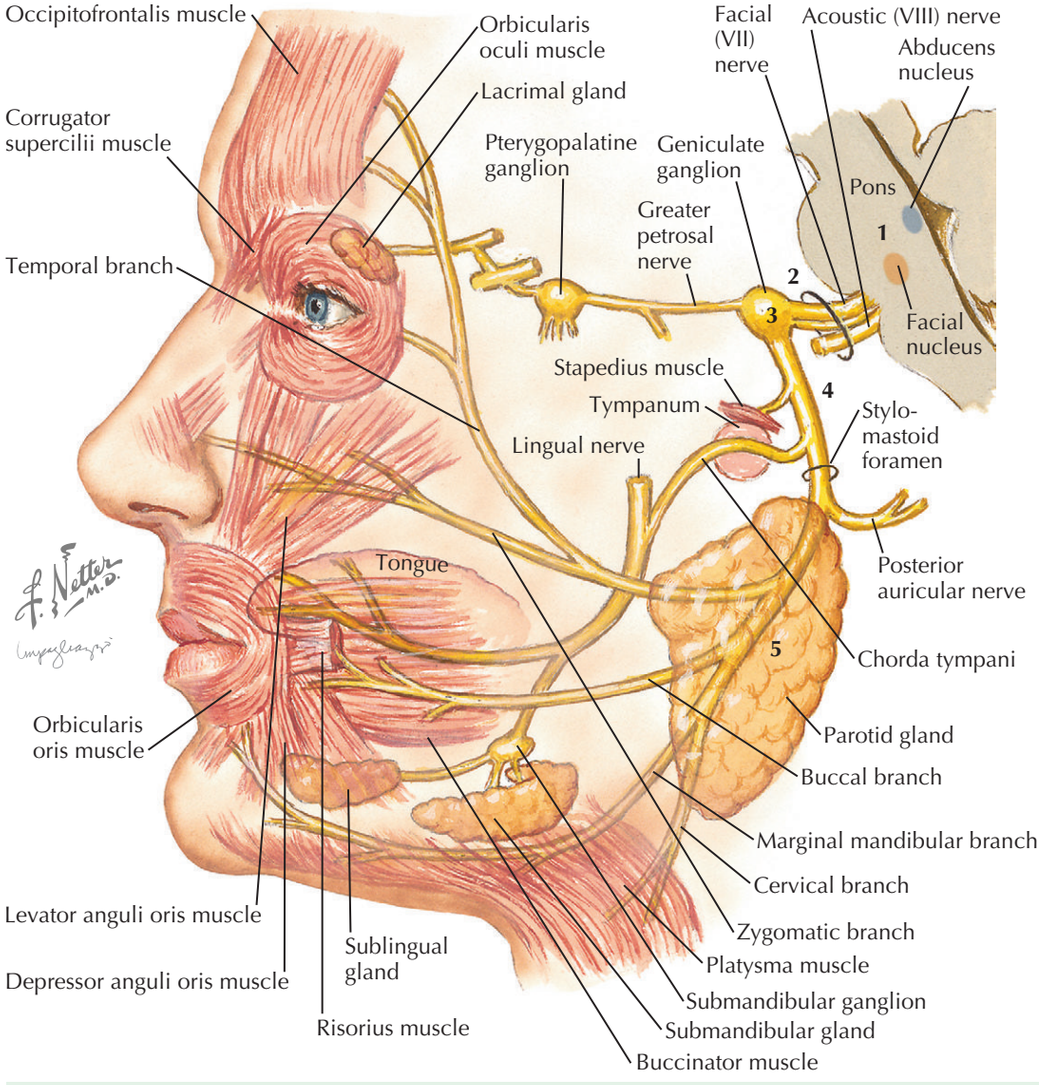
Bell palsy is a common cause of unilateral facial weakness. Onset of weakness is acute to subacute, evolving over hours to a few days. The lesion burden is usually proximal, with loss of total motor function on one side of the face, hyperacusis, disturbed taste, and decreased lacrimation. A preceding dull ache behind the ipsilateral ear is a common initial symptom. Nerve edema with subsequent compression and ischemia within the facial canal has been noted pathologically. The cause is believed to be reactivation of latent herpes simplex or varicella-zoster virus. A short course of corticosteroids, if given early in the course, reduces the duration of paralysis and risk of permanent impairment. The long-term prognosis is generally good, but severe cases may result in permanent partial facial paresis. Facial synkinesis, caused by aberrant regeneration of nerve, may manifest as ipsilateral eye closure occurring with smiling or ipsilateral lip and chin muscle activation during blinking. Excessive lacrimation when eating results from aberrant regeneration of salivatory fibers to the lacrimal glands ("crocodile tears").

OTHER ETIOLOGIES OF FACIAL NEUROPATHY

Lyme disease is a relatively common infectious cause of an acute unilateral or bilateral facial neuropathy. Symptoms typically include systemic symptoms (e.g., arthralgia, fever, rash), as well as other neurologic symptoms (e.g., headache, radiculitis, encephalopathy). Herpes zoster infection within the external auditory canal (Ramsay-Hunt syndrome), may cause facial paralysis that may precede the appearance of typical herpetic vesicles in the auditory canal. Extension of otitis media may rarely inflame and damage the facial nerve where it travels through the petrous bone. Leprosy may lead to bilateral facial nerve lesions. Unilateral or bilateral facial neuropathy is a common neurologic manifestation of sarcoidosis. Bilateral facial weakness is common in Guillain-Barré syndrome (acute inflammatory demyelinating polyradiculopathy).

Facial Palsy

Sites of facial (VII) nerve injury



Sites of lesions and their manifestations

1. Intrapontine lesions: Peripheral motor facial paralysis associated with eye movement abnormalities (ipsilateral abducens or horizontal gaze palsies) and contralateral motor paralysis.
2. Intracranial and/or internal auditory meatus: All symptoms of 3, 4, and 5, plus deafness due to involvement of eighth cranial nerve.
3. Geniculate ganglion: All symptoms of 4 and 5 with diminished lacrimation, plus pain behind ear. Herpes of tympanum and of external auditory meatus may occur.
4. Facial canal: All symptoms of 5, plus loss of taste in anterior tongue and decreased salivation on affected side due to chorda tympani involvement. Hyperacusis due to effect on nerve branch to stapedius muscle.
5. Below stylomastoid foramen (parotid gland tumor, trauma): Facial paralysis (mouth draws to opposite side) on affected side with patient unable to close eye or wrinkle forehead; food collects between teeth and cheek due to paralysis of buccinator muscle.

Taste Receptors and Pathways

Taste Receptors

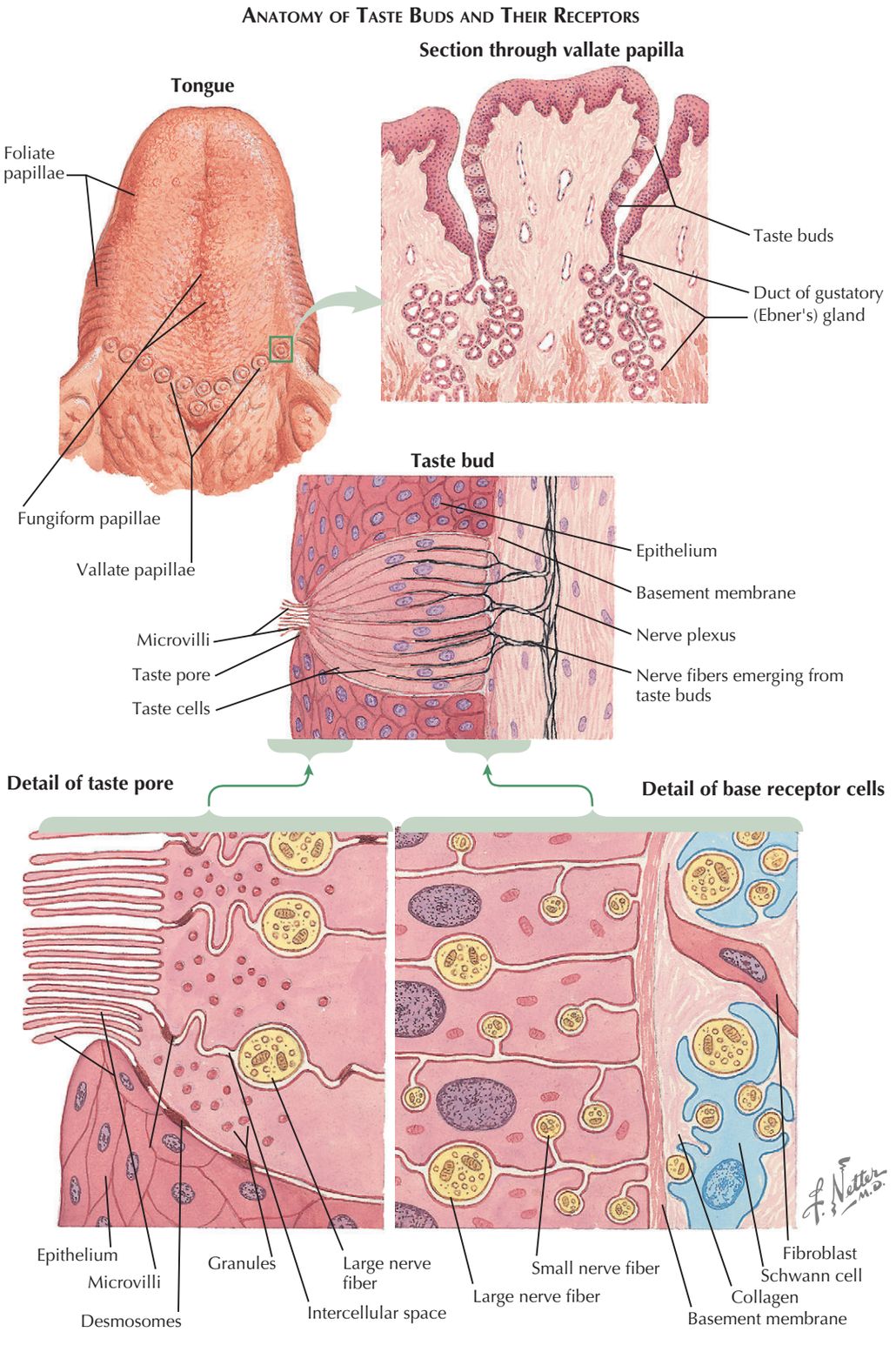
Taste buds contain the receptors responsible for taste sensation. They are located on the upper surface of the tongue, soft palate, epiglottis, and upper esophagus. The greatest concentration of taste buds is found on the raised protuberances of the tongue called the papillae. The vallate papillae are located at the back of the tongue in front of the sulcus terminalis and are innervated by the glossopharyngeal nerve. The fungiform papillae are located at the apex of the tongue and are innervated by the facial nerve. Foliate papillae are found on the roof of the mouth and are innervated by the facial and glossopharyngeal nerve.

Each taste bud consists of up to 100 polarized neuroepithelial cells that form "islands" of columnar pseudostratified cells embedded in the epithelium. Each bud has a central taste pore through which microvilli extend from the receptor cells. Just below their apical ends, the cells are joined by desmosomes, which seal off the intracellular spaces from the taste pore. There are three types of receptor cells (types I, II, and III) and basal cells that make up the taste bud. Taste buds are constantly being renewed.

Taste buds are innervated by both large and small fibers, which emerge from a subepithelial nerve plexus and enter the bud at its base. The larger fibers run in clefts between taste cells, while the smaller fibers (possibly terminal branches derived from large fibers) tend to run in invaginations found in the basal parts of taste cells.

The sensation of taste can be divided into five primary qualities: sweet (sucrose), sour (hydrochloric acid), salty (sodium chloride), bitter (quinine), and umami (L-glutamate and other L-amino acids). Sweet foods signal the presence of carbohydrates, which supply energy. Sour foods signal dietary acids and are frequently aversive. Salty taste sensation helps to regulate body water balance and blood pressure. Bitter taste is aversive and guards against poison consumption. Umami reflects food's protein content. The tip of the tongue is sensitive to all five stimuli but especially to sweet and salty substances, the sides of the tongue to sour substances, and the base of the tongue to bitter substances.

Water-soluble compounds evoke taste sensations by binding to the apical parts (microvilli) of the taste cells. Type I cells are the most abundant and function primarily by terminating synaptic transmission and regulating neurotransmitters. In type II cells, sweet, bitter, and umami ligands bind to taste receptors, resulting in an increase of cytoplasmic calcium and depolarization of the cell membrane, ultimately resulting in adenosine triphosphate (ATP) release. Sour taste excites type III presynaptic cells. The presynaptic type III cells also form synaptic junctions with nerve



Taste Receptors and Pathways *(Continued)*

terminals and also express proteins involved in synapses. These cells release both serotonin and norepinephrine. Salty taste is detected by direct permeation of sodium through membrane ion channels. The cell type underlying salty taste has not been identified, although type I cells have been implicated.

A single-taste cell responds to more than one of the five primary taste stimuli but not equally to each sensation. Similar multiple responses are observed in taste fibers, each of which synapses with several taste cells. The patterns of responses to the five taste stimuli by single fibers are not entirely random because experimental studies of large groups of fibers have revealed a tendency for certain fiber groups to respond specifically to certain sets of stimuli. For instance, a considerable number of fibers have been observed to respond well to both salt and acid stimuli, whereas fibers responding strongly to both salt and sweet stimuli are rare. Even within a given responding group, the relative sensitivity to different stimuli varies widely.

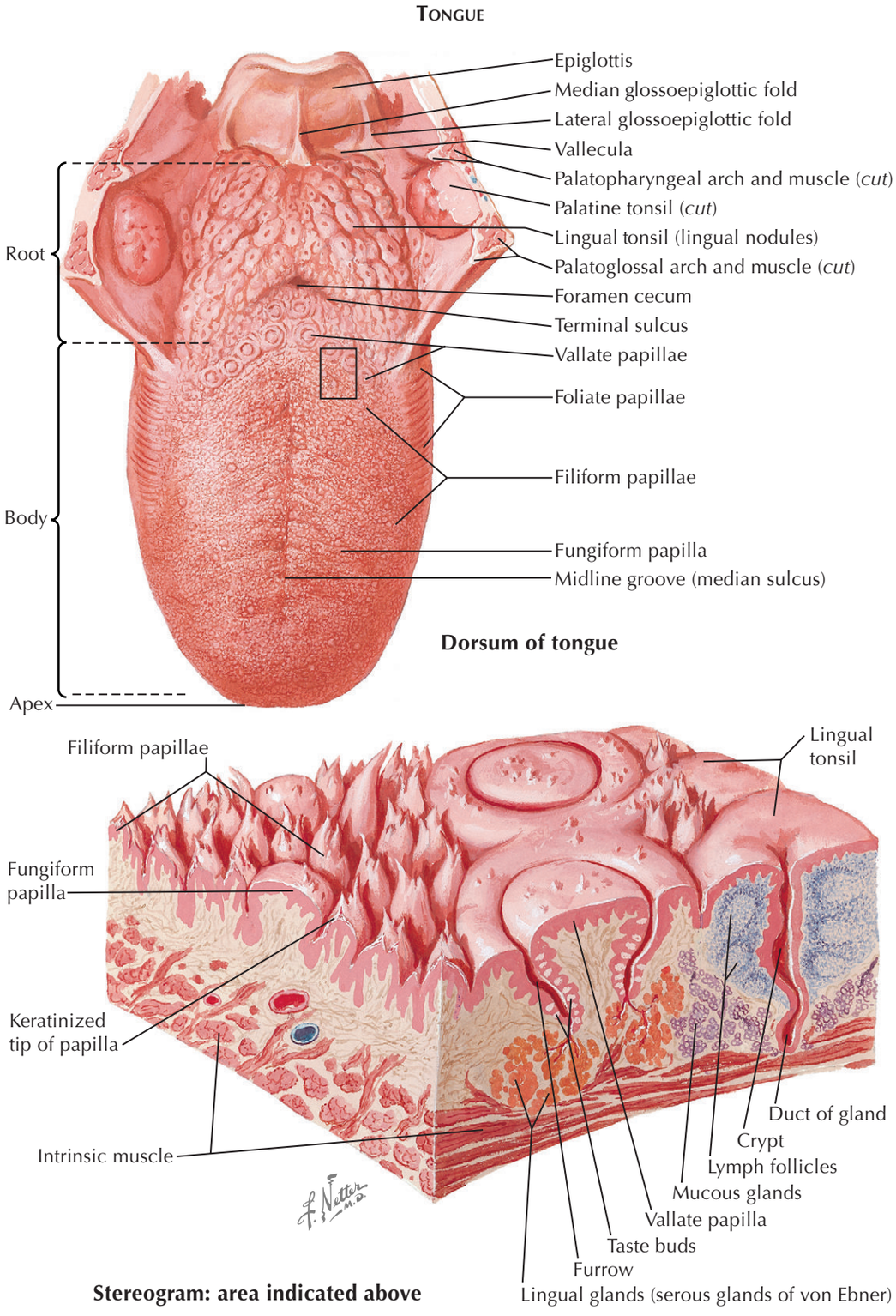
Taste Pathways

The chemosensitive cells found in the taste buds of the tongue, epiglottis, and larynx are innervated by three groups of sensory neurons.

Sensory Neurons. Taste cells synapse with sensory axons that run in the chorda tympani and greater superficial petrosal branches of the facial nerve, which carries taste sensation via the geniculate ganglion. The lingual branch of the glossopharyngeal nerve carries taste sensation via the petrosal (inferior) ganglion of the glossopharyngeal nerve. The superior laryngeal branch of the vagus nerve passes through the nodose (inferior) ganglion. All three groups of cells terminate in the medullary nucleus of the tract of solitarius.

Central Connections. From the nucleus of the tract of solitarius, second-order neurons project mostly ipsilateral (some fibers may cross over in the medial lemniscus) up the solitariothalamic bundle to the ipsilateral ventral posteromedial nucleus of the thalamus. Third-order neurons from the VPM nucleus pass through the posterior limb of the internal capsule to the taste region of the sensory cortex, located just below the face. The hypothalamic and amygdalar taste connections, on the other hand, appear to be primarily involved in reflex and motivational responses to taste stimuli, and thus control food intake.

The reflex-type brainstem connections between the taste nuclei and the autonomic nuclei for salivation (superior and inferior salivatory nuclei) mediate salivation reflexes that accompany taste responses to food stimuli on the tongue. "Gustation sweating," facial and forehead sweating in response to eating spicy foods, is a normal response, although it can be pathologic if profuse.

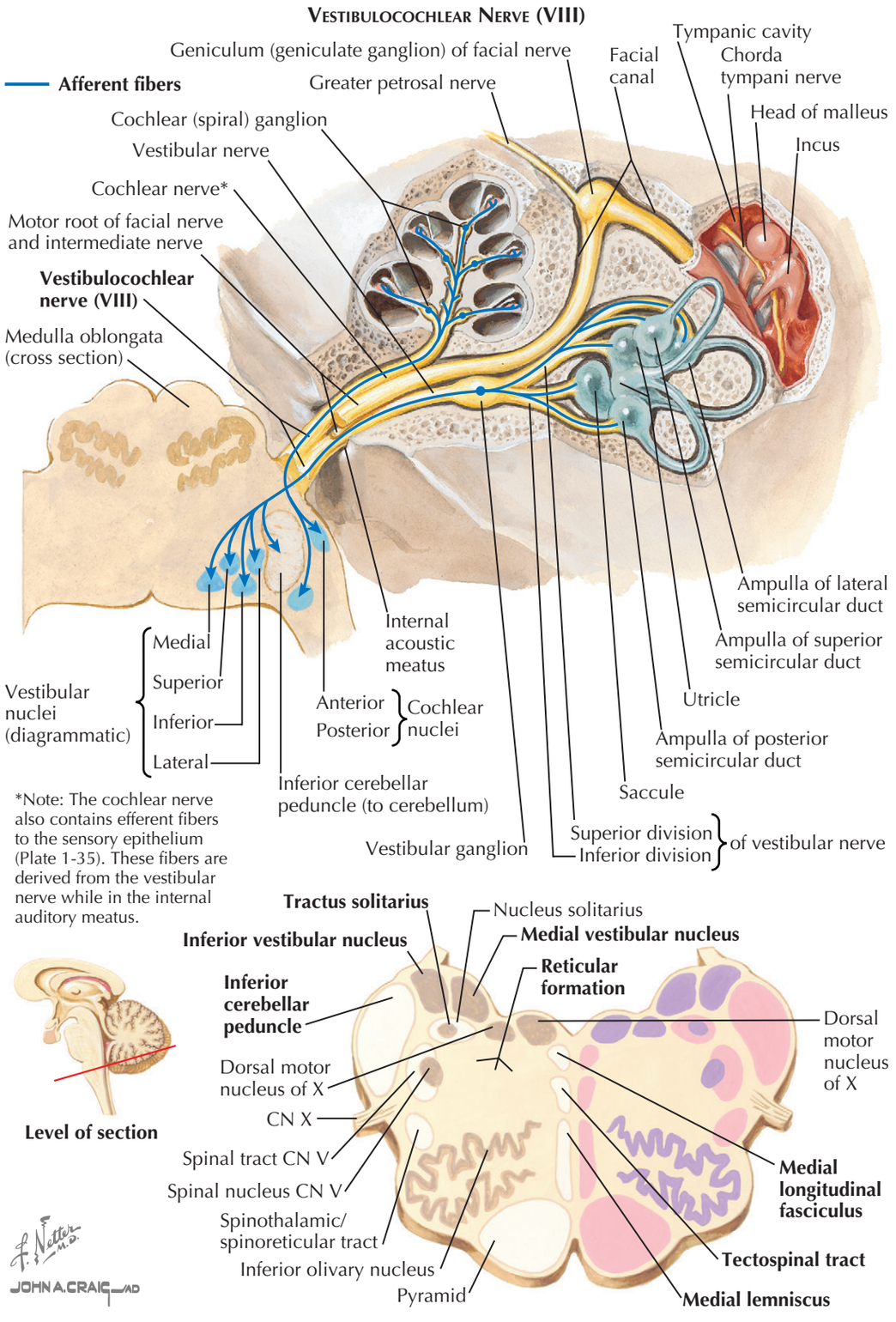


Cranial Nerve VIII: Vestibulocochlear Nerve

The vestibulocochlear nerve consists of two separate divisions, the vestibular and cochlear nerves. The vestibular labyrinth of the internal ear, including the semicircular ducts (canals) and the otolith organ (utricle and saccule), subserves equilibration, posture, and muscle tone. Linear acceleration is monitored by macules of the utricle and saccule, and angular acceleration is monitored by the cristae in the ampullae of the semicircular canals. The cochlea of the internal ear transmits auditory impulses from the spiral organ. The roots of the vestibular and cochlear nerves are attached behind the facial (VII) nerve, in the triangular area bounded by the pons, cerebellar flocculus, and medulla oblongata. The vestibular and cochlear nerves enter the brainstem separately and have different central connections. Sympathetic and parasympathetic fibers likely accompany both parts of the vestibulocochlear nerve. The vestibular and cochlear nerves usually unite over a variable distance and pass outward to enter the internal acoustic meatus, below the motor root of the facial nerve, with the nervus intermedius interposed.

VESTIBULAR NERVE

At the fundus of the internal acoustic meatus, the vestibular part of the vestibulocochlear nerve expands to form the vestibular ganglion before dividing into superior and inferior divisions. Both divisions contain peripheral processes of the vestibular bipolar cells, which penetrate tiny foramina in the superior and inferior vestibular areas of the fundus of the internal meatus. The peripheral processes spread to contact hair cell receptors embedded in the neuroepithelium lining the ampullae of the semicircular ducts (canals) and the maculae of the saccule and utricle. The longer central processes of the bipolar cells transmit impulses from these vestibular hair cells to the brainstem. Passing backward in the pontomedullary junctional area, the central processes divide into ascending and descending branches, which end predominantly in the superior (cranial), inferior (caudal), medial, and lateral vestibular nuclei located in the medulla oblongata and lower pons. Other branches proceed directly through the homolateral inferior cerebellar peduncle to the flocculonodular cerebellar lobe. Fibers from the superior nucleus enter the ipsilateral medial longitudinal fasciculus and ascend to end on cells of cranial nerves III, IV, and VI. Fibers from the inferior, medial, and lateral nuclei all terminate on the contralateral medial longitudinal fasciculus, in addition to connections with the autonomic nuclei, reticular formation, and the intermediolateral column of the cord. These connections play a crucial role in regulating posture and coordinating head, body, and eye movements. Separate vestibular-cerebellum pathways, mainly through the fastigial nuclei, also influence



Cranial Nerve VIII: Vestibulocochlear Nerve *(Continued)*

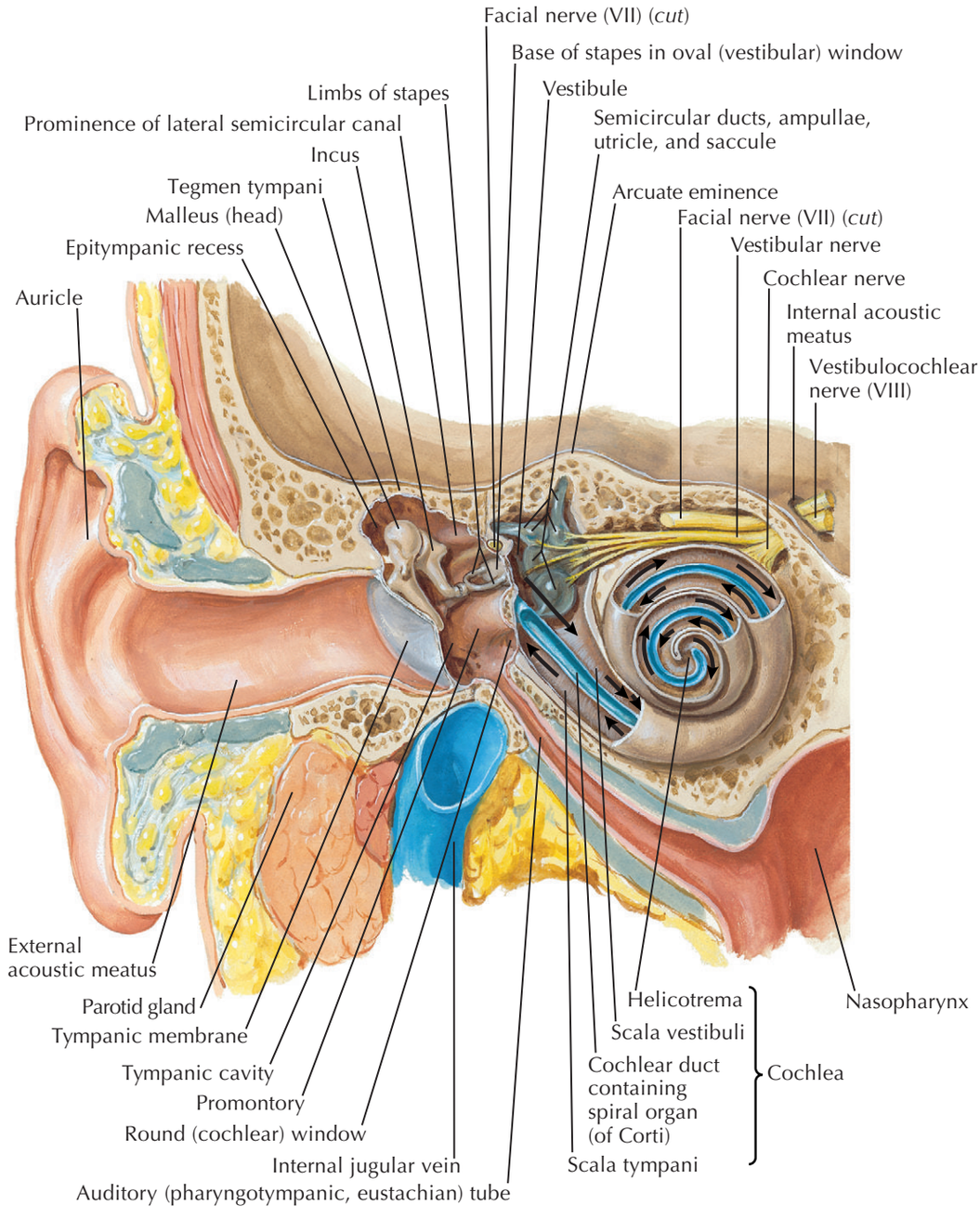
posture and movement coordination. Connections with the autonomic centers and the intermediolateral column likely account for the nausea and vomiting seen, at times, with overstimulation of the vestibular system.

COCHLEAR NERVE

The fibers in the cochlear part of the vestibulocochlear nerve traverse many small, spirally arranged foramina in the fundus of the internal acoustic meatus and enter the modiolus, the central pillar of the cochlea. The fibers run in tiny longitudinal and spiral canals into the conical central modiolus, with numerous enlargements of the spiral cochlear ganglia that contain bipolar nerve cells. The short peripheral processes of these bipolar cells end in special acoustic hair cells in the spiral organ of Corti in the cochlear duct. The hair cells located at the apex of the cochlea are stimulated by low-frequency tones, and those located at the base are stimulated by high-frequency tones. The relatively long central processes of the bipolar cells of the cochlear nerve reach the brainstem lateral to the vestibular part and end in the ventral and dorsal cochlear nuclei located on the lateral aspect of the inferior cerebellar peduncle in the superior medulla. The dorsal nuclei receive high-frequency fibers, and the ventral nuclei receive the low-frequency hair cells. Most cochlear nuclear fibers decussate through the trapezoid body before climbing in the lateral lemniscus to the inferior colliculus, while others synapse with neurons in the superior olivary nucleus. Third-order neurons from the inferior colliculus synapse in the medial geniculate body, which is the thalamic auditory relay nucleus. The fourth-order neurons proceed as the auditory radiations and courses laterally through the sublenticular portion of the internal capsule to the primary auditory cortex in the transverse temporal gyri of Heschl (Plate 1-34).

Pathway of Sound Reception

Frontal section



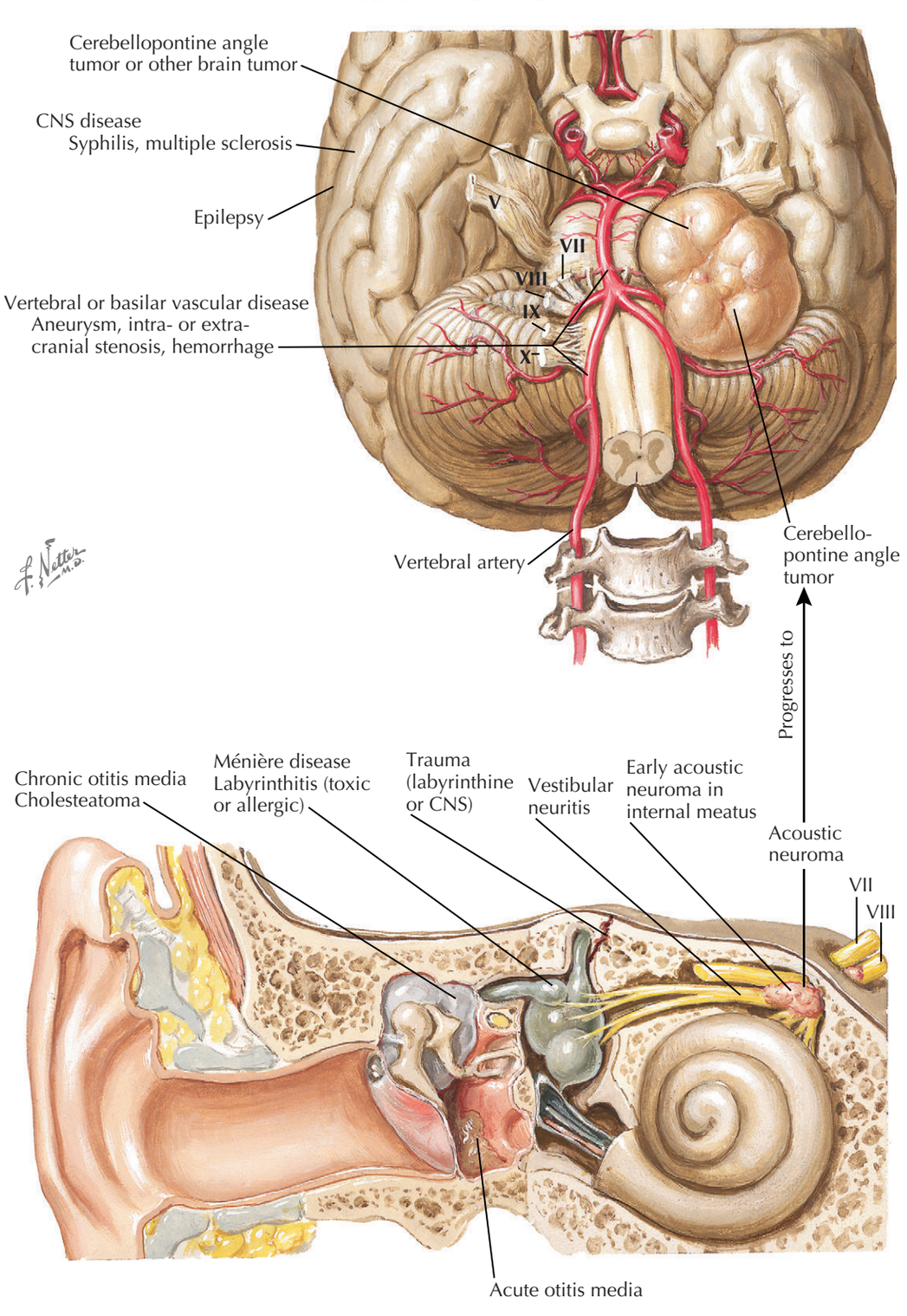
Note: Arrows indicate course of sound waves.

DISORDERS OF THE VESTIBULOCOCHLEAR NERVE AND SYSTEM

Vestibular

Ménière disease is an idiopathic process characterized by bouts of episodic vertigo, fluctuating but eventually progressive sensorineural hearing loss, tinnitus, and a sensation of aural fullness. Vestibular symptoms predominate especially early, and chronic imbalance may eventually ensue. Ménière disease is felt to be secondary to an imbalance of the inner ear's endolymph. Bilateral Ménière disease may have an autoimmune basis. Although Ménière disease is often associated with hearing loss and ear fullness, vestibular neuritis in contrast is characterized by prolonged vertigo without hearing loss. *Benign paroxysmal positional vertigo (BPPV)* is caused by errant otolith debris lodging into the semicircular canals and leading to overstimulation with head

Cranial Nerve VIII: Vestibulocochlear Nerve
(Continued)



movement. Upper respiratory and otologic infections, head trauma, and sustained unusual head postures are described triggers in many cases. Bedside maneuvers and vestibular rehabilitation help reposition errant otolith debris and reestablish equal tonic vestibular input (e.g., canalith repositioning or Epley maneuver).

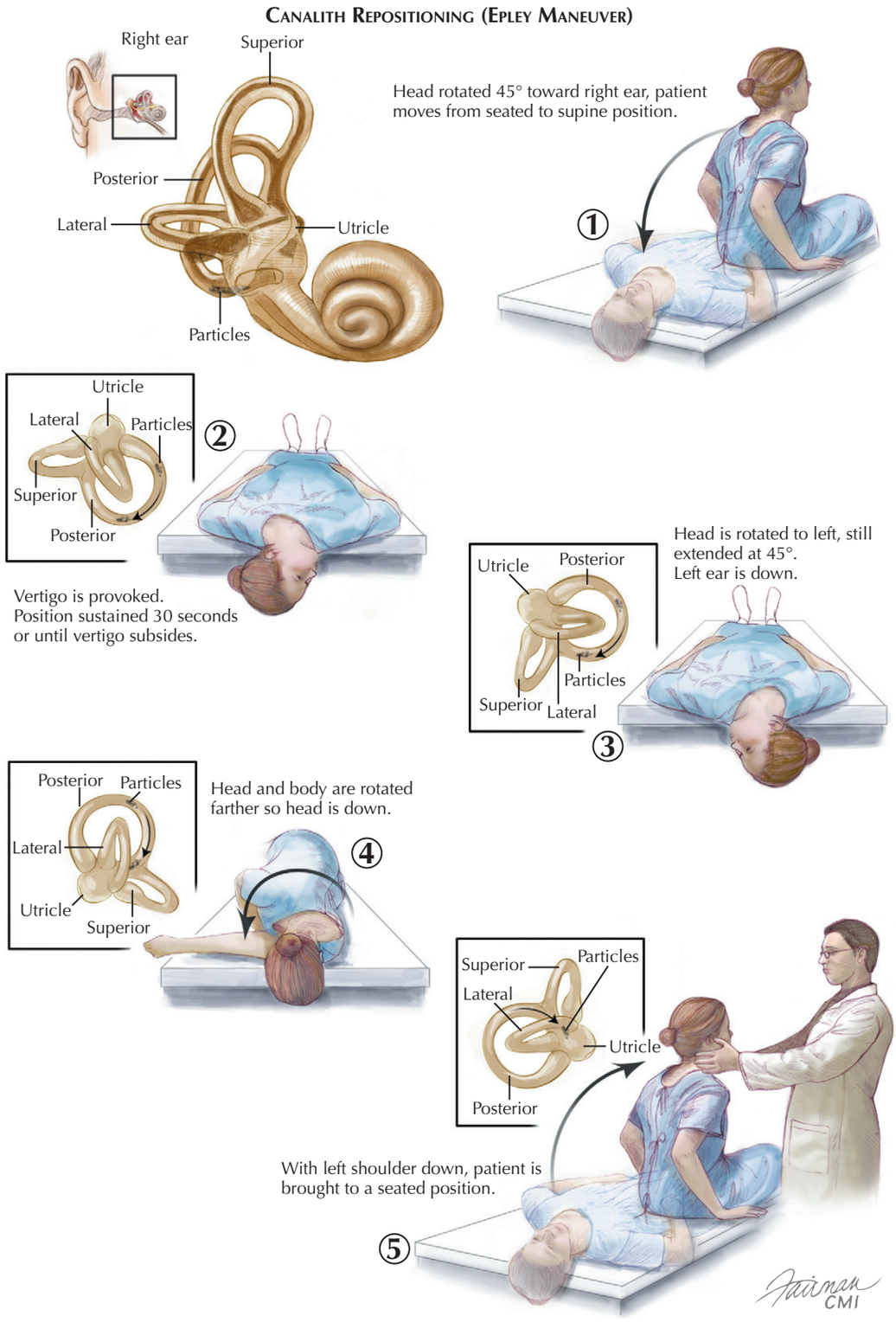
Vestibular schwannoma (also known by the misnomer "acoustic neuroma") is a benign Schwann cell tumor of the vestibular nerve that accounts for 6% of intracranial tumors. Vestibular schwannomas involve the adjacent cochlear division by compression against the walls of the internal auditory canal. Progressive hearing loss from stretching or compression of the cochlear nerve is the most common symptom, occurring in approximately 95% of patients. High-pitched unilateral tinnitus is often present, but vestibular symptoms are paradoxically infrequent as the contralateral vestibular system adjusts gradually to the imbalance. Large tumors can lead to facial or trigeminal nerve involvement and, at times, pontine compression.

The eighth cranial nerve is vulnerable to fractures involving the petrous part of the temporal bone and by tumors affecting the brainstem or cerebellum. Vertigo may be caused by central or peripheral pathology, but the distinction is not always readily clear, and thus, diagnostic circumspection is often warranted because posterior circulation strokes may manifest with the complaint of vertigo. Brainstem involvement from stroke or, at times, multiple sclerosis, may often be distinguished from a peripheral etiology by symptoms or signs indicating damage to other brainstem structures, such as dysmetria, diplopia, dysphagia, dysarthria, sensory loss, or weakness.

Cochlear

Conductive hearing loss refers to disrupted sound wave transmission to the cochlea from external ear canal, tympanic membrane, or ossicular dysfunction. *Sensorineural hearing loss* relates to impairment of the cochlea (sensory), cochlear nerve, or nuclei (neural), or any part of the brain auditory pathway (central).

Auditory nerve dysfunction usually results in subjective tinnitus in addition to sensorineural hearing loss. Tinnitus, the sensation of ringing in the ears without significant stimulus, is more frequently noted with peripheral than central lesions. Pulsatile tinnitus is often associated with vascular abnormalities such as arteriovenous malformations, glomus tumors, hemangiomas, meningiomas, vascular loops, high-grade carotid stenosis, intracranial aneurysm, and dural arteriovenous fistulae. Pulsatile tinnitus is also a feature of



Cranial Nerve VIII: Vestibulocochlear Nerve *(Continued)*

idiopathic intracranial hypertension. Although bilateral deficits reflect general processes such as ototoxicity (aminoglycosides, salicylates, or loop diuretics), noise exposure, and age-related hearing loss (presbycusis), unilateral hearing loss should raise concern of neoplastic, vascular, neurologic, or inflammatory etiologies. Fluctuating symptoms are seen in Ménière disease, while progressive loss may indicate tumor (e.g., vestibular schwannoma). Ménière disease typically results in low roaring tinnitus, while high-pitched tinnitus may suggest tumor or presbycusis. Sudden hearing loss occurs with viral neuritis or vascular processes that occlude the cochlear blood supply from the internal auditory artery, a terminal branch of the anterior inferior cerebellar artery or the basilar artery. This can also occur from compression by a tumor in the internal auditory canal. A stroke from occlusion of the anterior inferior cerebellar artery itself may cause infarction of the pons, with ipsilateral hearing loss, vestibular symptoms, gait ataxia, conjugate gaze palsy, ipsilateral facial paralysis, and sensory loss, as well as contralateral body loss of pain and temperature sensation. Combined symptoms of tinnitus and vertigo are inner ear symptoms and indicate involvement of the cochlea, vestibular labyrinth, auditory nerve, or a combination of structures.

Canalith Repositioning Maneuvers

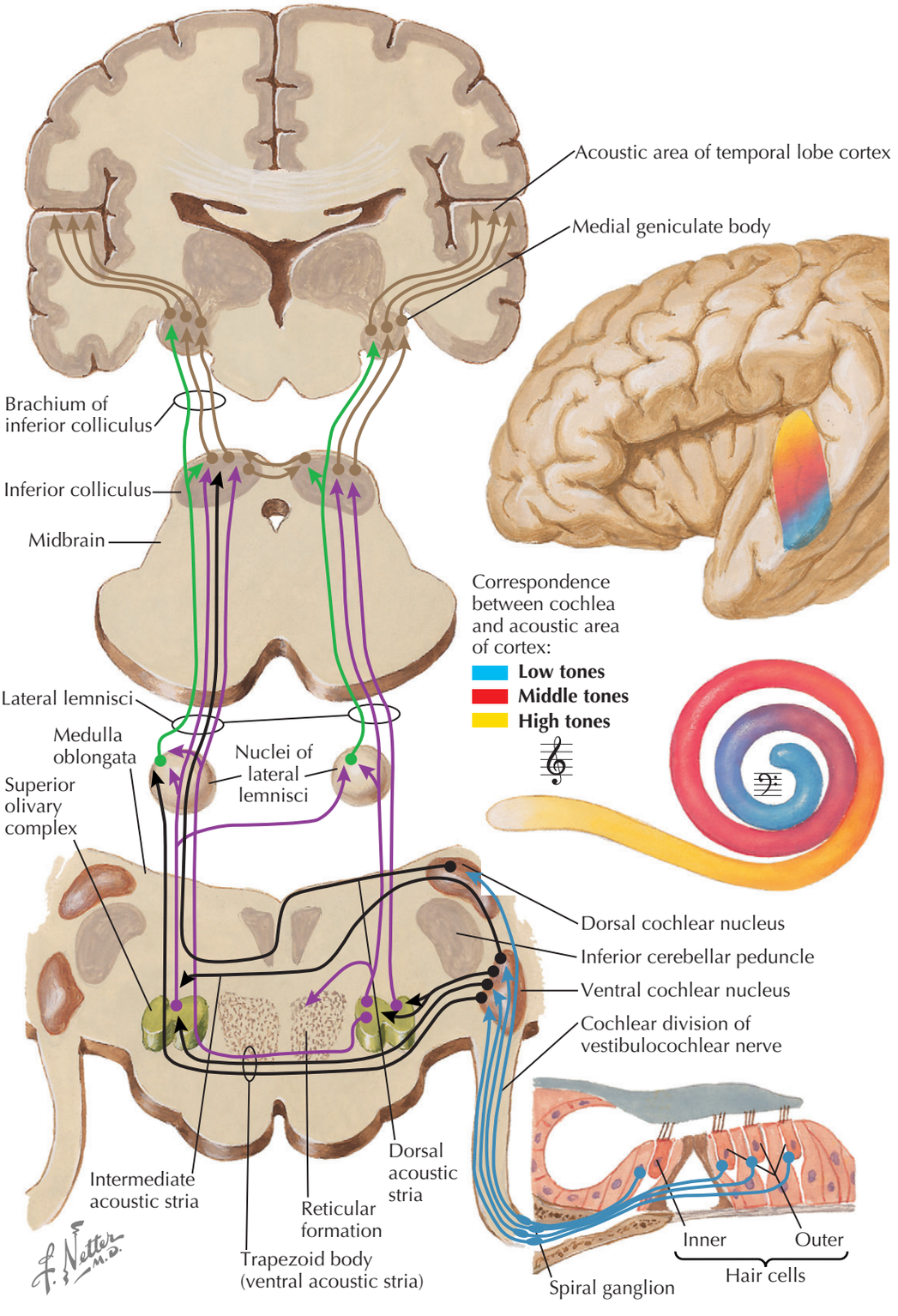
First-line therapy for benign paroxysmal positional vertigo (BPPV) includes canalith repositioning maneuvers such as the Epley maneuver. The maneuver uses gravity to pull the canalith debris out of the affected semicircular canal and into the utricle, where it lodges in the otolithic membrane of the macula (Plate 1-36). The maneuver requires sequential movement of the head into four positions, staying in each position for approximately 30 seconds. The Epley maneuver is most useful for posterior canal BPPV. The patient begins in the upright sitting position with the head turned 45 degrees toward the affected side (in the figure, the right ear is affected). The patient then lies down with the affected ear facing the ground and the head in 30 degrees of neck extension (Dix-Hallpike test). Vertigo and nystagmus is elicited, and the position is maintained until the nystagmus ceases. Then the head is rolled 180 degrees until the affected ear is facing up. The patient rolls onto their side until their nose points toward the floor. The patient then rapidly returns to the seated position, where he or she stays for 30 more seconds. The maneuver is repeated until no nystagmus is elicited.

Afferent Auditory Pathways

Auditory afferent fibers enter the brainstem as the vestibulocochlear nerve and then branch to the dorsal and ventral cochlear nuclei located in the medulla. Neurons in these nuclei have similar properties: each is excited by a relatively narrow range of sound frequencies and may be inhibited by tones outside that range. Within each nucleus, neurons sensitive to different frequencies are arranged in an orderly manner, which gives rise to a tonotopic distribution within the nucleus.

The fibers of the ventral cochlear nucleus then project to the superior olive located in the medulla. The fibers then project by way of the lateral lemniscus nuclei and other relays to the inferior colliculus. The dorsal cochlear nucleus projects directly to the inferior colliculus via the lateral lemniscus. Fibers from both the ventral and dorsal cochlear nucleus project from the inferior colliculus to the medial geniculate nucleus of the thalamus. Within the colliculi signals from both ears interact on their way toward the cerebral cortex. From the medial geniculate nucleus, the auditory signals travel to the primary auditory cortex, which is located in the temporal lobe and is Brodmann's area 41. Despite the extensive intermixing among afferent fibers, the bulk of the neural activity reaching the auditory cortex originates in the contralateral ear. Tonotopic ordering is preserved throughout the ascending pathway so that individual cortical regions are sensitive to specific frequencies. The width of the band of frequencies to which an individual neuron responds is approximately the same in area 41 as at the level of the cochlear nuclei.

In the analysis of acoustic information, relatively little is known about the function of the various stages along the auditory pathway. Neurons within the superior olivary complex are specifically adapted for analyzing the location of a sound in space. Olivary neurons receive excitatory input from the contralateral cochlear nuclei and inhibitory input from the ipsilateral cochlear nuclei. In the medial portion of the complex, where neurons are sensitive to sounds of low frequency, these opposing inputs result in individual neurons becoming attuned to a fixed time delay between the arrival of sound at each ear. In the lateral portion of the complex, where neurons are sensitive to higher frequencies, the opposing inputs result in neurons becoming sensitive to differences in the intensity of sound reaching each ear. The entire auditory pathway, including the auditory cortex, must be intact for sound localization to take place. Similarly, auditory structures as far as the level of the inferior colliculus are required for frequency discrimination, even though neurons at all levels of the auditory pathway are frequency selective.



Intensity discriminations, on the other hand, can be made following the destruction of the inferior colliculus and higher centers. Such discrimination may involve the collateral pathways that relay auditory signals to the brainstem reticular formation. These pathways are probably also involved in the reflex reaction to a sudden sound.

Disorders. A common auditory pathway deficit is vestibular schwannoma. The patient suffers loss of sound localization, diminished speech discrimination, tinnitus, imbalance, and diminution of the stapedius reflex. Nerve-type deafness can be caused by toxins (e.g., arsenic, lead, quinine) and by antibiotics such as streptomycin, which can also damage the cochlea directly. Because of the multisynaptic and highly complex system of crossed pathways, damage to auditory brainstem tracts and nuclei by trauma, tumors, or vascular disorders results in only slight hearing impairment.

Centrifugal Auditory Pathways

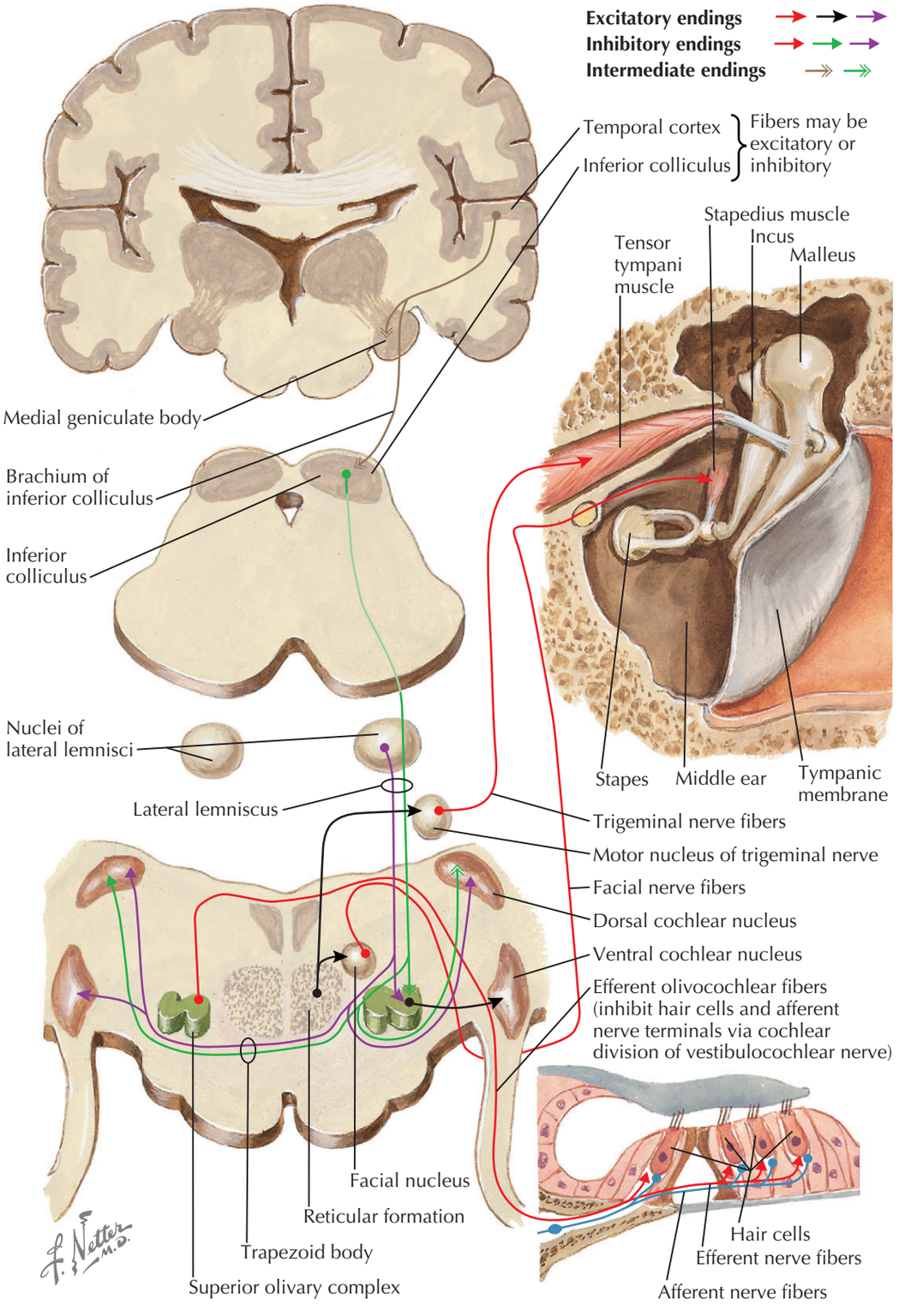
In addition to the afferent neural pathways that carry auditory information from the cochlea to the higher centers, there is a parallel, descending efferent pathway named the centrifugal pathway. Within the brain, such connections arise from each of the areas involved in the auditory system, including the primary auditory cortex, and project to nuclei one or two levels below their point of origin. Individual connections may be either excitatory or inhibitory, but the centrifugal pathways appear to be activated by the inhibition of transmission of auditory signals through the ascending auditory pathways.

Centrifugal auditory pathways also include efferent projections to the sensory hair cells of the cochlea and to the muscles of the middle ear. The cochlear efferent fibers originate from a group of neurons on the medial side of the contralateral superior olive and pass to the cochlea via the crossed olivocochlear bundle and the cochlear division of the vestibulocochlear nerve. They are joined by a smaller number of fibers, which originate in the ipsilateral superior olive. The olivocochlear efferent pathway comprises the medial olivocochlear system (MOCS) and the lateral olivocochlear system (LOCS). The MOCS has large cell bodies in the medial and anterior olivary regions and innervate the outer hair cells of the cochlea. The LOCS has small cell bodies in and around the lateral superior olive and innervate the afferent dendrites beneath the inner hair cells of the ipsilateral cochlea. The large outer hair cell endings are primarily cholinergic, whereas the axodendritic synapses beneath the inner hair cells contain acetylcholine, dopamine, enkephalins, and other peptides. The efferent fibers produce hyperpolarization in the cochlear hair cells and afferent nerve terminals, thereby decreasing the afferent response produced when sound reaches the cochlea. Fibers innervating the muscles of the middle ear originate in the trigeminal motor nucleus and the facial nucleus (the tensor tympani muscle and the stapedius muscle). By contracting, these muscles decrease the transmission of sound vibrations from the eardrum to the oval window by way of the ossicles (incus, malleus, and stapes).

Several functions have been proposed for the centrifugal auditory pathways. One possibility is that efferent impulses can suppress the auditory nerve afferent responses to sound, thus preventing damage from too strong a stimulus. The middle ear muscles contract during loud noises and self-initiated vocalization, thereby helping to prevent saturation or damage of the cochlear receptors. Sound-activated efferent fibers in the olivocochlear bundle may additionally contribute to the suppression of sensory input that could saturate the central nervous pathways. A related mechanism, possibly also mediated by olivocochlear fibers, is improved auditory discrimination by the attenuation of loud background noise.

The phenomenon of selective attention to auditory signals is likely also to be an effect of the centrifugal auditory pathways. This "attentional filter" is absent in de-efferented humans. Evidence also shows that habituation to repeated auditory stimuli occurs with inhibition of the cochlear nuclei.

Finally, efferent olivocochlear pathways participate in auditory discrimination. Neurons at higher levels of the auditory pathway tend to respond to transient changes in auditory input rather than to steady signals. Centrifugal inhibition may be a factor in eliminating responses to steady signals, thus accentuating sensitivity to transient ones. Together with the inhibition that takes place within each level of the auditory system, it may also contribute to the processes that sharpen neuronal responses by restricting the ranges of the frequencies to which each neuron responds.



Vestibular Receptors

The *membranous labyrinth* is a specialized structure that converts angular and linear accelerations of the head into neuronal signals. This labyrinth is filled with potassium-rich endolymph and is a system of thin-walled intercommunicating tubes and ducts situated within the petrous part of the temporal bone at the base of the skull. The membranous labyrinth consists of the otolith organ (utricle and saccule) and three semicircular canals. The utricle and saccule contain specialized receptors called maculae that specifically respond to linear acceleration. Connected to the utricle are the three semicircular canals oriented at right angles to each other, which respond to angular acceleration. Within swellings of the canals, called ampullae, are the specialized receptors, the cristae.

The vestibular labyrinth receives dual innervation. The distal axonal processes of the bipolar vestibular afferent neurons have cell bodies housed in the vestibular ganglion of the internal acoustic meatus. The afferent axons terminate on the mechanoreceptive vestibular hair cells that serve as the sensory transducers. The vestibular efferent fibers originate in the brainstem.

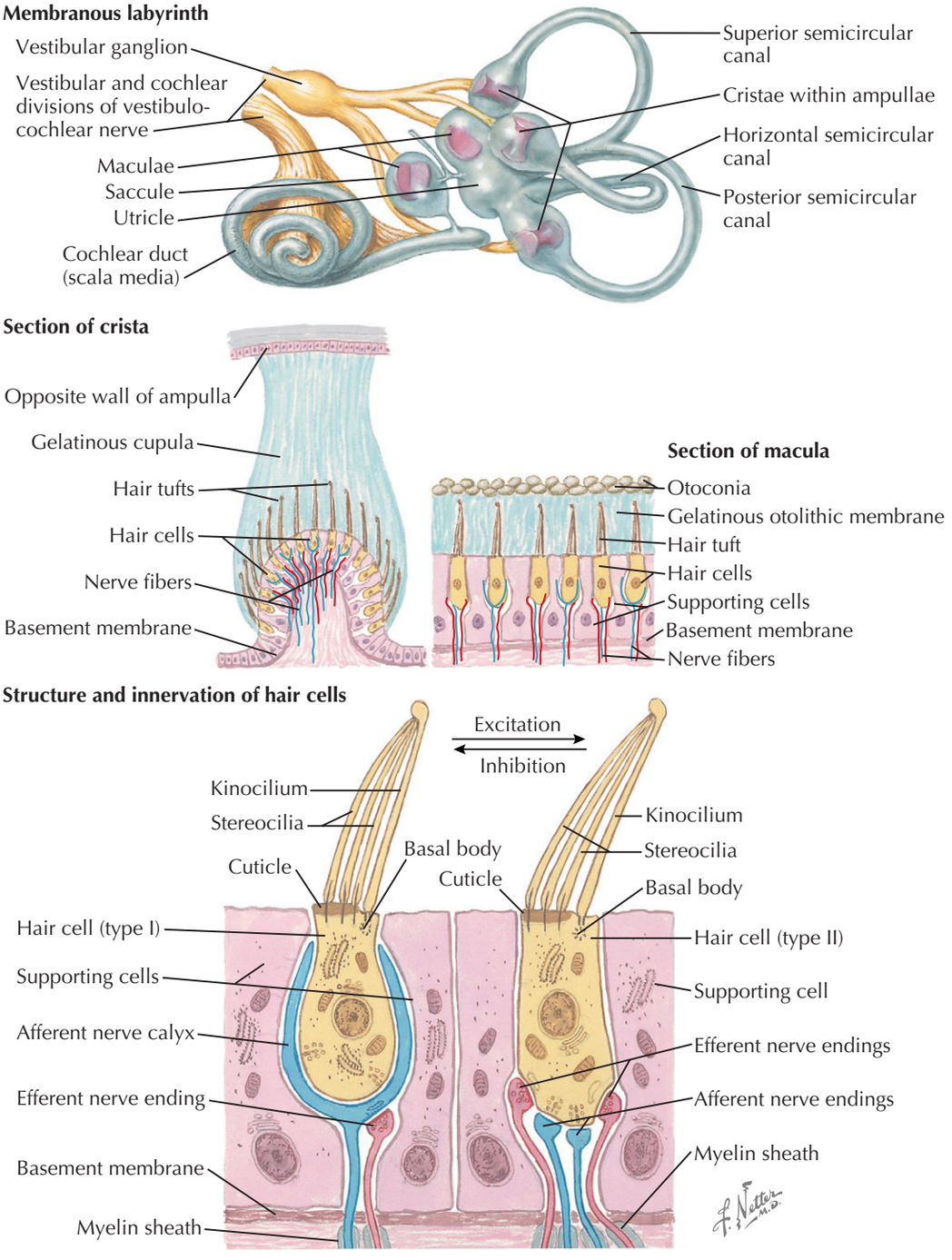
Hair cells are specialized epithelial cells that have ciliary tufts protruding from their apical surface. Type I cells are goblet shaped and are enclosed in a nerve chalice. Synaptic terminals packed with vesicles are in contact with the base of the chalice and are likely presynaptic terminals. Type II hair cells are more common and have small terminal synaptic boutons. They are innervated by thin nerve branches that form synaptic contact with the bottom of the cell. The efferent endings are presynaptic to the hair cell and filled with vesicles. Type I hair cells are thought to be more sensitive than those of type II. Efferent fibers form typical chemical synapses with hair cells or with afferent terminals, which act to increase the discharge rate of afferent fibers and to modulate their response to mechanical stimuli.

The apical ends of both types of hair cells bear a tuft of 40 or more sensory hairs, or stereocilia, whose bases are embedded in a stiff cuticle, and a single, lower kinocilium, which originates from a basal body and has a structure similar to that of a motile cilium. The entire group of hairs is joined together at its free end. The stimulus for the sensory hair cells is shearing displacement of the hair cells. Displacement of the sensory hair bundle in the direction in of the kinocilium is excitatory and results in depolarization of the hair cell and increased firing of the vestibular nerve fibers. In the opposite direction, the response is inhibitory and results in hyperpolarization of the hair cell and reduced firing of the vestibular nerve. Signal transduction in hair cells occurs via a direct gating mechanism in which the hair bundle deflection puts tension on membrane-bound, cation-selective ion channels located near the tip of the hair bundle. This increased tension opens the channel and allows calcium to enter the cell. The increased intracellular calcium promotes adaptation, which may activate molecular motors that adjust the tension of the transduction apparatus.

The cristae and maculae are especially sensitive to angular and linear acceleration and convert head movements to bending forces on the sensory hairs. The hair cells, the mechanoreceptors in the cristae, are embedded in a gelatinous mass called the cupula, which extends across the ampulla. During angular acceleration, there is displacement of the cupula and resultant bending of the sensory hairs. Because all hair cells in the cristae are oriented in the same direction as their kinocilia, this bending either increases or decreases the discharge rate of all the afferent fibers.

The hairs of the sensory cells found in the maculae of the saccule and utricle are embedded in a gelatinous otolithic membrane, which contains concretions of calcium carbonate called otoconia or otoliths. Because the otoconia are denser than the surrounding fluid, the otolithic membrane tends to move under the influence of linear acceleration. For instance, when the normally horizontal utricular macula is tilted, the pull of gravity tends to make the otolithic membrane slide downward, thus bending the sensory hairs. Because the macula contains hair cells that have two different orientations, this bending increases the discharge rate of some utricular afferent fibers and slows the discharge rate of others. These signals are analyzed by the central nervous system (CNS) for information on the position of the head. The macula of the saccule is in a vertical position and is therefore sensitive to vertical acceleration. The saccule may also contribute to the sensing of head position when the head is oriented with one ear down.

The vestibulospinal tracts are discussed in the spinal cord section.



Cochlear Receptors

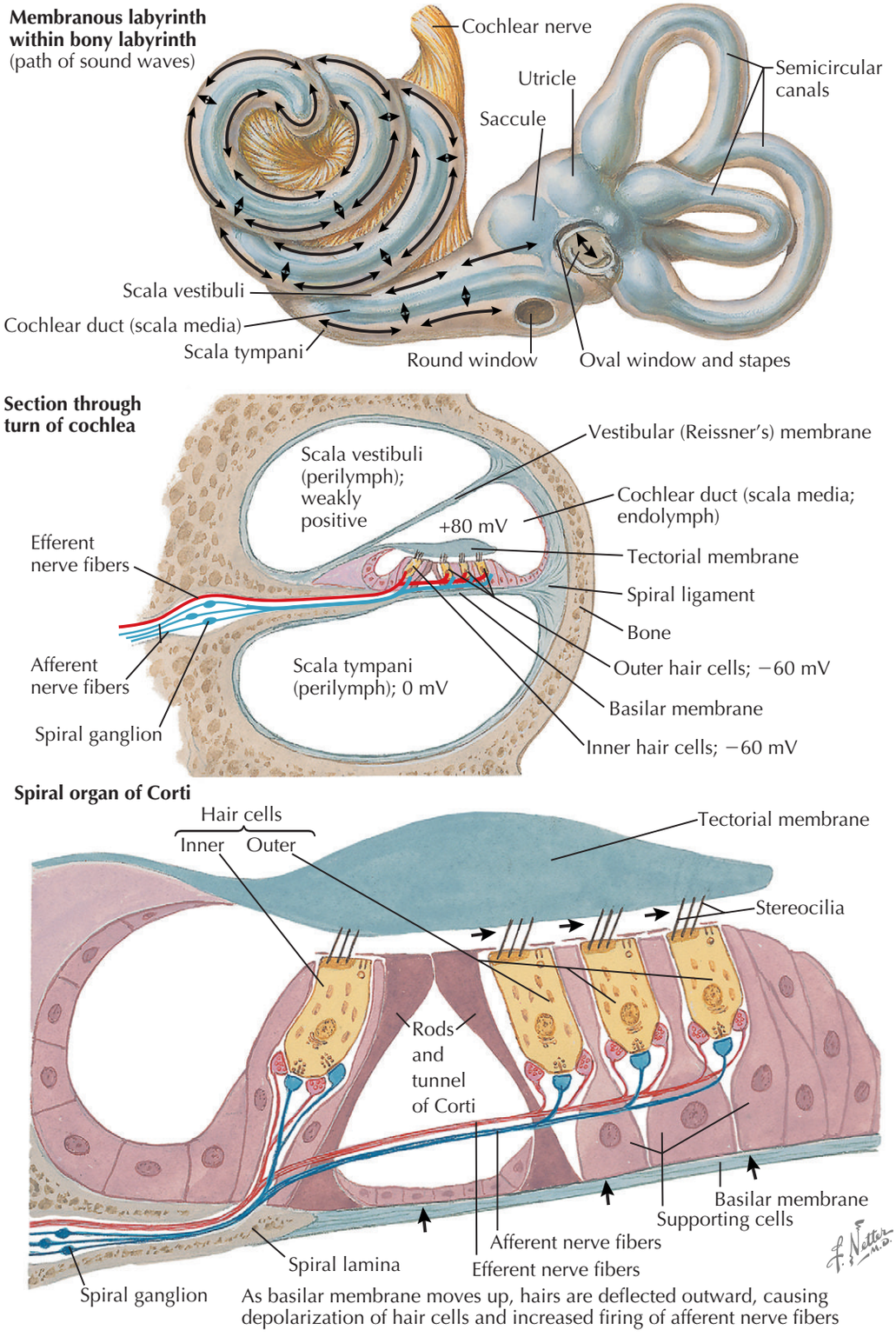
The human cochlea is a spiral channel located within the petrous portion of the temporal bone at the base of the skull. There are three fluid-filled chambers or scalae: the scala vestibuli, scala media, and scala tympani. The scala media is separated from the scala vestibuli by the vestibular (Reissner's) membrane and from the scala tympani by the stria vascularis. The scala media is filled with potassium-rich endolymph and is continuous with the vestibular labyrinth. The two remaining spaces, the scala vestibuli and the scala tympani, are external to the membranous labyrinth and are filled with perilymph. At the basal end of the scala vestibuli is the oval window, which is connected to the auditory ossicles that transmit vibration from the eardrum. At the basal end of the scala tympani is the membrane-covered round window, whose movements provide a compensatory release of the vibratory pressures at the oval window.

The cochlea receives dual innervation: afferent fibers, which originate from cell bodies in the adjacent spiral ganglion efferent fibers, which originate in the brainstem. Both types of fibers form synapses with sensory hair cells in the spiral organ of Corti (experimental studies have shown that activity in the efferent fibers can inhibit the discharge of cochlear afferent fibers). At the center of the organ of Corti is the tunnel of Corti, flanked by two sets of supporting rods of Corti (pillar cells). When hair cells are activated, impulse transmission is triggered in fibers of the spiral ganglion. The fibers then enter the brainstem as the cochlear nerve.

Hearing. The stapes ossicle bone transmits vibrations to the oval window on the outside of the cochlea. The perilymph vibrates in the scala vestibuli toward the helicotrema. Within the scala media is the receptor organ, the organ of Corti, which rests on top of the basilar membrane. The vibrations spread through the cochlea and induce vibrations in the basilar membrane, which are then transduced into afferent nerve excitation by the hair cells. The hair cells are arranged in inner and outer groups, and each cell is capped with 50 to 100 hairlike stereocilia that are imbedded in the tectorial membrane. The inner hair cells, about 3,500 in number, are arranged in a single row on the inner side of the inner rods of Corti; the 12,000 outer hair cells are longer and are arranged in three rows in the basal coil of the cochlea, and in four or five rows in the apical coil. Physiologic studies suggest that cochlear hair cells behave like their vestibular counterparts; bending of stereocilia in one direction leads to a depolarization of hair cells and an accelerated rate of nerve discharge, while bending in the opposite direction produces hyperpolarization and a slowing of discharge.

Another type of frequency analysis is based on the differences in the shape and stiffness of the basilar membrane located between the base and the apex of the cochlea. The basilar membrane vibrates to high frequencies at the base of the cochlea, where the basilar membrane is thinner and narrower, and to low frequencies at the apex. The dimensions of the basilar membrane gradually changes, so that for each vibration frequency between the two extremes, a somewhat restricted region of the membrane, and hence a certain group of afferent fibers, responds most vigorously. The cochlea is therefore said to be tonotopically organized: each afferent fiber will respond to some extent to a range of frequencies, while within the range is one frequency to which it will respond most readily.

Deafness. The cochlea is often the source of deafness, either to a specific pitch or to a broad range of frequencies. Head trauma can produce transient deafness, but severe injury involving a fracture of the petrous part of the temporal bone can cause permanent spiral ganglion or cochlear damage. Intense noise can cause temporary deafness; if it is sustained, permanent cochlear damage will result. The most common cause of deafness in adult life is otosclerosis, a non-neural process that results in the fixation of the stapes to the oval window.

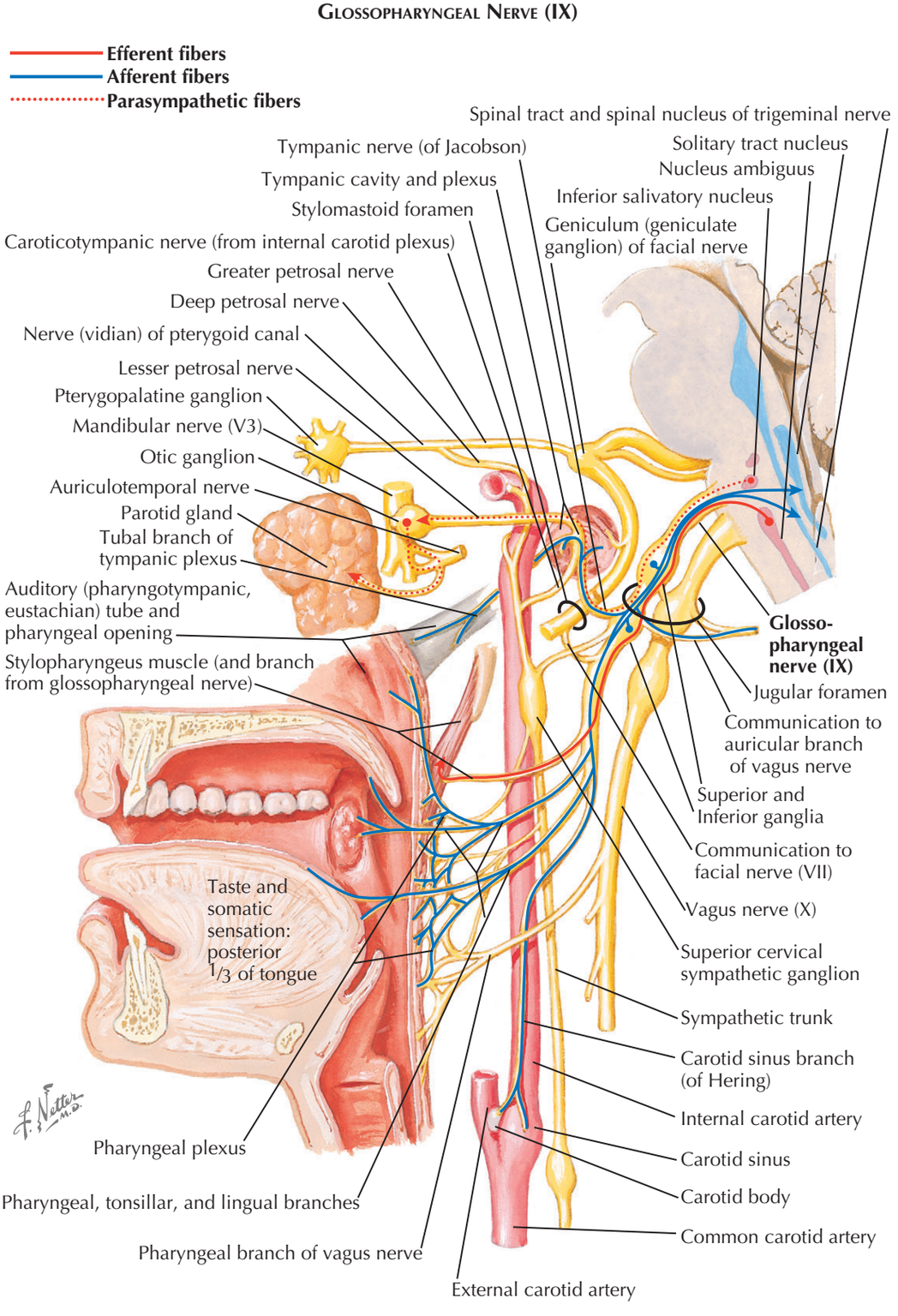


Cranial Nerve IX: Glossopharyngeal Nerve and Otic Ganglion

The glossopharyngeal nerve is closely related functionally and anatomically to the vagus nerve. The two share common nuclei of origin and terminate in the ambiguus and dorsal vagal nuclei. The glossopharyngeal nerve also carries secretomotor fibers from the inferior salivatory nuclei, which are scattered in the reticular formation. As its name implies, the glossopharyngeal nerve contains sensory, motor, and parasympathetic fibers that supply parts of the tongue and pharynx. Its rootlets emerge from the dorsolateral sulcus of the medulla oblongata, rostral to those of the vagus nerve. The rootlets unite, and the nerve joins the vagus nerve and spinal accessory nerve to leave the skull through the central part of the jugular foramen between the inferior petrosal and sigmoid sinuses. Two ganglia, a small superior ganglion and a larger inferior ganglion, are situated on the nerve. The pseudounipolar nerve cells contained in both ganglia transmit multiple afferent impulses: special visceral sensation (taste) from the posterior third of the tongue and part of the soft palate; general visceral sensation (touch, pain, temperature) from the posterior third and adjacent areas of the tongue, fauces and pharynx soft palate, nasopharynx, and tragus of the ear; general somatic afferent impulses, via the tympanic branch of the glossopharyngeal nerve, from small areas of postauricular skin and from the meninges in the posterior cranial fossa; and visceral afferent impulses from the carotid sinus and body. The central cell processes concerned with taste end in the nucleus of the solitary tract; those concerned with visceral sensation end in the combined dorsal glossopharyngeal-vagal nucleus, and those concerned with general somatic afferents likely end in the spinal tract and nucleus of the trigeminal nerve.

From the jugular foramen, the nerve arches forward between the internal jugular vein and internal carotid artery, then passes deep to the styloid process, and curves behind the stylopharyngeus muscle (which it supplies) to the side of the pharynx. It pierces the superior constrictor muscle (or passes between this muscle and the middle constrictor) to enter the base of the tongue. It finally divides into branches that supply the mucous membrane over the posterior third of the tongue, fauces, palatine tonsil, and adjacent part of the pharynx and glands and vessels in these areas.

The lingual branches convey special and general sensations from the vallate papillae and the tongue behind the sulcus terminalis. These branches are associated with small lingual ganglia. The ganglia act as relay centers for the preganglionic and postganglionic vasomotor and secretomotor neurons. Another glossopharyngeal branch is the tympanic nerve (or Jacobson's nerve), which arises from the inferior (petrous) ganglion and ascends through the tympanic canaliculus to the middle ear (tympanic cavity), where it contributes to the tympanic plexus and gives off the lesser petrosal nerve. The tympanic nerve contains sensory fibers that supply the middle ear, parasympathetic secretory fibers that serve the parotid gland, and sympathetic fibers that communicate with the carotid sinus. There are also communications with the auricular vagal branch, the superior vagal ganglion, the superior cervical sympathetic trunk ganglion, and the facial nerve. There is also a carotid sinus branch, a branch to supply the stylopharyngeus muscle, and several pharyngeal branches,



Cranial Nerve IX: Glossopharyngeal Nerve and Otic Ganglion *(Continued)*

which unite with similar vagal branches and sympathetic filaments to form a plexus on the surface of the pharynx.

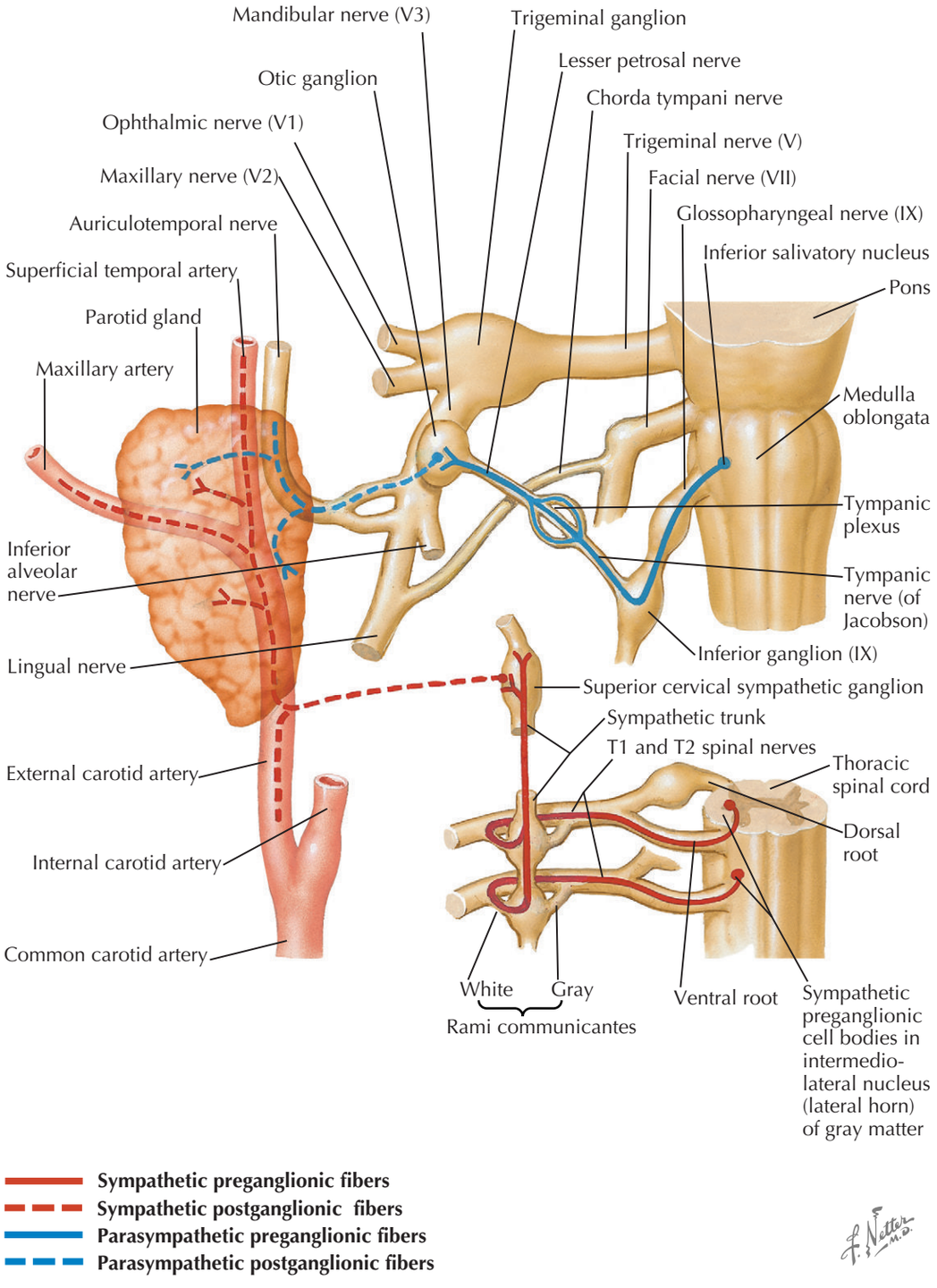
OTIC GANGLION

The otic ganglion lies directly below the foramen ovale between the mandibular nerve and the tensor veli palatini muscle, anterior to the middle meningeal artery. Its main parasympathetic root is the lesser petrosal nerve, which contains the parotid secretory and vasodilatory fibers. After relaying in the ganglion, these fibers reach the gland through the parotid branches of the auriculotemporal nerve (a branch of the trigeminal nerve). The sympathetic fibers of the otic ganglion are a filament from the middle meningeal plexus. The ganglion may also communicate with the nerve of the pterygoid canal, the medial pterygoid nerve, and the chorda tympani. Some taste fibers from the chorda tympani may pass through the communication with the ganglion and reach the facial nerve through its connection with the nerve of the pterygoid canal. The fibers from the medial pterygoid nerve traverse the ganglion without relay to supply the tensor veli palatini and tensor tympani muscles.

The pharyngeal reflex or gag reflex is elicited by stimulating the posterior pharyngeal wall and results in bilateral contraction of the pharyngeal muscles and brief elevation of the soft palate. The sensory limb is mediated by the glossopharyngeal nerve via the petrosal ganglion. The efferent limb is mediated by the vagus nerve and glossopharyngeal nerve. The vagus nerve originates in the rostral nucleus ambiguus of the medulla, then exits the brainstem dorsolateral to the inferior olive, and exits the skull via the jugular foramen and innervates the stylopharyngeus muscle and superior pharyngeal constrictors. If there is a glossopharyngeal nerve lesion, there is no response when touching the affected side of the pharynx. If there is vagal nerve damage, the soft palate elevates and pulls toward the intact side.

Lesions of the glossopharyngeal nerve rarely occur in isolation and usually are associated with vagus and spinal accessory nerve dysfunction, manifesting as dysphagia and dysphonia, ipsilateral palatal weakness, loss of gag reflex, homolateral vocal cord paralysis, altered taste and oropharyngeal sensation, decreased parotid secretion, and sternocleidomastoid and trapezius weakness. The major causes are trauma and tumors (especially paragangliomas), metastatic lesions to the skull base, extension of mastoid infections, or autoimmune disorders, such as giant cell arteritis.

Glossopharyngeal neuralgia is a disorder characterized by paroxysms of severe unilateral pain in the tongue, throat, ear, and tonsils. Symptoms of pain typically last from seconds to a few minutes and are triggered by chewing, talking, coughing, yawning, swallowing, and eating particular foods. The etiology is often unclear, but, some cases may be due to vascular compression of the nerve. There is usually no associated impairment of the glossopharyngeal nerve (e.g., no dysphagia) or any abnormal findings on the neurologic examination. The symptomatic treatment approaches are similar to those employed for trigeminal neuralgia. Surgical decompression of the nerve or rhizotomy is a second-line option.



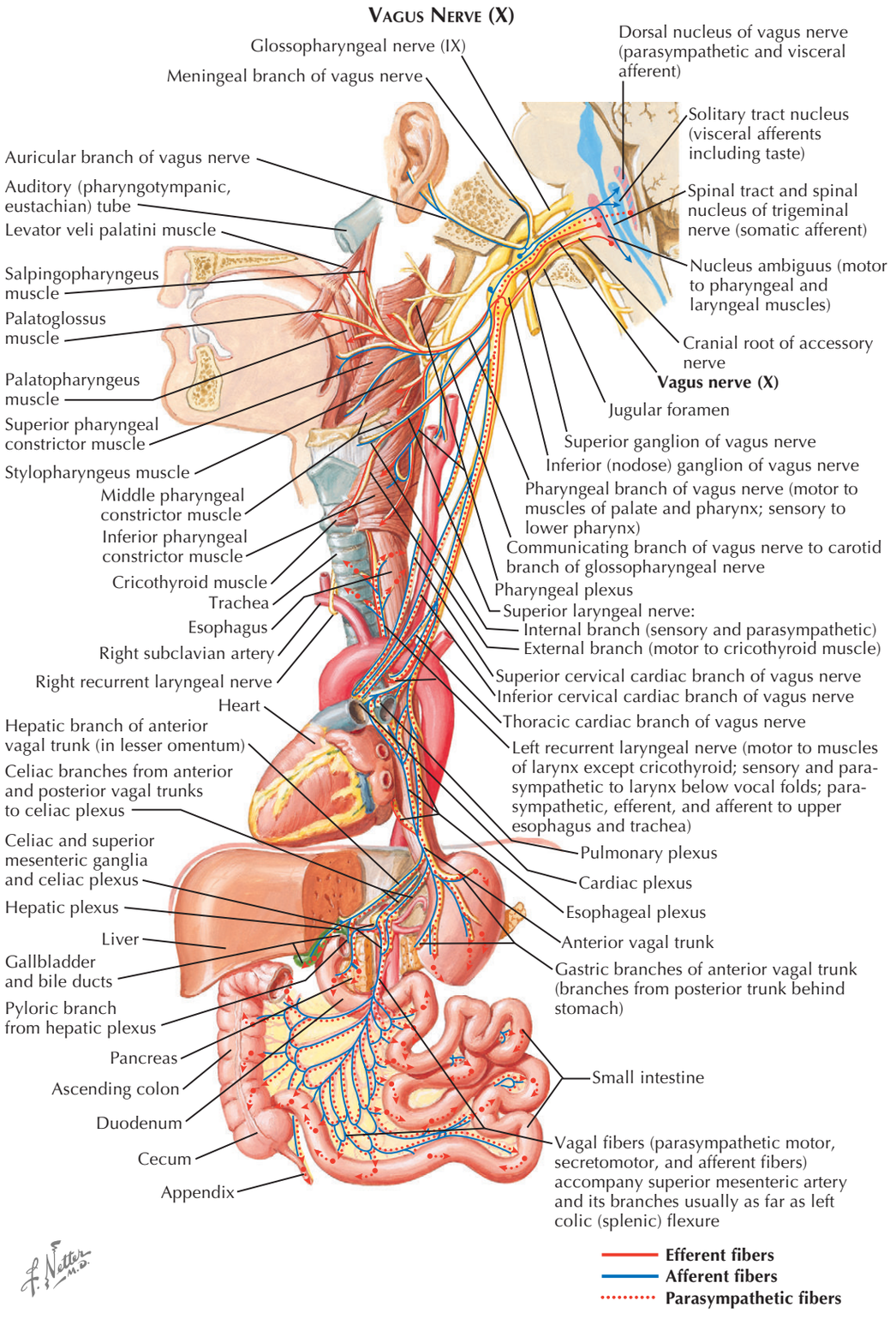
Cranial Nerve X: Vagus Nerve

VAGAL NUCLEI

The glossopharyngeal nerve, vagus nerve, and cranial parts of accessory nerves may be considered as a single nerve complex because all have central connections with the dorsal vagal nucleus, solitary tract nucleus, and nucleus ambiguus.

The dorsal vagal nucleus is a mixed nucleus that represents fused visceral afferent and efferent columns of neurons. It consists of a longitudinal column of cells lying beneath the vagal trigone in the fourth ventricle floor, lateral to the hypoglossal nucleus, extending nearly the length of the medulla oblongata. The special and general visceral afferent fibers ending in the nucleus are the central processes of pseudounipolar sensory cells in the inferior vagal ganglion (or nodose ganglion); peripheral processes of the sensory cells convey impulses from the heart, aorta, trachea, bronchi, lungs, most of the alimentary tract (from the lower pharynx almost to the left colic flexure), liver, pancreas, and possibly from the kidneys. Sensory fibers that carry taste sensation from the epiglottis, pharynx, and hard and soft palates are also located in the nodose ganglion. Preganglionic efferent fibers carrying impulses for the same structures originate in the dorsal vagal nuclei and are distributed through direct vagal branches to the viscera or through branches of the cardiac, celiac, and abdominal plexuses (anterior and posterior vagal trunks). Vagal preganglionic fibers synapse in ganglia located near or within the viscera they innervate. Because of this arrangement, vagal parasympathetic postganglionic fibers are relatively short and more limited in their distribution than their sympathetic counterparts. The general somatic afferent fibers are the pseudounipolar cells of the superior vagal ganglia (or jugular ganglia) involved with sensory impulses conducted through the auricular and meningeal vagal branches, although the fibers in the latter branches may be derived from interconnections between ganglia and upper cervical spinal nerves. Central processes of the superior vagal ganglion cells probably end in the spinal nuclei of the trigeminal nerves.

The solitary tract nucleus receives afferent special sensory taste fibers, traveling in the superior laryngeal vagal branches from the mucous membrane of the epiglottis and the epiglottic valleculae. In addition, general visceral sensations from the larynx, oropharynx, linings of the thorax, and abdominal viscera also project to the solitary tract nucleus. The nucleus ambiguus develops from special visceral efferent columns and forms a row of discrete, multipolar neurons located deeply in the reticular formation of the medulla oblongata. Its axons emerge in the glossopharyngeal and vagal nerves and in the cranial parts of the accessory nerves. The glossopharyngeal and vagal fibers distribute mainly to the intrinsic laryngeal and pharyngeal muscles (except tensor veli palatine [CN V] and stylopharyngeus [CN IX]), while the accessory fibers serve mainly the sternocleidomastoid and the trapezius muscles. The lower precentral gyrus controls vagal motor function.



VAGUS NERVE

The vagus nerve contains both afferent and efferent parasympathetic fibers that are widely distributed to visceral and vascular structures in the neck, thorax and abdomen, somatic sensory fibers in the auricular and meningeal branches, some special sensory fibers (taste) of the superior laryngeal branch, and special visceral efferent fibers that arise in the nucleus ambiguus and are distributed mainly to laryngeal and pharyngeal muscles.

Each vagus nerve emerges from the lateral medulla oblongata along the posterior sulcus as 8 to 10 rootlets above the rootlets of the glossopharyngeal nerve and cranial parts of the accessory nerve. The rootlets coalesce to form a nerve that exits the skull through the jugular foramen, together with the glossopharyngeal and accessory nerves, the sigmoid sinus, and several other blood vessels. Within or inferior to the jugular foramen, the vagus nerve expands into superior and inferior ganglia.

The superior vagal ganglion (jugular ganglion) communicates with the nearby superior cervical sympathetic trunk ganglion and the facial, glossopharyngeal and accessory nerves. It gives off a recurrent branch to the meninges of the posterior cranial fossa, an auricular branch that carries somatic sensory impulses from parts of the tympanic membrane and the external acoustic

Cranial Nerve X: Vagus Nerve *(Continued)*

meatus, and a pharyngeal branch that, along with the glossopharyngeal nerve, forms the pharyngeal plexus and sends motor fibers to the muscles of the soft palate and pharynx.

The inferior vagal ganglion (nodose ganglion) is connected with the cranial part of the accessory nerve. It communicates with the superior cervical sympathetic trunk ganglion, the hypoglossal nerve, and the loop between the first and second cervical spinal nerves. It gives off pharyngeal and superior laryngeal branches (which divide into a motor external ramus to the cricothyroid muscle and an internal ramus that pierces the thyrohyoid and sends sensory fibers to the larynx) and inconstant carotid rami, which assist the glossopharyngeal nerve in innervating the carotid sinus and body.

Below its inferior ganglion, the vagus nerve descends within a homolateral carotid sheath, shared with the internal jugular vein and carotid artery, to the thoracic inlet. The vagus nerve intercommunicates with filaments from the cervical sympathetic trunks or branches so that it is a mixed parasympathetic-sympathetic nerve from the neck downward. Within the neck, the vagus gives off the cardiac rami; these branches join the sympathetic fibers via the cardiac plexus of the heart.

VAGAL NERVE BRANCHES IN THE THORAX

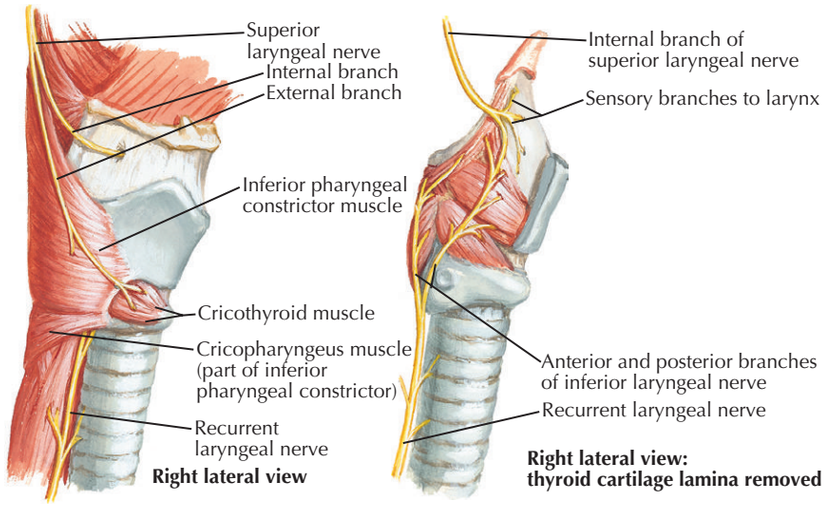
The right vagus nerve enters the thorax behind the internal jugular vein and in front of the first part of the subclavian artery. Here it gives off the right recurrent laryngeal nerve, which hooks under the artery before ascending to the larynx. The recurrent laryngeal nerves divide into anterior and posterior rami and supply the larynx. The main nerve climbs posteromedially, behind the right brachiocephalic vein and the superior vena cava, and runs medial to the azygos vein to reach the root of the right lung, where it splits into smaller anterior and larger posterior branches, both of which contribute rami to the anterior and posterior pulmonary plexuses.

The left vagus nerve enters the thorax between the left common carotid and left subclavian arteries, behind the left brachiocephalic vein. It crosses the left side of the aortic arch, giving off the left recurrent laryngeal nerve; thereafter, as on the right side, it participates in the formation of the pulmonary and esophageal plexuses. The left recurrent laryngeal nerve passes underneath the aorta on the outer side of the ligamentum arteriosum and then ascends to the larynx. The left recurrent laryngeal nerve, with the right recurrent laryngeal nerve, innervates the laryngeal muscles (all except the cricothyroids, which are supplied by the external ramus of the superior laryngeal nerve).

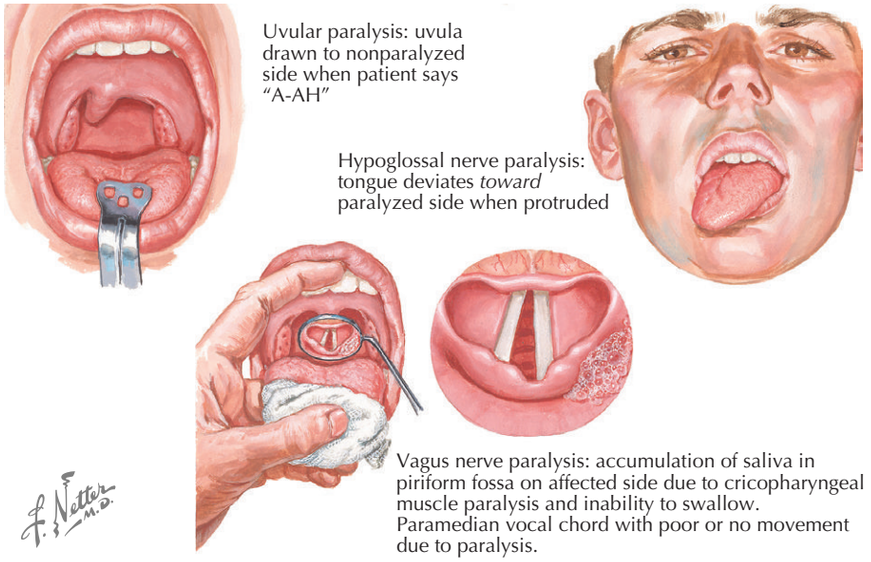
The vagal pulmonary branches, along with filaments derived from the second to fifth or sixth thoracic sympathetic trunk ganglia, form anterior and posterior pulmonary plexuses. The pulmonary plexuses become dispersed around the vascular and bronchial structures, and some of their terminal filaments reach the peripheral portion of the lungs. Along the course of the larger bronchi, small ganglia provide relay stations for the preganglionic parasympathetic (vagal) fibers. The sympathetic fibers relay outside the organs, primarily in the sympathetic trunk ganglia. Sympathetic and parasympathetic pulmonary afferent fibers are also present.

The esophageal plexus forms below the lung roots as the vagus nerves break up into two to four parts and travel on the esophagus as it descends through the posterior mediastinum, then divide and reunite to form the esophageal plexus. Filaments from the thoracic parts of the sympathetic trunks and from the thoracic splanchnic nerves then join the esophageal plexus. Most of the branches of the right vagus incline posteriorly, while most of those from the left vagus incline anteriorly. Above the esophageal hiatus in the diaphragm, the meshes of the esophageal plexus become reconstituted into two or more vagal trunks, which travel by way of the esophageal diaphragm to innervate the abdominal viscera.

Motor and sensory branches from the vagus nerve



Neurogenic disorders of mouth and pharynx (X and XII)



VAGAL NERVE DISORDERS

Bilateral supranuclear lesions may result in dysphagia, spastic dysarthria, emotional incontinence, pharyngeal and laryngeal incoordination, and altered sensation with an increased risk of aspiration. Unilateral supranuclear lesions rarely cause vagal dysfunction because the supranuclear control is bilateral. Dysphagia rarely occurs with unilateral precentral gyrus lesions.

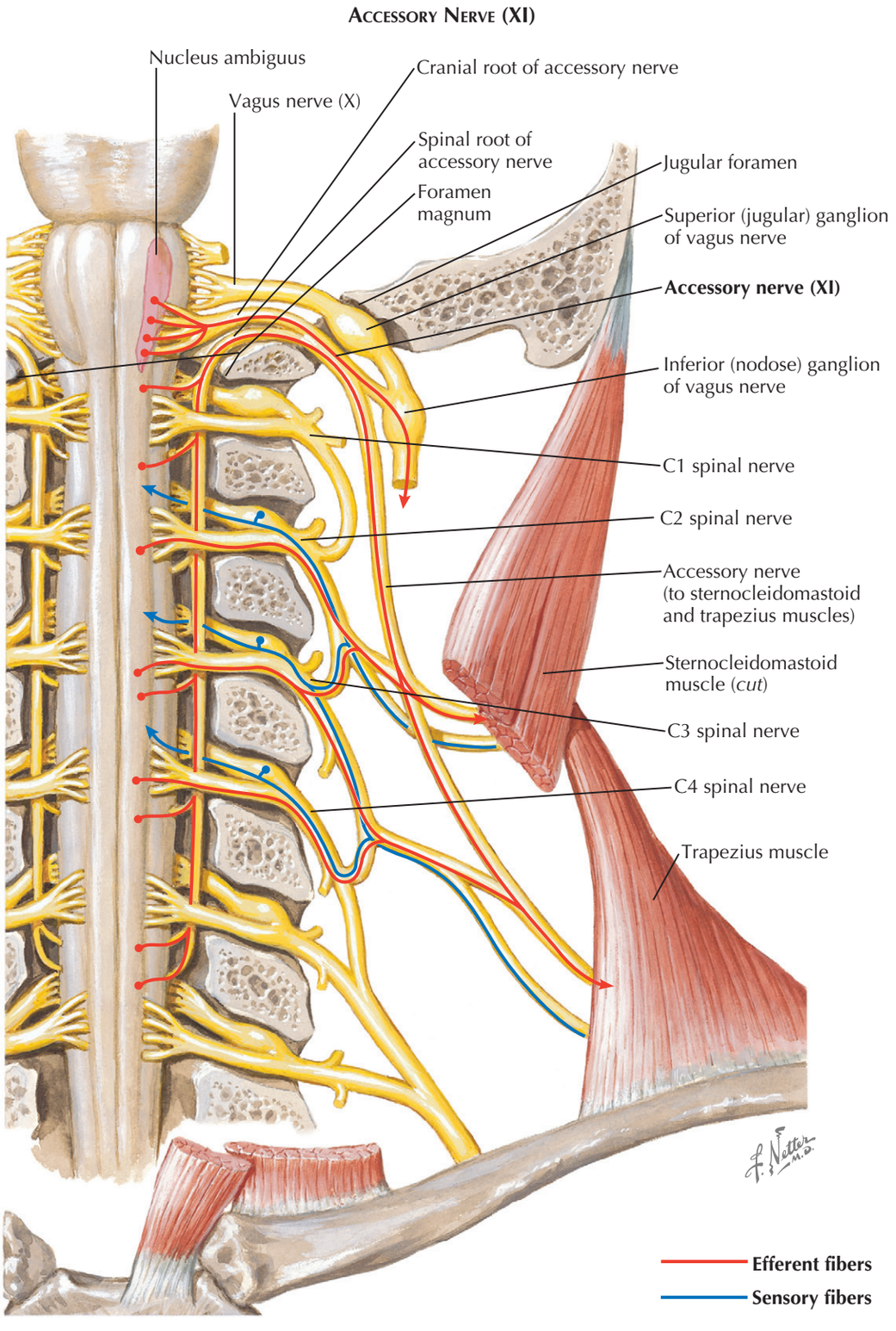
Isolated proximal vagus nerve injuries are rare because lesions at or around the jugular foramen, such as those caused by trauma or tumors (glomus vagale paragangliomas), usually also injure the glossopharyngeal and accessory nerves. Unilateral vagus neuropathy may cause ipsilateral pharyngeal (e.g., dysphagia) and laryngeal (e.g., change in voice) weakness and impaired sensation with inadequate airway protection. Ipsilateral soft palate weakness may manifest as nasal regurgitation and nasal speech. Ipsilateral vocal cord paralysis may be the result of superior laryngeal nerve injury (cricothyroid muscle for vocal cord lengthening and laryngeal sensation) or more distal recurrent laryngeal neuropathy (cricoarytenoids and thyroarytenoid muscles for adduction, abduction, and shortening of vocal cords). Recurrent laryngeal nerve lesions affect all laryngeal muscles, with the exception of the cricothyroid, which is innervated by the superior laryngeal nerve. Superior laryngeal neuropathy leads to loss of high vocal pitches, a weak voice, and aspiration due to altered laryngeal sensation. The causes include thyroiditis, local neck infections, or surgery; however, a good proportion of cases are idiopathic. Recurrent laryngeal nerve lesions cause variable symptoms, from slight voice fatigue and breathiness to significantly altered speech, hoarseness, and ineffective cough. When unilateral, they typically cause transient hoarseness. Common causes include thyroid, neck, and lung tumors; thoracic surgery; and, rarely, thyroiditis. Diabetes, amyloidosis, and other acquired etiologies of polyneuropathy may cause vagal neuropathy, usually accompanied by symptoms and signs of more widespread sensorimotor polyneuropathy.

Cranial Nerve XI: Accessory Nerve

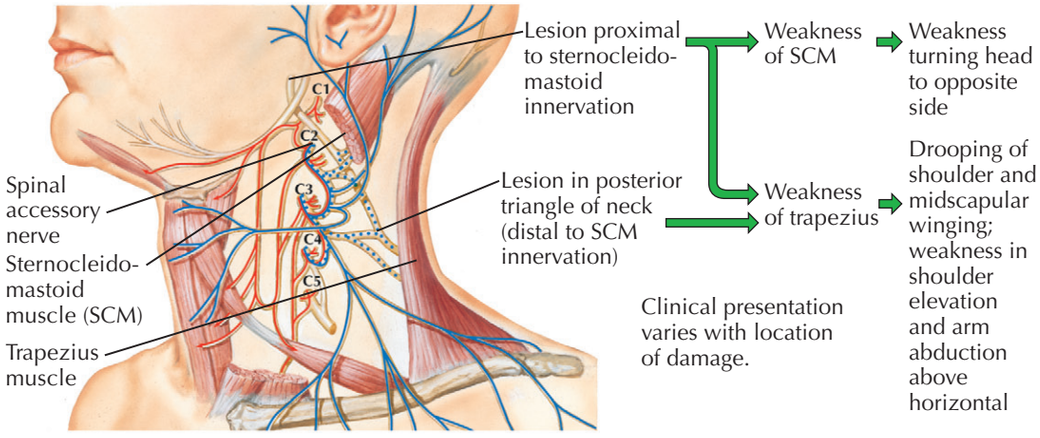
The spinal root fibers arise from an elongated strand of motor neurons, the *spinal nucleus of the accessory nerve*, which is a special visceral efferent column that extends from the lower medulla oblongata to the dorsolateral part of the ventral gray column of the upper five or six cervical cord segments. The fibers emerge as a series of rootlets from the side of the spinal cord via the lateral funiculus, about midway between the anterior and posterior rootlets of the upper five or six cervical spinal nerves, and coalesce as they ascend behind the denticulate ligament in the subarachnoid space to form the spinal root which enters the skull through the *foramen magnum* behind the vertebral artery. Arching upward and outward, the spinal root unites over a short distance with the cranial root to leave the skull through the *jugular foramen* in the same dural sheath as the vagus nerve.

The cranial root is the smaller of the two portions of the accessory nerve. Although it is discussed in this section, it is often considered as a part of the vagus nerve rather than the accessory nerve proper because the cranial component rapidly joins the vagus nerve and serves the same function as other vagal nerve fibers. The cranial nerve root fibers, classified as special visceral efferent, arise mainly from neurons in the caudal half of the *nucleus ambiguous* of the medulla, with probable minor contributions from the *dorsal vagal nucleus*. The fibers of the cranial root emerge as four to six rootlets from the dorsolateral sulcus, posterior to the olive, below the roots of the vagus nerve. The cranial root runs laterally to briefly join the larger spinal root before passing through the *jugular foramen* in the same dural and arachnoid sheath as the vagus nerve. The cranial root communicates by one or two filaments with the superior vagal ganglion; however, most of its fibers continue as the *internal branch of the accessory nerve*, which joins the vagus nerve at or near its inferior ganglion and provides most of the motor fibers to the pharynx and larynx. The *pharyngeal branches* supply the muscles of the soft palate (except the tensor veli palatini) and contribute motor fibers to the pharyngeal plexus. The fibers in the *recurrent laryngeal vagal branches* supply all the intrinsic laryngeal muscles except the cricothyroid.

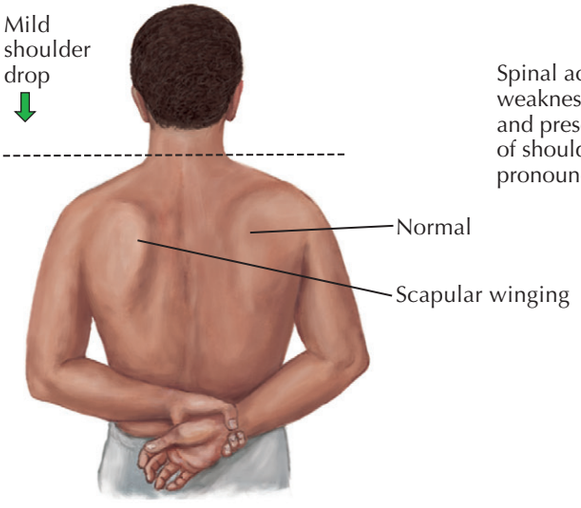
Course of Accessory Nerve. The cranial and spinal root fibers separate distal to the jugular foramen to form the *internal* and *external branches* of the accessory nerve. The internal branch joins the vagus nerve as described above. The external accessory branch innervates the sternocleidomastoid and trapezius muscles. The external branch of the accessory nerve usually passes between the internal carotid artery and the internal jugular vein and runs obliquely downward and backward over the transverse process of the atlas and deep to the styloid process, occipital artery, and posterior belly of the digastric muscle before piercing the deep



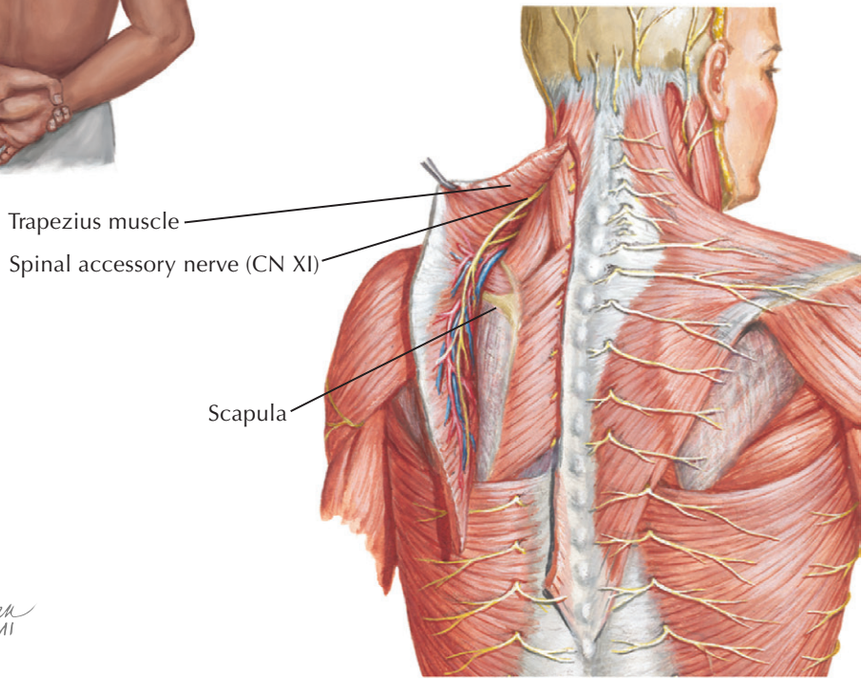
Clinical Findings in Cranial Nerve XI Damage



Clinical findings in CN XI nerve damage



Spinal accessory (CN XI) nerve lesions cause weakness of trapezius muscle on involved side and present with mild shoulder droop. Weakness of shoulder elevation and scapular winging most pronounced on arm abduction.



Cranial Nerve XI: Accessory Nerve *(Continued)*

surface of the *sternocleidomastoid muscle*. It passes through and supplies this muscle and emerges from the midpoint of the posterior sternocleidomastoid border. The external branch then descends across the posterior cervical triangle and crosses over the levator scapulae muscle to disappear under the trapezius muscle about 2 cm above the clavicle. Along its course, the external branch receives branches from the second, third, and fourth cervical nerves.

Supranuclear Innervation. The trapezius and sternocleidomastoid muscles receive supranuclear innervation from the lower precentral gyrus. The corticobulbar fibers supplying the trapezius are primarily crossed. The corticobulbar fibers controlling the sternocleidomastoid muscle are thought to terminate mainly in the ipsilateral nuclei.

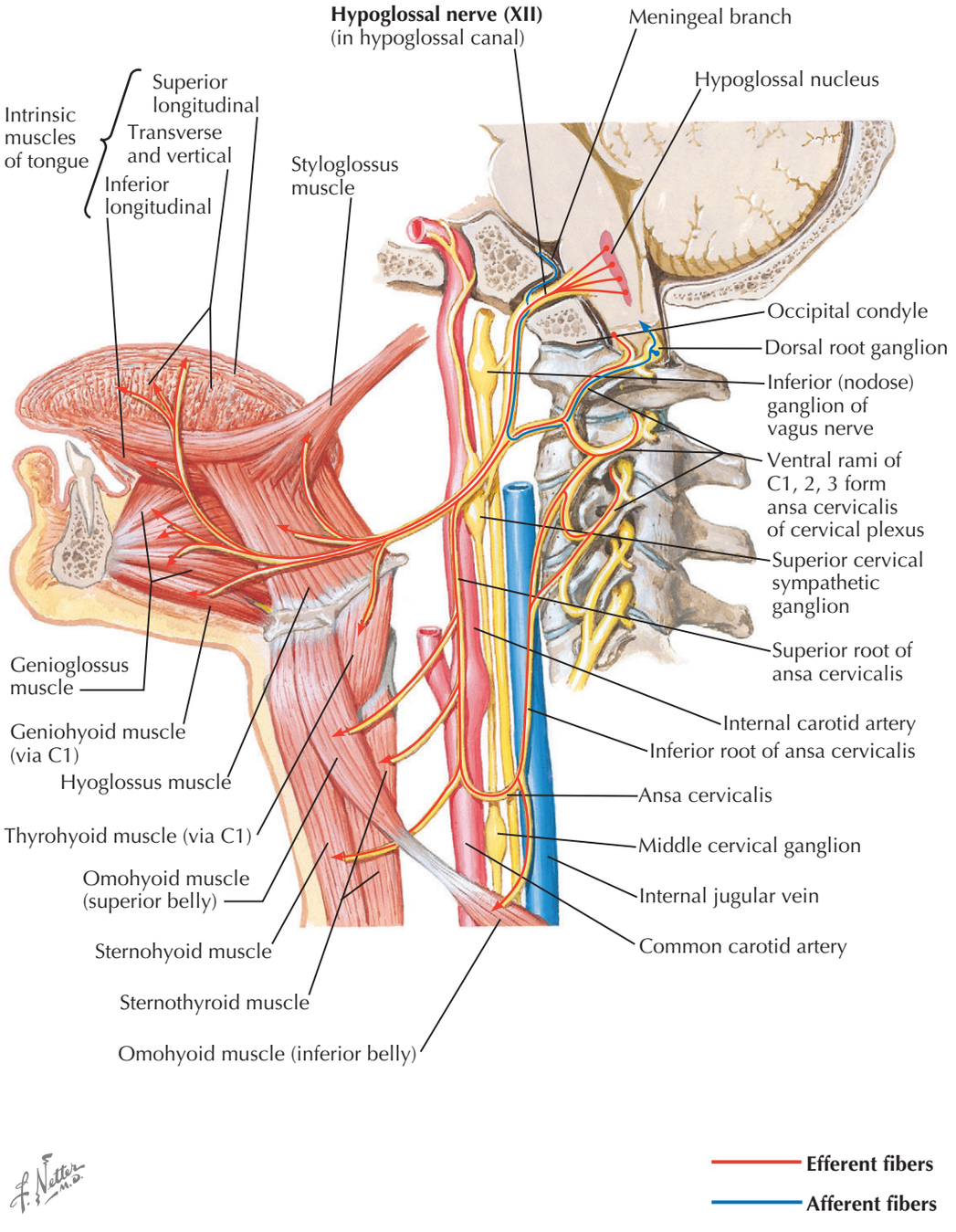
DISORDERS

Proximal spinal accessory nerve lesions cause weakness of the sternocleidomastoid and the trapezius muscles. Damage within the posterior triangle of the neck spares the sternocleidomastoid, resulting in trapezius weakness. With sternocleidomastoid weakness, there is weakness of turning the head to the opposite side. Involvement of the trapezius muscle manifests as drooping of the shoulder and mild upper scapular winging away from the chest wall, with slight lateral displacement. Weakness in shoulder elevation and arm abduction above horizontal is typical. Most individuals with accessory neuropathies also present with shoulder and neck pain.

The most common site of isolated accessory neuropathy is in the neck. The close association of the accessory nerve with the superficial cervical lymph nodes makes it vulnerable to iatrogenic damage during lymph node biopsy or radical neck dissection. The accessory nerve can also be directly compressed by swollen lymph nodes or other solid tumors. Rarely, accessory neuropathy occurs after blunt or penetrating neck trauma, or it is due to radiation injury with treatment of neck tumors. Damage can occur after carotid endarterectomy or jugular vein cannulation because of the nerve's proximity to large neck vessels. Accessory neuropathy is sometimes seen as part of brachial plexitis or Parsonage-Turner syndrome.

Intrinsic spinal cord lesions, posterior fossa meningiomas, or metastases near the jugular foramen or foramen magnum may injure the intraspinal and intracranial portions of the accessory nerve but usually also affect the glossopharyngeal and vagal nerves. At times, the hypoglossal nerve exiting through the adjacent hypoglossal foramen is involved, as well as the adjacent sympathetic chain fibers, resulting in an associated Horner syndrome. Disorders of the anterior horn cell, including motor neuron disease, syringomyelia, and poliomyelitis, may involve the nuclei of the accessory nerve.

Hypoglossal Nerve (XII)



Cranial Nerve XII: Hypoglossal Nerve

The hypoglossal nerve is the motor nerve of the tongue. The fibers of the hypoglossal nerve arise from the hypoglossal nucleus. This nucleus is a column of cells that lies beneath the hypoglossal trigone of the fourth ventricle floor in the medulla oblongata. It extends from the pontomedullary junction to the caudal most medulla oblongata. The main nucleus comprises subnuclei that are likely associated with the individual muscles they innervate. The fibers leave the hypoglossal nucleus and travel anterolaterally through the medullary reticular formation and the medial portion of the inferior olive and then course laterally to the medial longitudinal fasciculus, medial lemniscus, and pyramid. The hypoglossal nerve fibers leave the medulla between the inferior olivary complex and the pyramid. The fibers are positioned medial to cranial nerves IX, X, and XI. The rootlets fuse into two and then pass through the dura mater and hypoglossal canal of the skull. As the nerve roots exit into the upper neck, the two roots join to form a single nerve that runs near the internal carotid artery, internal jugular vein, and cranial nerves IX, X, and XI before passing over the internal and external carotid arteries and beneath the stylohyoid, mylohyoid, and digastric muscles. After passing between the mylohyoid and hypoglossal muscles, the nerve divides into many branches. These lingual branches convey general somatic efferent fiber to the tongue and supply most of the extrinsic (hyoglossus, styloglossus, genioglossus, and chondroglossus) and all the intrinsic muscles of the tongue (the transverse and vertical lingual muscles, as well as the superior and inferior longitudinal muscles). The other branches are derived from the cervical plexus and are not connected with the hypoglossal nuclei. These include the superior root of the ansa cervicalis, the meningeal branch, and nerves to the thyrohyoid and geniohyoid muscles. These are derived from the anterior rami of the first and second cervical nerves. The inferior root of the ansa cervicalis gives off branches to the omohyoid, sternothyroid, and sternohyoid muscles

Cranial Nerve XII: Hypoglossal Nerve *(Continued)*

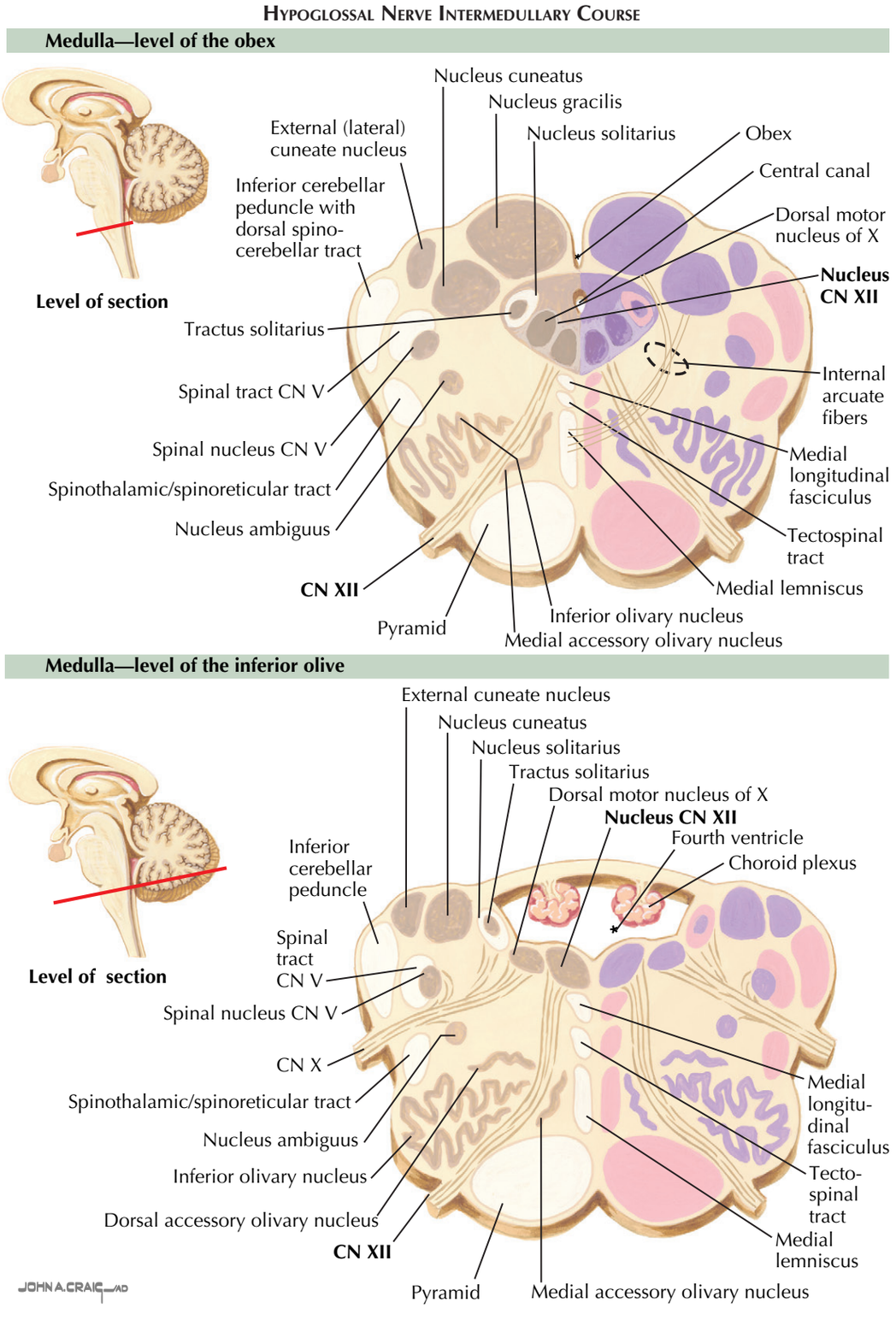
and is derived from the anterior rami of the second and third cervical nerves.

Supranuclear control of the tongue is mediated by the corticobulbar fibers, which originate in the lower portion of the precentral gyrus. The fibers controlling the genioglossus muscles are crossed, but other tongue muscles have bilateral supranuclear control.

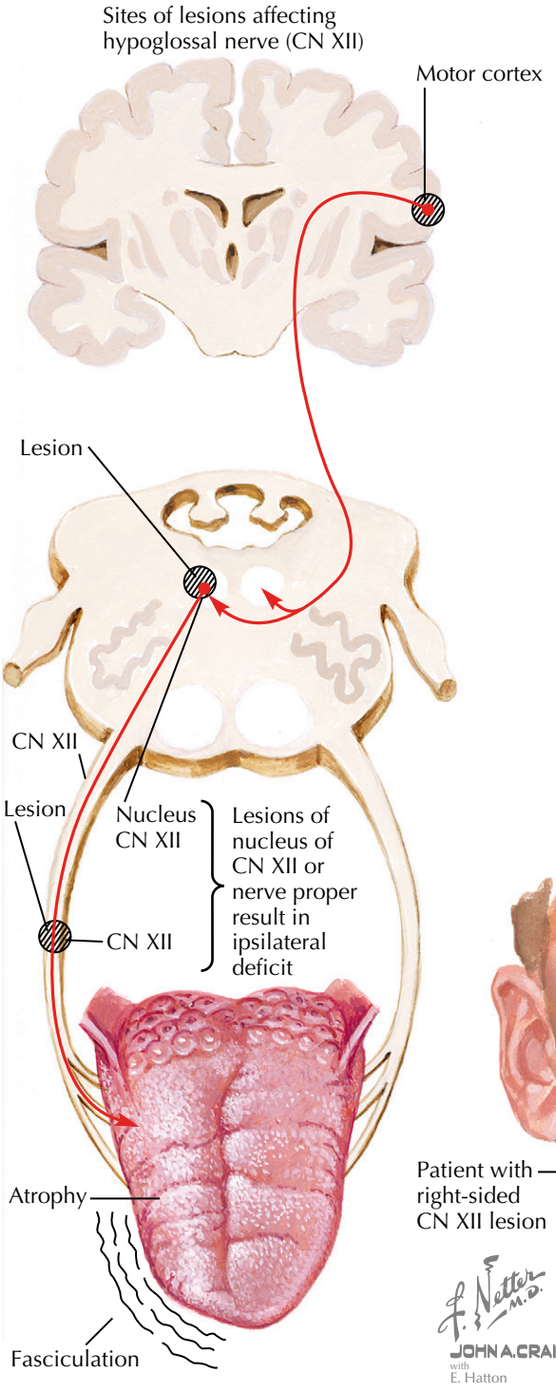
DISORDERS OF THE HYPOGLOSSAL NUCLEUS AND NERVE

Supranuclear lesions affecting the corticobulbar fibers above their decussation result in weakness of the contralateral half of the tongue. Bilateral upper motor neuron lesions affecting the corticobulbar tracts cause significant tongue dysfunction and spastic dysarthria. Dorsal medullary lesions causing bilateral lower motor neuron lesions of the tongue are extremely rare but are seen on occasion with tumors or syringobulbia. The medial medullary syndrome (Dejerine anterior bulbar syndrome) is caused by occlusion of the anterior spinal artery supplying the medial lemniscus, hypoglossal nerve, and ipsilateral pyramids. Intramedullary lesions may also result from cavernomas, multiple sclerosis, syringobulbia, and intramedullary tumors. These lesions may present with ipsilateral paresis, atrophy, and fasciculations of the tongue, often accompanied by contralateral hemiplegia and contralateral loss of position and vibratory sensation. Anterior horn cell disorders, such as amyotrophic lateral sclerosis, frequently affect the hypoglossal nucleus.

Peripheral nerve lesions of the hypoglossal nerve result in tongue deviation to the side of the lesion. Atrophy, fasciculations, and increased furrowing may be observed on the side of the lesion. It is best to allow the tongue to rest on the floor of the mouth when assessing for fasciculations. Because of the close proximity to cranial nerves IX, X, and XI in the hypoglossal canal,

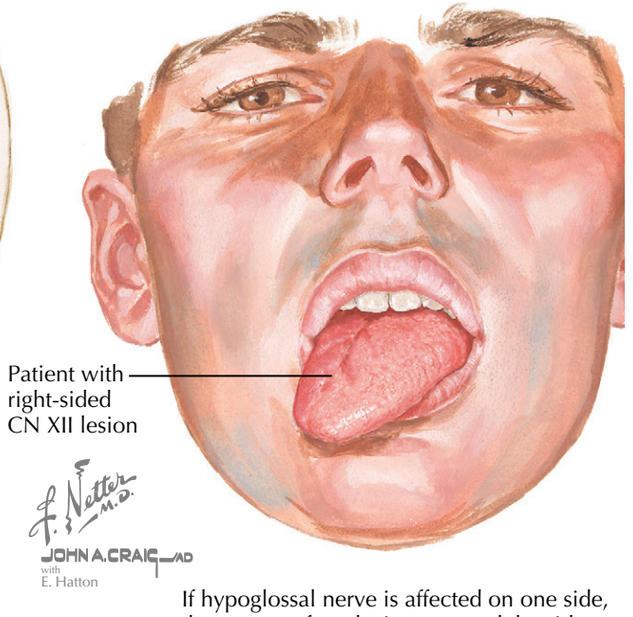


Disorders of Hypoglossal Nucleus and Nerve



When hypoglossal nerve or its nucleus is damaged, atrophy and fasciculation of the tongue are noted on evaluation

Subtle weakness of tongue may be tested by asking patient to press tongue against cheek (shown) or against a tongue depressor



If hypoglossal nerve is affected on one side, the tongue often deviates toward the side of the lesion on protrusion (due to imbalance of genioglossus contraction)

Cranial Nerve XII: Hypoglossal Nerve *(Continued)*

basilar skull lesions in this area may damage all four of these cranial nerves, resulting in weakness of the sternocleidomastoid, trapezius, tongue, pharyngeal and laryngeal muscles, accompanied by loss of taste on the posterior third of the tongue and hemianesthesia of the palate, pharynx, and larynx (Collard-Sicard syndrome). Occipital pain and ipsilateral hypoglossal nerve injury may occur with occipital condyle syndrome, which is usually the result of tumors or chronic inflammatory lesions. Isolated hypoglossal neuropathy may also occur as the result of carotid aneurysm, vascular entrapment, dissection, local infection, rheumatologic disease, neck radiation, or tumors.

Extra-axial intracranial lesions of the hypoglossal nerve are typically caused by neoplasm at the basal meninges or skull base. Examples of neoplasms that cause hypoglossal neuropathy include metastatic bronchial or breast carcinomas, lymphoma, meningiomas, chordoma, and cholesteatomas. The proximity of the hypoglossal and jugular foramina explains the frequent co-involvement of other lower cranial nerves (CN IX, X, XI) in cases caused by neoplasm. Jugular foramen lesions, such as glomus jugulare tumor (a rare hypervascular malignancy that arises from the paraganglionic tissue), can compress the hypoglossal nerve. Infectious or granulomatous lesions, such as tuberculosis and sarcoidosis, causing basal meningitis, may affect multiple cranial nerves, including the hypoglossal nerve. Primary bony processes (e.g., platybasia and Paget disease) have rarely been reported to affect the hypoglossal nerve. The close spatial relation between the hypoglossal nerve and the carotid artery makes this nerve vulnerable to primary carotid pathology within the neck and is occasionally seen with internal carotid artery dissection, neck surgery or carotid endarterectomy. Nasopharyngeal cancer and radiation therapy may damage the hypoglossal nerve in the neck.

SPINAL CORD: ANATOMY AND MYELOPATHIES

Spinal Cord

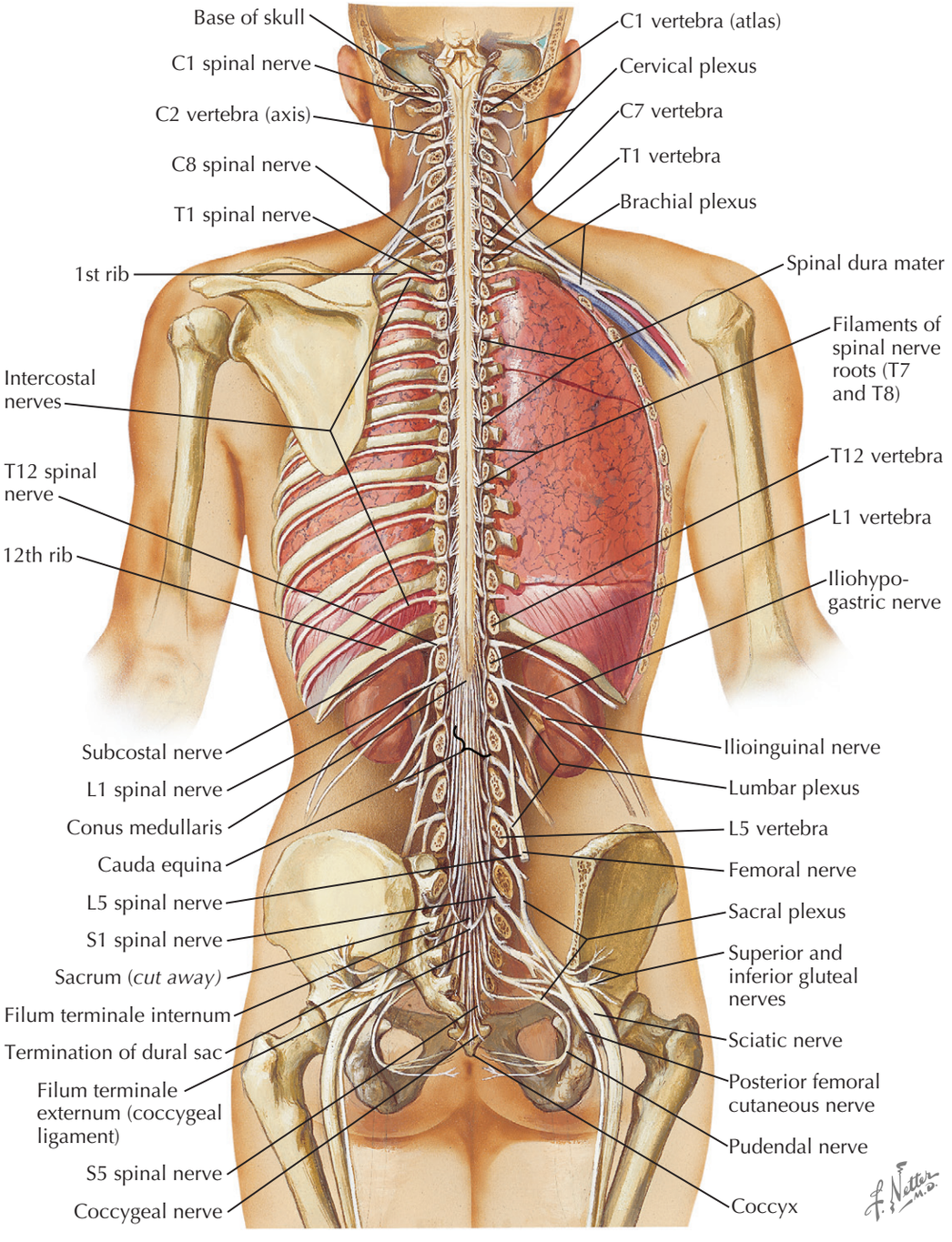
The spinal cord is the downward continuation of the medulla oblongata. It extends from the upper border of the atlas to end in a tapering extremity, the *conus medullaris*, opposite the lower border of the first lumbar vertebra, or at the level of the intervertebral disk between the upper two lumbar vertebrae (see Plate 2-1). From the conus, a slender, median, fibrous thread, the *filum terminale*, is prolonged as far as the back of the coccyx. The dura mater and arachnoid (and therefore the subarachnoid space) extend down to the level of the second sacral vertebra. Although generally cylindric, the cord is slightly flattened anteroposteriorly and shows *cervical* and *lumbar enlargements* that correspond to segments involved in supplying nerves to the upper and lower limbs. The nerve supply to the upper limb involves the fourth cervical to second thoracic spinal cord segments, and that to the lower limb, the third lumbar to third sacral spinal cord segments.

Meninges. The cord is surrounded by dura, arachnoid, and pia mater, which are continuous with the corresponding layers of the cerebral meninges at the foramen magnum. The *spinal dura mater*, unlike the cerebral, consists only of a meningeal layer that is not adherent to the vertebrae; it is separated from the boundaries of the vertebral canal by an epidural space containing fatty areolar tissue and many veins. The spinal and cranial *subarachnoid spaces* are continuous and contain cerebrospinal fluid. The *pia mater* closely invests the cord; on each side, it sends out a series of 22 triangular processes, the *denticulate ligaments*, which are attached to the dura mater and thus anchor the cord (see Plate 2-2). The spinal cord is considerably smaller than the vertebral canal; the meninges, the cerebrospinal fluid and the epidural fatty tissue and veins combine to cushion it against jarring contacts with its bony and ligamentous surroundings.

Spinal Nerves. There are 31 pairs (8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal) of symmetrically arranged *spinal nerves*, attached to the cord in linear series by anterior and posterior nerve rootlets, or filaments, which coalesce to form the nerve roots. Each posterior spinal nerve root possesses an oval enlargement, the *spinal (sensory) ganglion*.

In early embryonic life, the cord is as long as the vertebral canal, but as development proceeds, it lags behind the growth of the vertebral column. Consequently, the cord segments move upward in relation to the vertebrae, and the nerve roots, originally horizontal, assume an increasingly oblique direction from above downward as they proceed to their foramina of exit. In the adult, except in the upper cervical region, the cord segments lie at varying distances above the corresponding vertebrae. For clinical purposes, it is customary to localize them in relation to the vertebral spinous processes. In the lower cervical region, the vertebral spines are one lower in number than the corresponding cord segments; in the upper thoracic region, two lower in number; and in the lower thoracic region, three lower in number. For example, the fourth thoracic spinous process is approximately level with the sixth thoracic cord segment. The lumbar, sacral, and coccygeal segments of the cord are crowded together and occupy the space approximately opposite the ninth thoracic to the first lumbar vertebrae. These alterations of the cord segments relative to the vertebral segments explain why the cervical enlargement (C4 to T2) lies approximately opposite the corresponding vertebrae, whereas the lumbar enlargement (L3 to S3) lies opposite the last three thoracic vertebrae. The nerve roots attached to the lower part of the cord descend to their points of exit as the *cauda equina*, named for their resemblance to the tail of a horse.

Spinal Cord In Situ



Spinal Membranes and Nerve Roots

Meninges. The spinal cord is enveloped by meninges, which, at the level of the foramen magnum, are directly continuous with those surrounding the brain.

The external, tough, fibrous *dura mater* continues downward as far as the second sacral vertebra, where it ends blindly. It is separated from the wall of the vertebral canal by an *epidural space* containing fatty areolar tissue and a plexus of veins. The dura ensheathes the anterior and posterior spinal nerve roots, which lie close together when they pierce it; then the roots unite almost immediately to form a spinal nerve, and the dural sheath fuses with the epineurium. Between the dura mater and arachnoid is a potential *subdural space*, which normally contains the merest film of lymphlike fluid.

The spinal *arachnoid* is loose and tenuous and also ends at the level of the second sacral vertebra. It is separated from the pia mater by the *subarachnoid space*, which is traversed by delicate mesothelial septa and contains cerebrospinal fluid. The spinal nerve roots, up to the points at which they penetrate the dura mater, are loosely enclosed in arachnoid.

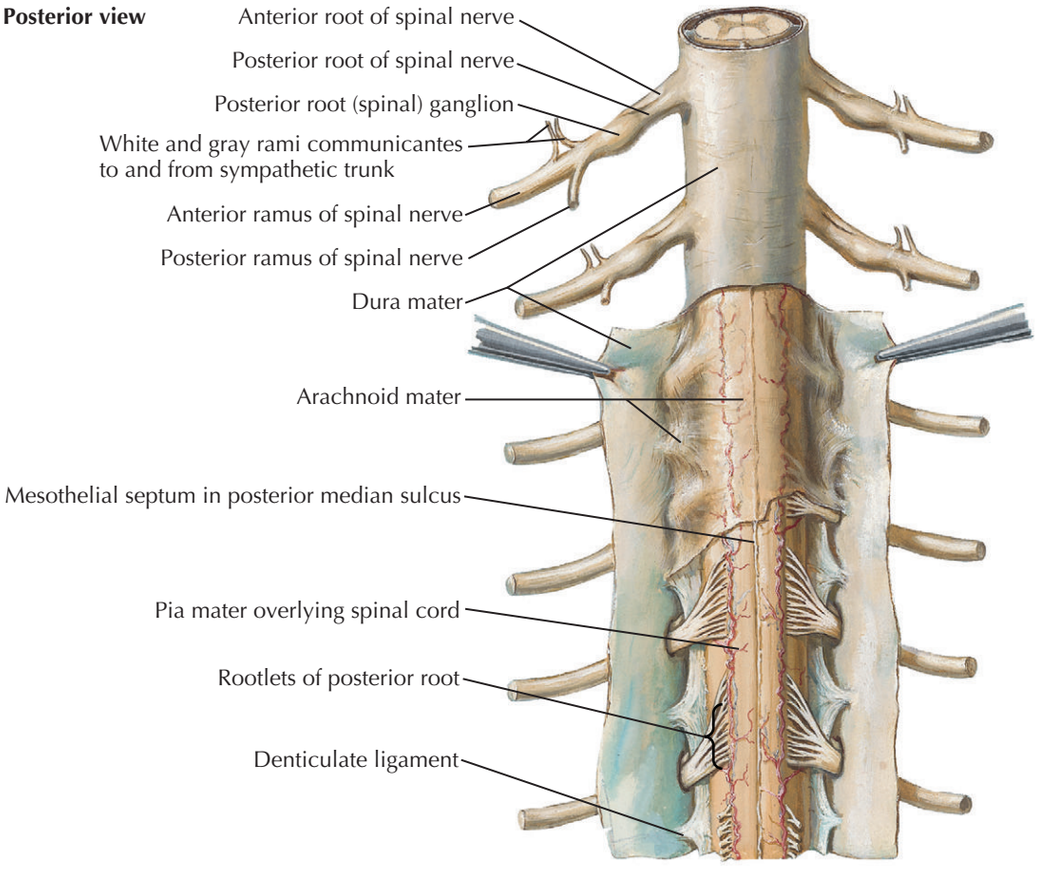
The *pia mater* is a thin layer of vascular connective tissue that intimately invests the spinal cord and its nerve roots. Below the conus medullaris, it is continuous with the slender *filum terminale* that descends in the midst of the cauda equina, pierces the terminal parts of the dura and arachnoid, and ends by blending with the connective tissue behind the first segment of the coccyx. On each side, the pia is attached to the dura by 22 pointed processes, the *denticulate ligaments*.

Nerve Roots. The spinal cord is a segmented structure, and this is indicated by the regular attachments of the pairs of *spinal nerves*. As explained earlier, the cord and vertebral segments coincide in early embryonic life, but the vertebral canal eventually becomes longer than the cord so that most of the spinal nerves run obliquely downward to their points of exit.

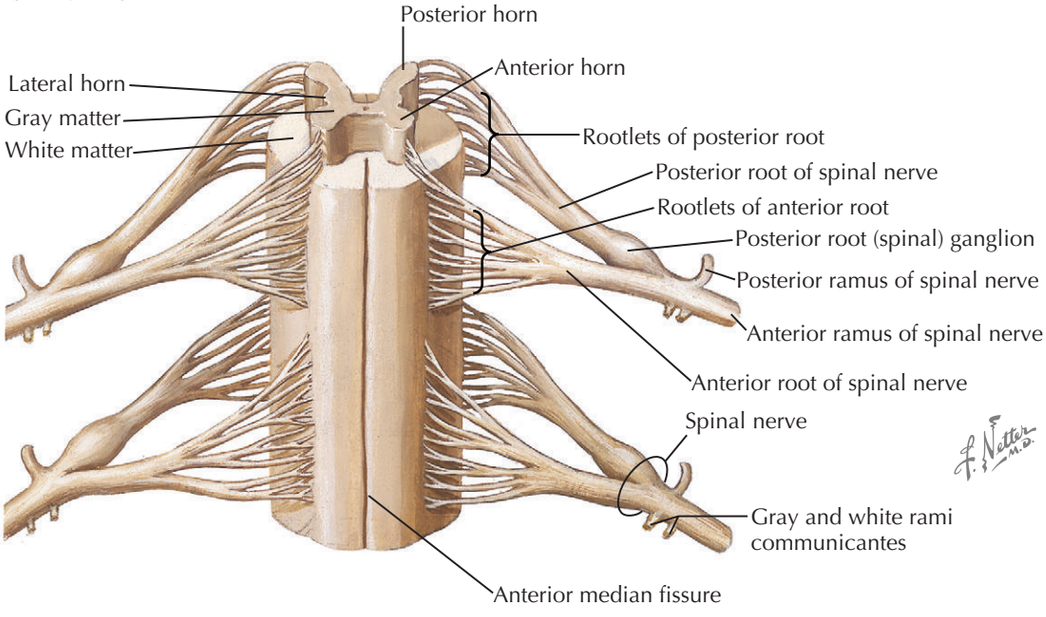
The nerve filaments, or rootlets, are attached to the cord along its anterolateral and posterolateral regions. The *anterior (ventral) filaments* emerge in two or three irregular rows. They are composed predominantly of efferent fibers, which are the axons of cells in the anterior columns, or horns, of gray matter, and they carry motor impulses to the voluntary muscles. In the thoracic and upper lumbar regions, the filaments also contain preganglionic sympathetic fibers, which are the axons of lateral columnar, or cornual, cells. The *posterior (dorsal) filaments* are attached in a regular series along a shallow groove, the posterolateral sulcus, and are collections of the central processes of nerve cells located in the spinal ganglia of the related dorsal nerve roots. The lateral cell processes pass on in spinal nerves and their branches to peripheral receptors, and they convey afferent impulses back to the spinal cord from somatic, visceral, and vascular sources.

The spinal cord shows an *anterior median fissure* and a shallow *posterior median sulcus* from which a *median septum* of neuroglia extends forward for 4 to 6 mm. The cord is divided into symmetric halves by the fissure, sulcus, and septum. The lines of attachment of the anterior and posterior nerve filaments are used to demarcate the white matter in each half of the cord into *anterior*, *lateral*, and *posterior columns*, or *funiculi*.

Posterior view



Membranes removed: anterior view
(greatly magnified)



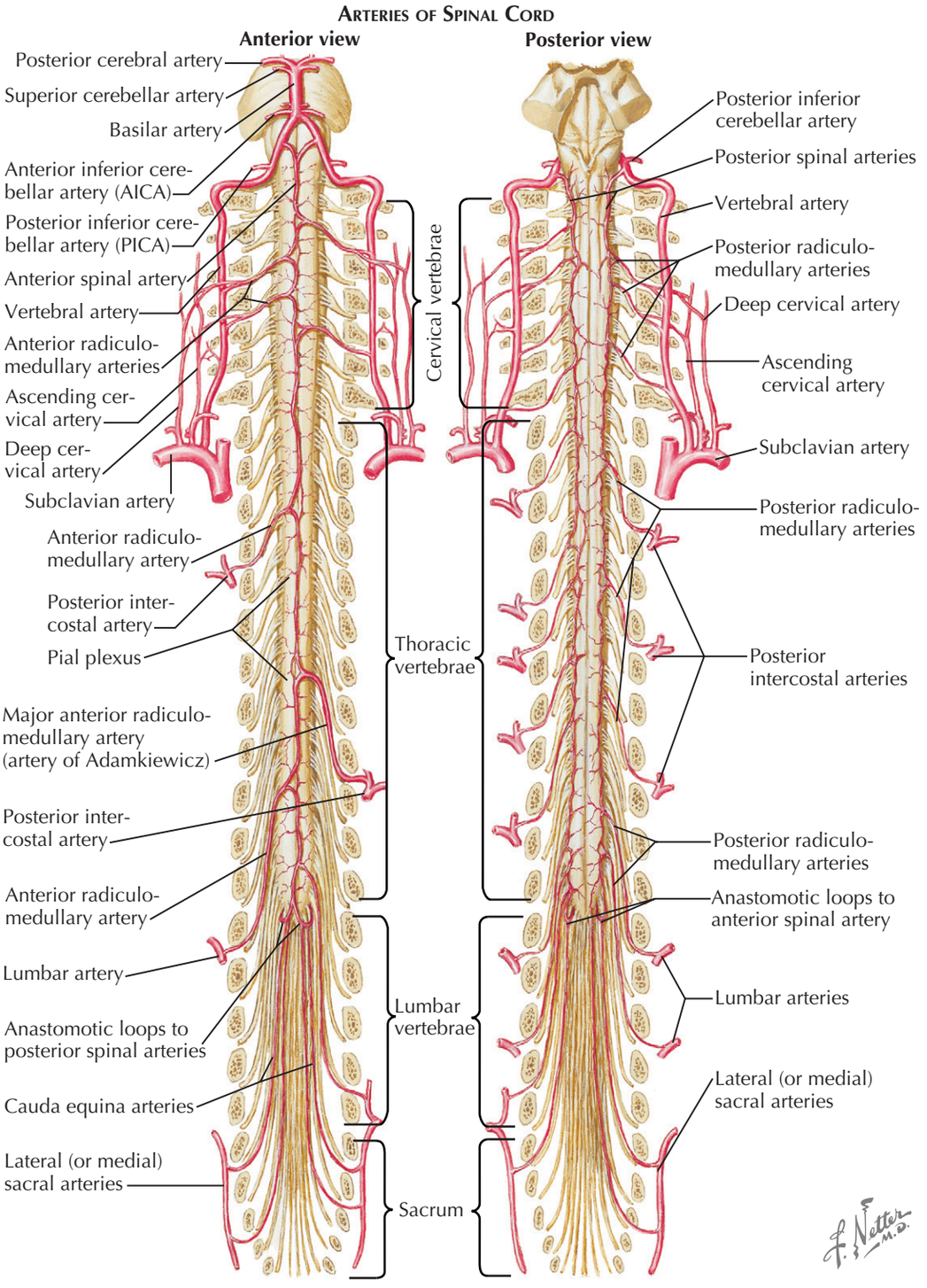
Arteries of Spinal Cord and Nerve Roots

The spinal cord is supplied by multiple *radicular arteries*, which form the *anterior spinal* and two *posterior spinal arteries*.

The radicular arteries arise from the lateral spinal arteries, which traverse the intervertebral foramina at each vertebral segment. Regardless of their origin, the many small radicular arteries pass medially to supply the anterior and posterior nerve roots. Most do not reach the spinal cord. However, some of the larger arteries reach the dura mater, where they give off small *meningeal branches* and then divide into *ascending* and *descending branches* to form the spinal arteries. The larger radicular arteries, which supply both the nerve roots and the spinal cord, are called *radiculomedullary arteries* to distinguish them from those radicular arteries that supply only the nerve roots.

The anterior spinal artery lies within the pia and runs the entire length of the spinal cord in the midline. It usually originates in the upper cervical region at the junction of the two *anterior spinal branches* that arise from the intracranial portion of the vertebral artery. Six to ten feeders—the *anterior radiculomedullary arteries*—contribute to it throughout its length, branching upward and downward. Occasionally, in the thoracic region, the anterior spinal artery narrows to such a degree that it is discontinuous. Blood from the anterior spinal artery is distributed to the anterior two thirds of the substance of the spinal cord via *central (*or *sulcocommissural) branches* and *penetrating branches* from the *pial plexus*.

The *cervical* and *first two thoracic segments of the spinal cord* are supplied by radiculomedullary arteries that arise from branches of the *subclavian artery*. Variability is common, and the branches may arise from either the right or the left (often alternately) to join the anterior spinal artery at an angle of 60 degrees to 80 degrees. Not uncommonly, one anterior radiculomedullary branch arises from the vertebral artery and accompanies the C3 nerve root, one branch arises from one of the branches of the costocervical trunk (often the deep cervical artery) and accompanies the C6 root, and one branch arises from the superior intercostal artery and accompanies the C8 root.



Note: All spinal nerve roots have associated **radicular** or **segmental radiculomedullary arteries**. Most roots have radicular arteries. Both types of arteries run along roots, but radicular arteries end before reaching the anterior or posterior spinal arteries; the larger radiculomedullary arteries continue on to supply a segment of these arteries.

The *midthoracic region of the spinal cord* (T3 to T7) usually receives only one radiculomedullary artery, which accompanies the T4 or T5 nerve root. Consequently, this section of the cord is characterized by its poor blood supply, and the anterior spinal artery may not be continuous at this level.

The *thoracolumbosacral part of the spinal cord* (T8 to the conus medullaris) derives its main arterial supply from the artery of Adamkiewicz, which arises from a left *intercostal* (or *lumbar*) *artery* in 80% of individuals. In 85% of instances, it reaches the cord with a nerve root between T9 and L2; in the 15% of cases in which it reaches the cord between T5 and T8, it is supplemented by a radiculomedullary artery (the artery of the conus medullaris) arising more inferiorly. The *artery of Adamkiewicz* has a large anterior and a smaller posterior branch. On reaching the anterior aspect of the spinal cord, the *anterior branch* ascends a short distance and

Arteries of Spinal Cord and Nerve Roots *(Continued)*

then makes a hairpin turn to give off a small ascending branch and a larger descending branch, which drops to the level of the conus medullaris, where it forms an anastomotic circle with the terminal branches of the two posterior spinal arteries.

The *cauda equina* is accompanied and supplied by one or two branches from the *lumbar*, *iliolumbar*, and *lateral* and *median sacral arteries*. These branches also ascend to contribute to the anastomotic arterial circle around the conus medullaris.

The central (sulcocommissural) branches of the anterior spinal artery pass back into the anterior median fissure to supply the central parts of the spinal cord. At the anterior commissure, the branches turn alternately right and left to supply the corresponding halves of the cord, except in the lumbar enlargement, where the left and right branches arise from a common trunk. The terminal branches ascend and descend within the cord, supplying overlapping territories. There are 5 to 8 central arteries for each centimeter length of the spinal cord in the cervical region, 2 to 6 in the thoracic region, and 5 to 12 in the lumbosacral area. Branches from each central artery overlap with those from adjacent arteries. The central arteries supply the anterior commissure and adjacent white matter of the anterior columns, anterior horns, bases of the posterior horns, Clarke's columns, corticospinal tracts, spinothalamic tracts, anterior parts of the gracile and cuneate fasciculi, and the region around the central canal.

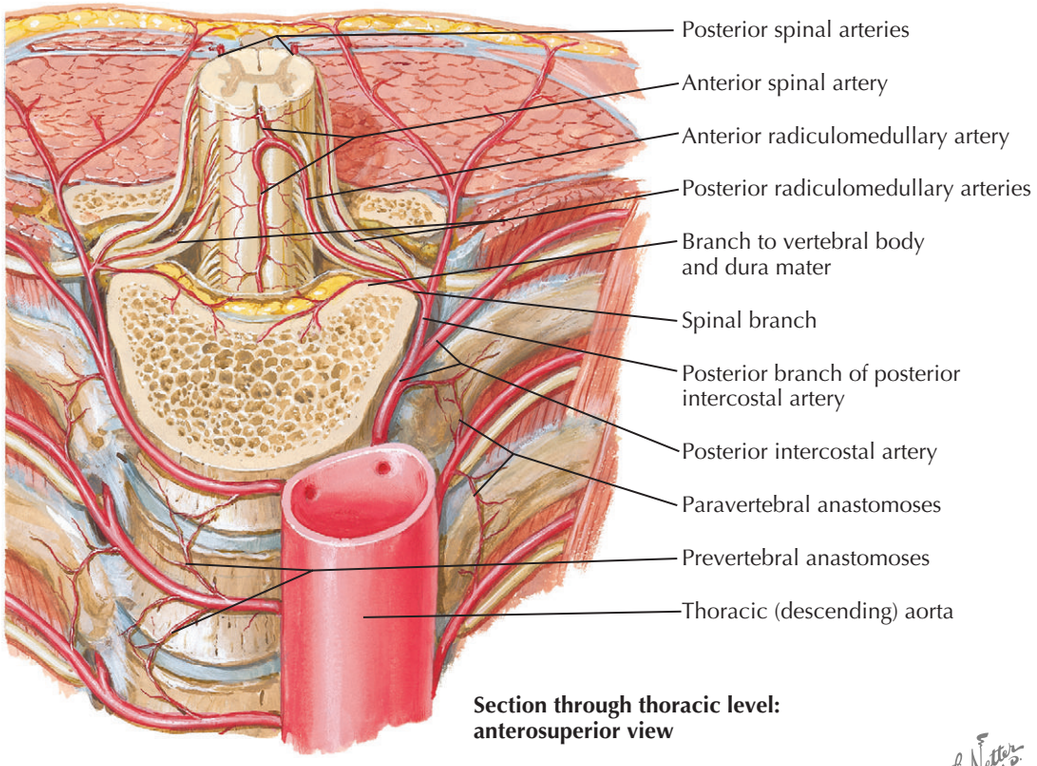
The posterior spinal arteries are paired arteries coursing on the posterolateral aspects of the entire length of the spinal cord, although they may become discontinuous at times. Each originates from the intracranial portion of the corresponding *vertebral artery*, and receives contributions from 10 to 23 *posterior radiculomedullary arteries*. The posterior spinal arteries distribute blood to the posterior third of their respective sides of the cord.

In the *cervicothoracic region*, the posterior spinal arteries receive one, and sometimes two, tributaries at each segment. *Between the T4 and T8 levels*, there are usually two or three posterior radiculomedullary branches, while in the *thoracolumbar region*, there are several feeders, one of which may be the *posterior radicular branch of the artery of Adamkiewicz*.

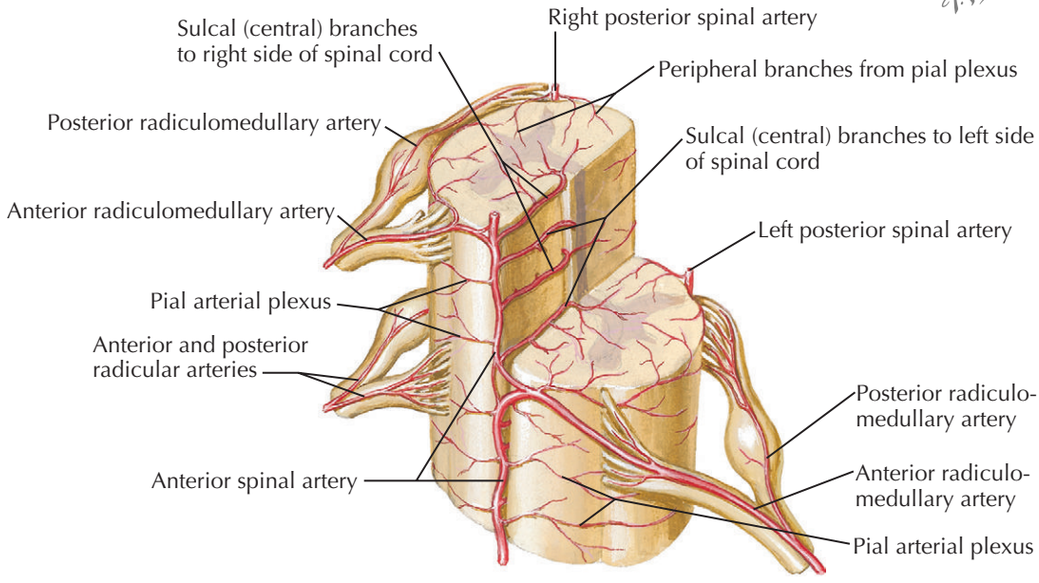
Pial Arterial Plexus. Small pial branches arise from the spinal arteries and ramify and interconnect on the surface of the cord to form a *pial plexus*. *Penetrating branches* of the plexus are radially oriented to supply the outer part of the substance of the cord; they follow the principal sulci of the cord (the posterior median sulcus and the posterior intermedian sulcus) to reach the anterior and posterior horns. The peripheral pial branches supply the outer portions of the posterior horns, most of the posterior columns, and the outer portion of the white matter of the periphery of the spinal cord.

There is some degree of overlap in the distribution of the peripheral and central arteries at the capillary level, but they do not anastomose at the arterial level, and hence both types are, in effect, *end arteries*.

Arteries of Spinal Cord: Intrinsic Distribution



Section through thoracic level: anterosuperior view



Arterial distribution

Although the anterior and posterior radiculomedullary arteries may contribute to their respective longitudinal spinal arteries at the same segmental level (as shown here for simplicity), this is usually not the case.

Veins of Spinal Cord, Nerve Roots, and Vertebrae

Two plexuses of veins, external and internal, extend along the entire length of the vertebral column and form a series of moderately distinct rings around each vertebra. The plexuses anastomose freely with each other, receive tributaries from the vertebrae, ligaments, and spinal cord and are relatively devoid of valves. Consequently, changes in the pressure of intrathoracic or cerebrospinal fluid may produce variations in the volume of blood, especially in the internal vertebral venous plexuses.

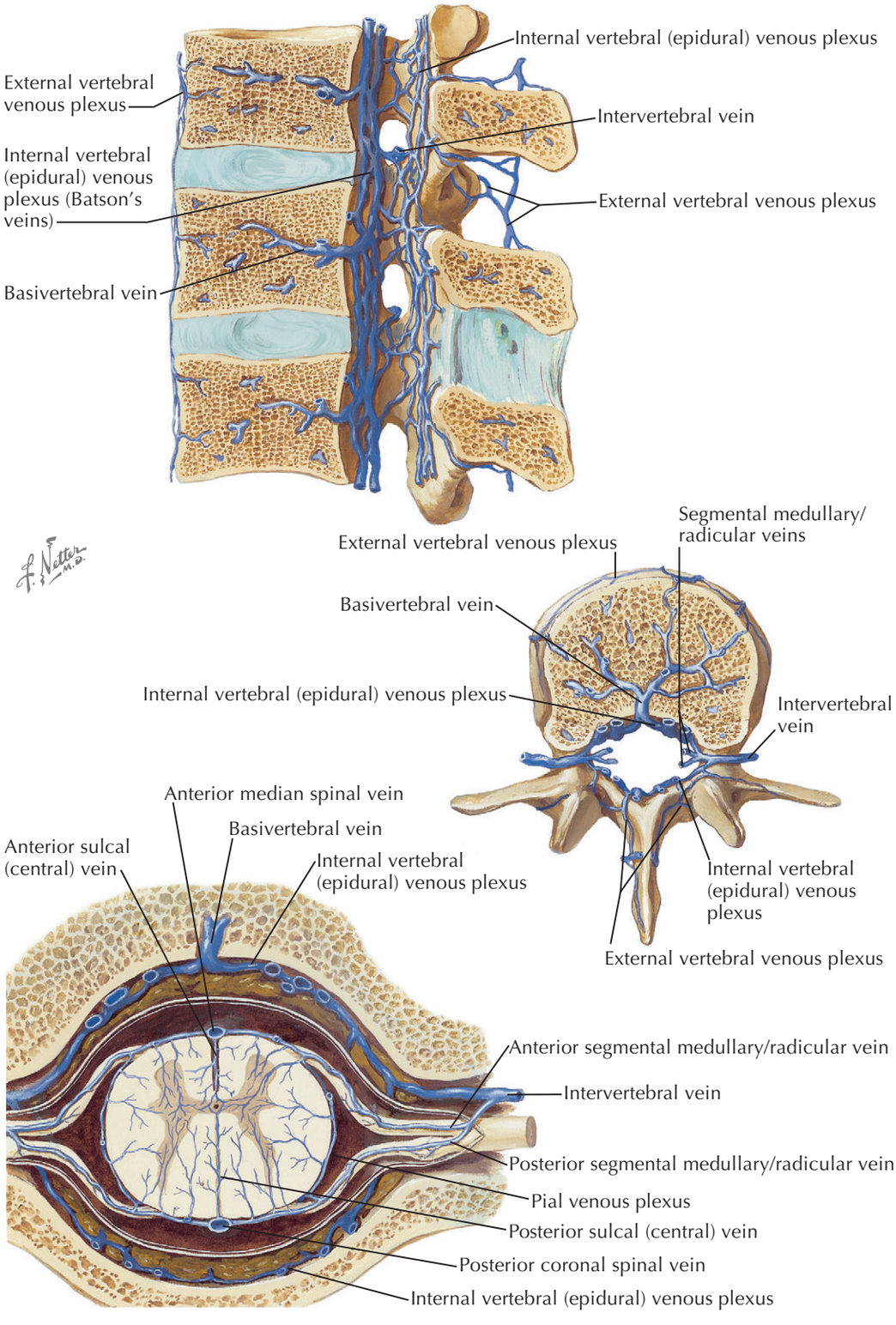
The external vertebral plexus consists of anterior and posterior parts, which anastomose freely. The veins forming the *anterior external plexus* lie in front of the vertebral bodies, from which they receive venous tributaries and through which they communicate with the basivertebral veins. The *posterior external plexus* is a network located over the vertebral laminae and extending around the spinous, transverse, and articular processes. In the upper cervical region, the posterior plexus communicates with the occipital veins and, via these, with the mastoid and occipital emissary veins. The posterior plexus also communicates with the vertebral and deep cervical veins, and a few channels pass through the foramen magnum to the dural sinuses in the posterior cranial fossa.

The internal vertebral plexus is formed by networks of veins lying in the epidural space within the vertebral canal. The networks are arranged in anterior and posterior groups, which are interconnected by many smaller oblique and transverse channels. The *anterior internal plexus* consists of longitudinal veins lying on the posterior surfaces of the vertebral bodies and intervertebral disks found on each side of the posterior longitudinal ligament. Interconnecting branches lie between the ligament and the vertebral bodies and receive the basivertebral veins. The longitudinal veins in the *posterior internal plexus* are smaller than their anterior counterparts. They are located on each side of the median plane in front of the vertebral arches and ligamenta flava. They anastomose with the veins of the posterior external vertebral plexus via small veins that pierce the ligaments and pass between them.

The basivertebral veins resemble the cranial diploë, and tunnel through the cancellous tissue of the vertebral bodies. They converge to form a comparatively large, single (occasionally, double) vein that emerges through the posterior surface of the vertebral body to end, via openings guarded by valves, in the transverse interconnections of the anterior internal vertebral plexus. The basivertebral veins also drain into the anterior external plexus through openings in the front and sides of the vertebral body.

The veins of the spinal cord resemble the related arteries in their distribution and form a tortuous plexus in the pia mater (see Plate 2-5). Intrinsic veins from the anteromedial region of the spinal cord and radial veins from the anterior funiculus drain into the *anterior median spinal (longitudinal)vein*, sometimes duplicated. Capillaries and venules from the rest of the spinal cord drain by radial veins into the *coronal veins* on the posterior and lateral surface of the spinal cord. These superficial veins drain, in turn, by the *anterior* and *posterior medullary veins*, sometimes called radicular veins, which accompany the nerve roots and radicular or radiculomedullary arteries. The medullary veins unite with radicular veins draining the nerve roots and with branches from the anterior and posterior internal vertebral plexuses to form the *intervertebral veins*. Above, the spinal veins communicate with veins draining the medulla oblongata and the inferior surface of the cerebellum through the foramen magnum.

The intervertebral veins drain most of the blood from the spinal cord and from the internal and external vertebral venous plexuses. They accompany the spinal nerves through the intervertebral foramina and end in the vertebral, posterior intercostal, subcostal, lumbar, and lateral sacral veins. Their orifices are usually protected by valves.



Principal Fiber Tracts of Spinal Cord

The spinal cord consists of a core of *gray matter*, surrounded by an outer fiber layer, the *white matter*. The gray matter consists of the cell bodies and dendrites of spinal neurons and the axons and axon terminals issuing from them or ending upon them (see Section 1, Normal and Abnormal Development, in Part I). The white matter consists of the axons of longitudinally running fiber tracts. The outlines of the gray and white matter are different at different spinal levels (Plate 2-6). The white matter is relatively massive in the cervical region and declines progressively in bulk in the lower levels. The gray matter is most highly developed in the cervical and lumbar enlargements, where it is made up of the neurons involved in the sensory and motor functions of the arms and the legs.

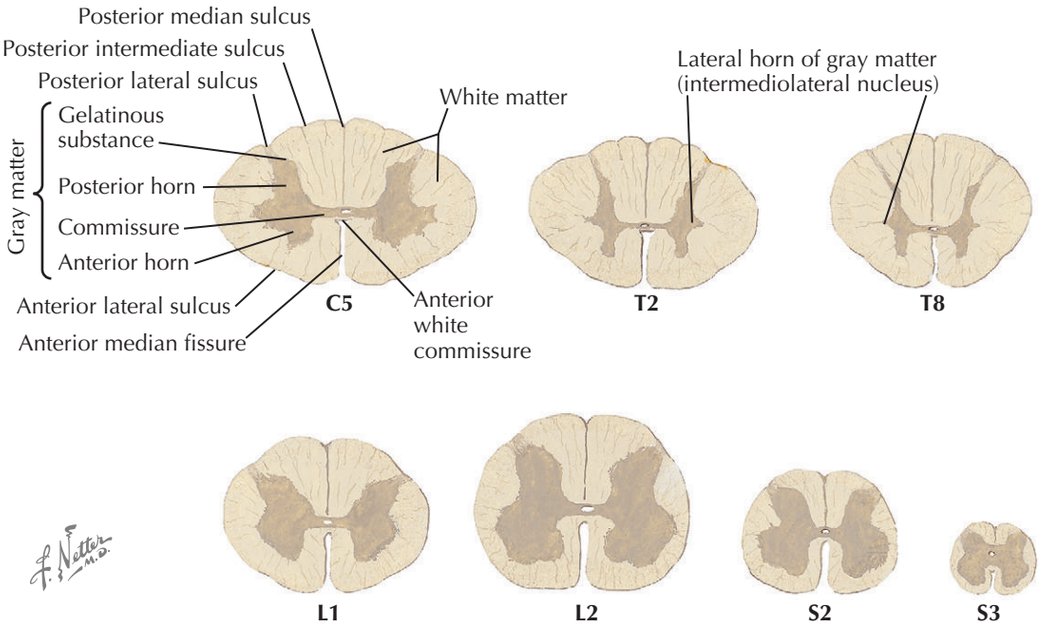
The schematic cross section in the lower part of the illustration shows the location of the principal fiber tracts within the spinal white matter. As indicated by the colors, the tracts can be divided into ascending (blue) and descending (red) pathways linking the spinal cord with the brain, and propriospinal (purple) pathways made up of fibers interconnecting different levels within the spinal cord itself.

The ascending pathways include the *fasciculus gracilis* and *fasciculus cuneatus* (part of the medial lemniscus system), which convey fine discriminative sensation from the lower and upper parts of the body, respectively. Less discriminative, higher-threshold sensations are carried by the *anterior* and *lateral spinothalamic tracts*; the latter is particularly important in conveying the sensations of pain and temperature. Other ascending pathways, which are more closely involved in reflex activity and motor control, include the *posterior* and *anterior spinocerebellar tracts* and the *spino-olivary*, *spinotectal*, and *spinoreticular tracts*.

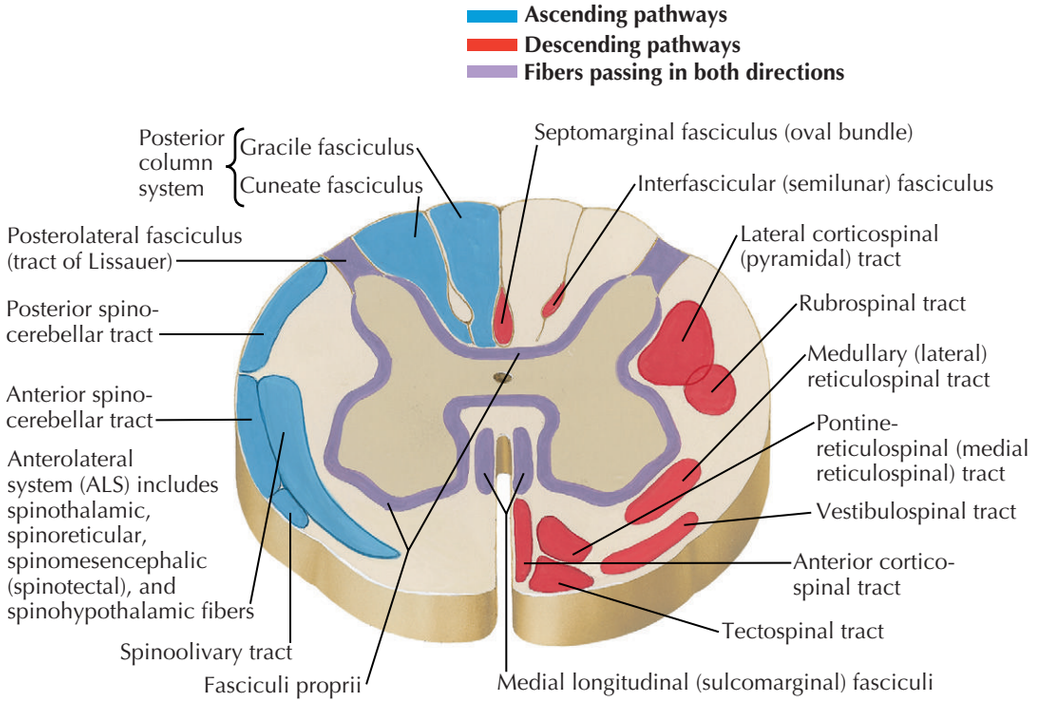
The descending pathways are divided into two groups. The first group includes the *corticospinal tracts* and the *rubrospinal tract*. It terminates preferentially in the posterolateral regions of the spinal cord, which contain the neurons controlling the distal muscles of the limbs. Damage to these pathways results in loss of fine-fractionated control of the extremities. The second group includes the *anterior* and *lateral reticulospinal tracts*, the *tectospinal tract*, the *lateral* and *medial vestibulospinal tracts*, and the *interstitiospinal tract* (from the *interstitial nucleus of Cajal* and *pretectal area)* that runs in the *medial longitudinal fasciculus* and terminates preferentially in the anteromedial regions of the spinal cord. These regions contain the neurons controlling axial and proximal limb muscles and regulate posture and righting. In addition to their motor action, both sets of descending pathways also include fibers that modulate sensory transmission by spinal pathways.

Propriospinal Pathways. Some of the propriospinal pathways consist of afferent fibers, which enter the spinal cord via the posterior roots and then ascend or descend in the *oval bundle*, *comma tract*, *posterolateral fasciculus (of Lissauer)*, *fasciculus gracilis*, or *fasciculus cuneatus* to terminate on spinal neurons at other levels of the spinal cord. Other propriospinal fibers originate from interneurons in the spinal gray matter itself. Collectively, propriospinal fibers are important in mediating spinal reflexes and coordinating activity at different levels of the spinal cord.

Sections through spinal cord at various levels



Principal fiber tracts of spinal cord



Somesthetic System of Body

Neural pathways conveying somatosensory information to the cerebral cortex can be divided into two major systems: posterior and anterolateral. The posterior pathways are involved in mediating fine tactile and kinesthetic sensations, whereas the anterolateral pathways conduct impulses for pain and temperature and for touch and deep pressure.

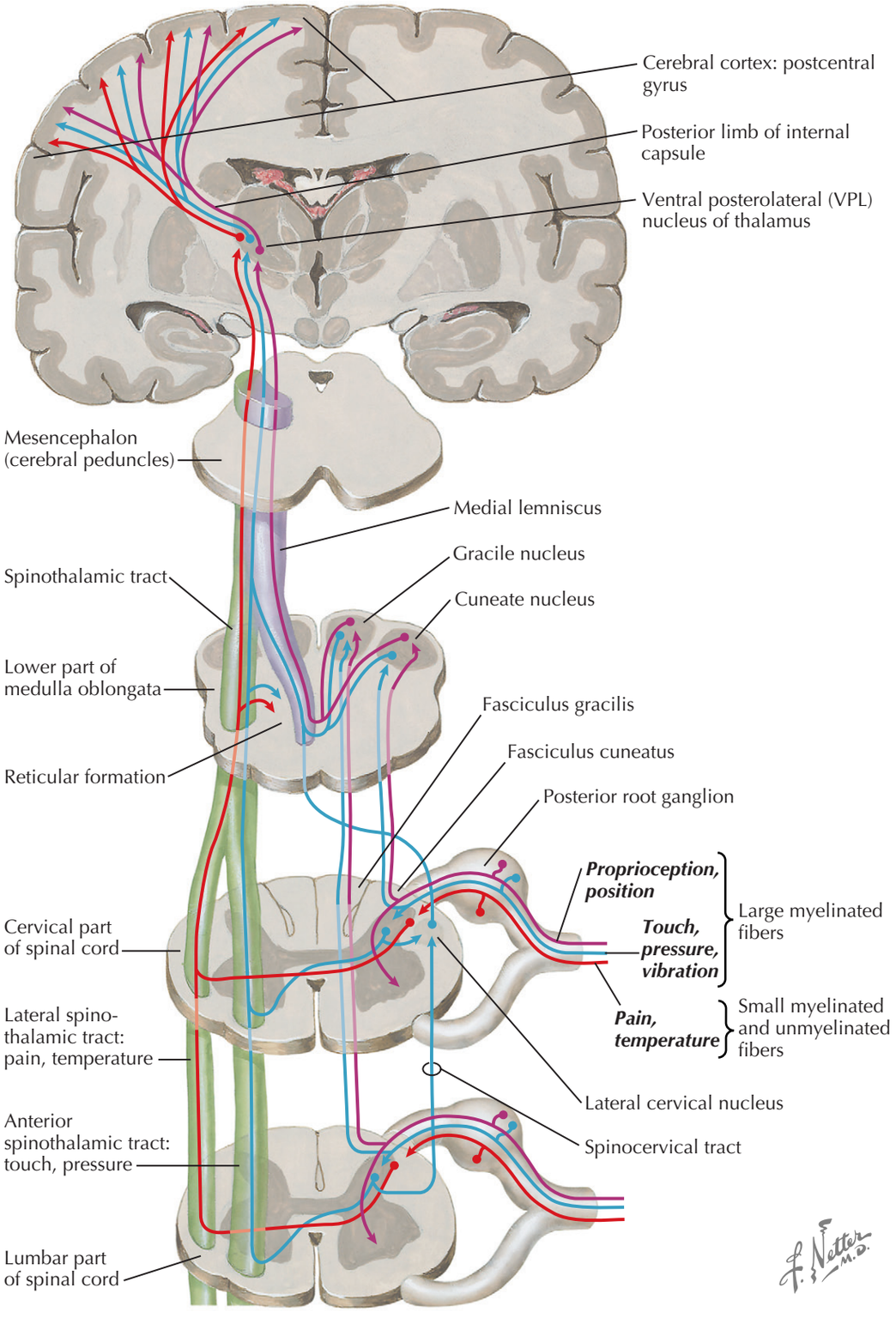
The posterior funiculus, made up of the *fasciculus gracilis* and the *fasciculus cuneatus*, carries fibers that signal discriminative touch or pressure, muscle length and tension, and joint position. Some afferent fibers, principally those from quickly adapting cutaneous receptors, ascend the entire length of the spinal cord to synapse directly with neurons in the *gracile* and *cuneate nuclei*, which relate to the lower and upper parts of the body. Other fibers leave the posterior columns and either activate spinal neurons for reflex purposes or project upward in the posterolateral funiculus. In humans, most of these secondary ascending fibers also end in the gracile or cuneate nuclei, although a small number of axons sometimes terminate in the upper cervical segments. All of the above nuclei send their axons via the *medial lemniscus* to the contralateral *ventral posterolateral (VPL) nucleus* of the thalamus, which projects to the *somatosensory regions* of the cerebral cortex.

The relay neurons in the gracile, cuneate, and VPL nuclei and the neurons of the primary somatosensory cortex are activated by a single sensory modality over a restricted receptive field. The receptive fields of neurons within each nucleus are arranged in an orderly fashion and give rise to a somatotopic representation of the body surface. Thus a high degree of specificity and order is maintained throughout the pathway.

Anterolateral Funiculus. Two somatosensory pathways ascend in the anterolateral spinal white matter: the lateral and anterior spinothalamic tracts and the smaller spinoreticulothalamic pathway. The *spinothalamic tracts* arise from neurons in the regions of the posterior horn of the spinal cord that correspond to laminae I, IV, V, and VI of Rexed (see Plate 2-13). Most axons cross in the anterior white commissure at about the level of their cell bodies and ascend in the contralateral lateral and anterior funiculi, although a few fibers ascend ipsilaterally. The spinothalamic axons end principally in the *VPL nucleus* and in the *posterior nuclear group* and *intralaminar nuclei*. Some spinothalamic neurons (especially those in lamina I) respond only to strong, noxious stimuli, but most of these neurons are excited by the activity of a wide variety of afferent fibers related to touch, pressure, vibration, and temperature sense. All spinothalamic neurons have large, unilateral receptive fields and transmit information about a wide variety of peripheral stimuli but with less specificity than is shown by neurons in the posterior spinal pathways.

The *spinoreticulothalamic pathway* (not shown) begins with neurons in the regions corresponding to laminae I and V to VIII, which ascend in the lateral and anterior funiculi to activate neurons in the *brainstem reticular formation*, which, in turn, project to the *intralaminar nuclei* of the thalamus. The spinoreticulothalamic neurons respond to the same stimuli as spinothalamic neurons, but tend to have large, bilateral receptive fields. This fact, together with the nonspecific nature of the intralaminar nuclei, suggests that this pathway is involved with poorly localizable pain sensation and is more important in generalized arousal reactions than in discriminative processing of sensation.

Lesions. Because the principal pathways of the posterior and anterolateral columns cross in the medulla and in the spinal cord, and because each pathway transmits specific modalities, damage from spinal cord lesions presents specific and characteristic deficits. *Posterior column destruction* results in ipsilateral loss of discriminatory touch and vibration sense, as well as loss of position sense below the level of the lesion. *Anterolateral column interruption* produces contralateral loss of pain and temperature sense accompanied by diminished touch sense below the lesion.

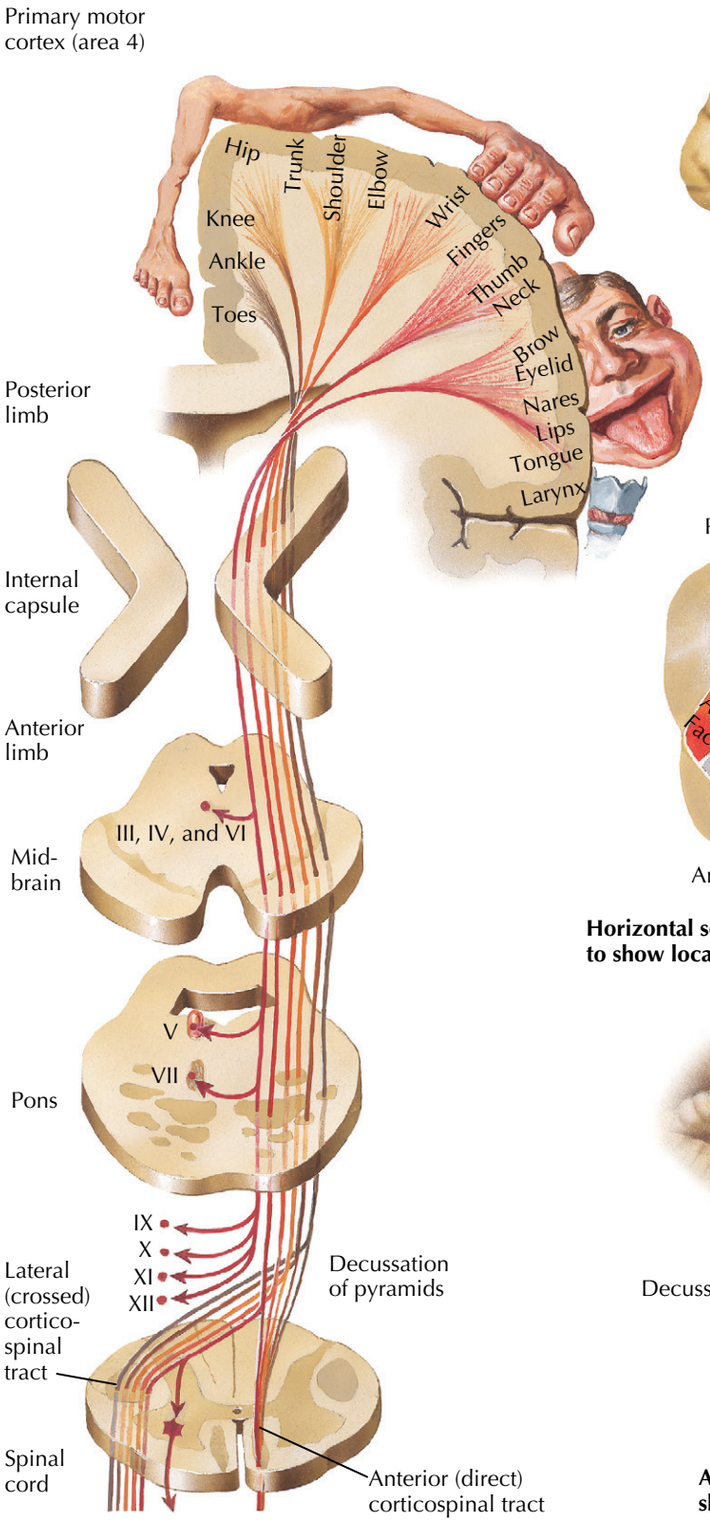


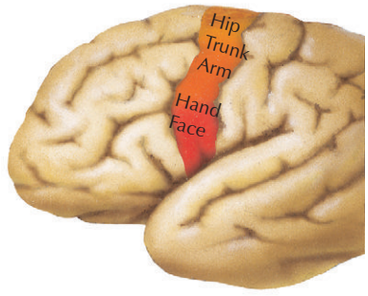
Corticospinal (Pyramidal) System: Motor Component

The corticospinal tract arises from wide regions of the cerebral cortex and is involved in multiple functions. It contributes to the control of somatosensory inputs and to motor activity. The motor component of the *corticospinal (pyramidal) tract* originates primarily in the cells of layer V in the primary motor cortex of the precentral gyrus (area 4) and projects to motor neurons and interneurons concerned with motor control throughout the central nervous system (CNS). Only the direct connections, by which cortical neurons excite motor neurons in the motor nuclei of the brainstem and spinal cord, are shown. Other illustrations show the projections of the motor cortex to the basal ganglia, thalamus, red nucleus (see Plate 2-9), reticular formation (see Plate 2-11), and intermediate spinal gray matter (see Plate 2-12).

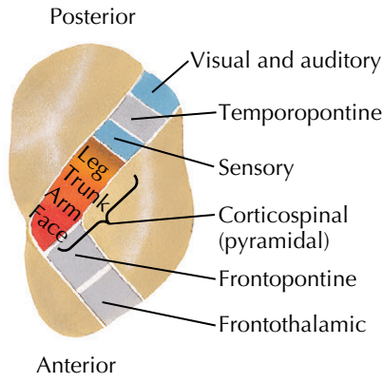
The direct motor component of the pyramidal tract runs from the precentral gyrus through the posterior limb of the internal capsule and into the midbrain, where it gives slips to the oculomotor, trochlear, and abducens nuclei. It then enters the pons, where it gives off fibers to the trigeminal motor and facial nuclei, which control the muscles of the face. From the pons, the tract continues through the medullary pyramids, giving off fibers to the nuclei of the ninth, tenth, eleventh, and twelfth cranial nerves. The major part of the tract then crosses to the opposite side of the brainstem at the *pyramidal decussation*, and the crossed fibers continue to all levels of the spinal cord as the *lateral corticospinal tract*. A smaller group of uncrossed fibers continues to the cervical spinal cord as the *anterior (direct) corticospinal tract*. The fibers end by synapsing with motor neurons in the anterior horn of the spinal cord (see Plate 2-13).

The pyramidal tract exhibits a *somatotopic organization* throughout its course. The homunculus at the top of the illustration indicates the orderly topographic arrangement of areas within the precentral gyrus, from which muscles in various parts of the body can be activated. The area controlling the face lies most laterally, with the areas related to the hand, arm, trunk, and hip following, in order, toward the midline. The areas representing the leg continue downward along the medial aspect of the cortex. Within each area, movements involving distal muscles are represented posteriorly, and proximal muscles, anteriorly. The initial somatotopic organization at the cortex persists in the arrangement of fibers along the course of the tract (see Plate 2-14). The control of voluntary movements probably relates, however, to distributed networks that are capable of modification rather than to discrete representations. There appears to be considerable plasticity of representations and cell properties in the primary motor cortex, probably related to the horizontal neuronal connections in the cortex. The primary motor cortex is not a simple static motor control structure but contains a dynamic substrate that participates in motor learning.

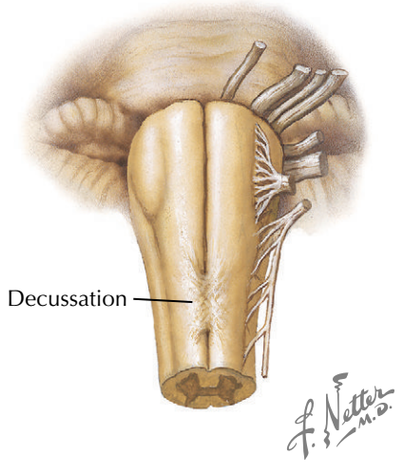




Lateral aspect of cerebal cortex to show topographic projection of motor centers on precentral gyrus



Horizontal section through internal capsule to show location of principal pathways



Anterior aspect of brainstem showing decussation of pyramids

Lesions of the motor cortex may produce discrete pareses, depending upon the type and size of the lesion and its somatotopic location. Irritative lesions of the cortex can lead to abnormal movements and ultimately to jacksonian seizures as the irritative focus spreads. Damage to the internal capsule produces contralateral paralysis, along with cranial nerve involvement.

In general, pyramidal tract disturbances produce an initial flaccid paralysis and areflexia, followed by spastic paralysis and hyperactive reflexes. Brainstem lesions cause paralysis contralateral to the lesion, accompanied by ipsilateral or contralateral cranial nerve deficits, depending on the level of the lesion. Spinal cord damage to the tract is usually accompanied by alterations in the autonomic and sensory systems.

Rubrospinal Tract

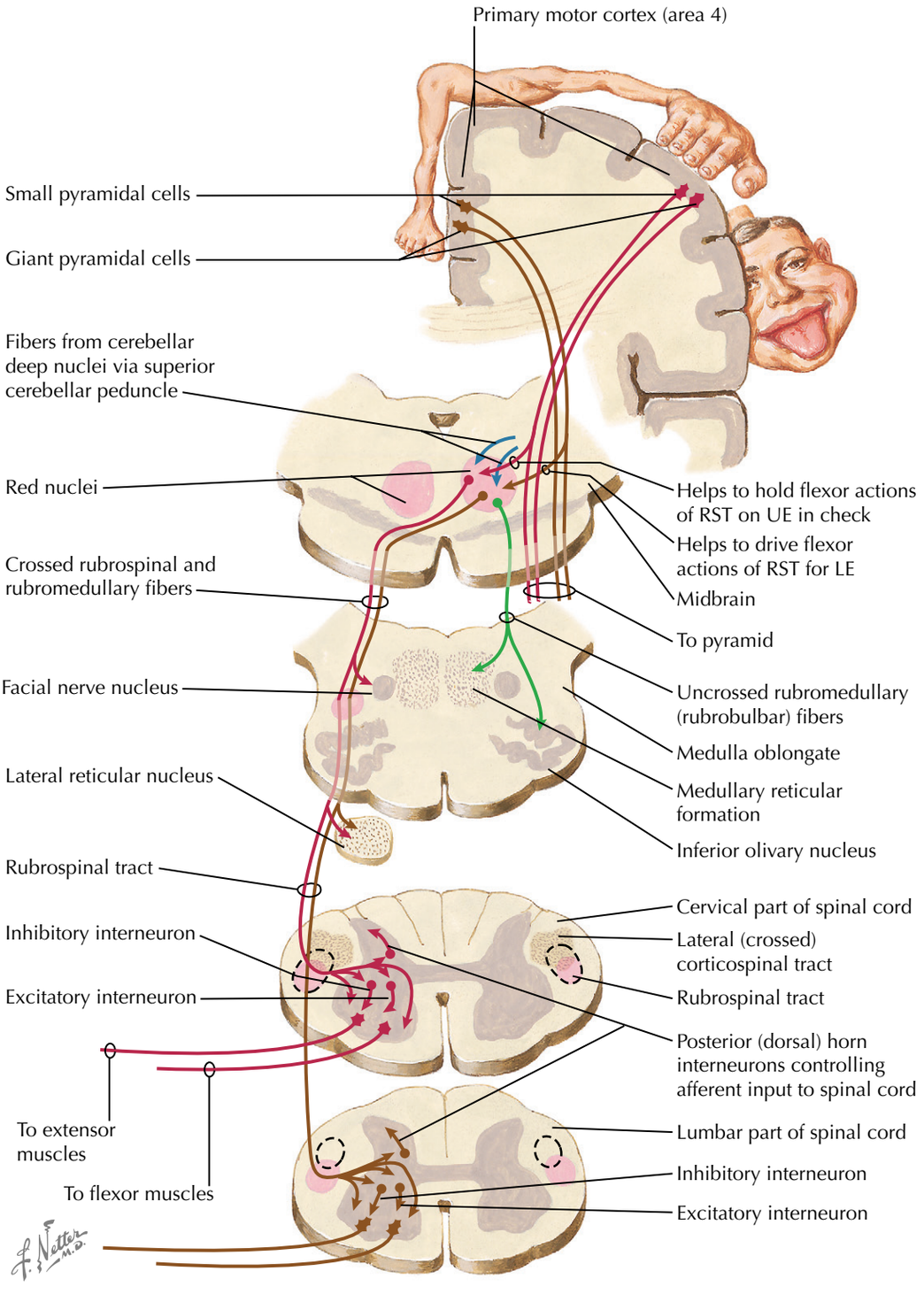
The *red nucleus* (so-called because of its reddish color in the fresh brain) is situated in the midbrain. It receives a large number of fibers from the contralateral cerebellum and the ipsilateral cerebral cortex and, in turn, has a major projection to the spinal cord, the rubrospinal tract. Knowledge of the rubrospinal tract in humans is limited. It seems to arise predominantly from the large neurons of the caudal part of the red nucleus, is arranged somatotopically, and extends the entire length of the spinal cord, influencing alpha and gamma motor neurons. The predominant target of its action is the motor apparatus controlling the distal muscles of the contralateral limbs, although the tract also acts to inhibit the action of cutaneous and muscle afferent fibers on spinal neurons. Within the brainstem, fibers branch from the rubrospinal tract to terminate in the facial nucleus (control of facial muscles), the lateral reticular nucleus (cerebellar afferent relay), and the gracile and cuneate nuclei (control of afferent input) (see Plate 2-7). In addition to being the source of the rubrospinal tract, the red nucleus sends fibers to the ipsilateral inferior olive (cerebellar afferent relay) and medial reticular formation (see Plate 2-11).

As shown in the illustration, *rubrospinal fibers decussate* almost immediately on leaving the red nucleus to descend through the lateral part of the brainstem to the spinal cord. In the cord, the tract lies in the *posterolateral funiculus*, just anterior to the lateral corticospinal tract. The distal branches of the rubrospinal fibers terminate in the intermediate regions and anterior horn (laminae V, VI, and VII) of the spinal gray matter (see Plate 2-12).

The rubrospinal tract influences the motor neurons in the anterior horns, primarily through its action on inhibitory or excitatory interneurons, but in primates some fibers end directly on anterior horn motor neurons. The predominant pattern of rubrospinal action is to facilitate flexor motor neurons and thus excite limb flexor muscles and to inhibit the corresponding extensor muscles via interneurons. However, a number of rubrospinal fibers have the opposite action. This allows a wide variety of movements to be executed by the selective activation of appropriate groups of rubrospinal neurons. The rubrospinal tract may thus be responsible for much of the relatively fine control of the extremities—discriminative movement that is retained when the pyramidal tract is damaged. In animals, lesions involving both the pyramidal and rubrospinal tracts result in a much greater deficit in distal movement than that obtained from a lesion of either tract alone.

Rubrospinal control of *afferent input* to the spinal cord takes the form of presynaptic inhibition acting at the central posterior horn terminals of fibers from Golgi tendon organs and cutaneous receptors.

The two major sources of the input that controls the activity of rubrospinal neurons are the *cerebellum* and the *cerebral cortex*. The cerebellar projection to the red nucleus consists primarily of fibers from the interposed (emboliform and globose) nuclei, which cross in the decussation of the superior cerebellar peduncle (brachium conjunctivum) to excite the red nucleus neurons of the opposite side. Neurons of the red nucleus are also excited by branches of small pyramidal cells from the ipsilateral motor cortex (see Plate 2-8). Afferents from the motor and premotor cerebral cortex synapse on their distal dendrites and from the cerebellum on their proximal dendrites and cell bodies. In addition, activity in pyramidal tract axons from giant neurons in the same cortical region exerts an opposite, inhibitory effect on rubrospinal neurons via inhibitory interneurons. The input as well as the output of the red nucleus is *somatotopically organized*. Thus rubrospinal fibers projecting to the lumbar part of the spinal cord originate from neurons in the lateral part of the nucleus. This same region receives input from regions of the cerebellar deep nuclei and motor cortex related to control of the lower limbs. Conversely, the medial part of the red nucleus, which contains neurons projecting to cervical levels of the spinal cord, receives input from cerebellar and cerebral regions responsible for control of the arms. This pattern of organization allows for the selective activation of individual extremities by different groups of rubrospinal neurons.



Vestibulospinal Tracts

The vestibular system is involved in the control of balance. *The vestibular nuclei* consist of four major groups of neurons—the *superior*, *medial*, *lateral*, and *inferior vestibular nuclei*—situated in the posterolateral part of the pons and medulla oblongata. Three of these neuronal groups, the medial, lateral (Deiters), and inferior (descending) vestibular nuclei—comprise the major central termination of the vestibular afferent fibers that supply the otolithic organs (utricle and saccule) of the labyrinth. Vestibular afferent fibers supplying the semicircular canals end primarily in the superior, medial, and lateral vestibular nuclei, but many fibers also terminate in the vestibulocerebellum. In addition to these vestibular afferent impulses, the vestibular nuclei also receive input from the spinal cord, cerebellum, reticular formation, and higher centers.

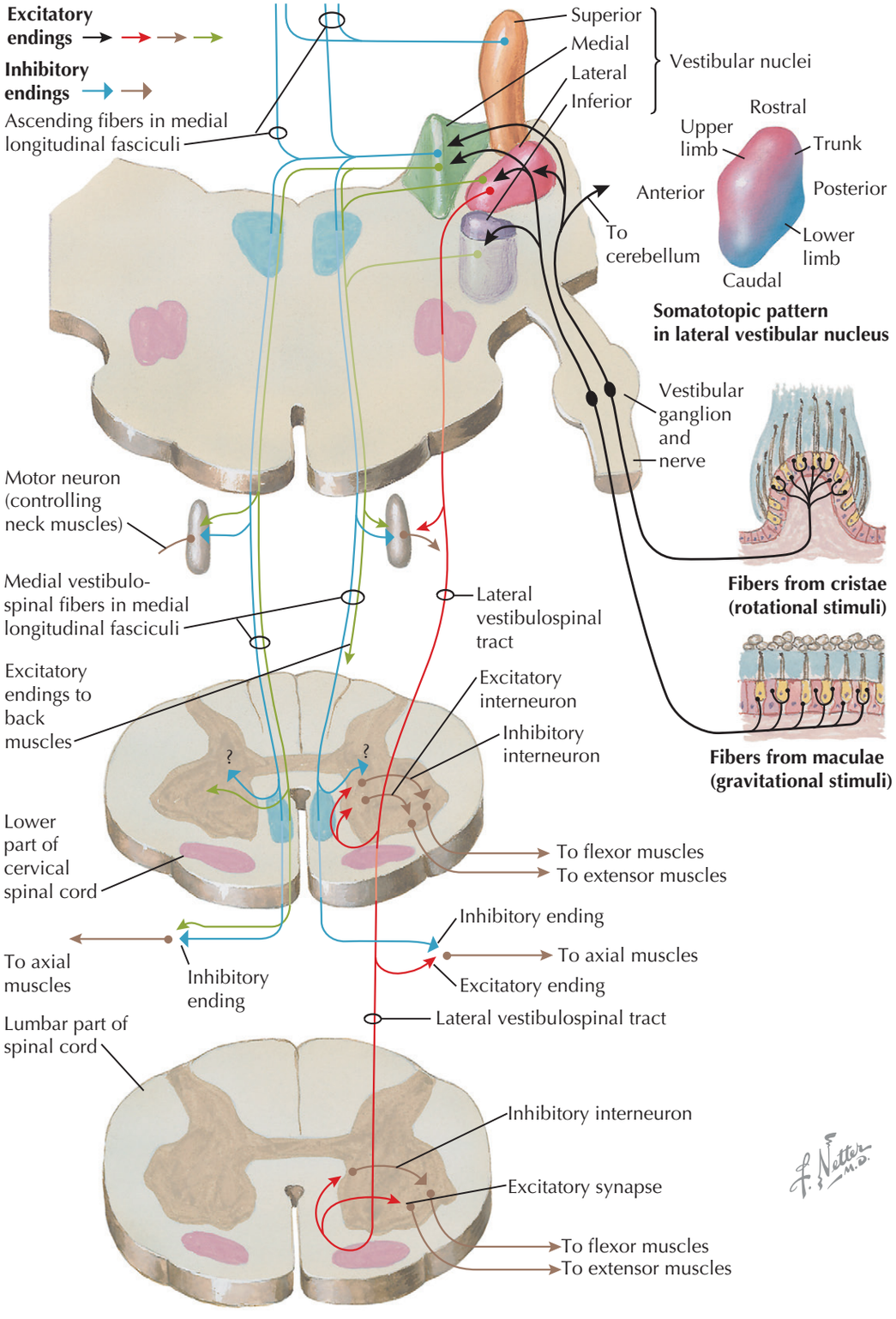
The known output pathways from the vestibular nuclei include projections to the spinal cord, oculomotor nuclei, cerebellum and reticular formation. Vestibular activity also reaches the thalamus, superior colliculus and other higher centers, but the exact pathways are not known.

Vestibulospinal Tracts. The illustration shows the projections of vestibular neurons to the spinal cord via the *lateral vestibulospinal tract (LVST)* and *medial vestibulospinal tract (MVST)*. These two tracts, which lie in the anterior and anteromedial funiculi (see Plate 2-12), act primarily on the motor apparatus that controls the proximal muscles and therefore are important in the regulation of postural equilibrium.

The *LVST* is uncrossed and originates primarily from the *lateral vestibular nucleus*. Some of its constituent fibers extend the entire length of the spinal cord, whereas others extend only part of this distance; they may branch to innervate several regions as they descend. The lateral nucleus is *somatotopically organized*: neurons projecting to the lower (hindlimb) levels of the spinal cord are located in the posterior and distal portion of the nucleus, and neurons ending at higher levels are situated more anteriorly and rostrally. The former region receives a heavy projection from the cerebellar vermis, whereas the latter region receives a heavy input of vestibular afferent fibers. The LVST ends in lamina VIII and parts of lamina VII; it acts on alpha and gamma neurons.

The predominant action of the LVST is to produce the contraction of extensor (antigravity) muscles and the relaxation of flexor muscles. In the case of neck, trunk, and some lower limb extensor muscles, contraction is produced in part by direct (monosynaptic) excitation of motor neurons. The excitation of other limb extensor muscles and the inhibition of flexor muscles are mediated by pathways that include spinal interneurons.

The *MVST*, which projects bilaterally to the cervical cord, is involved in reflex adjustments of the head and axial muscles to vestibular stimulation. It contains fibers that originate primarily in the *medial vestibular nucleus* and produce direct inhibition of motor neurons controlling neck and axial muscles. The tract seems to stop in the midthoracic region. The two vestibulospinal tracts are important factors in *vestibular reflex reactions* that are triggered by the movement of the head in space. Particularly significant in this regard is the strong vestibular action on the neck muscles, which helps to stabilize the position of the head. However, these tracts and the reticulospinal tracts (see Plate 2-11) also appear to play a much wider role in the control of the proximal musculature.



Reticulospinal and Corticoreticular Pathways

The reticulospinal pathways are important in controlling motor activity and in regulating the flow of afferent signals in the spinal cord. They consist of a series of descending fiber connections that originate in two regions of the brainstem and project to the spinal cord via two different *reticulospinal tracts*. Both regions of origin are in the medial, magnocellular part of the brainstem reticular formation. The more rostral region is in the nucleus reticularis pontis caudalis and nucleus reticularis pontis oralis of the *pontine reticular formation*; the more caudal region is in the nucleus gigantocellularis, in the rostromedial part of the *medullary reticular formation*. Their separate projections are described below.

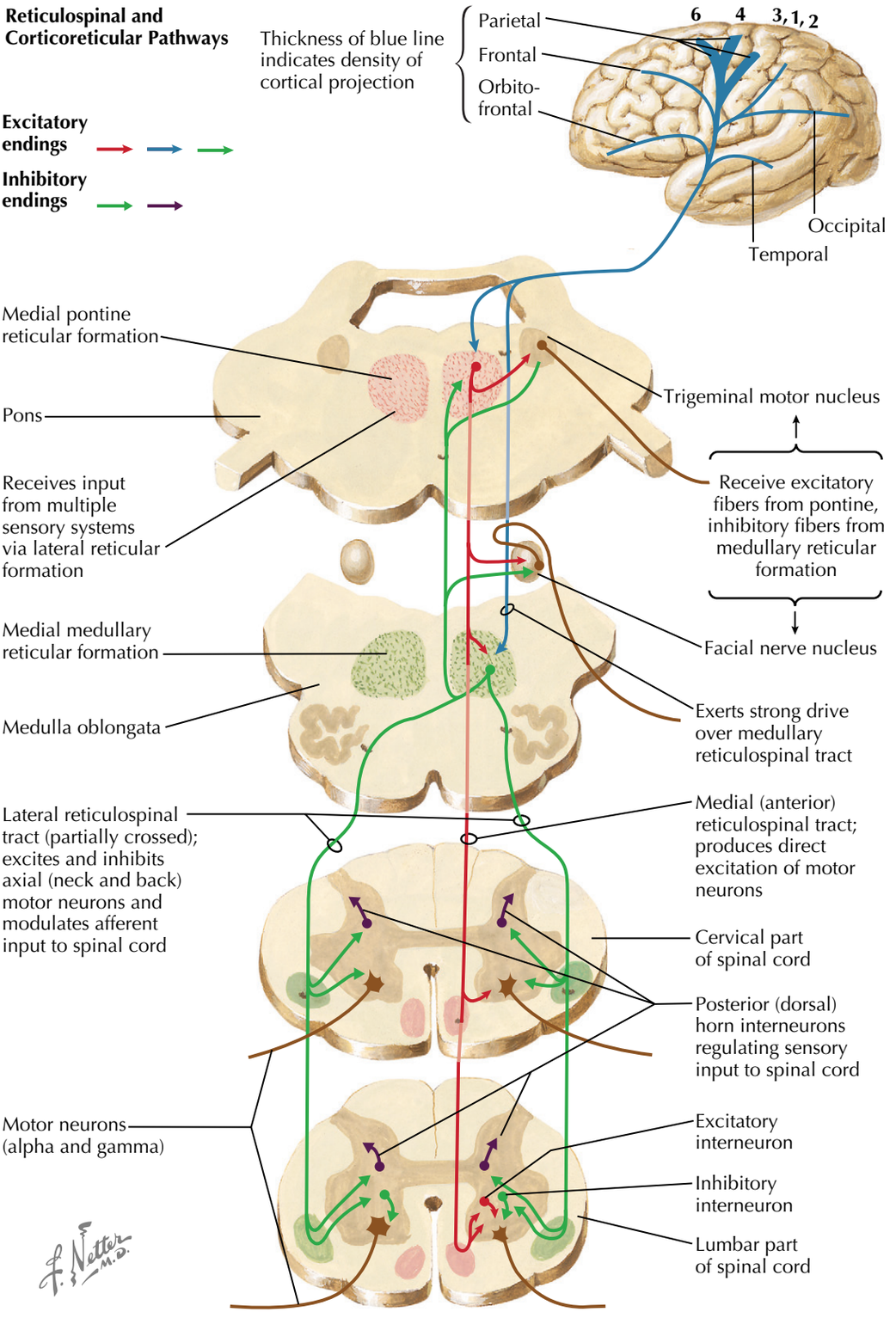
Pontine reticulospinal fibers project to the spinal cord *via the medial reticulospinal tract only*. This tract traverses the anterior funiculus ipsilaterally and extends along the entire length of the spinal cord, sending terminal branches to innervate the gray matter of the anterior horn (see Plate 2-12). It excites large numbers of spinal motor neurons of all types, especially flexor motor neurons and motor neurons controlling proximal (trunk and axial) muscles. The pontine system also has a strong, indirect influence on lumbar motor neurons, relayed by spinal interneurons (see bottom of illustration).

The medullary reticulospinal system has a more complex pattern of projection. Most fibers originating from the gigantocellular nucleus project to the spinal cord via the *ipsilateral lateral reticulospinal tract (RST)*, which is part of the lateral anterolateral funiculus. In addition, some medullary reticular neurons project via the *contralateral lateral reticulospinal tract*, and some join the *medial reticulospinal tract*. Within the spinal gray matter, terminations of medullary reticulospinal fibers cover an exceptionally wide area, encompassing most of the anterior horn and the basal portion of the posterior horn (see Plate 2-12).

The physiologic action of the medullary reticulospinal system on spinal motor neurons is twofold and quite complex. Stimulation of the *rostral part* of the *gigantocellular nucleus* produces *excitation* of motor neurons, whereas stimulation of its *caudal-anterior part* produces *inhibition*. Actions on axial motor neurons are mediated by direct connections, whereas those on limb motor neurons are relayed by spinal interneurons. Stimulation in the caudal-anterior area also produces inhibition of spinal interneurons and inhibition of afferent transmission to the spinal cord. The exact pathways mediating these various effects are unknown, but they appear to involve reticulospinal fibers descending in the posterolateral funiculus (not shown in illustration).

Reticulospinal fibers seem to be involved in the control of certain voluntary and reflex movements, the integration of sensory input to guide motor output, and the coordination of bilateral movements. They can influence both diffuse motor activity and more focused goal-directed movements. The reticulospinal tracts include descending autonomic fibers that terminate on sympathetic and parasympathetic preganglionic neurons and allow the hypothalamus to influence the autonomic outflow.

Input to the *medial brainstem reticular formation* originates from many sources. Most major sensory systems send collateral branches to one of its regions, and the most pronounced sensory input to the source of reticulospinal fibers comes from the cutaneous and high-threshold muscle receptors of the body. As indicated by the relative width of the particular lines in the illustration, physiologic studies demonstrate that the great majority of both pontine and medullary reticulospinal neurons receive strong excitatory input from structures involved in motor control, including the motor or premotor cerebral cortex, themselves a part of an extensive corticoreticular system originating from all parts of the cortex, the cerebellar fastigial nucleus, and the superior colliculus. The resulting *corticoreticulospinal connections* constitute an extrapyramidal pathway by which motor regions of the cortex can act on the spinal motor apparatus. The physiologic role of the projections from sensory regions of the cerebral cortex to reticulospinal neurons is less certain, but such pathways may be involved in the regulation of sensory input to the spinal cord through reticular-evoked presynaptic inhibition of spinal afferent fibers or through postsynaptic inhibition of spinal sensory interneurons.



Spinal Origin or Termination of Major Descending Tracts and Ascending Pathways

The spinal neurons receive input from, and send projections to, many parts of the brain (see Plate 2-6). The sections illustrated show the regions of the spinal gray matter, within which axons of the four major descending pathways terminate, and the locations within the spinal gray matter of neurons that project to the thalamus and cerebellum (see Plate 2-13).

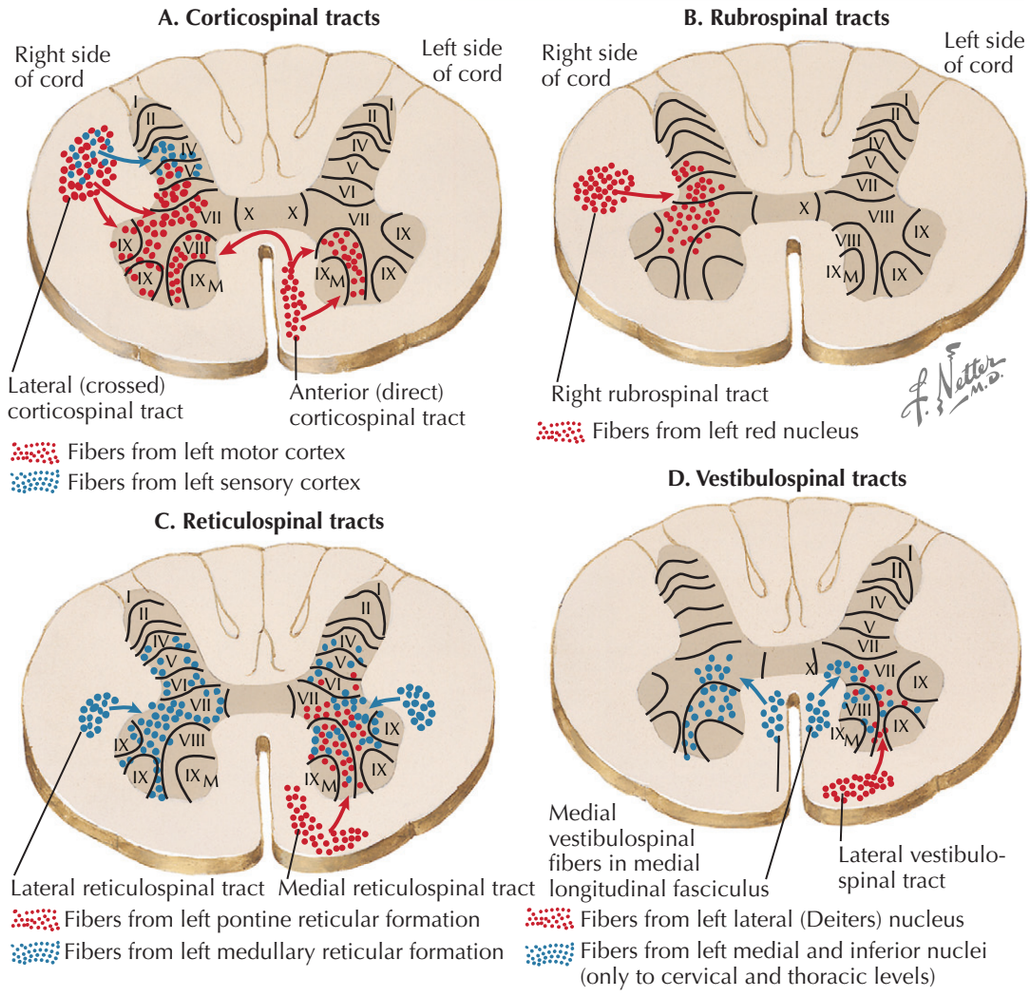
The descending pathways shown in parts A, B, C, and D have a variety of actions on spinal circuitry, including the modulation of somatosensory input and the production of motor output. Actions on the sensory apparatus are typically mediated by descending fibers that terminate upon neurons in the posterior horn (laminae I to VI) of the spinal cord. As shown in A, the specific spinal projections from the somatosensory cortex concerned with sensory control end almost entirely in the posterior horn. Some projections from the brainstem reticular formation, which also has a strong action on the sensory apparatus, also terminate in the posterior horn (C). Conversely, the vestibulospinal tracts (D), which have only a weak action on sensory processes, have relatively few terminals in the posterior horn. The rubrospinal tract (B), which has some inhibitory effect on spinal afferents, terminates in intermediate regions and in the rostral part of the anterior (ventral) horn.

The projections from the brain to the spinal cord have been divided into lateral and medial systems. The *lateral descending systems* include the lateral (crossed) corticospinal tract fibers originating in the motor cortex (A) and the rubrospinal tract (B) (see Plates 2-8 and 2-9). These tracts terminate predominantly in the lateral parts of laminae V, VI, VII, and IX, which are concerned with the control of the *distal musculature of the limbs*.

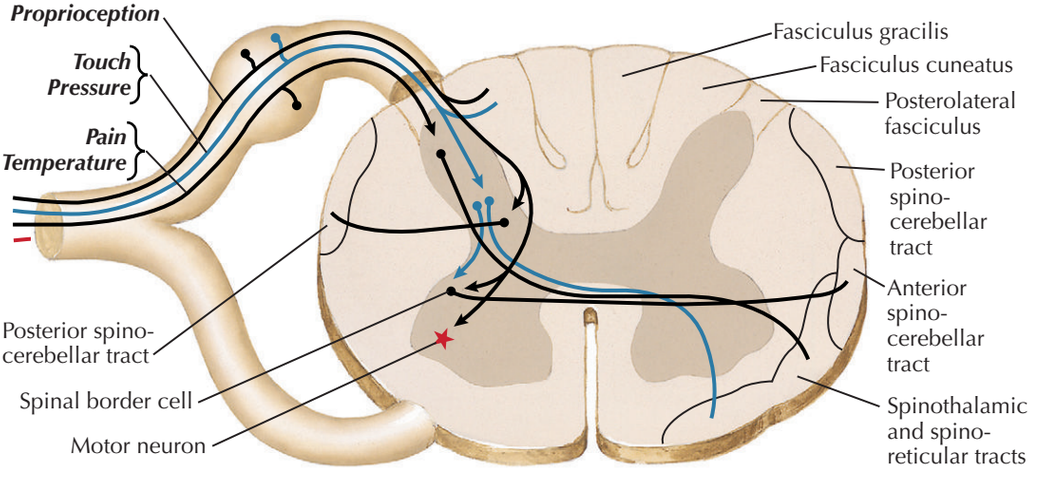
The *medial descending systems* include the reticulospinal tracts (C) and vestibulospinal tracts (D) (see Plates 2-10 and 2-11). These tracts end most heavily in laminae VIII and IX_M, which are involved in controlling neck and trunk muscles. Endings are also present in the medial parts of laminae VI, VII, and IX, which control the proximal muscles of the limbs. Thus the medial systems act predominantly upon *axial* and *proximal muscles*. The functional role of the *anterior (direct) corticospinal tract* is uncertain, although its endings in lamina VIII suggest that it may be involved in the cortical control of axial muscles.

Connections to Ascending Pathways. Ascending projections from the spinal cord to the brain arise from many parts of the spinal gray matter. In general, however, projections to sensory structures tend to originate in the posterior horn, which is the receiving area for somatosensory input arriving via the posterior roots. The illustration shows the *anterior* and *lateral* divisions of the *spinothalamic tract*, which are continuous with each other. One division originates primarily from neurons in lamina I, which respond chiefly to painful stimuli; the other originates from neurons located mainly in laminae IV to VI, which receive information related to a variety of somatosensory stimuli. Lamina IV also gives rise to projections to other sensory areas, such as the cuneate, gracile, and lateral cervical nuclei. Laminae V to VIII give origin to the spinoreticular tract.

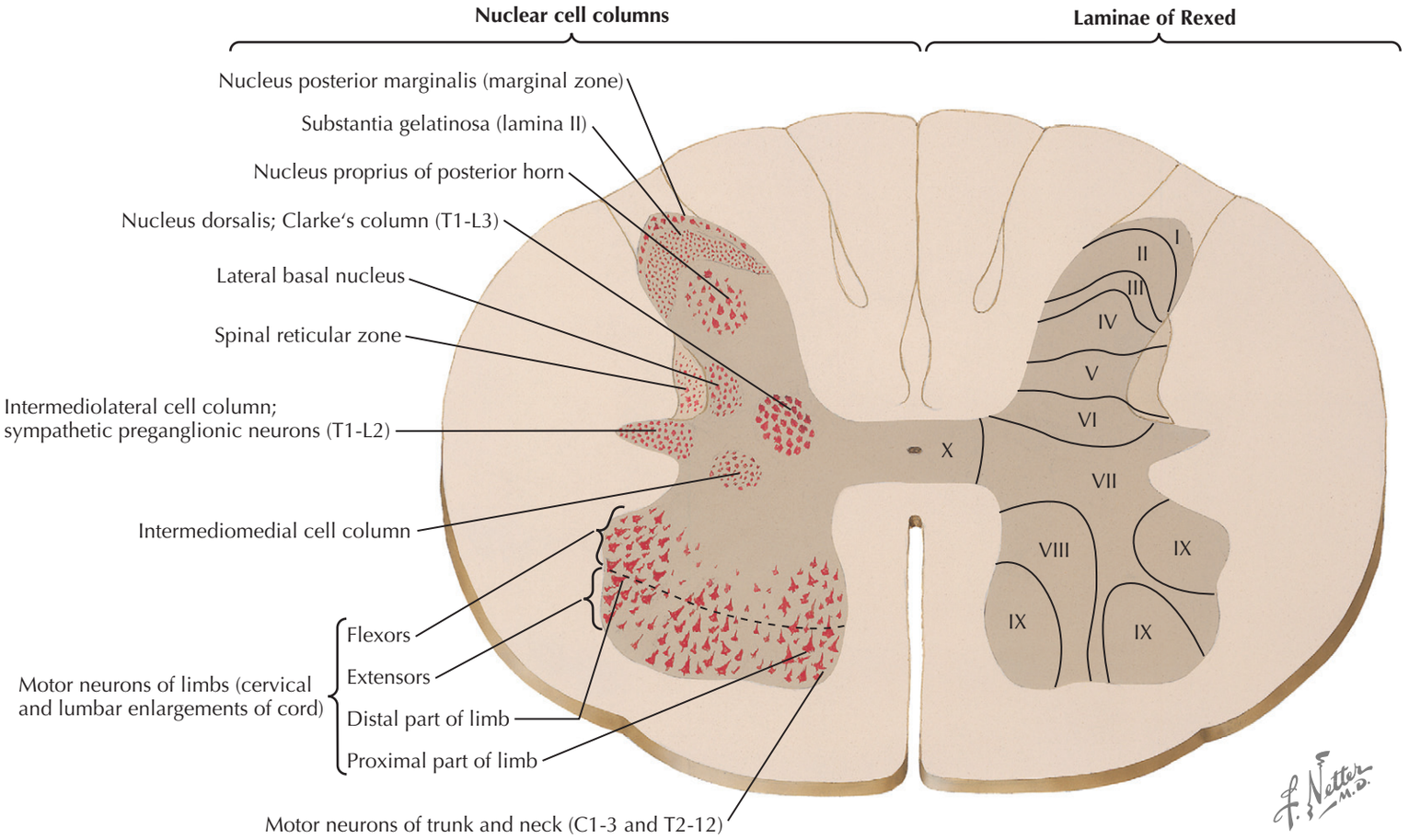
Termination of major descending tracts



Afferent connections to ascending pathways



Ascending projections to areas involved in motor control tend to arise from laminae VI to IX, which are related to motor movements. The illustration shows two ascending pathways related to motor activity, both of which terminate in the cerebellum. The *posterior spinocerebellar tract* originates from Clarke's column, a group of neurons located in lamina VI, and ascends in the ipsilateral posterolateral funiculus. The *anterior spinocerebellar tract* originates from spinal border cells at the edge of lamina VII and ascends via the contralateral anterolateral funiculus. As shown, neurons projecting in both tracts receive input from muscle proprioceptors; some also receive indirect cutaneous input. In addition to neurons projecting to the cerebellum, the anterior horn also contains neurons projecting to other structures related to motor control, such as the inferior olive and the reticular formation.



Cytoarchitecture of Spinal Cord Gray Matter

The gray matter of the spinal cord can be broadly divided into a *posterior (dorsal) horn* and an *anterior (ventral) horn*, which are further subdivided according to the size and structure of their component neuronal cell bodies. The left side of the illustration shows some of the clearly recognizable groups of neurons; the right side shows a more systematic subdivision of the spinal gray matter into 10 laminae, which were originally described by Rexed in the spinal cord of the cat, but which are useful in discussing human functional neuroanatomy.

Posterior Horn. Many neurons in the six laminae of the posterior horn receive direct synaptic input from spinal afferent fibers that enter the spinal cord via the posterior roots and are thus involved in sensation and in the generation of reflex responses to external or proprioceptive signals (see Plate 2-12).

Lamina I of the posterior horn is a thin layer of large cells, which gives origin to the pathway relaying information about painful stimuli to the thalamus. *Laminae II and III* comprise the *substantia gelatinosa*, a tightly packed mass of tiny neurons believed to play a role in regulating afferent input to the spinal cord. *Lamina IV* is a collection of larger neurons (sometimes referred to as the *nucleus proprius of the posterior horn*) that projects to three sensory structures: the lateral cervical nucleus, the posterior column nuclei, and the thalamus. Thus the connections of laminae I to IV indicate their importance in sensation.

Laminae V and VI contain neurons of medium-to-large size, many of which receive input from afferent fibers carrying proprioceptive information, as well as other sensory information also relayed by neurons in lamina IV. These neurons probably represent an intermediate stage in the transformation of sensory input to motor output. Laminae V and VI are also the sites of origin of ascending projections to higher centers. In spinal segments T1 to L3, lamina VI contains a group of large cells known as *Clarke's column*, which projects to the cerebellum via the posterior spinocerebellar tract.

The anterior horn contains the cell bodies of the motor neurons supplying the somatic muscles. These cell bodies are clustered into two distinct groups, referred to by Rexed as lamina IX and IX_M. Lamina IX_M contains the motor neurons supplying the muscles of the trunk and neck, while lamina IX contains motor neurons supplying the limbs. Lamina IX can be further divided into groups of motor neurons supplying flexor and extensor muscles in the proximal and distal parts of the limbs.

The anterior horn also contains *laminae VII and VIII*. These regions contain interneurons involved in reflex pathways and motor control, as well as neurons that project to motor regions of the brain. The neurons of lamina VIII are particularly related to lamina IX_M and thus participate in movements of the muscles in the trunk and neck. Conversely, neurons of lamina VII are particularly related to lamina IX and therefore participate in movements of the limb muscles. Laminae VII and IX are both highly developed in the spinal enlargements that control the arms and the legs (see Plate 2-8), whereas only laminae VIII and IX_M are found in the high cervical or thoracic segments that control the neck and trunk.

In the thoracic and sacral segments, the *intermediolateral cell column*, which is not considered part of either the posterior or the anterior horn, contains the neurons of origin of preganglionic autonomic fibers. *Lamina X* —the small area of gray matter around the central canal—contains neurons that project to the opposite side of the spinal cord, including those in the anterior and posterior commissural nuclei.

Spinal Effector Mechanisms

The illustration shows a schematic representation of the structure of the spinal motor nuclei and their segmental connections.

Motor Neurons. Except for muscles innervated by the cranial nerves, each somatic muscle receives its motor supply from a column of motor neurons arranged longitudinally in the anterior horn of the spinal cord. Motor neurons fall into three classes. The large *alpha motor neurons* supply the extrafusal fibers of the muscle, and each motor neuron may innervate several to more than one thousand fibers distributed throughout the muscle. A single motor neuron and all of the muscle fibers that it innervates are called a *motor unit*. The small *gamma motor neurons* (fusimotor neurons) innervate the intrafusal muscles of the spindles, thus regulating proprioceptive feedback of information about muscle length. The intermediate-sized *beta motor neurons* project to both extrafusal and intrafusal muscle fibers; their activity causes contraction and also adjusts length feedback to compensate for that contraction. The beta motor neurons are divided into dynamic and static, depending on the type of intrafusal muscle fibers that they innervate and their physiologic effects.

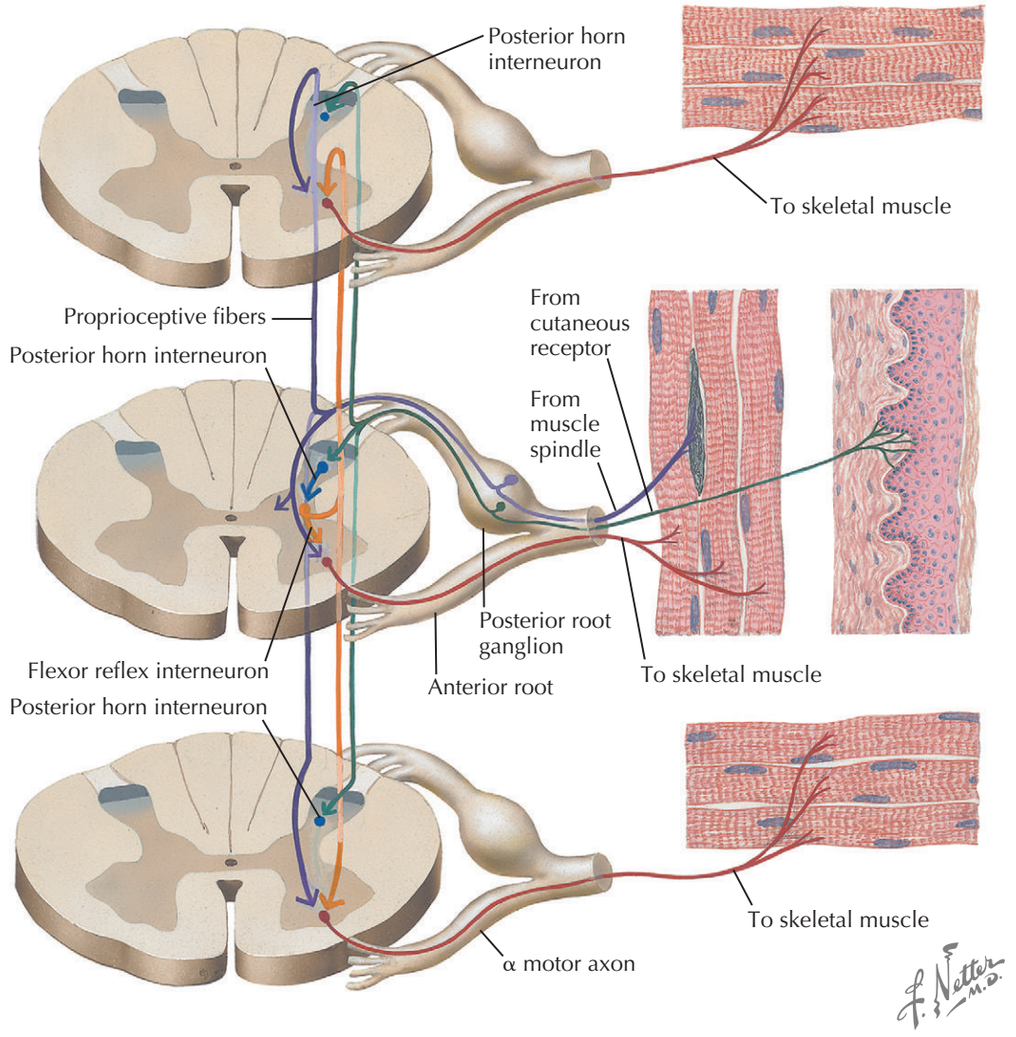
Motor nuclei may extend longitudinally over several segments of the spinal cord. Despite this, the nuclei supplying different muscles tend to be arranged in an orderly, somatotopic pattern (see Plate 2-13). In the upper cervical and the thoracic segments, which innervate only axial muscles, the anteromedial group is the only group of somatomotor neurons present; in the cervical and lumbar enlargements of the spinal cord (lower part of illustration), additional motor columns supplying limb muscles appear more laterally in the anterior horn. Moving from the rostral to the caudal end of the two enlargements, the motor nuclei supplying the proximal limb muscles appear first, lying adjacent to the anteromedial column. They are followed by the nuclei supplying the more distal muscles, which tend to lie more posteriorly and laterally. Nuclei supplying the extensor muscles also tend to lie anteriorly and laterally to those supplying the flexor muscles. Even the small movement of an extremity involves activity in the medial and lateral cell columns extending over several spinal cord segments.

Proprioceptive and Exteroceptive Fibers. Motor neurons can be influenced by both the proprioceptive and the exteroceptive fibers that enter the spinal cord. Upon entering the spinal cord (upper part of illustration), these fibers may give off ascending and descending branches that send terminal branches into the posterior or anterior horn over a distance of several segments, which approximately matches the extent of the corresponding motor nucleus. Further afferent fiber branches may continue rostrally to various sensory relay nuclei (see Plate 2-7).

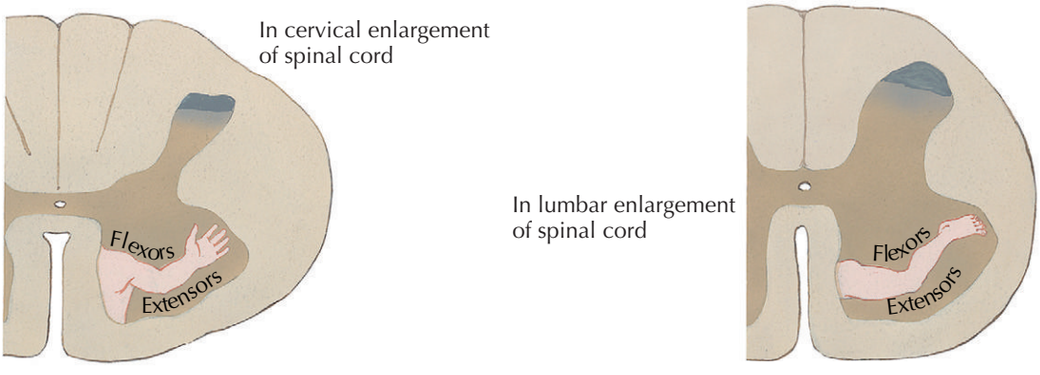
The most numerous *proprioceptive fibers* are those carrying information from muscle spindles (groups Ia and II fibers), and from Golgi tendon organs (group Ib fibers). The Ia fibers are unique in that they enter the anterior horn motor nuclei and establish direct connections with motor neurons. These connections form the basis of the *muscle stretch reflex* (see Plate 2-15). One Ia afferent fiber from a spindle in a given muscle produces direct excitation in virtually every motor neuron supplying that muscle and in a smaller proportion of motor neurons supplying closely related synergistic muscles. This selectivity may be explained by the fact that the terminal field of the la fiber is approximately coextensive with the motor nucleus of its muscle and overlaps slightly with synergist motor nuclei located nearby.

The principal reflex elicited by *exteroceptive fibers* is the *flexor withdrawal reflex* (see Plate 2-15). The distribution of motor effects in this reflex is much broader than that of the stretch reflex, comprising most of the flexor muscles of the limb, as well as crossed activation of the contralateral extensor muscles. This distribution does not derive from the projection pattern of the afferent fibers, however, but rather from the divergent projection of chains of interneurons in the posterior and anterior horns that subserve the withdrawal reflex.

Spinal effector mechanisms



Representation of motor neurons



Spinal Reflex Pathways

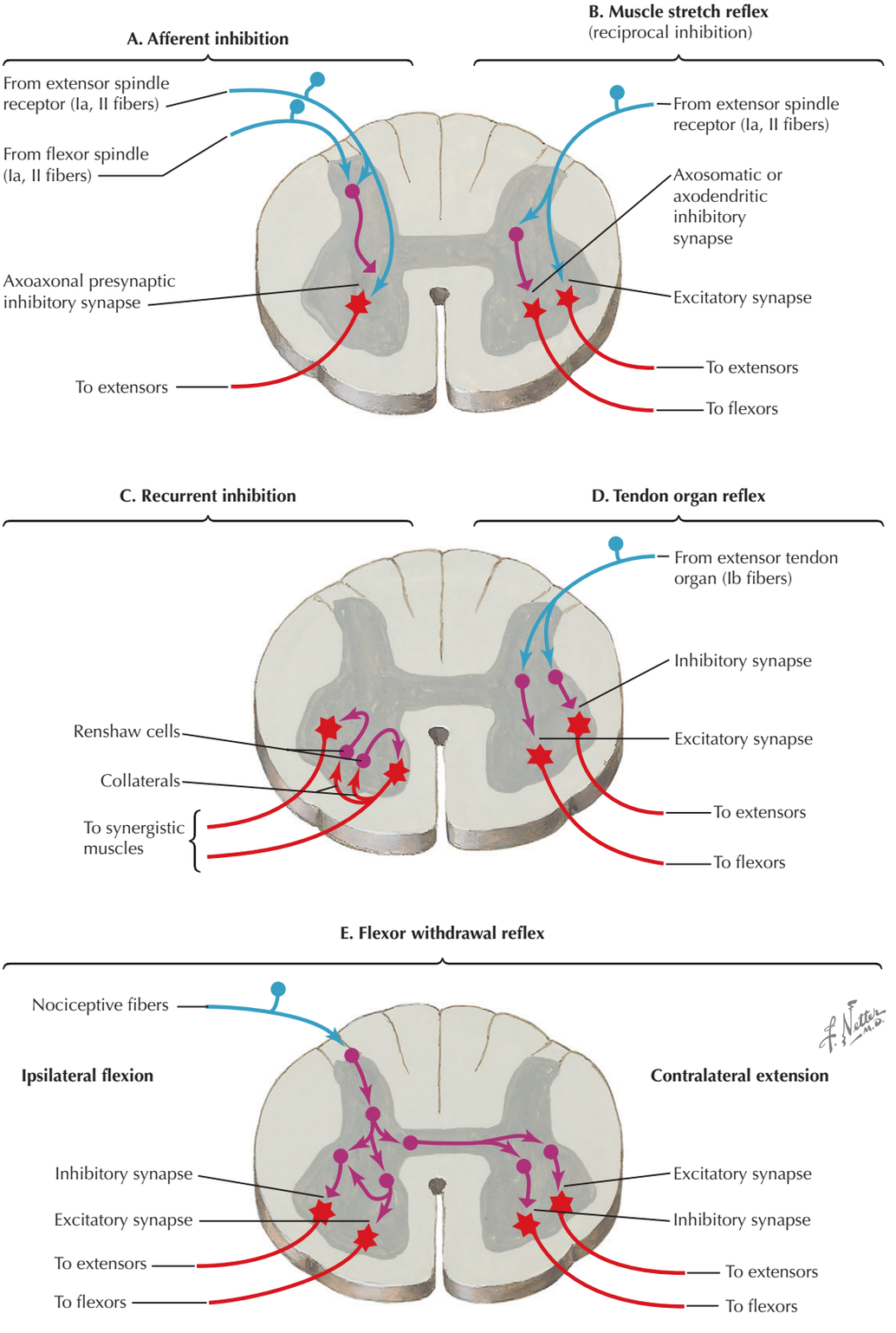
The intrinsic circuitry within the spinal cord influences the reflex activity of motor neurons. It is important to emphasize that these circuits are ordinarily under the control of higher centers (see Plates 2-8 to 2-11), but knowledge about them is an important step toward understanding motor behavior.

Muscle Stretch Reflex. Parts A and B show some of the connections made by groups Ia and II (not shown) afferent fibers from muscle spindle receptors. These afferent fibers are responsible for the muscle stretch reflex, in which the stretching of a muscle elicits a contraction of that muscle and its close synergists and a relaxation of its antagonists (see Plate 2-14). When the muscle is stretched, its spindle receptors are activated, thus causing increased firing of the spindle afferent fibers. The direct monosynaptic excitation of the motor neurons by these spindle afferent fibers contributes to the contraction of the stretched muscle and its synergists (B). Relaxation of the antagonist muscles is produced by a disynaptic inhibitory pathway involving an interneuron. The stretching of an extensor muscle leads to a reflex contraction of the extensors acting at that particular joint and to a simultaneous relaxation of the antagonistic flexor muscles.

Excitation and inhibition of motor neurons (B) are mediated by axosomatic or axodendritic synapses. Muscle spindle afferents, as well as other afferents, may also activate the circuits that modulate the action of afferent fibers by means of *presynaptic afferent inhibition* (A). Here, la fibers from either the flexors or the extensors activate an inhibitory neuron, which forms an axoaxonic synapse with a muscle spindle afferent fiber that terminates on an extensor motor neuron. The action of these synapses blocks or decreases the excitation of a motor neuron by muscle spindle afferents.

Recurrent inhibition is another type of neural interaction that controls the activity of motor neurons (C). It is produced by the collaterals of motor neurons that excite inhibitory interneurons known as Renshaw cells. When the motor neurons discharge, the Renshaw cells are activated by the motor neuron collaterals and fire a train of action potentials. The firing of the Renshaw cells causes inhibition of motor neurons of the same muscle and of other related, synergistic muscles. In addition to limiting the firing rate of motor neurons, this inhibition is also thought to restrict motor activity to the most intensely excited motor neurons.

Tendon Organ Reflex. Reflex actions evoked by Ib afferent fibers from Golgi tendon organs are shown in D. These fibers are activated by active (strong) tension in a muscle. When thus activated, the Ib fibers excite spinal interneurons, which inhibit the motor neurons that supply the particular muscle from which the Ib fibers originate and simultaneously excite the motor neurons that supply antagonist muscles. Thus the tendon organ reflex action is opposite to that produced by muscle spindle afferent fibers. The tendon organ reflex was once thought to play a role in protecting the muscles from excessive tension, but the excitatory influence of types Ia and II afferents during brief muscle contractions exceeds any inhibitory effects from the tendon organs. The tendon organ discharge may provide a "force feedback" signal whose inhibitory action opposes the excitatory "length feedback" signal provided by muscle spindle afferents during periods when the muscle is actively generating tension.



Flexor Withdrawal Reflex. Complex pathways are involved in the familiar flexor withdrawal reflex evoked by a painful stimulus (E). Such a stimulus activates nociceptive afferent fibers, which produce the firing of chains of neurons in the posterior horn of the spinal cord. These neurons, in turn, activate the interneurons in the anterior horn that excite flexor motor neurons and inhibit extensor motor neurons on the side of the painful stimulus. At the same time, commissural neurons activate circuits that excite extensor motor neurons and inhibit flexor motor neurons on the opposite side. The resulting reflex response is flexion or withdrawal of the stimulated limb and extension of the opposite limb.

Spinal Cord Dysfunction

A spinal cord lesion should be considered in any patient with numbness or weakness of one or more extremities, particularly if there is pain in the neck or back and sphincter dysfunction. Various combinations of symptoms and signs point to (1) extradural extramedullary, (2) intradural extramedullary, or (3) intradural intramedullary spinal cord lesions. *Spinal trauma* (see Section 3) may lead to neurologic dysfusion, depending on whether the spinal cord has been affected (for example, by compression, contusion, transection, hemorrhage, or shear injury) and on the site and extent of spinal cord involvement.

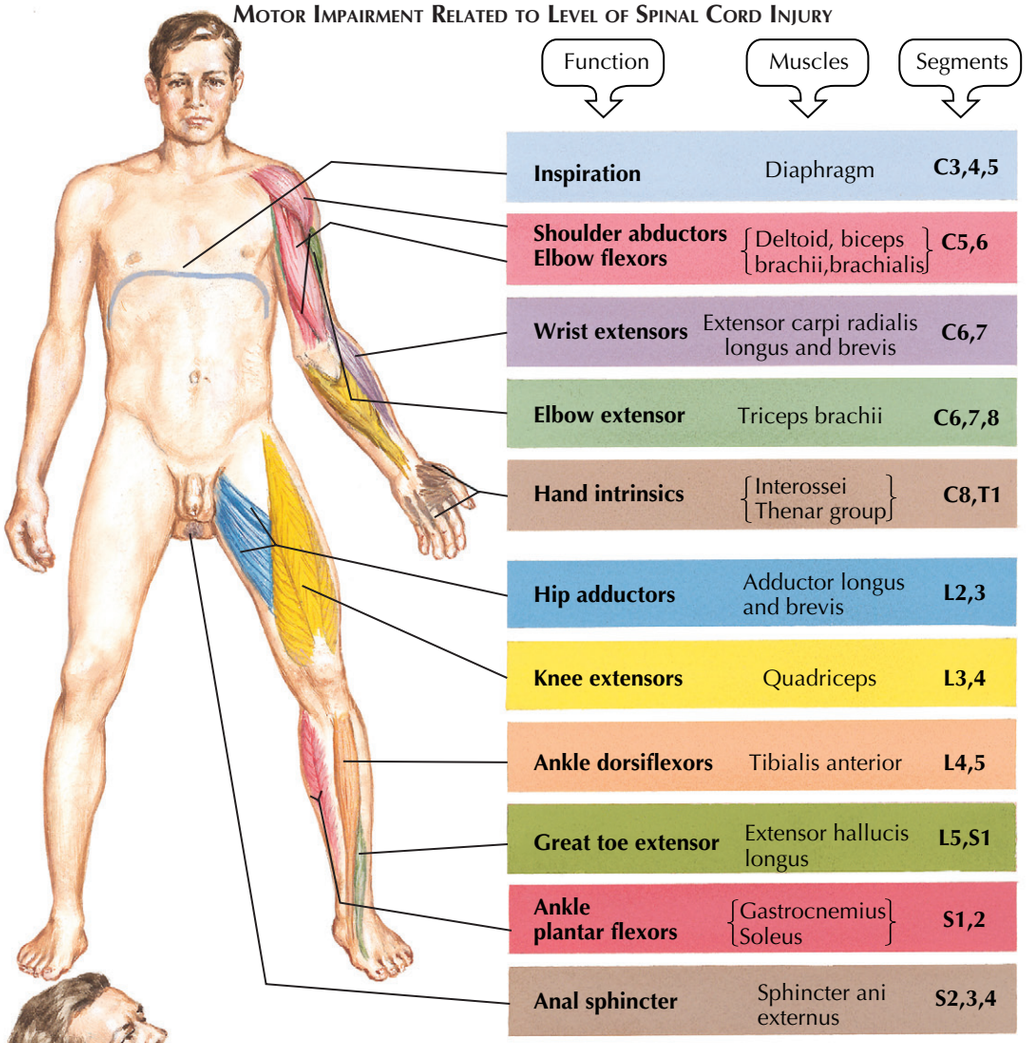
MOTOR IMPAIRMENT

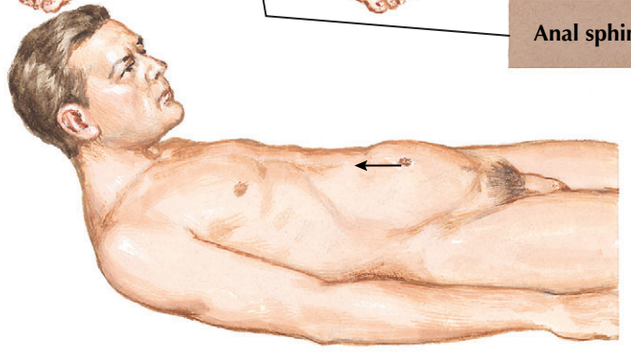
The degree of motor dysfunction depends on the extent of the spinal cord lesion. *Complete lesions* destroy all function below the affected level. *Incomplete lesions* cause partial weakness, atrophy, and hyporeflexia at the affected level, usually in combination with a distal upper motor neuron lesion, which may predominate and cause weakness, spasticity, and hyperreflexia. A search for subtle signs of a distal upper motor neuron lesion is imperative in any patient with an apparently isolated spinal nerve root lesion, particularly in the cervical region.

In contrast to a complete peripheral nerve lesion, in which motor function is completely lost in the distribution of that nerve, a complete nerve root lesion typically causes weakness (paresis), sometimes severe, but not total paralysis of the various muscles innervated by that nerve root. This is because each muscle is innervated by multiple nerve roots arising from more than one spinal level (see Plate 2-16).

The diaphragm is innervated by the C3, C4 and C5 segments; therefore a lesion high in the cervical spinal cord threatens respiratory function. Shoulder abduction is a good test of C5 function. In the presence of normal function of the deltoid muscle, weak elbow flexors, predominantly the biceps brachii muscles, suggest a C6 lesion. The elbow and wrist extensors, subserved primarily by the triceps brachii and extensor carpi radialis and ulnaris muscles, are innervated by C7. Function of the pronator teres muscle is also helpful in identifying a lesion at C7.

Lesions at C8 predominantly affect the intrinsic muscles of the hand, which are also innervated by T1.





Beevor sign

If patient actively flexes neck, abdominal muscles reflexly contract. If lower abdominal musculature (below T9) is relatively weaker than upper abdominal musculature, navel moves up (positive Beevor sign)

If upper abdominal musculature is	and lower abdominal musculature is	then Beevor sign is
Normal	Normal	Negative
Normal	Weak or nonfunctioning	Positive
Weak	Nonfunctioning	Positive
Nonfunctioning	Nonfunctioning	Negative

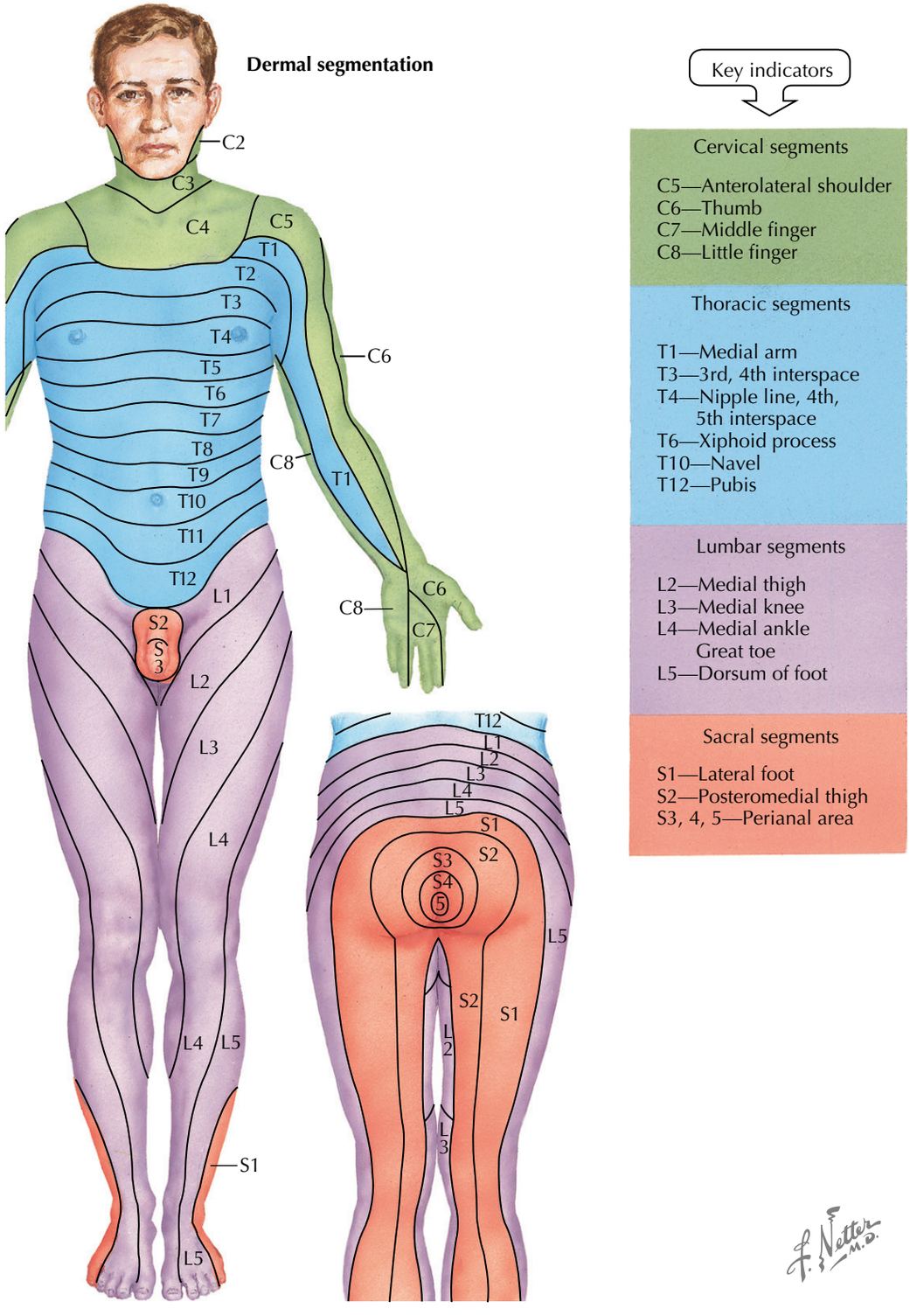
The abdominal musculature can be tested clinically for lesions that affect thoracic nerves; a positive Beevor sign indicates weakness below T9 or T10.

The hip flexors and adductors are innervated by L2 and predominantly by L3. The quadriceps femoris muscle is a good marker of L4 function. L5 innervates the ankle dorsiflexors and great toe extensors, while the ankle plantar flexors are innervated by S1 and S2. The lowest segments of the spinal cord (S2, S3, and S4) control the anal sphincter.

SENSORY IMPAIRMENT

Sensory examination often provides the most significant information in localizing a spinal cord lesion. However, if results of the examination are normal, the

Sensory Impairment Related to Level of Spinal Cord Injury



Spinal Cord Dysfunction
(Continued)

patient's symptoms may be the most important clue. The segmental distribution may be most useful in diagnosis when both the nerve root and spinal cord are involved, as seen in a dumbbell tumor, or neurilemmoma (see Plate 2-22).

The sensory dermatomal pattern shown in Plate 2-17 provides a useful guide. The C1 root has no significant sensory component; thus a lesion high in the cervical spinal cord at its most proximal limit affects C2, which involves the posterior part of the scalp. Because the descending spinal tract of the trigeminal (V) nerve extends into the upper cervical spinal cord, lesions at this level may produce changes in pain and temperature sensation over the temple and forehead, possibly with a diminished corneal reflex.

Segments C5 to T1 innervate the arm and hand, with the anterolateral aspect of the shoulder supplied by C5. The thumb and index finger are good markers for C6, the middle finger for C7, and the ring and little fingers for C8. T1 innervates the medial upper arm adjacent to the axilla. The nipple line is innervated by T4 and the area over the abdomen at the umbilicus by T10.

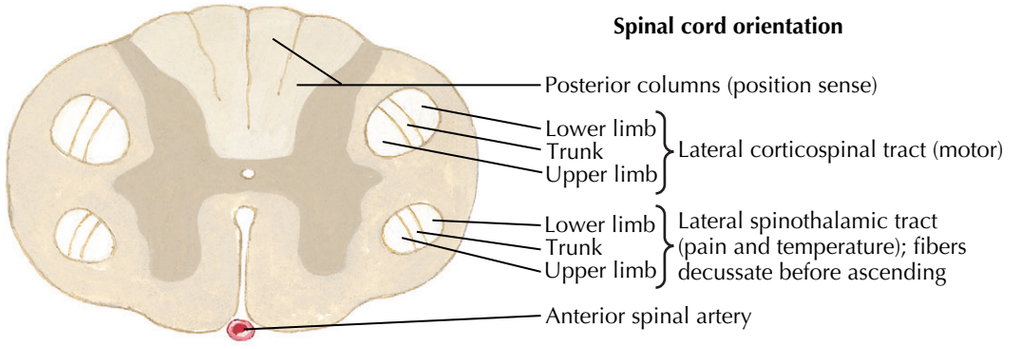
In the lower extremities, L3 and L4 segments innervate the anterior thigh and pretibial regions, respectively. The second, third, and fourth toes are innervated by L5, while S1 innervates the fifth toe and S2 the posterior medial thigh. The saddle area of the buttocks is innervated by segments S3, S4, and S5.

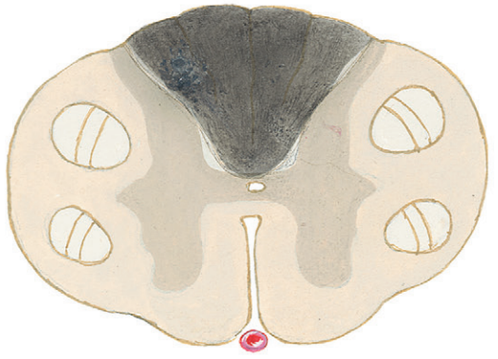
Paresthesias in the buttocks are an important sign of possible spinal cord dysfunction. Because segments S3, S4, and S5 are the lowest and most peripheral segments in the spinal cord, an *extramedullary lesion* at any level may first compress these fibers and affect pain and temperature sensation. If the saddle area of the buttocks is not examined for pain and temperature sensation, an early spinal cord lesion may not be suspected. In contrast, if an *intramedullary lesion* is present, the buttocks region is the last to be affected, with resultant sacral sparing.

Because the various ascending spinal tracts decussate at different levels of the spinal cord, several relatively specific patterns of dissociated sensory loss may be recognized clinically. The *Brown-Séquard syndrome* implies a hemisection or unilateral lesion of the spinal cord. This is characterized by ipsilateral diminution of touch, vibration, and position sense, and contralateral loss of pain and temperature sensation. Because the descending motor fibers decussate at the distal medulla, damage to these nerve fibers causes ipsilateral loss of function, with associated weakness and hyperreflexia (see Plate 2-18).

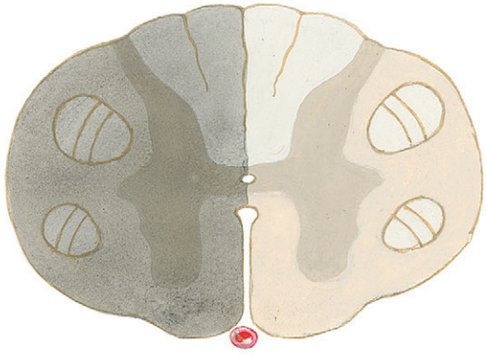
The *anterior spinal artery syndrome*, resulting from compression of this artery, occlusion of its feeders, trauma, or marked hypotension, affects the anterior two thirds of the spinal cord bilaterally, causing loss of pain and temperature sensation at approximately one to two segments below the level of the lesion, accompanied by

Incomplete Spinal Cord Syndromes

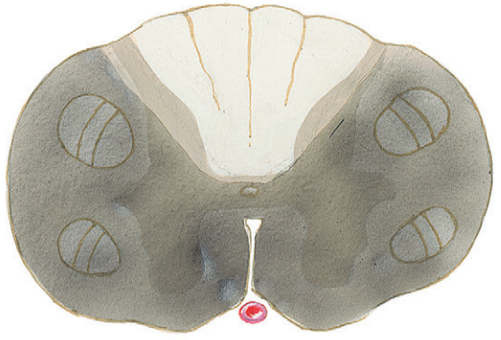




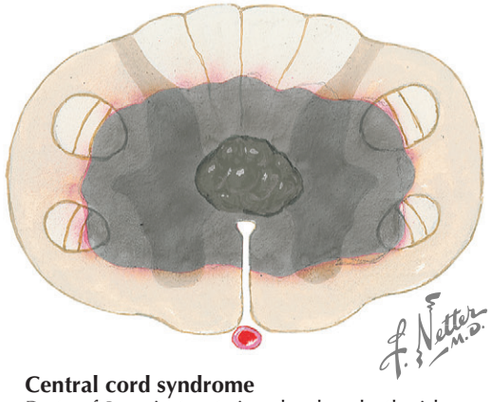
Posterior column syndrome (uncommon)
Loss of position sense below lesion



Brown-Séquard syndrome (lateral cord hemisection) Ipsilateral paralysis and loss of position sense; contralateral analgesia



Anterior spinal artery syndrome
Bilateral paralysis and dissociated sensory loss below lesion (analgesia but preserved position sense)



Central cord syndrome
Parts of 3 main tracts involved on both sides; upper limbs more affected than lower limbs

Spinal Cord Dysfunction
(Continued)

paraplegia. However, because the posterior columns are preserved, touch, vibration, and position sense is normal bilaterally. The rare *posterior spinal artery syndrome* is characterized by loss of position sense but preserved pain appreciation and motor function below the lesion.

Intramedullary central cord *lesions*, such as with certain tumors, after injury, or in *syringomyelia*, affect decussating spinothalamic fibers in the central gray matter of the spinal cord. When the lesion is in the cervical region, this produces a capelike loss of pain and temperature sensation, with preservation of posterior column function. Pain and temperature sensation is preserved below the involved levels, because the lateral spinothalamic tract is not affected by this central spinal cord syndrome. A concomitant lower motor neuron lesion commonly causing atrophy and fasciculations of the hands and arms is usually seen at the level of the dysfunction.

AUTONOMIC IMPAIRMENT

In addition to its somatic components, the spinal cord also contains autonomic nerve fibers, carried in the intermediolateral columns. A lesion at any level may cause sphincter dysfunction. Spinal cord lesions may damage the upper motor neuron pathways that control the bladder and rectum, but incontinence does not develop unless there is a severe bilateral lesion.

Other signs of autonomic dysfunction include *erectile dysfunction in men; changes in sweating*, with anhidrosis below the level of the lesion; and *Horner syndrome*, which includes ipsilateral miosis, ptosis, and decreased facial sweating secondary to damage to sympathetic fibers at C8-T1. A variety of gastrointestinal disturbances may also occur.

OTHER ABNORMALITIES

Café au lait spots may suggest the presence of a *meningioma* or a *neurofibroma*. A tuft of hair or dimple in the midline, particularly in the lower spine, may point to an underlying *congenital vertebral defect*. In rare cases, a cutaneous angioma may overlie or be segmentally related to a spinal cord or dural *arteriovenous fistula*.

Although *scoliosis* is usually idiopathic, it rarely is the first sign of an evolving spinal cord tumor. *Pes cavus* may be seen with distal spinal cord lesions. A *short neck* may suggest the Klippel-Feil syndrome, which is sometimes associated with other cervical spine lesions.

Spinal cord dysfunction can be identified early if the patient's history and the results of neurologic examination are carefully assessed, with particular attention to the distribution of motor, reflex, and sensory changes associated with autonomic dysfunction and the presence of various skeletal and cutaneous changes.

Acute Spinal Cord Syndromes

Spinal injury (see Section 3) may lead to a neurologic deficit from spinal cord involvement, but this is generally recognized by the context in which the deficit develops. The recognition of disease processes that can cause acute spinal cord damage is important. If the disorder is diagnosed early, some patients with spinal cord damage can be successfully treated. However, when the subtleties of the clinical picture are not recognized, the course may be disastrous, often culminating in lifelong paraplegia (see Plate 2-19).

The common mechanism in the patient with a potentially reversible condition is the presence of a mass lesion that has reached a critical size. Because the spinal cord lies within the bony spinal canal, an obstructive extradural or intradural extramedullary process causes compression of the cord and its vessels. If treatment is initiated before severe damage to spinal cord tissue causes total paraplegia, useful recovery is possible.

The acute onset of *back pain* in any patient, and particularly in a patient with cancer, should alert the physician to the potential for an impending spinal disaster. Often, however, the patient is not seen until further symptoms have developed.

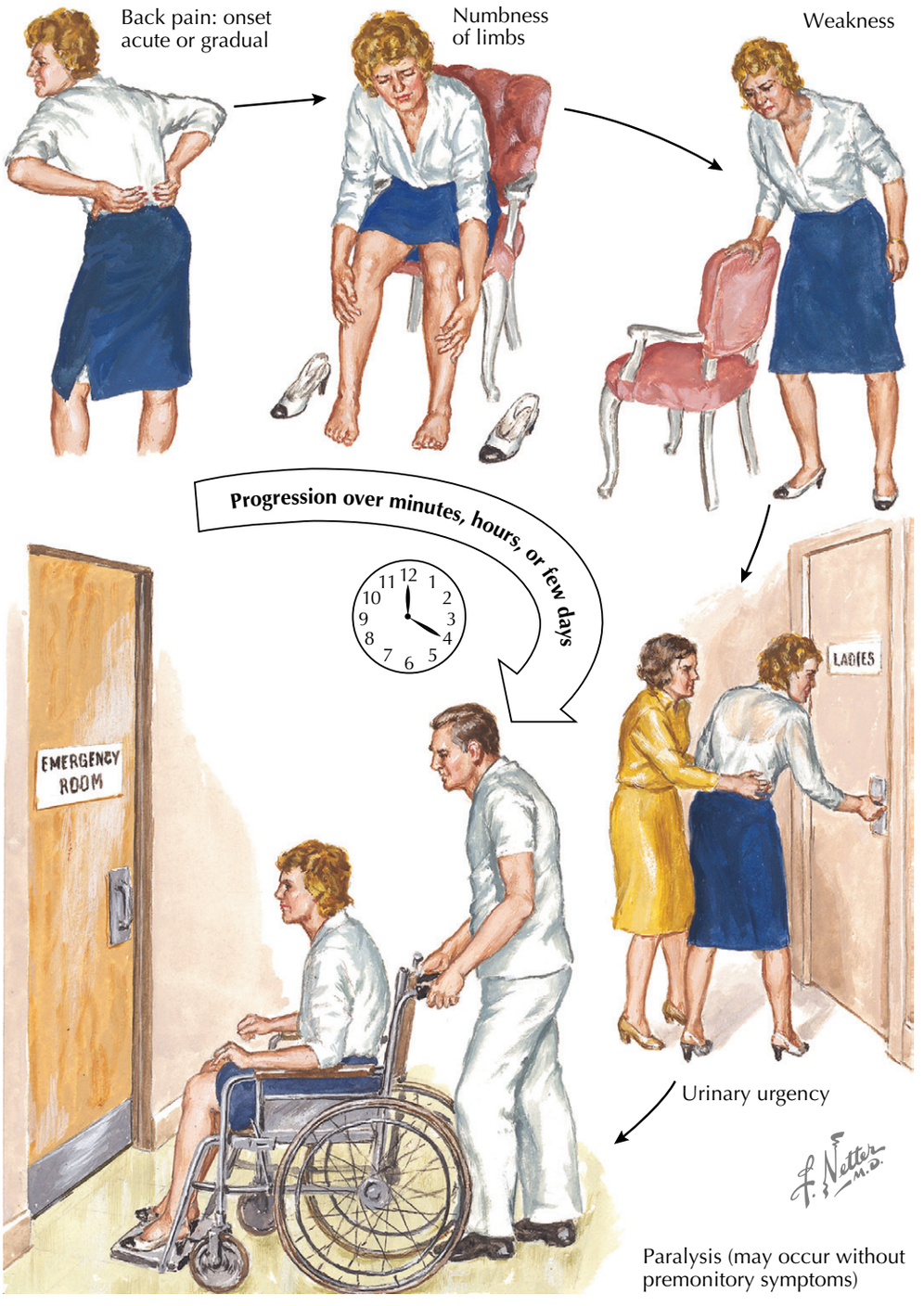
PREDISPOSING CAUSES

Metastatic Deposits. The most common cause of an acute spinal cord syndrome, particularly in patients in the middle to late decades of life, is epidural spinal cord compression from metastatic cancer. Most patients have a known preexisting malignancy, but a spinal metastatic lesion may be the first indication of a primary tumor elsewhere, and particularly of prostate, breast, or lung cancer; other common causes are non–Hodgkin lymphoma and plasmacytoma or multiple myeloma (see Plate 2-21). Patients have leg weakness and an impaired gait and frequently complain also of ascending numbness and paresthesias. A spinal sensory level may be present but may be one to several levels below that where the cord is compressed. A "saddle" sensory loss may be present with cauda equina lesions. Depending on the site of spinal involvement, muscle stretch reflexes may be exaggerated if the spinal cord is compressed or lost with cauda equina lesions. Bladder and bowel involvement occur later, most often with urinary retention. Magnetic resonance imaging (MRI) of the entire spine is mandatory; computed tomography (CT) myelography provides similar and sometimes complementary information.

Infarction. Occlusion of the anterior spinal artery affects the anterior two thirds of the spinal cord (see Plates 2-18 and 2-20). Spinal cord infarction is usually precipitous. The clinical findings include paraparesis or paraplegia in combination with dissociated sensory loss, that is, loss of pain and temperature sensation, with preservation of position and vibration sense. During the acute stage, tone is flaccid and muscle stretch reflexes are lost; spasticity and hyperreflexia develop subsequently. Sphincter control is lost. Back pain, often at a segmental level, may be present.

Although in many cases spinal cord infarction may be idiopathic, in other instances it relates to aortic dissection that compromises the artery of Adamkiewicz (major anterior radiculomedullary artery), emboli from aortic atheroma, profound hypotension, or various types of arteritis. It may also occur as a complication of cardiac or aortic surgery.

Acute Spinal Cord Syndromes: Evolution of Symptoms

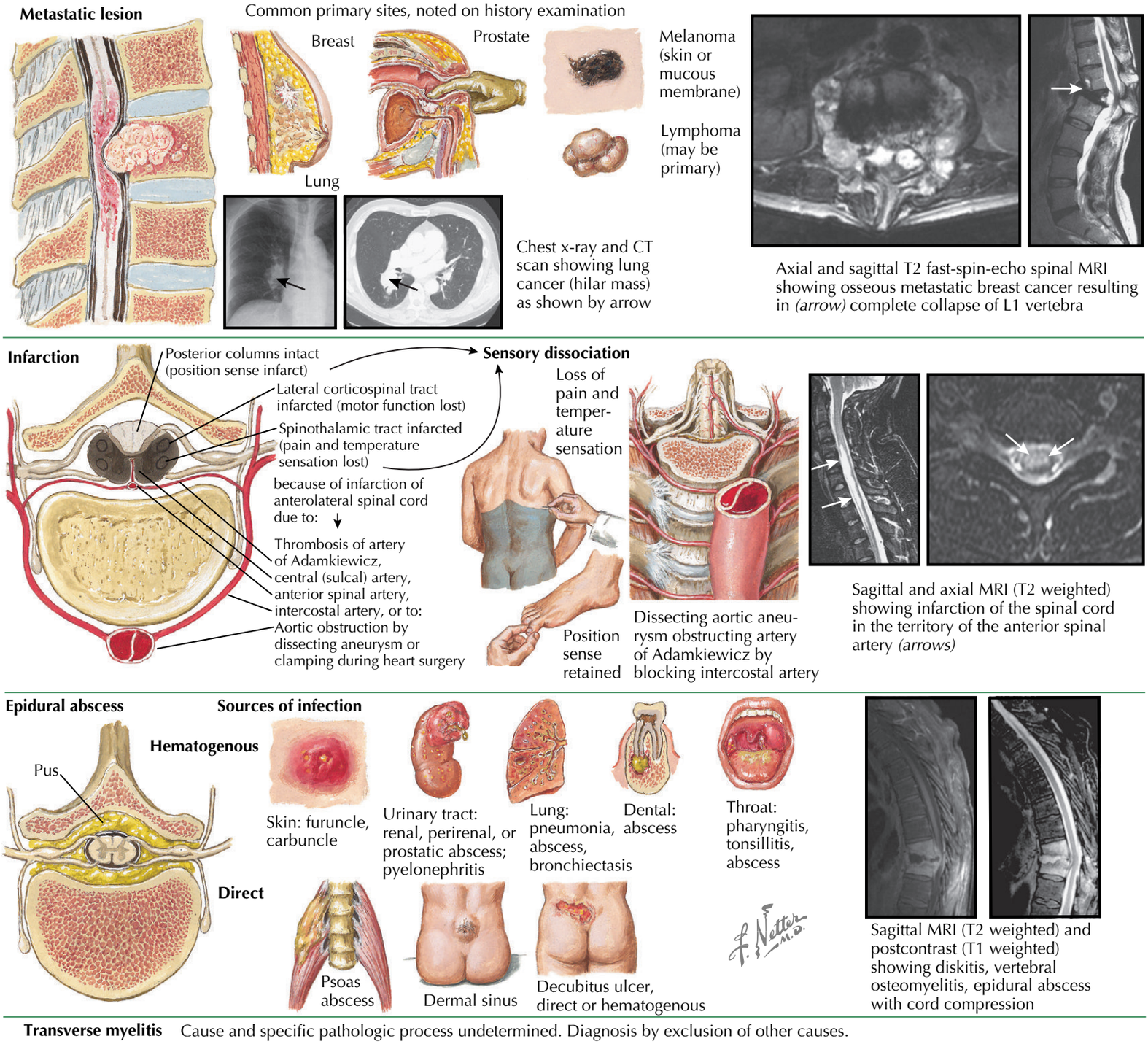


Spinal MRI or CT myelography is indicated to exclude other (compressive) lesions, including spontaneous epidural hematoma. The MRI may also confirm that infarction of the spinal cord has occurred. Spinal angiography may help to confirm the diagnosis. Aortic dissection must be excluded. Treatment is based on the underlying pathology. The prognosis for recovery of useful function is poor.

Epidural Abscess. This lesion has a fairly characteristic clinical setting (see Plate 2-20). The vast majority of patients are febrile, and most are acutely ill, sometimes becoming disoriented but always complaining of severe back and nerve root pain. Examination demonstrates exquisite tenderness on percussion over the affected spinal process and signs of spinal cord impairment. Weakness, sensory changes, and bladder or bowel dysfunction, occur with progression. If the abscess remains untreated, paralysis develops and may not be reversible.

There is often an apparent predisposing source of infection; staphylococci and gram-negative bacilli are the predominant causative organisms. Risk factors include epidural catheter placement (e.g., for anesthesia), spinal surgery, paraspinal injections, impaired immunity, alcoholism, diabetes mellitus, and intravenous drug use.

Acute Spinal Cord Syndromes: Pathology, Etiology, and Diagnosis



Transverse myelitis Cause and specific pathologic process undetermined. Diagnosis by exclusion of other causes.

Acute Spinal Cord Syndromes *(Continued)*

Spinal MRI is important in confirming the diagnosis and localizing the lesion, but CT myelography may also be revealing. Surgery should be performed early to open and drain the area. Antibiotic therapy is administered according to the pathogen isolated in cultures from the abscess or blood, to eradicate the causal organism.

Transverse Myelitis. This syndrome of acute segmental spinal cord dysfunction results from inflammatory disease. Initial symptoms include limb weakness, loss of all sensation, and sphincter involvement. Nerve root pain and back pain are common. Early in the course, muscle stretch reflexes are either depressed or absent; spasticity and hyperreflexia subsequently develop.

The disorder may have an autoimmune basis. It occurs in multiple sclerosis, sometimes as the presenting feature, in neuromyelitis optica (a disorder limited to the optic nerve and spinal cord and characterized by the presence of specific circulating antibodies against the aquaporin-4 antigen), and in various connective tissue diseases. In many instances, it is idiopathic. The diagnosis is one of exclusion in a patient who has a complete acute spinal cord syndrome. Involvement of all sensory modalities in acute transverse myelitis differentiates this disorder from spinal cord infarction, in which dissociated sensory loss is present. Spinal MRI shows gadolinium-enhancing signal abnormality, with involvement over one or more segments of the spinal cord. In neuromyelitis optica, these changes extend over at least three or more vertebral segments.

Treatment is of the underlying disorder. Patients with idiopathic transverse myelitis often make a partial recovery with time but may be left with a significant residual disability. Recovery is unlikely if improvement fails to occur within about 3 months.

Spinal Tumors

Tumors involving the spine are usually classified as either extradural or intradural. The intradural tumors are further divided into extramedullary and intramedullary lesions. The anatomic location of the tumor provides a clue to the pathologic diagnosis, but accurate diagnosis is based on histologic studies.

EXTRADURAL TUMORS

Extradural tumors are usually *metastases* to the vertebrae that subsequently invade the epidural space (see Plate 2-21). Almost any neoplasm can spread to the spine, but spinal metastases most commonly occur from a primary tumor in the lung, breast, or prostate. The tumor metastasizes through the arterial circulation or Batson's venous plexus, although direct extension from lung cancer or lymphoma is possible. Primary bone tumors, such as *osteogenic sarcoma* and *giant cell tumor*, are also seen, as are benign *hemangiomas* of bone. In most cases, pain is the first symptom of a vertebral tumor. Spinal cord compression, with associated symptoms, usually develops late and may be slowly progressive, but a rapidly growing tumor may cause acute neurologic deterioration secondary to infarction of the spinal cord.

A patient with a known primary cancer in whom spinal pain develops must be assumed to have a metastasis. A bone scan reveals a lesion earlier than plain radiographs but may fail to reveal neoplasms without increased blood flow or new bone formation. Furthermore, bone scanning is not informative about thecal sac compression Spinal magnetic resonance imaging (MRI) is the preferred imaging modality and has largely replaced computed tomography (CT) myelography. Epidural tumor deposits are often multiple, so the entire spine should be imaged.

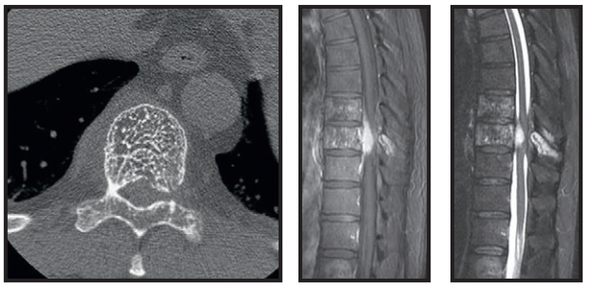
Epidural tumors must be treated before serious spinal cord dysfunction develops, but treatment is controversial. High-dose corticosteroids should be administered, and the lesion irradiated if the primary lesion is known. If there is no known primary tumor, if the tumor is known not to be radiosensitive, or if the neurologic status is rapidly deteriorating, surgical decompression should be done. Radiation therapy is usually administered postoperatively.

INTRADURAL TUMORS

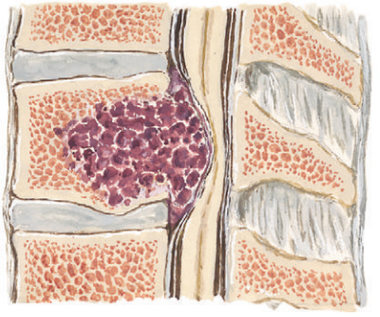
Intradural extramedullary tumors include the benign *meningiomas* and nerve sheath tumors (*neurilemmomas*) and the *neurofibromas* associated with neurofibromatosis. Local and radicular pain is an early symptom. A spinal cord deficit results from compression of the spinal cord, usually develops gradually, and leads to

Benign

Primary



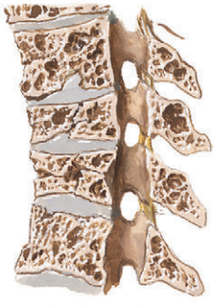
Axial CT scan and MRIs (sagittal T1 postcontrast and T2) of vertebral hemangioma



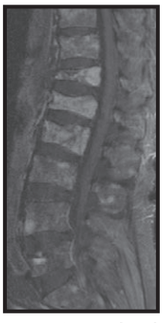
Hemangioma

Malignant

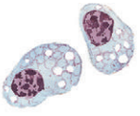
Primary



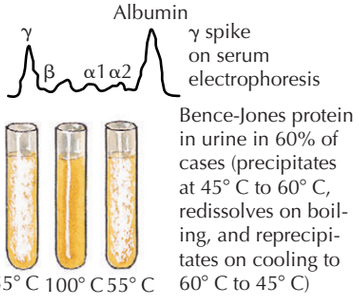
Multiple myeloma



MRI (T1 weighted) of lumbar spine in patient with multiple myeloma and multiple compression fractures of spine

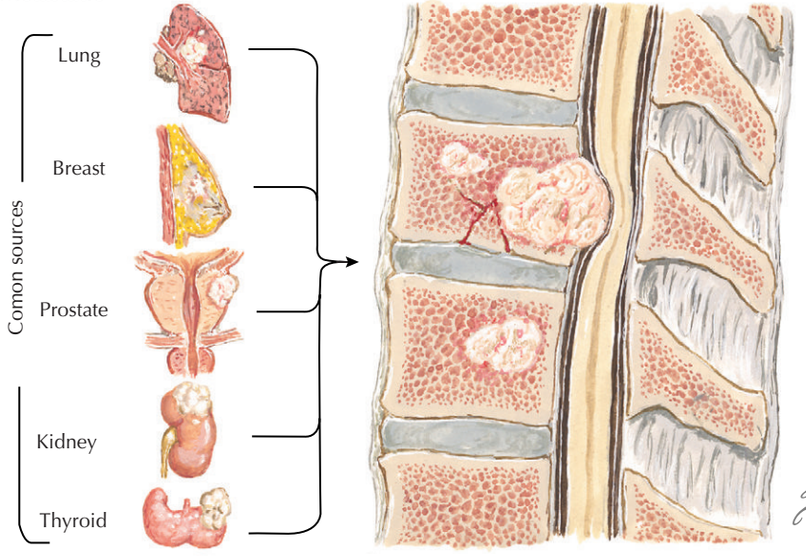


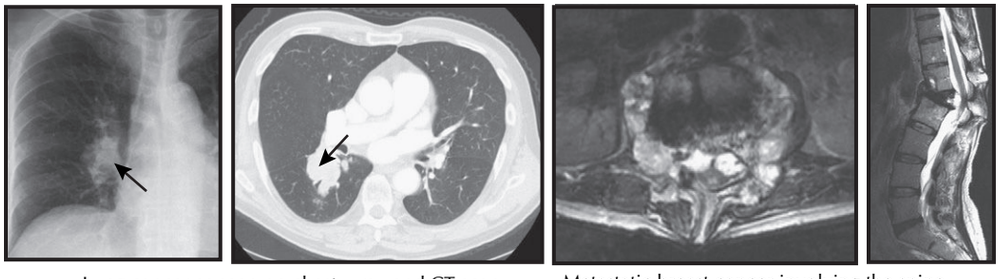
Malignant myeloma cells in biopsy specimen of bone marrow



Bence-Jones protein in urine in 60% of cases (precipitates at 45° C to 60° C, redissolves on boiling, and reprecipitates on cooling to 60° C to 45° C)

Metastatic





Lung cancer as seen on chest x-ray and CT scan *(arrows)*

Metastatic breast cancer involving the spine, shown on axial and sagittal T2 fast-spin-echo spinal MRI. There is osseous metastatic breast cancer resulting in collapse of L1 vertebra.

SPINAL TUMORS *(Continued)*

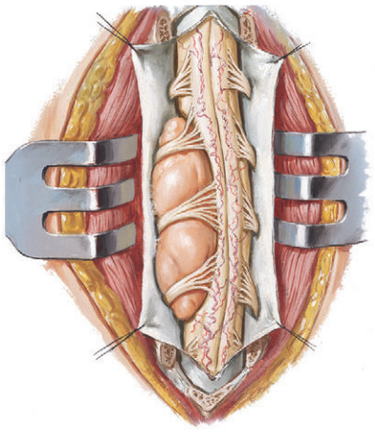
sensory complaints, weakness, and sphincter disturbances. Plain radiographs are not helpful in diagnosis unless a neurilemmoma has caused widening of the intervertebral foramen by extending through it in the shape of a dumbbell (see Plate 2-22). MRI allows the entire thecal sac and adjacent bone and soft tissue to be studied (see Plates 2-22 and 2-23). CT myelography is sometimes helpful. These tumors can be completely resected. Nerve roots in the thoracic region may be sectioned to provide better exposure, but damage to radicular arteries must be avoided.

Intramedullary tumors may involve just a short segment of the spinal cord or extend almost to its full length. They are the most difficult tumors to diagnose and treat. Diagnosis is confirmed by spinal MRI, which provides good visualization of the spinal cord and adjacent structures, with enhancement by gadolinium, or by CT myelography, especially when MRI cannot be undertaken. The cord may be expanded, and cystic changes are sometimes present (see Plates 2-22 and 2-23). However, demonstrating a swollen spinal cord with even the most sensitive radiographic studies does not confirm the diagnosis of intramedullary tumor. If the diagnosis is in doubt and the patient is deteriorating, the spinal cord should be explored surgically.

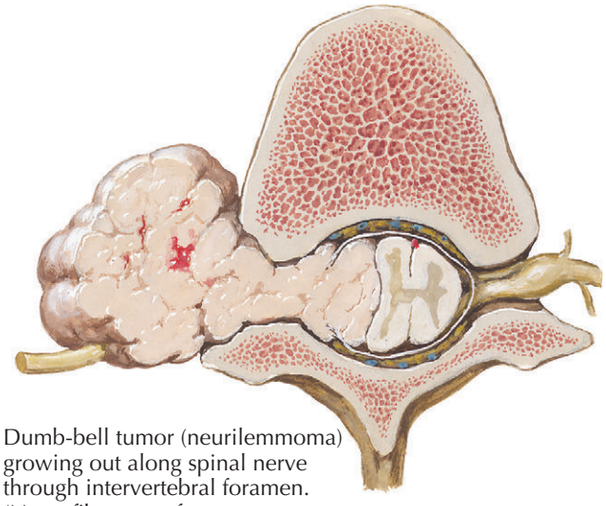
The two most common intramedullary tumors are *astrocytomas* and *ependymomas.* Astrocytomas are infiltrative, and total excision is not possible; however, there is frequently a well-demarcated plane around ependymomas, permitting their excision. Intramedullary metastatic deposits also occur, and improved imaging has resulted in their being recognized with increasing frequency. Surgery on the spinal cord demands the most meticulous technique. If the tumor is not completely excised, radiation therapy may be indicated.

Intradural tumors of the lumbar spine involve the conus medullaris, filum terminale, and cauda equina. Both ependymomas and astrocytomas may arise from the conus medullaris. These tumors produce early deficits of sphincter and sexual function, and are difficult to remove without incurring significant neurologic deficit. Ependymomas of the filum terminale (see Plate 2-22) cause pain, often without significant neurologic findings, and can be cured by surgical excision.

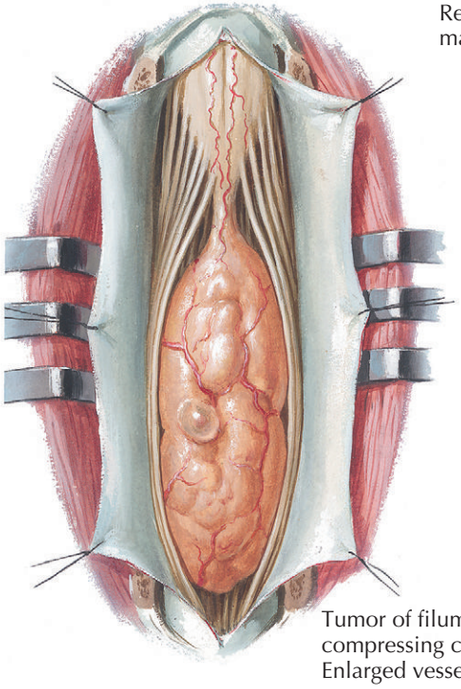
The diffuse myxopapillary ependymoma, which involves the roots of the cauda equina, is difficult to excise and should receive postoperative radiation therapy. A neurilemmoma or a meningioma can be successfully removed. Lipoma of the cauda equina arises from fetal rests and is associated with spina bifida occulta. Excision of this tumor is difficult, but meticulous microsurgery can reduce the tumor and preserve neurologic function.



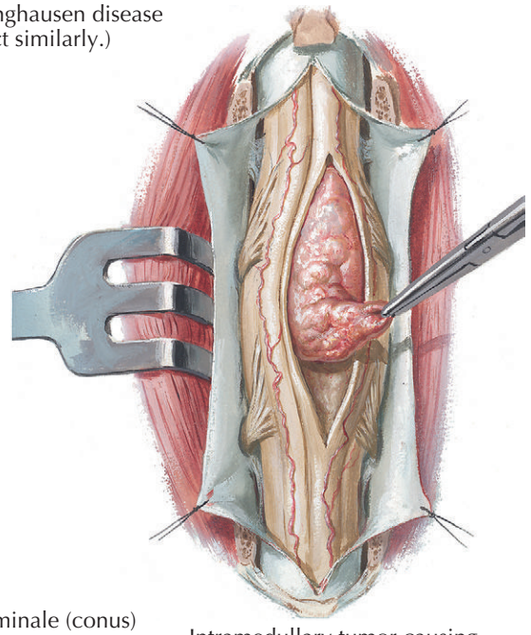
Intradural extramedullary tumor (meningioma) compressing spinal cord and deforming nerve roots



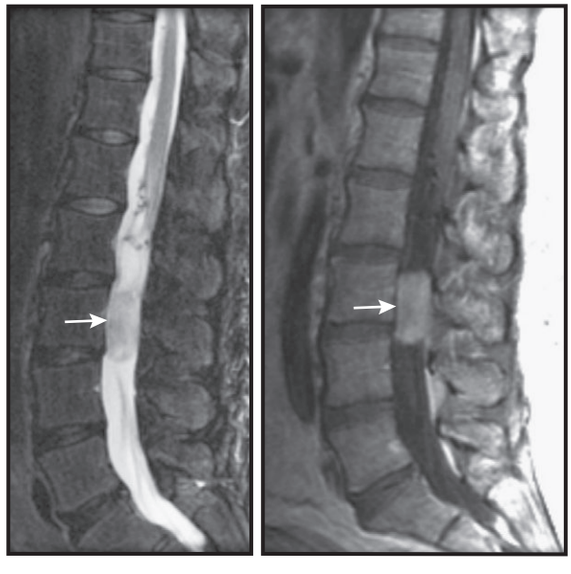
Dumb-bell tumor (neurilemmoma) growing out along spinal nerve through intervertebral foramen. (Neurofibromas of von Recklinghausen disease may act similarly.)



Tumor of filum terminale (conus) compressing caud equina. Enlarged vessels feed tumor.



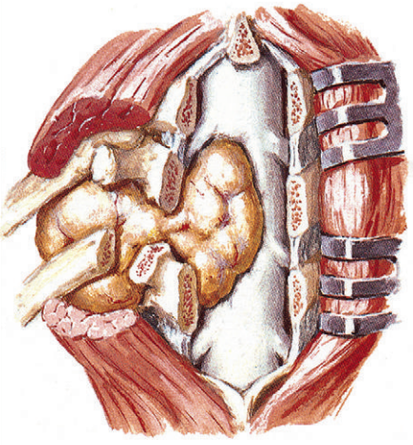
Intramedullary tumor causing widening of spinal cord



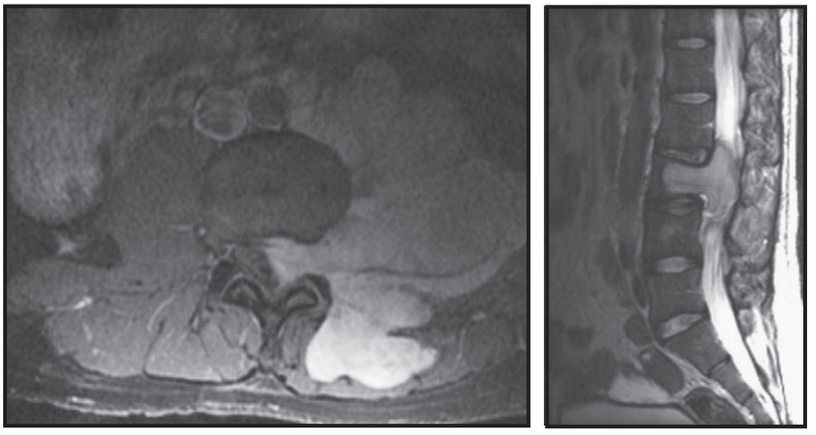
Filum ependymoma. Sagittal T2 fast-spin-echo (left) and T1 postgadolinium (right) images of lumbar spine. Intradural extramedullary enhancing mass posterior to L3 vertebral body.

Neuroimaging (MRI) Characteristics of Spinal Tumors

Extradural tumors

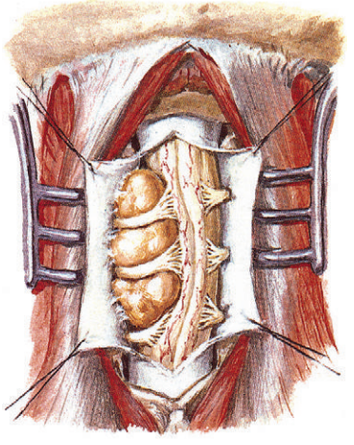


Lymphoma invading spinal canal via intervertebral foramen, compressing dura mater and spinal cord

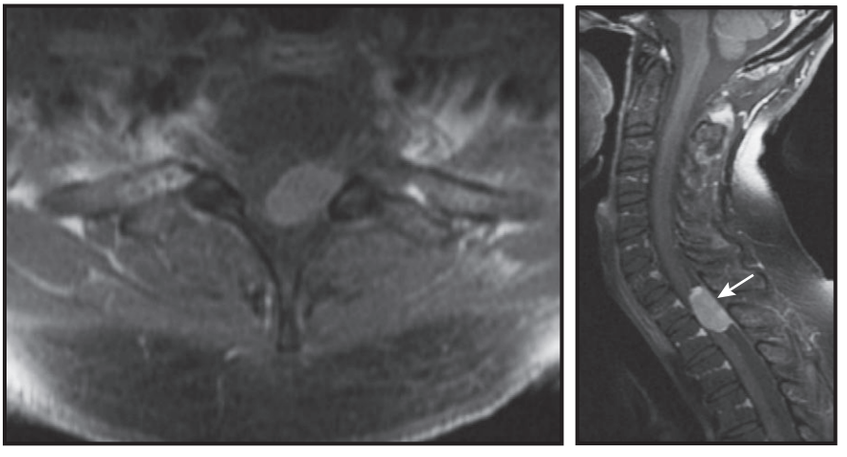


Axial postgadolinium T1 and sagittal T2 fast-spin-echo MRIs demonstrating extradural schwannoma (nerve sheath tumor), causing expansion of left L3-4 neural foramen and vertebral body scalloping

Intradural extramedullary tumors

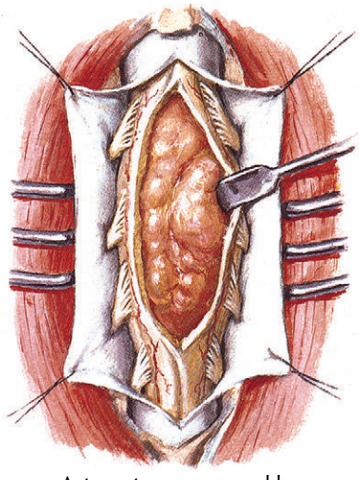


Meningioma compressing spinal cord and distorting nerve roots

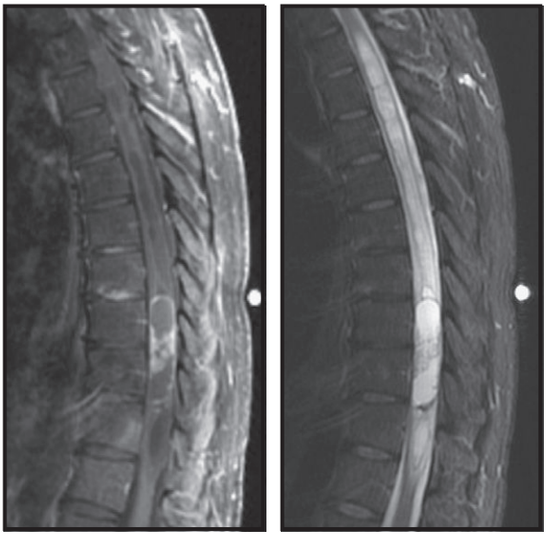


T1 postgadolinium axial and sagittal MRIs showing intradural extramedullary mass in left aspect of spinal canal at the T1-T2 level *(arrow)*. Signal characteristics are most characteristic of a meningioma.

Intramedullary tumors



Astrocytoma exposed by longitudinal incision in bulging spinal cord



Sagittal T1 postgadolinium and T2 MRI of spinal astrocytoma

SYRINGOMYELIA

Syringomyelia is a condition in which a tubular cavity, or syrinx, in the central area of the spinal cord gradually expands and produces neuronal and tract damage.

When *congenital*, the syrinx develops most frequently in the cervical and upper thoracic segments. Serial sections of pathologic material show that it arises as a diverticulum from the central canal of the spinal cord. It may then dissect into the posterior or anterior gray matter on one side or enlarge symmetrically into a large, fluid-filled cavity, which, in turn, causes transverse enlargement of the spinal cord. Anterior horn neurons and pain and temperature fibers crossing in the central gray matter are destroyed. Long tracts, first the pyramidal and later the posterior column, may be compressed. In some cases, the syrinx extends from the cervical area into the posterolateral medulla, producing syringobulbia. Lumbar extension is rare.

Pathogenesis. The pathogenesis of syringomyelia is poorly understood. Almost all patients with congenital syringomyelia have an associated type I Arnold-Chiari malformation, which may itself produce symptoms of medullary or upper cervical compression. Other associated developmental defects include basilar impression, the Dandy-Walker syndrome, and atresia of the foramen of Magendie. Some patients have hydrocephalus. It has been suggested that the presence of an Arnold-Chiari malformation means that flow of cerebrospinal fluid (CSF) from the fourth ventricle is diminished, and increased pressure forces fluid into the central canal, producing a gradually expanding syrinx. A communication between the fourth ventricle, central canal, and the syrinx is not always evident, but abnormalities in the hindbrain and CSF dynamics may still be present.

Some cavities appear to be caused by spinal cord trauma and may develop months or even years after injury. Spinal arachnoiditis and intramedullary tumors are also associated with syrinx formation, as occasionally are infectious or inflammatory states. In such circumstances, the *secondary or acquired* cavitation may occur in any part of the cord, depending on the site of the original pathology. A progressive neurologic deficit develops after a period of stability after the original injury.

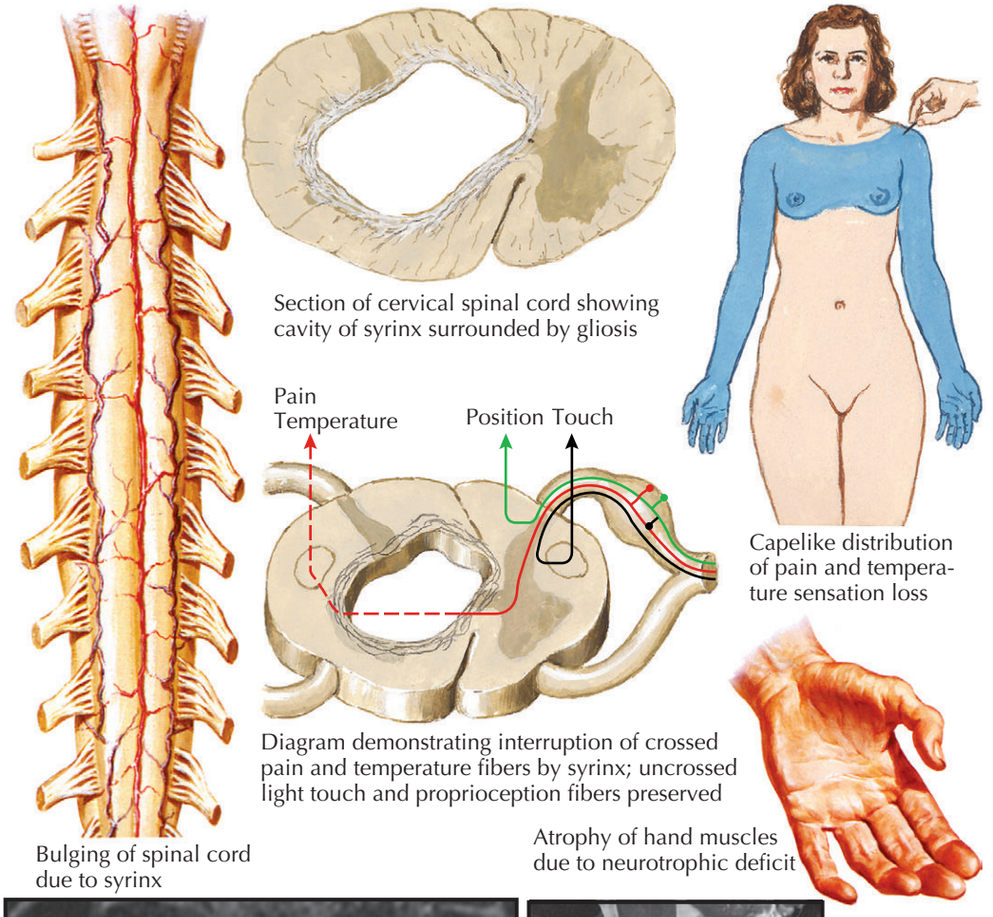
Clinical Manifestations. Syringomyelia is rare, with a prevalence of 8 per 100,000 persons. The syrinx may be asymptomatic, being discovered incidentally on spinal cord imaging. Symptoms usually appear late in the second decade through the fifth. Average age at onset is 30 years. The disease progresses at a variable rate; some patients become quadriplegic in 10 years, while others have a more benign course with long periods of stabilization. By 20 years, however, probably 50% of patients have become wheelchair-bound.

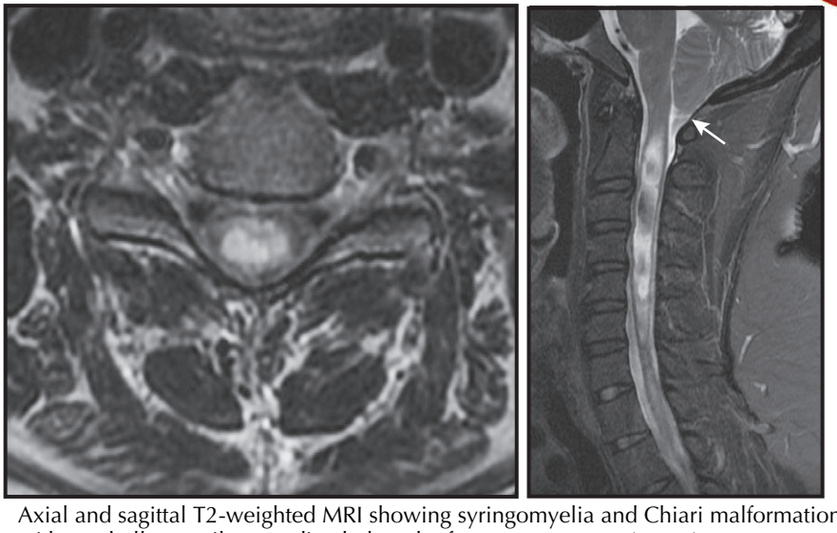
The classic sign of cervical syringomyelia is *dissociated anesthesia*, or loss of pain and temperature sensation in a capelike distribution, with preservation of light touch sensation and proprioception. Fibers carrying pain and temperature sensation cross in the central gray matter near the central canal and then form the spinothalamic tract in the anterolateral portion of the spinal cord. These fibers are damaged near the central canal or in the posterior horn before they cross. Fibers carrying light touch and proprioception information do not cross and course rostrally in the posterior columns. Centrally generated pain is sometimes problematic and has a segmental distribution.

Trophic changes occur, and the appearance of Charcot's joints is not uncommon. When the cavity expands into the anterior horn, atrophy and motor weakness become apparent. Fasciculations may be seen, and kyphoscoliosis resulting from paraspinal muscle weakness is common. Thus presentation is with a progressive central cord syndrome. As the lesion expands further, it compresses the corticospinal and spinothalamic tracts. Progressive spastic paraparesis with a sensory level then becomes apparent.

Diagnosis. Syringomyelia is readily diagnosed with the use of spinal MRI and CT myelography. The spinal cord may be expanded, and the intramedullary cavity and an Arnold-Chiari malformation may be seen.

Treatment. The cause of the syrinx dictates the appropriate treatment. In most cases, an Arnold-Chiari malformation is present, and decompression of the area with suboccipital craniectomy and upper cervical laminectomy may be sufficient. In patients with no cervicomedullary abnormality, syringostomy may be considered. A plastic tube is placed into the syrinx cavity to provide communication to the subarachnoid space. If the tube remains patent, the process may stabilize. Syringoperitoneal or syringopleural shunting may also be worthwhile. Symptomatic hydrocephalus is treated with ventriculoperitoneal shunting.





Axial and sagittal T2-weighted MRI showing syringomyelia and Chiari malformation, with cerebellar tonsils extending below the foramen magnum *(arrow)*

Subacute Combined Degeneration

Subacute combined degeneration of the spinal cord refers to degeneration of the posterior and lateral spinal columns. This may results from vitamin B_{12} deficiency, usually as a consequence of addisonian *pernicious anemia*, with atrophy of gastric parietal cells and absence of intrinsic factor. The same neurologic picture may appear in any condition in which vitamin B_{12} absorption is impaired or its dietary intake is insufficient. Cases have been reported in strict vegans and in patients who have sprue, Crohn disease, fistula of the small intestine, or fish tapeworm infestation, or who have had a bowel resection or gastrectomy. Vitamin B_{12} deficiency may also lead to mental changes. Early manifestations are subtle and include fatigue, irritability and mild depression. Delirium, dementia, and paranoid psychosis are major cerebral manifestations. Rarely, seizures or visual blurring occur. A glove-and-stocking anesthesia, although uncommon, is a reflection of peripheral neuropathy.

Subacute combined degeneration may also result from *nitrous oxide* abuse, which leads to inactivation of vitamin B_{12}. A similar syndrome is also seen with *copper deficiency*, which may be a consequence of total parenteral hyperalimentation, copper deficiency in enteral feeding, malabsorption, gastric surgery, or excessive zinc ingestion, which inhibits the intestinal absorption of copper.

Pathology. The earliest neuropathologic lesion in this disorder is myelin swelling in the thoracic and lower cervical posterior columns. Later, demyelination and axonal destruction occur, and still later, the lateral columns and spinocerebellar tracts are involved. Ascending secondary degeneration may be seen in the posterior columns, and descending degeneration may be seen in the corticospinal tract. Small foci of demyelination are scattered throughout the cerebral white matter and optic (II) nerve. Secondary degeneration of association tracts may be present. Mild changes occur in peripheral nerves, and damage to cortical neurons has been described.

Clinical Manifestations. Fatigue, weight loss, abdominal distress, diarrhea, and sore tongue are the most common general symptoms of pernicious anemia. Examination reveals glossitis and a lemon-yellow tint to the skin.

The most common neurologic symptoms relate to *involvement of the posterior columns.* Tingling, burning, and numbness of the distal extremities are the earliest symptoms. Depending on the site of initial demyelination, the feet or hands may be involved first, or paresthesias may occur simultaneously in all four extremities. Occasionally, Lhermitte's sign is present. Due to proprioceptive loss, imbalance, which worsens in the dark, may be an early sign.

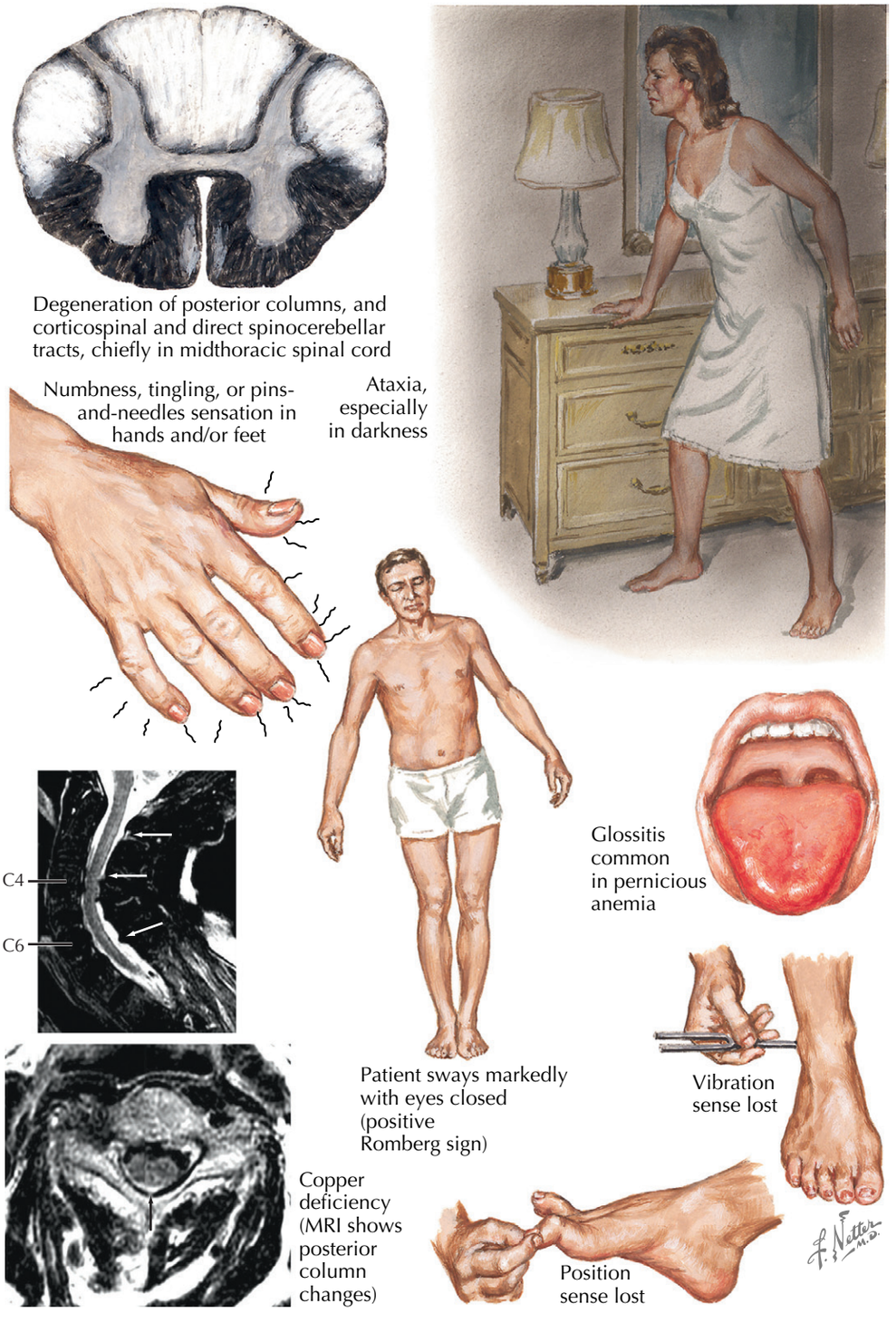
Stiffness is often the first sign of *lateral column dysfunction* but usually occurs after the onset of paresthesias. Later, overt spasticity develops, and if the disease remains untreated, paraplegia with bowel and bladder incontinence ensues.

The cardinal neurologic sign is diminution of vibration sense. Position sense is affected to a lesser degree, but the Romberg sign is often positive. Involvement of the posterior columns and spinocerebellar tract may cause severely disabling sensory ataxia. With extensive spinal cord damage, a sensory level may be noted, usually in the middle or lower thoracic segment. Hyperreflexia, spasticity, clonus, and the Babinski sign signify lateral column damage. A hyperactive bladder may be an associated finding. In severe untreated cases, paraplegia with flexor spasms may develop.

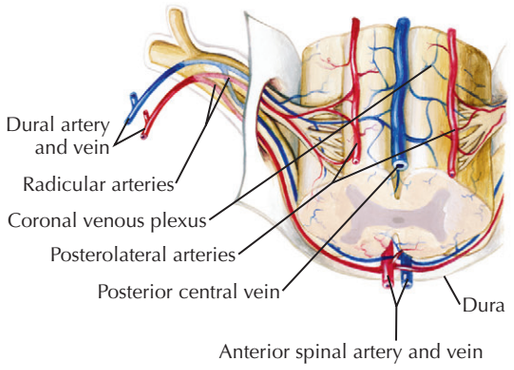
Diagnosis. Subacute combined degeneration is diagnosed clinically by recognition of posterior and lateral column involvement. Determination of the serum vitamin B_{12} level and the Schilling test are usually sufficient for confirming a diagnosis of pernicious anemia. It has long been recognized that neurologic signs and symptoms may precede the appearance of anemia. The red blood cell count and the mean corpuscular volume, however, are often abnormal in the face of normal hemoglobin and hematocrit values.

Treatment. For patients with a permanent impairment of vitamin B_{12} absorption (e.g., with pernicious anemia or gastrointestinal resection), treatment will need to be continued indefinitely. Loading doses of intramuscularly administered vitamin B_{12} are given several times per week for several months, followed by a maintenance dosage of at least 1000 µg/month for life. When the cause of the vitamin B_{12} deficiency is reversible (e.g., diet, nitrous oxide exposure, certain malabsorption syndromes), treatment can be stopped when the vitamin deficiency is completely reversed and its cause eliminated. In patients with copper deficiency, supplementation may halt disease progression; ingestion of zinc should be discontinued or strictly limited.

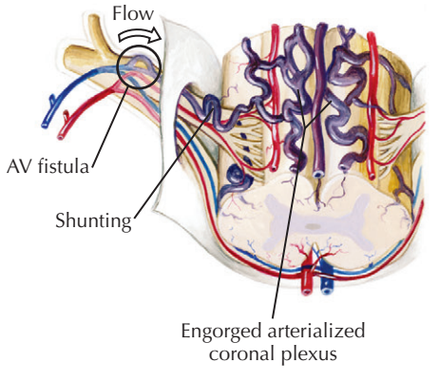
Mild paresthesias and mental changes of recent onset may completely resolve with treatment, but when symptoms have been present for several months, complete recovery is unlikely.



Spinal Dural Fistulas and Arteriovenous Malformations



The spinal cord is supplied via radiculomedullary arteries, which supply the anterior spinal and posterolateral spinal arteries.



In a dural AVM, the nidus is usually a low-flow AV shunt located within dura of intervertebral foramen. Supplied by a radicular artery and drained via a single vein into the coronal plexus on the posterior, or less commonly, the anterior surface of the cord. Coronal plexus is "arterialized" and becomes coiled, dilated, and elongated.

JOHN A. CRAIG, MD

Spinal dural fistulas (also called arteriovenous malformations or AVMs) consist primarily of an abnormal arteriovenous communication without intervening capillaries. They may occur at any level but are most common in the thoracolumbar region, where generally only one or two arterial feeding vessels are present. These are a radicular or dural branch of a segmental artery that does not supply the spinal cord itself. The AVM nidus is typically a low-flow shunt drained by a vein that joins the posterior coronal venous plexus. The coronal plexus is arterialized by the fistula and becomes dilated, coiled, and elongated. The increased venous pressure (resulting from the abnormal arteriovenous communication) leads to a reduced arteriovenous pressure gradient across the cord and thus to reduced blood flow. The resulting ischemia/hypoxia leads to a progressive myelopathy.

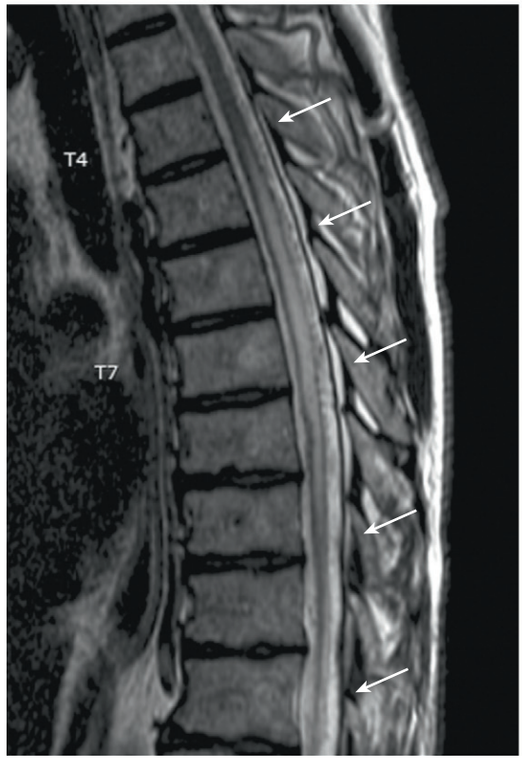
Symptoms typically develop gradually after age 40 and progress slowly. They consist of some combination of back or radicular pain, weakness, sensory disturbances, and impaired sphincter function. Neurogenic claudication may be present. Examination commonly reveals mixed upper and lower motor neuron deficits, sensory abnormalities, and reflex changes in the legs. Without treatment, the gait becomes progressively more impaired until the patient is chair-bound. A discrete or vague sensory level is sometimes present. A bruit may be audible over the spine.

Intradural AVMs may occur at any level but are more common in the cervical region. There may be one or multiple feeding vessels, which arise from a radiculomedullary vessel supplying the anterior spinal artery or from one of the branches to the spinal cord. The nidus may be intramedullary, in the pia (i.e., extramedullary), or both intramedullary and extramedullary. These are high-volume, high-pressure shunts with rapid blood flow, from which spontaneous intraparenchymal or subarachnoid hemorrhage may occur. Symptoms develop usually during early adult life. Patients present with sudden back pain and a neurologic deficit in the limbs, perhaps accompanied by impaired consciousness when hemorrhage has occurred, or with a progressive myelopathy. When the lesion is located cervically, both upper and lower extremities may be affected. Recurrent hemorrhages leads to clinical deterioration.

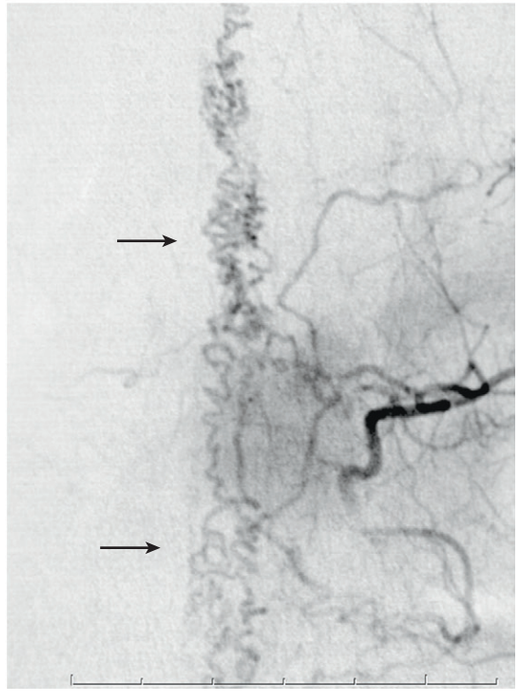
Cavernous angiomas or malformations are rare, isolated, or multiple lesions that can spontaneously hemorrhage and are best shown by magnetic resonance imaging. Spinal arteriography is normal.

In patients with spinal dural fistulas, MRI demonstrates serpentine filling defects of reduced signal in the subarachnoid space, corresponding to blood flow in the dilated, tortuous coronal venous plexus. Sometimes cord signal is increased from edema or venous congestion. Low cord signal may reflect an intradural nidus. Computed tomography (CT) myelography may demonstrate serpentine linear defects, but its use has largely been supplanted by MRI. Selective spinal arteriography defines the precise site of the nidus, its arterial feeders, and the normal blood supply to the spinal cord. Endovascular occlusion of feeding vessels is often undertaken during the procedure and may obliterate the lesion or, at least, reduce its size so that it is easier to remove surgically. Intramedullary lesions may be inoperable, but embolization can occlude feeding vessels and the nidus, reducing flow and allowing lesion thrombosis. It is important to maintain the vascular supply to the spinal cord to prevent damage from subsequent ischemia. After nonoperative obliterative procedures, feeding vessels may recanalize or new feeders can open up, requiring further treatment.

Early detection and treatment can improve gait disturbances, and sometimes bladder or bowel dysfunction, and a previously progressive course can be arrested.

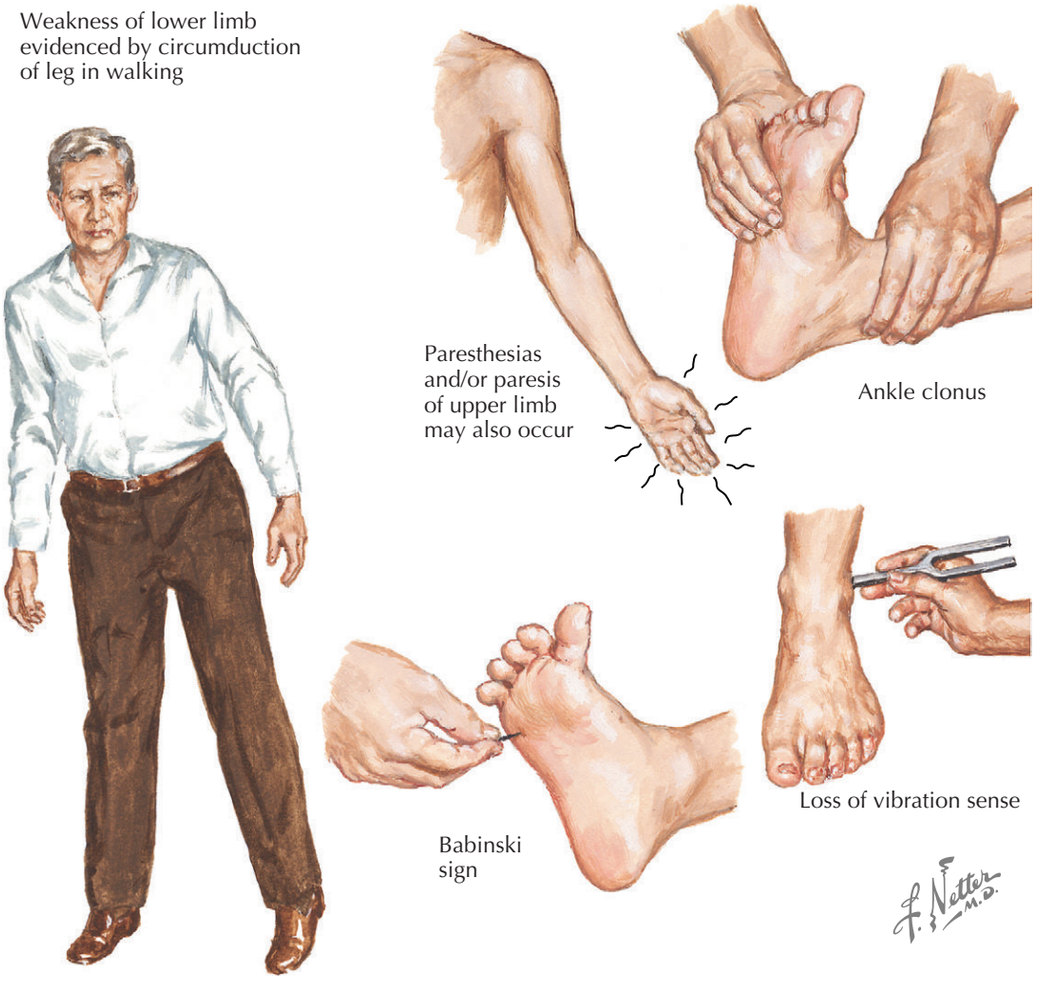


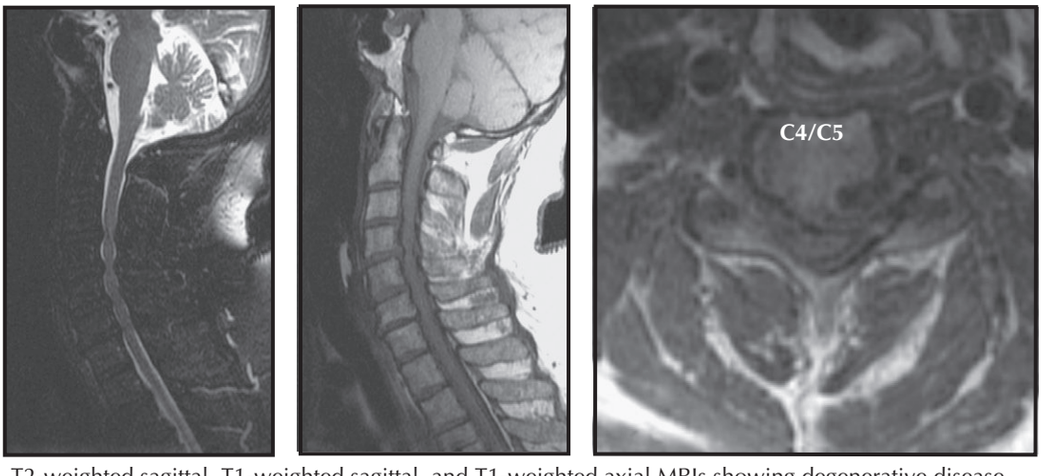
Sagittal T2 MRI shows increased T2 signal in the central cord representing edema and/or gliosis. Multiple signal voids behind the spinal cord are secondary to tortuous vessels from the malformation.



Spinal angiogram of radicular artery, left T6, with arteriovenous fistula filling multiple draining veins at the dural level. These join to form a complex medullary venous plexus.

Cervical Spondylosis





T2-weighted sagittal, T1-weighted sagittal, and T1-weighted axial MRIs showing degenerative disease with spinal cord compression. Idiopathic spinal stenosis with disk protrusion anteriorly and hypertrophy of ligamentum flavum posteriorly, most extreme at C4-5.

The pathologic process in cervical spondylosis is a gradually progressive degeneration of intervertebral disks, with subsequent changes in vertebrae and meninges. Disk degeneration may result from desiccation of the nucleus pulposus that begins in the fifth decade and progresses rapidly thereafter. At the same time, the annulus fibrosus may weaken to allow bulging of the nucleus pulposus. Disk material extrudes when portions of the annulus rupture. Osteophytes (bony spurs) appear on the margins of the vertebral bodies, zygapophyseal joints, and articular cartilages, probably as a result of trauma and disk degeneration. If osteophytes or protruding disks project posteriorly or posterolaterally, they may compress the spinal cord or cervical nerve roots. As disks degenerate and bulge posteriorly, so-called spondylotic bars may be formed, which also may compress the spinal cord or neural foramina. The anteroposterior diameter of the spinal canal is also important. The average sagittal diameter is about 17 mm, while the average spinal cord diameter is 10 mm. The canal narrows about 2 mm with maximal neck extension. In most patients, large cervical bars or osteophytes are necessary to produce spinal cord compression, but in those with an already narrowed canal (spinal stenosis), compression may occur with lesser degenerative changes.

Finally, as disk spaces narrow secondary to degeneration, the cervical spine shortens. This can produce infolding of the ligamentum flavum, which narrows the anteroposterior diameter of the spinal canal. The vertebral column shortens, but the length of the spinal cord remains unchanged, resulting in traction on the lower cervical nerve roots.

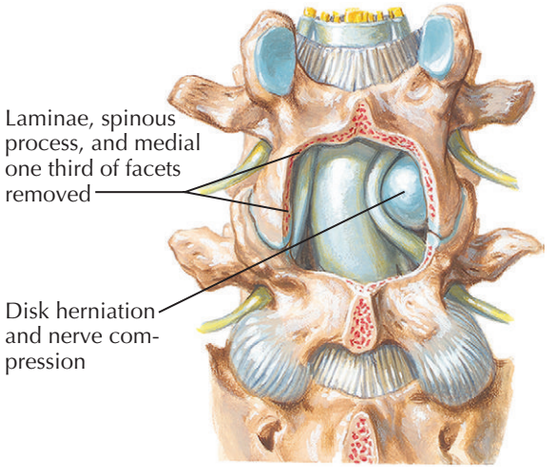
When spinal cord compression occurs, pathologic examination shows flattening and distortion of the cord. Several indentations may be present, depending on the number of spondylotic bars. Demyelination of the lateral and posterior columns and neuronal damage at the points of compression are the primary microscopic findings.

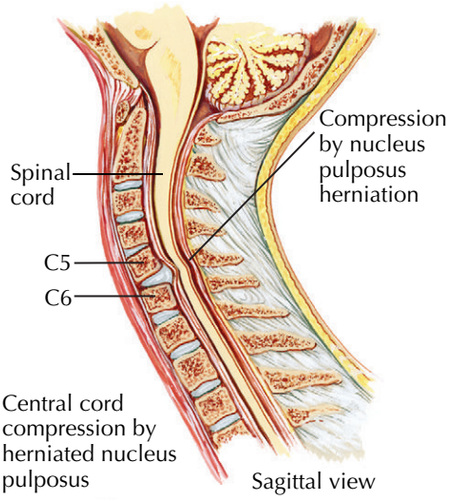
Clinical Manifestations. Cervical spondylotic radiculomyelopathy or myelopathy is the commonest myelopathy of later life. Its onset is usually insidious. *Paresthesias* of the hand may occur early, and the patient may experience numbness and tingling in a radicular distribution, as well as *radicular pain.* Weakness and atrophy in the upper extremities vary, depending on the spinal cord segments or nerve roots compressed. Because the fifth and sixth cervical segments are most frequently compressed, stretch reflexes of the biceps and triceps, respectively, may be diminished. In the lower extremities, a *spastic paraparesis* is common, but one leg may be more severely involved than the other. Vibration and position sense are often diminished in the feet. The gait is spastic and sometimes ataxic because of impaired position sense. Sphincter disturbances (especially urinary urgency, frequency, or retention) and sensory levels are seen only in later stages. The spastic paraparesis is insidious and slowly progressive in some cases and more acute in onset in others; muscle fasciculations, atrophy, and weakness of the upper extremities may develop in conjunction with it, sometimes simulating motor neuron disease when sensory or sphincter disturbances are absent.

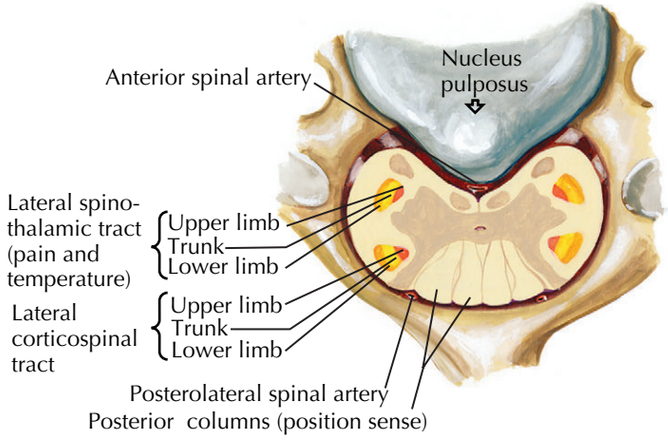
Diagnosis. Spinal magnetic resonance imaging (MRI) or computed tomography (CT) myelography is required to establish the presence of spinal cord compression, confirm the cause, and exclude other pathologic processes. Narrowing of the anteroposterior sagittal diameter to 11 mm or less in any area of the cervical spine increases the risk of cord compression. Multilevel disease is common. Cerebrospinal fluid (CSF) is normal or shows a mild to moderately elevated protein content.

Treatment. Nonoperative treatment may involve analgesics and immobilization of the neck, for example, in a cervical collar. Although most nerve root syndromes subside spontaneously, spondylotic myelopathy, if progressive, requires surgical intervention. Some patients improve after surgery, but only stabilization can be realistically expected.

Spinal cord decompression may be done through either an anterior or a posterior approach, and it is not clear which approach is best. About 75% of patients stabilize or improve after surgery, whereas up to 25% may worsen or progress. There is no agreement on factors that predict the surgical outcome.







Cervical Disk Herniation Causing Cord Compression

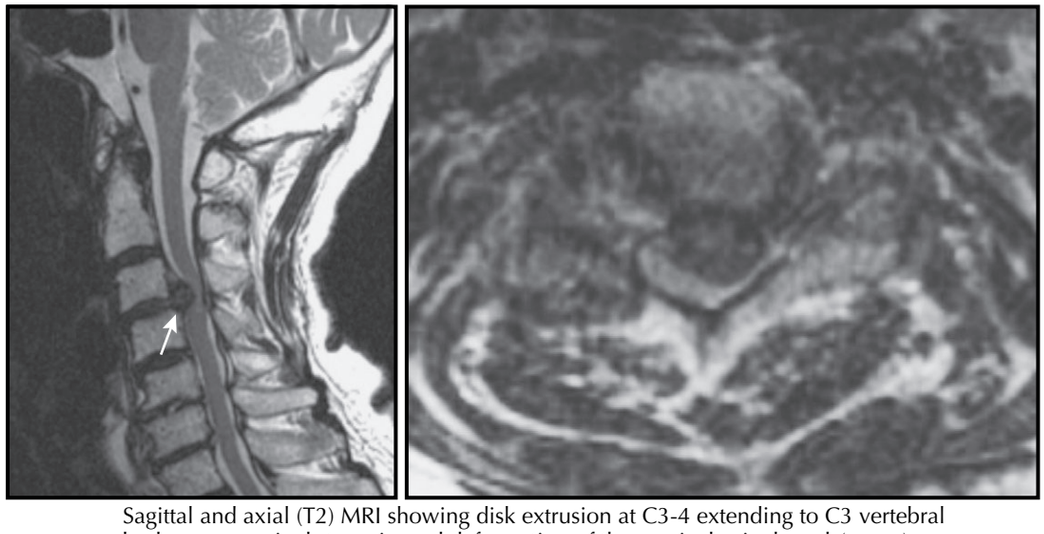
Cervical disk disease is a common disorder, accounting for 1% to 2% of all hospital admissions in the United States. Its etiology is multifactorial. It is sometimes attributed to preceding injury or exertion, but, in most instances, no specific precipitant can be identified.

With age, the nucleus pulposus of the disk dehydrates, placing more stress on the annulus fibrosus (outer lining). Tears in the annulus may permit a sudden herniation of the nucleus—a *ruptured disc.* Alternatively, chronic annular bulging or nuclear herniation may lead to the formation of extensive bony spurs (osteophytes), typically located along the anterior portion of the disk interspace or posteriorly within the nerve root foramen. Osteophytes or ruptured disks produce symptoms only if they compress the spinal cord or nerve roots against posteriorly located structures, including the posterior nerve root foramen and ligamentum flavum.

Clinical Manifestations. The first manifestation of cervical disk disease is often cervical radiculopathy, with symptoms and signs referable to compression of a cervical nerve root. Cervical and unilateral arm pain, frequently acute in onset, is a common symptom of cervical disk disease, and patients often complain also of numbness, paresthesias, or, less commonly, of weakness in the involved arm in a radicular distribution. Examination may show sensory, motor, or reflex abnormalities depending on the involved nerve roots. Gait disturbances, leg weakness, or sphincter disturbances suggest an associated compressive myelopathy.

Diagnosis. Spinal MRI is the imaging modality of choice, but CT myelography may be required in those with a normal MRI when a strong clinical suspicion of the diagnosis remains. Electrodiagnostic studies (needle electromyography to detect signs of denervation in muscles) are helpful in indicating the functional significance of any anatomic abnormalities seen on imaging studies.

Treatment. Many patients with cervical radiculopathy respond to *conservative treatment*, including short-term use of a soft cervical collar to immobilize the neck, mild analgesics, physical therapy, and muscle relaxants as required. A brief course of oral steroids is sometimes worthwhile. Many believe that cervical traction is also helpful, provided imaging reveals no contraindication. If symptoms persist after 4 to 6 weeks, further testing, including spinal MRI, is indicated. If imaging shows compression of the clinically appropriate nerve root, *surgical therapy* is often undertaken. Surgery is also often performed if patients have clinical evidence of myelopathy and imaging evidence of spinal cord compression. Some neurosurgeons strongly advocate an anterior approach, and others, a posterior approach in treatment. In skilled hands, either route leads to excellent relief of symptoms in many patients, but the evidence that surgery is beneficial is incomplete.



Sagittal and axial (T2) MRI showing disk extrusion at C3-4 extending to C3 vertebral body, severe spinal stenosis, and deformation of the cervical spinal cord *(arrow)*

Infectious and Hereditary Myelopathies

Several infectious myelopathies merit brief comment. *AIDS-associated vacuolar myelopathy* is discussed in the section on infections of the nervous system (Plate 11-13).

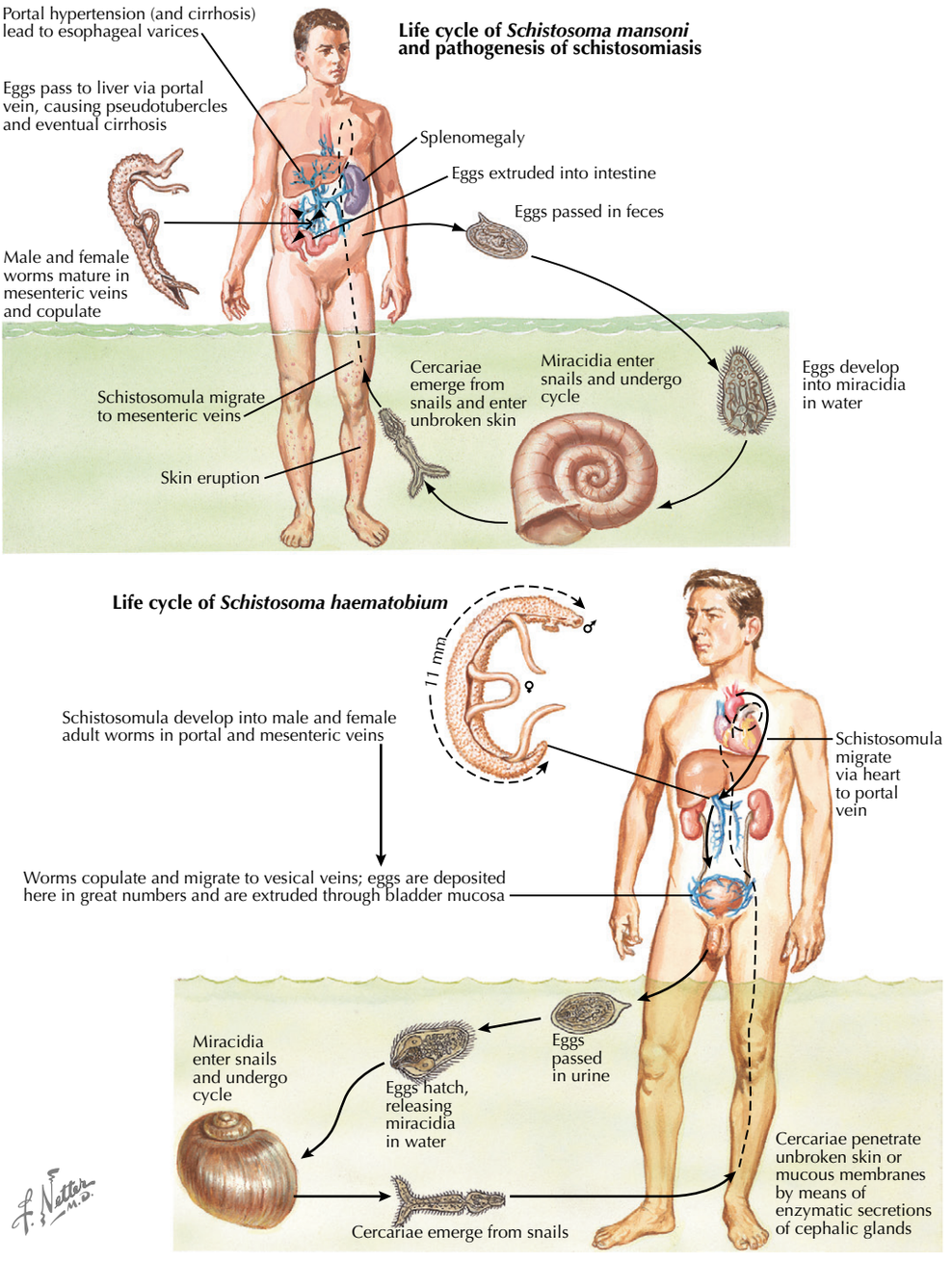
Human T-cell Lymphocytic Virus-1 (HTLV-1) Myelopathy. This disorder, also known as tropical spastic paraparesis/HTLV-1–associated myelopathy (TSP/HAM), may be acquired as a sexually transmitted disease, particularly in the Caribbean, eastern South America, equatorial Africa, and southern Japan, where HTLV-1 is endemic. Transmission is by semen, blood or its products, and breast milk. Only a small proportion of HTLV-1 carriers develop the myelopathy after a latent period that may be many years. The mid- to lower thoracic cord is most severely affected, especially the lateral columns and corticospinal tracts. Patients typically present in the midfourth to fifth decades with a slowly progressive spastic paraparesis and paraparesthesia. Bladder disturbances, impotence, and constipation also develop. Cerebral, cerebellar, and cranial and peripheral nerve dysfunction may occur, as may HTLV-1–associated systemic disorders.

MRI may show spinal atrophy and sometimes the presence of cerebral periventricular white matter lesions. The cerebrospinal fluid (CSF) may contain a mononuclear pleocytosis or elevated protein concentration, with oligoclonal bands. Anti–HTLV-1 antibodies are present in CSF, and polymerase chain reaction (PCR) is positive for the virus. There is no effective treatment for HTLV-1–related myelopathy other than symptomatic measures. Preventive measures to reduce transmission include screening blood products, sexual education, and use of formula rather than breast milk of infected mothers.

Schistosomal Myelopathy. Millions of persons worldwide are infected with schistosomes, parasitic blood flukes that are transmitted to humans in contact with fresh water. Neurologic involvement is relatively uncommon in schistosomiasis, but an inflammatory myeloradiculopathy may occur, especially with *Schistosoma mansoni* and *S. haematobium* infection (cerebral involvement is more common with *S. japonicum infection)*. *Schistosoma* organisms are found in tropical areas such as the Nile and Amazon River basins, Lake Victoria in East-Central Africa, the Caribbean, and Middle East. Infective larvae (cercariae) are released into fresh water by infected snails (the intermediate host). After they penetrate the skin of humans, the parasite migrates to selected vascular beds, depending on species. After reproduction of adult male and female parasites, eggs are deposited in various tissues and eventually exit the body in urine or feces; in the right context, the eggs open to release free-swimming larvae (*miracidia)* that infect snails. Involvement of the human nervous system probably occurs by transport of eggs into the central nervous system (CNS) circulation by collateral veins or by aberrant migration of adult worms.

Spinal cord involvement, often at the level of the conus medullaris, often follows an initial radiculopathy and may progress acutely or subacutely. Patients may present with back or root pain, paraparesis, sensory abnormalities, and bladder dysfunction. Expanding granulomatous inflammation may lead to a progressive myelopathy; in some instances, an acute transverse myelitis leads to a catastrophic deficit.

The diagnosis should be suspected in any recent traveler to an endemic area. An eosinophilia in the blood, and sometimes the CSF, is suggestive but may not be present. Enlargement and gadolinium enhancement of the thoracolumbar spinal cord may be evident on magnetic resonance imaging (MRI). Serologic tests may reveal evidence of schistosomal exposure. Rapid diagnosis and early treatment with praziquantel and corticosteroids improves the ultimate prognosis.

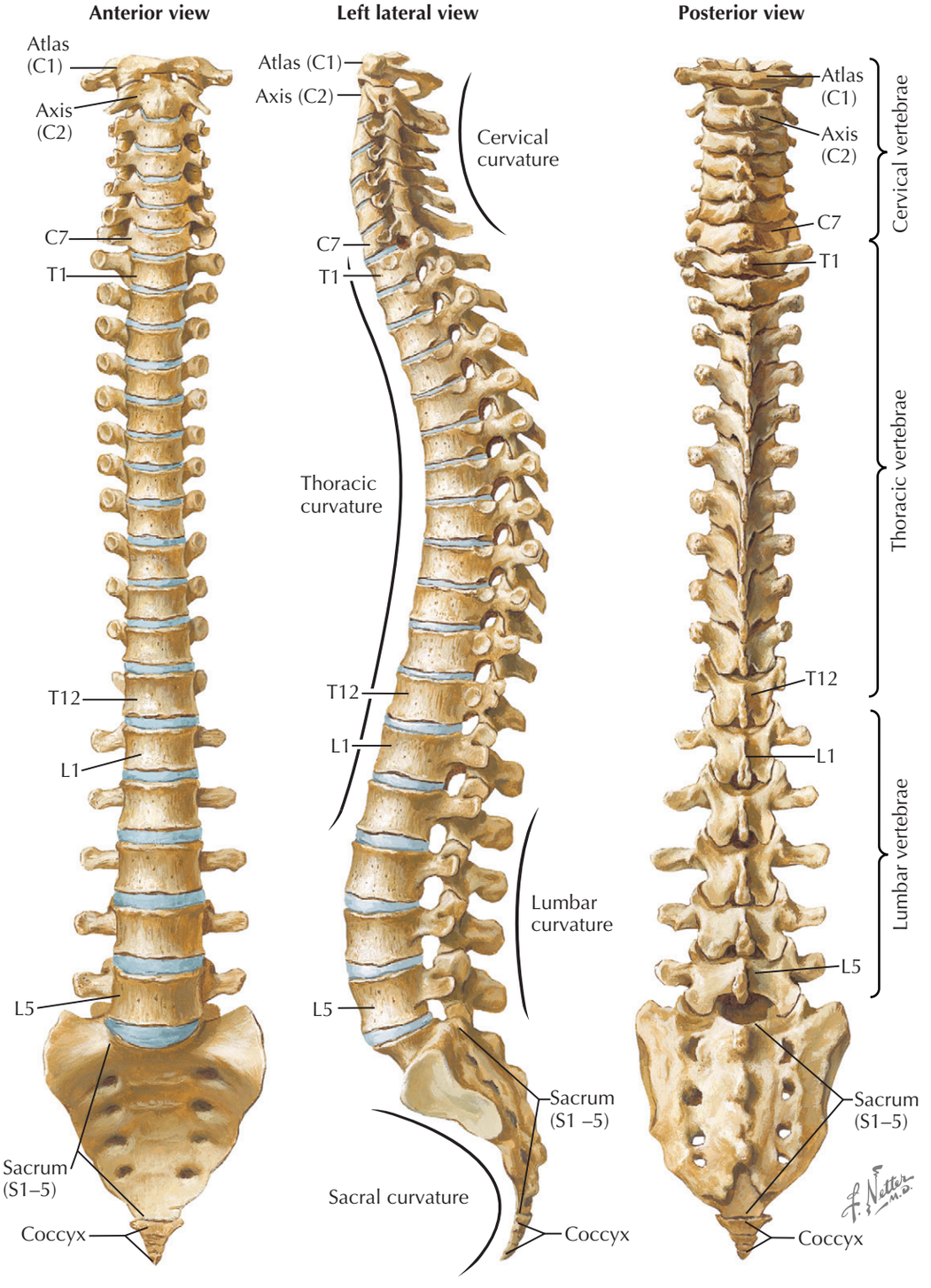


Hereditary Spastic Paraplegia. This term refers to a group of clinically heterogeneous hereditary disorders in which a progressive spastic weakness affects the lower extremities. Patients differ according to the mode of inheritance and genetic locus (when known). Age at onset and the severity of symptoms also vary widely. Corticospinal tract and posterior column involvement occurs from a dying-back process affecting the distal ends of long axons, causing the motor and sensory deficits. The disorder occurs most often with autosomal dominant inheritance, but autosomal recessive and X-linked inheritance also occur. Many different genes and genetic loci have been identified.

Patients with the "pure" form of the disorder present with progressive spasticity, hyperreflexia, and weakness of the lower extremities. Vibratory sensation is sometimes mildly decreased. Occasional patients experience sphincter disturbances manifested by a spastic bladder with urgency and frequency. In the *complicated form*, other findings include cognitive impairment, aphasia, dysarthria, dysphagia, pale optic discs, nystagmus, cataracts, upper extremity weakness, motor neuronopathy, sphincter disturbances, and muscle wasting; neuroimaging may reveal cerebellar or cerebral atrophy, hydrocephalus, white matter changes, and a thin corpus callosum.

A positive family history is one of the most important diagnostic clues. Genetic screening may be supportive, but, in many cases, the genetic abnormality has yet to be identified. MRI helps to exclude other structural causes of the patient's symptoms and sometimes reveals marked spinal atrophy. No specific therapy is available. Management is therefore supportive and treatment is symptomatic.

SPINAL TRAUMA



Spinal Column

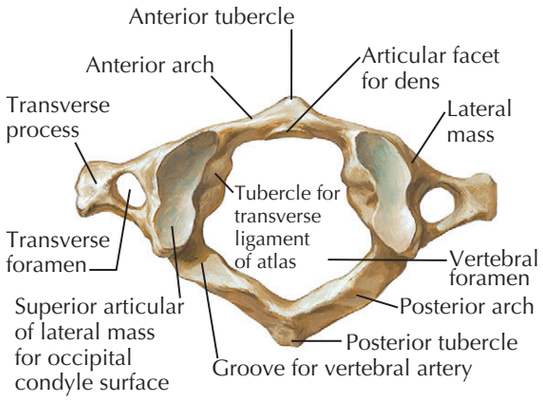
The spinal column is built up from alternating bony vertebrae and fibrocartilaginous disks, which are intimately connected by strong ligaments and supported by powerful musculotendinous masses. The individual bony elements and ligaments are described in Plates 3-2 to 3-10. There are 33 vertebrae (7 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 4 coccygeal), although the sacral and coccygeal vertebrae are usually fused to form the sacrum and coccyx.

All vertebrae conform to a basic plan, but individual variations occur in the different regions. A typical vertebra consists of an anterior, more-or-less cylindric *body* and a posterior *arch* composed of two *pedicles* and two *laminae*, the latter united posteriorly to form a *spinous process*. These processes vary in shape, size, and direction in the various regions of the spine. On each side, the arch also supports a *transverse process* and *superior* and *inferior articular processes*; the latter form synovial joints with corresponding processes on adjacent vertebrae, and the spinous and transverse processes provide levers for the many muscles attached to them. The increasing size of the vertebral bodies from above downward is related to the increasing weights and stresses borne by successive segments, and the sacral vertebrae are fused to form a solid wedge-shaped base—the keystone in a bridge whose arches curve down toward the hip joints. The *intervertebral disks* act as elastic buffers to absorb the numerous mechanical shocks sustained by the spinal column.

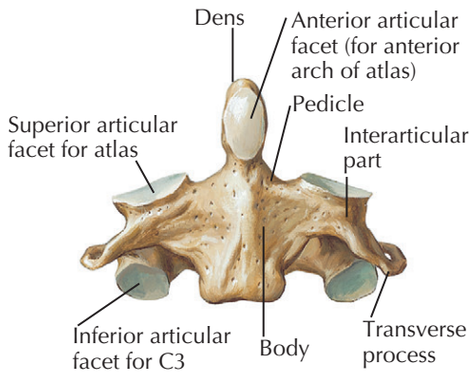
Only limited movements are possible between adjacent vertebrae, but the sum of these movements confers a considerable range of mobility on the vertebral column as a whole. Flexion, extension, lateral bending, rotation, and circumduction are all possible, and these actions are freer in the cervical and lumbar regions than in the thoracic. Such differences exist because the disks are thicker in the cervical and lumbar areas, the splinting effect produced by the thoracic cage is lacking, the cervical and lumbar spinous processes are shorter and less closely apposed, and the articular processes are shaped and arranged differently.

At birth, the spinal column presents a general posterior convexity, but later, the cervical and lumbar regions become curved in the opposite directions—when the infant reaches the stages of holding up its head (3 to 4 months) and sitting upright (6 to 9 months). The posterior convexities are *primary curves* associated with the fetal uterine position, whereas the cervical and lumbar anterior *secondary curves* are compensatory to permit the assumption of the upright position. There may be additional slight lateral deviations due to unequal muscular traction in right-handed and left-handed persons.

Human evolution from a quadrupedal to a bipedal posture was mainly effected by the tilting of the sacrum between the hip bones, by an increase in lumbosacral angulation, and by minor adjustments of the anterior and posterior depths of various vertebrae and disks. An erect posture greatly increases the load borne by the lower spinal joints, and, good as these ancestral adaptations were, some static and dynamic imperfections remain and predispose to strain and backache. The length of the vertebral column averages 72 cm in the adult male and 7 to 10 cm less in the female. The *vertebral canal* extends through the entire length of the column and provides an excellent protection for the spinal cord, the cauda equina, and their coverings. The spinal vessels and nerves pass through *intervertebral foramina* formed by notches on the superior and inferior borders of the pedicles of adjacent vertebrae, bounded anteriorly by the corresponding intervertebral disks, and posteriorly, by the joints between the articular processes of adjoining vertebrae. Pathologic or traumatic conditions affecting any of these structures may produce pressure on the nerves or vessels they transmit.



Atlas (C1): superior view



Axis (C2): anterior view

Atlas and Axis

The atlas and axis are the first and second cervical vertebrae, and both are atypical. They are linked together and to the skull and other cervical vertebrae by a layered pattern of craniocervical ligaments (see Plates 3-4 and 3-5).

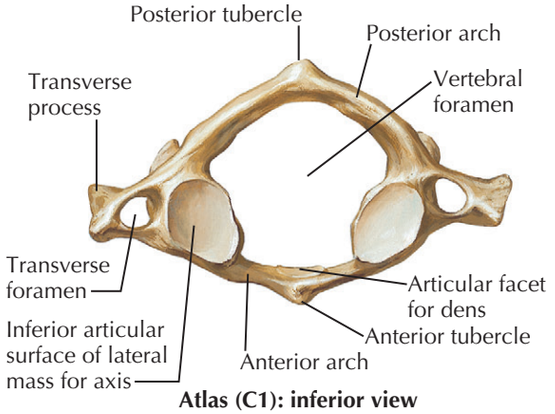
The atlas (named after the mythical giant who carried the earth on his shoulders) supports the globe of the skull. It lacks a body and forms a ring consisting of shorter anterior and longer posterior arches, with two lateral masses. The enclosed *vertebral foramen* is relatively large.

The *anterior arch* is slightly curved, with an anterior midline tubercle and a posterior midline facet for articulation with the dens of the axis. The *lateral masses* bear superior and inferior articular facets and transverse processes. The *superior articular facets* are concave and ovoid (often waisted, or reniform) and are directed upward and inward as shallow cups, or foveae, for the reception of the occipital condyles. Nodding movements of the head mainly occur at these atlanto-occipital joints. The *inferior articular facets* are almost circular, gently concave, and face downward and slightly medially and backward; they articulate with the superior articular facets on the axis. The *transverse processes* are each pierced by a foramen for the vertebral artery, and project so far laterally that they can be easily palpated by pressing inward between the mandibular angles and the mastoid processes. They provide attachments and levers for some of the muscles involved in head rotation. On the anteromedial aspect of each lateral mass is a small tubercle for the attachment of the transverse ligament of the atlas.

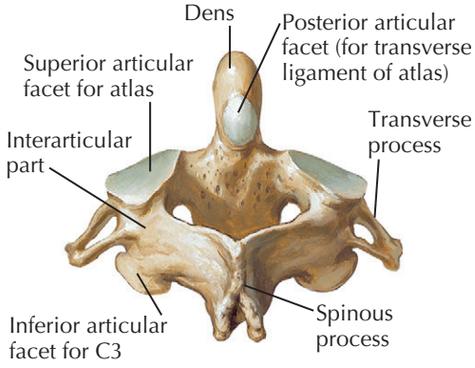
The *posterior arch* is more curved than the anterior and has a small *posterior tubercle*, which is a rudimentary spinous process. Just behind each superior articular facet is a shallow *groove for the vertebral artery* and first cervical spinal nerve, the nerve lying between the artery and the bone.

The axis, or second cervical vertebra, has a toothlike process, or dens, projecting upward from its body. The *dens* is really the divorced body of the atlas that has united with the axis to form a pivot around which the atlas and the superjacent skull can rotate. Its anterior surface has an oval *anterior facet* for articulation with the facet on the back of the anterior arch of the atlas, and a smaller *posterior facet* lower down on its posterior surface, which is separated from the transverse ligament of the atlas by a small bursa. The apex of the dens is attached to the lower end of the apical ligament, and the alar ligaments are attached to its sides.

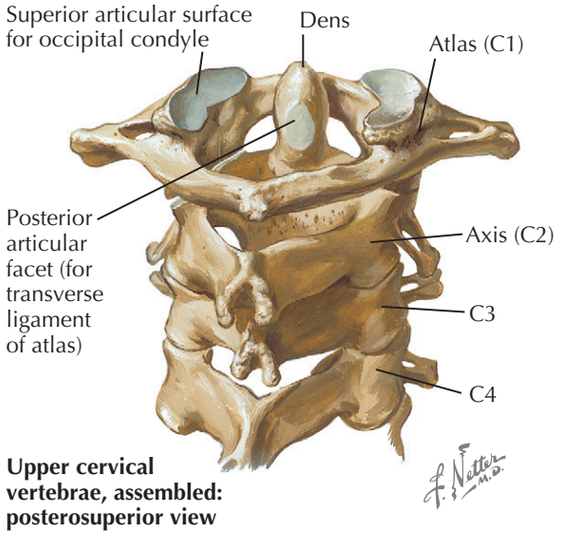
The *body* of the axis has a lower liplike projection that overlaps the anterosuperior border of the third cervical vertebra. Its anterior surface shows a median ridge separating slight depressions for slips of the longus colli muscles. The posteroinferior border of the body is less prominent, and attached to it are the tectorial membrane and the posterior longitudinal spinal ligament. The *pedicles* and *laminae* are stout, and the latter end in a strong, bifid *spinous process*. The *vertebral foramen* of the axis is somewhat smaller than that of the atlas. On each side of the body are superior and inferior articular and transverse processes. The *articular processes* are offset, because the superior pair is anterior in position to the inferior pair. They articulate with the adjoining processes of the atlas and third cervical vertebra. The *transverse processes* are smaller and shorter than those of the atlas, and their foramina are inclined superolaterally to allow the contained vertebral arteries and nerves to pass easily into the more widely spaced transverse foramina of the atlas.



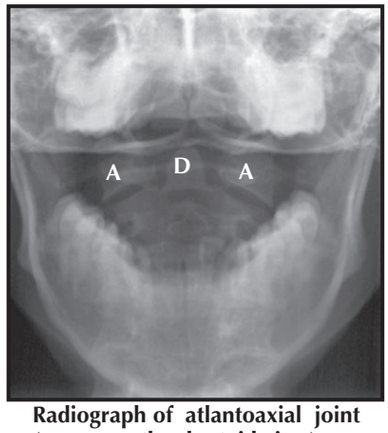
Atlas (C1): inferior view



Axis (C2): posterosuperior view

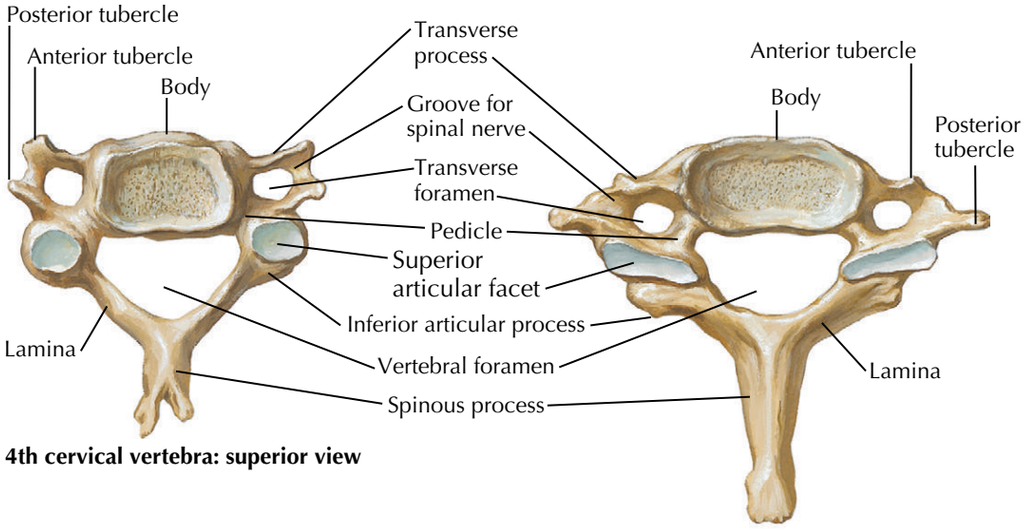


Upper cervical vertebrae, assembled: posterosuperior view



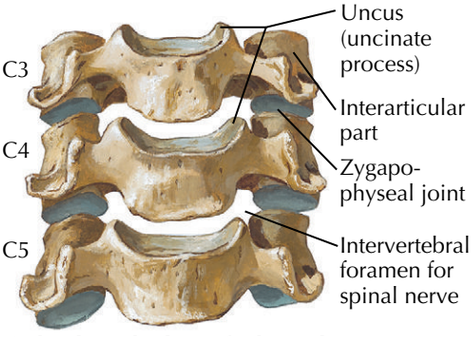
Radiograph of atlantoaxial joint (open mouth odontoid view)

A Lateral masses of atlas (C1 vertebra)
D Dens of axis (C2 vertebra)

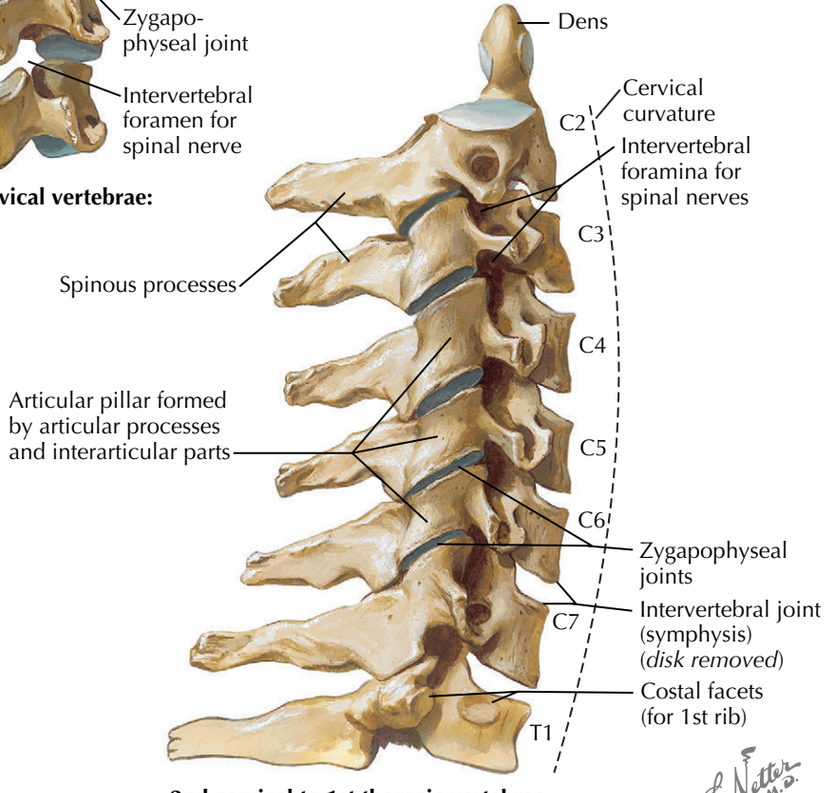


4th cervical vertebra: superior view

7th cervical vertebra: superior view



3rd, 4th, and 5th cervical vertebrae: anterior view



2nd cervical to 1st thoracic vertebrae: right lateral view

Cervical Vertebrae

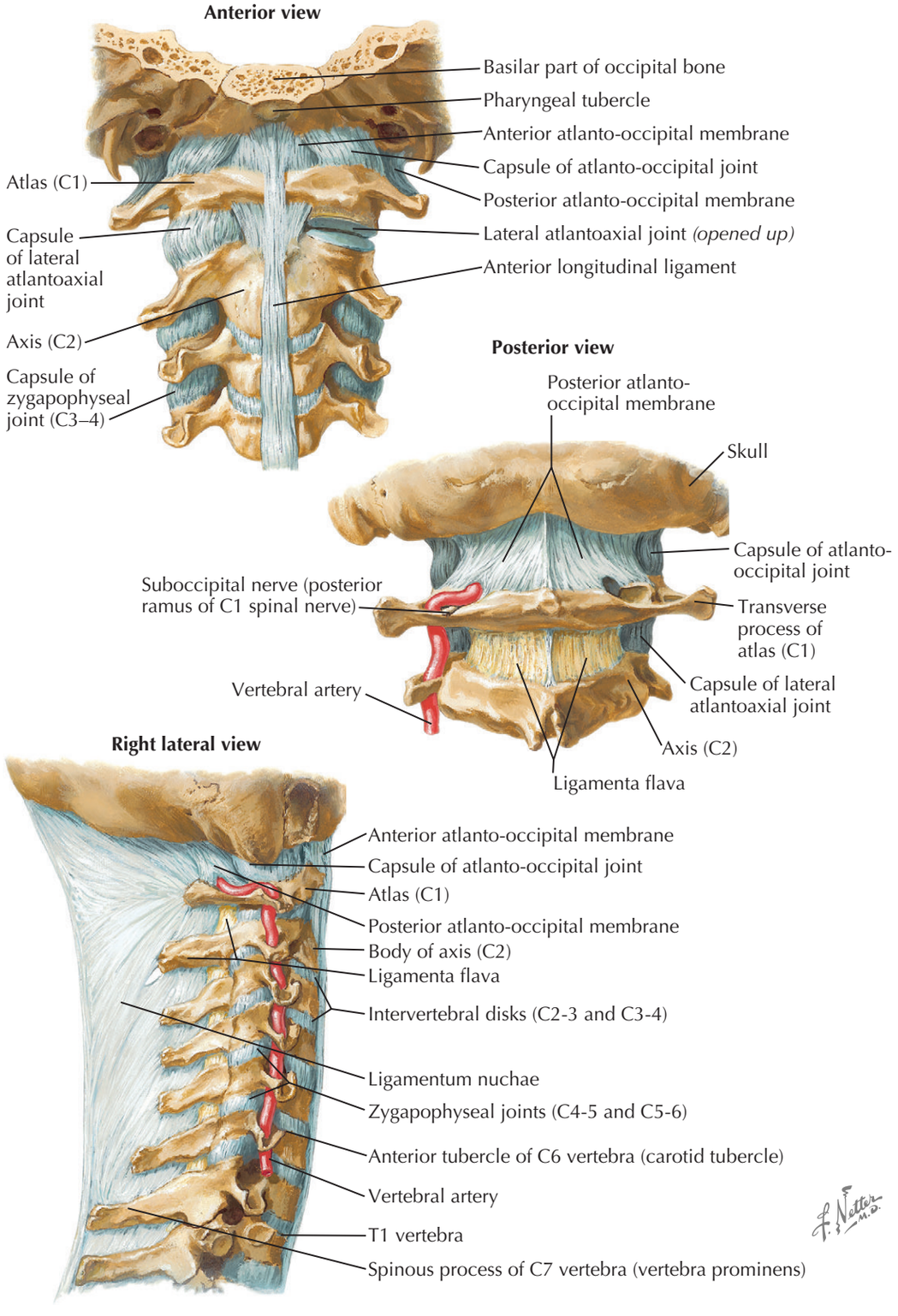
The first two cervical vertebrae, the atlas and the axis, are illustrated in Plate 3-2. The other five (C3 to C7) show the general vertebral features, but cervical vertebrae are easily distinguishable by the presence of foramina in their transverse processes, which (except in the case of the seventh vertebra) transmit the vertebral vessels and nerves (see Plate 3-2).

The cervical *vertebral bodies* are smaller than those of the other movable vertebrae and increase in size from above downward; they are broader in the transverse diameter than anteroposteriorly. The superior body surfaces are concave from side to side and slightly convex from front to back, whereas the inferior surfaces are reciprocally curved or saddle shaped. The lateral edges of the superior body surface are raised, whereas those of the lower surface are beveled, and small clefts exist between them. Some claim these are miniature synovial joints, but others believe they are merely spaces in the lateral parts of the corresponding intervertebral disks.

The *vertebral foramina* are comparatively large in order to accommodate the cervical enlargement of the spinal cord; they are bounded by the bodies, pedicles, and laminae of the vertebrae. The *pedicles* project posterolaterally from the bodies and are grooved by superior and inferior vertebral notches of almost equal depth, which form the intervertebral foramina by connecting with similar notches on adjacent vertebrae. The medially directed *laminae* are thin and relatively long and fuse posteriorly to form short, bifid *spinous processes*. Projecting laterally from the junction of the pedicles and laminae are articular pillars supporting *superior* and *inferior articular facets*.

Each *transverse process* is pierced by a foramen, bounded by narrow bony bars ending in anterior and posterior tubercles; these are interconnected lateral to the foramen by the so-called *costotransverse bar*. Only the medial part of the posterior bar represents the true transverse process; the anterior and costotransverse bars and the lateral portion of the posterior bar constitute the costal element. These elements, especially in the seventh and/or sixth cervical vertebrae, may develop abnormally to form cervical ribs. The upper surfaces of the costotransverse bars are grooved and lodge the anterior primary rami of the spinal nerves. The anterior tubercles of the sixth cervical vertebra are large and are termed the *carotid tubercles* because the common carotid arteries lie just anteriorly and can be compressed against them.

The seventh cervical vertebra is called the *vertebra prominens* because its spinous process is long and ends in a tubercle that is easily palpable at the lower end of the nuchal furrow; the spinous process of the first thoracic vertebra is just as prominent. The seventh cervical vertebra sometimes lacks a transverse foramen on one or both sides; when present, the foramina transmit only small accessory vertebral veins.



External Craniocervical Ligaments

The ligaments uniting the cranium, atlas, and axis allow free, yet safe, movement of the head, and extra security is provided by the ligamentous action of the surrounding muscles. Ligaments best seen from the external aspect are shown in the illustration.

The *anterior atlanto-occipital membrane* is a wide, dense, fibroelastic band extending between the anterior margin of the foramen magnum and the upper border of the anterior arch of the atlas. Laterally, it is continuous with the articular capsules of the atlanto-occipital joints. In the midline, it is reinforced by the upward continuation of the anterior longitudinal ligament.

The *posterior atlanto-occipital membrane* is broader and thinner than the anterior one and connects the posterior margin of the foramen magnum with the upper border of the posterior arch of the atlas. On each side, it arches over the groove for the vertebral artery, leaving an opening for the upward passage of the artery and the outward passage of the first cervical spinal nerve.

Articular capsules surround the joints between the occipital condyles and the superior atlantal facets. The capsules are rather loose, allowing nodding movements of the head, and are thin medially; laterally, they are thickened and form the *lateral atlanto-occipital ligaments*, which limit lateral tilting of the head.

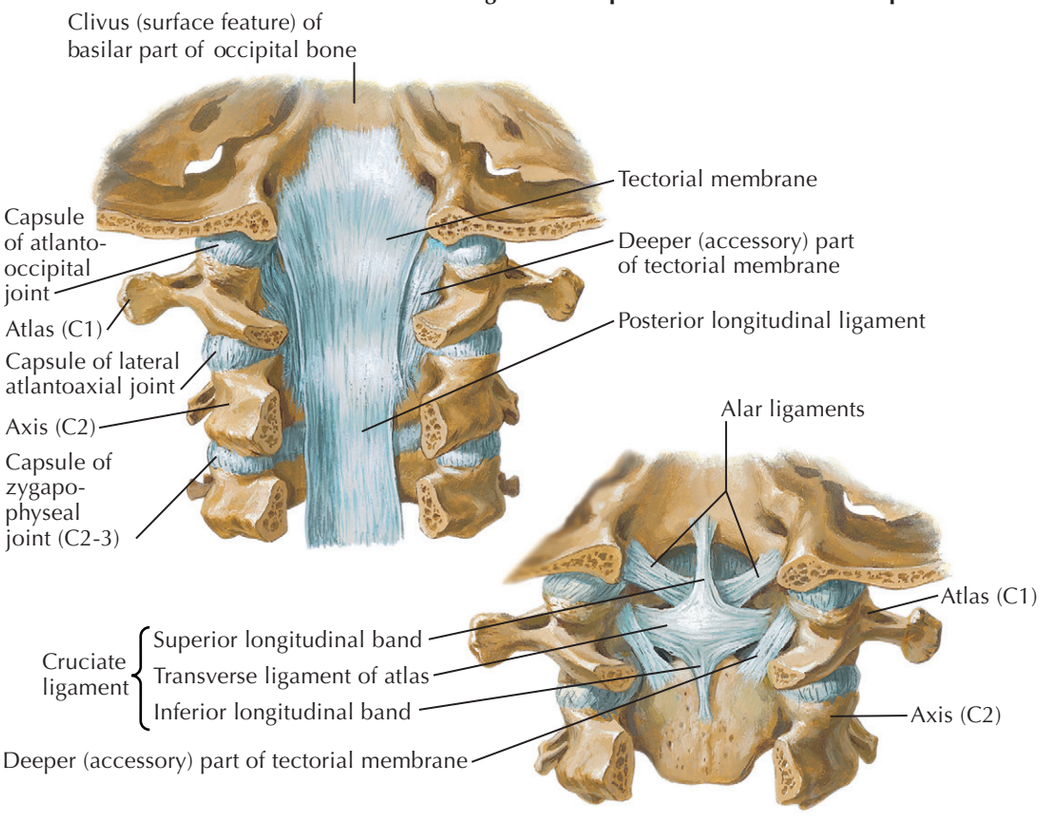
The *anterior longitudinal ligament* extends from the base of the skull to the sacrum. Its uppermost part reinforces the anterior atlanto-occipital membrane in the midline. The part between the anterior tubercle of the atlas and the anterior median ridge on the axis may have lateral extensions—the *atlantoaxial (epistrophic) ligaments*.

The *ligamentum nuchae* is a dense fibroelastic membrane stretching from the external occipital protuberance and crest to the posterior tubercle of the atlas and the spinous processes of all the other cervical vertebrae. It provides areas for muscular attachments and forms a midline septum between the posterior cervical muscles. The ligamentum nuchae is better developed in quadrupeds than in humans.

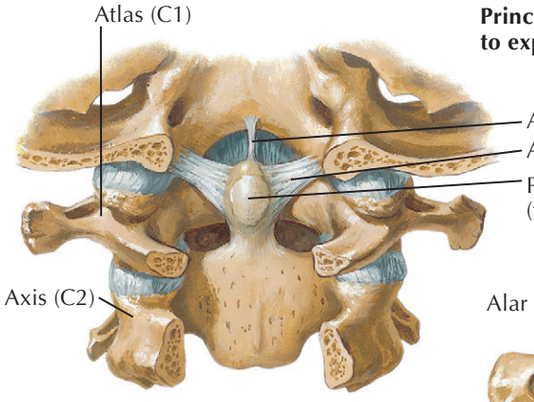
The *ligamenta flava* contain a high proportion of yellow elastic fibers and connect the laminae of adjacent vertebrae. They are present between the posterior arch of the atlas and the laminae of the axis but absent between the atlas and skull.

Intervertebral disks are lacking between the occiput and atlas and between the atlas and axis.

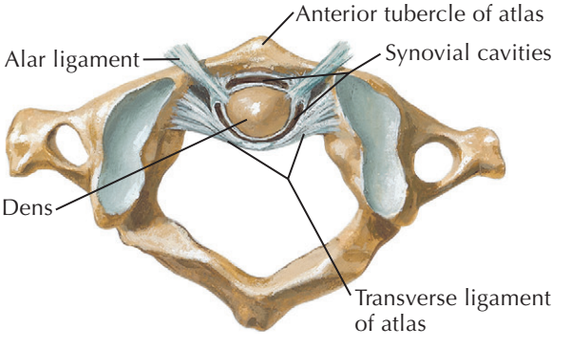
Upper part of vertebral canal with spinous processes and parts of vertebral arches removed to expose ligaments on posterior vertebral bodies: posterior view



Principal part of tectorial membrane removed to expose deeper ligaments: posterior view



Cruciate ligament removed to show deepest ligaments: posterior view



Median atlantoaxial joint: superior view

Internal Craniocervical Ligaments

The ligaments on the posterior aspects of the vertebral bodies contribute added strength to the craniocervical region, and some are specifically arranged to check excessive movements, such as rotation at the median and lateral atlantoaxial joints.

The broad, strong *tectorial membrane* lies within the vertebral canal. It prolongs the *posterior longitudinal ligament* upward from the posterior surface of the body of the axis to the anterior and anterolateral margins of the foramen magnum, where it blends with the dura mater. It covers the dens and its ligaments and gives added protection to the junctional area between the medulla oblongata and spinal cord.

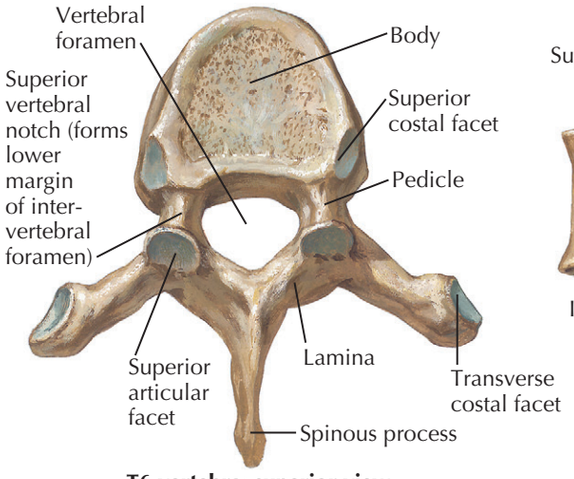
The *median atlantoaxial pivot joint* lies between the dens of the axis and the ring formed by the anterior arch and transverse ligament of the atlas (see Plate 3-2). Two small synovial cavities surrounded by thin articular capsules are present between the dens and the anterior arch in front, and the transverse ligament of the atlas behind.

The *transverse ligament of the atlas* is a strong band passing horizontally behind the dens and attached on each side to a tubercle on the medial side of the lateral mass of the atlas. From its midpoint, bands pass vertically upward and downward to become fixed, respectively, to the basilar part of the occipital bone between the tectorial membrane and the apical ligament of the dens and to the posterior surface of the body of the axis: the *superior* and *inferior longitudinal fascicles*. These transverse and vertical bands together form the *cruciform ligament*.

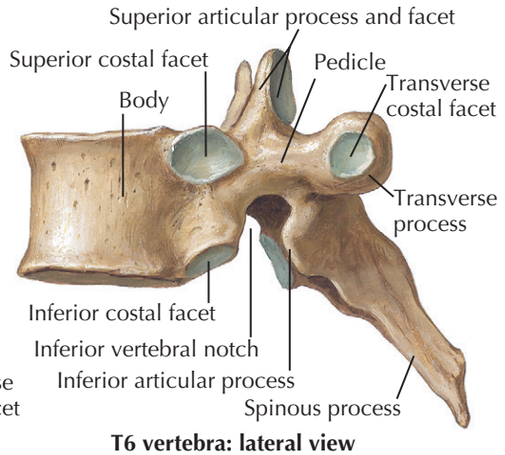
The *apical ligament* is a slender cord connecting the apex of the dens to the anterior midpoint of the foramen magnum, lying between the anterior atlanto-occipital membrane and the upper limb of the cruciform ligament.

The *alar ligaments* are two fibrous bands stretching upward and outward from the superolateral aspects of the dens to the medial sides of the occipital condyles. They check excessive rotation at the median atlanto-occipital joint.

Lateral atlantoaxial joints are formed between the almost-flat inferior articular facets on the lateral masses of the atlas and the superior articular facets of the axis. They are synovial joints with thin, loose articular capsules. An *accessory ligament* extends from near the base of the dens to the lateral mass of the atlas, close to the attachment of the transverse ligament. It assists the alar ligaments in restricting atlantoaxial rotation.



T6 vertebra: superior view



T6 vertebra: lateral view

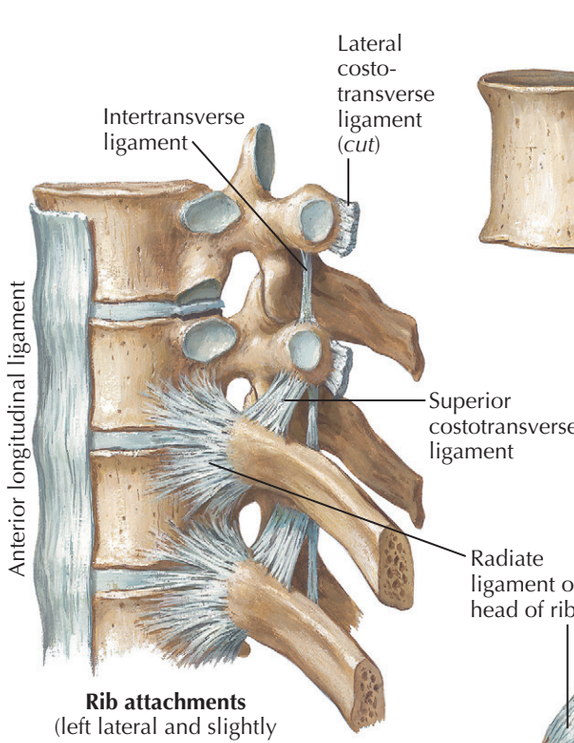
THORACIC VERTEBRAE

The 12 thoracic vertebrae are intermediate in size between the smaller cervical and larger lumbar vertebrae. The *vertebral bodies* are heart shaped and are slightly deeper posteriorly than anteriorly. They are easily recognized by costal facets on both sides of the bodies and on all the transverse processes (except those of the eleventh and twelfth thoracic vertebrae), which articulate, respectively, with facets on the heads and tubercles of the corresponding ribs.

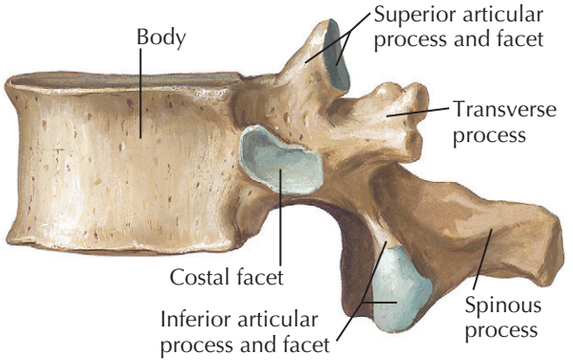
The *vertebral foramina* are smaller and more rounded than those in the cervical region, and so conform to the reduced size and more circular shape of the spinal cord in the thoracic region. They are bounded by the posterior surfaces of the vertebral bodies and by the pedicles and laminae forming the vertebral arches. The stout *pedicles* are directed backward; they have very shallow superior and much deeper inferior vertebral notches. The *laminae* are short, relatively thick, and partly overlap each other from above downward. The typical thoracic *superior articular processes* project upward from the junctions of the pedicles and laminae, and their facets slant backward and slightly upward and outward. The *inferior articular processes* project downward from the anterior parts of the laminae, and their facets face forward and slightly downward and inward. The processes and facets in the cervicothoracic and thoracolumbar junctional areas show gradual transitional changes.

Most of the thoracic *spinous processes* are long and are inclined downward and backward. Those of the upper and lower thoracic vertebrae are more horizontal. The *transverse processes* are also relatively long and extend posterolaterally from the junctions of the pedicles and laminae. Except for those of the lowest two or, occasionally, three thoracic vertebrae, the transverse processes have small oval facets near their tips, which articulate with similar facets on the corresponding rib tubercles.

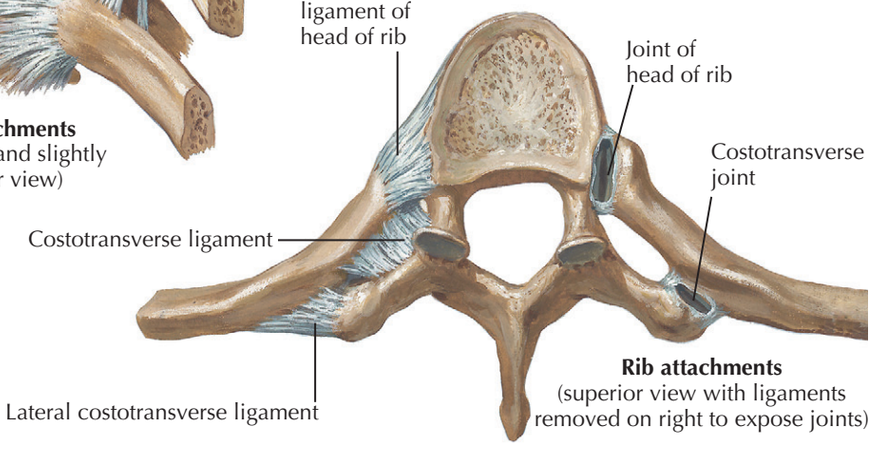
Adjacent vertebral bodies are connected by *intervertebral disks* and by *anterior* and *posterior longitudinal ligaments*; the transverse processes, by *intertransverse ligaments*; the laminae, by *ligamenta flava*; and the spinous processes, by *supraspinal* and *interspinal ligaments*. The joints between the articular processes are surrounded by fibrous *articular capsules*.



Rib attachments
(left lateral and slightly anterior view)



T12 vertebra: lateral view



Rib attachments
(superior view with ligaments removed on right to expose joints)

Costovertebral Joints. The ribs are connected to the vertebral bodies and transverse processes by various ligaments. The *costocentral joints* between the bodies and rib heads have *articular capsules*, and the second to tenth costal heads, each of which articulates with two vertebrae, are connected to the corresponding intervertebral disks by *intra-articular ligaments*. *Radiate (stellate) ligaments* unite the anterior aspects of the rib heads with the sides of the vertebral bodies above and below, and with the intervening disks.

The *costotransverse joints* between the facets on the transverse processes and on the tubercles of the ribs are also surrounded by *articular capsules*. They are reinforced by a (middle) *costotransverse ligament* between the rib neck and the adjoining transverse process, a *superior costotransverse ligament* between the rib neck and the transverse process of the vertebra above, and a *lateral costotransverse ligament* interconnecting the end of a transverse process to the nonarticular part of the related costal tubercle.

Lumbar Vertebrae and Intervertebral Disk

The five lumbar vertebrae are the largest separate vertebrae and are distinguished by the absence of transverse foramina and costal facets. The *vertebral bodies* are wider from side to side than from front to back, and the upper and lower surfaces are kidney shaped and almost parallel, except in the case of the fifth vertebral body, which is slightly wedge shaped. The triangular *vertebral foramina* are larger in the thoracic vertebrae and smaller in the cervical vertebrae.

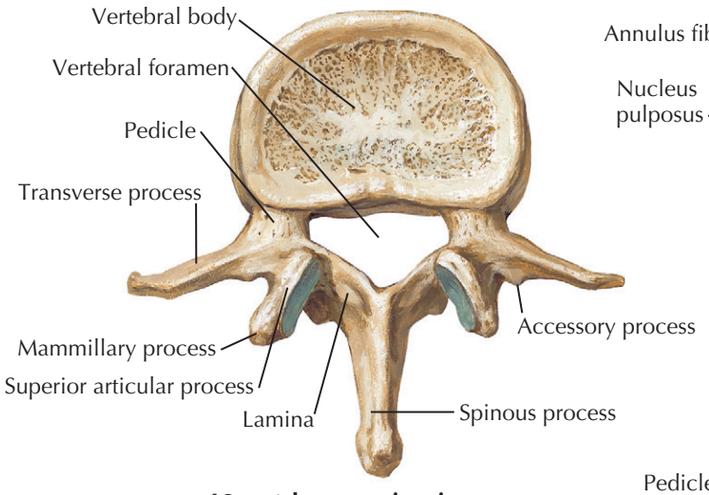
The *pedicles* are short and strong and arise from the upper and posterolateral aspects of the bodies; the superior vertebral notches are therefore less deep than the inferior notches. The *laminae* are short, broad plates that meet in the midline to form the quadrangular and almost horizontal *spinous processes*. The intervals between adjacent laminae and spinous processes are relatively wide.

The *articular processes* project vertically upward and downward from the junctional areas between the pedicles and the laminae. The superior facets are gently concave and face posteromedially to embrace the inferior facets of the vertebra above, which are curved and disposed in a reciprocal fashion. This arrangement permits some flexion and extension but very little rotation. The *transverse processes* of the upper three lumbar vertebrae are long and slender, whereas those of the fourth, and especially of the fifth, are more pyramidal.

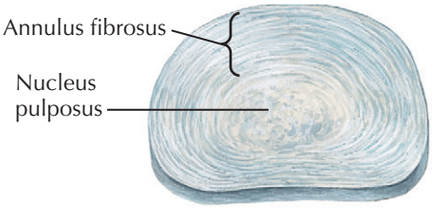
Near the roots of each transverse process are small *accessory processes*; other small, rounded *mammillary processes* protrude from the posterior margins of the superior articular processes. The former may represent the true transverse processes (or their tips) because many of the so-called transverse processes are really costal elements. In the first lumbar vertebra, these elements occasionally develop into lumbar ribs.

The *fifth lumbar vertebra* is atypical. It is the largest, its body is deeper anteriorly, its inferior articular facets face almost forward and are set more widely apart, and the roots of its stumpy transverse processes are continuous with the posterolateral parts of the body and with the entire lateral surfaces of the pedicles.

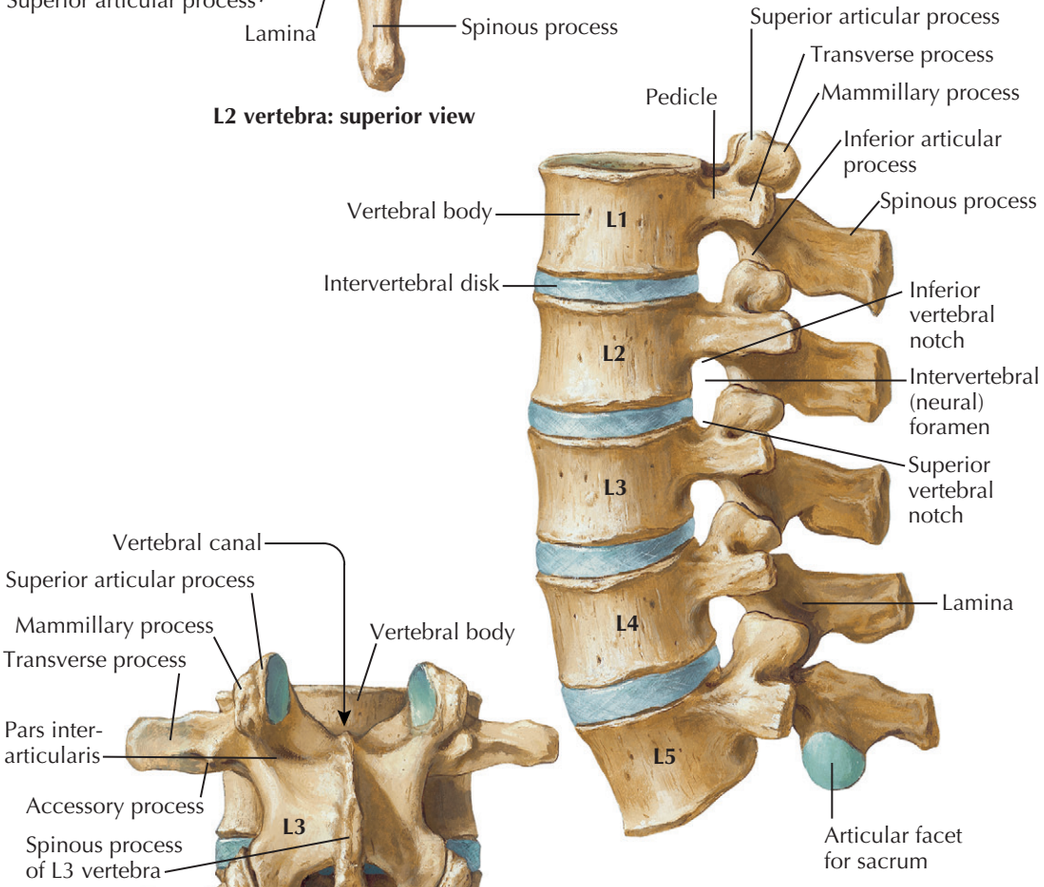
The intervertebral disks are interposed between the adjacent vertebral bodies from the axis to the sacrum and are immensely strong fibrocartilaginous structures that provide powerful bonds and elastic buffers. They consist of outer concentric layers of fibrous tissue—the *annulus fibrosus* (the fibers in adjacent layers are arranged obliquely but in opposite directions, to assist in resisting torsion)—and a central springy, pulpy zone, the *nucleus pulposus*. The blood and nerve supplies to the disks are inconspicuous. If the annular fibers give way as a result of injury or disease, the enclosed turgid nucleus pulposus may prolapse and press on related nervous and vascular structures.



L2 vertebra: superior view



Intervertebral disk



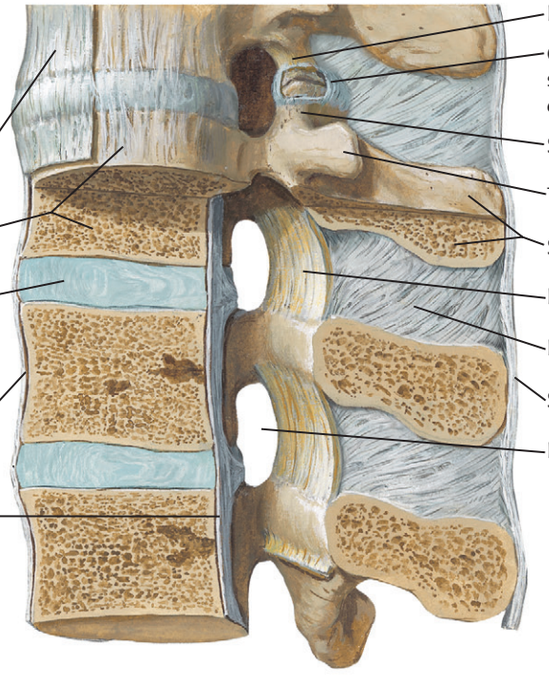
Lumbar vertebrae, assembled: left lateral view

L3 and L4 vertebrae: posterior view

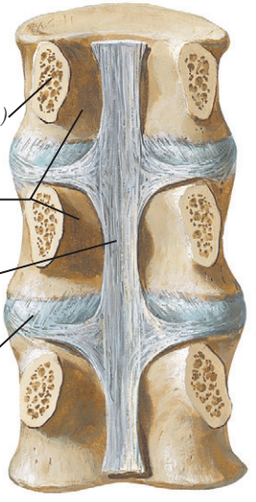
In health and maturity, the intervertebral disks account for almost 25% of the length of the vertebral column; they are thinnest in the upper thoracic region and thickest in the lumbar region. In vertical section, the lumbar disks are rather wedge shaped, with the thicker edge anteriorly. The forward convexity of the lumbar spine is due more to the shape of the disks than to disparities between the anterior and posterior depths of the lumbar vertebrae. The more defined wedge shape of the lumbosacral disk helps to minimize the effects of the marked lumbosacral angulation.

As age advances, the nucleus pulposus undergoes changes: its water content decreases, its mucoid matrix is gradually replaced by fibrocartilage, and it ultimately comes to resemble the annulus fibrosus. The resultant loss of depth in each disk is small, but overall, it may amount to a decrease of 2 to 3 cm in the height of the spinal column.

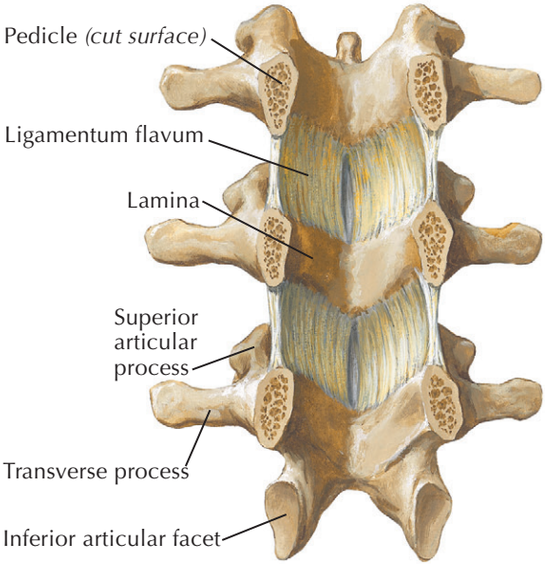
Left lateral view
(partially sectioned in median plane)



Anterior vertebral segments: posterior view
(pedicles sectioned)



Posterior vertebral segments: anterior view



Ligaments of Spinal Column

The vertebrae from the axis to the upper sacrum are united by intervertebral disks and by various other ligaments that interconnect the vertebral bodies, arches, and processes. Additional ligaments link the skull, atlas, and axis (see Plates 3-4 and 3-5); the ribs and the thoracic vertebra; and the lower lumbar, sacral, and coccygeal vertebrae and the hip bones.

The *anterior longitudinal ligament* is a straplike band that increases in width from above downward and extends from the anterior tubercle of the atlas to the sacrum. It is firmly attached to the anterior margins of the vertebral bodies and the intervertebral disks. The superficial fibers cross over several vertebrae, and the shorter, deeper fibers interconnect adjacent bodies and disks. The anterior longitudinal ligament is thicker in the thoracic region than in the other regions of the spinal column.

The *posterior longitudinal ligament* is broader above than below and lies within the vertebral canal behind the vertebral bodies. Its upper end is continuous with the tectorial membrane, and it extends from the axis to the sacrum. The edges of the ligament are serrated, especially in the lower thoracic and lumbar regions, because it spreads outward between its attachments to the borders of the vertebral bodies to blend with the annular fibers of the disks. It is separated from the posterior surfaces of the vertebral bodies by the basivertebral veins that join the anterior internal vertebral venous plexus.

The *ligamenta flava*, largely composed of yellow elastic tissue, join adjacent laminae. They extend from the anteroinferior aspect of the lamina above to the posterosuperior surface of the lamina below, and from the midline to the articular capsules laterally. Small gaps for the passage of veins from the internal to the external vertebral venous plexuses exist between them in the midline. The ligaments increase in thickness from the cervical to the lumbar region.

The *supraspinal ligaments* interconnect the tips of the spinous processes from the seventh cervical vertebra to the sacrum. They are continuous with the ligamentum nuchae above and with the interspinal ligaments in front and increase in thickness from above down. The *interspinal ligaments* are thin, membranous structures extending between the roots and apexes of the spines; they are best developed in the lumbar region.

Articular capsules surround the joints between adjacent articular processes. They are relatively lax in the cervical region.

The *intertransverse ligaments* connect adjoining transverse processes. They are often filamentous in the cervical and lumbar regions but form distinct cords in the thoracic region.

Sacrum and Coccyx

The sacrum consists of five fused vertebrae and is wedge shaped from above down and from before back. It forms most of the posterior pelvic wall and is fixed between the hip bones at an angle so that its curved pelvic surface is inclined downward and forward.

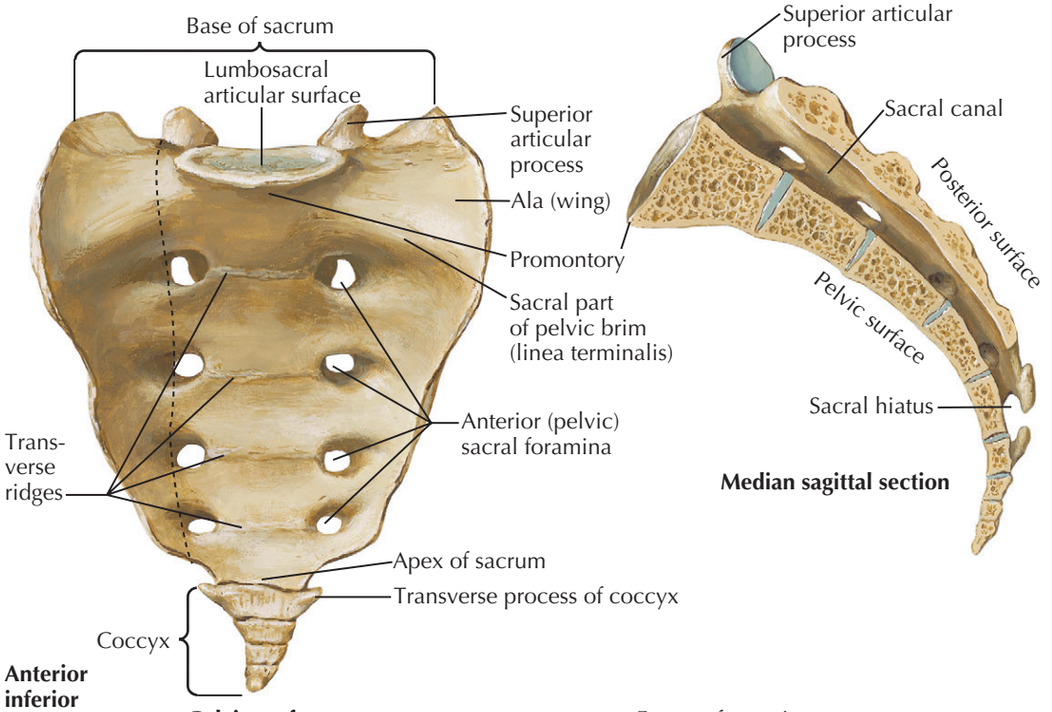
The broader *base* of the sacrum faces anterosuperiorly toward the abdomen; its elevated central third is the upper part of the first sacral vertebral body and bears a smooth oval area for the attachment of the lumbosacral intervertebral disk. Its projecting anterior border is the sacral *promontory*. On each side, the costotransverse elements of the first vertebra are fused to form a wing-shaped lateral mass (sacral *ala*), separated from the pelvic surface by a curved line, which is the sacral portion of the arcuate pelvic brim. The articular processes are fused, like most of the other components of the sacral vertebrae, but the *superior articular processes* of the first vertebra remain and project upward for articulation with the inferior articular processes of the fifth lumbar vertebra. They are flattened and face almost directly backward to assist in preventing subluxation (spondylolisthesis) of the last lumbar vertebra at the angulated lumbosacral junction.

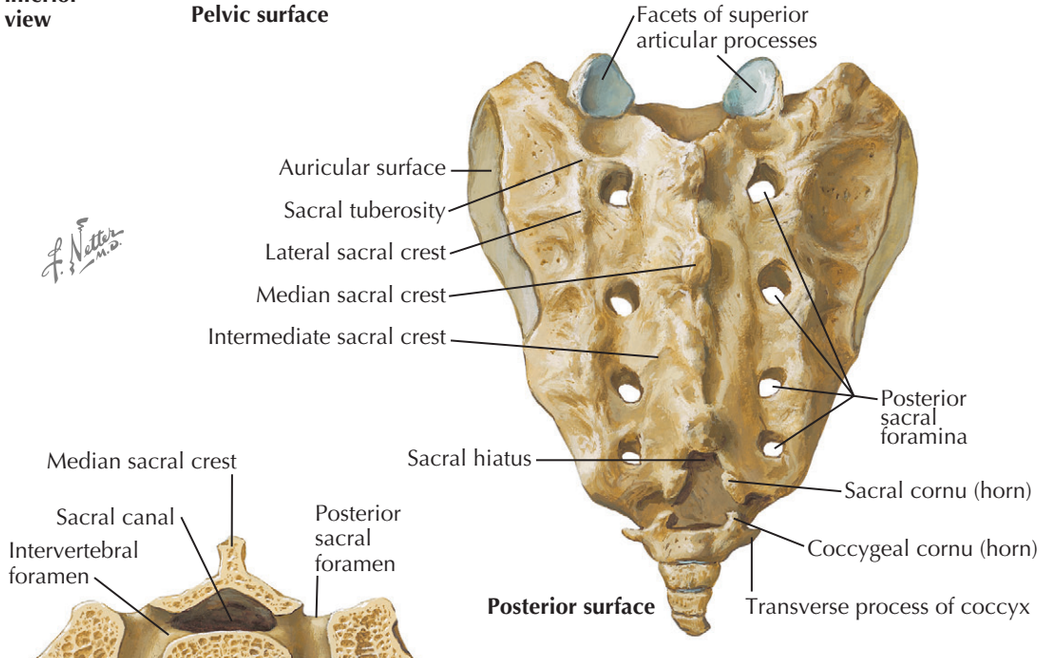
The narrow *apex* is the lower end of the sacrum and articulates with the coccyx. The pelvic surface is concave both vertically and horizontally and shows four *transverse ridges* indicating the lines of fusion between the bodies of the original five vertebrae. On either side of the ridges, four *pelvic sacral foramina* permit the passage of the anterior rami of the first four sacral nerves and their associated vessels.

The convex posterior surface shows irregular *median*, *intermediate*, and *lateral sacral crests* representing, respectively, the fused spinous, articular, and transverse processes. The areas between the median and intermediate crests are the fused laminae, and there are four pairs of *posterior sacral foramina* for the passage of the posterior rami of the upper four sacral nerves. The laminae of the fifth and, occasionally, the fourth vertebra fail to unite and thus leave a *hiatus*, which is exploited for the injection of epidural anesthetics. The hiatus is bounded on each side by a *cornu*, a relic of the inferior articular process, and transmits the small fifth sacral and coccygeal nerves.

The parts of the sacrum lateral to the sacral foramina are produced by the fusion of the costal, transverse, and pedicular elements of the five vertebrae. The upper, broader parts of their lateral surfaces bear uneven *auricular*, or ear-shaped, surfaces for articulation with similar surfaces on the iliac parts of the hip bones. This canal surrounds and protects the terminations of the dural and arachnoid sheaths and the subarachnoid space, which end at about the level of the second sacral vertebra and enclose the sacral and coccygeal roots of the cauda equina and the lower intrathecal portion of the filum terminale. The dura mater is separated from the walls of the canal by fibrofatty tissue, fine arteries, and nerves and sacral internal vertebral venous plexuses.

Coccyx. The small, triangular coccyx is formed by the fusion of four (occasionally, three or five) rudimentary tail vertebrae. Its base articulates with the sacral apex, and its apex is a mere button of bone. Most of the features of a typical vertebra are lacking, but the first coccygeal vertebra has small *transverse processes* and a *cornu* on each side, which is sometimes large enough to articulate with the corresponding sacral cornu. Transverse sections of the sacrum reveal the triangular sacral end of the *vertebral canal*.





Ligaments of Sacrum and Coccyx

Because the lumbosacral and sacroiliac joints transmit the entire weight of the body to the hip bones and thence to the lower limbs, their ligaments are most important.

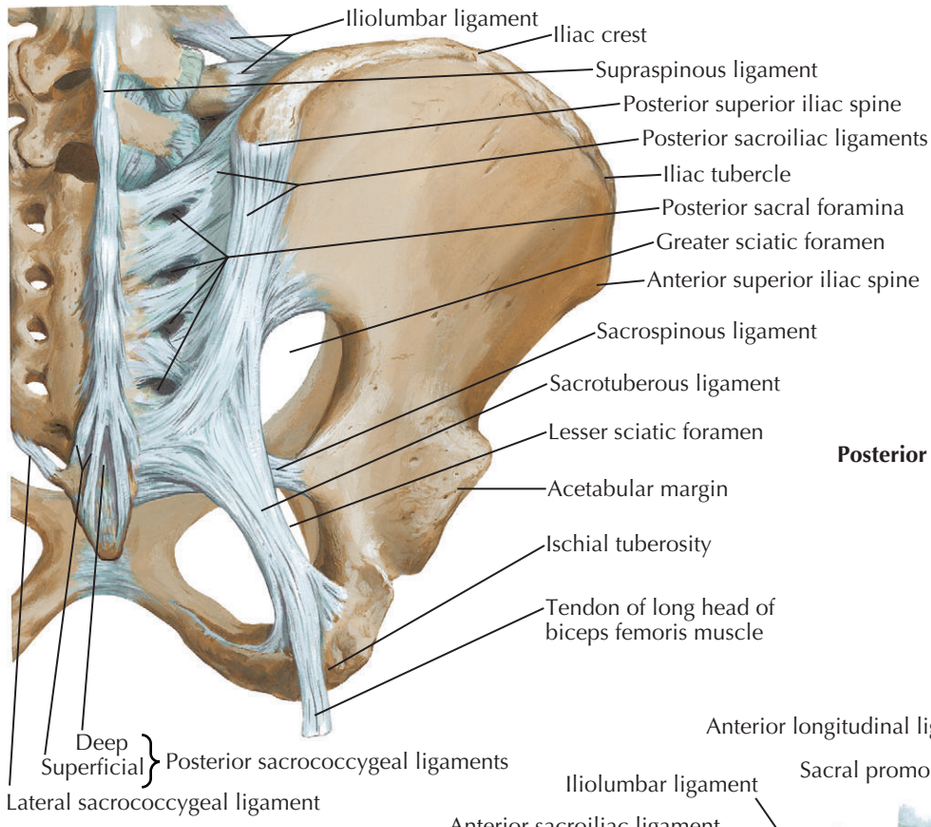
The lumbosacral junction is mechanically imperfect because of its angulation and the consequent sloping platform provided for the fifth lumbar vertebra by the first sacral vertebra (see Plate 3-9). The tendency to subluxation (spondylolisthesis) is resisted by the impingement of the almost sagittally arranged lumbosacral articular processes, and this bony check is strongly augmented by the last *intervertebral disk*, the *anterior* and *posterior longitudinal ligaments*, the *ligamenta flava*, and the *supraspinal* and *interspinal ligaments*. These ligaments are further reinforced by the erector spinae and other muscles and by the *iliolumbar ligaments*, which are strong bands uniting the transverse processes of the fourth and fifth lumbar vertebrae and the posterior parts of the iliac crests and sacral alae. The iliolumbar ligaments are really the expanded lower margins of the anterior and middle layers of the thoracolumbar fascia that encloses the quadratus lumborum muscles. They blend below with the anterior sacroiliac ligaments.

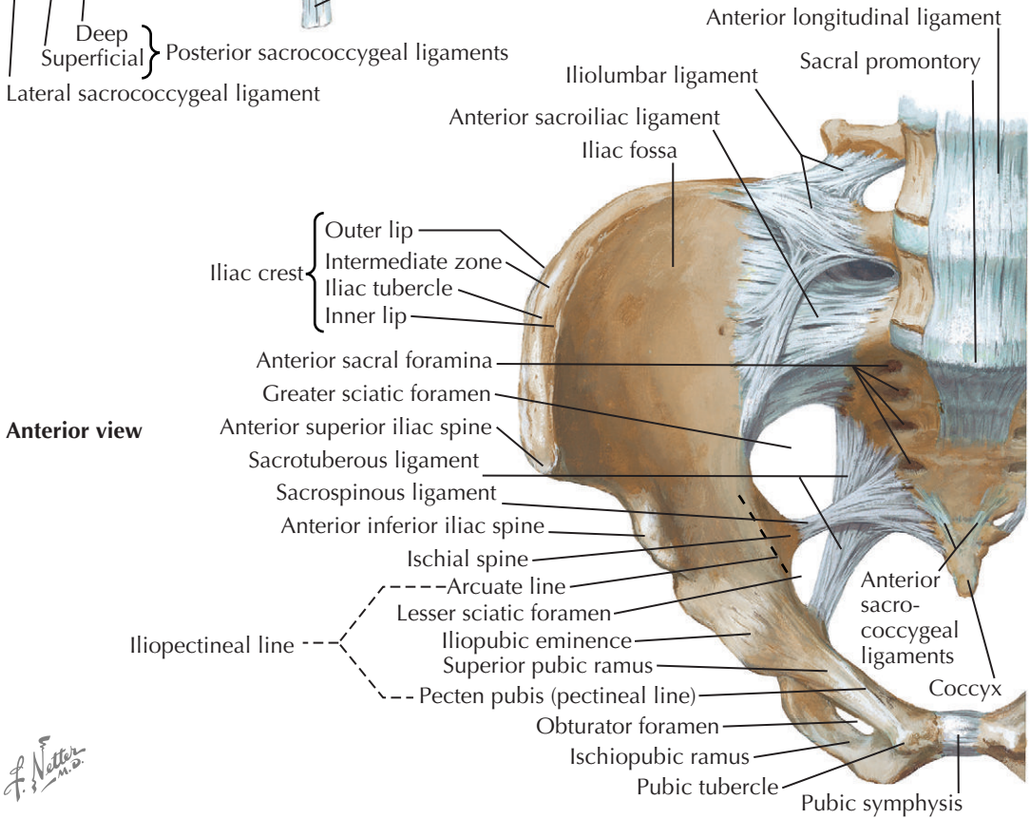
The sacroiliac joints between the auricular surfaces of the sacrum and ilia are synovial in type. Movements are limited, however, because of the interlocking elevations and depressions on the opposed articular surfaces, the way the sacrum is wedged between the hip bones, and the restraining influence of the anterior, posterior, and interosseous sacroiliac ligaments and the accessory sacrotuberal and sacrospinal ligaments.

The anterior *sacroiliac ligament* is a thin, wide, fibrous layer reinforcing the anterior part of the articular capsule and stretching from the ala and pelvic surface of the sacrum to the adjoining parts of the iliac bone.

The posterior *sacroiliac ligament* consists of more superficial, longer bundles and deeper, shorter bundles. The fibers of the long posterior sacroiliac ligament interconnect the posterior superior iliac spine and the lateral parts of the third and fourth sacral segments; its outer fibers interdigitate with those of the sacrotuberal ligament. The short posterior sacroiliac ligament interconnects the medial surface of the iliac bone to the lateral parts of the first and second sacral segments and is often considered to be a part of the interosseous ligament.

The *interosseous sacroiliac ligament* is formed by short, thick bundles of fibers interconnecting the sacral and iliac tuberosities—the rough areas behind and above the auricular surfaces of both bones. It is the most powerful bond between the bones and, indeed, is one of the strongest ligaments in the body. It lies deep to the posterior sacroiliac ligament and is not shown in the illustration.



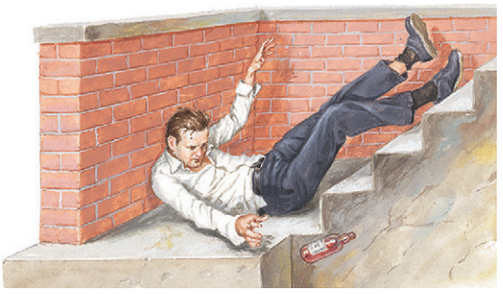


The *sacrotuberal* and *sacrospinal ligaments* act as accessory ligaments of the sacroiliac joints because they assist in regulating joint movements. The downward thrust at the lumbosacral junction tends to push the upper part of the sacrum down, with coincident upward tilting of its lower part as the sacrum seesaws on a transverse axis through the middle of the sacroiliac joints. The illustration shows how these accessory ligaments anchor the lower sacrum and coccyx to the ischial tuberosity and spine, thus limiting the seesaw movement.

The sacrum and coccyx are connected by a small, fibrocartilaginous *intervertebral disk* and by thin bands on the anterior, posterior, and lateral sides of the junction—the *anterior*, *posterior*, and *lateral sacrococcygeal ligaments*. The posterior ligament has a superficial part, which partly fills in the sacral hiatus, and a deep part, which represents the posterior spinal longitudinal ligament.

Mechanism

Head-on collision with stationary or moving object. Occupant not restrained by seat belt: head strikes steering wheel, windshield, or roof. Head hyperflexed on trunk.



Blow to back of head from falling against hard surface when balance is compromised

Distractive Flexion

Distractive flexion refers to acute, severe flexion of the neck with associated rotation and is one of the most commonly seen spinal injuries. The posterior ligaments are injured initially, manifested as a widening of the distance between two spinous processes. With increasing degrees of force, the facet capsules are disrupted, and there is shearing through the posterior longitudinal ligament, the disk space, and the anterior longitudinal ligament.

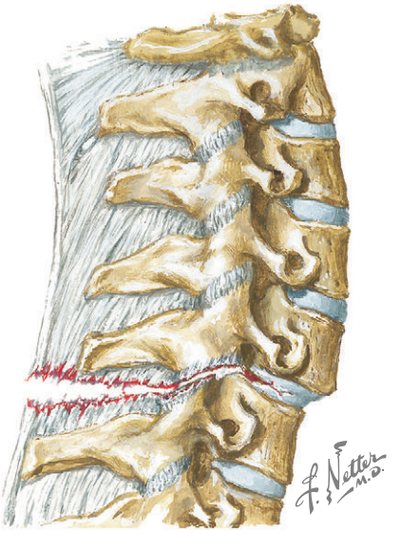
In the first phase of injury, the posterior ligaments fail, allowing the facets to displace anteriorly. In the second phase, there is unilateral facet dislocation as the interspinous ligament, facet capsule, and posterior longitudinal ligaments give way. With further force, the second facet capsule ruptures and bilateral facet dislocation occurs.

Approximately one third of spinal cord injuries occur as a result of distractive flexion forces, and the injuries are typically complete, especially with bilateral facet dislocation (see Plates 2-16 to 2-20).

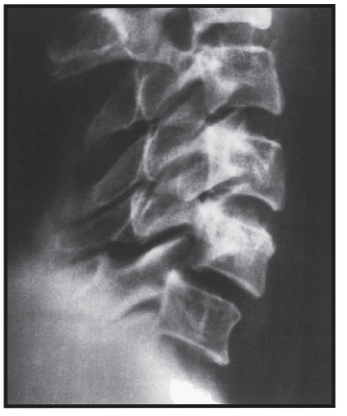
Radiographically, unilateral or bilateral facet dislocations are typical, with associated vertebral body subluxation. The difference between these injuries is readily distinguishable radiographically. With a unilateral facet dislocation, there is approximately 25% anterior subluxation of one vertebral body on another. With bilateral facet dislocation, there is greater than 50% anterior subluxation. These injuries are generally highly unstable, are associated with significant neurologic deficits and commonly require internal reduction and stabilization.

Traction will usually reduce a unilateral facet dislocation. If there are fractures of the facet, once realignment has been accomplished, treatment with a halo may allow for stable healing. Bilateral locked facets are rarely reduced with traction and can be treated through an anterior or posterior surgical approach. On occasion, both anterior and posterior surgical approaches are required to achieve reduction and stabilization.

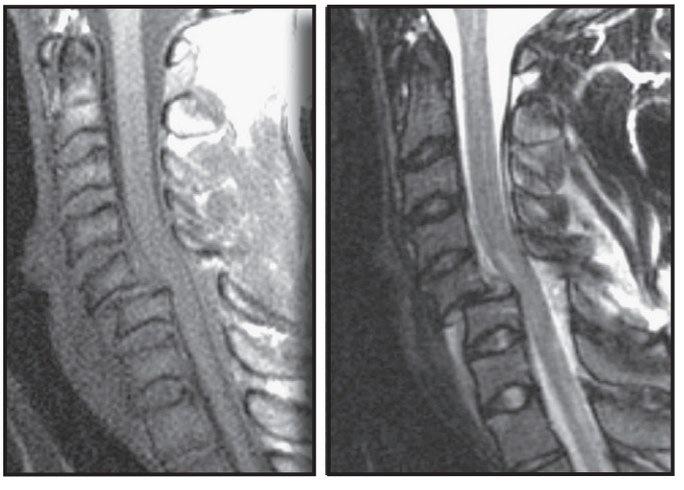
There is, however, one significant caveat in the use of traction with facet dislocations. It has been reported that up to 25% of these patients will have an associated traumatic herniated disk at the level of injury. Realigning the spine in the face of an anterior compressive mass, such as a traumatic herniated disk, could potentially result in additional spinal cord compression and further spinal cord injury. It has thus been recommended that patients with facet dislocations and an incomplete spinal cord injury syndrome undergo magnetic resonance imaging (MRI) to look for a traumatic herniated disk before realignment is attempted.



Anterior dislocation of C5-6 with tear of interspinal ligament, facet capsules, and posterior fibers of intervertbral disk

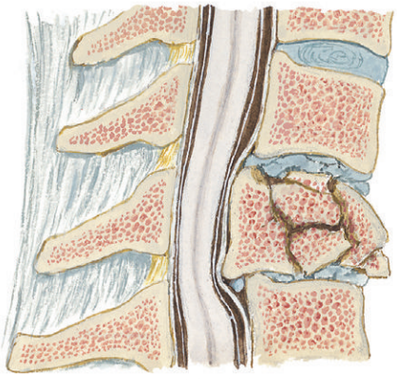


X-ray film (lateral view) showing bilateral interfacet dislocation at C5-6



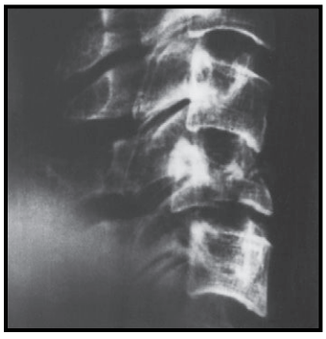
MRI of the cervical spine demonstrating subluxation of C4-C6 consistent with bilateral facet dislocation. There is an associated small acute traumatic disk herniation as well as hyperintense signal cord at the level of the injury.

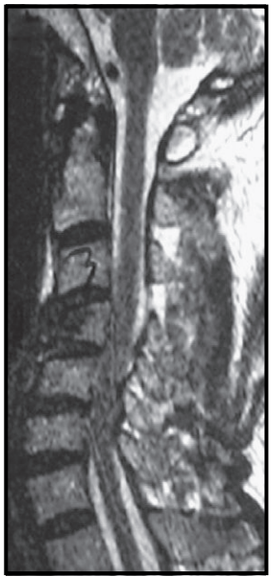
Mechanism. Vertical blow on head as in diving or surfing accident, being thrown from car, or football injury.



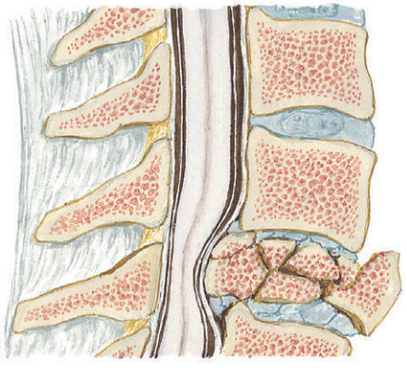
Burst fracture with characteristic vertical fracture through vertebral body

Radiograph showing fracture of C5

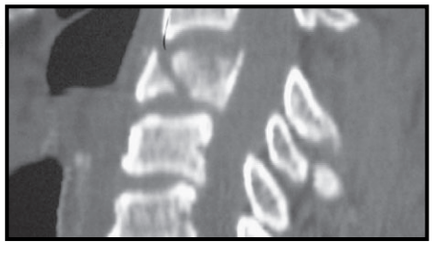




Sagittal MRI of a C4 burst fracture showing swelling of the spinal cord from C4-6



More severe trauma explodes vertbral body. Posteriorly displaced bone fragments frequently produce spinal cord injury.



Sagittal reconstructed CT in a patient with a C4 burst fracture demonstrating an anterior fracture line with retropulsion of bone into the spinal canal

Compressive Flexion

Compressive flexion injuries occur when there is a combination of axial loading (vertical compression) associated with acute severe flexion of the neck. Such an injury may occur in patients diving into shallow water or being thrown from a moving vehicle. With lesser degrees of force, there is typically only compression of the anterior aspect of a vertebral body; however, as the forces increase, the vertebral body "bursts," and retropulsion of bony fragments into the spinal canal results in severe neurologic injury.

Initially, as force is progressively applied, there is blunting of the anterosuperior aspect of the vertebral body, with the subsequent development of oblique fracture lines through the centrum of the body. Eventually, there is fragmentation of the centrum with peripheral displacement of the bony fragments.

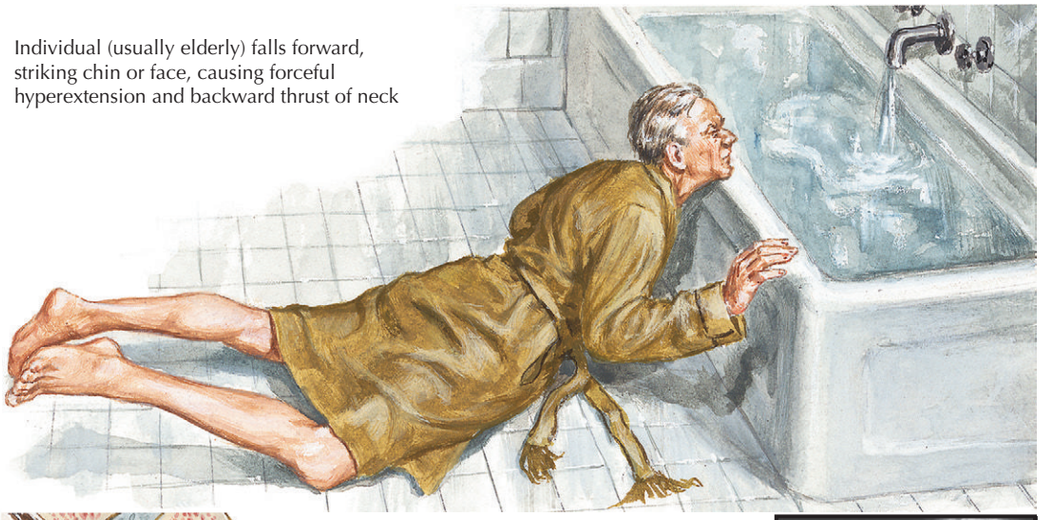
This biomechanical mechanism reinforces the three-column theory of spinal stability. The anterior column extends from the anterior longitudinal ligament to the midpoint of the vertebral body. The middle column includes the posterior half of the vertebral body and the posterior longitudinal ligament. The posterior column includes pedicles, lamina, facets, and spinous processes along with all supporting ligaments. Any injury involving two of the three columns is generally unstable.

Compressive failure of the anterior aspect of the vertebral body rarely leads to neurologic injury. However, with ligamentous failure and posterior movement of the vertebral body, the incidence of complete spinal cord injury significantly increases (see Plates 2-16 to 2-20). Approximately one third of spine injuries result from compressive flexion, with a high occurrence at the mid-cervical levels.

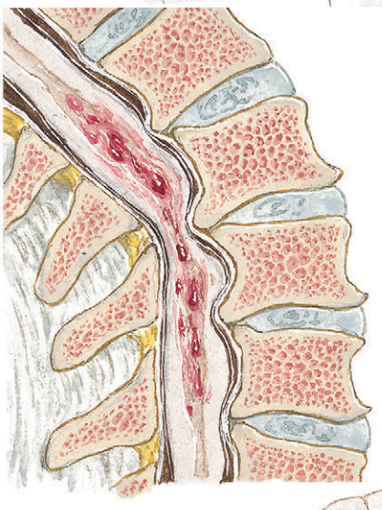
Traction is rarely indicated, unless there is an associated facet dislocation or other injury that might be amenable to realignment. Magnetic resonance imaging (MRI) scan will clearly show the degree and extent of spinal canal compromise as well as blood and/or edema within the spinal cord.

Compressive flexion injuries comprise approximately one third of cervical spine injuries and most commonly occur at the C4-5 and C5-6 levels.

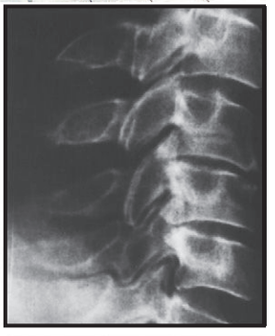
Anterior vertebral body compression and minor burst fractures may be treated with external orthoses such as the halo. These types of fractures will heal stably in more than 70% of patients. Burst fractures with greater than 3 mm retropulsion and significant canal compromise usually require anterior and, on occasion, posterior operative decompression and stabilization as well. Such is also the case if there has been significant associated ligamentous disruption.



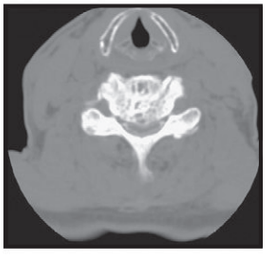
Individual (usually elderly) falls forward, striking chin or face, causing forceful hyperextension and backward thrust of neck



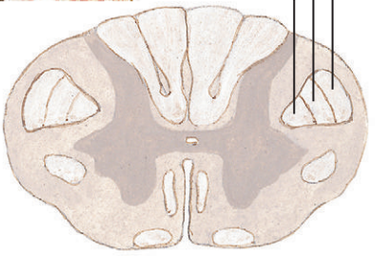
Osteophytes compressing spinal cord. Hyperextension injury results in cord contusion, self-destructive edema, and intramedullary hemorrhage with rapidly developing quadriplegia.



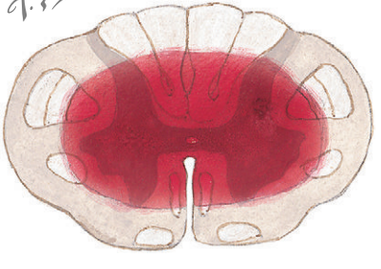
Radiograph (lateral view) showing osteophytes



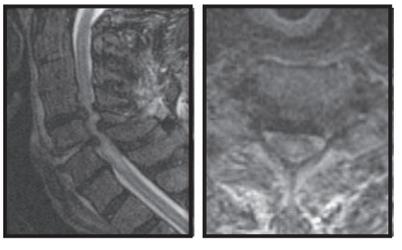
Typical CT findings in a patient with central cord syndrome. On axial view the spinal canal is reduced to 7 mm (normal, 15 mm) by a large osteophyte.



Section of cervical spinal cord showing orientation of fibers in lateral corticospinal tracts



Central cord syndrome: central hemorrhage may damage medial part of lateral corticospinal tract and anterior horn cells, resulting in paralysis of upper limbs, leaving lower limbs intact



Sagittal *(left)* and axial *(right)* MRIs in a patient with central cord injury. Although there is not acute traumatic injury, the spinal canal is significantly narrowed at C4-6 by anterior osteophytes and posterior in-buckling of the ligamentum flavum.

Distractive Extension

Distractive extension injury occurs with acute hyperextension of the spine. In its most minor form, this is termed a "whiplash" injury. In its more severe form, a common scenario for such an injury is the elderly patient with preexisting cervical spondylosis or stenosis who falls, striking the forehead. There is usually no traumatic radiographic abnormality. The spinal cord is pinched between the anterior osteophytes and the in-buckled ligamentum flavum. There are varying degrees of associated injury, including the central cord syndrome (see Plates 2-16 to 2-20). The vertebral injury is rarely unstable, but surgical intervention may be indicated in an attempt to improve neurologic recovery.

In its more severe forms, the forces producing distractive flexion result in progressive anterior to posterior ligament failure in one or more cervical motion segments. With complete ligamentous failure, the upper vertebrae displace posteriorly, creating significant spinal canal narrowing. When there is no significant bony injury, the ligamentous disruption may be very difficult to detect. With patients in the neutral position, there may very well be no subluxation. Thus magnetic resonance imaging (MRI) is strongly indicated when this mechanism of injury is suspected.

This type of injury pattern occurs in only 1% to 5% of all spine injuries.

Compressive Extension

Compressive extension involves axial loading in association with hyperextension. This may produce injuries as minor as a laminar fracture or as severe as the highly unstable "teardrop" fracture. In the latter, the anterior longitudinal ligament is ruptured, avulsing a small bone fragment from the superior aspect of a vertebral body and causing fractures of the lateral masses, pedicles, and lamina.

As force progressively increases, there may be a linear fracture through the facet in association with a pedicle and laminar fracture; bilateral posterior arch fractures and ultimately ligamentous injury. The majority of the most unstable fractures occur at the C6-7 level and account for less than 5% of spine injury.

A comparative study was undertaken of patients with distractive flexion and compressive extension cervical spine injuries. There was no significant difference with respect to severity of injury, level of injury, or neurologic sequelae. Sixteen percent of patients with either type of injury suffered complete spinal cord injury.

Cervical Spine Injury: Prehospital, Emergency Room, and Acute Management

Prehospital Management

Spinal injury may lead to neurologic impairment from *spinal cord involvement*. Initial management of a patient suspected of having a spinal cord injury begins at the accident scene, with early, aggressive resuscitation and spinal immobilization. Altered mental status, focal neurologic deficits, intoxication, spinal pain or tenderness, and/or distracting injuries are all potential risk factors for spinal cord injury (see Plates 2-16 to 2-20) and indications for immobilization. Up to 10% of spinal cord injuries occur after the initial traumatic injury, during extrication, transport, or early in the course of management.

The entire spinal column is at risk; 15% of fractures are multiple and involve different spinal segments. The cervical spine can be partially immobilized by a hard cervical collar, but the efficacy of a collar is limited unless used with a hard, full-length backboard. A wide variety of hard cervical collars are available; superiority of one over another has not been shown. Immobilizing the cervical spine is accomplished by simultaneous control of head and trunk motion. This is most reliably accomplished by combining a hard cervical collar with a full-length backboard. Bolsters (or, alternatively, sandbags) on either side of the neck, secured by straps (or tape) across the head, maximally limits movement of the neck, whereas strapping the rest of the body to the backboard prevents truncal movement. This appears to provide the most safe and effective method of spine immobilization for transport.

Airway protection is paramount. If intubation is necessary, in-line cervical traction with efforts to minimize cervical extension should be undertaken, if at all possible. Immobilization precautions must be taken until spinal injury can be excluded or more definitive spine treatment initiated. It is important, however, to remove the backboard as soon as possible, keeping the patient on a firm padded surface while maintaining spinal alignment. In an insensate patient with spinal cord injury (SCI), skin breakdown, leading to decubitus ulcers, can begin within 2 hours of lying on a hard backboard. When transfers are necessary, the technique of logrolling should be employed in an attempt to maintain spinal alignment.

In certain patients with preexisting spinal deformities, providing care in the position of greatest comfort for the patient may take precedence over maximum spinal stabilization.

Emergency Room and Acute Management

Initially, it is important to follow advanced trauma life support (ATLS) evaluation and resuscitation protocols, determine the degree and extent of neurologic loss, and prevent any further loss of function. This is accomplished by ensuring an adequate airway and oxygenation, establishing and maintaining a systolic blood pressure greater than 90 mm Hg, serial complete neurologic examinations, radiographic identification of the degree and extent of spinal column injury, spinal realignment, and ensuring acute stabilization.

The most widely used neurologic examination protocol is that of the American Spinal Injury Association (ASIA). Sensory examination includes testing of all sensory modalities across the 28 dermatomes from C2 to S5. The major muscle groups are tested in the arms and legs and graded from 0 (no movement) to 5 (normal active movement against full resistance). The neurologic findings direct the radiographic assessment.

Plain spine radiographs have for the most part been supplanted by computed tomography (CT) scanning with reconstruction. Even if the CT findings are "normal," magnetic resonance imaging (MRI) is always indicated in the presence of SCI to look for traumatic herniated disks, intraspinal hematomas, or significant ligamentous injury.

There continues to be controversy over the pharmacologic treatment of SCI. The National Acute Spinal Cord Injury Studies (NASCIS) demonstrated statistically significant improved neurologic recovery if methylprednisolone was administered within 8 hours of injury. However, the functional significance of this recovery has been questioned, and meta-analysis of published data fails to confirm any benefit of this approach. If methylprednisolone is to be used, the loading dose is 30 mg/kg, with a maintenance dose of 5.4 mg/kg/hr for 24 hours.

It is important to be vigilant for the presence of neurogenic shock and provide appropriate treatment. With mid-level to high-level cervical SCI, there is loss of sympathetic function and associated loss of vascular tone. This can result in significant pooling of blood in the lower extremities and associated hypotension. Volume resuscitation is ineffective in this setting, and pressors must be utilized early. Because SCI patients may also have multiple injuries, the distinction between hypovolemic and neurogenic shock must be recognized. In hypovolemic shock, there is tachycardia, cold clammy skin, altered mental status, and low urine output. In neurogenic shock, there is bradycardia, warm dry skin, normal mental status, and normal urinary output.

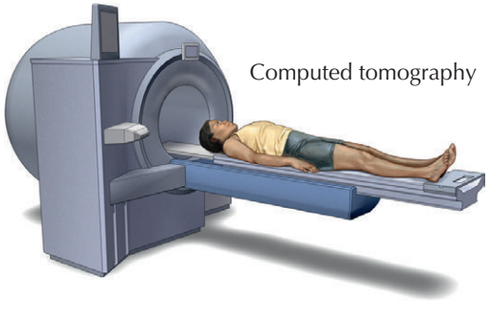
Once the SCI patient has been stabilized, the specific treatment required for the spinal injury is determined. Certain injuries may be treated with traction and bracing, whereas others require surgical intervention.

Treatment at site of accident

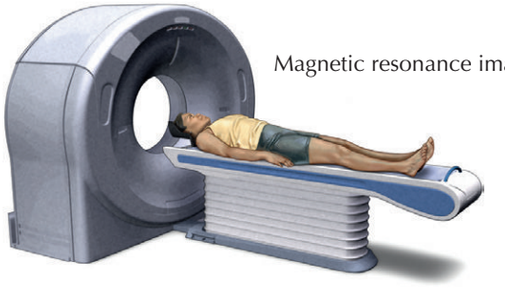
Patient's head is held securely between attendant's elbow, and shoulders are supported by attendant's hands during lift. Cervical collar applied before lift.

Three-man lift: useful if limited help available for placing patient on board or carrying patient short distances. Head, trunk, and legs must be aligned in straight line, and head must be supported from underneath and laterally.

Emergency room and acute management

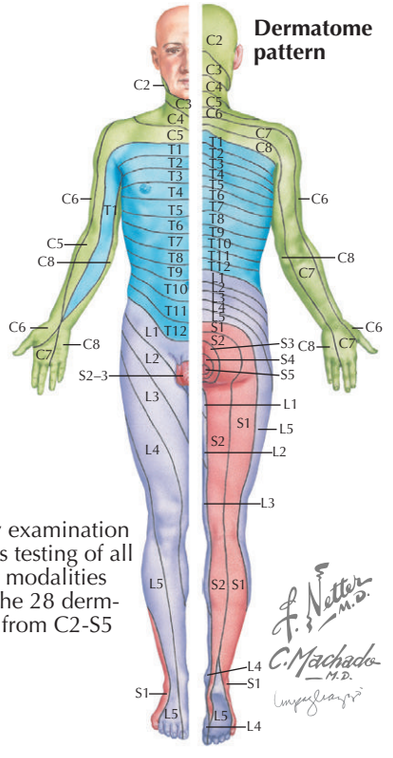


Computed tomography



Magnetic resonance imaging

CTs and MRIs are used more than plain spine-xrays, to look for traumatic herniated disks, intraspinal hematomas, or significant ligamentous injury



Sensory examination includes testing of all sensory modalities across the 28 dermatomes from C2-S5

A halo vest is frequently used to treat many types of bony cervical spine injury

A molded thoracolumbosacral orthosis (TLSO) vest can be used to treat spine injuries from the upper thoracic spine to the lower lumbar spine

Traction and Bracing

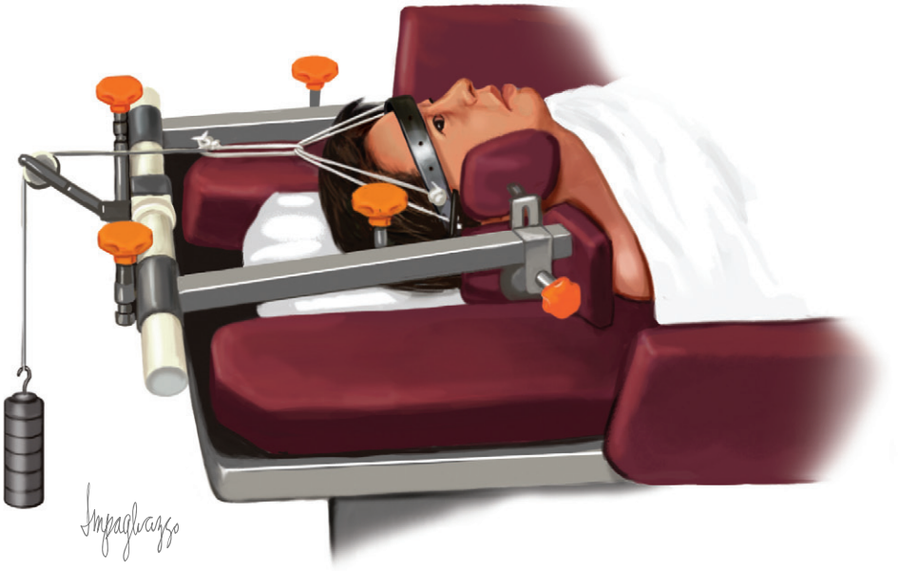
Opinions vary on the means and methods of spinal realignment in patients with cervical spine subluxations. Various techniques have been advocated to realign the spine and decompress the spinal canal in an effort to preserve or improve neurologic function and recovery. In 1933, Crutchfield first used cranial tongs for spinal realignment. This device or various modifications remained in widespread clinical use for five decades. In 1973, the Gardner-Wells tongs were introduced, and the ease of their use led to widespread adoption. Gardner-Wells tongs are still used occasionally, and a graphite version compatible with magnetic resonance imaging (MRI) is available. The most common device in clinical use today is the MRI-compatible halo ring. Because the halo device is frequently used as the definitive treatment for many types of cervical spine injury, its use for spinal realignment expedites treatment. Halo ring placement requires both local anesthesia and intravenous sedation to minimize patient discomfort. Four skull pins are needed. The ring should be sized for 1 cm of clearance between the scalp and the ring around the circumference of the head. The frontal pins are typically placed 1 cm above and just lateral to the supraorbital notch so as to avoid injury to the supraorbital and supratrochlear nerves and the frontal sinus. The patient should be asked to close the eyes as tightly as possible so as to minimize retracting the forehead skin, which would make subsequent eye closure difficult. The occipital pins are placed several centimeters behind and in line with the tops of the ears.

The pins are first tightened by hand, then with a torque wrench to 6 to 8 lb to engage the outer table of the skull. The torque should be rechecked within the next 48 hours.

Few problems have been associated with acute halo use, the most significant being pin loosening and pin infection, occurring in up to 25% of instances. This is generally manifested by local pain and discomfort and is helped by careful daily cleaning of the pin sites.

After the halo has been applied, the amount of traction to be used must be determined. A very general guideline is no more than 5 lb of traction per injury level so that 30 to 35 lb may be used for an injury at C6-7. On a practical level, however, for injuries such as bilateral locked facets, up to 80 to 90 lb may be necessary to achieve reduction.

Once traction is instituted, it is important to monitor response by clinical findings and radiographic studies. It is a generally accepted procedure to add cervical traction in increments of 5 to 10 lb every 20 to 30 minutes until reduction is achieved, there is clinical or radiographic evidence of overdistraction, or a maximum weight has been reached. Because there is often significant cervical muscle spasm, it is may be necessary to administer muscle relaxants to aid in realignment.



A halo ring can be used to stabilize cervical fractures that will require operative intervention or by applying traction that can reduce cervical spine subluxations

For certain injuries, especially those with a significant ligamentous disruption, such as atlantoaxial dislocation, any traction may be contraindicated. A specific concern over bilateral facet dislocation is the possibility of an associated traumatic disk herniation, estimated by some to be as high as 25%. Realignment of the spine in such a setting could cause significantly increased spinal cord compression. Although not universally agreed, obtaining an MRI before the application of traction is advisable.

Traction is not used for thoracolumbar spine injuries. Those injuries not requiring internal stabilization are generally successfully treated with a thoracolumbosacral orthosis. For injuries involving the lumbosacral junction, a hip extension added to the orthosis provides increased stability.

Anterior Cervical Spine Decompression and Stabilization

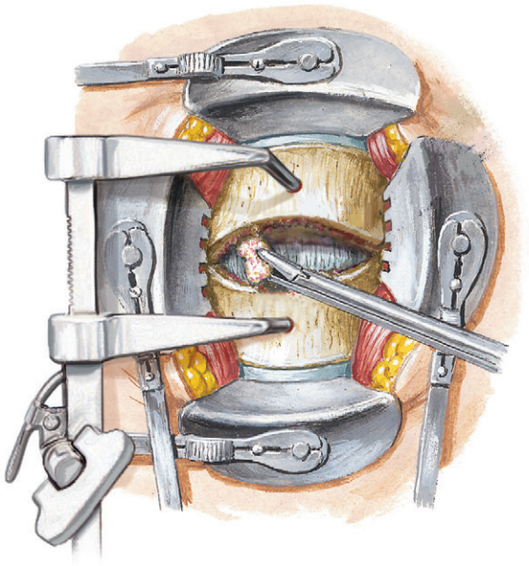
Although a significant number of traumatic cervical spine injuries may be treated with external immobilization—that is, a halo vest or hard cervical collar—there are certain types that require internal stabilization with or without decompression. The types of such injuries which most often require an anterior approach include certain odontoid fractures, traumatic disk herniations (with pain or neurologic deficit), burst fractures, and teardrop fractures.

The surgical approach to the anterior cervical spine has not significantly changed for decades, but the various means of stabilization have changed dramatically. Typically, a transverse incision centered on the medial boarder of the sternocleidomastoid muscle, is made on the right side of the neck. Special precautions, however, may be necessary in a spinal cord injury (SCI) patient who has already required tracheostomy. The platysma is divided, and the sternocleidomastoid is sharply dissected from the medial strap musculature down to the prevertebral fascia, which is often swollen and filled with hematoma from the underlying injury. Retractors are used to protect the carotid artery laterally and the esophagus medially. The prevertebral fascia is bluntly dissected off the anterior longitudinal ligament, which may be disrupted from the injury. Even if the injury is obvious, a lateral plain radiograph (or fluoroscopy) is done to confirm the operative level.

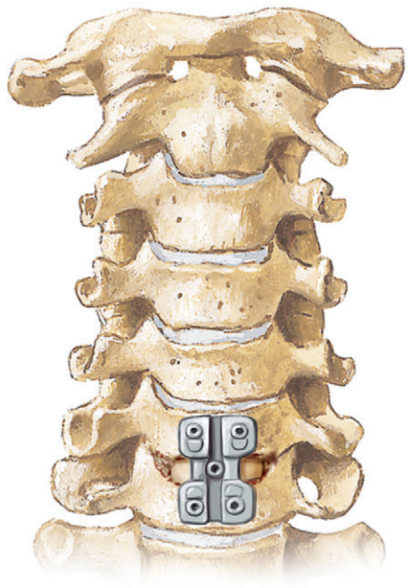
If the primary injury is a traumatic herniated disk, the affected disk space is incised and the disk material and end plates of the vertebral bodies above and below are removed in piecemeal fashion using pituitary rongeurs and curettes. Most surgeons use an operating microscope to visualize the posterior aspect of the disk space. Once the disk is removed, the anterior longitudinal ligament—unless already breached by the injury—is removed and complete decompression of the dura is observed. The spine is then stabilized by using a proper-sized piece of allograft bone. A few surgeons still prefer autogenous bone, but for most patients, the discomfort from iliac crest bone harvesting (unless insensate from SCI) outweighs any advantages. The bone is securely wedged between the affected vertebral bodies.

Although stable fusion rates are high with this approach, supplementation with an anterior cervical titanium plate, secured by screws into the affected vertebral bodies, has become popular in recent years. This follows the general biologic principle of bone healing: the two elements of most importance in achieving a bony fusion are compression and immobilization. A wide variety of plates are available; all provide for immediate compression and immobilization, with subsequent high fusion rates.

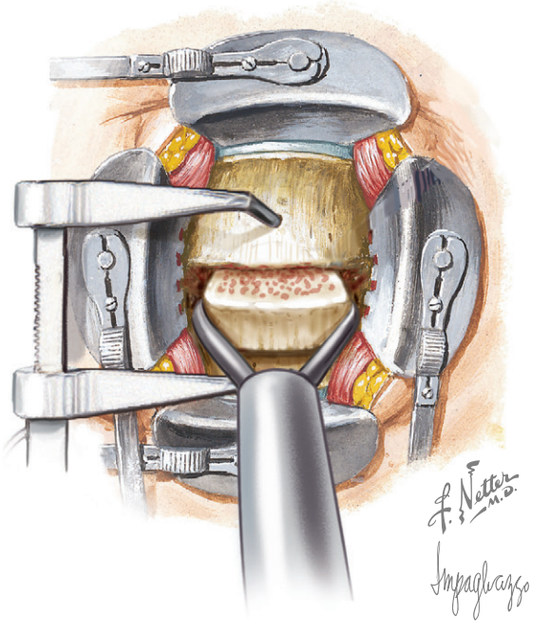
For burst fractures at single or multiple levels, an anterior approach is required to adequately decompress the spinal canal. The approach is the same as for a diskectomy, but all portions of the affected bone are removed. Before the late 1990s, the most common form of reconstruction of the spine after corpectomy was with an iliac strut or fibular graft with or without supplementation by an anterior plate. More recently, there has been increasing use of interbody cages, which are intended to provide immediate structural stability. The cage is generally packed with osteoinductive or osteoconductive materials to facilitate fusion.



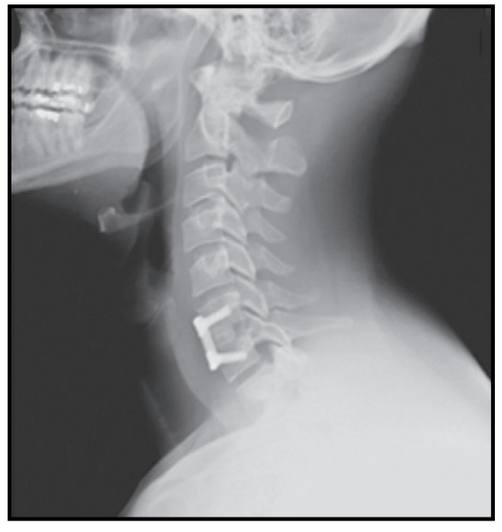
Spine exposed by progressive dissection and self-retaining retractors inserted. Disk, osteophytes, and bone fragments removed piecemeal.



Fusion completed with titanium compression plate and screws



Autogenous bone graft wedged securely in intervertebral space



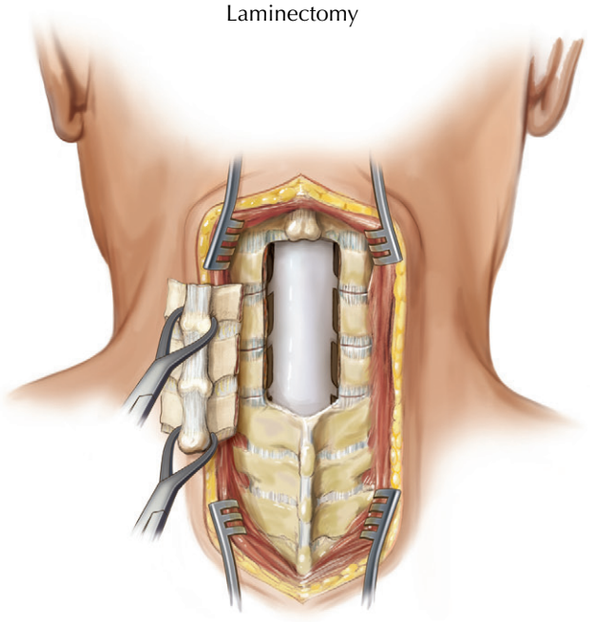
Lateral cervical radiograph demonstrating anterior cervical interbody fusion and plating at C6-7

Tear drop fractures are unstable anteriorly and posteriorly due to disk and ligamentous injury. Thus both an anterior stabilization—cervical diskectomy and fusion with plate—and posterior stabilization are required.

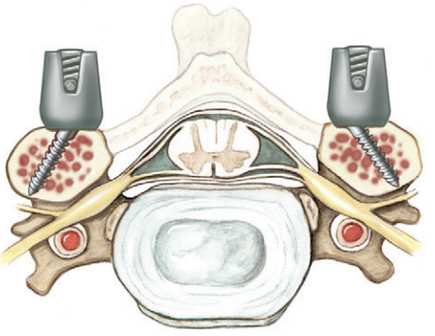
For unstable odontoid fractures, anterior screw fixation may be quite appropriate. As opposed to posterior fixation, this preserves C1-2 mobility and may be better tolerated. A small incision is made near the C5-6 level and, under biplanar fluoroscopy, a guide is passed up to the C2-3 level. Through the guide, a small pilot hole is drilled into the base of C2. An appropriate-length screw is then passed to the tip of C2. If reduction of the fracture is desired, a lag screw will pull the fracture fragments together. Success of fusion exceeds 90%.

Complications from anterior decompression and stabilization are generally acceptable. Development of new neurologic dysfunction occurs generally in less than 2% of cases. Issues related to carotid or esophageal injury are likewise small. The risk of a significant infection leading to diskitis or osteomyelitis is less than 1%. On rare occasions, there can be failure of the fusion/plate/cage construct, leading to injury to surrounding neck structures, instability, and the need for reoperation.

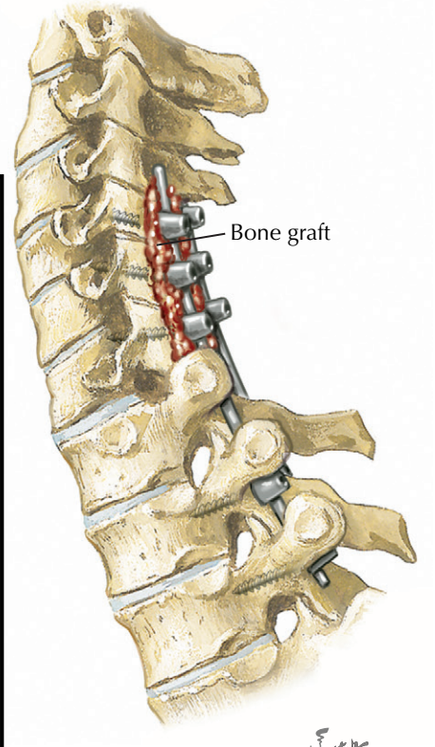
Laminectomy

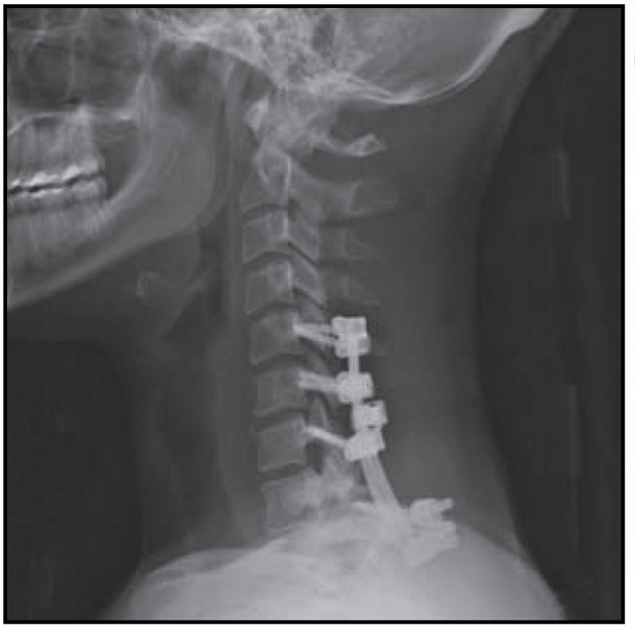


Placement of screws



Placement of rod system





Lateral cervical spine radiograph after posterior decompression and pedicle screw fixation from the midcervical to the upper thoracic spine

Posterior Cervical Stabilization and Fusion

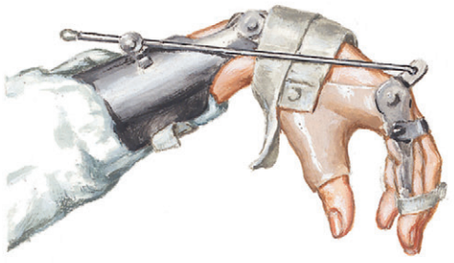
In the 1940s, posterior cervical spinal stabilization was generally limited to interspinous process wiring and bone fusion. Gallie popularized C1–C2 fusion using fine steel wires around the lamina or spines and leaving a bone graft between the spines, tightening the wires over it. Brooks further refined this technique However, neither of these procedures prevented rotation at the level of the injury, leading to the development of techniques of intrafacetal wiring that eventually evolved into the use of various forms of plates and screws.

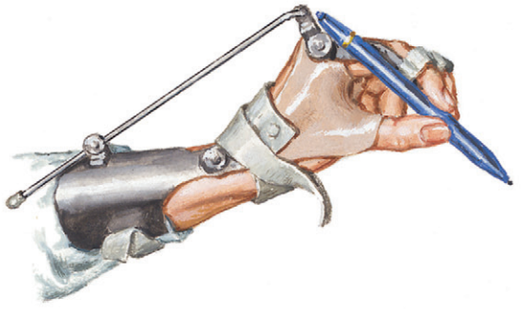
Regardless of technique, the ultimate goal is to achieve a stable bony fusion in flexion, extension, and rotation as soon as possible. Metallic internal fixation devices provide stability and increase the fusion rate. Plates and screws can be used to stabilize temporarily the cervical spine from the occiput to C7. Screws can be placed into the C2 pedicles, the C1-2 facets, and the C3-7 lateral masses, and various forms of plates are available to add strength to the metal construct. The screws, fixed on each side, can also be connected together by a metal rod on each side of the spine (Plate 3-17).

Operative exposure is common to all levels of the posterior cervical spine, using a midline cervical incision with dissection of the paraspinal musculature and bony exposure at the affected levels. On most occasions, the only bone work necessary is eburnation of the bony surfaces to facilitate fusion. On occasion, a laminectomy may be necessary for spinal decompression, for example, for central cord syndrome from spinal stenosis. If there is significant facet subluxation, with "locking" of the facets, it is usually necessary to drill off the superior aspect of the affected inferior facet to allow reduction of the subluxation.

For lateral mass screws, the entry point is 1 mm medial to the center of the lateral mass, angled 20 to 30 degrees rostrally and 20 to 30 degrees laterally. Screw placement needs to be precise so as to minimize injury to the vertebral artery or nerve roots.

Cervical Spine Injury: Rehabilitation of Patient





Functional wrist orthotic device aids in prehension and in maintaining metacarpophalangeal alignment. Extension of wrist opposes fingers to thumb, providing grasping action.

Spinal Cord Injury Medical Issues

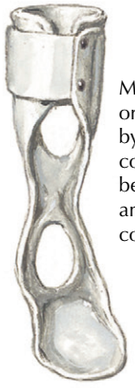
Spinal cord injury (SCI) patients are prone to many medical complications requiring vigilance and preventative strategies. The loss of sensation and immobility leads to a high risk for development of decubitus ulcers. The areas at greatest risk are over bony prominences, such as the sacrum. Prevention requires frequent examination of the areas at risk, use of pressure reduction mattresses (or cushions if the patient is able to be out of bed), frequent repositioning, and education of family or other caregivers. It is also important to regularly check the skin at the edges of orthoses.

Deep vein thrombosis (DVT) occurs in more than 50% of patients who do not receive prophylactic measures. The first-line preventive measure are mechanical compression devices on the lower extremities, but studies have shown that although this minimizes venous stasis, it is relatively ineffective in preventing DVT when used alone. Thus, unless contraindicated, compression devices should be supplemented with low-molecular-weight heparin, such as enoxaparin, or with unfractionated heparin.

Bladder dysfunction from SCI requires a variety of interventions. In acute cases, an indwelling Foley catheter is appropriate and should be used until the patient is hemodynamically stable. However, because of the risk of infection, the catheter should be removed as soon as medically possible and intermittent catheterization substituted. The prophylactic use of antibiotics acutely or chronically does not reduce infection rates.

SCI has been shown to be an independent risk factor for gastrointestinal (GI) ulcers and upper GI bleeding. There are two forms of pharmacologic prophylaxis: histamine H2 receptor antagonists and proton pump inhibitors. Based on present evidence, both are equally safe and effective in preventing stress ulceration in SCI patients.

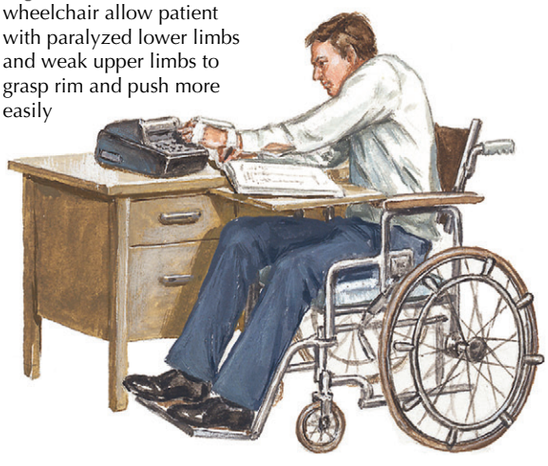
Loss of lower GI motility is universal in SCI patients and requires early attention. Once enteral nutrition is instituted, bowel movements should be facilitated. This requires the use of oral medications, suppositories, and digital stimulation.



Molded polypropylene orthotic device preferred by many patients to conventional braces because of lighter weight and more pleasing cosmetic appearance

Patient wearing conventional double-metal upright below-knee brace for weakness of foot dorsiflexors and evertors

Paraplegic girl wearing full-length lower limb braces, facilitating ambulation by " swing-through " gait



Pegs on hand rim of wheelchair allow patient with paralyzed lower limbs and weak upper limbs to grasp rim and push more easily

Disabled athlete competing in a race

EARLY SPINAL CORD INJURY REHABILITATION

It is important that rehabilitation specialists are involved early in the care of the SCI patient. In acute cases, this is intended to maintain range of motion and to begin strengthening exercises as well as to initiate mobilization, thereby minimizing the risk of joint contracture. In SCI patients with pulmonary problems, respiratory therapists can enhance pulmonary hygiene. Pulmonary interventions, such as suctioning, percussion, vibration, and training of accessory respiratory muscles, reduce the incidence of pneumonia and shorten time in acute care.

One of the primary obstacles to early mobilization is orthostatic hypotension, which limits tolerance to being upright. Nonpharmacologic therapeutic measures include leg-compression stockings, abdominal binders, and a tilt table to gradually elevate the patient as tolerated. Pharmacologic treatments typically include adrenergic agents to enhance vascular tone.

Attention to skin integrity is important during the process of mobilization. SCI creates a number of psychologic, psychosocial, and family issues. These may include grief and denial reactions, major depression, and, in the most severe cases, decisions to remove life support. It is thus important to provide psychologic and social services support to the patient and family.

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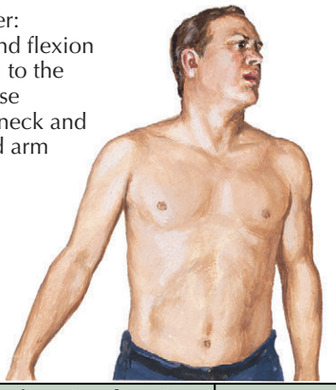
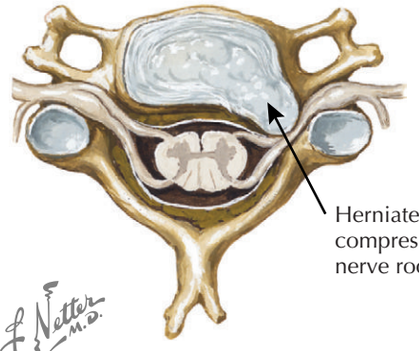
NERVE ROOTS AND PLEXUS DISORDERS

Cervical Disk Herniation

Spurling maneuver: hyperextension and flexion of neck ipsilateral to the side of lesion cause radicular pain in neck and down the affected arm





Level	Motor signs (weakness)	Reflex signs	Sensory loss
C5	Deltoid	None	
C6	Biceps brachii	Biceps brachii; Weak or absent reflex	
C7	Triceps brachii	Triceps brachii; Weak or absent reflex	
C8	Interossei	None	

Cervical disk disease is a common disorder, accounting for 1% to 2% of all hospital admissions in the United States. Unlike lumbar disk disease, which is approximately six times more common, cervical disk disease is rarely caused by trauma. In fact, severe degenerative cervical disk disease often develops in indolent patients.

Etiology. Cervical disk disease is likely multifactorial, with contributing factors ranging from advancing age to neck trauma to heavy lifting to smoking. The nucleus pulposus in the middle of the disk dehydrates with age, placing more stress on the circumferential annulus fibrosus. Tears in the annulus may permit a sudden herniation of the nucleus—a *ruptured disk.* Alternatively, chronic annular bulging or nuclear herniation may incite a bony reparative process (spondylosis), leading to the formation of extensive bony spurs (osteophytes). These spurs are generally located along the anterior portion of the disk interspace or posteriorly, within the intervertebral foramen.

Osteophytes or ruptured disks produce neurologic symptoms when they compress the spinal cord or adjacent spinal nerve roots. The cervical nerve roots are most susceptible to injury at the point where they enter the intervertebral foramen (neuroforamen), a space delineated by the uncovertebral joint (anteromedially), the facet joint (posterolaterally), intervertebral disks and the vertebral end plates (medially), and by the pedicles of the vertebral bodies (above and below).

Symptoms. The first manifestation of cervical disk disease is often cervical radiculopathy, with symptoms and signs referable to compression of a cervical nerve root. The cervical nerve roots exit above the vertebral body of the same number, with the exception of the C8 root, which emerges at the C7-T1 interspace. Thus a lesion of the C5-6 disk produces C6 radiculopathy. Spondylosis is implicated in cervical nerve root compression about three times more often than acute disk rupture and most frequently involves the C6 or C7 nerve root. The C5 and C8 nerve roots are involved less often and the T1 root only rarely.

Cervical and unilateral arm pain is the most common symptom of cervical disk disease, and patients often complain of numbness or weakness in the involved arm. Occasionally, pain also involves the shoulder, occiput, or anterior chest. Cervical tenderness is present, and range of motion in the neck is decreased. Hyperextension and rotation of the neck toward the painful side (Spurling's maneuver) decrease the diameter of the neural foramen and may exacerbate radicular symptoms.

Clinical Diagnosis. Neurologic examination, with careful attention to motor, reflex, and sensory findings in the upper extremities, often reveals a diagnostic constellation of signs. *C5* radiculopathy usually causes weakness of shoulder external rotation (infraspinatus muscle) and shoulder abduction (supraspinatus and deltoid muscles), with decreased biceps and brachioradialis reflexes and hypalgesia over the lateral shoulder. *C6* radiculopathy is characterized by diminished sensation over the thumb and index finger; however, the pattern of weakness and abnormal reflexes may be difficult to distinguish from C5 radiculopathy due to overlap between the C5 and C6 myotomes. Of note, forearm pronation (pronator teres muscle) is more likely to be involved with injury to the C6 root. In C7 radiculopathy, weakness is noted in the triceps brachii and extensor muscles of the wrist. The triceps reflex is usually decreased or absent, and sensation over the index and middle fingers is often decreased. *C8* radiculopathy causes intrinsic hand muscle weakness affecting the finger abductors, adductors, and flexors. The triceps reflex may also be decreased, and sensation may be diminished over the ring and little fingers. The rare *T1* radiculopathy may be associated with weakness of the intrinsic hand muscles, particularly abduction of the thumb (abductor pollicis brevis muscle), and Horner syndrome (ptosis, miosis, and anhidrosis), which results from disruption of the sympathetic outflow to the face and eye via the root of C8 or T1, or both.

Treatment. The majority of patients who have symptoms and signs of cervical radiculopathy respond to *conservative treatment*, including activity modification, use of a soft cervical collar to immobilize the neck for a brief period, mild analgesics, anti-inflammatory medications, and muscle relaxants as required. In some cases, cervical traction and epidural steroid injections may also be considered. If symptoms persist beyond 2 to 4 weeks, further testing, including cervical magnetic resonance imaging (MRI) and electromyography (EMG) may be indicated. If the findings suggest significant nerve root compression in the setting of progressive neurologic deficits or intractable pain, *surgical therapy* may be considered. Cervical root decompression may be accomplished by an anterior or posterior approach through the neck. However, epidemiologic data suggest that up to 90% of patients improve with conservative treatment alone.

Radiographic Diagnosis of Radiculopathy

Herniation of an intervertebral disk, alone or in combination with spondylosis, is the most common cause of surgically remediable lumbar and cervical radiculopathy. In patients with signs and symptoms of radiculopathy, the clinician can often localize the problem to within one or two spinal segments. However, when conservative management has failed or when excruciating, unrelenting pain or severe weakness with or without loss of sphincter control forces consideration of surgery, precise anatomic localization of the disk herniation is necessary. Magnetic resonance imaging (MRI) is the most reliable diagnostic procedure in most cases.

MRI effectively demonstrates the bony architecture of the spine, the contours of the intervertebral disk, the paraspinal soft tissues, and the contents of the spinal canal. Various MRI sequences can be used to confirm disk herniation and visualize degenerative or traumatic changes, such as annular tears and end-plate edema. Changes that would suggest the presence of a radiculopathy include foraminal narrowing as well as a decreased amount of adipose tissue surrounding neuroforaminal nerve roots and dorsal root ganglia.

Computed tomography (CT) myelography, a fluoroscopic procedure in which a water-soluble contrast medium is injected into the spinal canal, followed by CT imaging of the spine, may also help with localization in that it can further delineate the extradural, bony and paraspinal tissues, especially in patients who have undergone previous spine surgery, resulting in technical artifacts that can obscure the MRI.

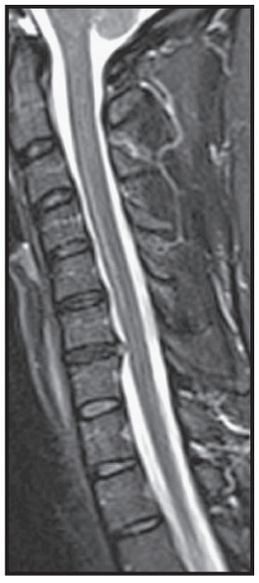
The *cervical region* has little, if any, epidural fat, and frequently only a small fragment of disk is enough to cause severe nerve root compression. Because of the lack of epidural fat and the small size of disk herniations, CT is less effective than myelography for diagnosing cervical radiculopathy. In disk herniation, myelography commonly demonstrates displacement of the dural sac, impaired filling or displacement of an axillary sleeve, or nerve root swelling.

When either MRI or CT myelography fails to suggest a clear-cut diagnosis, the other procedure should be considered. CT myelography may be more effective in patients with a prior history of spine surgery and metal hardware placement or when MRI is contraindicated, as when the patient has an internal cardiac pacemaker.

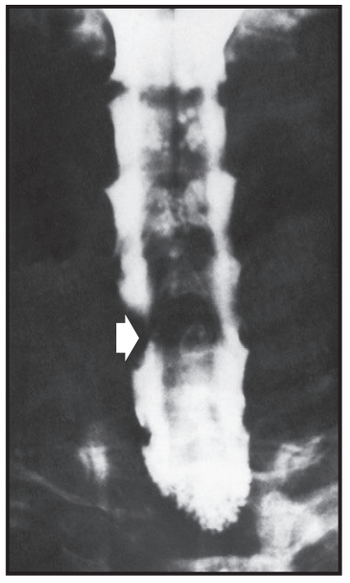
In the cervical region, CT and myelography are complementary. The combination of both studies clearly shows the nature and degree of spinal cord distortion, which is valuable in determining the proper treatment. The diagnosis of cervical spinal nerve root avulsion from traction injury of the arm is best visualized with a combination of CT and myelography; imaging identifies the diagnostic leakage of cerebrospinal fluid (CSF) into the neuroforaminal and extraspinal space.

Clinical localization of *cauda equina compression* may be difficult. In this case, MRI of the lumbosacral spine (LS) is helpful in localizing the compressive lesion. In the majority of patients with cauda equina compression related to disk disease, the MRI will demonstrate extensive disk material occupying over one third of the intraspinal canal space. CT myelogram may also demonstrate a myelographic block, the degree of which can help quantitate the severity of neural compression and be monitored in several different patient positions.

However, MRI is the test of choice because it is more rapidly performed with minimal risk of complications; characterization of the LS spine with MRI in conjunction with the clinical picture may be sufficient for planning surgery.

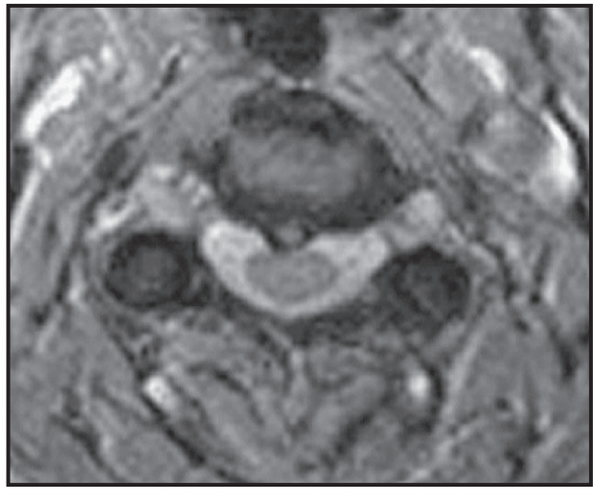


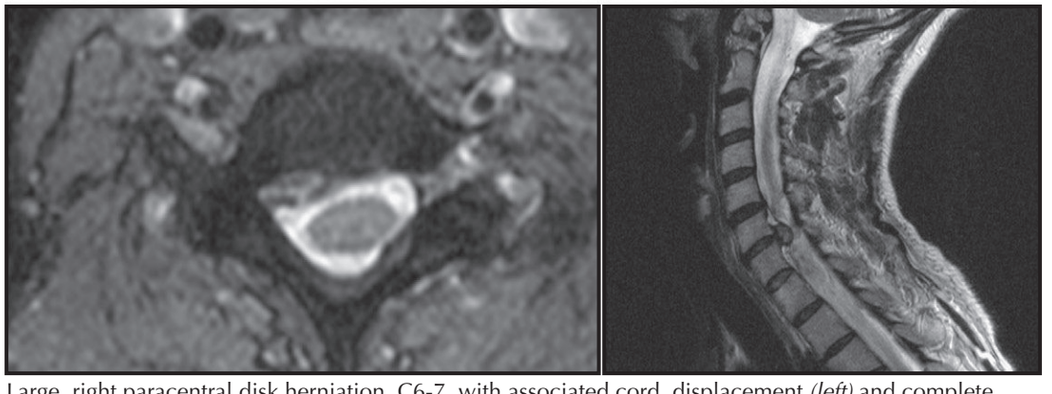
Central disk herniation, sagittal view



Myelogram (anteroposterior view) showing prominent extradural defect *(open arrow)* at C6-7

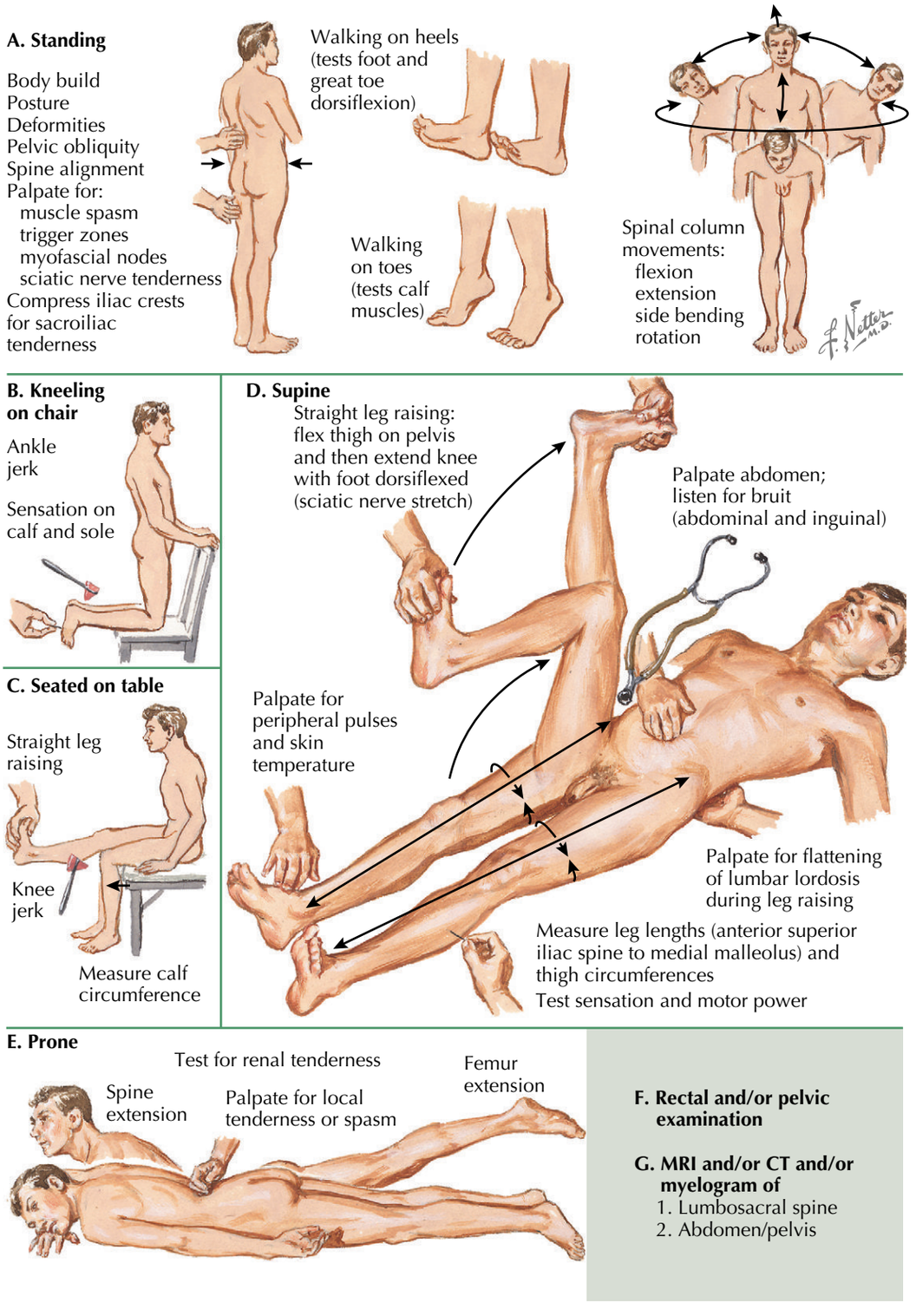
Central disk herniation, axial view





Large, right paracentral disk herniation, C6-7, with associated cord displacement *(left)* and complete right neural foraminal compromise *(right)*.

Examination of Patient with Low Back Pain



Back Pain and Lumbar Disk Disease

Lumbar disk disease causing low back and nerve root pain is a common problem that relates to the five lumbar vertebrae and the sacrum. The adjacent vertebrae are joined by strong ligaments at the articular facets and the vertebral bodies. Cartilage lines the articular surfaces of the vertebral bodies. The disk fills the space between the cartilaginous end plates and is normally a tough fibrocartilaginous structure. The dural sac contains the nerve roots of the cauda equina and extends through the spinal canal. As they exit the spinal canal at each segment, the nerve roots course caudad to the facet before passing through the intervertebral foramen. With aging, the disk degenerates, fragments, and loses its adherent properties. Thus appropriate mechanical forces can cause the fragment to move, usually posterolateral at the point of least ligamentous resistance, where the nerve root exits the spine. Pressure on the nerve root may produce pain and neurologic deficit.

As a result of abnormal movement at the facet joint, a hypertrophic, osteoarthritic process known as spondylosis develops. Enlargement of the facet joints by this spondylotic process narrows the intervertebral foramen, which may cause mechanical pressure on the exiting nerve root. In some persons, the anteroposterior diameter of the spinal canal is narrow, with deep lateral recesses. Thus the spondylotic process produces spinal stenosis, which causes pressure on the dural sac and cauda equina.

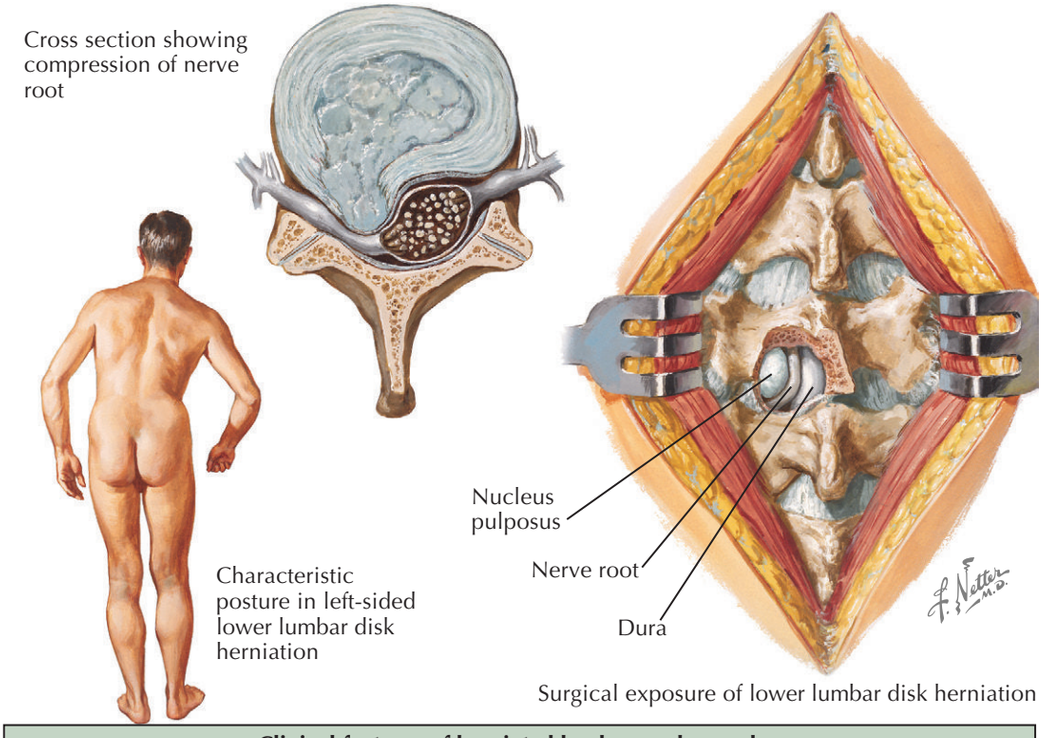
Clinical Manifestations

Lumbar spine disease may be manifested by pain in the low back, a monoradicular syndrome, a cauda equina syndrome, or spinal stenosis. As an isolated symptom, low back pain is usually self-limited and responds to conservative measures.

Initially, only a detailed history and physical examination may be necessary (see Plate 4-3). However, increasing pain with or without neurologic symptoms in a person who has systemic symptoms raises the question of a destructive lesion and merits further investigation, especially if the response to treatment has been limited. Back pain that is not helped by lying down is non-specific but occurs with cancer or infections.

The monoradicular syndromes are the classic syndromes of a ruptured disk. Most disk ruptures occur at L5-S1 and L4-5. The herniated disk at L5-S1 usually compresses the S1 root as it passes the interspace on its way beneath the S1 facet. In the same manner, the L4-5 disk compresses the L5 root, and the L3-4 disk compresses the L4 root. Rarely, the disk extrudes laterally into the intervertebral foramen, and then the L5-S1 disk produces an L5 root syndrome; the L4-5 disk, an L4 root syndrome; and the L3-4 disk, an L3 root

Lumbar Disk Herniation: Clinical Manifestations



Surgical exposure of lower lumbar disk herniation

Back Pain and Lumbar Disk Disease *(Continued)*

syndrome. Failure to diagnose these problems accurately results in inadequate treatment.

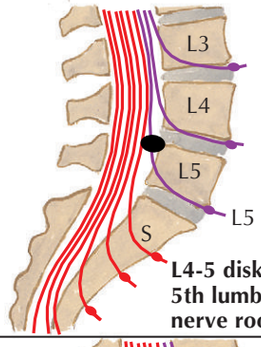
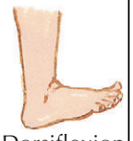
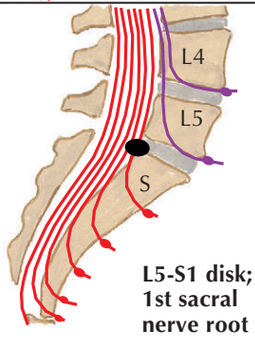
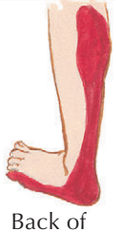
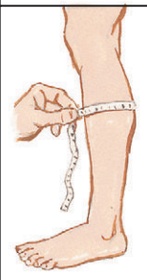
The *S1 root syndrome* includes sciatic pain ("sciatica") from the buttock to the posterior thigh, to the posterior or lateral calf, and into the foot. When due to disk herniation, it often increases with coughing or sneezing. Numbness and paresthesias commonly occur on the lateral aspect of the foot, the sole, and the heel. Weakness, if present, is in plantar flexion of the ankle and foot. The ankle jerk is absent.

The sciatic pain of the *L5 root syndrome* is indistinguishable from that of the S1 root syndrome. Dorsiflexion of the foot and eversion and inversion of the ankle may be weak. The ankle and knee jerk are normal, but the internal hamstring reflex may be diminished or absent. Sensory change develops in the dorsal and medial aspects of the foot and great toe. In the less common *L4 root syndrome*, pain radiates to the lateral and anterior thigh. The quadriceps muscle is weak and atrophied, and the knee jerk is lost. Sensory change occurs in the anterior thigh and pretibial regions. The clinical manifestations of herniation at L4-5 and L5-S1 are summarized in Plate 4-4.

Compression of the cauda equina by a midline disk herniation or tumor may lead to bladder or bowel dysfunction, often with bilateral sciatica, saddle anesthesia, and leg weakness. This is a surgical emergency because deficits may become irreversible if treatment is delayed,

In *lumbar spinal stenosis*, congenital or acquired narrowing of the spinal canal or intervertebral foramina is caused by disk bulging or protrusion, bony hypertrophic changes, or thickening of the ligamentum flavum. In addition to back pain that is relieved by sitting or bending forward, symptoms include pain or other sensory disturbances occurring in one or both legs with exercise, occasionally in a radicular distribution, and resolving with rest. Such "neurogenic claudication" is distinguished from vascular claudication by the lack of any circulatory abnormality in the legs; the arterial pulses are normal.

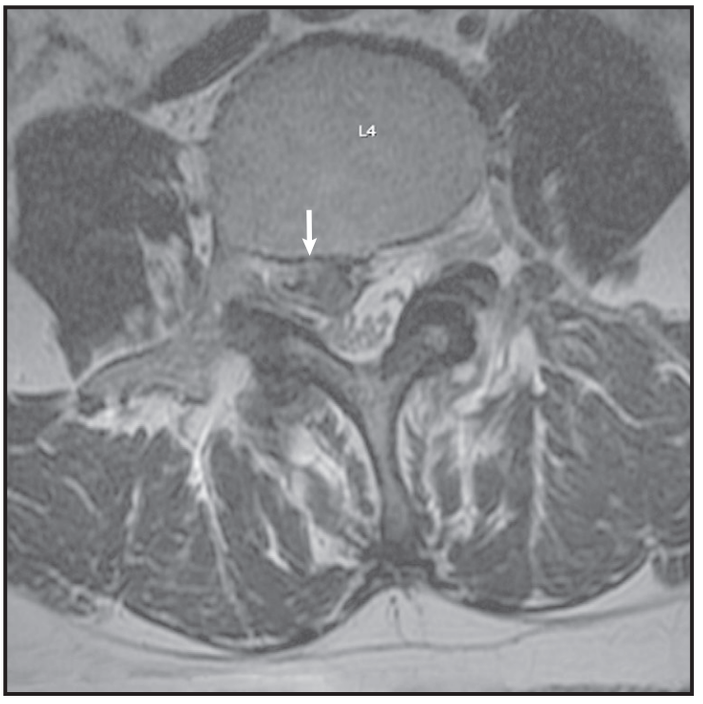
Clinical features of herniated lumbar nucleus pulposus

Level of herniation	Pain	Numbness	Weakness	Atrophy	Reflexes
 **L4-5 disk; 5th lumbar nerve root**	 Over sacroiliac joint, hip, lateral thigh and leg	 Lateral leg, first 3 toes	 Dorsiflexion of great toe and foot; difficulty walking on heels; foot drop may occur	Minor	Changes uncommon in knee and ankle jerks, but internal hamstring reflex diminished or absent
 **L5-S1 disk; 1st sacral nerve root**	 Over sacroiliac joint, hip, posterolateral thigh and leg to heel	 Back of calf, lateral heel, foot to toe	Plantar flexion of foot and great toe may be affected; difficulty walking on toes	 Gastrocnemius and soleus	 Ankle jerk diminished or absent

Treatment

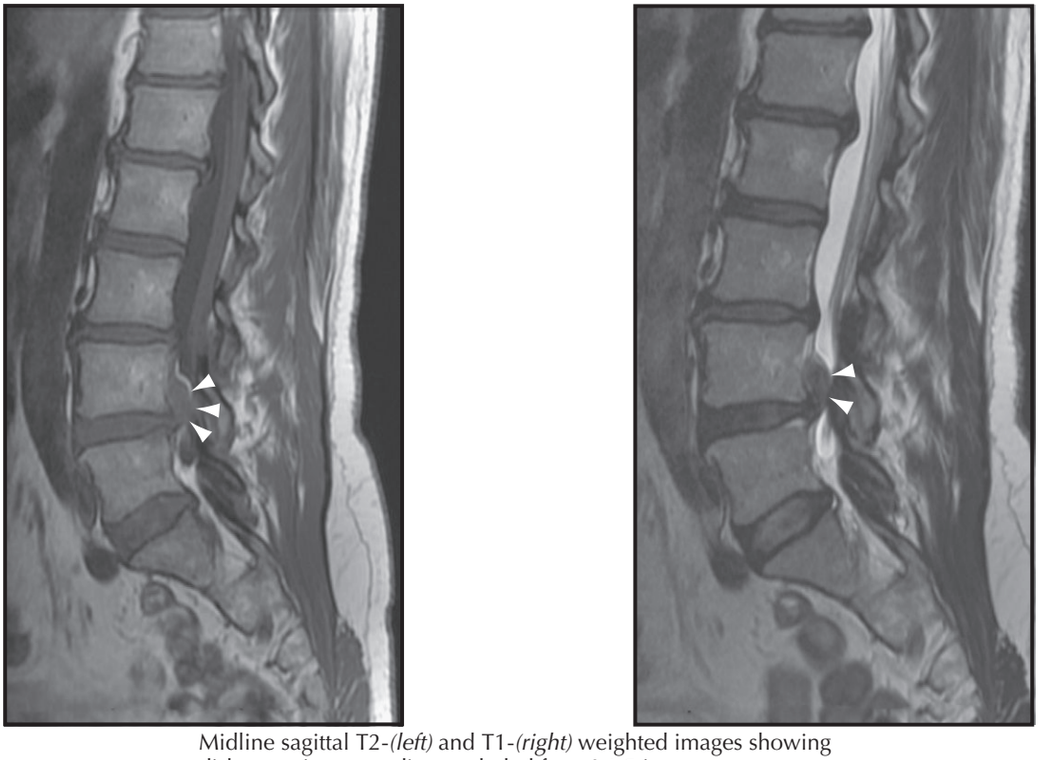
Most of the monoradicular syndromes, even those with mild neurologic deficit, respond to conservative care for several weeks; this involves a short period of bed rest (generally not more than 2 or 3 days), followed by mobilization and an exercise program. For patients with a definite diagnosis of radiculopathy secondary to a herniated disk who do not improve, options are limited. Some choose more prolonged rest, whereas some with mild symptoms may choose to return to activities of daily living despite the pain.

L4-5 Disk Extrusion



Axial T2-weighted image at L4 shows large paracentral disk extrusion extending into the right lateral recess and neuroforamen

Back Pain and Lumbar Disk Disease *(Continued)*



Midline sagittal T2-*(left)* and T1-*(right)* weighted images showing disk extrusion extending cephalad from L4-5 interspace

In patients in whom further treatment is necessary because of pain or neurologic deficit, surgery must be considered and must be preceded by imaging of the lumbosacral spine to rule out a destructive lesion or an anomaly such as spondylolisthesis. The important tests are spinal magnetic resonance imaging (MRI) or, less often, computed tomography (CT) myelography.

If no destructive lesion is present and test results show that the pain and neurologic deficit are caused by the herniated disk, surgery is indicated. The surgeon must keep in mind that the important structure is the nerve root. Adequate exposure is essential to expose the root cephalad and caudad to the extruded fragment and to the lateral margin of the spinal canal. This allows maximal exposure of the disk and nerve root, which can be minimally manipulated. The extruded disk is removed and foraminotomy is done. The root is then retracted medially, the annulus is exposed, and the disk is removed from the interspace to reduce the chance of recurrence. The patient is discharged 1 to 3 days postoperatively and can return to a sedentary job in 2 weeks. Diskectomy, with use of the operating microscope, is also a satisfactory procedure if done at the correct level to adequately expose the root.

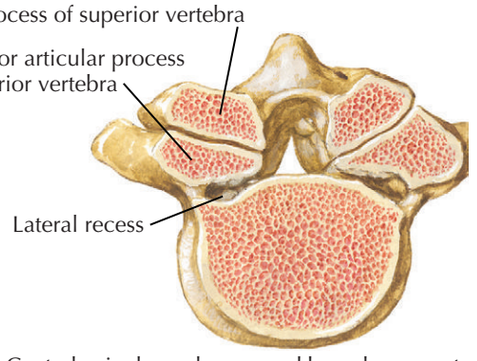
The *midline disk herniation* is a much more serious problem. The entire cauda equina can be compressed at the level of the rupture. Because of the danger of irreversible neurologic damage, bilateral sciatica demands more urgent evaluation than unilateral sciatica. Any suggestion of sphincter disturbance should lead to urgent spinal MRI or CT myelography, and, if necessary, to decompressive laminectomy with disk removal.

Conservative treatment for lumbar spinal stenosis includes weight loss, physical therapy (to improve posture, strengthen abdominal muscles, and increase lumbar flexion) and nonsteroidal anti-inflammatory agents. Surgery may be required to relieve symptoms or prevent further deterioration and usually involves single or multilevel decompressive laminectomy, sometimes with lumbar fusion.

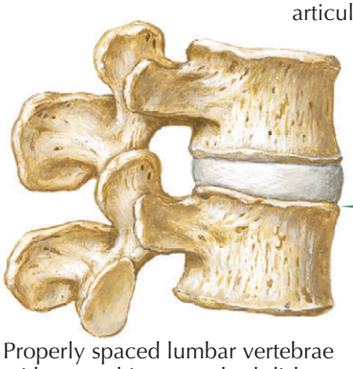
The patient who does not improve after surgery should be reevaluated to rule out a recurrent disk fragment and to establish that surgery was done at the correct level. If no surgical lesion is found, the patient should be encouraged to exercise and to return to work and attempt to live with the symptoms. Analgesic drugs, especially narcotics and tranquilizing medications, should be avoided. Pain clinics have been helpful in rehabilitating some of these patients. Those with persistent lumbar disk signs but no clinical or radiographic findings should not have any type of surgery. Rehabilitation should be attempted.

Lumbosacral Spinal Stenosis

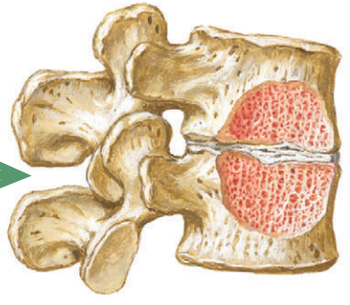
Patient assumes characteristic bent-over posture, with neck, spine, hips, and knees flexed; back is flat or convex, with absence of normal lordotic curvature. Pressure on cauda equina and resultant pain thus relieved.



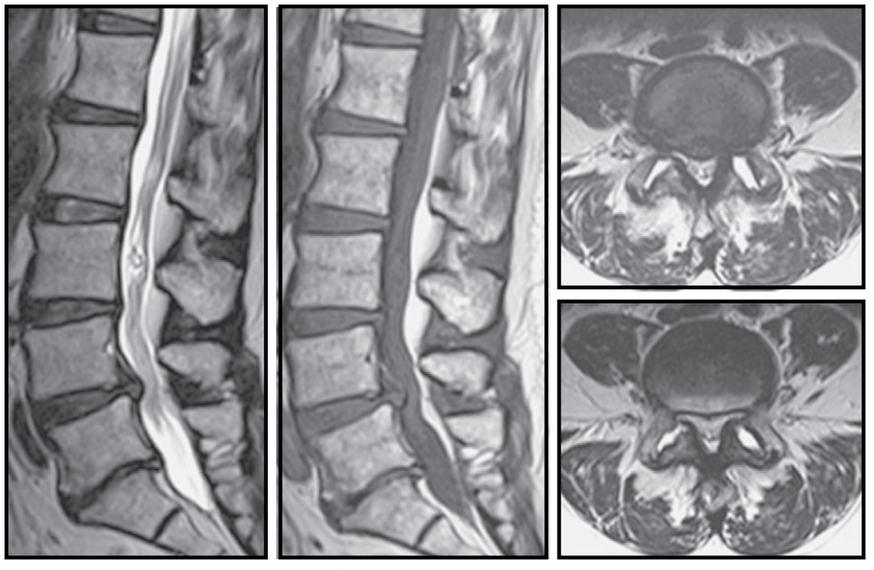
Central spinal canal narrowed by enlargement of inferior articular process of superior vertebra. Lateral recesses narrowed by subluxation and osteophytic enlargement of superior articular processes of inferior vertebra.



Properly spaced lumbar vertebrae with normal intervertebral disk



Vertebrae approximated due to loss of disk height. Subluxated articular process of inferior vertebra has encroached on foramen. Internal disruption of disk shown in cut section.



Combined spinal stenosis

In contrast to patients with a herniated disk, which is usually symptomatic at the level of just one spinal nerve root, some patients develop acute or chronically progressive narrowing of the central spinal canal, known as spinal stenosis. Progressive disk degeneration due to aging, trauma, or other factors can lead to disk protrusion and/or loss of disk height, resulting in pressure on posterior elements of the spine, including the facet joints. Facet joint arthropathy and osteophyte formation follow, along with hypertrophy of the ligamentum flavum. All of these processes (facet osteophytes, ligamentum flavum hypertrophy, and disk bulging) can encroach on the central canal and the neural foramina at one or multiple segmental levels, producing the anatomic picture of spinal stenosis, especially at the L3-5 segmental levels.

Spondylolisthesis, in which one vertebral body translates anteriorly or posteriorly with respect to an adjacent vertebral body, can also occur, exacerbating the spinal canal narrowing. The L4-5 level is most commonly involved, followed by L5-S1 and L3-4.

The majority of patients with spinal stenosis are men, and most are in at least their sixth decade of life. However, spinal stenosis may occur early in life in patients with certain developmental bony abnormalities, such as achondroplasia, osteochondrodystrophy, and mucopolysaccharidosis.

Clinical Manifestations. The classic clinical presentation of lumbar spinal stenosis is neurogenic (or pseudo) claudication, characterized by symptoms of pain or aching in the legs to be exacerbated with walking, standing, and/or maintaining certain postures (especially extension of the spine), and relieved with sitting or lying. Many patients with lumbar spinal stenosis (LSS) are symptomatic only when active. The symptoms are similar to vascular claudication of the leg(s) due to arterial insufficiency exacerbated by walking. Symptoms of neurogenic claudication are reported in the majority of patients with lumbar spinal stenosis. Other common symptoms include paresthesia, low back pain, and weakness. Symptoms are bilateral in over half of patients, but are often asymmetric. Often, the whole leg is symptomatic, including the hip, buttock, thigh, and leg.

Patients with spinal stenosis can pedal long distances on a bicycle or push a grocery cart throughout a store as long as they maintain a fully flexed position, in contrast to patients with arterial insufficiency. Walking uphill or upstairs involves hyperextension of the spine and so is more likely to cause exacerbation of symptoms in patients with lumbar spinal stenosis, in contrast to walking downhill or downstairs when the spine is in a flexed position. As the degree of canal stenosis increases, spinal nerve roots are continuously compressed, and symptoms and weakness become constant, even at rest.

Diagnosis. Results of examination of the patient with spinal stenosis may be relatively benign, especially in comparison with results in patients in whom a herniated nucleus pulposus produces nerve root disease. At rest, these patients are usually comfortable and have no back pain, muscle spasm or loss of lumbar lordosis. Straight leg raising does not aggravate symptoms, as it does in disk disease. In contrast, in spinal stenosis, hyperextension of the spine precipitates symptoms, which may be relieved by forward flexion. At times, the physician does not consider the patient's symptoms to be serious because testing of strength, reflexes, and sensation often fails to reveal any deficit. When exercise fails to elicit changes in pulses, the unwary physician may cease the evaluation. The precise mechanism that produces spinal stenosis is not clear. It has been postulated that interaction occurs between mechanical compression and exercise-precipitated nerve root ischemia.

Plain radiographs of the spine demonstrate spondylosis. MRI usually shows high-grade stenosis of the central canal, while CT myelography may demonstrate severe obstruction or complete block. Frequently, multiple levels are involved, usually L2 or L3-5. In contrast to acute disk rupture, L5-S1 is rarely involved.

Treatment. Wide laminectomy of the affected levels, with unroofing of the most symptomatic nerve roots, is the treatment of choice. The surgeon must search for extruded disk fragments. Postoperatively, neurogenic claudication is fully relieved in most patients, allowing them to lead much fuller lives. It should be stressed that in contrast to midline disk herniation, which can also produce bilateral paresthesias, surgery is not urgent. Rather, the patient and surgeon may wish to follow a conservative course of observation until the symptoms produce significant discomfort and interfere with normal leg patterns.

Spinal Nerves

The *ventral (anterior)* and *dorsal (posterior) nerve roots* are closely covered by pia mater and loosely invested by arachnoid. As each pair emerges through an intervertebral foramen, the roots are enclosed in a sheath of dura mater, surrounded by fatty areolar tissue containing a plexus of veins. The roots lie close together as they pierce the dura and unite almost immediately to form a *spinal nerve*, their dural sheaths becoming continuous with the epineurium.

The upper cervical spinal nerves lie horizontally, but all the others assume an increasingly oblique and downward direction as they proceed to their foramina of exit. In the adult, the lumbar, sacral, and coccygeal cord segments lie opposite the last three thoracic and first lumbar vertebrae, and their attached nerve roots descend as a sheath around the filum terminale to constitute the *cauda equina*.

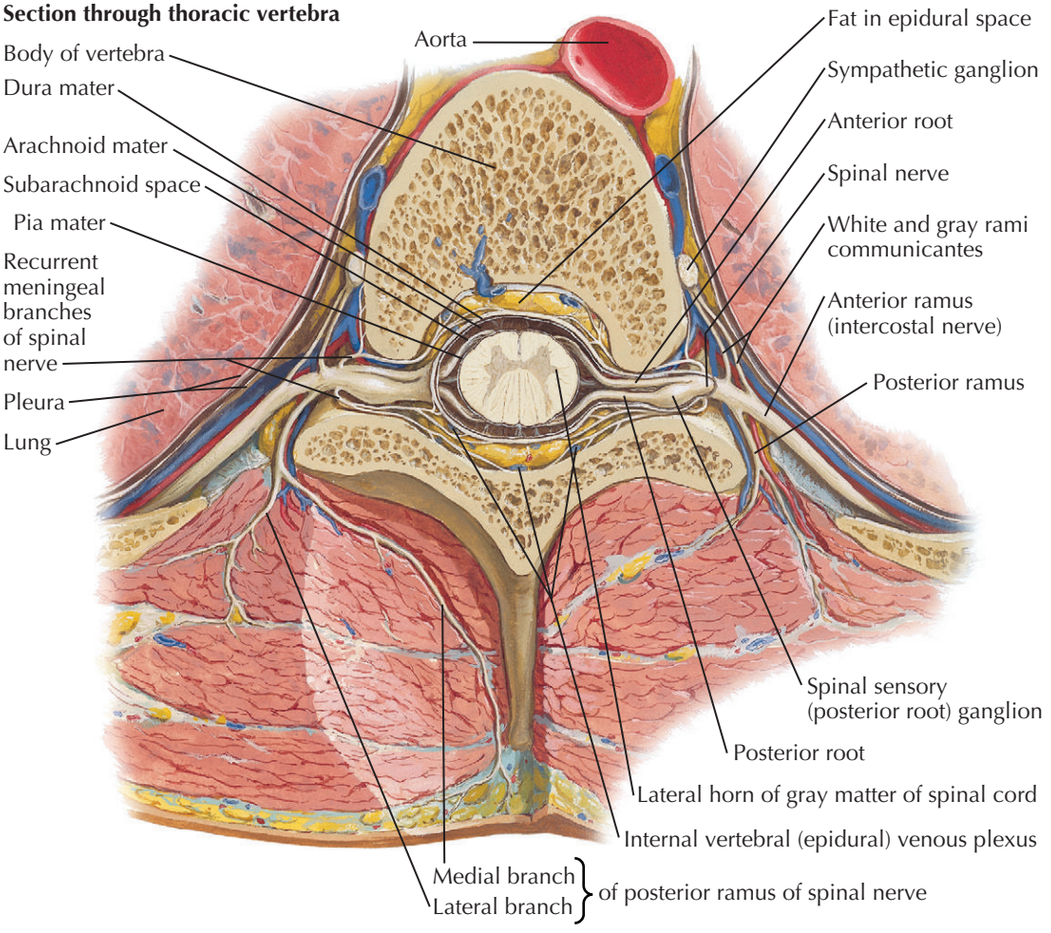
The spinal nerves are connected with adjacent sympathetic trunk ganglia by *rami communicantes*. These rami contribute efferent and afferent sympathetic fibers to the spinal nerves, which consist primarily of efferent and afferent somatic fibers derived from the ventral and dorsal nerve roots.

Shortly after emerging from the intervertebral foramina, the spinal nerves give off small *recurrent meningeal branches*, which supply the meninges and their vessels; they also supply filaments to adjacent articular and ligamentous structures. They then divide into *ventral (anterior)* and *dorsal (posterior primary)* rami, which contain fibers from both nerve roots and a variable number of sympathetic fibers.

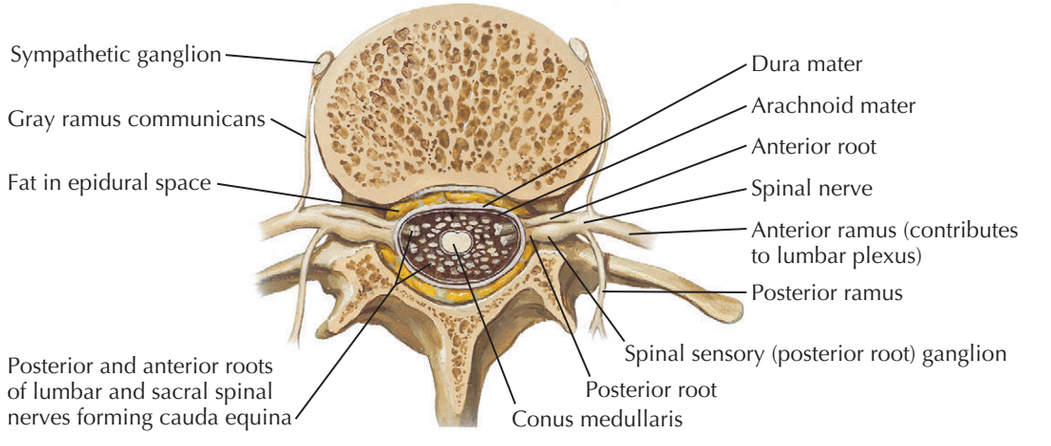
The ventral rami supply the anterior and lateral parts of the neck and trunk and make up the nerves of the perineum and limbs. Except in the thoracic region, where they retain their separate identities as intercostal and subcostal nerves, the ventral rami divide and reunite in differing patterns to form the following nerve plexuses: the *cervical plexus*, from the ventral rami of the first four cervical nerves; the *brachial plexus*, from the ventral rami of the lower four cervical and first thoracic nerves; the *lumbar plexus*, from the ventral rami of the first three lumbar nerves and from most of the ventral ramus of the fourth lumbar nerve; the *sacral plexus*, from the remainder of the ventral ramus of the fourth lumbar nerve and from the ventral rami of the fifth lumbar and first three sacral nerves; and the small *sacrococcygeal plexus*, from the ventral rami of the fourth and fifth sacral nerves and from the coccygeal nerve. (The plexuses and their branches are described in detail in Plates 4-12 and 4-13.

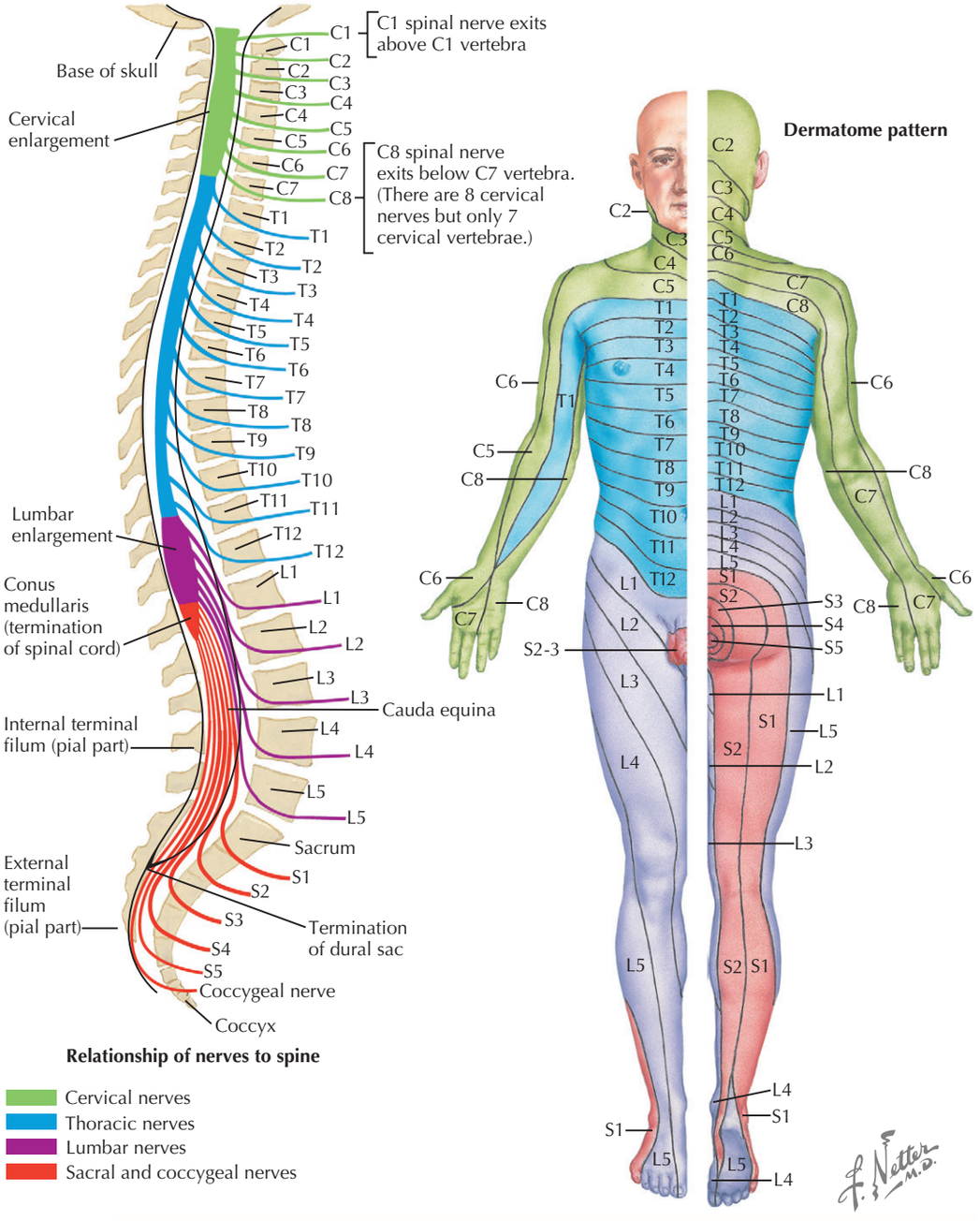
The dorsal rami turn dorsally and are distributed to cutaneous, muscular, and other structures of the back of the neck and trunk. Although some dorsal rami join to form loops, their branches do not form true plexuses as do branches derived from the ventral rami. Also, the dorsal rami (with the exception of those from the first and second cervical nerves) are generally smaller than the corresponding ventral rami. All the dorsal rami, except those from the first cervical, fourth and fifth sacral, and coccygeal nerves, divide into larger *medial* and smaller *lateral branches*. Most medial branches supply the muscles and the skin, whereas the lateral branches end in the muscles. However, the lateral branches tend to increase in size from above downward, so that those from the last thoracic, five lumbar, and five sacral nerves provide both muscular and cutaneous filaments.

Section through thoracic vertebra



Section through lumbar vertebra





Dermal Segmentation

The cutaneous area supplied by a single spinal nerve is called a *dermatome*. The cell bodies of the afferent fibers involved are located in the dorsal spinal nerve root ganglia and in ganglia on cranial nerves V, VII, IX, and X. One exception should be mentioned: the cell bodies of the trigeminal nerve proprioceptive fibers conveyed from the facial and masticatory muscles are located in the trigeminal mesencephalic nucleus and not in the trigeminal ganglion.

The spinal cord is segmental in character, and the spinal nerves are distributed to structures developed from the associated segments, or metameres (see Plate 2-1). In the trunk, the correspondence between neural and bodily segments is clearly apparent because they are arranged in consecutive encircling bands. In the limbs, however, due to plexus formation and interchange of nerve fibers in the nerves supplying them, the segmental distribution is obscured, although the arrangement is explicable embryologically. As the limb buds develop, they draw out parts of certain segments, together with their mesodermal cores, ectodermal coverings, and corresponding segmental nerves and vessels. Thus the more proximal dermatomes are elongated strips situated along the preaxial (outer) sides of the limbs, and the more distal ones are situated along their postaxial (medial sides). The oblique disposition in the lower limbs is due to the fact that during development, the limbs rotate medially around a longitudinal axis.

The fifth cervical to first thoracic metameres and the first lumbar to third sacral metameres contribute, respectively, to the formation of the upper and lower limbs. This is reflected in their nerve supplies and explains why in the neck, trunk, and upper limb the C5 and T1 dermatomes are in parts contiguous, and why in the trunk, perineum, and lower limbs the L1 and L2 dermatomes are in places adjacent to those of S2 and S3—the intervening segments have migrated into the more distal parts of the limbs.

The nerves supplying neighboring dermatomes overlap, and thus division of one dorsal nerve root produces *hypoesthesia* rather than *anesthesia*. To effect complete cutaneous anesthesia in any area, at least three adjoining spinal nerves or their dorsal roots must be blocked or divided. The exception to this general rule is that section of the dorsal root of C2 produces an area of complete anesthesia in the occipital region of the scalp. The degree of nerve overlap varies for different sensations, being greater for touch than for pain and temperature. The segmental muscular supplies also overlap so that most of the larger muscles (especially those in the limbs) are innervated by fibers from several ventral nerve roots. Therefore *paresis* occurs if only one or two roots are affected, but *paralysis* results if more roots are damaged or destroyed.

Knowledge of the dermatomes enables the clinician to locate lesions affecting the spinal cord or spinal nerves, and the dermatomes of the hand and foot deserve special attention.

Levels of principal dermatomes

C5	Clavicles
C5, 6, 7	Lateral parts of upper limbs
C8; T1	Medial sides of upper limbs
C6	Thumb
C6, 7, 8	Hand
C8	Ring and little fingers
T4	Level of nipples
T10	Level of umbilicus
T12	Inguinal or groin regions
L1, 2, 3, 4	Anterior and inner surfaces of lower limbs
L4, 5; S1	Foot
L4	Medial side of great toe
L5; S1, 2	Outer and posterior sides of lower limbs
S1	Lateral margin of foot and little toe
S2, 3, 4	Perineum

Thoracic Nerves

The 12 pairs of thoracic nerves resemble other typical spinal nerves in their segmental attachments to the cord by *dorsal* and *ventral nerve roots*. These roots unite to form short *spinal nerve trunks*, which emerge through the corresponding intervertebral foramina, give off recurrent meningeal filaments, establish connections through white and gray rami communicantes with adjacent sympathetic trunk ganglia, and divide into larger *ventral* and smaller *dorsal rami*. (See Plates 7-3 and 7-4 for greater detail of these general arrangements.)

The dorsal rami of the thoracic nerves run backward near the zygapophyseal joints, which they supply, and divide into medial and lateral branches. Both sets of branches pass through the groups of muscles constituting the erector spinae and give off branches to them. The terminations of the upper six or seven *medial branches* innervate the skin adjacent to the corresponding spinous processes, but the lower five or six often fail to reach the skin. The terminations of all the *lateral branches* usually pierce the thoracolumbar fascia over the erector spinae muscles and divide into *medial* and *lateral cutaneous branches*, which innervate much of the skin of the posterior thoracic wall and upper lumbar regions.

The ventral rami of most of the thoracic nerves, unlike those in other regions, do not form plexuses. They retain their segmental character, and each pair runs separately in the corresponding intercostal spaces as the *intercostal nerves*. The first pair, however, divides into larger and smaller branches; the former, usually joined by twigs from the second pair, participate in the formation of the *brachial plexuses* (Plate 4-13), whereas the smaller branches are the first pair of intercostal nerves. The last (twelfth) pair of ventral rami course below the lowest ribs and are therefore termed the *subcostal nerves*.

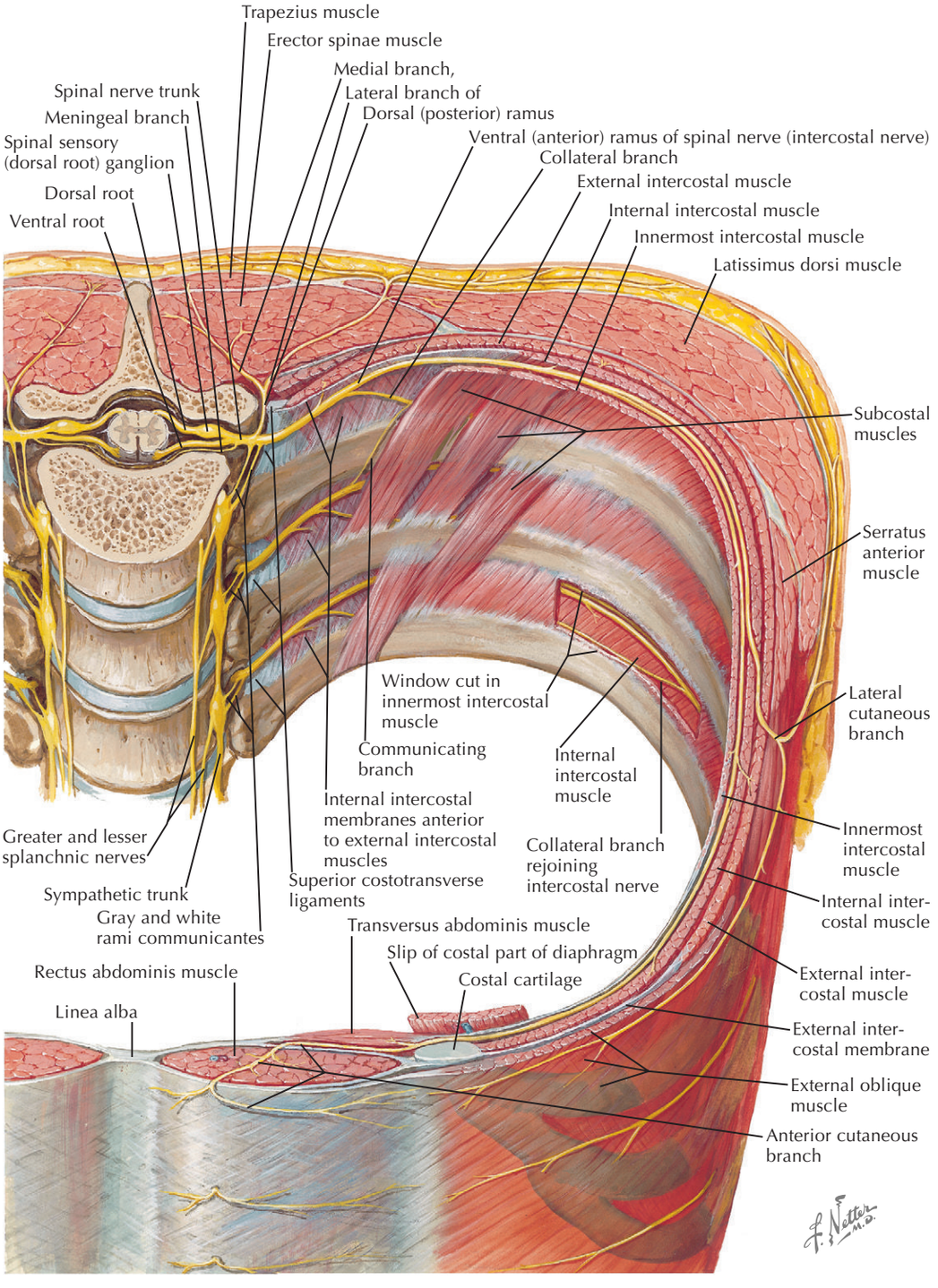
The intercostal nerves are distributed mainly to structures in the thoracic and abdominal walls. The upper six pairs are limited to the thoracic parietes, whereas the lower five pairs extend from the thoracic into the abdominal walls and also contribute fibers to the diaphragm. The intercostal nerves give off *muscular*, *anterior* and *lateral cutaneous*, *mammary*, and *collateral branches*, and supply filaments to adjacent vessels, periosteum, parietal pleura, and peritoneum.

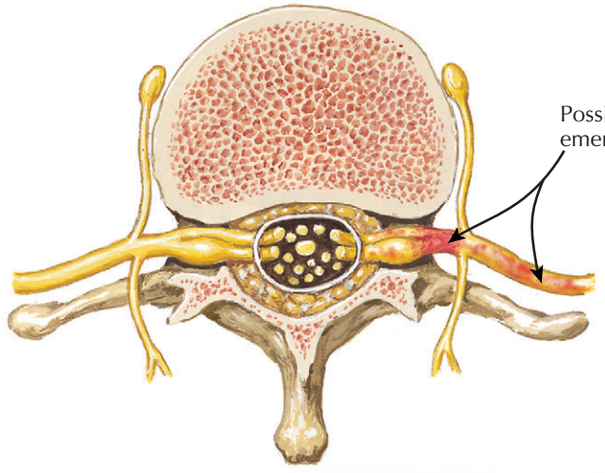
The upper six pairs supply *muscular branches* to the corresponding intercostal muscles and also to the subcostal, serratus posterior superior, and transverse thoracic muscles. The lower five pairs supply the lower intercostal muscles and the subcostal, serratus posterior inferior, transverse, oblique, and rectus abdominal muscles. Fascicles from the lower intercostal nerves also enter the margins of the diaphragm, but they are sensory. The subcostal nerves supply the pyramidalis muscles.

The *anterior cutaneous branches* supply the front of the thorax. The *lateral cutaneous branches* pierce the internal and external intercostal muscles and end by dividing into branches that extend forward and backward to innervate the skin covering the lateral sides of the thorax and abdomen. The small *lateral branch* of the *first intercostal nerve* supplies the skin of the axilla, and the lateral branch of the second is the *intercostobrachial nerve*, which is distributed to the skin on the medial side of the arm. The *lateral cutaneous branch* of the *subcostal nerve* pierces the internal and external oblique abdominal muscles and descends over the iliac crest to supply the skin of the anterior part of the gluteal region.

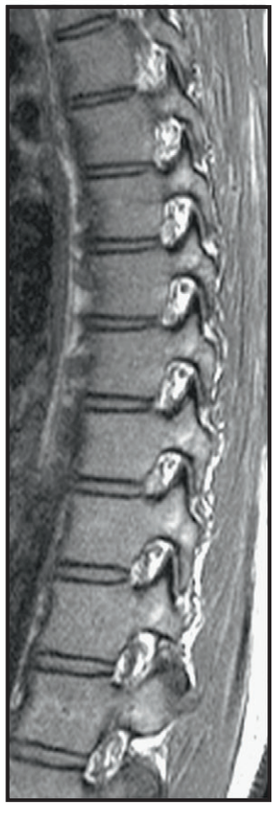
The *mammary glands* receive filaments from the lateral and anterior cutaneous branches of the fourth, fifth, and sixth intercostal nerves, which convey autonomic and sensory fibers to and from the glands.

Thoracoabdominal Nerves





Possible site of lesion roots of spinal nerve at emergence from spinal canal or proximal plexus



Normal thoracic spinal nerve roots in their neuroforamina, sagittal view

Thoracic Spinal Nerve Root Disorders

The common occurrence of disk herniation and spinal nerve root compression seen at cervical and lumbosacral levels is not the case at the thoracic levels because of the rib cage, which stabilizes the spine and minimizes the forces leading to disk rupture and spondylosis. Disk herniation at the T1-2 level is more common than at other thoracic levels, with subsequent clinical manifestations of a T1 radiculopathy: numbness and pain in the medial hand and forearm, with weakness of thumb abduction. Mass lesions are relatively more common, including meningiomas and schwannomas. Varicella-zoster reactivation occurs frequently at thoracic spinal root levels, producing a characteristic radicular vesicular rash that follows a radicular pattern from the spine circumferentially around the torso to the abdominal wall. Acute herpes zoster neuropathy is manifested by pain and then anesthesia in a similar distribution conforming to the involved dermatomal segment. At times the motor spinal nerve root fibers are also affected, producing weakness in abdominal wall muscles of the affected myotomes. This is clinically manifested as a unilateral bulge of the abdominal wall when contracted, such as during a sit-up maneuver. Post–herpetic neuralgia describes the chronic pain and numbness that persist after the rash resolves, especially prevalent in older individuals. Diabetic thoracic radiculopathy presents with similar symptom and signs but without rash. Lyme disease can demonstrate neurologic manifestations, such as multifocal radiculitis, including at the thoracic levels. For all these disorders, when the motor fibers at the T9-12 segmental levels are affected, unilateral or bilateral weakness of rectus abdominis muscles and muscle bulging can be seen.

Diabetic Lumbosacral Radiculoplexus Neuropathy

Patients with diabetes mellitus are predisposed to a variety of peripheral nervous system disorders, the most common of which is the insidiously progressive, predominantly sensory symmetric distal polyneuropathy. In addition, a variety of other neuropathic disorders may develop, including an asymmetric neuropathy, that is, mononeuritis multiplex; an acute oculomotor nerve palsy that mimics an aneurysm, except for pupillary sparing; sensitivity to compression or entrapment neuropathies; and an acute lumbosacral radiculoplexus neuropathy.

Diabetic lumbosacral radiculoplexus neuropathy is a painful condition that causes severe weakness and muscle wasting of the lower extremities. A number of clinical terms have been applied to this syndrome, including diabetic amyotrophy, femoral neuropathy of diabetes, diabetic asymmetric proximal motor neuropathy, and diabetic lumbosacral plexopathy. Differences in terminology have reflected various opinions as to the primary anatomic site of the lesion and underlying pathology. Although the syndrome was initially thought to be limited to the proximal muscles of the thigh, more recent studies have demonstrated that most cases are widespread, affecting both proximal and distal segments in bilateral lower extremities. Pathologic findings on nerve biopsy include microvasculitic changes and inflammation, suggestive of an underlying immune-mediated vasculitis; however, the exact mechanism of injury is still unknown.

Clinical Manifestations. The onset of symptoms is typically focal, beginning with severe pain in the anterior thigh and hip and weakness of the thigh muscles. It is also often accompanied by weight loss. Over time, the symptoms progress to involve distal segments and eventually the contralateral limb. Less commonly, there may be additional thoracic nerve root involvement resulting in truncal pain and paresthesias. The cervical dermatomes are usually not affected, although there may be a concomitant mononeuropathy of the upper limb, such as an ulnar mononeuropathy.

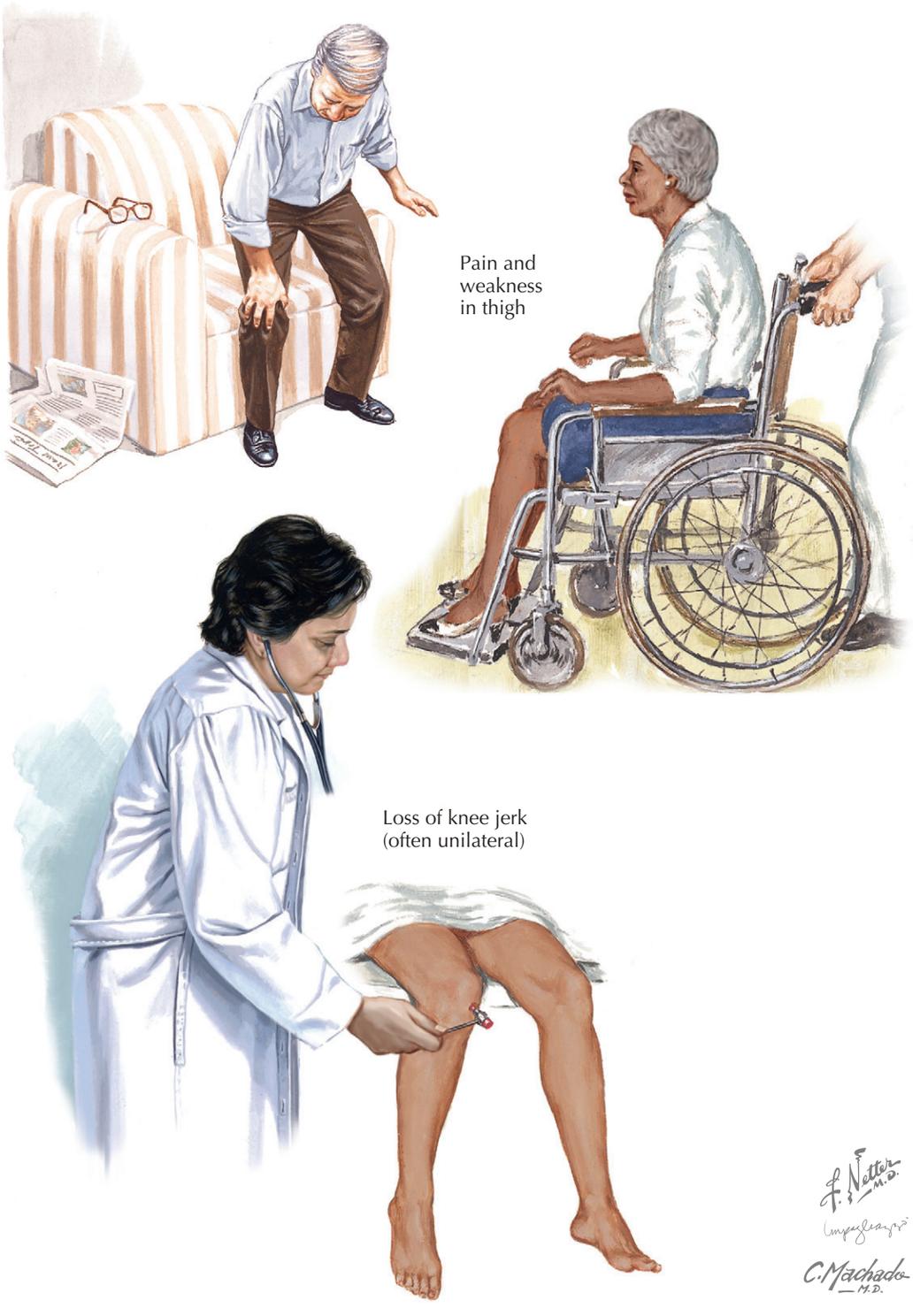
Although the onset of symptoms is often fairly acute or even precipitous, the course may be insidiously progressive in some patients. Pain is the most common initial complaint. In contrast to the patient with disk disease, who can usually find a comfortable position at night, the patient with diabetic lumbosacral radiculoplexus neuropathy often has nocturnal exacerbations. The pain frequently has a dysesthetic quality evoked by touch or exacerbated by clothing, such as brassiere straps or garments fitting tightly over the thigh. When thoracic dermatomes are involved, the pain is sometimes severe enough to mimic an abdominal or cardiac crisis.

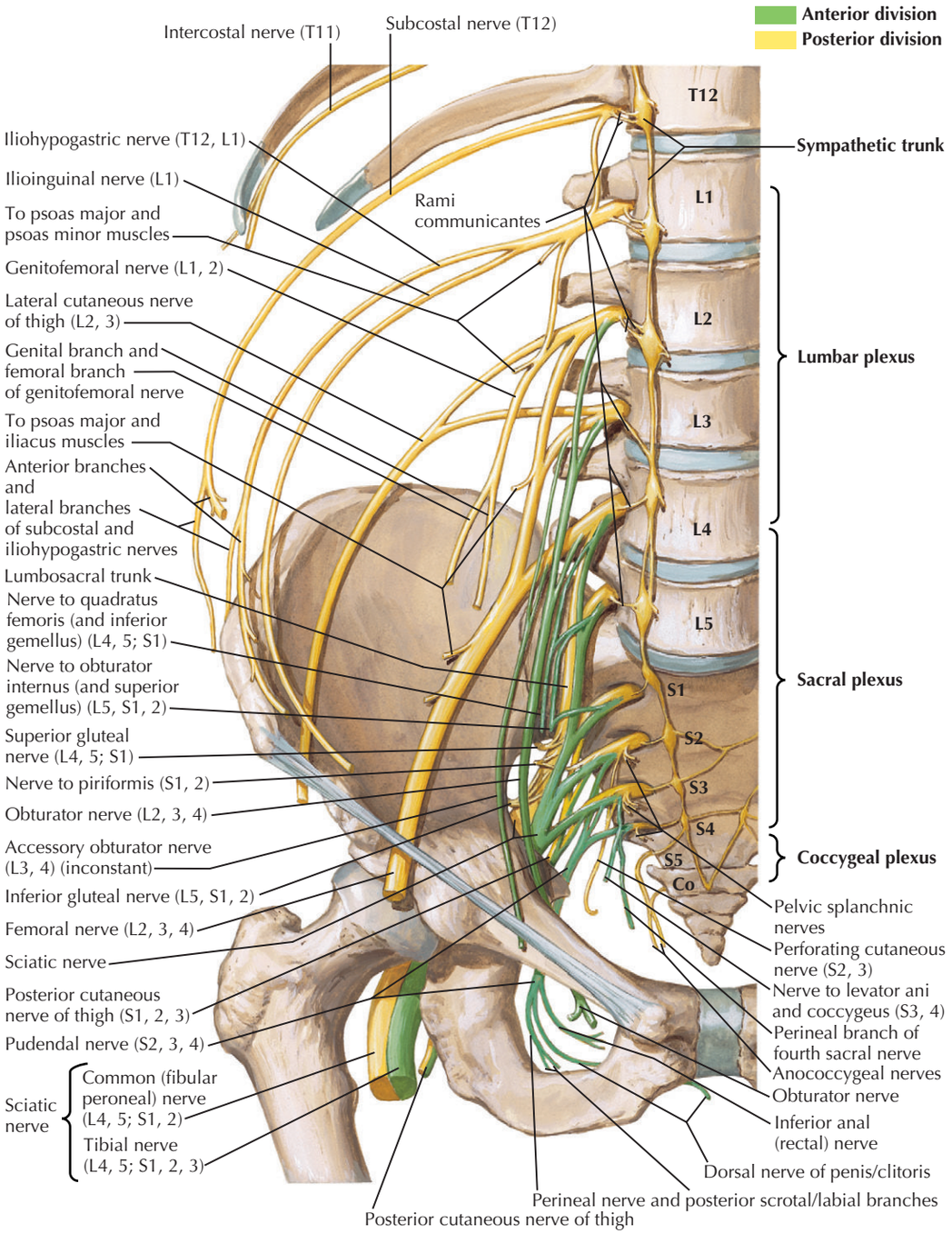
Weakness without sensory loss may be the first sign in some patients. Involvement of the quadriceps femoris and iliopsoas muscles may compromise climbing stairs or arising from a squatting position. With more distal weakness, the patient may experience gait difficulty due to a footdrop.

Diagnosis. Physical examination confirms the radicular or plexus pattern of motor loss. Deep tendon reflexes, particularly the knee jerk, are often absent. Sensory loss may be difficult to define, although the area of hyperpathia may sometimes mimic a nerve root distribution. A moderate number of patients show signs of coexisting mild symmetric distal polyneuropathy, although sensory abnormalities in the feet may also be related to distal limb involvement.

Reduced amplitudes of sensory and motor nerve conduction responses are seen on electromyogram (EMG), with needle examination findings of active denervation and neurogenic motor unit potential changes in the distribution of multiple nerve roots, including paraspinal muscles. Cerebrospinal fluid (CSF) protein is often elevated. Imaging studies of the lumbosacral spine are typically normal.

Course and Treatment. In most cases, improvement occurs spontaneously over a period of 6 to 18 months, but immune-modulating therapy may expedite recovery with regard to pain and weakness. Symptomatic management with optimal pain control and physical therapy is crucial. Relapse may occur in approximately one in five patients.





Lumbar, Sacral, and Coccygeal Plexuses

The lumbar, sacral, and coccygeal plexuses are interlinked and are formed from the ventral rami of the first three lumbar nerves and the greater part of the fourth, with a contribution from the subcostal nerve. The plexus lies anterior to the lumbar vertebral transverse processes, embedded in the posterior part of the psoas major muscle.

The first lumbar nerve receives a fascicle from the subcostal nerve and divides into upper and lower branches; the upper branch splits into the iliohypogastric and ilioinguinal nerves, whereas the lower branch joins a twig from the second lumbar nerve and becomes the genitofemoral nerve. Except near their terminations, all three nerves run parallel to the lower intercostal nerves and help to supply the transverse and oblique abdominal muscles. The *iliohypogastric nerve* gives off a lateral cutaneous branch to the skin on the anterolateral aspect of the buttock and ends as the anterior cutaneous branch to the skin above the pubis. The *ilioinguinal nerve* pierces the internal oblique muscle above the anterior part of the iliac crest and then runs above and parallel to the inguinal ligament to traverse the inguinal canal and supply the skin over the root of the penis, the adjoining part of the femoral triangle, and the upper part of the scrotum (mons pubis and adjacent part of labium majus in the female). The *genitofemoral nerve* penetrates the psoas major muscle and divides into *genital* and *femoral branches*. The genital branch in males passes through the inguinal canal and supplies the cremaster muscle and the skin of the scrotum; in females, it ends in the mons pubis and labia majora. The femoral branch in both males and females supplies the skin over the upper part of the femoral triangle.

The larger part of the second lumbar nerve, the entire third lumbar nerve, and the offshoot from the fourth lumbar nerve to the lumbar plexus split into ventral (anterior) and dorsal (posterior) divisions, which unite to constitute, respectively, the *obturator* and *femoral nerves* (see Plates 5-15 and 5-16). The *lateral femoral cutaneous nerve* (see Plate 5-16) is formed by offshoots from the second and third posterior divisions.

The lower part of the ventral ramus of the fourth lumbar nerve joins the ventral ramus of the fifth to form the *lumbosacral trunk*. The trunk and the ventral rami of the first three sacral nerves and the upper part of the fourth sacral ramus constitute the *sacral plexus*.

The sacral plexus, by convergence and fusion of its roots, becomes a flattened band that gives rise to many branches before its largest part passes below the piriformis muscle and through the greater sciatic foramen as the *sciatic nerve* (see Plate 5-17). The rami forming the sacral plexus divide into ventral (anterior) and dorsal (posterior) divisions, which subdivide and regroup to become branches of the plexus.

Coccygeal Plexus. The lower part of the ventral ramus of the fourth and fifth sacral nerves and the coccygeal nerves form the small coccygeal plexus. It consists of two loops on the pelvic surface of the coccygeus and levator ani muscles. Twigs are given off to these muscles, and fine *anococcygeal nerves* supply the skin between the anus and coccyx.

Brachial Plexus

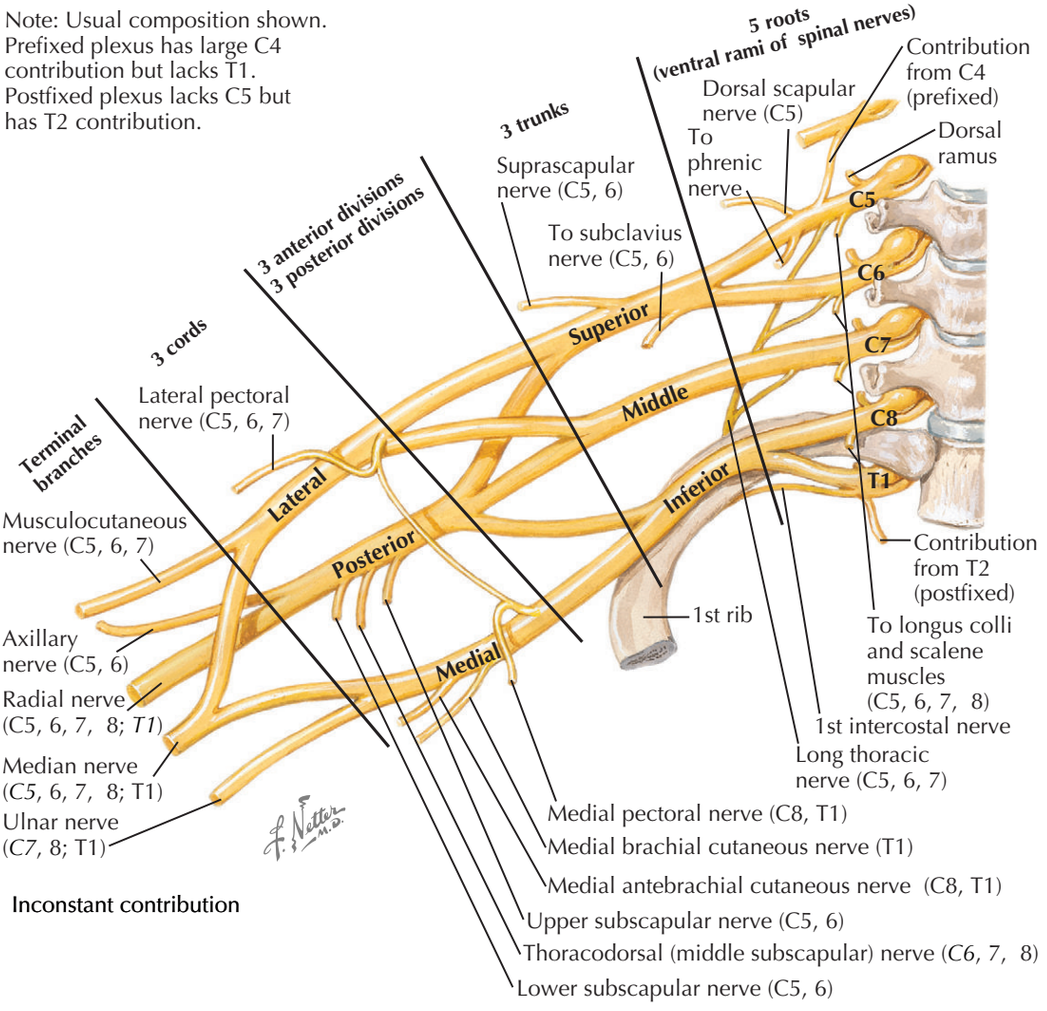
Roots. The brachial plexus is formed by the union of the ventral (anterior) rami of the *fifth*, *sixth*, *seventh*, and *eighth cervical nerves* and the greater part of the *first thoracic nerve*—the roots of the plexus. Usually, a small branch from C4 joins the C5 root, and one from T2 joins the T1 root; thus C4 and T2 often provide minor contributions to the plexus. However, the contributions are variable in size, especially if so-called prefixation or postfixation exists. A "prefixed" plexus shows a cranial shift and the C4 contribution is large, whereas the plexus from T1 is small and that from T2 is often absent. In a "postfixed" plexus, the condition is reversed: the contribution from T2 is large, that from C5 is small, and that from C4 is often missing. The roots lie between the anterior and middle scalene muscles.

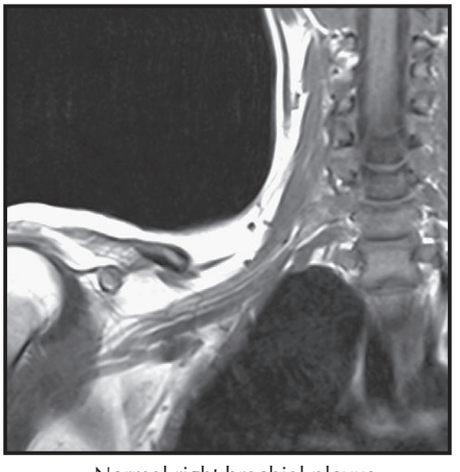
The plexus formation allows rearrangements of the efferent and afferent somatic and autonomic fibers (the latter reach the roots of the plexus through sympathetic rami communicantes) so that they are redirected through the various trunks, divisions, and cords into the most appropriate channels—the terminal branches—for distribution to the muscles, skin, vessels, and glands in the upper limbs.

Trunks. The upper roots (C5, C6) unite to form the *superior trunk*, the C7 root continues alone as the *middle trunk*, and the lower roots (C8, T1) constitute the *inferior trunk* of the plexus. The trunks lie in the lower part of the posterior cervical triangle.

Divisions and Cords. Each trunk divides into three *ventral* (anterior) and three *dorsal* (posterior) *divisions*, which supply the ventral (flexor) and dorsal (extensor) structures in the upper limb. In the axilla, the divisions become regrouped as follows: the *ventral division* of the *inferior trunk* continues as the *medial cord* (C8, T1), the *ventral divisions* of the *superior* and *middle trunks* unite to form the *lateral cord* (C5, C6, C7), and all *three dorsal divisions* of the *trunks* join to produce the *posterior cord* (C5 to C8, T1). (The terms "medial," "lateral," and "posterior" indicate the relationships of the cords to the second part of the axillary artery.)

Branches. Most of the branches of the plexus originate in the axilla from the *cords* located below the level of the clavicle—*infraclavicular branches*. However, several branches arise from the *roots* and *trunks* in the posterior cervical triangle above the clavicle—*supraclavicular branches*. Nerves derived from a cord do not necessarily contain fibers from all its constituent roots; for instance, the axillary nerve arising from the posterior cord (C5 to C8, T1) contains fibers from only C5 and C6.





Normal right brachial plexus, T1-weighted coronal view

Supraclavicular branches	
From plexus roots or spinal cord	
To longus colli and scalene mm.	C5, 6, 7, 8
Dorsal scapular	C5
Branch to phrenic	C5
Long thoracic	C5, 6, 7
Spinal accessory	Cervical spinal cord (and C3, 4)
From superior trunk	
Suprascapular	C5, 6
To subclavius m.	C5, 6

Infraclavicular branches	
From lateral cord	
Lateral pectoral	C5, 6, 7
Musculocutaneous	C(4), 5, 6, 7
Lateral root of median	C(5), 6, 7
From medial cord	
Medial pectoral	C8, T1
Medial cutaneous n. of arm	T1
Medial cutaneous n. of forearm	(C8), T1
Ulnar	C(7), 8, T1
Medial root of median	C8, T1
From posterior cord	
Upper subscapular	C5, 6, (7)
Lower subscapular	C5, 6
Axillary (circumflex humeral)	C5, 6
Thoracodorsal	C6, 7, 8
Radial	C5, 6, 7, 8; T1

Brachial Plexus and/or Cervical Nerve Root Injuries at Birth

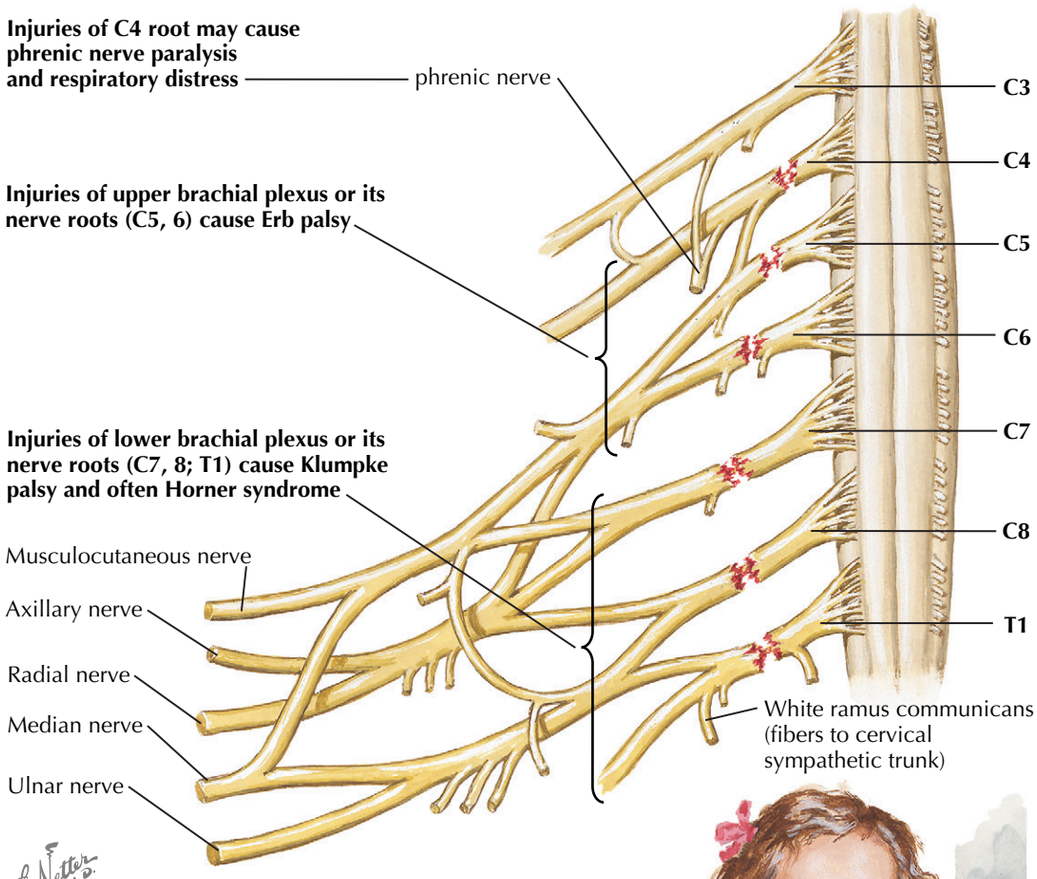
Brachial plexus injuries in the newborn now occur much less commonly than formerly, although the incidence is still approximately 1 to 2 per 1000 live births. The injury results from traction forces in delivering the shoulder in vertex deliveries and delivering the head in breech deliveries. The associated obstetric factors are occipitoposterior or transverse presentation, the use of oxytocin, shoulder dystocia, and large babies (weighing over 3500 g) with low Apgar scores.

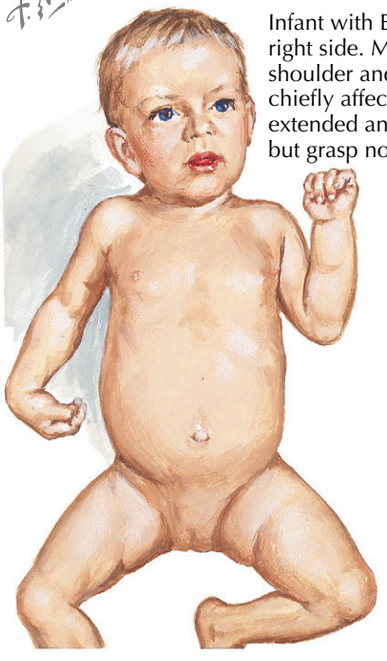
Neonatal brachial plexopathy is believed to be secondary to stretching of the plexus by traction, the nerve roots being anchored by the spinal column and cord. Lesion severity depends on the degree of stretch, but axonal injury is the usual result. If the epineurial nerve sheath remains intact, nerve regeneration down to the denervated muscles occurs at a rate of about 1 mm per day. Complete rupture of the nerve sheath as well as the axons leads to poor reinnervation. With severe traction injuries, there may be additional damage to spinal nerve roots, including root avulsion. Diagnosis requires imaging, and computed tomography (CT) myelography remains more reliable than magnetic resonance imaging (MRI). Upper brachial plexus injuries involve the junction of C5 and C6 roots (Erb's point), and lower injuries involve the junction of C8 and T1 roots.

Upper Brachial Plexus Injury (Erb Palsy). This is the most common of the brachial plexus injuries, affecting muscles supplied by C5 and C6 and accounting for 90% of the total incidence. An *asymmetric Moro response* is usually the first indication of the injury. The upper extremity assumes the "waiter's tip" position: the shoulder is adducted and internally rotated, the elbow is extended, and the forearm is pronated, with the hand in flexion. A mild sensory loss may develop over the lateral aspect of the shoulder and arm, but is difficult to elicit. Associated fractures of the clavicle or humerus must be ruled out, and fluoroscopic examination should be carried out to exclude the rare diaphragmatic paralysis caused mainly by a C4 lesion.

Lower Brachial Plexus Injury (Klumpke Palsy). A pure lower brachial plexus injury is uncommon, and most cases of Klumpke palsy involve the more proximal muscles supplied by C7 or C6. An *absent grasp reflex* is the most prominent clinical feature. There may be involvement of sympathetic fibers from T1, causing Horner syndrome (ptosis, miosis, anhidrosis). A significant sensory deficit is usually present, occasionally resulting in unwitting trauma to fingers. Prognosis for full recovery in these infants is poor. The upper extremity often remains small and distally foreshortened.

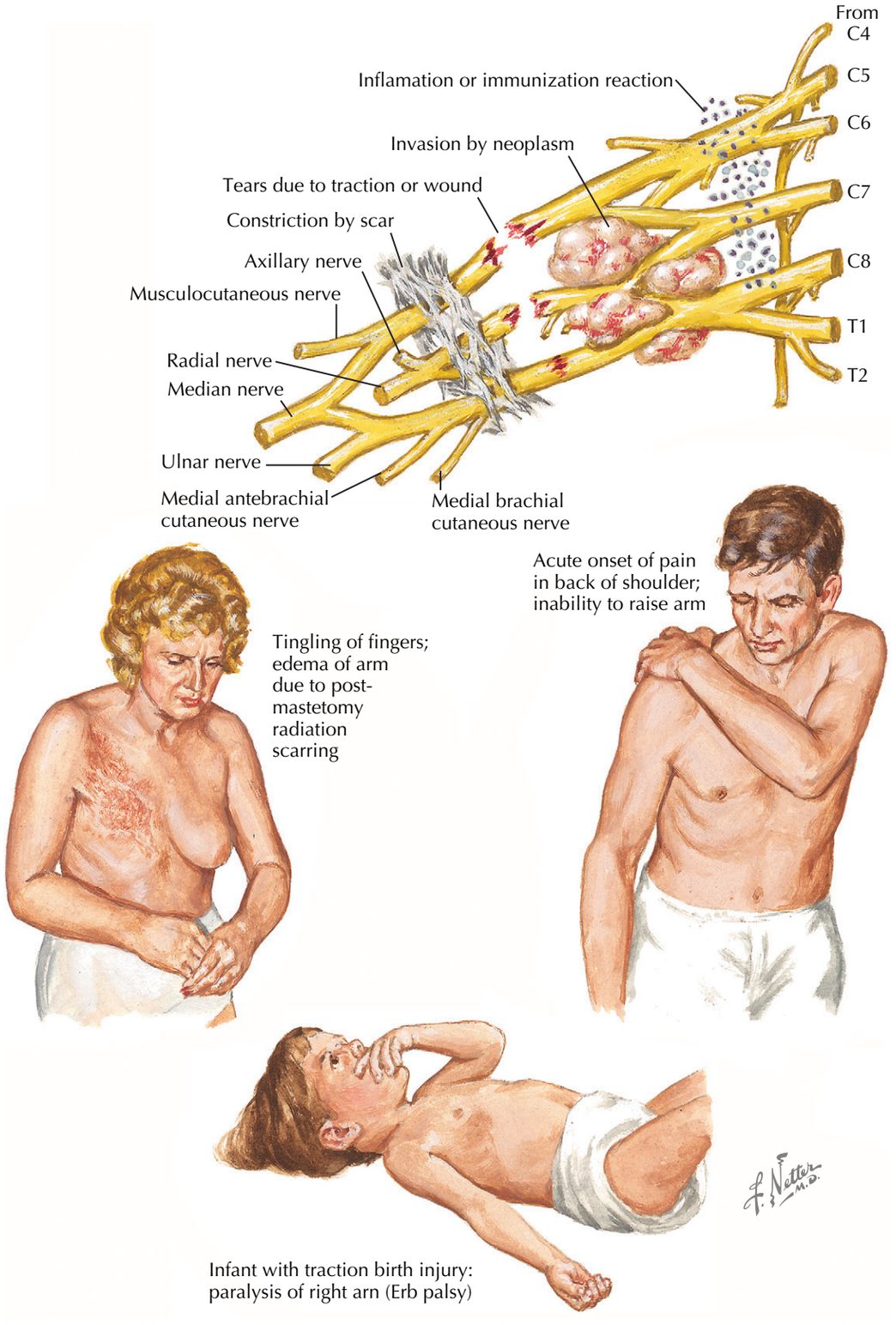
Management. Immediate management should include evaluation for underlying structural lesions of the neck and shoulder. Over the initial 3 to 6 months, there may be significant spontaneous improvement, aided by functional positioning, passive range-of-motion exercises, and splinting. Electrodiagnostic testing can aid in assessing the extent of motor and sensory axon injury and presence of reinnervation. Treatment of neonatal brachial plexus injury is conservative. No surgical procedure is likely to improve the immediate situation or the prognosis. The limb should be placed in its best functional position, that is, across the chest, not abducted and flexed. Gentle, passive, range-of-motion exercise should be initiated within 7 to 10 days of birth. Hand and wrist splints can be constructed later as necessary. Failure to show any clinical improvement over 3 to 6 months is an indication at some centers for surgical exploration, neurolysis, and cable nerve grafting. Electrodiagnostic studies are of diagnostic value in determining the extent of the injury but have not been proven useful, to date, in identifying patients best suited for surgical intervention. After the child is 5 to 6 years of age, muscle transfers may be helpful.





Infant with Erb palsy on right side. Muscles of shoulder and upper arm chiefly affected. Elbow extended and wrist flexed, but grasp normal.

Young girl with Klumpke palsy on right side. Muscles of forearm and hand chiefly affected. Grasp weak and affected limb small. Horner syndrome present, due to interruption of fibers to cervical sympathetic trunk.



Brachial Plexopathy

Trauma is responsible for many acute brachial plexus lesions. The prognosis depends on the severity of the lesion and the distance between the lesion and the muscles innervated by the affected nerve fibers. Thus the likelihood of reinnervation is better for upper trunk/lateral cord lesions and worse for lower trunk/medial cord lesions. Spinal nerve root avulsion precludes reinnervation in the affected segment. Surgical trauma to the brachial plexus can occur in open-heart surgery, when rib cage retraction causes fracture of the first thoracic rib at the costo-vertebral joint and migration of the rib up and entrapment of the C8 anterior primary ramus proximal to its point of combination with the T1 segment to form the lower trunk. The clinical presentation is severe pain and numbness in the medial hand with weakness of finger abduction, and finger extension.

Neuralgic amyotrophy (acute brachial plexitis) is a disorder of acute nerve injury often triggered by an acute infectious illness, immunization, or surgery. It has many potential presentations but usually affects nerve trunks of the shoulder girdle, upper trunk nerve fibers, and parts of peripheral nerve trunks of the arm. Winging of the scapula from long thoracic neuropathy, inability to externally rotate the shoulder from suprascapular neuropathy, and inability to abduct the shoulder from axillary neuropathy are common presentations. Spontaneous improvement occurs in most individuals over 6 to 12 months.

Progressive brachial plexus lesions may result from infiltrative processes, such as malignancy, that spread from local structures, such as the lung (Pancoast tumor) and breast. These tumors tend to involve the lower trunk/medial cord first, producing sensory loss in the fourth and fifth fingers and weakness of intrinsic muscles of the hand. A progressive brachial plexopathy can also result from radiation therapy close to the brachial plexus performed years earlier for treatment of these malignancies.

A slowly progressive lower trunk brachial plexopathy (neurogenic thoracic outlet syndrome) can arise from a fibrous band extending from an elongated C7 transverse process to the first thoracic rib. This anatomic anomaly causes compression of the T1 anterior primary ramus before it merges with the C8 segment to form the lower trunk, producing a classic clinical presentation of numbness of the medial hand and forearm, along with weakness and atrophy of thumb and other intrinsic hand muscles. Progression of weakness is halted by surgical section of the offending fibrous band.

Lumbosacral Plexopathy

The clinical presentation of a lumbosacral plexopathy varies depending on which portion of the plexus is affected: the lumbar, the sacral, or both. Patients with lesions of the lumbar plexus will note prominent hip flexion weakness, although knee extensors and hip adductors may also be involved. This is often accompanied by pain and sensory loss in the distribution of the inguinal region, most of the thigh, and medial lower leg. With lesions affecting the sacral plexus, footdrop is a common presenting complaint, along with weakness in hip extensors, hip abductors, knee flexors, and foot/ankle movements. Pain and sensory changes may be seen in the posterior thigh, most of the lower leg, and throughout the foot. Lesions affecting both parts of the lumbosacral plexus are uncommon but can lead to extensive weakness and sensory changes involving the entire leg.

In contrast to the brachial plexus, traumatic lesions of the lumbosacral plexus are relatively uncommon due to its protective location within the pelvis. Injuries such as gunshot wounds, falls, and motor vehicle accidents, which often result in pelvic fractures, can cause an acute and diffuse lumbosacral plexopathy via blunt force or nerve avulsion.

Malignancy may also cause an extensive lesion of the lumbosacral plexus. Tumor invasion from lymphoma, metastatic disease, or malignancies arising from neighboring structures, for instance, gynecologic tumors and colorectal cancer, may cause compression or direct infiltration of the plexus. Another cancer-related cause is radiation injury, which is a slowly progressive lesion that occurs several years after radiation treatment for cancers within the pelvis. Radiation injuries typically affect the sacral plexus (lower portion), causing weakness, sensory loss, and sometimes pain in the corresponding distributions.

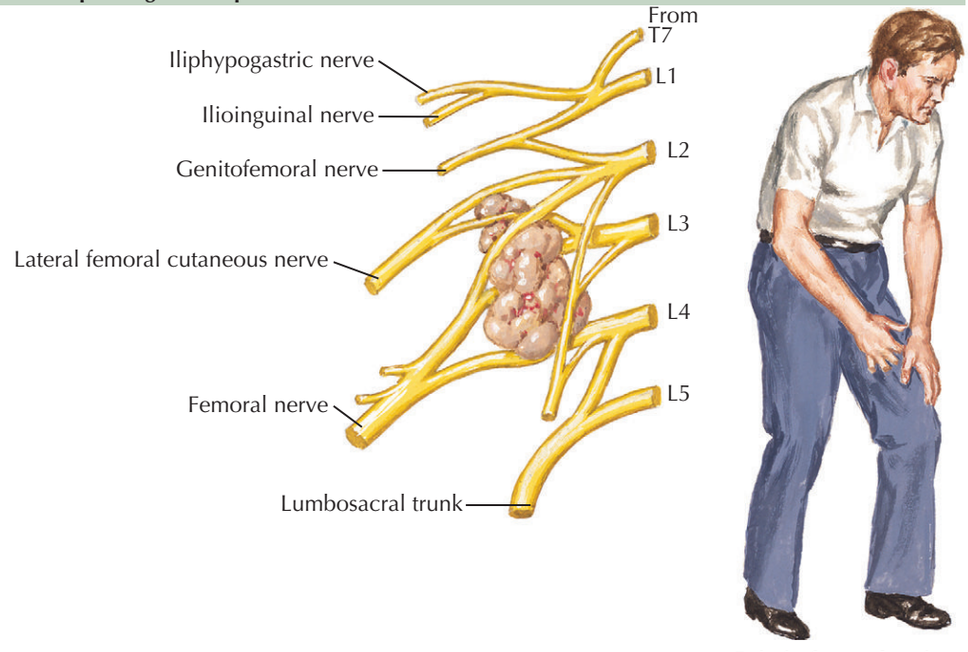
In diabetic patients, an immune-mediated vasculitic lesion may lead to a syndrome called diabetic lumbosacral radiculoplexus neuropathy, which causes severe pain and muscle weakness in lumbosacral plexus–innervated muscles, with corresponding sensory loss (see Plate 4-11). Also known as diabetic amyotrophy, the syndrome may initially mimic a femoral neuropathy, but soon progresses to involve more distal segments and eventually the contralateral lower extremity. Nondiabetic patients may experience a similar clinical syndrome, which is also thought to be due to an immune-mediated microvasculitis. Spontaneous recovery over several months typically occurs in both types, although immune-modulating therapies have been shown in small studies to improve pain and weakness.

A more recently described etiology is maternal lumbosacral plexopathy, which occurs primarily in petite women due to compression of the lumbosacral trunk (L5 nerve root with posterior portion of L4) by the descending fetal head at the pelvic brim. Following a difficult or prolonged labor that, in many cases, necessitates a forceps delivery or cesarean section, the patient will notice a footdrop on attempts to stand or walk. Fortunately, the underlying pathophysiology of the lesion is thought to be demyelinating conduction block, and most patients spontaneously recover within 3 months.

Retroperitoneal hematomas in patients receiving anticoagulation or after experiencing blunt trauma may compress the lumbar plexus and result in acute weakness of hip flexors, with pain in the groin, hip, or lower abdomen. The hemorrhage is usually seen on computed tomography (CT) of the abdomen and pelvis, and can be accompanied by a sudden drop in the hematocrit level.

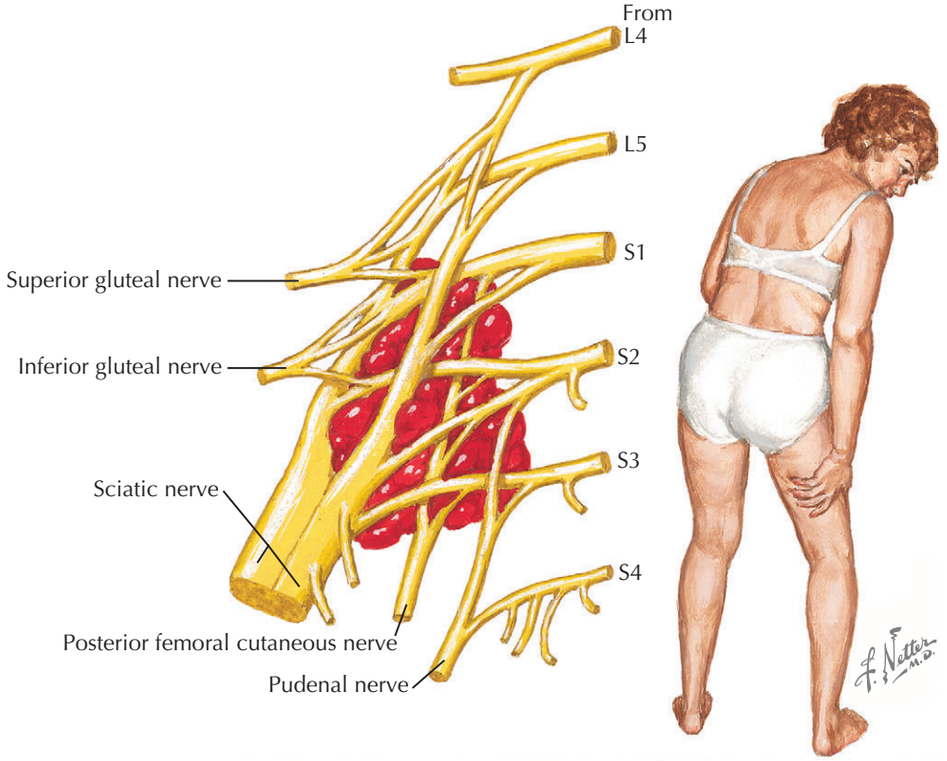
Finally, infection may cause a lumbosacral plexopathy through a compressive mechanism due to an infra-abdominal abscess or infiltrative lesion, such as that seen with herpes simplex or cytomegalovirus infections.

Tumor compressing lumbar plexus

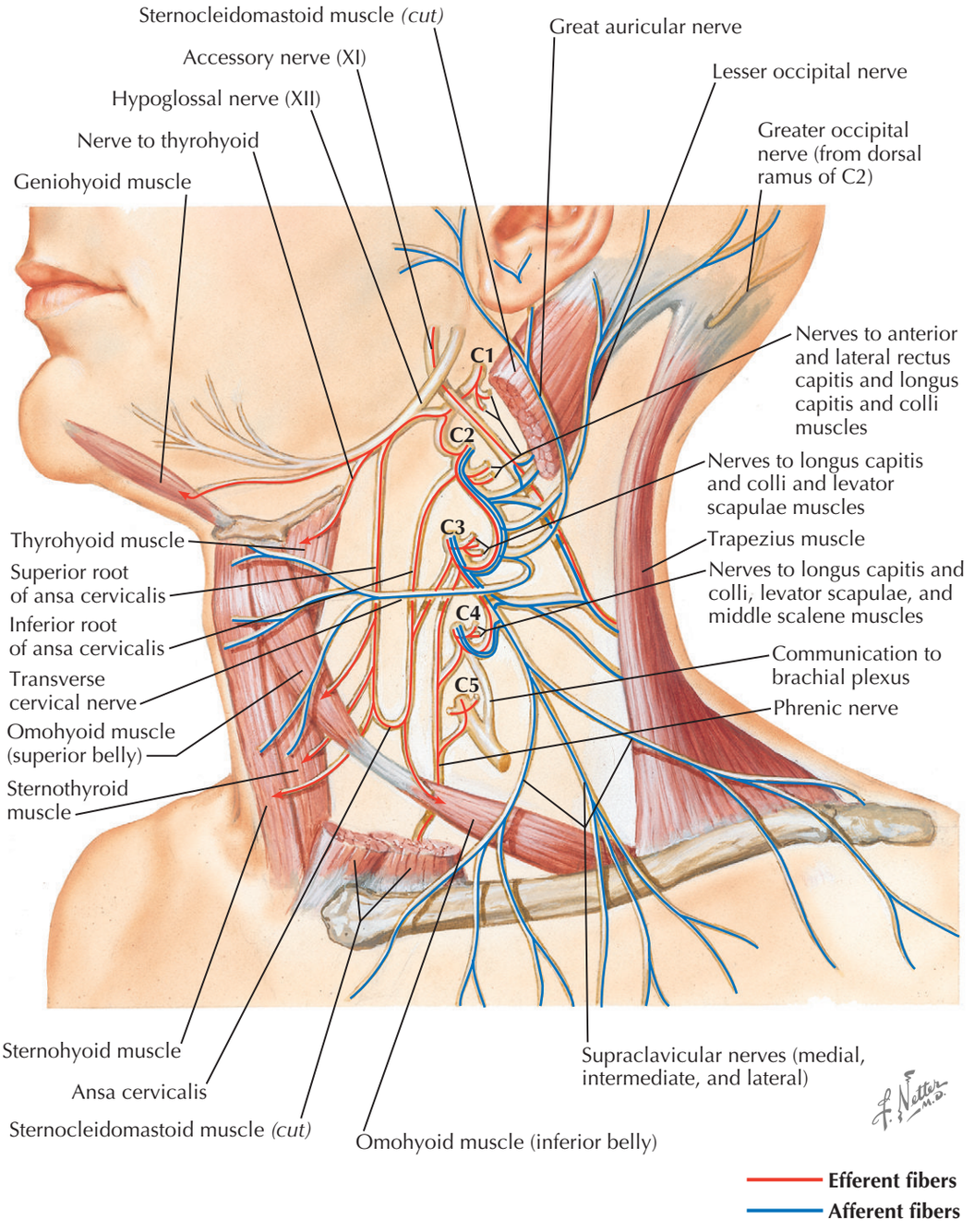


Pain in femoral region

Hematoma compressing sacral plexus



Pain in back of thigh



Cervical Plexus

The cervical plexus lies deep to the sternocleidomastoid muscle. Its branches convey motor fibers (to many cervical muscles and to the diaphragm), sensory fibers (from parts of the scalp, neck and chest), and autonomic fibers (to vessels and glands). The superficial branches perforate the cervical fascia to supply cutaneous structures, whereas the deep branches supply mainly muscles and joints.

The superficial branches are the lesser (minor) occipital, great auricular, transverse (cutaneous) cervical, and supraclavicular nerves.

The *lesser occipital nerve* (C2, C3) curves around the accessory (XI) nerve, ascends near the posterior border of the sternocleidomastoid muscle, and divides into branches that supply the skin on the superolateral aspects of the neck, the upper part of the auricle, and the adjacent area of the scalp.

The *great auricular nerve* (C2, C3) is larger than the lesser occipital and passes obliquely upward over the sternocleidomastoid muscle, lying near the external jugular vein before dividing into anterior and posterior branches. The former passes over or through the parotid gland to supply the skin of the posteroinferior part of the face. The latter supplies the skin over the mastoid process and over the medial and lateral surfaces of the lower part of the auricle.

The *transverse cervical nerve* (C2, C3) runs forward beneath the external jugular vein to divide into superior and inferior branches, which supply the skin over the anterolateral aspects of the neck from the mandible above to the sternum below.

The *supraclavicular nerves* (C3, C4) arise from a common trunk, which descends for a variable distance before dividing into medial, intermediate, and lateral supraclavicular nerves. These supply the skin over the lower neck from near the midline to the acromioclavicular region and above the shoulder. They then pass in front of the clavicle to innervate the skin of the anterior chest wall to the level of the sternal angle and the second rib. The medial and lateral nerves, respectively, send twigs to the sternoclavicular and acromioclavicular joints.

The deep branches are mainly motor, but they also carry proprioceptive, osseous, articular, and autonomic fibers to and from muscles, bones, joints, and vessels in their areas of distribution. Some motor branches pass *medially* to supply the rectus capitis anterior and rectus capitis lateralis (C1, C2), longus capitis (CI, C2, C3), longus colli and intertransverse (C2, C3, C4) muscles, and the diaphragm through the phrenic nerve. Other muscular branches pass *laterally* to the sternocleidomastoid (C2, C3), trapezius (C3, C4), levator scapulae (C3, C4), and scalenus anterior and scalenus medius (C3, C4) muscles; the branches to the sternocleidomastoid and trapezius muscles are reputedly proprioceptive, but they nevertheless communicate with motor branches of the accessory nerve to these muscles.

A branch from the loop between C1 and C2 joins the hypoglossal (XII) nerve. Some of these fibers continue onward, along with the hypoglossal nerve, to supply the thyrohyoid and geniohyoid muscles, whereas others leave it as a filament running downward, anterolateral to the carotid sheath, the *superior root* (*descendens hypoglossi*) of the *ansa cervicalis*, or *ansa hypoglossi*. The ansa ("loop") is completed by the *inferior root* (*descendens cervicalis*) derived from C2 and C3. Branches from the ansa supply the sternohyoid, sternothyroid, and omohyoid muscles.

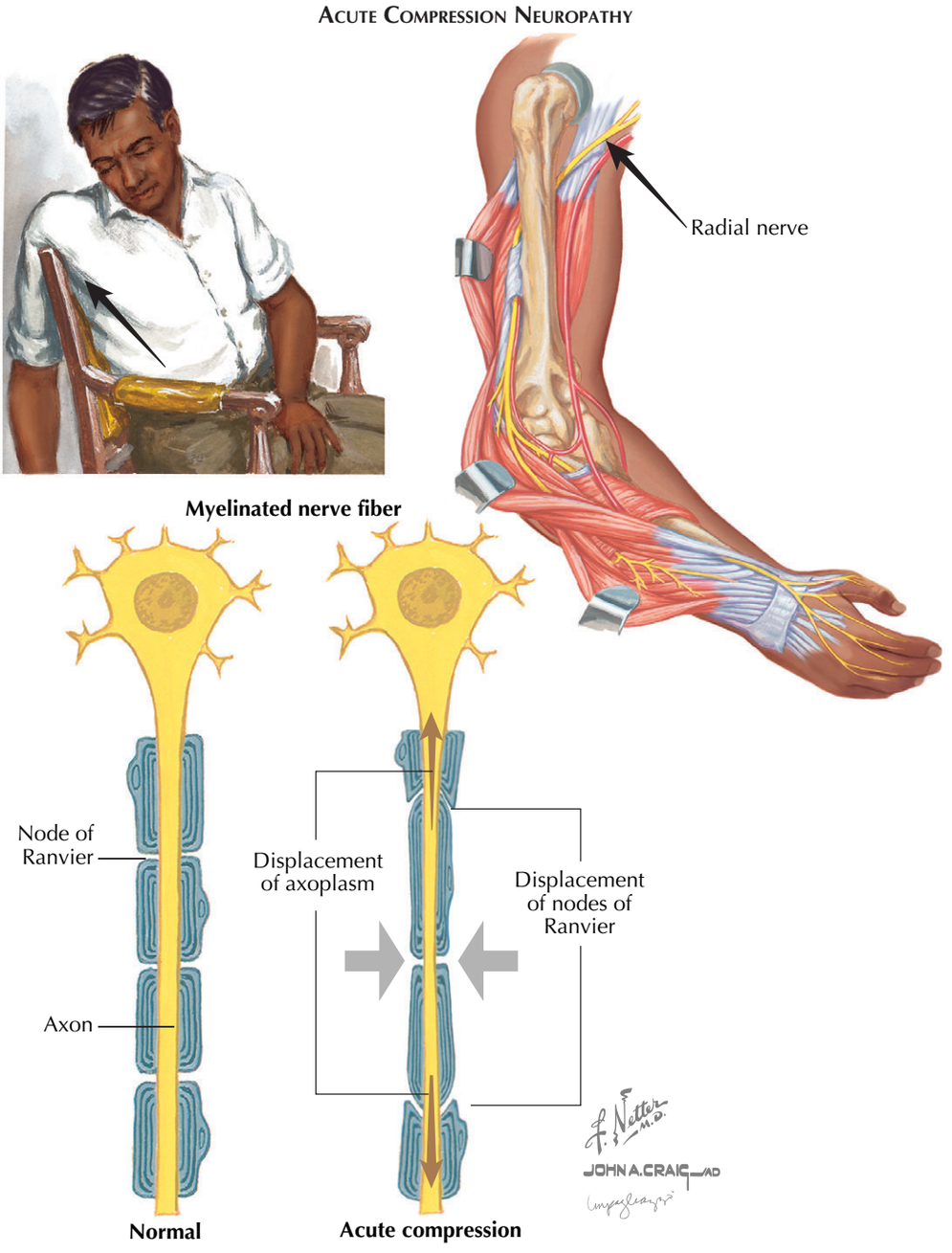
MONONEUROPATHIES

Compression Neuropathies

Compression neuropathies occur acutely (e.g., proximal radial nerve palsy, peroneal neuropathy at the fibular hear) or more gradually (e.g., median neuropathy at the wrist, ulnar neuropathy at the elbow). Acute compressive neuropathies typically develop at sites where external pressure can compress the nerve against a harder surface, such as the radial nerve at the humerus' spiral groove. Chronic mononeuropathies (e.g., entrapment neuropathies) occur where nerve passes through tissue tunnels with a propensity to narrow with time, eventually entrapping the nerve itself.

Acute neuropathies tend to manifest more with predominant motor manifestations, for instance, peroneal neuropathy—a footdrop, and radial neuropathy—a wristdrop; sensory disturbances are relatively mild. Entrapment neuropathies usually present with paresthesias (tingling) predating focal weakness by months and often years, as well as overshadowing it. Median neuropathies at the wrist initially are characterized by hand tingling at night or with various hand activities, particularly driving; only later in the course does weakness of the thumb, particularly the abductor pollicis brevis, become evident. Diabetes mellitus, myxedema, or, rarely, hereditary neuropathy with liability to pressure palsy makes nerves more susceptible to compression injury.

Peripheral nerves are made up of many myelinated and unmyelinated nerve fibers originating from either the anterior horn cell (motor) or the posterior root ganglia (sensory) and traveling the nerve's entire length. Nerve fibers are organized into *fascicle*s, of which there are many within one peripheral nerve. Elements contained within the fascicles represent the *endoneurium*. The *perineurium*, a protective sheath of connective tissue, surrounds each fascicle. *Schwann cells* concentrically wrap their cytoplasmic processes around axons many times, creating the myelinated nerve fiber. Each nerve segment is associated with one adjacent Schwann cell. When many Schwann cells are lined up contiguously, the entire nerve fiber becomes myelinated. An *internode* consists of one *myelinated segment*. *Nodes of Ranvier* represent areas lacking myelin, thus interrupting the internodal sections and containing high concentrations of *voltage-gated sodium channels*. *Juxtaparanodal* and *paranodal regions* are distinctive myelin folds at internode edges containing high concentrations of *voltage-gated potassium channels*. These areas are integral to conduction of action potentials down the axon.



Acute Nerve Compression

When nerve tissues are subjected to mechanical compression, some of the compressed tissues are displaced to sites of lower pressure. This is especially the case for acute compression neuropathies, such as proximal radial neuropathy ("Saturday night palsy") and neuropathies secondary to tourniquet compression. With acute nerve compression, damage is concentrated at the compression edges. The predominant injury at this level implies that the pressure gradient itself, rather than the absolute pressure, is the critical factor for acute compression neuropathy.

In the setting of experimental acute compression, the earliest histopathologic change seen within just a few hours is *an invagination of one paranodal segment* into its adjacent paranode. Directed toward the uncompressed tissue, paranodal myelin, tethered to the axon, may be grossly distorted, resulting in invagination on one side and passive stretching on the other side. Longitudinal movement of the axon relative to the Schwann cell accompanies the paranodal myelin alterations. In extreme cases, myelin lamellae may be ruptured. These findings are reminiscent of intussusception of the bowel, suggesting that that the pressure gradient between compressed and uncompressed nerve provides definitive forces causing axoplasm extrusion "similar to toothpaste from a tube."

The sequential events of acute, focal compression initially include an early combined extrusion of endoneurial fluid (i.e., the fluid between fibers), axonal fluid, and cytoskeletal elements, and subsequently distortion of myelin and Schwann cell elements. A second slower phase is attributed to further endoneurial and axonal fluid extrusion, paranodal disruption, Schwann cell cytoplasm extrusion, and displacement of other tissue elements. Additional damage (e.g., of the cytoskeletal network) may occur at more extreme pressures or with protracted compression. Nodes of Ranvier are frequently obscured or lengthened because of displaced paranodal myelin.

Classic nerve conduction studies provide a means to measure the magnitude of the nerve action potential conduction block as well as focal conduction slowing. These findings correlate with the degree and duration of compression. Focal ischemia may also contribute in some compression neuropathies, particularly in combination with the direct effects of pressure. Transient nerve block, for instance, when a limb "goes to sleep" for a few seconds, may be related to modest external pressures, and/or may be primarily caused by focal ischemia because no recognizable structural nerve pathology has been convincingly demonstrated. For more severe cases of acute compression, nerve fiber remyelination may occur weeks to months after resolution of the acute compression.

Chronic Nerve Compression

The earliest histopathologic change observed in chronic nerve compression is an asymmetric distortion of the large myelinated fiber internodes; there is tapering of the internodes at one side and swelling of the internodes at the other. A modified axoplasm accumulation occurs, possibly caused by interference of axon flow. The direction of tapering (i.e., polarity) reverses on the other side of the compressive lesion. In cases of chronic ulnar neuropathy, the reversal of polarity appears to lie under the aponeurosis of the flexor carpi ulnaris muscle. Similarly, with chronic median neuropathies, the reversal of polarity is under or near the flexor retinaculum over the carpal tunnel. In contrast to the pathologic changes of acute nerve compression, there is no displacement of nodes of Ranvier. Subsequently, these myelinated fiber paranodal changes are followed by demyelination and remyelination, events probably occurring repeatedly during chronic compression.

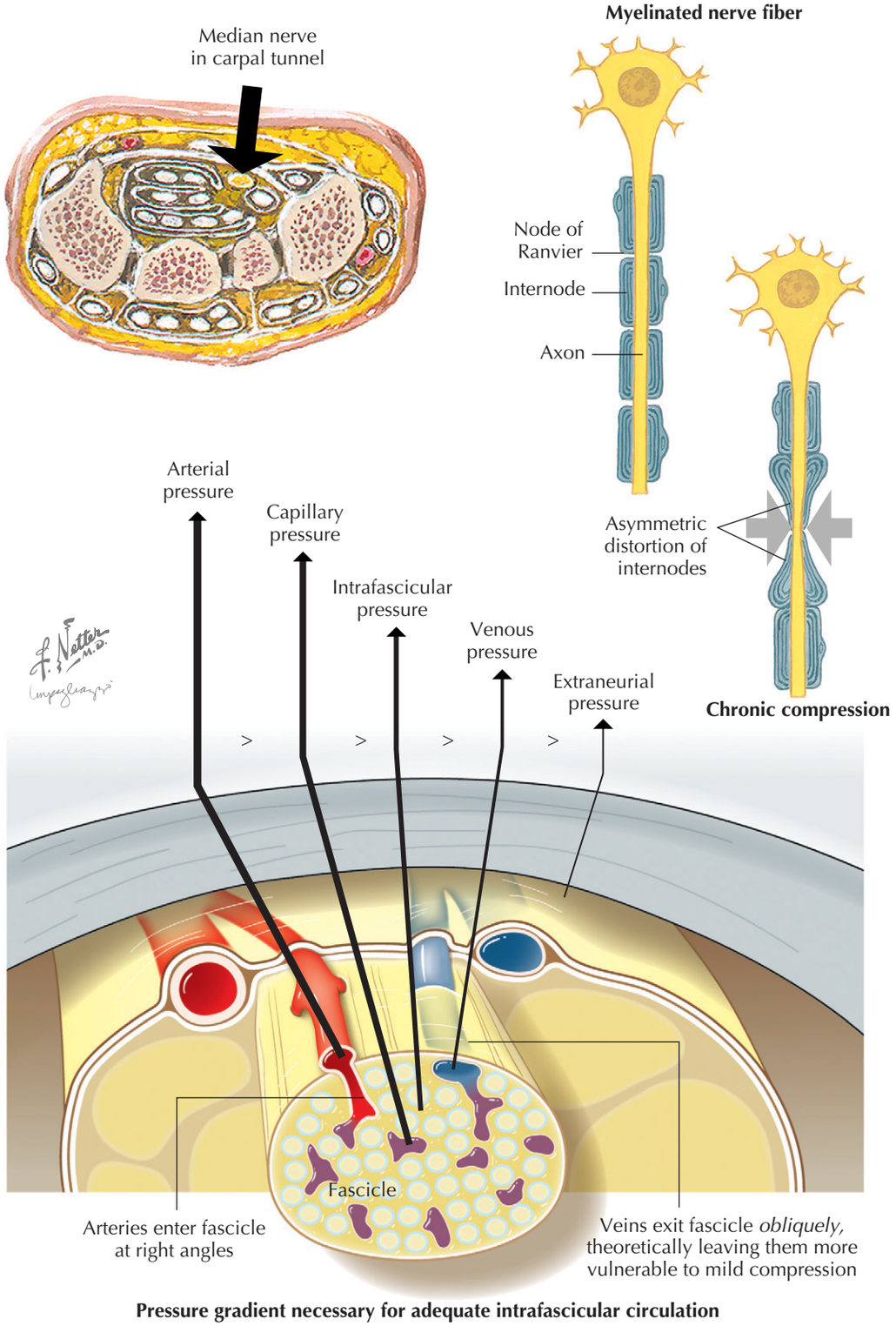
Ischemia and endoneurial edema also contribute to the pathology of nerves that sustain chronic compression; modest pressure magnitudes develop, such as occurs with median nerve compression in the carpal tunnel and ulnar neuropathy at the elbow. The ischemic hypothesis has focused on the *transperineurial vascular system*. This includes an intrafascicular circulation, composed mostly of capillaries running longitudinally within the endoneurium and an extrafascicular network within the epineurium, composed predominantly of venules and arterioles. The extrinsic vessels penetrate the relatively rigid perineurium to anastomose with the intrinsic circulation, and it is this transperineurial vessel network that may be particularly susceptible to focal compression, especially because these vessels traverse the perineurium at oblique angles.

These transperineurial vessels, especially the venules, are vulnerable to constriction caused by endoneurial edema and elevated (intrinsic) endoneurial fluid pressure. Constriction of these vessels causes venous congestion, endoneurial capillary leakage, and elevated endoneurial fluid pressures. These effects introduce metabolic disturbances to the microenvironment, with subsequent damage to the peripheral nerve anatomy and nerve function. Thus chronic external compression may induce ischemia and endoneurial edema with concomitantly elevated endoneurial fluid pressures. These two effects impair nerve function by altering the metabolic microenvironment as well as contributing to nerve injury by further constricting transperineurial venules. Thus a precarious cycle of venous congestion, ischemia, and metabolic disturbances is initiated that eventually leads to a "*miniature compartment syndrome.*"

In cases of median neuropathy at the wrist (i.e., carpal tunnel syndrome), it is thought that carpal tunnel pressures may rise to abnormal levels, increasing the endoneurial fluid pressure and thereby impairing the transperineurial microcirculation. Carpal tunnel pressure and consequently endoneurial fluid pressures probably rise significantly at night in the setting of carpal tunnel syndrome because the limb venous return is impeded by limb posture and reduced limb movement. *Endoneurial edema* due to other causes, for instance, diabetes, further increases nerve susceptibility to compression.

Moderately elevated pressures also disturb axonal transport. Retrograde axonal transport is critical for communication with the nerve cell body. Fast and slow anterograde axonal transport may also be reversibly impaired after compression. The blocking of axonal transport with compression is a graded effect, related to the magnitude and duration of compression. For example, the susceptibility to entrapment in diabetic polyneuropathy may be in part due to the combination of widespread endoneurial edema (diabetes) and focal (entrapment) impairment of axonal flow.

The gliding capacity of a peripheral nerve is another important factor inherent to chronic compression neuropathies. This is particularly relevant at common sites of entrapment, such as the wrist and elbow. Gliding of nerves is necessary during movement of limbs and is made possible by conjunctiva-like adventitia that allow longitudinal excursion of a nerve trunk. Restriction of glide may occur with extraneural and intraneural fibrosis, especially at sites of entrapment, inducing nerve stretch lesions, edema, inflammation, and further fibrosis. Stretch may contribute to nerve injury at common sites of entrapment, although it is unlikely to be the major factor in injury and is likely overshadowed by the consequences of direct pressure and perhaps ischemia.



Pressure gradient necessary for adequate intrafascicular circulation

Evaluation of Mononeuropathies

Clinical Assessment

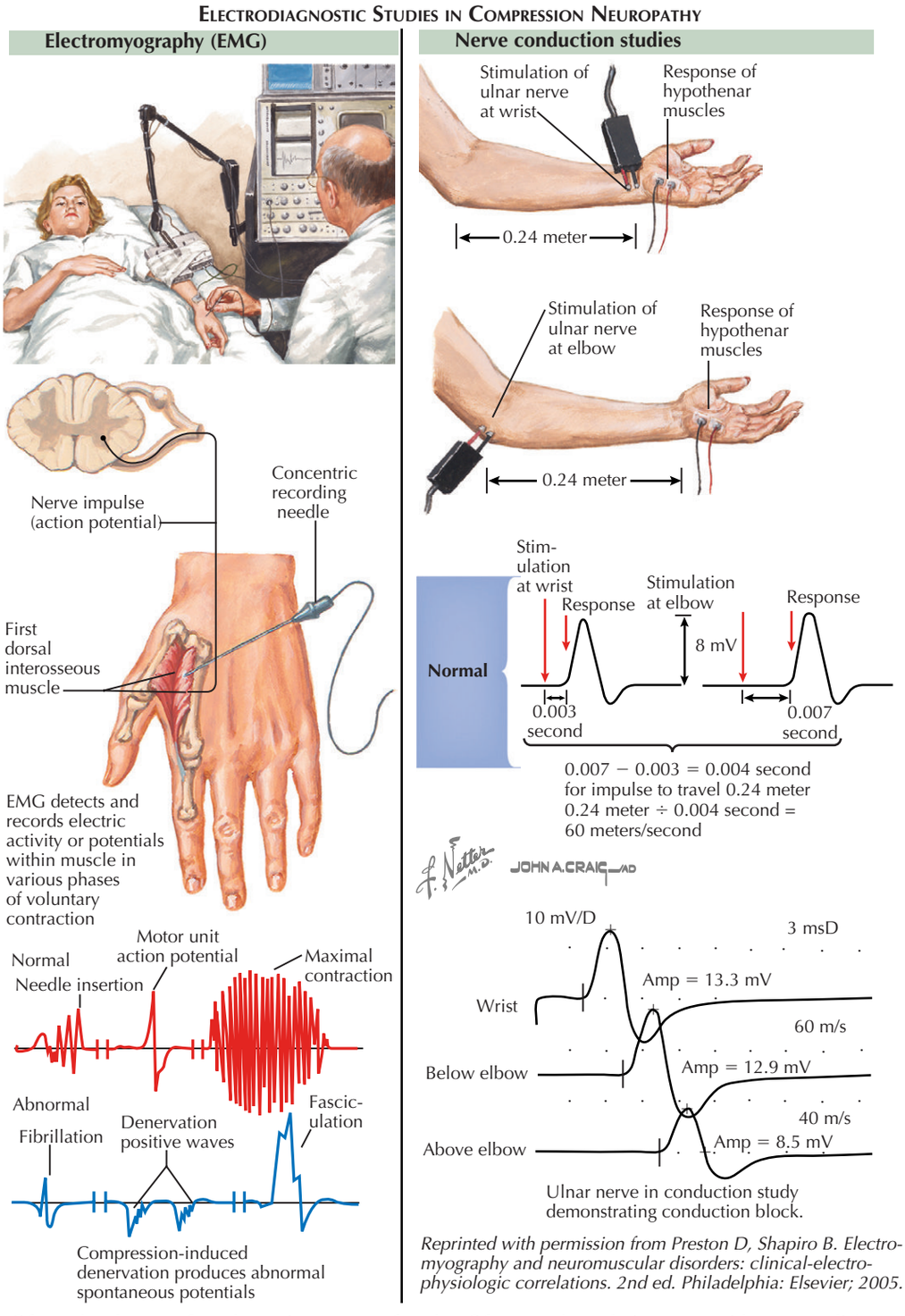
Careful history and meticulous neurologic examination are essential for evaluation of mononeuropathies. Initially, one defines the precise motor and sensory deficits and next decides whether this fits an individual peripheral nerve's anatomic distribution. This is relatively easily accomplished with acute nerve trauma, that is, a laceration or gunshot wound. In contrast, most mononeuropathies have a relatively ingravescent course characterized first by intermittent paresthesias initially not producing clinically definable functional loss.

Each peripheral nerve has a unique clinical anatomic signature vis-à-vis motor and sensory deficits when these nerves are compromised. This is illustrated by the seemingly complicated cutaneous sensory distribution of the median, radial, and ulnar nerves in the hand. With this knowledge, clinicians are often able to outline characteristic clinical features of a specific pattern of compromised function appropriate to a mononeuropathy. Frequently, symptoms of a mononeuropathy are stereotyped and sometimes evanescent, such as with the carpal tunnel syndrome.

Occasionally, underlying systemic illnesses predispose to the occurrence of more than one acute mononeuropathy, that is, mononeuritis multiplex. A sudden footdrop secondary to a fibular (peroneal) nerve lesion is followed in days to weeks by another mononeuropathy, such as a wristdrop from an acute radial nerve lesion, and soon thereafter another nerve becomes acutely compromised. Systemic vasculitides, such as occurs in polyarteritis nodosa, are often responsible. Hereditary neuropathies with liability to pressure palsies (HNPP) lead to recurrent multiple neuropathies in a chronic setting (see Plate 5-22). Sometimes symptoms of a possible mononeuropathy actually represent an initial sign of a plexus, nerve root, spinal cord, or brain lesion.

Patients with recurrent hand numbness or weakness require consideration for transient cerebral ischemic attacks or, rarely, an intracranial tumor such as a meningioma. Parasagittal cerebral lesions may occasionally manifest primarily with foot weakness. Individuals presenting with hand weakness but no sensory loss or pain may have a deep ulnar motor lesion within their medial palm or even motor neuron disease.

Neck or low back *pain* usually indicates a protruded or herniated disk (nucleus pulposus) affecting one specific nerve root. Often this discomfort *radiates into an arm or a leg and is associated with tingling and numbness (paresthesias), and sometimes weakness* is confined to the distribution of a nerve root. However, this clinical picture is not always straightforward enough to allow for simple clinical judgment to make a diagnosis based on history alone. For example, in the common setting of a footdrop, the clinician needs to examine carefully the leg muscles to define whether the affected muscles have only a peroneal nerve distribution with weakness confined to dorsiflexors (tibialis anterior) and evertors (peroneus longus). In contrast, the affected muscles may have an L5 nerve root derivation, that is, tibialis anterior primarily, but also a subtle inability to invert the foot because of weakness of the tibialis posterior. These muscles are innervated by two different peripheral nerves, fibular and tibial, and the weakness is thus compatible with a specific L5 radiculopathy. This distinction is sometimes difficult to make initially, and thus electromyography (EMG) is the first study of choice.



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Often, the degree of weakness is more profound in a mononeuropathy than a nerve root lesion because the affected muscles are solely dependent on that nerve, whereas a nerve root lesion does not affect all fibers going to the affected muscles. For example, with a wristdrop where there is concomitant C6 and C7 root supply, if just the C7 root is affected, the muscles continue to have partial innervation from the C6 root, and thus there is not a total paralysis of the wrist and finger extensors. In contrast, if the radial nerve is damaged, there is no overlapping safety feature of multiple innervations as in nerve root disorders. Here the deficit's severity is directly related to how significant the damage is within that nerve itself. Often, total paralysis occurs with acute radial nerve damage. Muscle atrophy develops when there is significant peripheral denervation.

Measuring extremity circumference may document significant side-to-side asymmetries representative of muscle atrophy and, by inference, anterior horn cell, nerve root, or peripheral nerve damage. Patients with brachial or lumbosacral plexus lesions are less likely to have neck or back pain but, rather, pain within the affected extremity. Here the numbness may be more diffuse, and muscles are weakened within the distribution of multiple peripheral nerves/nerve roots.

Numbness rather than pain is much more common with early mononeuropathies. The symptom onset and

Evaluation of Mononeuropathies *(Continued)*

progression can help in diagnosis. Because sensory examination is the most subjective part of the neurologic examination, occasionally this is difficult to define clearly. Sometimes the patient can provide the most accurate assessment by roughly outlining the area in question using a finger to demonstrate the area of diminished sensation; this is best demonstrated with meralgia paresthetica (see Plates 5-15 and 5-16), where the patient outlines an elliptic loss of sensation on the lateral thigh. These assessments often clarify whether the pattern of sensory loss is specific to one peripheral nerve or nerve root dermatome. Meralgia paresthetica best illustrates this with lateral thigh sensory loss secondary to a lateral femoral cutaneous nerve lesion. Often, it is easier for the patient to outline the precise deficit than the clinician.

Percussion over an affected nerve frequently elicits paresthesias within its specific distribution: the *Tinel sign*. This is best performed using the small head of a percussion hammer; this can be elicited in many mononeuropathies, particularly the median nerve at the wrist, (i.e., carpal tunnel syndrome [CTS]), ulnar nerve at the elbow, radial nerve over the humerus spiral groove, and fibular (peroneal) nerve at the fibular head.

Mononeuropathy: Diagnostic Studies

Sometimes clinical neurologic examination is not precise enough to provide early diagnosis of mononeuropathies. Electrodiagnostic studies are the method of choice for defining the precise anatomic distribution of peripheral nerve damage. This includes nerve conduction studies (NCS) and needle EMG. Thus it is possible to assess the quality of peripheral nerve conduction as well as whether there is damage to muscles specifically innervated by that nerve. NCS allows identification of the site of nerve damage whenever the nerve's myelin is chronically damaged. Examples include chronic ligamentous thickening over the carpal tunnel (see Plate 5-10), sudden sustained acute pressure over the radial nerve at the humerus (see Plate 5-13), or fibular (peroneal) compression at the knee (see Plate 5-19).

Early signs of a carpal tunnel syndrome are best defined by sensory NCS, and later motor NCS, demonstrating prolongation of the time for nerve conduction across the wrist (distal latency). Motor NCS are especially useful for defining more proximal nerve blocks, that is, at the elbow (ulnar nerve), midhumerus (radial nerve), and knee (fibular [peroneal] nerve). This leads to a diminution of the compound muscle action potential (CMAP) just above the site of nerve block (see Plate 5-3). Conduction slowing provides another means to identify a nerve block. Here there is focal motor NC slowing (by 30%-40%, i.e., 10-20 m/sec) at the site of anatomic compromise, that is, across the fibular head for the fibular (peroneal) nerve.

Needle EMG also may provide a precise means to specifically define the affected muscles. When the nerve's axon is partially damaged, spontaneous firing of small muscle fibers occurs. These are known as denervation potentials, that is, fibrillation potentials and positive waves. Similarly, when the nerve lesion leads to significant damage, there is a diminution in the number of motor units firing. The healthy remaining motor units (MUPs) attempt to compensate by reinnervation; this results in larger MUPs that are recruited at increased frequency.

Patients with a footdrop secondary to a fibular (peroneal) nerve lesion demonstrate denervation signs confined to fibular-innervated muscles. However, if the footdrop is secondary to an L5 root lesion, signs of denervation are demonstrated not only in fibular (peroneal) muscles but also L5 muscles innervated by both peroneal and posterior tibial nerves. These include the posterior tibial, the gluteus medius, and the lumbosacral paraspinal musculature. Thus by combining NCS and EMG, the electromyographer has the ability to literally map the precise pathoanatomy of the nerve lesion.

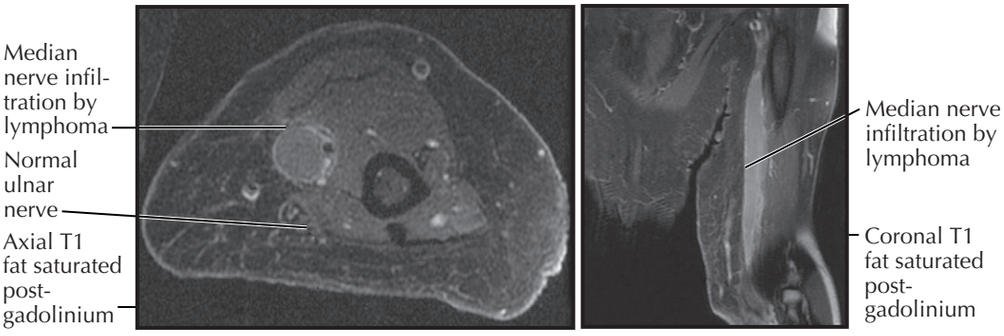
Magnetic Resonance Imaging. MRI studies provide an increasingly used means to evaluate for occult tumors or congenital lesions (Plate 5-4). Very rarely, certain congenital or acquired lesions, such as fibrous bands, may entrap the nerve without MRI identification. In this instance, surgical exploration based on the clinical and EMG findings may lead to a diagnosis.

Ultrasound. This modality is gaining an increased presence in some centers for more rapid identification of sites of nerve compression or entrapment.

Skeletal Radiograph. Rarely, bony abnormalities entrap a peripheral nerve. Examples include popliteal fossa bony exostoses entrapping the tibial nerve. The sciatic nerve is rarely entrapped at the pelvic ischium in babies.

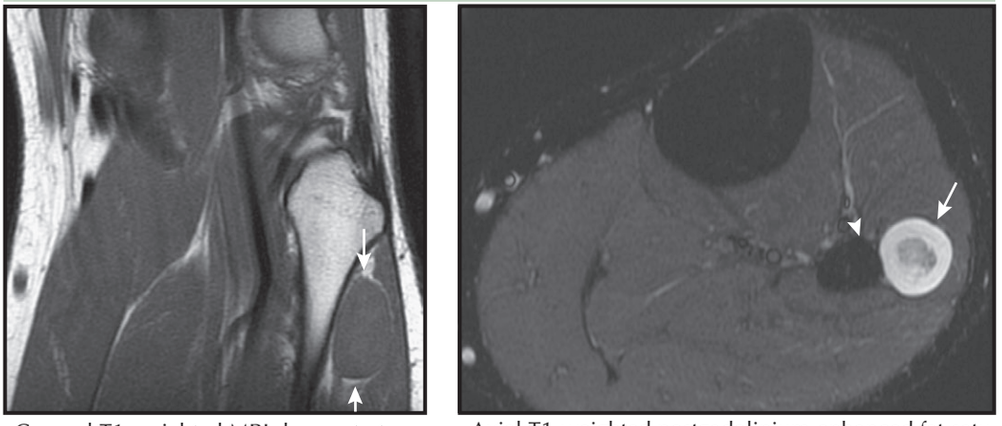
Radiologic Studies in Compression Neuropathy

Median nerve lymphoma



Fusiform enlargement of the median nerve extending from the upper humerus to the elbow. This mass enhanced with gadolinium but without periosteal involvement.

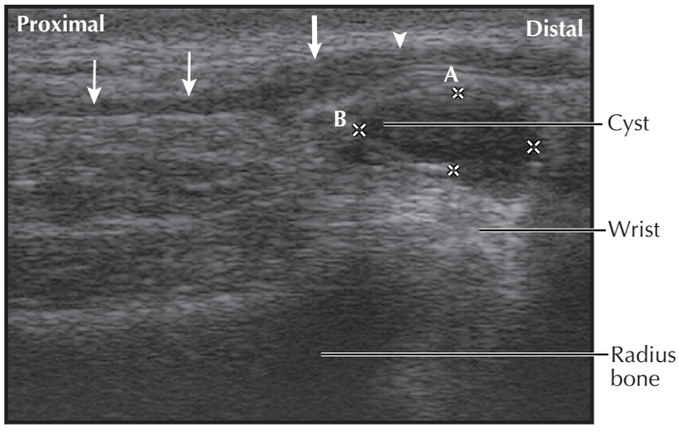
Peroneal nerve schwannoma



Coronal T1-weighted MRI demonstrates an oval mass of left peroneal nerve *(arrows)*

Axial T1-weighted postgadolinium-enhanced fat-saturated MRI demonstrating enhancing peroneal nerve schwannoma with central myxoid degeneration *(arrow)* near fibula *(arrowhead).*

Median nerve entrapment



Longitudinal ultrasound image of the median nerve within the wrist (Toshiba Nemio XG, 14.0 MHz linear array transducer). The nerve *(arrows)* is compressed from below by a fluid-filled structure *(arrowhead)*, consistent with a ganglion cyst *(A, stars)*. Compression-related swelling of the median nerve can be appreciated at the proximal end of the cyst *(B)*. *(Ultrasound courtesy Steven Shook, MD.)*

Proximal Nerves of the Upper Extremity

Shoulder girdle mononeuropathies are relatively uncommon when compared with the frequency of most other mononeuropathies encountered in clinical practice. However, each nerve has its own unique function. When evaluating the patient with shoulder pain or weakness, it is most important to appreciate these anatomic intricacies. Variable degrees of discomfort within the shoulder or a focal proximal weakness are often the cardinal symptoms. These patients with proximal arm neuropathies need to be differentiated from fifth cervical nerve root disorders as well as a primary orthopedic shoulder joint lesions.

The clinical demonstration of weakness and atrophy specific to one of these nerves provides important differential diagnostic clues. Typically, the patient with a primary orthopedic problem, such as a rotator cuff injury or calcific bicipital tendonitis, also usually has significant shoulder pain, but, in contrast to these proximal neuropathies, they lack weakness. The patient with one of these orthopedic problems may be a challenge to examine because his or her joint-related pain will initially lead them to report having weakness, because often it is initially *"too painful"* for them to cooperate. However, a skillful neurologic or orthopedic examination can often sort out these anatomic challenges by asking the patient to give full effort, for just a few seconds, to eliminate the pain component limitation. This becomes more confusing when there is major shoulder joint trauma because both the joint and its proximate nerves are affected. In this setting, the combination of careful electromyography and magnetic resonance imaging (MRI) will allow definition of the nature of the lesion.

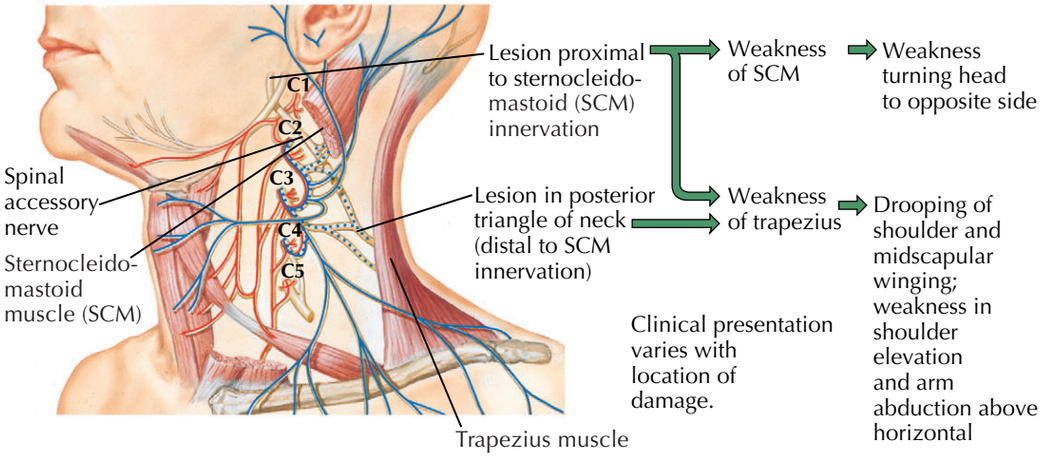
The *spinal accessory nerve* is unique in that it is derived from two seemingly disparate motor neuron populations. However, in fact, these are in continuity. One set originates intracranially from *bulbar fibers*, originating in line with the nucleus ambiguous within the medulla. However, the primary source for the spinal accessory nerve lies within *cervical spinal cord segments C1-5, 6*. Here its cell bodies are found within the lateral anterior gray column's posterolateral anterior horn. This nerve exits the skull via the *jugular foramen*, accompanying the vagus nerve. The cranial fibers innervate some of the laryngeal muscles, whereas the primary portion of the spinal accessory nerve fibers innervates the sternocleidomastoid and trapezius muscles. The spinal portion is joined by fibers from the third and fourth upper cervical rami; these innervate the caudal trapezius muscle. In contrast, the remainder of the trapezius and the entire sternocleidomastoid are supplied by the accessory portion of this nerve.

Injury to the spinal accessory nerve rarely occurs and usually is secondary to surgical procedures involving the posterior triangle of the neck, where it is particularly at risk with lymph node biopsies. Spinal accessory nerve injury can lead to scapular winging secondary to loss of some innervation of the trapezius muscle. This is characterized by one of the two forms of scapular winging that is recognized by lateral scapula deviation (see Plate 5-5). This needs to be differentiated from long thoracic nerve palsy.

The *long thoracic nerve* originates directly from C5 to C7 roots immediately before the formation of the brachial plexus. It primarily innervates the *serratus anterior* muscle that stabilizes the scapula for pushing movements and elevates the arm above 90 degrees. There is no cutaneous sensory innervation. *Long thoracic neuropathy* is the common cause for scapular winging. This is best recognized by having a patient extend the arms and then push against a wall; in this instance, the inferior medial scapular border is prominently projected away from the chest. Unilateral scapular winging can also be caused by weakness of the trapezius *(spinal accessory neuropathy)* or the rhomboid muscles *(dorsal scapular neuropathy)*. These neuropathies produce a lateral scapula deviation, in contrast to the long thoracic medial scapula deviation. The long thoracic nerve may be damaged by acute brachial neuritis, mechanical factors, and surgical procedures, including mastectomy or thoracotomy. Occasionally, patients present with bilateral scapular winging. This is most commonly related to facioscapulohumeral muscular dystrophy because it is unusual to have bilateral long thoracic nerve palsies.

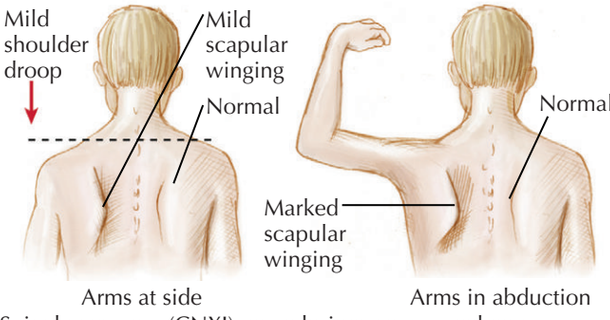
The *dorsal scapular nerve (C5)* arises from the *uppermost root* of the brachial plexus. It pierces the scalenus

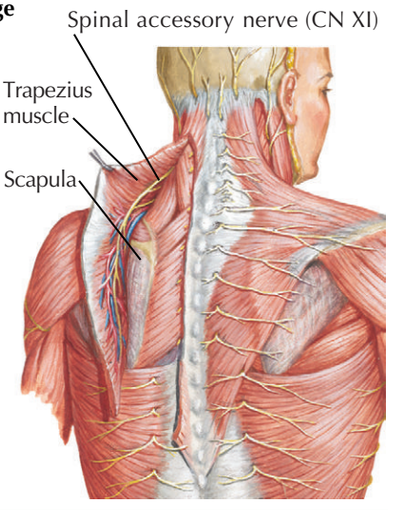
Clinical Comparison of Winged Scapula Cranial Nerve XI and Long Thoracic Nerve Palsy



Comparison of clinical findings in CN XI and long thoracic nerve damage

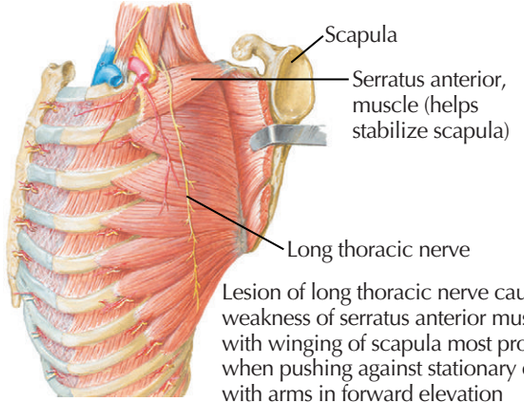
CN XI damage



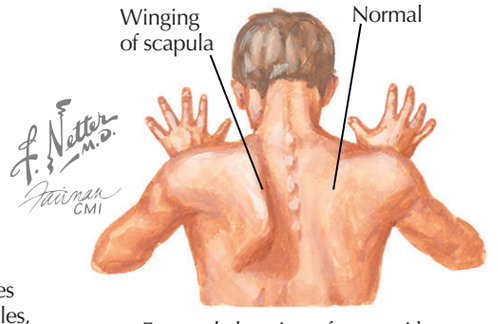


Spinal accessory (CNXI) nerve lesions cause weakness of trapezius muscle on involved side and manifest with mild shoulder droop. Weakness of shoulder elevation and scapular winging most pronounced on arm abduction.

Long thoracic nerve damage



Lesion of long thoracic nerve causes weakness of serratus anterior muscles, with winging of scapula most pronounced when pushing against stationary object with arms in forward elevation



Forward elevation of arms with push against stationary object

Proximal Nerves of the Upper Extremity *(Continued)*

medius, runs deep to the *levator scapulae*, helping to innervate this muscle. It terminates by supplying the *rhomboid muscles (C5)*. These muscles stabilize and rotate the scapula in a medial-inferior direction as well as elevate the arm (see Plate 5-6). *Rhomboid* weakness presents with scapular winging, most prominent when the patient raises the arm overhead. The patient typically notes difficulty reaching into a back pocket of his or her slacks or trying to scratch the back. These rare dorsal scapular neuropathies have varying pathophysiologic mechanisms, including shoulder dislocation, weightlifting, and entrapment by the scalenus medius muscle.

The *suprascapular nerve (C5, 6)* arises from the *upper trunk* of the brachial plexus. It runs outward, deep to the trapezius, enters the *supraspinous fossa* through the scapular notch, and winds around the lateral border of the scapular spine to reach the *infraspinous fossa*. It supplies both the *supraspinatus (C5, 6)*, an initiating abductor of the shoulder, and the *infraspinatus (C5, 6)*, the predominant lateral rotator of the arm. This is a purely motor nerve, having no cutaneous component. The *suprascapular notch* is a site of potential entrapment. There are two other potential sites for suprascapular entrapment. These include the place where this nerve passes under the *transverse scapular ligament*, affecting both the supraspinatus and infraspinatus muscle, or, more distally, at the *spinoglenoid notch*, affecting the infraspinatus alone. Acute-onset *suprascapular neuropathies* result from brachial plexus neuritis, blunt shoulder trauma, or forceful anterior rotation of the scapula. Chronic suprascapular neuropathies develop subsequent to postfracture callous formation, entrapment at the suprascapular or spinoglenoid notch, compression from a ganglion, or traction from repetitive overhead activities, such as volleyball or tennis.

The *axillary (circumflex humeral) (C5, 6)* and *radial (C6, 7)* nerves are the primary derivatives of the posterior cord of the brachial plexus. Descending behind the axillary vessels, the axillary nerve curves posteriorly and below the *subscapularis (C5, 6)* muscle. It next passes through a *quadrangular space*, bounded above by the *teres minor (C5)*, below by the *teres major (C5-7)*, medially by the *triceps brachii* long head, and laterally by the humerus. An *anterior branch* passes to innervate the *deltoid* muscle. The *posterior branch* innervates both the deltoid and the *teres minor muscle*. The axillary nerve terminates as the *superior lateral cutaneous nerve of the arm, supplying the most upper portion of the arm immediately below the shoulder.*

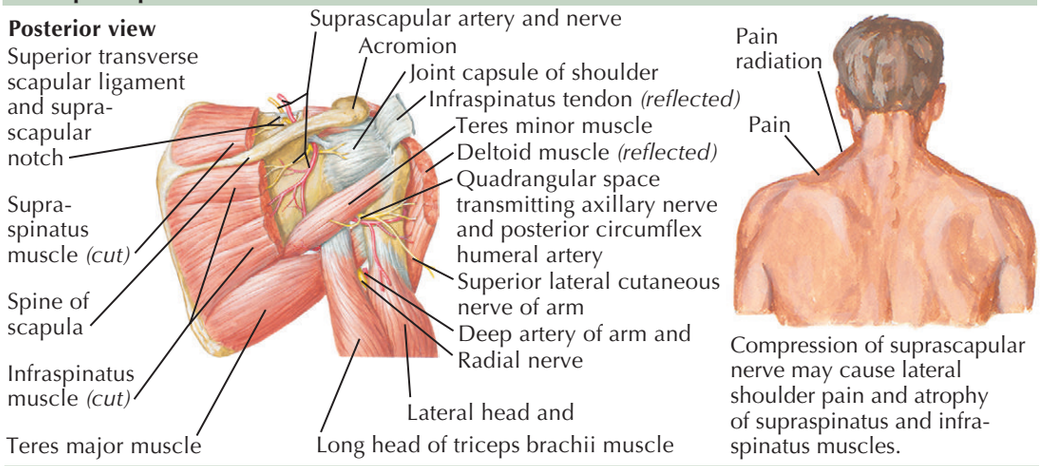
Axillary neuropathies are characterized by shoulder abduction weakness and diminished cutaneous sensation of the lateral shoulder, an area having C5 dermatome representation. Acute axillary neuropathies most typically result from blunt trauma, anterior shoulder dislocations, and/or humerus fractures, or perhaps from an autoimmune disorder, such as a forme fruste of *brachial plexus neuritis*. These primarily require differentiation from C5 radiculopathies. Electromyography is particularly helpful because the *deltoid* and *teres minor* are the only two muscles innervated by this nerve. Denervation confined to these muscles is diagnostic of a primary axillary nerve lesion, whereas the concomitant finding of infraspinatus/supraspinatus and/or rhomboid denervation favors a C5 radiculopathy.

The *musculocutaneous nerve* originates directly from the lateral cord of the brachial plexus innervating the *biceps brachii*, *brachialis*, *and coracobrachialis (C5, 6)* muscles. It terminates as the *lateral antebrachial cutaneous* nerve, supplying sensation to the forearm from immediately below the elbow to just proximal to the thumb. Isolated *musculocutaneous neuropathies* are rare. These may occur as a forme fruste of an acute brachial plexus neuritis. Other settings predisposing to such a condition include weight lifting, postsurgical procedures, and prolonged pressure during sleep. Patients present with weakness of forearm flexion and supination, with sensory loss of the lateral dorsovolar forearm. More distal lesions, primarily affecting the lateral antebrachial cutaneous nerve, may result from attempted cannulation of the basilic vein in the antecubital fossa.

The *thoracodorsal nerve* is derived from the posterior cord of the brachial plexus and innervates the *latissimus dorsi (C6, 7, 8)*. Isolated lesions are rare; latissimus dorsi atrophy very rarely develops subsequent to chest tube insertion.

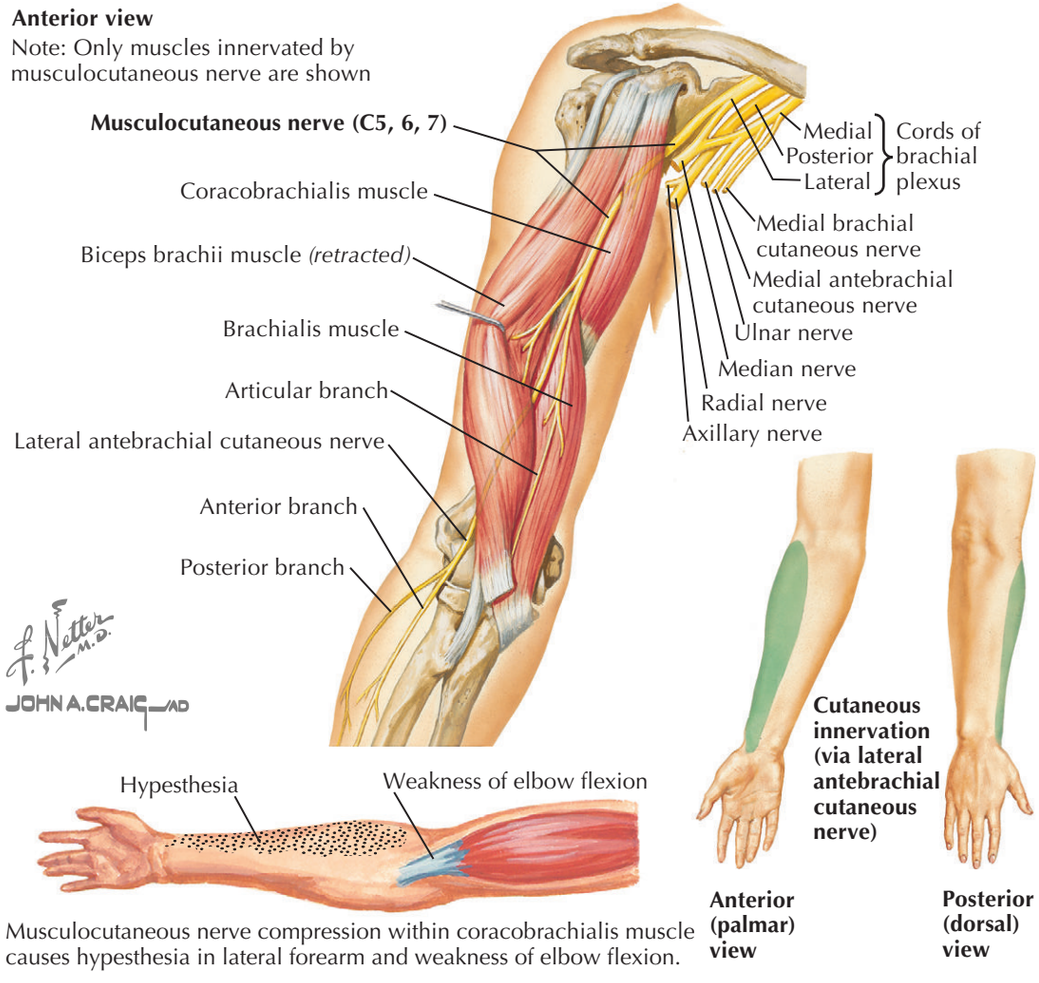
Suprascapular and Musculocutaneous Nerves

Suprascapular nerve



Compression of suprascapular nerve may cause lateral shoulder pain and atrophy of supraspinatus and infra-spinatus muscles.

Musculocutaneous nerve



Musculocutaneous nerve compression within coracobrachialis muscle causes hypesthesia in lateral forearm and weakness of elbow flexion.

Median Nerve

Teleologically, the *median nerve* support a higher primate's unique ability to grip and to pinch the thumb and index fingers. Concomitantly, it provides discriminatory sensory function for our thumb, index, and middle fingers. Writers, artists, musicians, physicians, and craftsmen, for example, absolutely depend on median nerve motor/sensory attributes.

UPPER ARM

The *median nerve* is derived from the major cervical nerve roots (C5-8) and a minor first thoracic (T1) nerve root contribution. Within the axilla, *various fascicles* of these nerve roots join to form the lateral, medial, and posterior cords of the brachial plexus. Subsequently, a significant portion of the lateral and medial cords fuse to form the median nerve adjacent to the axillary artery. As the median nerve travels through the axilla and into the arm, it lies lateral to the brachial artery. Lower, near the coracobrachialis muscle insertion, the nerve moves medially over the brachial artery, descending toward the cubital fossa at the elbow. Occasionally, just above the elbow, the ligament of Struthers, a fibrous band extending from a small supracondylar spur to the medial epicondyle of the humerus, forms the roof of a tunnel for the median nerve and brachial artery to concomitantly pass through as they approach the elbow. Here the median nerve lies posterior to the bicipital aponeurosis (lacertus fibrosis), the intermediate cubital vein and superficial to the insertion of the brachialis muscle at the ulna tuberosity.

When performing venipuncture or arterial puncture, the close proximity of the median nerve to the intermediate basilic vein and brachial artery always must be considered. It is important to perform venipuncture immediately lateral to the bicipital tendon to avoid the brachial artery, which lies just medial to this prominent tendon. There are no significant median nerve motor or sensory branches within the arm.

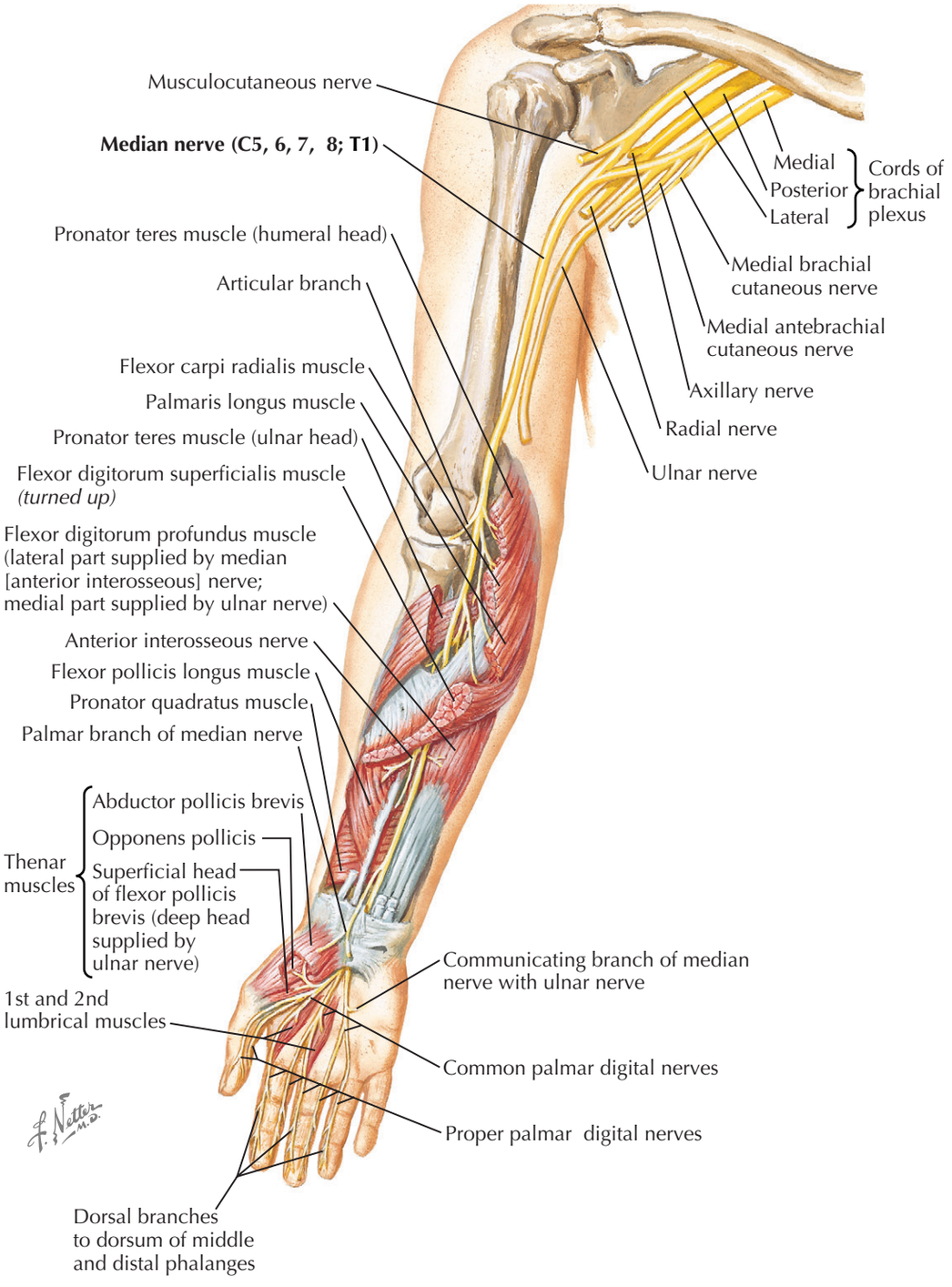
FOREARM

The median nerve enters the forearm between the long and short heads of the biceps muscle. Initially, it innervates the *pronator teres* (PT) muscle (C6, 7). Subsequently, it innervates three other forearm muscles: *flexor carpi radialis* (FCR; C6, 7), *palmaris longus* (C7, 8, T1), and *flexor digitorum superficialis* (FDS; C7, 8). It also provides articular twigs to the elbow and proximal radioulnar joints.

Within the very upper forearm, the *anterior interosseous nerve (AIN; the primary median nerve motor branch)* is derived from the primary trunk of the median nerve. This is a primarily motor branch, coursing distally, superficial to the anterior interosseous ligament, accompanied by its anterior interosseous artery. The AIN innervates the *lateral head of the flexor digitorum profundus* (FDP; C7, 8) a muscle providing tendons that flex the most distal interphalangeal joints of the index and middle fingers, In addition, the AIN supplies the *flexor pollicis longus* (FPL; C7, 8, T1), which flexes the distal phalanx of the thumb, and the *pronator quadratus* (C7, 8, T1), which aids in wrist pronation. Thus the AIN, through its innervation of the FDP and the *flexor pollicis longus (FPL)*, provides the essential means for allowing the most important very fine movements, leading to flexion of the most distal phalange of the index and middle fingers, and for allowing the thumb to make the all important pinch movement possible.

Anterior view

Note: Only muscles innervated by median nerve are shown



In the lower forearm, the main trunk of the median nerve lies deep to the *FDS* and superficial to the *FDP*. Eventually, the primary median nerve trunk becomes more superficial, lying between the tendons of the *palmaris longus and the flexor carpi radialis, (FCR; C6, 7)*. Here the *median palmar cutaneous branch* originates, arising 3 to 4 cm above the flexor retinaculum and descending over this area to supply the skin of the median palm and the thenar eminence. This is the first and only median sensory branch that is defined before the median nerve enters the hand.

In the forearm, the median and ulnar nerves are occasionally interconnected by fibers passing between these nerves. The most common are the median-ulnar anastomosis *(Martin-Gruber syndrome)*, wherein portions of the median nerve branch off within the forearm to join the ulnar nerve. Typically, when this ulnar nerve variant reaches the hand, these median fibers will subsequently innervate their appropriate median intrinsic muscles. This is important for electromyographers to recognize, especially when looking for ulnar nerve block at the elbow as discussed on the ulnar nerve plates.

Proximal Median Neuropathies

Proximal median nerve lesions are quite unusual, except relatively so in children, where they occur as frequently as wrist lesions. These are situated near the elbow or the pronator teres muscle, affecting the main median nerve trunk or its anterior interosseous division.

PRIMARY MEDIAN TRUNK

All median nerve function is potentially compromised with very proximal lesions. In contrast to the patient with carpal tunnel syndrome (CTS) experiencing finger paresthesias, median trunk lesions present with combined sensory/motor dysfunction not only affecting the classic 3.5 lateral digits but also diminished palmar sensation because of *median palmar cutaneous branch* involvement, something not characteristic of CTS. All median-innervated muscles may be affected. Often, these very proximal median lesions are idiopathic, although some may represent another brachial neuritis variant.

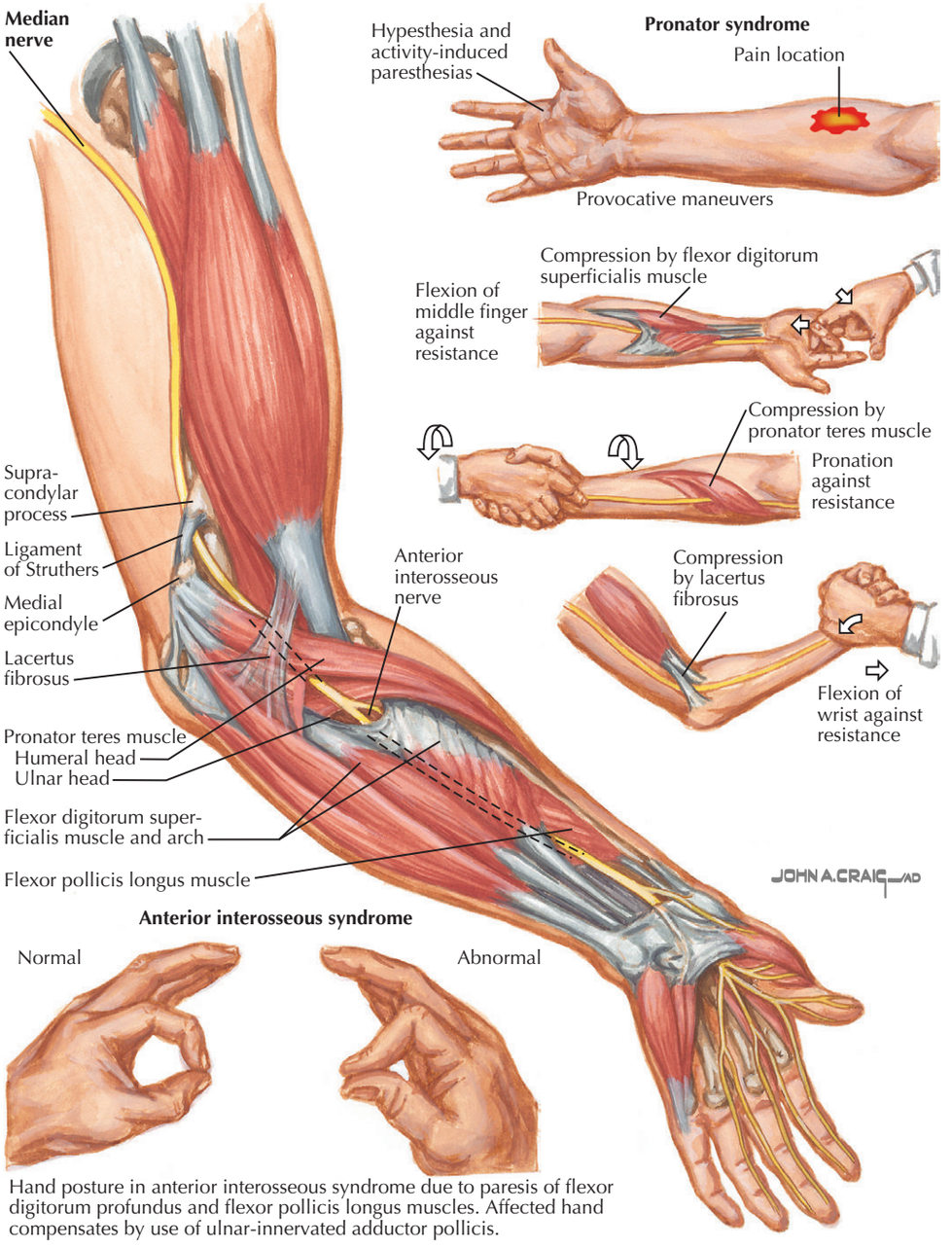
Supracondylar humerus fractures leading to nerve compression, entrapment, or total laceration are common causes of proximal median nerve lesions. The primary median nerve trunk is usually damaged; however, occasionally, because of the fascicular characteristics of peripheral nerves, the anterior interosseous nerve may be traumatized in isolation at a proximal site. Elbow dislocations, hyperextension of the arm, shoulder falls, lacerations, blunt nerve trauma, arterial or venous puncture, and repetitive pronation/supination are other mechanisms.

Median nerve entrapment rarely occurs just above the elbow at the ligament of Struthers. This is a fibrous band extending from a small supracondylar spur on the humerus to its medial epicondyle. Here it forms the roof of a tunnel, radiographically identifiable in about 2% of the population. Median entrapment has occurred with a distal humeral osteoid osteoma and congenital fibromuscular bands. Lipofibromas, hamartomas, neurofibromas, hemangiomas, juvenile cutaneous mucinosis, calcified flexor digitorum superficialis tendons, and abscess have also led to proximal median nerve lesions.

ANTERIOR INTEROSSEOUS NERVE (AIN)

Sometimes clinical involvement of the AIN is referred to as the *pronator syndrome;* however, this is not a well-accepted terminology because multiple other mechanisms, besides entrapment within the pronator teres, may be operative at this level. These patients present with a characteristic clinical picture, wherein they initially report difficulty with handwriting or placing a key in a lock. This symptom is related to an inability to pinch because concomitant damage to the *flexor pollicis longus (FPL) and flexor digitorum profundus (FDP; C8, T1)* muscles limit the patient's ability to flex the distal interphalangeal joints of both the index finger and thumb. The third muscle innervated by the AIN, the *pronator quadratus (PQ, C8, T1)* is clinically silent but provides localizing value with needle electromyography (EMG).

Some instances of *idiopathic anterior interosseous neuropathies*, having an acute onset and possibly representing an autoimmune process, have also been likened to a partial brachial neuritis variant. One interesting modification is a syndrome of acute median nerve compression by the bicipital aponeurosis at the elbow. Here an acute elbow pain develops during a maximal and vigorous contraction of the biceps brachii muscle. Examination demonstrates severe pain on median nerve palpation at the elbow as well as with triceps contraction when extending the elbow, but there is no neurologic compromise.



Hand posture in anterior interosseous syndrome due to paresis of flexor digitorum profundus and flexor pollicis longus muscles. Affected hand compensates by use of ulnar-innervated adductor pollicis.

EVALUATION

EMG is the primary means for identifying these proximal median nerve lesions as discussed above. The role of ultrasound and magnetic resonance imaging (MRI) await prospective analysis, but it is expected that these modalities will be particularly useful for both localization and sometimes identification of the pathology.

THERAPY AND PROGNOSIS

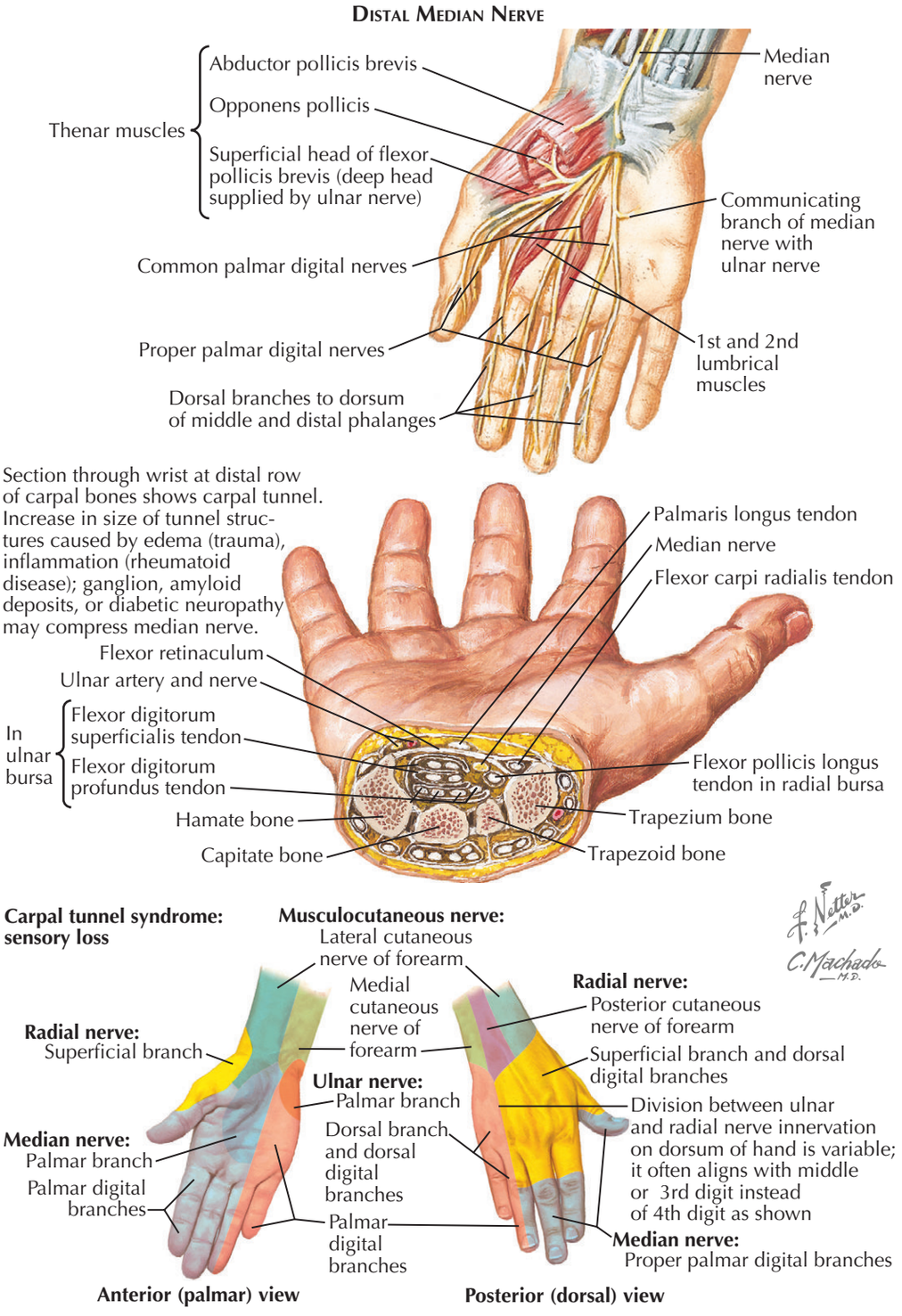
The decision to pursue surgical exploration for diagnosis and therapeutic potential is a difficult one. At times, this is indicated for the syndrome of acute painful median nerve compression at the elbow, as previously noted. In this instance, exploratory surgery sometimes defines an acute median nerve entrapment at the ligament of Struthers, lacertus fibrosis, pronator teres, or flexor digitorum superficialis, requiring decompression. In more chronic settings, good results occur variously with local corticosteroid injection, surgical explorations, as well as conservative management. However, in the last instance, if signs of a progressive median deficit develop, surgical exploration is definitely in order. Although the region of the pronator teres may be a prime site from which to start, unless a well-defined lesion is identified there, the incision needs to be extended to avoid missing an adjacent occult site of entrapment. If an entrapment site is identified and the nerve decompressed, the prognosis will depend on the degree of axonal damage and the chronicity of the lesion. The spontaneously occurring, possibly autoimmune, AIN lesions often resolve on their own.

Distal Median Neuropathies: Carpal Tunnel Syndrome

The *median nerve* is the most commonly compromised single peripheral nerve. This is due to its relation to the carpal tunnel, where it can potentially be entrapped at the wrist. As the median nerve enters the palm, it passes through the central lateral aspect of the anatomically relatively restricted *carpal tunnel*. If the canal thickens enough to entrap the median nerve over time, the common *carpal tunnel syndrome* (CTS) develops. Although this malady can be symptomatically annoying, it is the most treatable mononeuropathy (see Plate 5-10).

Anteriorly, within the carpal tunnel, the median nerve is bounded by the stiff *flexor retinaculum* and posteriorly by the carpal bones. In contrast, the ulnar nerve does not travel through the carpal tunnel; rather, it has a very medial position, reaching the hand through the much less restrictive *Guyon canal*. Thus it is relatively uncommon to have both the median and ulnar nerves affected concomitantly *at the wrist*, unless there is a diffuse polyneuropathy, such as found in a patient with diabetes mellitus, or amyloidosis. Once the *median nerve* leaves this anatomically defined tunnel, it divides into its *terminal sensory and motor branches*, providing motor and sensory function to 60% of the hand. These branches directly accompany tendons originating from the digital flexor muscles, including the flexor digitorum superficialis, flexor digitorum profundus, and the flexor pollicis longus. The *muscular branch* arises close to, or is initially united with, the *common palmar digital nerve to the thumb*. This curves outward over or through the *flexor pollicis brevis* to supply its superficial head before dividing to innervate the *abductor pollicis brevis* and *opponens pollicis* muscles, all C8, T1–innervated muscles. In addition, this muscular branch usually innervates both the *first and second lumbrical* muscles. Only one thenar muscle, the *adductor pollicis* (C8, T1) is not innervated by the median nerve; this has an ulnar nerve innervation.

There is one other rare motor variant within the hand—*Riche-Cannieu anastomosis*. Here the deep ulnar branch of the ulnar nerve (C8, T1) communicates with the *terminal motor branch of the median* nerve. Because the former nerve has its own clinical presentation, such a variation can rarely lead to diagnostic confusion. Another rare, important anatomic variation occurs if the distal median motor nerve branches off earlier than usual within the carpal tunnel, exiting it by directly piercing the flexor retinaculum, rather than leaving the carpal tunnel at its most distal extent near the thenar eminence. This *anatomic variant* is of potential clinical concern if an incision is made through this area when operating on a patient with CTS symptoms In the circumstance wherein this unusual branch is not recognized, the motor function of the thumb may be inadvertently and severely compromised if this unexpected branch is severed. Thus the surgeon needs to carefully inspect the site at the time of the operation to avoid damage to this branch, if present.



Carpal Tunnel Syndrome

Carpal tunnel syndrome (CTS) is the most common adult mononeuropathy; it is three times more common in women, usually manifesting in middle to late life. In contrast, CTS rarely occurs in young children. The symptoms of CTS include feelings of numbness and tingling in the fingers of one or both hands. Although some patients report that their hand is simply "asleep," at times, these paresthesias have an annoying, allodynic quality. Many individuals report that *all* their fingers are affected. This is conceivable when one considers that the cortical representation of the thumb, index, and middle fingers covers a much larger portion of the parietal cortex than is available for the ring and little fingers, thus allowing the misperception that all fingers are affected. Rarely, there is a component of dysautonomia with changes in temperature, color, and sweating.

Typically, these symptoms occur at night, awakening the patient from sleep. In addition, many patients also note similar symptoms on first awakening in the morning or later in the day while driving, related to holding a steering wheel. Very often, CTS patients believe that they have been sleeping on the hand, and this is thought to be supported by their observation that a simple shaking of the fingers and hand will abort symptoms. Occasionally, there is radiation of the pain into the volar forearm; rarely, this will spread into the upper arm.

Occupational activities requiring continued use of the hands, such as in carpenters, bakers, electricians, or painters, predispose to CTS at a younger age, that is, in the 30s and 40s, whereas persons without such predisposing activities present in later life. Various hobbies,

Distal Median Neuropathies: Carpal Tunnel Syndrome
(Continued)

including artistic painting, sewing, crocheting, or sculpturing, may also predispose the artisan to classic CTS symptoms. Athletic endeavors, including skiing, rowing, and bicycle riding, also provide the potential for CTS development. Of interest, although many of us use computer keyboards for many hours a day, there is no increased occurrence of CTS in this setting.

Some systemic disorders, including diabetes mellitus, rheumatoid arthritis, hypothyroidism, acromegaly, and systemic amyloidosis, predispose adult patients to developing CTS. There is a broader set of possible mechanisms in children, including congenital carpal tunnel canal stenosis, leading to a familial CTS. Thickening of the flexor retinaculum occurs in the mucopolysaccharidoses, and here the motor fibers are primarily affected, leading to painless thumb atrophy.

The clinical signs of CTS may be quite variable on neurologic examination; early, there are often no specific findings. In this instance, sometimes typical CTS symptoms can be precipitated by tapping over the nerve at the wrist. This maneuver is known as the *Tinel sign*; parenthetically, this is not specific to CTS but rather to any site of focal nerve damage where percussion produces sensory symptoms distal to the site of clinical involvement. This is also particularly useful with ulnar lesions at the elbow, radial nerve lesions in the mid–upper arm, and fibular (peroneal) nerve lesions below and just lateral to the knee.

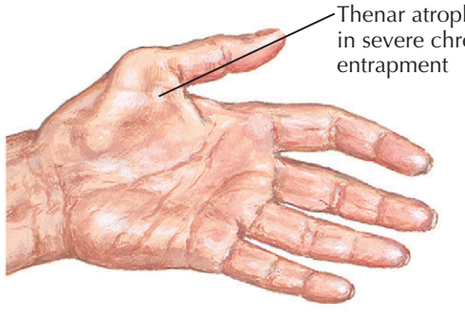
Early, when clinically defined CTS deficits develop, these are usually confined to loss of sensation in the median-innervated finger tips, sparing the palm because the palmar branch of the median nerve leads off from the primary median trunk proximal to the carpal tunnel and thus passes superficial to the same and is not subject to entrapment. Two-point discrimination, light touch, and pinprick sensory modalities may be affected with early sensory loss. As the degree of entrapment increases, the motor branches become affected. This leads to weakness and atrophy of the thenar eminence, particularly affecting thumb abduction and opposition. Atrophy of these muscles leads to a hollowing out of the most lateral (radial) portion of the thumb.

Differential diagnosis is usually straightforward. Cervical radiculopathies, particularly at C6 or C7, are the most common consideration. These patients often first experience unilateral intrascapular pain and/or develop significant cervical radicular pain and persistent sensory paresthesias unrelated to time of day, in contrast to nocturnal expression with early CTS. Cervical spine and spinal cord magnetic resonance imaging (MRI) is useful in making this differential diagnosis.

Other considerations in the differential diagnosis, particularly when there is thenar atrophy, include proximal median nerve lesions, motor neuron disease, multifocal motor neuropathy, and the rare thoracic outlet syndrome. The last condition is related to compression of the upper medial portion of the brachial plexus, affecting the T1 root. In contrast to involvement in a median nerve distribution with feelings of numbness in the thumb, index, and middle fingers, patients with the thoracic outlet have sensory loss in an ulnar nerve distribution. Before the development of electrodiagnostic techniques, many patients with ulnar nerve lesions were incorrectly presumed to have thoracic outlet lesions and were surgically decompressed without any improvement.

Presentation

Patient awakened by tingling, pain, or both in sensory distribution of median nerve



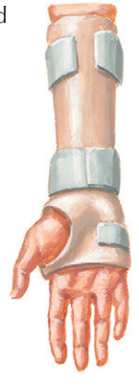
Thenar atrophy in severe chronic entrapment

Gradual numbness of fingers while driving

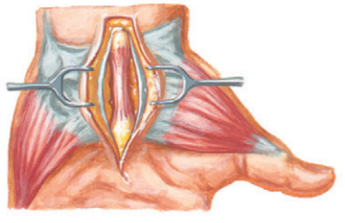
F. Netter M.D.
C. Machado M.D.

Treatment

Find possible causes and avoid these actions. Avoid repetitive movements, such as vibrating hand tools.



Wrist splint at night can be helpful



If pain does not improve, wrist surgery to decompress median nerve in the carpal tunnel may be recommended

In addition, when the clinical and electrodiagnostic findings do not support a CTS diagnosis, the outside chance of a central nervous system lesion always needs to be considered. Syringomyelia or other intramedullary spinal disorders may lead to an atrophic thumb. However, observing the classic cape-type sensory loss and obtaining a cervical spine MRI allow for this diagnosis. Lastly, especially with intermittent symptoms, carotid atherosclerosis producing transient ischemic attacks or a slow-growing intracranial tumor, such as meningioma or glioma, may initially mimic CTS.

DIAGNOSIS AND THERAPY

Nerve conduction studies (NCS) are the primary means for confirming a CTS diagnosis. These demonstrate delayed conduction across the carpal tunnel; the sensory components are most sensitive to early change. Although conservative therapy with wrist splints (used while sleeping), are helpful early, most patients with significant CTS changes require simple outpatient surgical decompression. This is successful in the vast majority of patients.

Ulnar Nerve

The *C8, T1, and occasionally the C7 nerve roots*, provide the primary spinal derivations for the ulnar nerve. These nerve roots join soon after leaving the spinal cord to form the *medial cord of the brachial plexus*, eventually terminating as either the ulnar nerve or the medial portion of the median nerve within the lower axilla. Here the ulnar nerve lies between the axillary artery and vein; entering the arm, it lies medial to the brachial artery. After piercing the medial intermuscular septum, midway down the arm, the ulnar nerve descends anterior to the medial head of the triceps brachii muscle. Proximal to the elbow, this *initial ulnar nerve segment* has no branches throughout the upper arm. Above the elbow, the ulnar nerve inclines posteriorly, passing through a groove between the medial humeral epicondyle and the olecranon to reach the forearm. Here it occupies a superficial plane covered with fascia and skin; it is very palpable and easily rolled between the fingers. This positioning allows for a slight trauma to send a shocklike sensation distally into the medial two fingers. The layman refers to the elbow's medial epicondyle and adjacent ulnar nerve as the "funny bone."

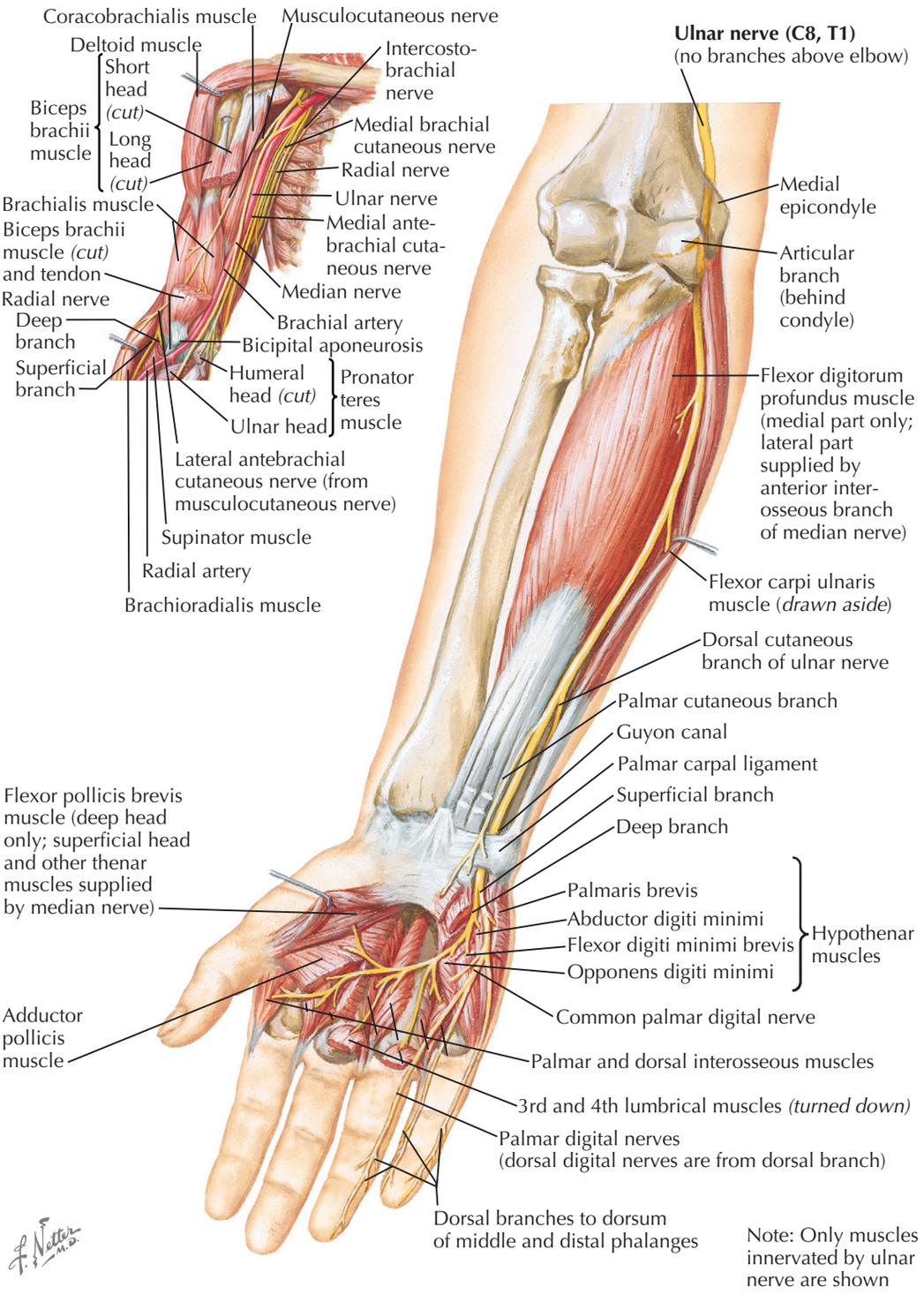
Within the proximal forearm, the ulnar nerve courses along the length of the medial forearm, lying on the ulnar collateral ligament immediately below the elbow; it subsequently passes between the two heads of the *flexor carpi ulnaris* (C7, 8, T1), while innervating this muscle, and the *medial flexor digitorum profundus (C8,T1)*, providing flexion of the fourth and fifth distal interphalangeal joints. The palmar and dorsal cutaneous sensory branches leave the ulnar nerve within the lower forearm. As the flexor carpi ulnaris narrows into its tendon, the nerve and artery emerge from under its lateral edge, where it is covered just by skin and fascia.

Entering the hand through the *Guyon canal*, the ulnar nerve passes anterior, that is, superficial to the flexor retinaculum, almost immediately splitting into its superficial and deep terminal branches. This contrasts with the median nerve, which passes deep to the flexor retinaculum and thereby provides a potential entrapment site. At the wrist, the ulnar nerve divides into the superficial and deep branches. The *superficial branch* innervates the *palmaris brevis* muscle and then splits into its terminal sensory nerves, providing sensation to the entire fifth digit and medial ring finger. The *deep terminal motor branch (C8, T1)* has a purely muscular function, supplying all hypothenar muscles, including the *abductor digiti minimi*, *opponens digiti minimi*, *and flexor digiti minimi*. Subsequently, it curves along the palm, providing motor branches to the *third and fourth lumbricals*, *the four dorsal and three palmar interossei*, *the adductor pollicis*, *and the deep head of the flexor pollicis brevis.*

The *ulnar palmar cutaneous branch* arises 7 cm above the wrist, descends near the ulnar artery, pierces the deep fascia, supplying the hypothenar eminence; it communicates with the medial cutaneous nerve of the forearm and the palmar cutaneous branch of the median nerve. The *dorsal ulnar branch* arises 5 to 10 cm above the wrist, passes posteriorly, deep to the tendon of flexor carpi ulnaris, pierces the deep fascia, and continues distally along the posteromedial side of the wrist.

Proximal Ulnar Nerve in the Axilla and Upper Arm

Anterior view



Here it divides into branches that supply the *palmaris brevis* muscle, and as the *superficial terminal branch*, the skin on the medial side of the back of the hand and fingers. There are usually two or three *dorsal digital nerves:* one, the *proper palmar digital nerve*, supplying the medial side of the little finger, the other splitting into *a common palmar digital nerve*, communicating with the adjoining common palmar digital branch of the median nerve before dividing into the two *proper palmar digital nerves* for the adjacent sides of the little and ring fingers. Very rarely, the ulnar nerve supplies 2.5 rather than 1.5 digits, in which case the areas supplied by the median and radial nerves are reciprocally reduced.

There are a variety of interconnections between the ulnar and median nerves, allowing interchanges of fibers from different nerve roots. Their clinical implications are important, allowing explanations for seemingly "*nonanatomic*" findings.

Ulnar Mononeuropathies: Potential Entrapment Sites

Ulnar nerve dysfunction occurs at two anatomic loci; primarily the elbow and, uncommonly, the wrist. Proximal ulnar lesions at the elbow are the second most common adult mononeuropathy; however, these are less than 10% as frequent as median nerve lesions from carpal tunnel syndrome. In contrast, ulnar nerve elbow lesions are the most common childhood mononeuropathy.

PROXIMAL ULNAR NERVE LESIONS

Chronic ulnar nerve elbow lesions primarily exist at the *cubital tunnel* or *condylar groove*. Patients with these lesions present with numbness and tingling, and/or sensory loss over the entire fifth and medial fourth fingers. The ulnar nerve does not provide sensory innervation until reaching the wrist; thus medial forearm paresthesias indicate a medial brachial plexus lesion or a C8 radiculopathy. Indolent ulnar damage presents with the classic "*papal blessing hand*," with hyperextension of the fourth and fifth metacarpophalangeal (MCP) joints and flexion of proximal interphalangeal joints. This is due to unopposed flexion of the proximal and distal interphalangeal (PIP/DIP) joints because of the loss of function of the ulnar-innervated *third and fourth lumbrical muscles*, primarily extending the PIP/DIP joints. Unopposed contraction of radial nerve innervated *extensor digitorum muscles* keeps the proximal phalanxes extended. Although ulnar forearm muscle weakness is rarely apparent to patients, the *medial flexor digitorum profundus* for the fourth and fifth fingers' distal PIP joints is weakened with nerve entrapment at the elbow.

Typically, *ulnar nerve elbow entrapment* occurs at the ulnar *condyle*, presumably after remote elbow trauma *(tardy ulnar palsy)*, or just distal to the elbow joint *(cubital tunnel syndrome)*. Although *chronic ulnar neuropathies* are relatively common, a precise etiology is often not identified. Constant pressure from leaning the elbow on a chair arm or desk top may predispose to such a condition. Uncommonly, idiopathic focal hypertrophic neuropathy, tumors, and hamartomas affect the ulnar nerve. Leprosy is responsible for the majority of chronic ulnar nerve lesions in economically underdeveloped countries. Elbow fractures or dislocations commonly produce acute ulnar nerve compromise. Other acute mechanisms include external compression in anesthetized patients, hemorrhage in hemophiliacs, intravenous fluid extravasation leading to a compartment syndrome, and burns.

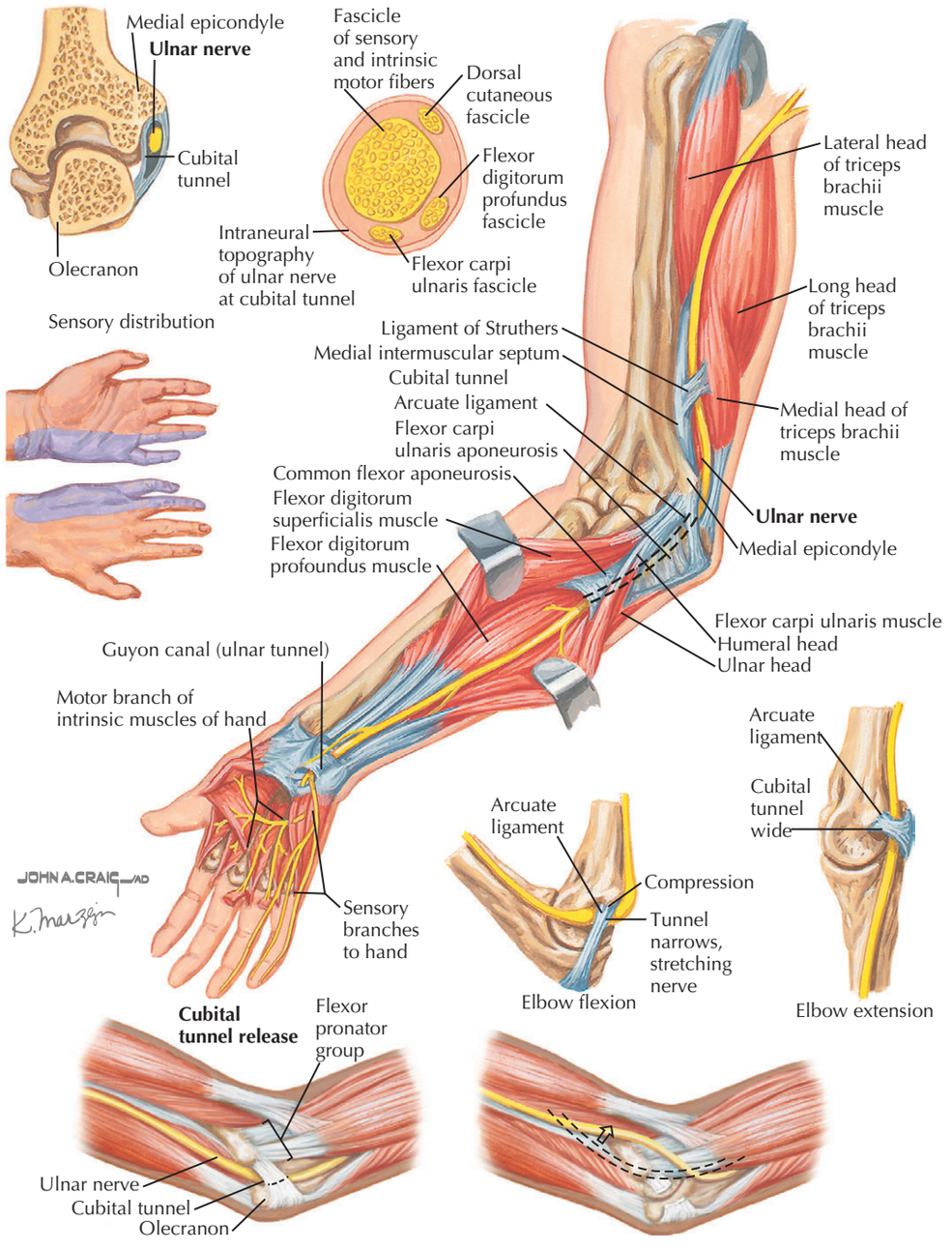
DISTAL ULNAR NERVE LESIONS

Ulnar neuropathies at the wrist or palm are uncommon. Entrapment at the ulnar tunnel, that is, the Guyon canal, may occur after wrist fractures or with rheumatoid arthritis and ganglion cysts. Sensory symptoms may or may not develop. When a sensory loss is demonstrated on the dorsal medial hand, compatible with involvement of the dorsal ulnar cutaneous nerve, the lesion is proximal to the wrist. In contrast, when ulnar-innervated muscle weakness is identified as confined to the intrinsic hand muscles, that is, both the hypothenar abductors and opponens as well as the thumb adductors (without sensory loss), this localizes a pure motor distal ulnar neuropathy at or distal to the Guyon canal. The most distal pure motor ulnar lesion involves the deep ulnar motor branch within the palm. This is characterized by weakness of the adductor pollicis, the primary thenar muscle not innervated by the median nerve, as well as concomitant weakness of the first dorsal interosseous muscle. The preservation of fifth-finger abduction provides the key to localizing the compression site to the lateral palmar hypothenar eminence.

Primary palmar lesions usually result from repetitive hand injury, for instance, from bicycling or from occupations using tools requiring significant intermittent pressure over the distal ulnar motor fibers at the hypothenar eminence. Typically, these patients have difficulty adducting the thumb and index finger, leading to problems placing a key in a lock. When the inciting mechanism is discontinued, significant recovery frequently occurs.

DIFFERENTIAL DIAGNOSIS

Motor neuron disease (MND) is a primary consideration in patients presenting with asymmetric painless atrophy of the hand intrinsic muscles, with no associated sensory deficits. The presence of concomitant median-innervated thenar weakness and atrophy usually occurs in MND because these muscles similarly have C8, T1 innervation. *Lower brachial plexus* lesions characteristically include both motor and sensory dysfunction in multiple peripheral nerve and nerve root territories within the arm. *Thoracic outlet syndrome* is a rare medial plexus lesion mimicking an ulnar neuropathy. However, these patients have greater thenar than hypothenar muscle weakness. *C8 radiculopathies* are uncommon lesions; neck pain is very important in clinical differentiation from an ulnar neuropathy. However, weakness of non–ulnar-innervated C8 muscles (the thenar eminence, the flexor pollicis longus (FPL), and the extensor indicis proprius) with medial forearm numbness provides major diagnostic distinctions.



RADIAL NERVE

The radial nerve (C5-8, T1) is primarily derived from the *posterior cord of the brachial plexus*. This is the only nerve that innervates muscles in both the arm and forearm. Its primary function is an extensor; however, it also contributes to arm flexion by its innervation of the *brachioradialis muscle*. The radial nerve provides cutaneous innervation of *the posterior arm*, forearm, and the posterior 3.5 lateral fingers up to the distal interphalangeal (DIP) joint.

Within the axilla, the radial nerve lies posterior to the axillary artery, and subsequently upon the *subscapularis and latissimus dorsi* muscles while anterior to the teres major muscle. Here it is vulnerable to compression injuries, such as inappropriate positioning of crutches. As the radial nerve exits the axilla, entering the arm, it lies between the brachial artery and the *triceps brachii long head* innervating the triceps long and medial heads as it passes deep to this muscle.

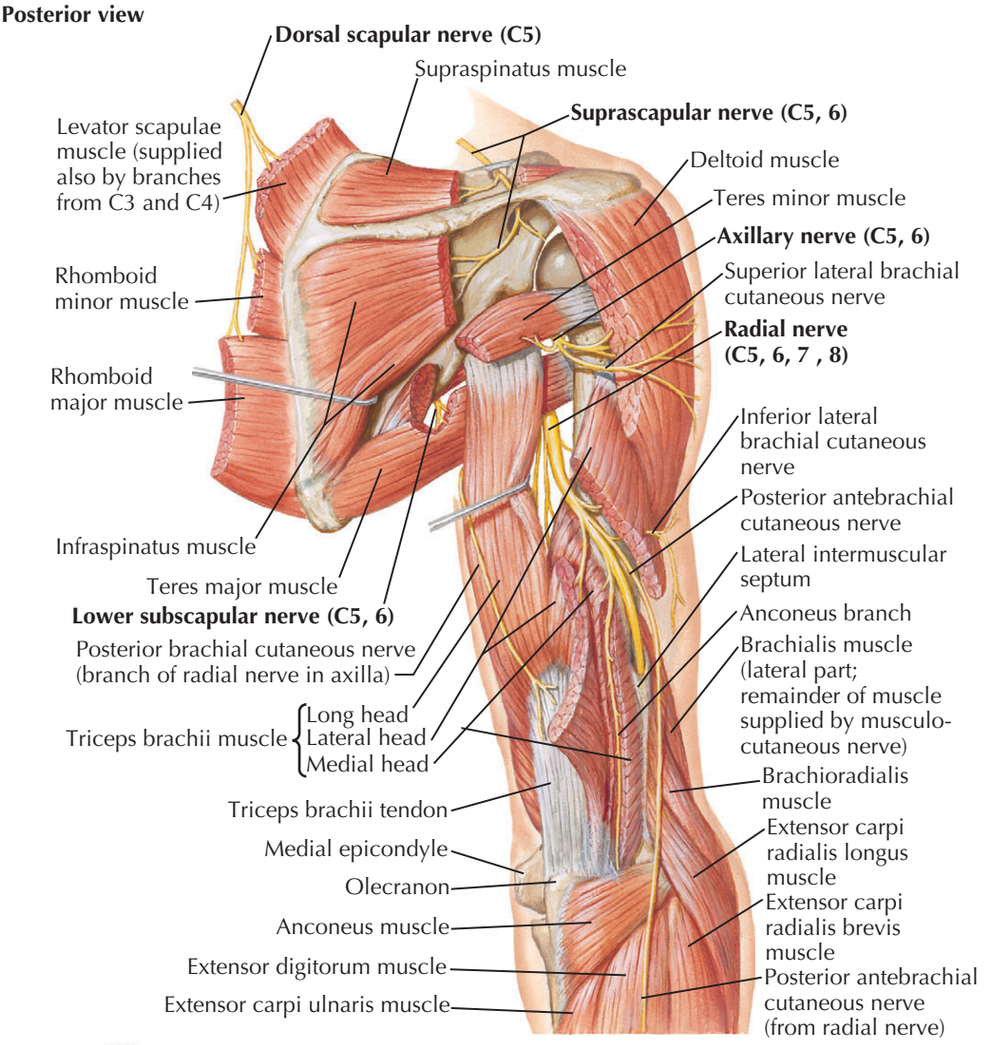
Proximal to the spiral groove, the *posterior cutaneous nerve of the arm* arises from the radial nerve. The *primary radial nerve trunk (C5, 6)* then passes distally, accompanying the brachial artery within the shallow *radial (spiral) groove of the posterior humerus*, where it is vulnerable to external compression with pressure against the humerus, potentially leading to wristdrop. More distally, the radial nerve takes a medial to posterolateral direction. The *radial posterior muscular branches* innervate the *lateral and medial heads of the triceps muscle* (C6, 7) as well as a long, slender branch to the distal *anconeus* muscle *(C6, 7)* at the elbow. This small forearm extensor muscle, lying adjacent to the lateral epicondyle of the humerus, sometimes helps localize the primary site of radial neuropathies. If electromyography (EMG) demonstrates anconeus denervation, the lesion site approximates the spiral groove, that is, midhumerus; if the anconeus is unaffected, the injury is distal to the radial groove. The *posterior cutaneous nerve of the forearm* crosses above the anconeus muscle.

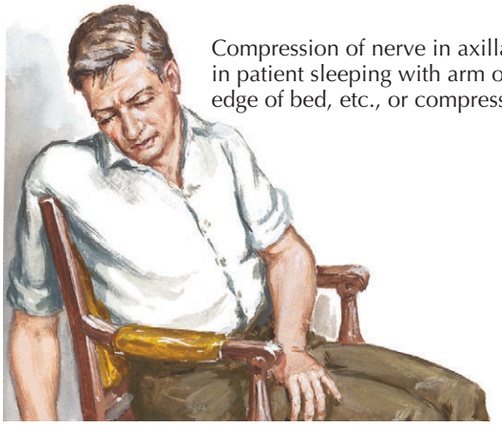
Distal to the spiral groove, adjacent to the lower humerus, the radial nerve lies within the furrow between the medial *brachialis (C5, 6)* muscle and the *brachioradialis (C5, 6) /extensor carpi radialis longus (C6, 7)* laterally, innervating these muscles. There are three cutaneous radial nerve branches originating proximal to the elbow: (1) the *posterior cutaneous and* (2) *lower lateral cutaneous nerves of the arm*, and (3) the *posterior cutaneous nerve of the forearm*.

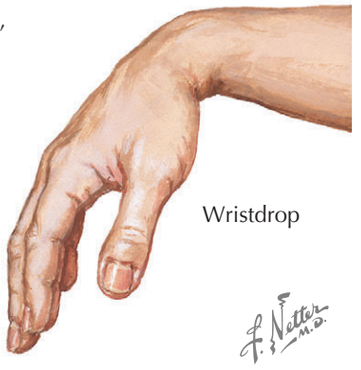
RADIAL NERVE IN FOREARM

As the radial nerve enters the forearm, piercing the *lateral intermuscular septum* while descending anterior to the *lateral humeral epicondyle*, it soon supplies *lateral muscular branches*, innervating the most proximal *brachioradialis and extensor carpi radialis* muscles. Here the radial nerve bifurcates into its *superficial* and *deep terminal branches*. The *superficial sensory radial branch* (SSRB) descends within the forearm deep to the brachioradialis and extensor carpi radialis muscles, eventually emerging in the distal forearm as the *superficial terminal sensory radial branch (STSRB)*, descending along the anterolateral side of the forearm. In its upper third, the STSRB *branch* and the radial artery converge meeting midway down the lateral forearm, only again to diverge in the distal forearm as the STSRB inclines posterolaterally, deep to the brachioradialis tendon. Here it pierces the deep fascia, subdividing into a *lateral branch* supplying the radial side of the thumb and a *medial branch* splitting into four or five *dorsal digital nerves*. This cutaneous sensory innervation extends just to the distal interphalangeal joints, whereas the most distal phalanges are supplied, respectively, by the median (digits 1-3.5) and ulnar (digits 4.5 and 5) nerves. The cutaneous hand areas supplied by the radial, median, and ulnar nerves can have individual variations due to intrabranch communication and minor overlap.

The terminal deep muscular radial *branch* winds posteroinferiorly around the lateral side of the radius innervating the brachioradialis (C5, 6), extensor carpi radialis longus (C6, 7), and supinator (C5, 6, 7). It enters the *supinator muscle* through the *arcade of Frohse* between its superficial and deep heads, reaching the posterior forearm as the *posterior interosseous nerve (PIN)*. This accompanies the posterior interosseous artery between the superficial and deep extensor forearm musculature innervating the *extensor carpi radialis brevis (C6, 7)*, *extensor digitorum and minimi (C7, 8)*, *extensor carpi ulnaris (C7, 8)*, *abductor pollicis longus (C7, 8)*, *extensor pollicis longus (C7, 8) and brevis (C8)*, *and extensor indicis proprius (C8)*. The radial nerve terminates as a small nodule, a pseudoganglion, sending filaments to the distal bones, joints, and ligaments.




Compression of nerve in axilla or upper arm in patient sleeping with arm over chair back, edge of bed, etc., or compression by crutch


Wristdrop

Radial Nerve Compression/ Entrapment Neuropathies

PROXIMAL RADIAL NEUROPATHIES

These radial compression neuropathies frequently occur at the midhumerus spiral groove and, rarely, the axilla. External compression leads to painless wrist and finger extensor weakness, referred to as wristdrop. Elbow extension is spared, except with axilla lesions, because the radial branches to the triceps originate proximal to the spiral groove. A potentially confounding examination feature initially is an apparent concomitant weakness of ulnar-innervated finger abduction. Appreciation of the full strength of ulnar muscles requires at least partial wrist extension. In the presence of a radial nerve palsy, full-strength finger abduction (median and ulnar innervation) must be tested by placing the hand and forearm flat on a firm surface. This prevents a false localization to the plexus, spinal cord, or even the brain. Sensory signs and symptoms are sometimes elusive because the motor loss predominates clinically The brachioradialis reflex is typically diminished or lost, whereas the triceps and biceps reflexes are normal.

Patients unexpectedly assuming a prolonged posture, with an arm resting posteriorly against a hard surface, are liable to develop *acute radial nerve palsies*. Examples include sleeping with weight on an arm, such as a loved one's head over the spiral groove *(honeymooner's palsy);* in patients lying on a hospital gurney, when an arm becomes inadvertently draped over a side rail; or in individuals becoming stuporous secondary to alcohol/drug intoxication in a posture that compresses the radial nerve at the axilla, such as when seated with an arm draped over the back of a chair. *("Saturday night palsy")* (see Plate 5-13). Continued pressure on the radial nerve sequentially produces focal demyelination, conduction block, and clinical weakness. In these circumstances, on awakening, the patient, or a nurse discovering such a condition, may initially think a stroke occurred. However, clinical evaluation demonstrates weakness limited to radial-innervated musculature, and not the more global character of a cerebral infarct, wherein not only radial but also median/ulnar–innervated muscles are affected. Primary radial nerve lesions are more severe than those found with a C6 or C7 cervical radiculopathy. Neck or intrascapular pain is the more prominent symptom with cervical root lesions.

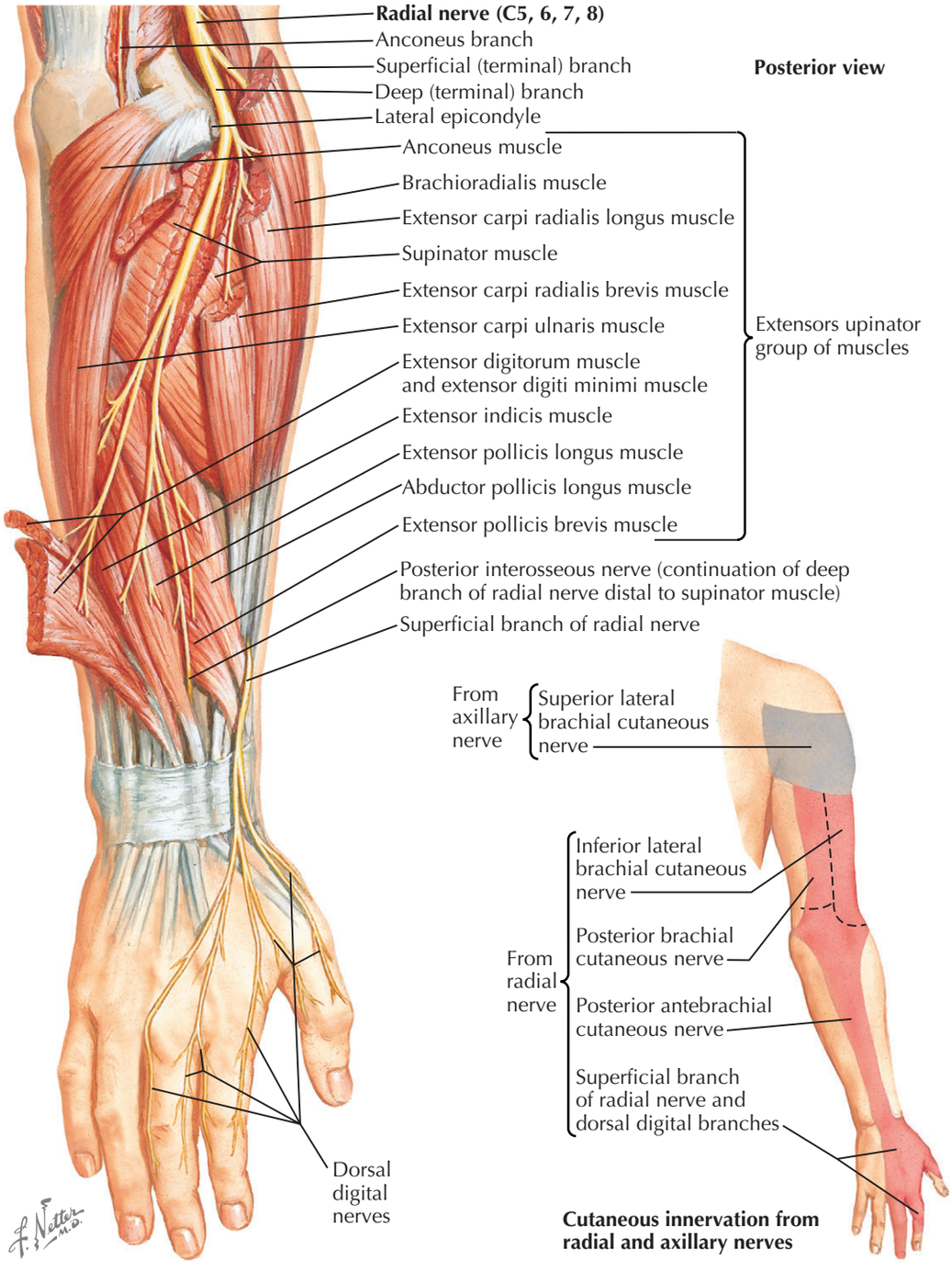
DISTAL RADIAL NEUROPATHIES

The *posterior interosseous nerve (PIN)* is analogous to the anterior interosseous nerve, being a distal, predominantly motor branch of a major peripheral nerve trunk. The *extensor carpi radialis longus/brevis (C6, 7) and brachioradialis (C5, 6) muscles* are innervated by radial nerve branches exiting the main trunk before the PIN origin in the upper forearm; therefore, fingerdrop, rather than wristdrop, is the predominant manifestation of a PIN neuropathy. Because the *extensor carpi ulnaris* is affected and not the extensor carpi radialis, radial hand deviation occurs during wrist extension. There are no clinical PIN sensory accompaniments. However, the one exception is pain near the lateral humerus epicondyle, which extends distally as the PIN gives off sensory fibers supplying the interosseous membrane and hand joints near the forearm.

Posterior interosseous neuropathies are quite uncommon, rarely occurring acutely with fractures of the proximal radius Very exceptionally, the PIN is chronically compromised by a soft tissue mass or ligamentous structure near or within the supinator muscle. Posterior interosseous neuropathies may develop precipitously in patients performing repetitious and strenuous pronation/supination movements, such as recurrent hammering or serving at tennis. Occasionally, instances of this activity lead to intermittent PIN entrapment by the fibrous *arcade of Frohse* at the proximal *supinator muscle* or a hypertrophied or anomalous supinator.

Predominant Sensory Radial Neuropathies. The superficial terminal radial primary sensory branch may be injured in isolation with external pressure at the wrist, for example, with handcuff injuries. These lesions are readily recognized by the distribution of sensory symptoms on the posterolateral portion of the hand, particularly the thumb. Weakness does not occur. An intermittent radial sensory occupational neuropathy, characterized by recurrent numbness of the thumb and fingers, may occur when the wrist is dorsiflexed, such as by an artist holding a paint brush for a prolonged period of time, leading to a temporary entrapment. Sensory symptoms on the posterior forearm from isolated injuries to the posterior cutaneous nerve of the forearm are equally rare.

In children, more than 50% of radial neuropathies occur secondary to trauma, either fractures or lacerations. Forty percent are due to compression, either intrauterine from prolonged labor or varied mechanisms similar to those in adults. Very occasionally, benign tumors, such as lipomas, ganglia, fibromas, neuromas, and hemangiomas, may affect the radial nerve.



Femoral and Lateral Femoral Cutaneous Nerves

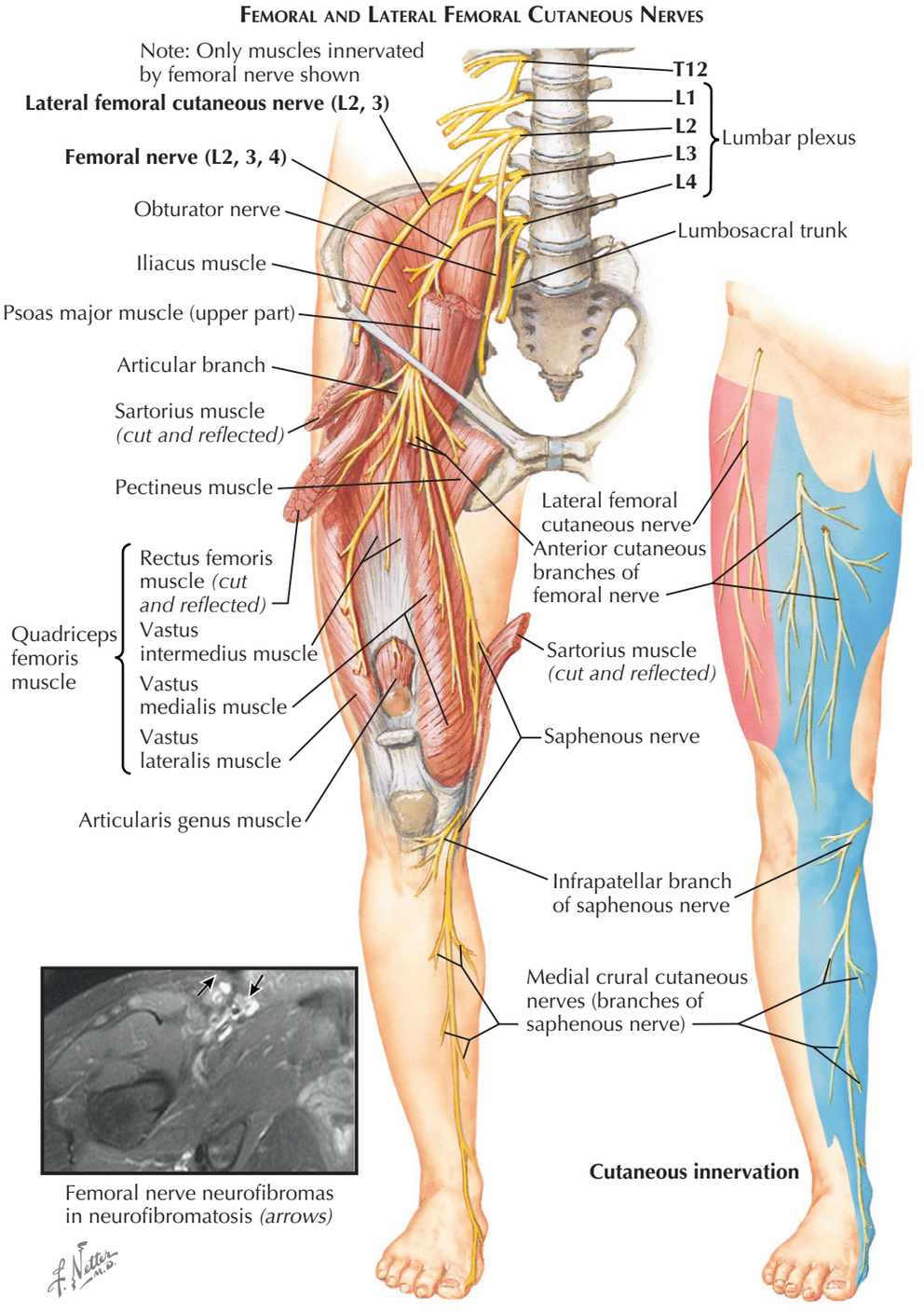
Femoral Nerve

Anatomy. The *femoral nerve* (L2-4) is the largest branch of the lumbar plexus, initially exiting this plexus and passing inferolaterally beneath the psoas muscle and then coursing within the pelvis between the *iliacus and psoas (L2, 3) muscles* to innervate same. The femoral nerve enters the thigh descending beneath the inguinal ligament lateral to the femoral vascular sheath, thus lateral to the femoral artery pulse, with the femoral vein placed medially. Muscular branches then supply, in order, the *sartorius, pectineus, and quadriceps femoris*, (all L3, 4) innervated. The *anterior femoral cutaneous nerves* supply the skin and fascia over the front and medial sides of the thigh. The *saphenous nerve* communicates with the anterior femoral cutaneous and obturator nerves, then gives off its infrapatellar branch, descends medial to the knee onto the medial foreleg (close to the great saphenous vein), and distally subdivides at the ankle, distributing to the medial arch and dorsum of the foot.

Clinical. An *iliacus syndrome (L2, 3)* occurs when the femoral nerve is entrapped during its initial course within the pelvis and groin, affecting the iliopsoas and quadriceps femoris muscles. The former leads to unilateral hip flexion weakness and the latter to knee extension weakness. When severe, this leads to total loss of knee extension, precluding walking as leg stability is totally compromised from lack of quadriceps femoris function. With partial lesions, patients first note difficulty going down stairs as their ability to lock their knee to support their weight is compromised. The patellar muscle stretch reflex is diminished or absent. Groin and thigh pain may also occur. Sensory symptoms involve the anteromedial thigh and medial lower leg. A somewhat unusual pure motor syndrome with primary quadriceps weakness occurs with lesions distal to the origin of the saphenous nerve.

Femoral mononeuropathies are infrequent. Acute femoral nerve deficits may occur when an expanding mass, particularly a spontaneous hematoma, develops within the *iliopsoas* muscle in a medically anticoagulated patient. *Diabetes mellitus* is the most common associated disorder occurring with a "*femoral neuropathy.*" Although these lesions clinically mimic a painful femoral neuropathy, electromyography (EMG) studies typically demonstrate that the disorder is more extensive; these lesions are better considered as *femoral radiculoplexopathies*. Often, there is an autoimmune vasculitic component not unlike polyarteritis nodosa. With either illness, the femoral neuropathy may be the initial sign of mononeuritis multiplex. Occasionally, femoral neuropathies manifest in patients having prolonged pelvic surgery or childbirth requiring a lithotomy position. Other iatrogenic mechanisms include postoperative hematomas or abscesses, misplaced femoral artery or venous puncture, and direct nerve injury subsequent to nephrectomy or hip arthroplasty. Tumors, either benign ones such as neurofibromas, or infiltrating malignant lesions, such as lymphoma, rarely cause femoral neuropathies. Isolated saphenous nerve injuries may result from knee arthroscopy, femoral-popliteal artery bypass surgery, and in the course of coronary artery bypass graft surgery.

Femoral mononeuropathies are extremely rare in children, occurring subsequent to orthopedic or renal transplant surgery, with stretch injuries, spontaneous intrapelvic hemophiliac-related intraneural or extraneural hematomas, perineuromas, and neurofibromas.



Differential Diagnosis. *L3 and L4 nerve root and lumbosacral plexus* lesions are the two primary possibilities. If there is no pain or sensory loss, *early motor neuron disease* is always a possibility. Very rarely, a *lumbosacral plexitis* occurs in children. This mimics the immunologically mediated Parsonage-Turner brachial plexitis.

Evaluation. Electromyelography with computed tomography (CT) and/or magnetic resonance imaging (MRI) is most useful. Relevant blood studies include serum glucose, perhaps a 2-hour glucose tolerance test if there is a lot of pain typical of diabetes, and an erythrocyte sedimentation test and/or C-reactive protein when an autoimmune process, such as polyarteritis nodosa, is a clinical possibility.

Treatment and Prognosis. Rehabilitation, particularly utilizing bracing lending to knee stabilization, is essential. The degree of axonal damage and subsequent reinnervation determines the patient's outcome. Physical therapy is important.

Lateral Femoral Cutaneous Nerve

The lateral femoral cutaneous nerve *(LFCN)* has a *pure sensory* function. It is derived from the L2 and L3 nerve roots to emerge from the *lateral psoas* muscle, passing obliquely over the *iliacus*, to course toward the anterior superior iliac spine. Eventually, it enters the thigh by passing above or through the most lateral portion of the inguinal ligament. The LFCN next passes over or through the proximal *sartorius* muscle, descending deep to the *fascia lata*. After a number of small branches are delivered to the overlying skin, the LCFN pierces the

Femoral and Lateral Femoral Cutaneous Nerves
(Continued)

fascia about 10 cm below the inguinal ligament to innervate the anterolateral thigh.

Damage to this cutaneous nerve is one of the most commonly observed adult mononeuropathies; in contrast, LFC neuropathies are extremely rare in children. Classically, patients report vague lateral thigh numbness and annoying paresthesias referred to as *meralgia paresthetica*. With a few exceptions, there is usually no serious pain. This contrasts with patients having a radiculopathy or, rarely, a primary bone or muscle tumor, where pain is often prominent.

On neurologic examination, the patient is asked to outline the distribution of discomfort. He or she can invariably do so by taking a finger to delineate areas of abnormal sensation; typically this is a small football-like elliptic area of dysesthesias. The remaining neurologic examination is normal and, in particular, there is no weakness in the femoral-innervated muscles.

Almost all LFCNs develop insidiously without the identification of a specific pathophysiologic mechanism. On rare occasions, an individual unaccustomed to utilizing a tight harness or a backpack belt tightly positioned across the iliac crest, may report more painful dysesthesias appropriate to the LCFN innervation. Other mechanisms include compression with orthopedic appliances or athletic injuries—from direct blunt trauma to the thigh in high-energy sports or, in female gymnasts, due to the repetitive impact on the thigh by parallel bars. Almost all idiopathic LFCN lesions gradually resolve. Reporting this to the patient is very reassuring.

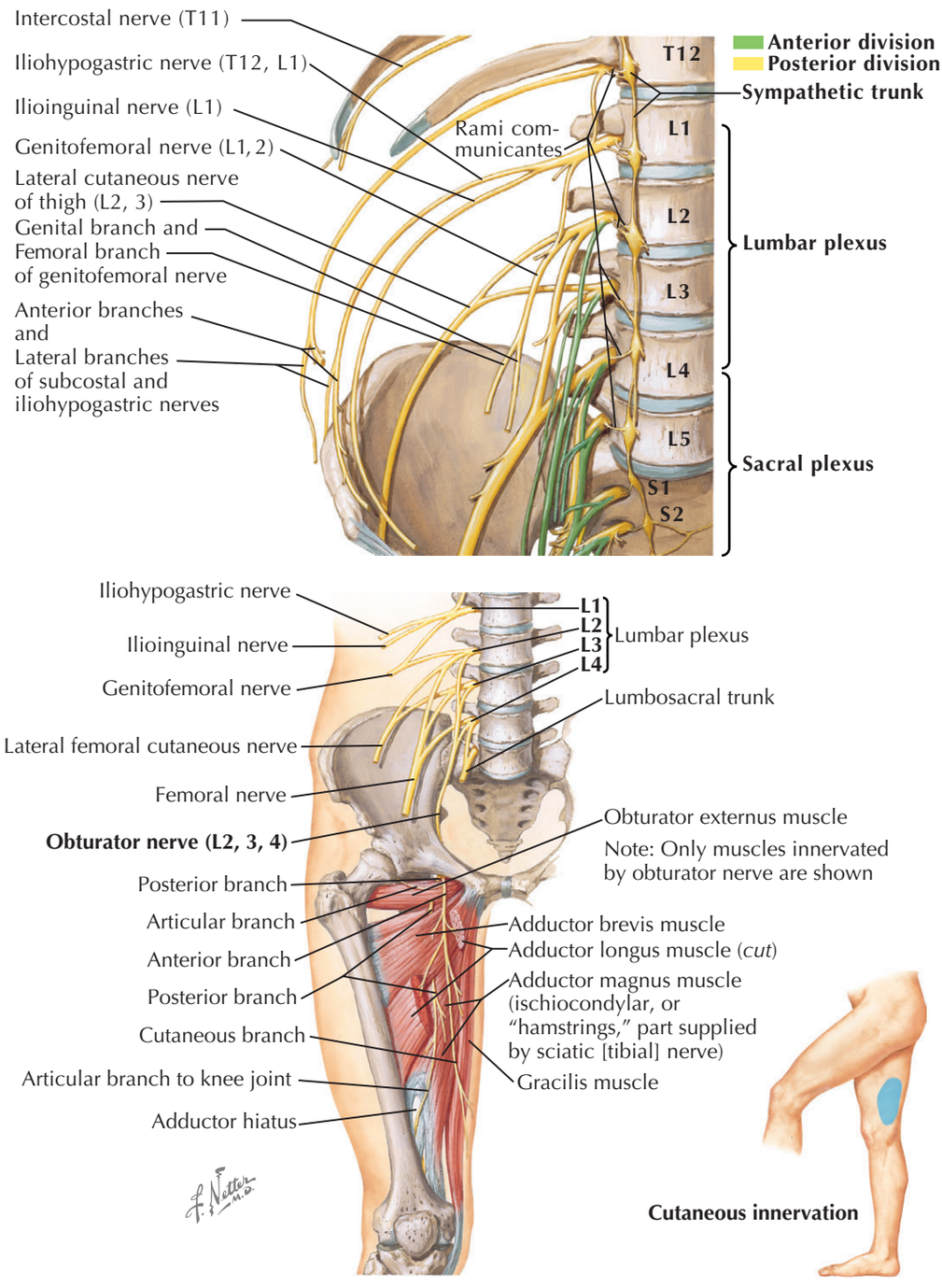
When the patient's history is atypical, such as because of constant boring pain leading to postural changes or difficulty sleeping, it is important to obtain CT scans or MRIs to evaluate the possibility of other lesions, such as a potentially fatal soft tissue sarcoma.

Iliohypogastric, Ilioinguinal, and Genitofemoral Nerves

The *iliohypogastric, ilioinguinal, and genitofemoral* nerves are primary sensory nerves innervating the lower abdomen, inguinal region, the upper and medial anterior thigh, and part of the genitalia. Each has an L1 origin; sometimes there are T12 and L2 contributions. The *iliohypogastric and ilioinguinal nerves* track laterally, similar to other cutaneous thoracoabdominal nerves. The genitofemoral nerve descends distally through the psoas, emerging to pass under the inguinal ligament, dividing into genital and femoral branches. Its *genital branch* accompanies the ilioinguinal nerve and has a similar cutaneous distribution; it also innervates the cremaster muscle. The *femoral branch*, and the *ilioinguinal nerve* innervate small areas of the most proximal anterior thigh. The *ilioinguinal nerve* innervates the skin above the inguinal ligament; the base of the penis and upper scrotum in men, or, in women, the mons pubis and labium majus; and the upper medial thigh. The *iliohypogastric nerve* innervates the distal abdominal wall musculature, its adjacent skin, a small area above the pubis, and a minor portion of the upper buttocks.

These nerves are most likely to be affected subsequent to inguinal hernia repair. Entrapment may occur as the ilioinguinal nerve emerges from the abdominal wall near the iliac crest. This is typified by iliac fossa, inguinal allodynia, or hyperesthesia radiating to the genitalia, often exacerbated by walking and hip extension. Relief may occur with hip flexion. This neuropathy is often clinically difficult to prove; sometimes a local nerve block may confirm the diagnosis and provide therapy. Either a retroperitoneal lymphoma or intrapelvic/inguinal endometriosis merits differential diagnostic consideration.

Iliohypogastric, Ilioinguinal, Genitofemoral, and Obturator Nerves



Obturator Nerve

Originating within the lumbar plexus and derived from the anterior divisions of the L2, 3, 4 nerve roots, these nerves unite within the posterior psoas muscle, forming the obturator nerve. This descends through the iliopsoas to emerge medially near the upper sacroiliac joint. The obturator nerve then courses along the pelvis, lying lateral to the ureter and internal iliac vessels, and bending anteroinferiorly to follow the lateral pelvic wall. It next passes anterior to the obturator vessels while lying on the obturator internus muscle, to reach the obturator groove, and then it enters the obturator canal. Here it descends to the medial thigh, supplying the obturator externus, pectineus, adductor longus, adductor brevis, and gracilis muscles, as well as hip and knee joints and medial thigh.

Obturator mononeuropathies are exceedingly rare in both adults and children. Various pathophysiologic mechanisms include pelvic and hip fractures, rarely obturator hernias, malignancies, surgery involving the hip and pelvis, particularly when patients are placed in the lithotomy position, and various laparoscopic interventions.

Sciatic and Gluteal Nerves

Gluteal/Proximal Sciatic Nerves

The *gluteal nerves* originate from the anterior divisions of the lumbosacral trunk. Both gluteal nerves leave the company of the adjacent sciatic nerve within the buttocks near the sciatic notch. The *superior gluteal nerve*, primarily L5 in origin, emerges above the piriformis muscle to innervate the *gluteus medius and tensor fasciae lata muscles*, both important abductors of the hip. Concomitantly, *the inferior gluteal nerve*, having a predominant S1 origin, emerges below the piriformis muscle, innervating the *gluteus maximus* muscle, the primary extensor of the thigh. The gluteal nerves provide an important clinical localization for the electromyographer because, in the patient presenting with a sciatic neuropathy, the absence of denervation in the gluteal muscles provides support for a localization of the lesion immediately at or distal to the sciatic notch.

Sciatic/Posterior Femoral Cutaneous Nerves

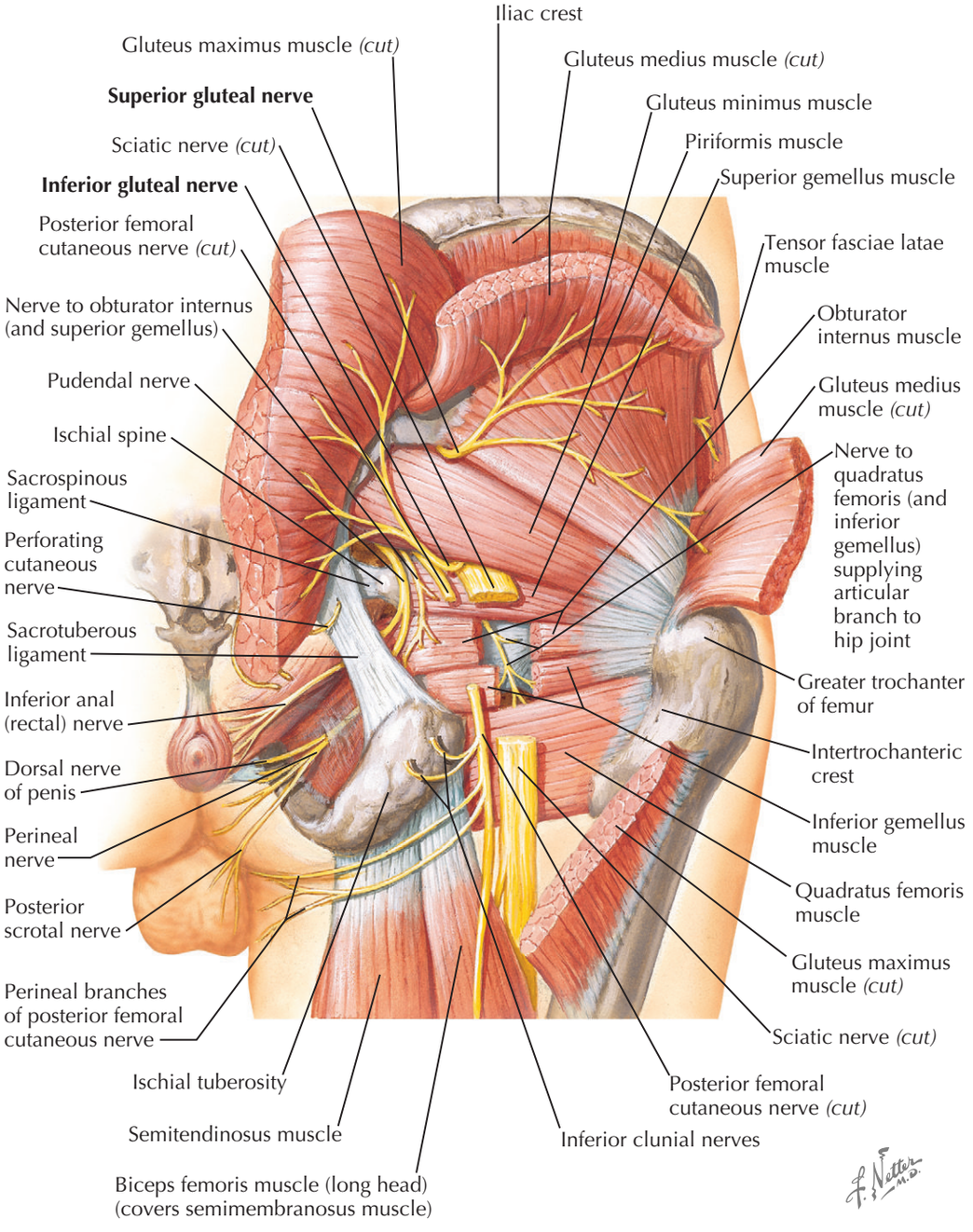
Anatomy

The sciatic and the gluteal nerves share common derivations originating from the anterior rami of the fourth lumbar through the third sacral nerve roots, immediately forming the lumbosacral plexus. The *sciatic nerve* (SN) is a very large single elliptic trunk, 2.0 cm in diameter, that inclines laterally beneath the gluteus maximus muscle while resting on the posterior ischium and the nerve to the quadratus femoris. The *posterior femoral cutaneous nerve* (PFCN), lying immediately adjacent to the medial edge of the sciatic nerve, provides cutaneous innervation to the posterior thigh. Concomitantly, the sciatic nerve is also accompanied by the inferior gluteal artery (IGA), providing primary blood supply to this nerve. On reaching a point about midway between the ischial tuberosity and the greater trochanter, the SN turns downward over the *gemelli*, the obturator internus tendon, and the *quadratus femoris* muscle, separating it from the hip joint to exit the buttock and enter the thigh beneath the lower border of the *gluteus maximus*, then emerging from the pelvis through the sciatic notch. Here it is found lying just anterior to the piriformis muscle; however, in about 10% to 15% of individuals, part or all of the SN pierces the piriformis muscle.

After passing through the *sciatic notch*, the sciatic nerve descends into the thigh, where it innervates the *semitendinosus (L5, L4-S2)*, *semimembranosus (L5)*, *biceps femoris (S1, 2)*, *and distal part of the adductor magnus (L5)* muscles. The sciatic nerve then descends near the mid-posterior thigh, initially directly posterior to the *adductor magnus*, the distal portion of which it also innervates. It soon travels obliquely over the long head of the *biceps femoris*. Just above the apex of the popliteal fossa, it is overlapped by the contiguous margins of the biceps femoris and *semimembranosus muscles*.

The sciatic nerve trunk has two well-defined divisions, namely the *lateral fibular (peroneal)*, derived from the anterior divisions of the anterior rami of the L4-S2 roots and *medial tibial* derived from the posterior divisions of the anterior rami of the L4-S3 nerve roots. The tibial division innervates all posterior thigh muscles, with the exception of the short head of biceps femoris, which is innervated by the fibular division. In approximately 90% of individuals, these two divisions share a common sheath from the pelvis to the popliteal fossa. However, in 10% of individuals, the anatomic separation of the sciatic divisions occurs higher in the thigh. Rarely, the common fibular and tibial nerves arise independently from the sacral plexus itself, pursuing similar courses until truly separating at the apex of the *popliteal fossa* into its two terminal branches, the common fibular (peroneal) and tibial nerves.

Gluteal Nerves



Clinical

Acute proximal sciatic neuropathies manifest with distal leg weakness affecting both fibular- and tibial-innervated muscles—in the most severe instances, leading to severe footdrop (secondary to weakness of the *tibialis anterior*) and weakness of eversion (*peroneus longus* muscles), plantar flexion (*gastrocnemius*), and inversion (*tibialis posterior* muscles). Concomitantly, the more proximal SN-innervated *hamstring muscles* are weakened. The ankle jerk and hamstring muscle stretch reflexes are usually depressed or absent with primary SN lesions. Sensory loss and painful dysesthesias of the sole and dorsum of the foot and posterolateral lower leg are common concomitant sensory findings. Sciatic nerve lesions in children are as frequent as fibular nerve lesions, in contrast to adults, where the latter are much more prevalent.

In the setting of an *acute gluteal compartment syndrome*, secondary to an expanding hematoma compressing the SN, there is often increasingly severe pain within the buttocks. The sciatic notch and gluteal musculature must be palpated to search for tenderness or fullness compatible with a hematoma or other infiltrating lesion. Occasionally, because of the SN's fascicular anatomy, a proximal sciatic neuropathy manifests with a more predominant fibular division deficit manifested

Sciatic and Gluteal Nerves
(Continued)

by an isolated footdrop requiring differentiation from the more common fibular (peroneal) neuropathy (FN) at the fibular head. The presence of clinical or electromyographic (EMG) evidence of hamstring weakness helps differentiate between primary SN and FN lesions. Involvement of the *gluteal muscles* will confirm a proximal *lumbosacral plexus* or L5, S1 nerve root lesion with combined sciatic and gluteal nerve involvement.

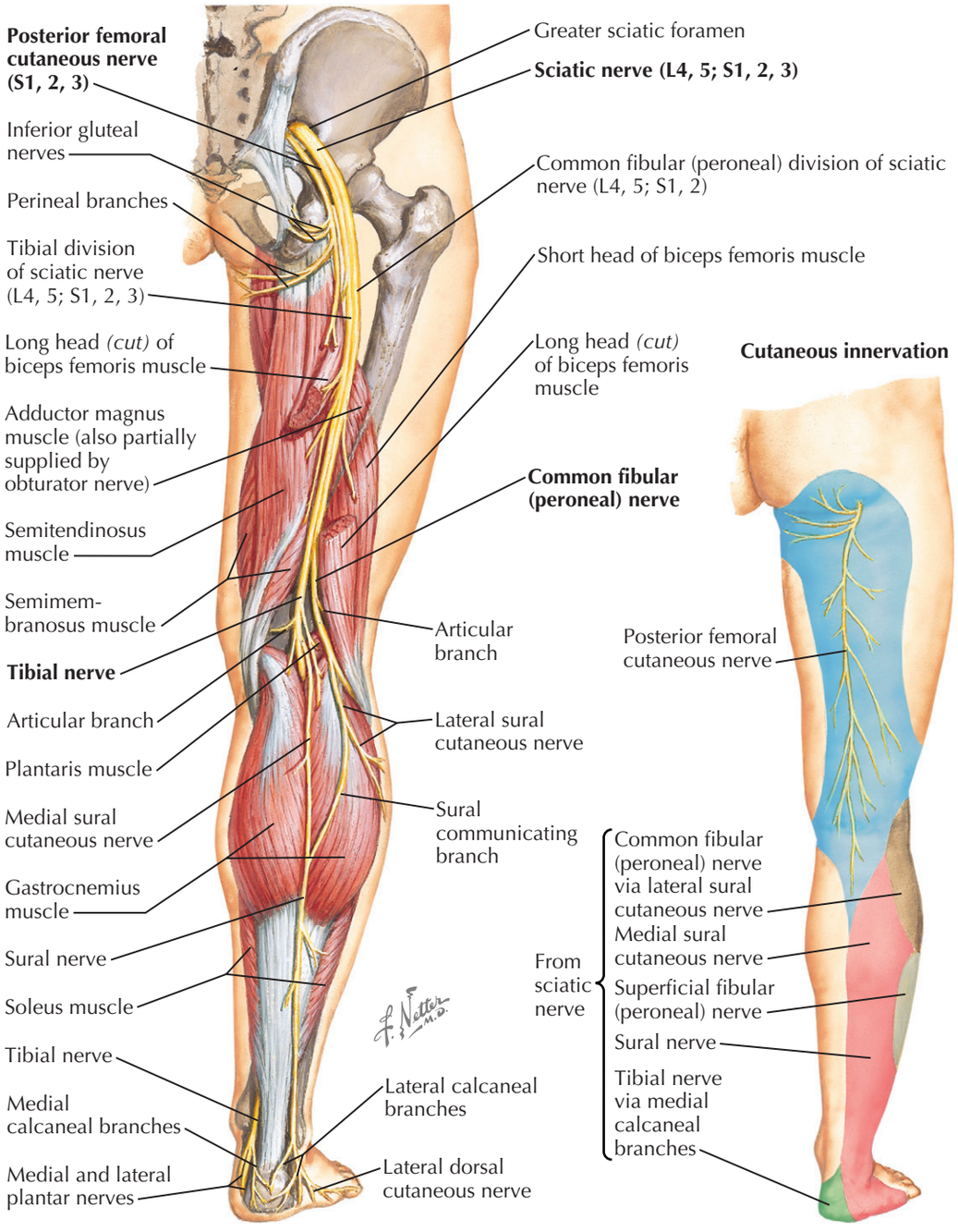
Etiology

The sciatic nerve is particularly vulnerable to trauma because it is situated immediately behind the bony pelvis and adjacent to the hip joint, predisposing it to bony pelvic or femoral fractures and/or posterior hip dislocations. Sciatic neuropathies occasionally occur subsequent to hip arthroplasty. Similar to femoral neuropathies, sciatic lesions occasionally occur subsequent to prolonged surgery with the patient in the prolonged lithotomy position, presumably from nerve stretch, compression, or vascular (vasa nervorum) injury in lean individuals who are anatomically predisposed in a nonpredictable fashion.

Rarely, sciatic neuropathies develop secondary to external pressure, producing a compression injury in comatose or immobilized patients. Very slender individuals who pass out after using toxic substances while seated on a very hard surface, such as a bench or a toilet seat, may develop severe SN damage. If there is significant axonal damage, there may be little chance for nerve recovery over such a long distance. Other traumatic mechanisms leading to a severe SN occur with misplaced injections into the inferior medial quadrant of the buttocks. Fortunately, intramuscular medications are now avoided in this area. Various benign nerve sheath or malignant tumors, such as lymphomas, affect the sciatic nerve in rare instances. Iliac artery aneurysms, systemic vasculitis, or endometriosis are extremely rarely causes of SNs. Congenital fibrous bands may entrap the SN in the midthigh.

Pediatric sciatic neuropathies are primarily related to trauma or iatrogenic orthopedic or miscellaneous surgeries. Other examples of prolonged extrinsic compression leading to sciatic neuropathies include heel compression in an orthopneic child who slept with a foot tucked under his buttock, after prolonged lithotomy surgical positioning, and the consequences of sitting in the lotus posture. The precise mechanism of injury is unclear; these are possibly due to ischemia, stretch, or external compression. Damage to a persistent sciatic artery at the pelvic notch may predispose to sciatic nerve compression and infarction. A variety of tumors affect SN function in children, including neurofibromas, lymphomas, pelvic neuroblastomas, and chloromas. Various vascular lesions occur, including hemophilia, arteriovenous malformations, hypereosinophilic or meningococcemia vasculitis, and hematocolpos. The sciatic nerve is at risk during rare newborn crises, wherein analeptic agents are inadvertently injected into an umbilical artery rather than the umbilical vein. Because the umbilical artery supplies the inferior gluteal artery (IGA), and thus the embryologic-derived sciatic artery, severe IGA vasoconstriction or thromboembolism leads to sciatic nerve ischemia. Congenital iliac anomalies or myofascial bands deep within the thigh are rare causes of a pediatric SN. Occasionally, no specific pathophysiologic mechanism is defined, even in the face of a progressive clinical deficit.

Sciatic and Posterior Femoral Cutaneous Nerves



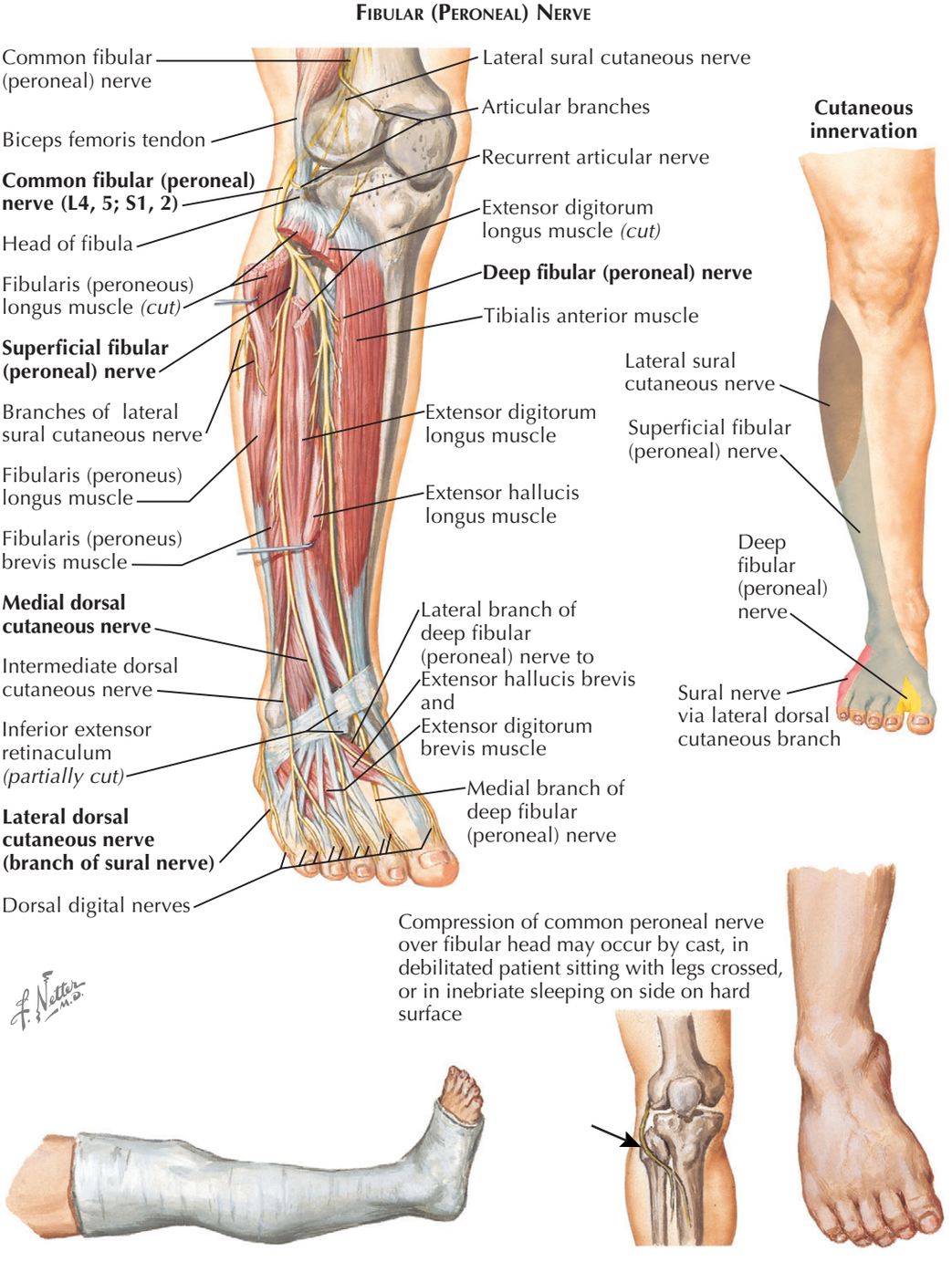
Differential Diagnosis

Nerve root lesions, particularly at L5, S1 or a *lumbosacral plexus* lesion, provide the primary differential diagnostic consideration in most SNs, when findings clearly encompass not only fibular but also tibial and or proximal sciatic nerve damage. Diminished sensation on the posterior thigh points to a concomitant posterior femoral cutaneous neuropathy near the greater sciatic foramen. Injury to the *perineal branches of the sacral plexus* nerves leads to sensory loss on the scrotum or labia majora.

Hip extension and abduction, dependent on gluteal nerve and muscle function, are preserved in primary SNs unless there is concomitant involvement of the superior and inferior gluteal nerves. When clinical or EMG evidence defines gluteal muscle involvement, primary lesions adjacent to the pelvis, such as malignant processes—particularly lymphoma or benign tumors, (e.g., schwannomas)—require consideration. The possibility of a piriformis syndrome is mentioned for completeness. It is a poorly defined entity that has no proved clinical definition despite a modest literature on the subject. Objective clinical or electrodiagnostic evidence of sciatic neuropathy is not confirmed in most patients in whom piriformis syndrome is suspected.

Fibular (Peroneal) and Tibial Nerves

Fibular (Peroneal) Nerve



Fibular (Peroneal) Nerve

The *common fibular (peroneal) nerve* (CFN) is one of the two major subdivisions of the sciatic nerve, having a lateral, more superficial locus within the sciatic nerve sheath. It is derived from the *posterior* divisions of the fourth and fifth lumbar anterior rami and the first and second sacral nerves. Transcending the thigh, usually within the sciatic trunk, it enters the popliteal fossa, where it and the tibial division bifurcate as separate entities. At the knee, the CFN descends along the lateral popliteal fossa, initially overlapped by the medial biceps femoris tendon; it passes between the biceps tendon and the lateral gastrocnemius head and behind the fibular head to wind around the fibula's bony surface.

This nerve next passes between the two heads of the *fibularis (peroneus) longus* (L5) muscle; here it is particularly vulnerable to being compressed against the fibular bone, leading to footdrop. The CFN divides into the *superficial* and *deep fibular nerves* here. Concomitantly, two superficial sensory nerves take origin. The *lateral sural cutaneous nerve* supplies the skin and fascia on the lateral and adjacent parts of the anteroposterior leg. The *peroneal communicating branch* joins the *sural nerve, a branch of the tibial nerve*, to be distributed with it.

The superficial fibular nerve initially descends between the *extensor digitorum longus and brevis* (L5, S1) muscles to innervate the *fibularis (peroneus) longus (L5) and brevis (L5) muscles*. The *accessory fibular* (peroneal) nerve, a motor branch of the superficial fibular nerve, is an important *anatomic variation* found in 10% of individuals. This provides partial innervation to the extensor digitorum brevis. Subsequently, the superficial fibular nerve pierces the deep fascia in the lower leg, dividing into two cutaneous nerves. The *medial dorsal cutaneous nerve innervates* the skin on the anterior distal leg; then it travels across the anterior ankle to the dorsum of the foot and across the lower inferior extensor retinaculum. It divides into two *medial dorsal digital nerves;* one supplies the medial and posterior aspects of the foot and great toe, and the other innervates the second and third toes. The *intermediate dorsal cutaneous nerve* courses along the lateral dorsal foot, supplying its adjacent skin and fascia. The *lateral dorsal digital nerves* innervate the skin and fascia of the third through fifth toes.

The deep fibular (peroneal) nerve (DFN) originates at the fibular head, passing obliquely downward around the proximal fibular neck, between the *fibularis (peroneus) longus* and *extensor digitorum longus (L5, S1)*, muscles that it innervates, to then descend lateral to the *tibialis anterior (L4, 5)* and medial to the *extensor digitorum longus and brevis* (L5, S1) and *extensor hallucis longus (L5, S1)*. *The DFN* innervates each of these muscles and the fibularis (peroneus) tertius muscles. The DFN divides at the ankle. Its *medial terminal branch* gives rise to a *dorsal digital nerve*, whose two branches supply the contiguous surfaces of the first two toes. Its *lateral terminal branch* curves outward under the extensor digitorum brevis muscle, which it supplies.

Clinical. Most *fibular (peroneal) neuropathies* occur at the fibular head with 60% of cases involving the CFN, whereas about 10% affect the deep fibular, and 5% the superficial fibular nerve. The other 25% are difficult to localize precisely. *Compression* is the primary pathophysiologic mechanism for fibular neuropathies; a typical example occurs when sleeping on one's side on a hard surface, resting directly on the fibular head, and thereby compressing this nerve as it winds around the fibular neck. This typically occurs in a narcotized, often alcoholically intoxicated individual not moving during deep sleep. Anorectic malnourished adolescents often sit for long periods with legs crossed, compressing their fibular heads and the CFN, and leading to a footdrop. When this occurs among patients who are on strict diets, it is known as *"slimmer's palsy."* Occupations requiring prolonged squatting, such as farm laborers, strawberry pickers, and carpet layers, may compress this nerve between the biceps femoris tendon and lateral gastrocnemius origin. Very occasionally, iatrogenic mechanisms lead to compression injuries and footdrop; these include too tightly applied casts at the fibular head, Buck traction, Velcro straps, and intravenous footboards.

Entrapment. Sometimes a progressive footdrop develops secondary to *common or deep fibular nerve* entrapment at the knee. The proximal tendon of the *fibularis longus* rarely entraps the fibular nerve within the fibular tunnel at the fibular head. Mass lesions, including schwannomas, hemangiomas, bony exostoses, osteochondromas, perineuromas, or intraneural ganglia or synovial cysts within the popliteal fossa, may variably entrap the fibular nerves. Occasionally, runners inadvertently step into a hole, inverting the ankle and concomitantly stretching and/or avulsing the CFN at its anatomic fixation to the fibular head, producing a

Fibular (Peroneal) and Tibial Nerves *(Continued)*

footdrop. A post-traumatic anterior tibial compartment syndrome rarely leads to similar outcomes. An urgent limited fasciectomy is indicated. The *lateral cutaneous nerve of the calf* can be entrapped in the lateral popliteal fossa, leading to popliteal fossa and lateral calf pain, exacerbated when seated and aided by extension of the knee.

Many of the above noted mechanisms are operative in children. We have seen a newborn with a primary fibular nerve lesion resulting in a footdrop. The rapid recovery suggested there must have been a neurapraxic mechanism, presumably secondary to the uterus being pushed against the pelvic brim.

TIBIAL NERVE

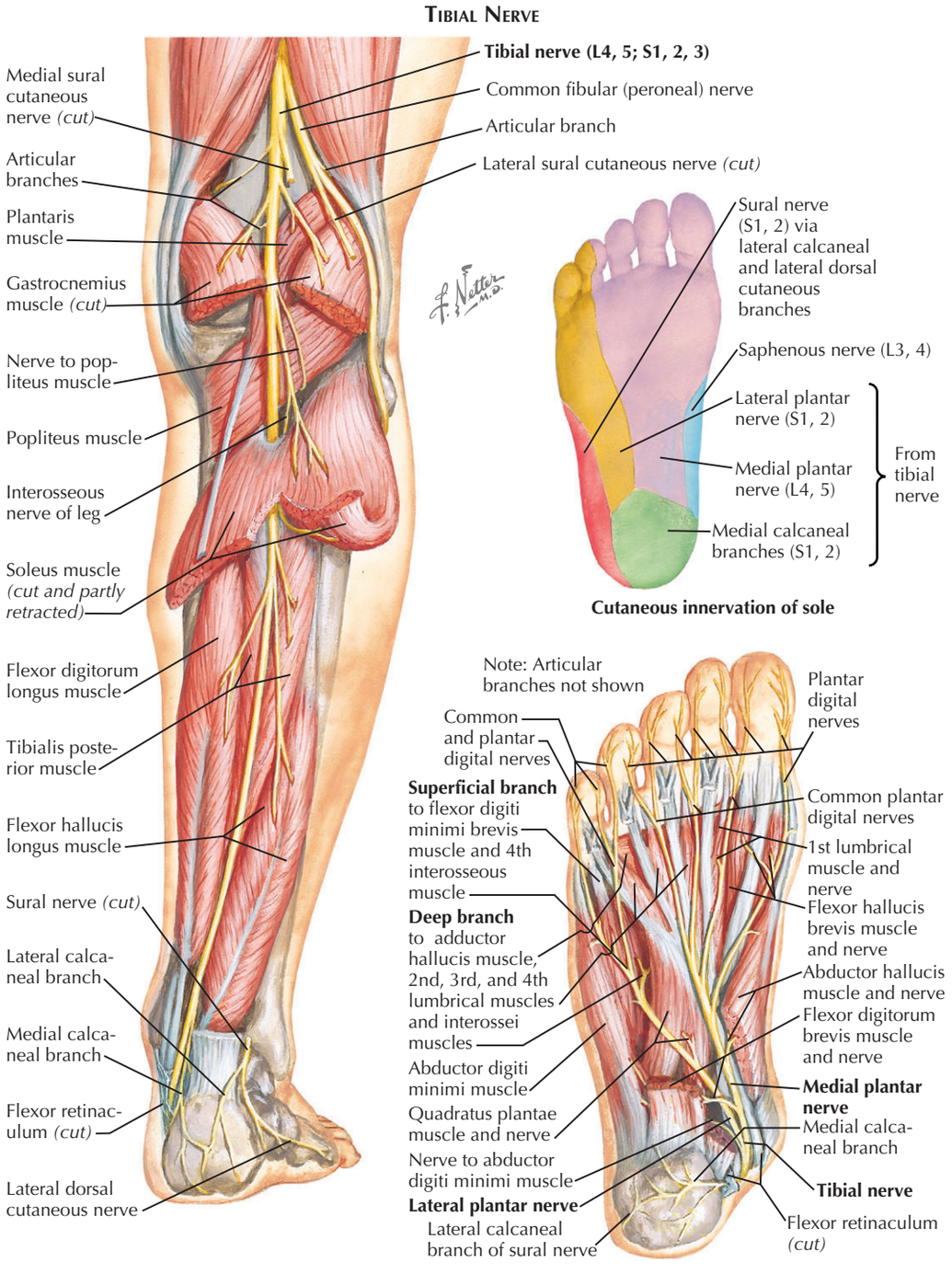
This is the larger and medial terminal branch of the sciatic nerve. Its fibers are derived from the anterior divisions of the anterior rami of the fourth and fifth lumbar and the first, second and third sacral nerves. In the distal thigh, after its origin from the sciatic bifurcation, the tibial nerve is overlapped by the semimembranosus and biceps femoris muscles, becoming more superficial in the popliteal fossa; proceeding into the leg beneath the heads of the *gastrocnemius lateral (L5, S1) and medial (S1, 2)* and *plantaris* muscles; and descending to be above the *popliteus* muscle and under the *soleus (S1, 2)*, to travel between the gastrocnemius medial and lateral heads of the tibialis posterior and, subsequently, between the *flexor digitorum longus (L5, S1) and flexor hallucis longus* muscles, innervating each of these muscles as well as *plantaris* and *popliteus* muscles. Distally, the nerve lies superficially, descending to the ankle, medial to the Achilles tendon; curving anteroinferiorly and posteriorly to the medial malleolus. Here it enters the tarsal tunnel, proceeding into the foot deep to the flexor retinaculum between the flexor hallucis longus and flexor digitorum longus tendons. Here it terminates, dividing into the medial and lateral plantar nerves that innervate all intrinsic foot muscles (S1, 2) and provide the sensation for the plantar surface of the foot.

The sural nerve, a cutaneous branch, arises from the tibial nerve at the popliteal fossa, descends between the gastrocnemius heads, pierces the deep fascia, gives off a small *medial sural cutaneous nerve* (it may be larger and arise directly from the tibial nerve), and is joined by the *fibular communicating branch of the lateral sural cutaneous nerve*, next passing over and lateral to the Achilles tendon. It provides cutaneous innervation to the posterior lateral lower leg, the lateral ankle, and heel. The terminal portion courses forward as the *lateral* dorsal cutaneous nerve of the foot.

The medial plantar nerve can be compared with the median nerve in the hand. It originates under the flexor retinaculum, traveling deep to the *abductor hallucis*, innervating it and subsequently the *flexor digitorum brevis* and *flexor hallucis brevis* muscles all (S1, 2). At the tarsometatarsal joints, this nerve ends by dividing into a *proper plantar digital nerve* that supplies the medial great toe and three *common plantar digital nerves* in a fashion similar to the median nerve of the hand.

The lateral plantar nerve is homologous with the ulnar nerve in the hand, arising deep to the flexor retinaculum; passing outward to innervate the lateral sole, the *flexor digitorum brevis*, *the quadratus plantae*, *and the abductor digiti minimi* all (S1, 2); and ending near the fifth metatarsal bone. Lastly, it divides into two branches: the *superficial branch* that splits into *proper and common plantar digital nerves* that innervate the plantar lateral small toe and the *flexor digiti minimi and interossei* muscles (S1, 2) of the fourth intermetatarsal space. The *common plantar digital nerve* divides into two *proper plantar digital nerves* supplying the fourth and fifth toes. A *deep branch* supplies the *adductor hallucis*, the second to fourth *lumbricals*, and the medial three *interossei muscles (S1, 2)*.

Clinical. Isolated *tibial neuropathies* are very uncommon. This nerve is very well protected within the entirety of its course from the sciatic notch, through the thigh, within the popliteal fossa, and deep within the calf. It is not at risk for compression or entrapment. However, various traumas, such as localized lacerations, fractures, and hematomas, may involve the tibial nerve. A Baker cyst within the knee joint or a ganglion within the tibiofibular joint occasionally compromises this nerve. Intrinsic nerve tumors may affect the tibial nerve anywhere along its course. Depending on the site of involvement, there can be calf and/or foot muscle weakness and atrophy, as well as sensory loss appropriate to the lesion site. Other sites of involvement can lead to a painful or numb foot, as seen in the very uncommon tarsal tunnel syndrome or distal Morton neuroma.



Dermatomal and Cutaneous Nerve Patterns

Feelings of numbness, tingling, or sensory loss are very common complaints, particularly with the various neuropathies. Knowledge of the cutaneous sensory supply of the individual peripheral nerves and nerve roots is essential. These symptoms can emanate from almost any level of the somatosensory system. However, sensory evaluation is the most subjective part of the neurologic examination; depending on the patient's perceived symptoms, it may be difficult to clearly define their origin. With cerebral cortex involvement, the patient reports a more global deficit, for example, of the entire hand, arm, and, often concomitantly, the face, rather than a partial deficit. Alternatively, numbness can involve the entire side, including both ipsilateral extremities, when the thalamus or internal capsule is affected.

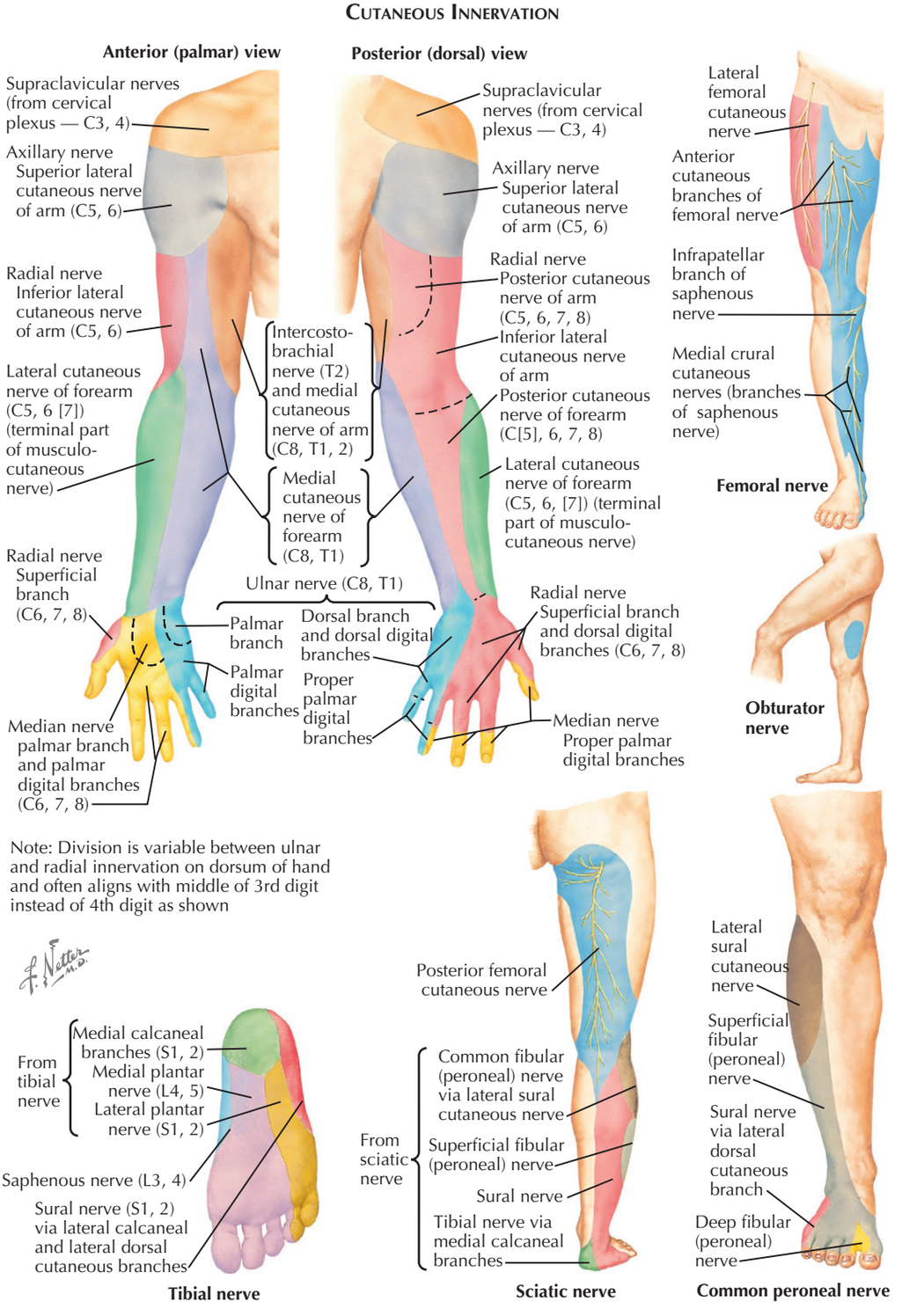
Clinical definition of the distribution of sensory changes affecting a specific area within one extremity implies a single nerve root, portion of a plexus, or peripheral nerve damage. Focal complaints involving a few digits or a distinct area within an extremity (such as the lateral outer thigh), almost always define a peripheral nervous system (PNS) lesion, either the cervical or lumbosacral nerve root or a specific mononeuropathy.

A careful neurologic examination allows differentiation of specific anatomic sites of involvement. Finger numbness is a very familiar clinical neurologic complaint. The carpal tunnel syndrome results from median nerve entrapment at the wrist; this is the most common mononeuropathy. Here, sensory symptoms are predominant early in this disorder. The clinical history of nocturnal awakening or symptoms present on awakening in the morning or precipitated by various activities, particularly driving or working with the hand, helps the clinician differentiate this disorder from other somatosensory system lesions. Sometimes the patient provides the most accurate assessment by roughly defining the area in question using a finger to outline the area of diminished sensation. Often, it then becomes clear that the pattern of sensory loss fits the distribution of a particular peripheral nerve or nerve root dermatome.

Unfortunately, sometimes the symptom distribution is not clearly defined by patients, particularly those who are not good self-observers. Often, they are unable to decide whether their symptoms involve the classic lateral 3.5 digits of the hand, namely the thumb, index, and middle fingers, and the lateral aspect of the ring finger, typical of a median nerve lesion, versus all fingers—raising the possibility of a cerebral cortical lesion. However, when there is concomitant focal *weakness* with *numbness*, it is much easier to differentiate a peripheral nerve lesion from a nerve root lesion.

Median nerve lesions primarily affect the *palmar aspects of fingers 1 to 3.5*; the dorsal tips of these fingers are also compromised to the distal interphalangeal joints (DIPs). In contrast, *ulnar neuropathies* also manifest with finger numbness but with a different anatomic distribution involving the *medial 1.5 fingers*, specifically the entire little (fifth) finger, and the medial aspect of the ring (fourth) finger. The *ulnar nerve* is the only nerve in the hand to equally affect the palmar and posterior portions of the fingers and hand. Parenthetically, an early *medial cord or lower trunk brachial plexus lesion* may also present with numbness mimicking the ulnar nerve, that is, the medial fingers of the hand. Although a *C-8 radiculopathy* has a similar sensory distribution, it is usually accompanied by significant neck pain. The *radial nerve* primarily innervates the dorsum of the proximal thumb, index, middle, and lateral half of the ring finger to the DIPs, as well as the *dorsum of the hand* in continuity with these fingers, thus sparing the fingertips because of their full median innervation. Thus when the finger tips are involved, there is either a median or ulnar nerve lesion or a nerve root lesion present.

A cervical radiculopathy, C6 to C8, is the other common disorder that leads to numbness developing in the fingers. The C6 and C7 nerve roots are the two most commonly compromised sites at the nerve root level. Often, the history of nerve root impingement is relatively abrupt in onset, commonly preceded by intrascapular or neck pain. Sometimes the patient may not present to their physician until after the painful lesion has resolved and its history is then no longer important to the individual and thus forgotten. Annoying finger numbness may be the only clinical residua of a recent C6, C7, and/or C8 nerve root irritation. In contrast to



Dermatomal and Cutaneous Nerve Patterns *(Continued)*

a peripheral nerve lesion affecting primarily the palmar surface, such as the median nerve in the carpal tunnel syndrome, a C6 or C7 nerve root lesion will compromise sensation of both palmar and posterior finger surfaces. Thus three separate and distinct peripheral nerves, namely the median, ulnar, and radial, as well as C6 to C8 radiculopathies, and most uncommonly a medial plexus lesion, when affected, can manifest with a numb finger.

Similarly, within the leg and foot, when there is numbness and tingling of the toes, either the fibular (peroneal) or tibial nerve are affected or nerve roots L5 and S1 are damaged. Lumbosacral (LS) back pain, that is, sciatica, is a common accompaniment when a LS nerve root lesion is responsible for partial foot numbness. More *generalized peripheral neuropathies* usually lead to bilaterally symmetric symptoms initially having a stocking-like, and later glove-type, distribution. These are related to disorders predominantly affecting the distal portions of multiple peripheral nerves; there may or may not be a motor component, and thus some degree of weakness is sometimes detected. When there is a pure distal, sometimes more global, symmetric sensory loss, one needs to consider the remote possibility of a disorder primarily affecting the posterior root ganglion cells, also known as a *sensory ganglionopathy*.

Two unusual peripheral nerve variants occasionally occur. One includes the initial acute involvement of an individual nerve, soon thereafter followed by involvement of another anatomically distinct mononeuropathy, and subsequently, in short order, yet another individual nerve becomes involved; these soon fuse into what might appear to the unwary historian/examiner to be a primary generalized polyneuropathy because all nerves eventually become involved, leading to a picture mimicking a much more common generalized polyneuropathy. Usually, there is a concomitant motor component that helps define the specific affected peripheral nerves. After more than one nerve is semiacutely involved in a steplike fashion, it becomes clear that the patient has an evolving *mononeuritis multiplex (MNM)*.

Typically, these patients note both an acute sensory deficit as well as acute weakness, such as a footdrop, in the distribution of one specific peripheral nerve, here the fibular nerve. These disorders are quite uncommon. The acuity of onset mimics a stroke, and indeed that is exactly what is occurring as the small arterioles, *vasa nervorum*, that supply the individual nerve develop a vasculitis, leading to nerve infarcts. The two most common MNM etiologies are an arteritis, such as occurs with diabetes mellitus, or a systemic vasculitis, such as polyarteritis nodosa.

Hereditary neuropathy with predisposition to pressure palsies (HNPP) is a different pathologic entity that can also affect multiple individual peripheral nerves in a varied sequence. However, this is subacute and rarely leads to a clinical fusion of findings as with a vasculitis. HNPP is an autosomal dominant form of demyelination that is secondary to a PMP-22 deletion on the short arm of chromosome (17p11.2). Of interest, duplication here leads to Charcot-Marie-Tooth disease, the most common hereditary neuropathy.

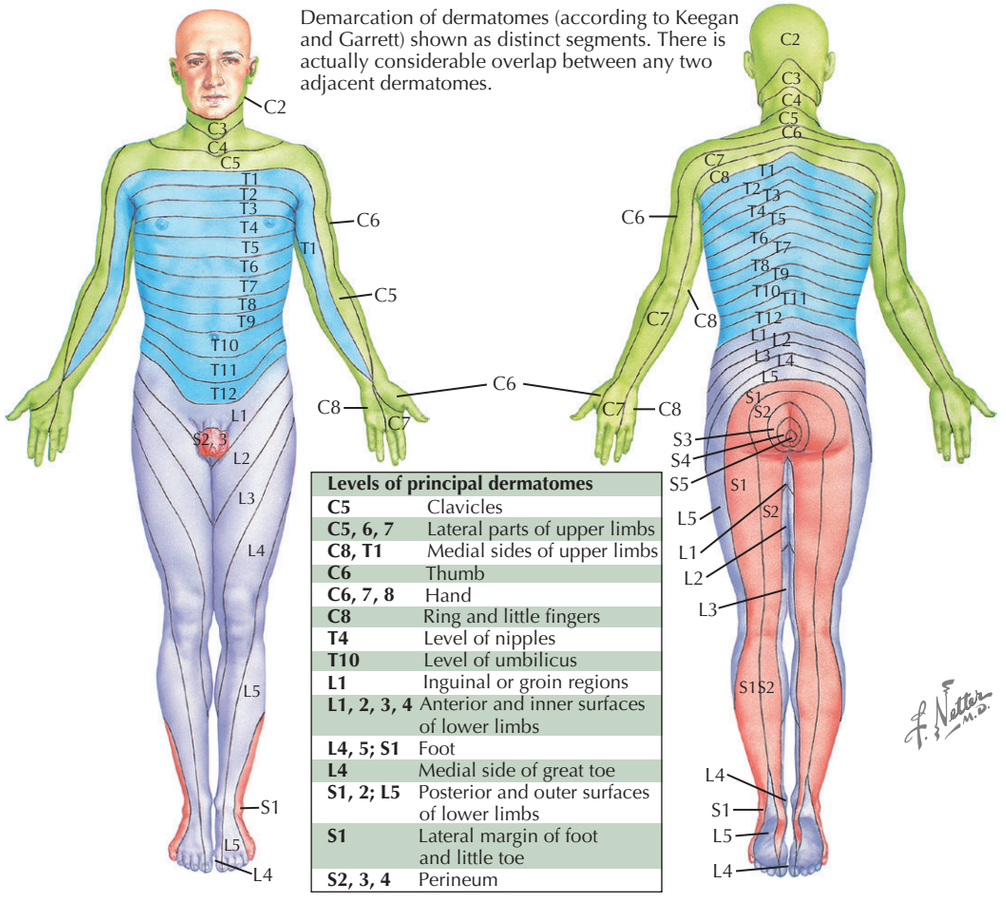
Some peripheral mononeuropathies manifest predominantly with weakness, particularly the wristdrop of radial nerve lesions or footdrop of fibular (peroneal) nerve lesions. Sometimes these are mistaken for a stroke. A clear appreciation of each individual peripheral nerve's motor distribution ultimately aids in the correct diagnosis. Rarely, lesions as high as the parasagittal region of the brain may also manifest with foot weakness.

Atrophy of muscles innervated by the involved nerve occurs with significant chronic denervation. Concomitantly, fasciculations may also be present. Measuring extremity circumference may document significant side-to-side asymmetries and, by inference, muscle atrophy secondary to anterior horn cell, nerve root, or peripheral nerve damage. It is most important here to carefully search for sensory loss, such as one finds with the ulnar nerve lesion, often manifesting with painless intrinsic hand muscle atrophy, to exclude the possibility of a pure motor nerve lesion mimicking amyotrophic lateral sclerosis (ALS) or syringomyelia.

In summary, careful understanding of the precise distribution of peripheral nerve or dermatomal innervation may be immensely helpful in differential diagnosis; when this is not clear, electromyography can help define the problem.

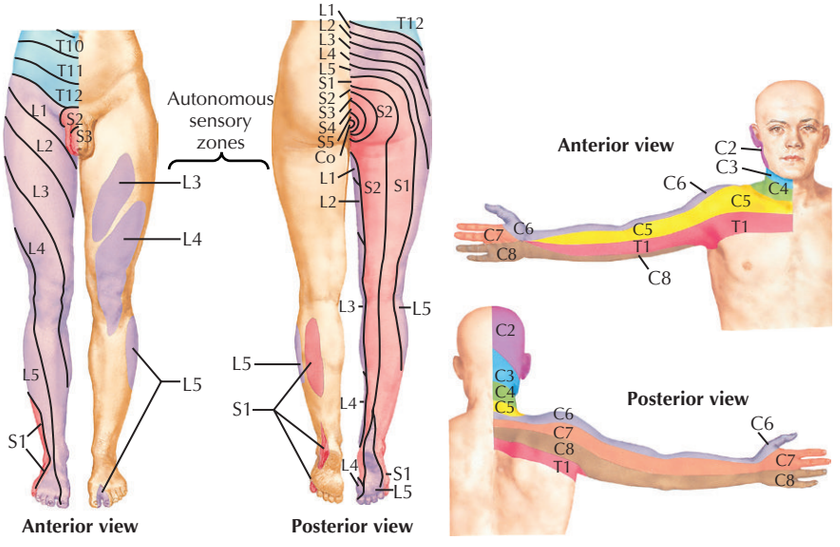
Dermatomes

Demarcation of dermatomes (according to Keegan and Garrett) shown as distinct segments. There is actually considerable overlap between any two adjacent dermatomes.



Levels of principal dermatomes	
C5	Clavicles
C5, 6, 7	Lateral parts of upper limbs
C8, T1	Medial sides of upper limbs
C6	Thumb
C6, 7, 8	Hand
C8	Ring and little fingers
T4	Level of nipples
T10	Level of umbilicus
L1	Inguinal or groin regions
L1, 2, 3, 4	Anterior and inner surfaces of lower limbs
L4, 5; S1	Foot
L4	Medial side of great toe
S1, 2; L5	Posterior and outer surfaces of lower limbs
S1	Lateral margin of foot and little toe
S2, 3, 4	Perineum

Demarcation of dermatomes (according to Keegan and Garrett) shown as distinct segments. There is actually considerable overlap between any two adjacent dermatomes.



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PERIPHERAL NEUROPATHIES

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Peripheral Nerve

The main function of the peripheral nerve is to rapidly conduct electrical signals between the central nervous system and end organs. The *neuronal cell body* is the main functional component that maintains the neuron and *produces* important *structural proteins and neurotransmitters* that are necessary for nerve function. The peripheral *nerve axon* is the major component of the neuron that, through a cascade of physiologic reactions, conducts the electrical signals between different sites. The anatomic structure of the peripheral nerve consists of more than simply the axon and its surrounding myelin; supportive connective tissue structures, intracellular structural proteins, and accompanying vasculature are necessary to maintain the structure and function of the nerve.

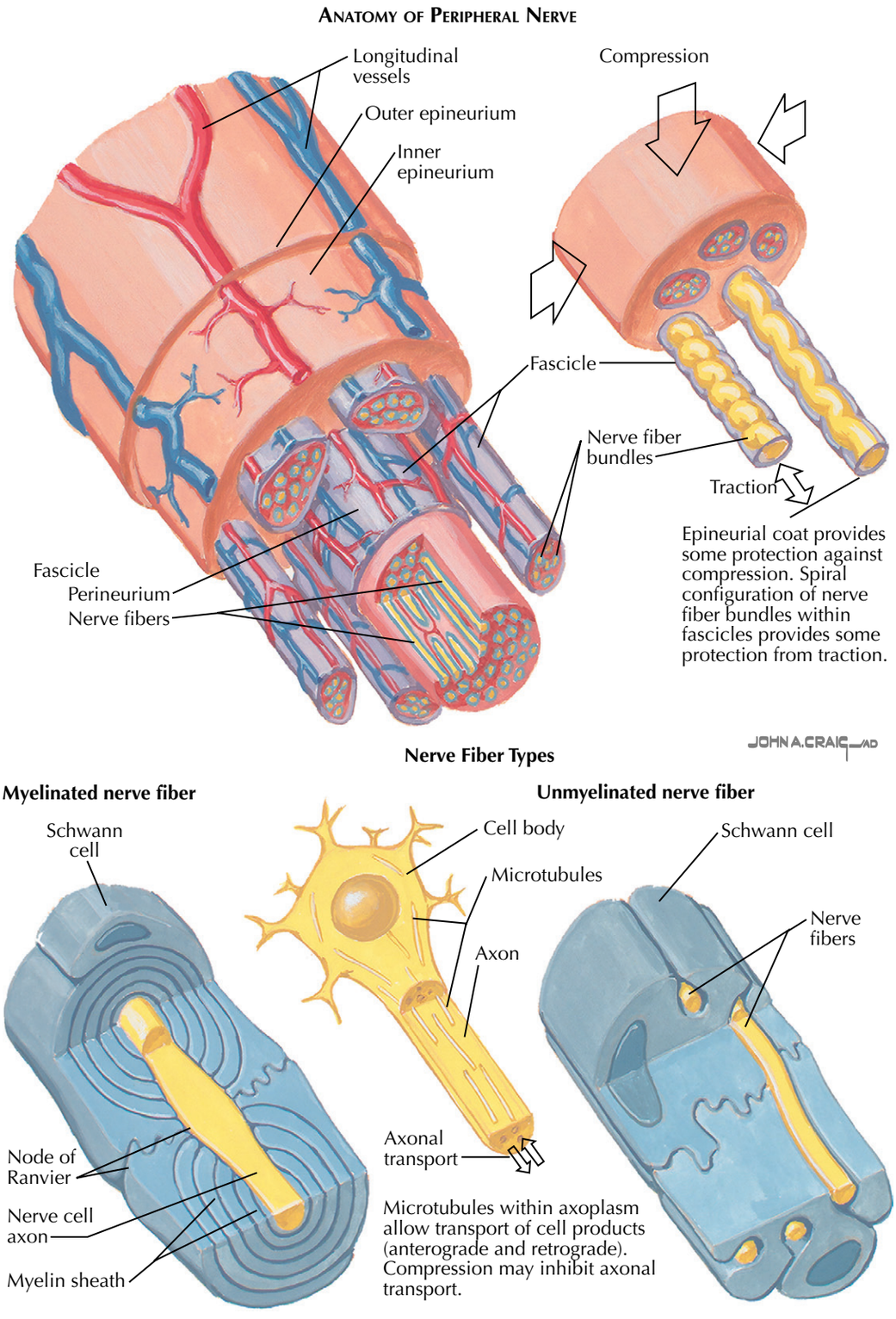
A single nerve, such as the median or ulnar nerve, is composed of thousands of axons that are grouped into several distinct *nerve fascicles* (see Plate 6-1, top left). Each of the fascicles is held together by the *epineurium*, the connective tissue sheath that maintains the structure of the entire nerve. Longitudinal vessels, *arterioles and venules*, course along the *surface* of the *epineurium*; these provide the necessary vascular supply to the nerve. Compromise of this vascular supply—by compression, ischemia, or inflammation—can result in *infarction* of an entire nerve or individual fascicles, producing acute or subacute nerve dysfunction. Clinical examples of nerve injury resulting from vascular compromise include those that occur with peripheral nerve vasculitis. The group of axons within a single nerve fascicle is surrounded by additional connective tissue called the *perineurium*. Within the perineurium are also small vessels providing vascular supply to the individual fascicles and axons. Each fascicle is composed of a number of individual nerve fibers, the main functional component of a nerve.

The *epineurium* and *perineurium* have important roles in maintaining the structure of the nerve, but also in providing a safety mechanism protecting the nerve from physical stresses that may injure the axons. Not only do they provide the framework for the nerves to remain adjacent and in close proximity to each other, but they protect the nerves from physical stress or injury (see Plate 6-1, top right). Physical compromise of a nerve can occur by direct external compression, such as from repetitive physical compression of superficial nerves (e.g., habitual leg crossing compressing the fibular nerve at the fibular head, habitual leaning on the elbow compressing the ulnar nerve as it courses superficially behind the medial epicondyle, or long-distance bicycle riding compressing the ulnar nerve at the wrist). Although the connective tissue structures provide some degree of protection, with severe or repetitive compression, damage to the myelin sheaths and eventually the axons can occur.

In addition, the supportive structures and the *spiral configuration of the nerve fiber bundles* within each fascicle help to protect the nerve from traction injuries, in which the nerve may be suddenly extended longitudinally. This type of injury often occurs with sudden, direct blunt trauma to the limb or neck region in the case of the nerves in the brachial plexus, such as with trauma after high-speed collisions. Although the spiral configuration protects the nerves from relatively minor traction injuries, it does not prevent injury from more severe injuries (e.g., nerve root avulsion from the spinal cord).

There are two main anatomic types of individual nerves: those that are myelinated and those that are unmyelinated (see Plate 6-1, bottom). *Myelinated fibers* consist of an axon surrounded by multiple *Schwann cells* that are present longitudinally along the course of the axon. The cytoplasm of the Schwann cells wrap around a 0.5- to 1.0-mm longitudinal segment of the axon in a spiral formation, producing *lamellae*. The plasma membrane of the Schwann cells that encircle the axon is composed of lipids (including cholesterol, cerebrosides, sulfatides, proteolipids, sphingomyelin, glycolipids, and glycoproteins) and proteins, and the concentric layers of the membrane that wrap around the axons form the "myelin." The function of the myelin is to form "insulation" around segments of the nerve. Between the segments of myelin are small unmyelinated regions called *nodes of Ranvier*, the sites at which there is a high concentration of sodium and potassium channels. As a result, the *action potentials* that are generated along the nerve are *rapidly transmitted* from node to node, producing a very rapid "*saltatory*" *conduction.*

In contrast to myelinated fibers, *unmyelinated fibers* consist of an axon that is embedded within several Schwann cells, and a single Schwann cell surrounds a



PERIPHERAL NERVE *(Continued)*

number of unmyelinated axons. In these fibers, rather than each axon having multiple Schwann cells wrap their cytoplasm around the axon, many axons are embedded in fewer Schwann cells. Although there is a small amount of protective myelin, there are no nodes of Ranvier, and sodium channels are equally dispersed along the entire course of the axon, resulting in *slower action potential propagation* along the nerve.

Both types of nerve fibers contain the other basic structures of a neuron: dendrites, a cell body, the axon, and the nerve terminals. Within the axon are a number of other proteins that provide axonal structure and assist in transporting proteins and waste back and forth from the cell body to the nerve terminals. The largest of these proteins are *microtubules*, which transport products from the axon to the nerve terminal, that is, *anterograde transport*, and from the nerve terminal to the cell body, that is, *retrograde transport*. Other proteins, such as intermediate filaments, help to maintain the structure of the axon.

The structures of the nerve can be identified microscopically. At different magnifications, the definition and various individual components of the nerves can be identified. The upper image (see Plate 6-2) shows a light micrograph transverse section of a peripheral nerve at a magnification of 200× (Masson trichrome stain). In this image, four individual nerve fascicles are seen. The *epineurium (Ep)* is the *connective tissue* that envelops and supports the individual fascicles. Each fascicle is surrounded by a dark-appearing band of connective tissue, the *perineurium (Pe)*, which also provides tensile support of the axons. The individual axons within the perineurium and the connective tissue surrounding the axons (endoneurium) are difficult to identify at this magnification.

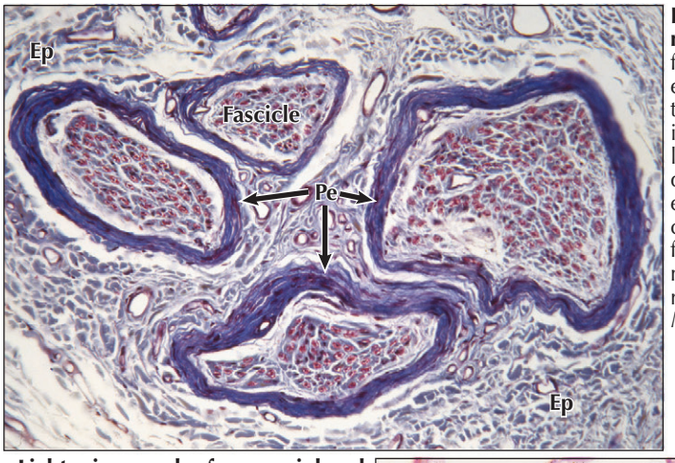
In the middle light micrograph image (see Plate 6-2), a transverse section of a single nerve fascicle is seen on the light micrography at medium magnification (280×, hematoxylin and eosin [H&E] stain). In this image, the darker-stained perineurium (Pe) can be seen forming a surrounding protective support for the axons within. Inside the perineurium are multiple nerve fibers that are sectioned transversely or obliquely. Many of the fibers are surrounded by myelin sheaths, although the myelin is difficult to see well as a result of the lipid content. Surrounding the individual axons are nuclei of fibroblasts, Schwann cells, and capillary endothelia cells.

The bottom electron micrograph image (see Plate 6-2), is a transverse section of a single individual axon as visualized on electron microscopy at very high magnification (30,000×). The axon is surrounded by *perineurial* cells (Pe) and collagen fibrils (CF) that constitute the supportive endoneurium. The Schwann cell surrounding the axon is composed of cytoplasm (SC) that wraps around the axon in *lamellae forming the myelin sheath* (MS); this appears as a thin "onion" covering wrapping around the axon. The thin external basal lamina of the myelin can also be identified. Within the myelin is the axon. Individual organelles, including mitochondria (Mi), neurofilaments, and microtubules can also be seen.

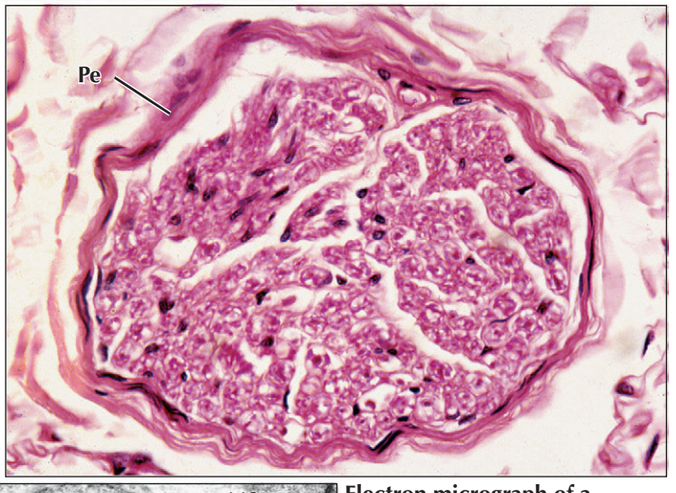
Peripheral nerves and their respective muscle fiber integrity and sensory pathway function are assessed through electrodiagnostic testing (electromyography [EMG]), including motor and sensory nerve conduction studies and needle electromyography. Injury or dysfunction at any motor unit site may lead to limited motor unit function. EMG abnormalities help to identify the site and physiologic basis of the motor unit dysfunction. The peripheral nerves are most commonly affected by genetically determined abnormalities, such as Charcot-Marie-Tooth disease (CMT1a), that are often autosomal dominant. Metabolic-derived conditions, including diabetes mellitus and chronic renal disorders and often occult malignancies producing a paraneoplastic process, as well as various toxins, including medications and certain environmental risks such as arsenic, can also affect peripheral nerve function.

Individual peripheral nerves may be affected by local factors, such as thickening of the transverse carpal ligament producing a carpal tunnel syndrome (CTS) or crossing one's knees, thus entrapping the common peroneal nerve at the fibular head. With sufficient loss of motor units in a muscle, or with inability of an impulse to conduct along the motor unit, muscle strength diminishes. Primary or conjoint sensory dysfunction is studied with EMG, noting sensory nerve action potentials (SNAPs) absence secondary to an axonal process or prolonged conduction across the transverse carpal ligament typical of the carpal tunnel syndrome.

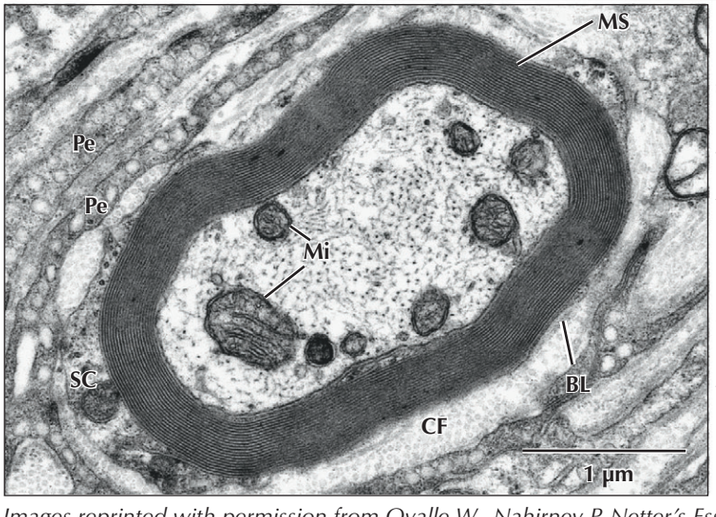
HISTOLOGY OF PERIPHERAL NERVE



Light micrograph of a peripheral nerve in transverse section. Several fascicles that make up this nerve are enveloped by connective tissue of the epineurium (**Ep**), which merges imperceptibly with surrounding loose connective tissue. A more deeply stained perineurium (**Pe**) encloses the fascicles. Each fascicle consists of large numbers of nerve fibers, which are embedded in a more delicate endoneurium (not well resolved at this magnification). 200×. *Masson trichrome.*



Light micrograph of one peripheral nerve fascicle in transverse section at medium magnification. The perineurium (**Pe**) forms an investment around the fascicle. This small nerve has a single fascicle in the connective tissue, so it lacks an epineurium. The interior has numerous nerve fibers sectioned transversely or obliquely and embedded in loose connective tissue of the endoneurium. Many nerve fibers are surrounded by myelin sheaths, which appear washed out because of lipid content. Within the fascicle are nuclei of occasional fibroblasts, Schwann cells, and capillary endothelial cells between nerve fibers. 280×. *H&E.*



Electron micrograph of a peripheral nervous system nerve fiber in transverse section. The axon is surrounded by a myelin sheath (**MS**) composed of multiple lamellae formed by the plasma membrane of a Schwann cell. A thin rim of Schwann cell cytoplasm (**SC**) envelops the myelin and is invested externally by a thin basal lamina (**BL**). Collagen fibrils (**CF**) of the endoneurium and flattened perineurial cells (**Pe**) are in the surrounding area. The nerve fiber axoplasm contains mitochondria (**Mi**), neurofilaments, and a few microtubules. 30,000×.

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Cell Types of Nervous System

SENSORY NEURONS

Sensory neurons carry information from the periphery to the central nervous system (CNS) in the form of sequences of action potentials. The *cell bodies* of these neurons lie in ganglia generally found outside the brain or spinal cord. The *proximal (central) processes* of these cells enter the CNS via the cranial nerves or the dorsal (posterior) spinal roots and terminate synaptically either on interneurons or, in the case of group I muscle spindle afferents, on skeletal motor neurons. The *distal (peripheral) processes* of sensory neurons, which may be either myelinated or unmyelinated, terminate in one of three ways:

1. In the *free nerve ending*, the peripheral process branches widely and ends without obvious specialization. These endings respond primarily to intense stimuli, and are thought to play a role in the perception of pain.
2. In the *encapsulated ending*, the terminal of the peripheral process is enveloped in an accessory structure modifying the stimulus before it reaches the part of the nerve terminal membrane where the actual stimulus transduction occurs. Examples of encapsulated endings are Ruffini and Golgi endings and pacinian and paciniform corpuscles. The muscle spindle and Golgi tendon organ are highly specialized forms of encapsulated endings in which the sensory nerve terminal also performs stimulus transduction.
3. In the *taste buds* and the *cochlear* and *vestibular systems*, sensory fibers end as synaptic terminals on the bodies of specialized receptor cells, which transduce chemical or mechanical stimulation into a shift in membrane potential, which is then synaptically transmitted.

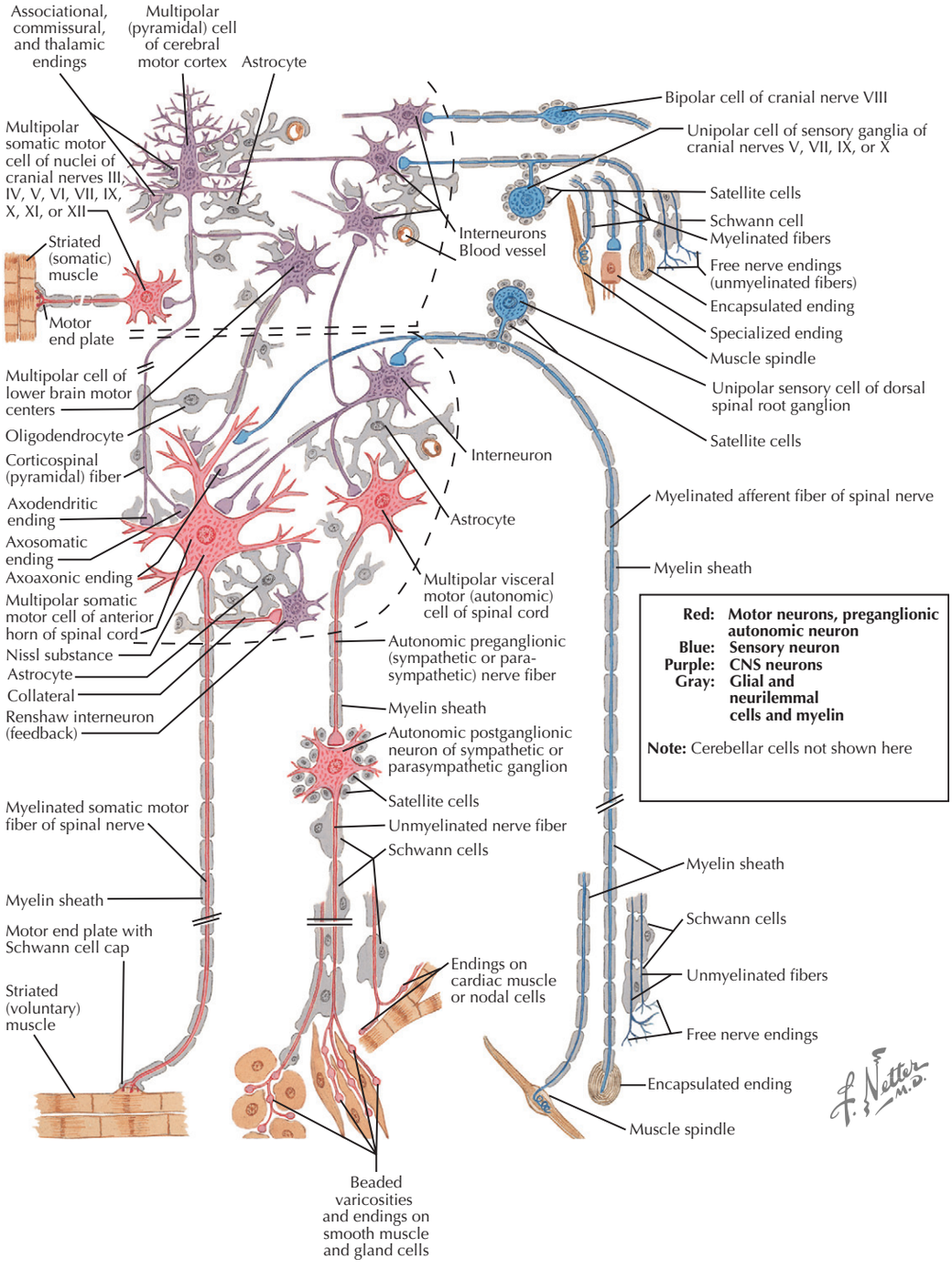
Olfactory and *optic afferent neurons* do not fit into any of these categories. Olfactory stimuli are detected by specialized receptor cells with axons projecting directly to interneurons of the olfactory bulb. The retina, which is formed by an outgrowth of the brain, contains both receptor cells and several types of interneurons. The optic nerve, therefore, corresponds more to a central sensory tract than a sensory nerve.

MOTOR NEURONS

All neurons sending efferent axons to the periphery can be described as effector, or motor, neurons. These are typically medium-to-large, multipolar cells with long myelinated axons. There are three classes of motor neurons:

1. *Motor neurons supplying skeletal muscles* are located in the anterior horn of the spinal cord and project to the periphery via the anterior (ventral) spinal roots. Motor neurons supplying muscles of the face and some muscles of the neck and throat are located in the brainstem motor nuclei and project to their target muscles via the fifth, seventh, and ninth to twelfth cranial nerves. Motor neurons supplying skeletal muscles are of two kinds: *alpha motor neurons*, which supply the main extrafusal muscle fibers, and *fusimotor (gamma motor) neurons*, which supply the intrafusal fibers of muscle spindles. The alpha motor neurons have conduction velocities ranging from 50 to 100 m/sec; fusimotor axons have velocities of 20 to 40 m/sec.

   Skeletal motor neurons are often referred to as the "final common path," because they integrate all CNS activity controlling a given muscle, from spindle afferent fibers, spinal interneurons involved in spinal reflexes, brainstem nuclei, and cortical pyramidal cells.
2. *Extraocular motor neurons* are located in the nuclei of the third, fourth, and sixth cranial nerves. Because human extraocular muscles lack muscle spindles, these neurons are all of the alpha motor type. The contractions of these muscles in various combinations direct the eyes during slow (pursuit, vestibulo-ocular) and rapid (saccadic) eye movements.
3. *The motor innervation of the autonomic nervous system* differs from the innervation of skeletal and extraocular muscles because two neurons are involved. The first, called the *preganglionic neuron*, is located in the intermediate horn of the spinal cord or in the brainstem and sends a thin myelinated axon to one of the various sympathetic or parasympathetic ganglia. The sympathetic ganglia are located near the spinal cord, whereas parasympathetic ganglia are located close to or within the organ being innervated. Within the ganglion, the preganglionic fiber forms an excitatory (cholinergic) synapse with a ganglionic neuron. The ganglionic neuron then sends an unmyelinated *postganglionic axon* to innervate the target structure.



Resting Membrane Potential

Rapid transmission of electrical signals along neurons relies on the generation and propagation of electrical charges along the membrane. A complex and constantly occurring series of processes along the axon membrane are necessary for the development of the action potential. The axon membrane potential electrical gradient at rest provides the foundation for the changes that occur during action potential generation. Several structures along the axonal plasma membrane are responsible for the generation of the resting membrane potential—the sodium (Na^+), potassium (K^+), and chloride ($C1^-$) channels and the adenosine triphosphate (ATP)-dependent Na^+-K^+ pump.

The *transmembrane ion concentrations* at rest is dependent upon the passive diffusion of ions from the site of higher concentration to the site of lower concentration through ion channels, as well as the active adenosine triphosphatase (ATPase)-dependent transport of ions against a concentration gradient. At rest, the concentrations of sodium, chloride, and calcium ions are higher extracellularly, whereas the concentrations of potassium ions and impermeable protein anions are higher intracellularly. As a result, sodium and chloride are forced to move from the extracellular to intracellular space and potassium in the opposite direction. With the diffusion of ions across the cell membrane, a separation of charges develops because the nondiffusible negatively charged intracellular ions have a charge opposite that of the diffusible ions. As a result, an electrical potential difference develops between the intracellular and extracellular axon membrane. This electrical potential difference produces an electrical pressure that opposes the physical movement of the ion. The net ionic movement continues until the electrical pressure equals the diffusion pressure, and there is no net movement of ions. The resulting electrical potential across the membrane is called the *equilibrium potential*.

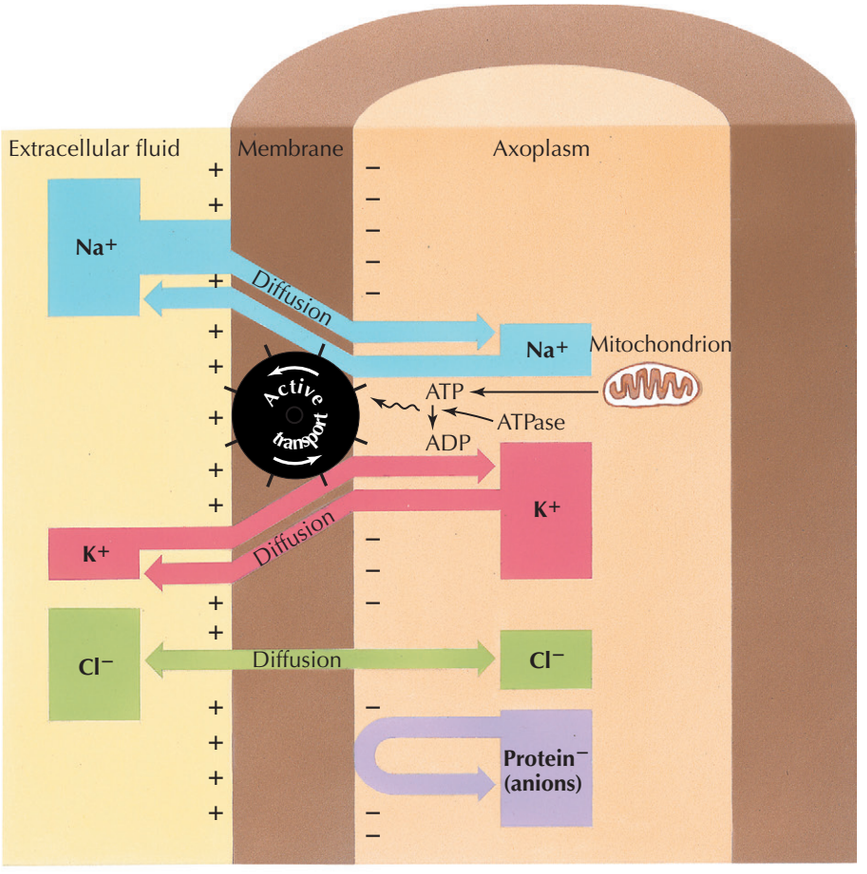
The equilibrium potential of each ion (E_{ion}) is the voltage difference across the membrane that exactly offsets the diffusion pressure of an ion to move down its concentration gradient. This potential is different for each ion and can be defined by the *Nernst equation*, which defines the equilibrium potential, E_m, inside the cell for any ion in terms of its concentration extracellularly [Xe] and intracellularly [Xi].

$$E_m = (61.5\ \text{mV}/Z_i)\log_{10}([X_e]/[X_i])$$

In the resting state, the approximate equilibrium potentials of the major ions are

$K^+ = -90$ mV, $Na^+ = +50$ mV, and $Cl^- = -70$ mV.

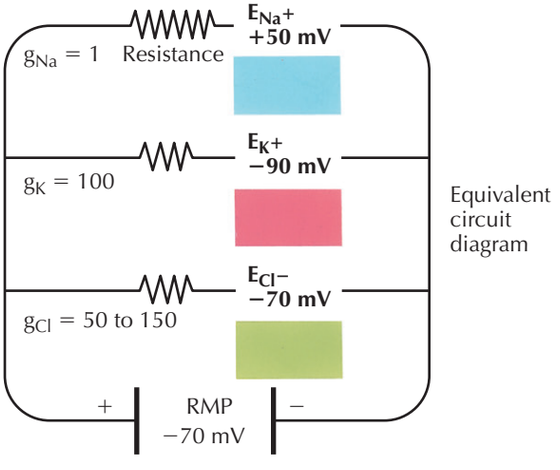
The contribution of a given ion to the actual resting transmembrane voltage depends not only on the ion's concentration gradient but also the permeability of the membrane to that ion as a result of the opening or closing of the ion channel. Increased permeability (i.e., opening of the channel) to a particular ion brings the membrane potential toward the equilibrium potential of that ion. If a membrane is permeable to multiple ions that are present in differing concentrations on either side of the membrane, the resultant membrane potential is a function of the concentrations of each of the ions and of their relative permeabilities. The Goldman equation combines these factors for the major ions (Na^+, K^+, and Cl^-) that influence the membrane potential and is used to calculate the resting membrane potential.



$$E_K = 61 \log \frac{[K^+\ \text{outside}]}{K^+\ \text{inside}}$$

$$E_{Na} = 61 \log \frac{[Na^+\ \text{outside}]}{Na^+\ \text{inside}}$$

$$E_{Cl} = -61 \log \frac{[Cl^-\ \text{outside}]}{Cl^-\ \text{inside}}$$



An electrical circuit model using Ohm's law (E = IR) can be used to demonstrate the contribution of each ion to the resting membrane potential. The movement of ions across the membrane is expressed as an ion current. By Ohm's law, this current depends on the driving force of the ion (the difference between the membrane potential and the equilibrium potential of that ion) and conductance of the ion (g). Using this model, the *conductance* (g) (or the reciprocal of the resistance) for a particular ion is dependent on the ion channel permeability of each ion. The concentration ratios of the different ions are represented by their respective equilibrium potentials (E_{Na}, E_K, E_{Cl}); their ionic permeabilities are represented by their respective conductances. Therefore, at rest, the conductance of the potassium ions is high, whereas sodium conductance is low and chloride conductance is moderate. As a result, the flow of potassium ions is the predominant contributor to the membrane potential at rest. The resting membrane potential (RMP) is the sum of the conductances of all the open channels permeable to each ion.

Ion Channel Mechanics and Action Potential Generation

The role of the neuron is to generate and rapidly transmit electrical signals over relatively long distances. This function relies on the membrane potential and its effect on the gating of the sodium channels, which play a critical role in action potential generation and propagation.

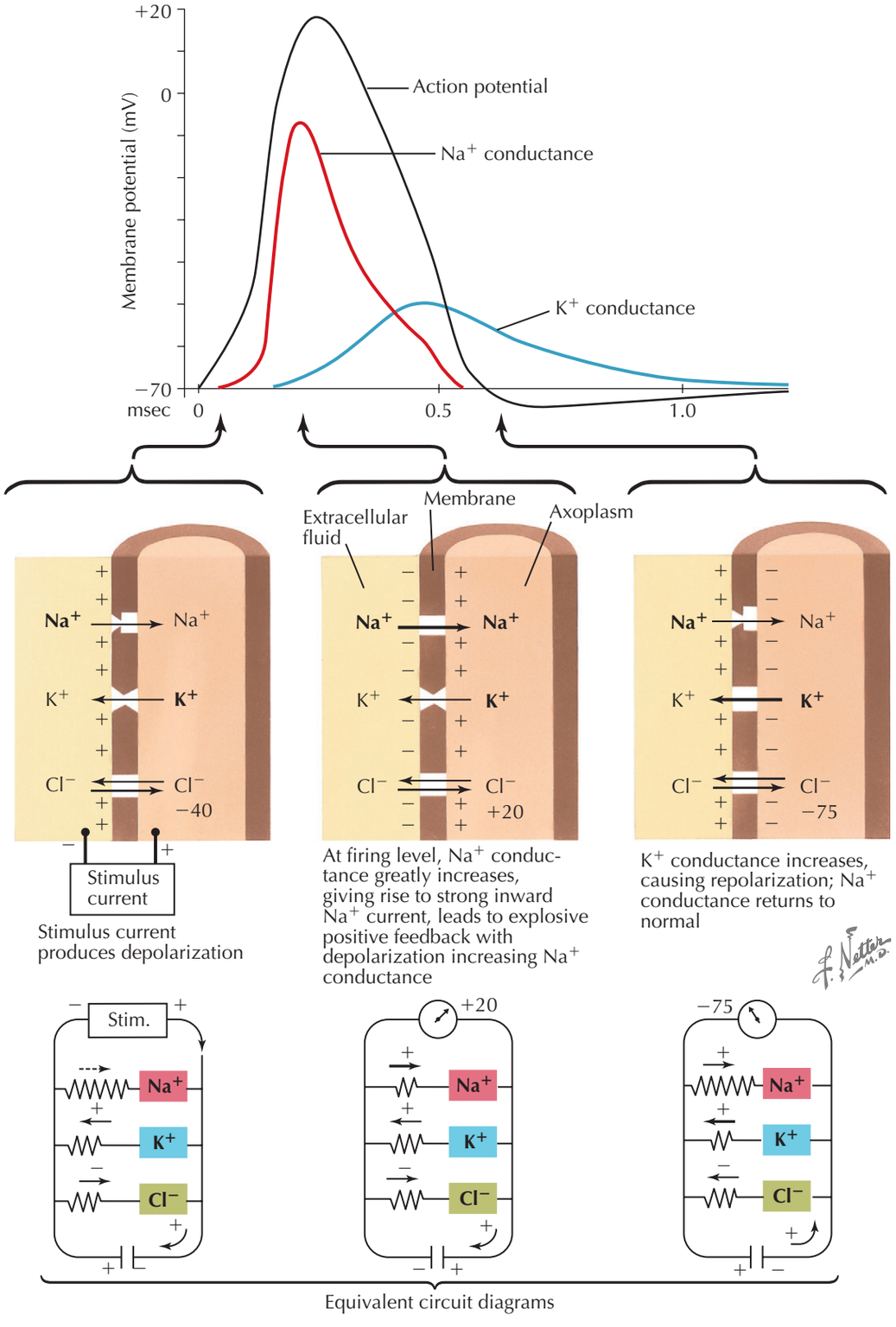
At rest, the resting membrane potential, or the absolute difference in electrical potential between the inside and the outside of the inactive neuron, results predominantly from the membrane permeability to potassium as a result of the open state of the potassium leak channels. This resting membrane potential is approximately −70 mV. If an electrical circuit diagram is used to demonstrate the transmembrane potential at rest, with conductance and resistance of Na^+, K^+, and Cl^- shown in parallel, the contribution of conductance of K^+ and Cl^- are responsible for the overall current flow and membrane potential.

When a negatively charged stimulus (physiologic or external) is applied to the extracellular axon membrane, there is a decrease in the value of the resting membrane potential as the charge difference between the extracellular and intracellular membranes decreases (called depolarization). If the membrane is depolarized only a small degree, only a few sodium channels are activated, and a local potential is generated. If this charge difference reaches the *excitation threshold* for opening of many voltage-gated sodium channels (approximately −50 to −55 mV) the conductance of sodium rapidly becomes greater than that of K^+, and Na^+ ions rapidly move from the extracellular to intracellular space, resulting in a movement of the transmembrane potential difference toward the equilibrium potential of sodium (+60 mV). This *depolarization* locally reverses the polarity of the membrane, the inside becoming positive with respect to the outside.

This rapid change in conductance results in the *action potential*. Action potentials are "all-or-none," allowing for rapid transmission of information over long distances along the nerve. The change in sodium conductance is transient and lasts only a few milliseconds. As the sodium channels become inactive and the potassium channels re-open, the sodium conductance decreases and potassium conductance increases, resulting in an increase in flow of potassium out of the cell and *repolarization* of the membrane.

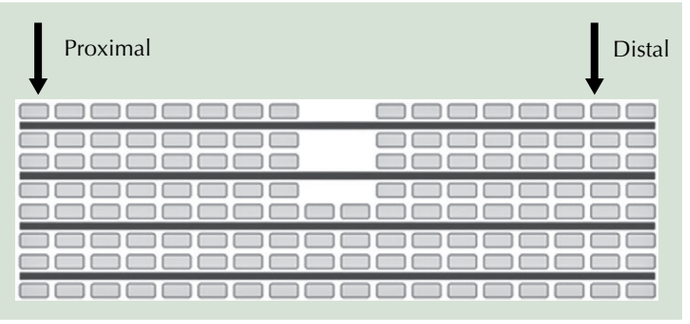
The rate of return of the membrane potential to the baseline slows after sodium conductance has returned to baseline, producing a small residual on the negative component of the action potential, which is called the *negative afterpotential*. This afterpotential is positive when the membrane potential is recorded with a microelectrode within the cell, but it is negative when recorded with an extracellular electrode. The increase in potassium conductance persists and results in a *hyperpolarization* after the spike component of the action potential—the after-hyperpolarization—which is due to continued efflux of potassium ions, with a greater than resting difference in potential between the inside and the outside of the cell. The after-hyperpolarization is positive when measured with extracellular electrodes and therefore is called a *positive afterpotential*.

The changes in Na^+ and K^+ channel activation and inactivation overlap to a degree. As a result, the membrane potential is a function of the ratios of the conductances of the Na^+, K^+, and Cl^- ions. These can be demonstrated in an electrical circuit diagram, demonstrating current flow relative to the conductances (ion channel permeability) of Na^+, K^+, and Cl^- in the resting states and after a threshold-reaching stimulus.



Conduction Block and Temporal Dispersion

Neurophysiology and Peripheral Nerve Demyelination



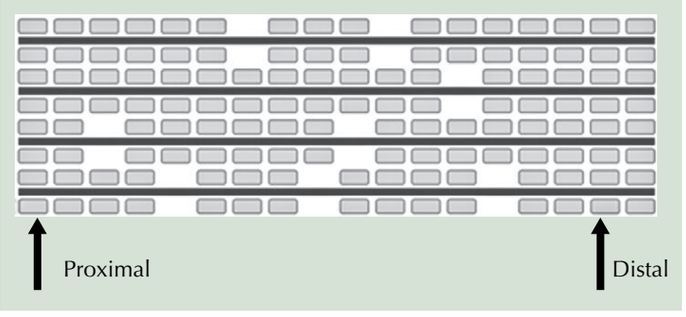
Schematic showing focal demyelination of 50% of axons within a nerve, ("conduction block")

Several different pathologic changes within the nerves may occur as a result of disease. Nerve injury occurs in three stages of severity—neurapraxia, axonotmesis, and neurotmesis. In *neurapraxia*, there is a block of conduction of the action potential across the region of nerve injury. This is a relatively common clinical lesion that occurs when external pressure is applied against a single nerve resting against a bony surface. An example of focal neurapraxia is the wristdrop that develops from subacute pressure against the radial nerve passing through the spiral groove within the midhumerus. Some diffuse peripheral nerve disorders, such as the autoimmune Guillain-Barré syndrome, are also characterized by neurapraxia, but here there are multiple areas of asymmetric focal demyelination. In both settings, the axon and supporting structures may remain intact structurally; however, action potential conduction across the abnormal demyelinated axon is slowed or blocked. Conduction of action potentials and the structural integrity of the proximal and distal portions of the region of neurapraxia are maintained. Focal demyelination is the predominant pathologic alteration of this stage. A similar physiologic response may also develop when there is alteration of the cell membrane or channels, such as with local anesthetic.

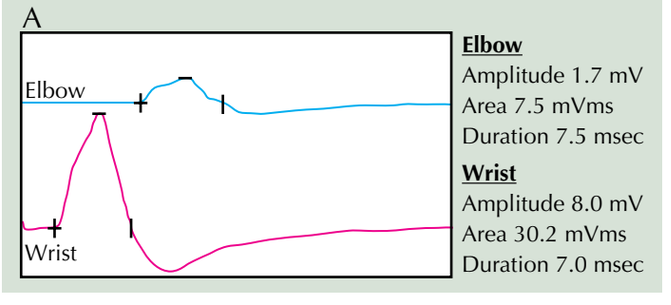
On neurophysiologic testing with motor nerve conduction studies (NCS), the pattern of changes in the recorded responses differs when focal neurapraxia occurs to the same degree and at the same site along multiple axons within a nerve compared with differing degrees of focal demyelination among different axons within the nerve. In disorders where *uniform demyelination* occurs at a focal site along a nerve (*conduction block*), stimulation of the nerve distal to the site will elicit a normal compound muscle action potential (CMAP) response, whereas stimulation proximal to the site will elicit a CMAP that is of lower amplitude and area but of similar morphology. (A) In contrast, when *multifocal demyelination* occurs among the axons within the nerve, the *degree of slowing or block varies* among different axons. As a result, stimulation distal to the areas of demyelination will result in a normal CMAP response, but stimulation at a proximal site will elicit a response that is of lower amplitude and area as well as increased in duration (*temporally dispersed*) (B).

With both *axonotmesis* and *neurotmesis*, the continuity of the axon is disrupted, and the portion of the axon separated from the anterior horn cell or posterior root ganglia undergoes *wallerian degeneration*. *Axonotmesis occurs* when axonal continuity is disrupted; however, the connective tissue, including the *endoneurium*, *is preserved*. Axonal regeneration and regrowth along the endoneurial tubes is still possible as long as the connective tissue along the endoneurial tube remains intact. *Neurotmesis* is a more severe stage of injury, where the *axon*, *myelin*, *and connective tissue sheath*, *including the epineurium*, are *disrupted* and the two ends of the nerve are separated. In this stage, effective recovery is very unlikely or impossible, depending on the amount of separation of the two ends of the nerve.

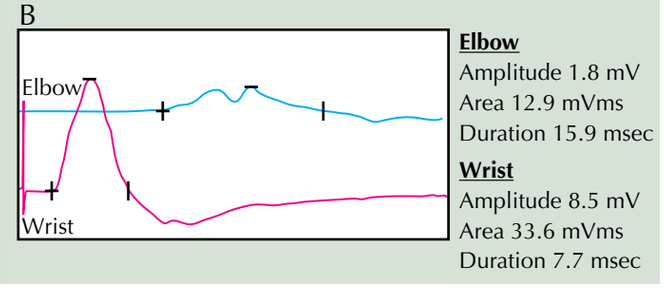
When NCS are performed in this setting during the first week after an *axonotmetic* or *neurotmetic* injury, and a nerve is stimulated electrically distal to the site of injury, the portion of the axon that is separated from the cell body will temporarily continue to have the ability to propagate an action potential. However, once an entire week of axonal wallerian degeneration occurs, the disconnected segment of the axon can no longer respond to electrical stimulation to conduct an action potential. Therefore the CMAP amplitude will be reduced or absent with distal and proximal stimulation sites. The motor fibers are more sensitive and lose their ability to conduct at about 7 days, whereas one may still obtain a sensory nerve action potential (SNAP) up to about 10 days.



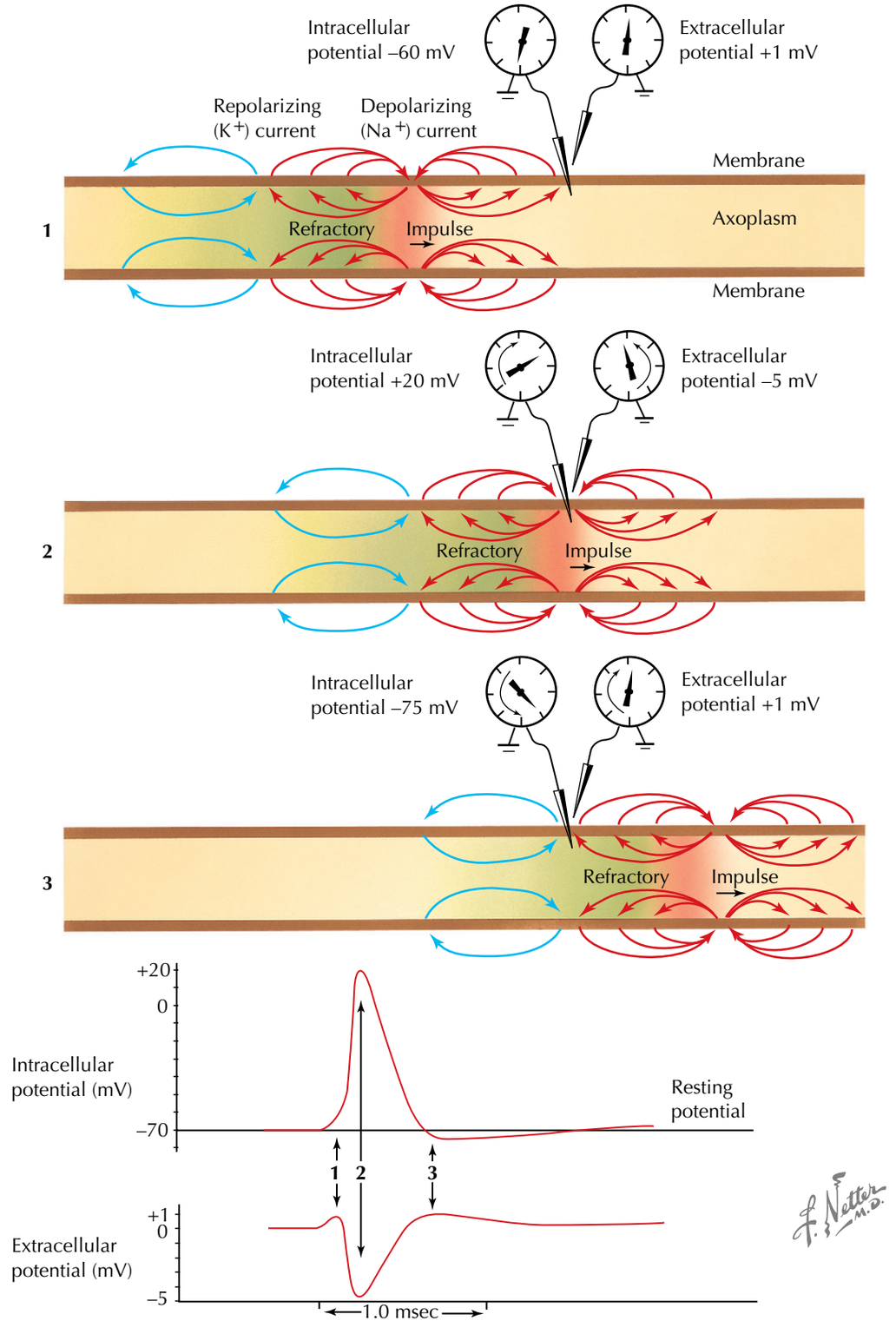
Schematic of segmental and varying degrees of demyelination of axons within a nerve



Amplitude and area reduction seen on an ulnar motor nerve conduction study in a patient with a severe partial focal conduction block



Reduction in amplitude an area with an increase in duration, with proximal compared to distal nerve stimulation, an ulnar motor nerve conduction study (indicative of "temporal dispersion")



Impulse Propagation

In the normal propagating action potential, only a small section of the membrane is active at one time. As a result, part of the current associated with the action potential in the active region passes through adjacent, inactive parts of the axonal membrane. This spread of current is the factor responsible for the propagation of nerve impulses.

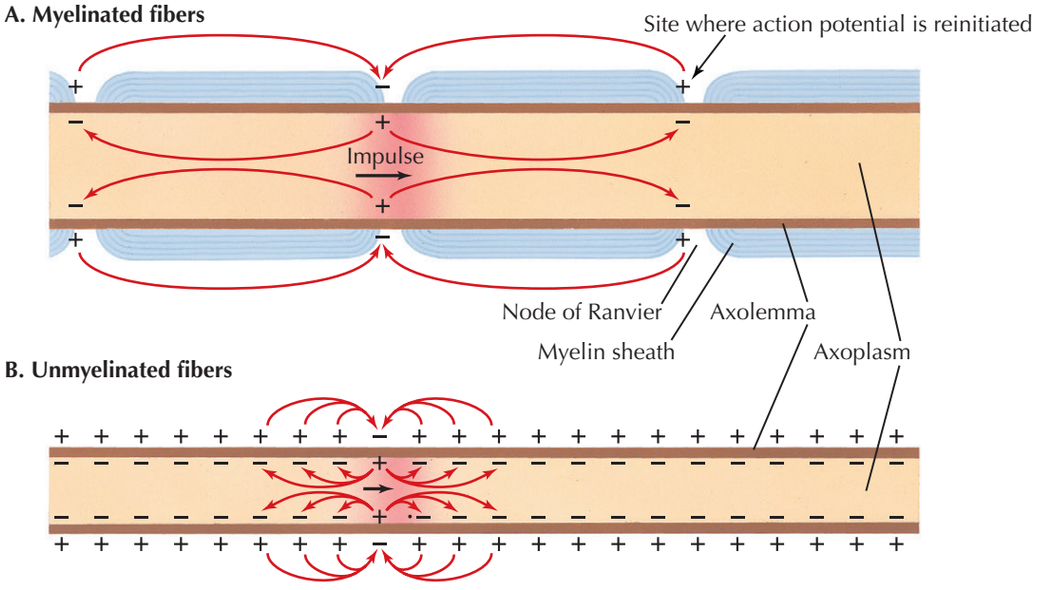
Action Potential Propagation. Three stages illustrate the propagation of an action potential past a point on an axon at which microelectrodes have been positioned to record intracellular and extracellular potentials, each with respect to "ground" (the bath fluid). The intracellular electrode records the transmembrane potential, while the extracellular electrode records the much smaller voltage changes produced by the flow of current through the extracellular fluid.

Stage 1. The nerve impulse is approaching the recording point from the left. Inward current flow at the active region gives rise to compensatory outward current flow through a section of axonal membrane on either side of the active region. (The inward flow of sodium ion [Na^+] current in excess of that required to charge the membrane capacitance must be balanced by the outward flow of other ionic currents.) The outward current flow is passive in that it is not initiated by a change in membrane permeability, as is the inward Na^+ current. According to Ohm's law, such a passive flow of outward current through the membrane resistance causes a voltage drop that depolarizes the axonal membrane at the recording point. The intracellular electrode therefore records depolarization of the membrane, and the extracellular electrode records a positive voltage shift caused by the outward flow of current away from the recording point.

Stage 2. As the activity approaches, the transmembrane depolarization at the recording point becomes greater, until it reaches the threshold for action potential initiation. At this point, the membrane becomes active. The passive outward current flow shifts to an active inward flow of Na^+ current. In accordance with this reversal in the direction of current flow, the voltage recorded by the extracellular electrode shifts from positive to negative. Rather than changing sign, however, the intracellular potential moves farther in the depolarizing direction. This happens because the inward current flow is caused by a change in membrane permeability to Na^+, which shifts the membrane potential toward E_{Na}+ (+50 mV).

The strong flow of inward current at the recording point gives rise to a passive flow of outward current through the axonal membrane to the right and to the left. Depolarization caused by this current triggers an action potential in the axon to the right. Re-excitation of the axon to the left does not occur immediately because the membrane is temporarily refractory as a result of the passage of the nerve impulse.

Stage 3. The axon to the right has become active, while the potential at the recording point has fallen to –75 mV. This takes place because Na^+ inactivation has returned Na^+ permeability to a low level, and potassium ion (K^+) permeability has increased, thus moving the potential toward E_{K^+} (–90 mV). The increase in K^+ permeability and the active zone to the right give rise to an outward current flow, which is revealed by a final positive extracellular voltage. Because of the altered permeability of the membrane to K^+ and Na^+ inactivation during the refractory period, this outward current cannot give rise to another action potential.



Conduction Velocity

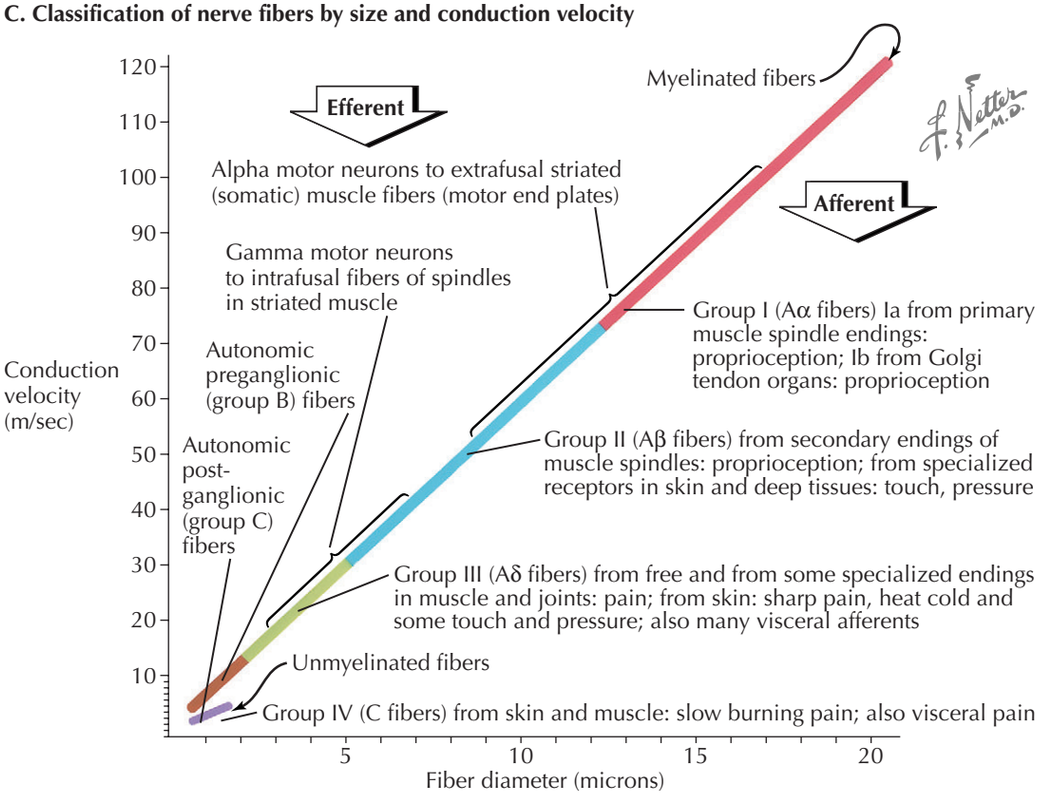
The velocity of action potential propagation along an axon depends on the distance that suprathreshold depolarization spreads in front of the active zone. This distance can be increased either by increasing the axonal diameter (which decreases the longitudinal resistance of the axoplasm), or by increasing the transverse resistance of the outer covering of the axon. Increasing the axonal diameter alone (as would be needed in unmyelinated fibers) would require excessively large diameters to attain the high action potential conduction velocities observed in the human nervous system. In myelinated fibers, where the transverse resistance is increased by the addition of the myelin sheath, conduction velocities in excess of 100 m/sec are achieved with axonal diameters of less than 20 µm.

In a myelinated nerve fiber, successive 1- to 2-mm segments of axon, called *internodes*, are enveloped by multiple layers of Schwann cell membrane. Between these segments are short lengths of axon with little or no covering, called *nodes of Ranvier*. According to the saltatory conduction theory, myelin increases the transverse resistance of the internodes, while the resistance at the nodes remains normal. As a result, when the axonal membrane at a node becomes active (part A), the passive outward currents produced by this activity are prevented from flowing through the membrane of the adjacent internode; instead, they flow through the membrane of the next node.

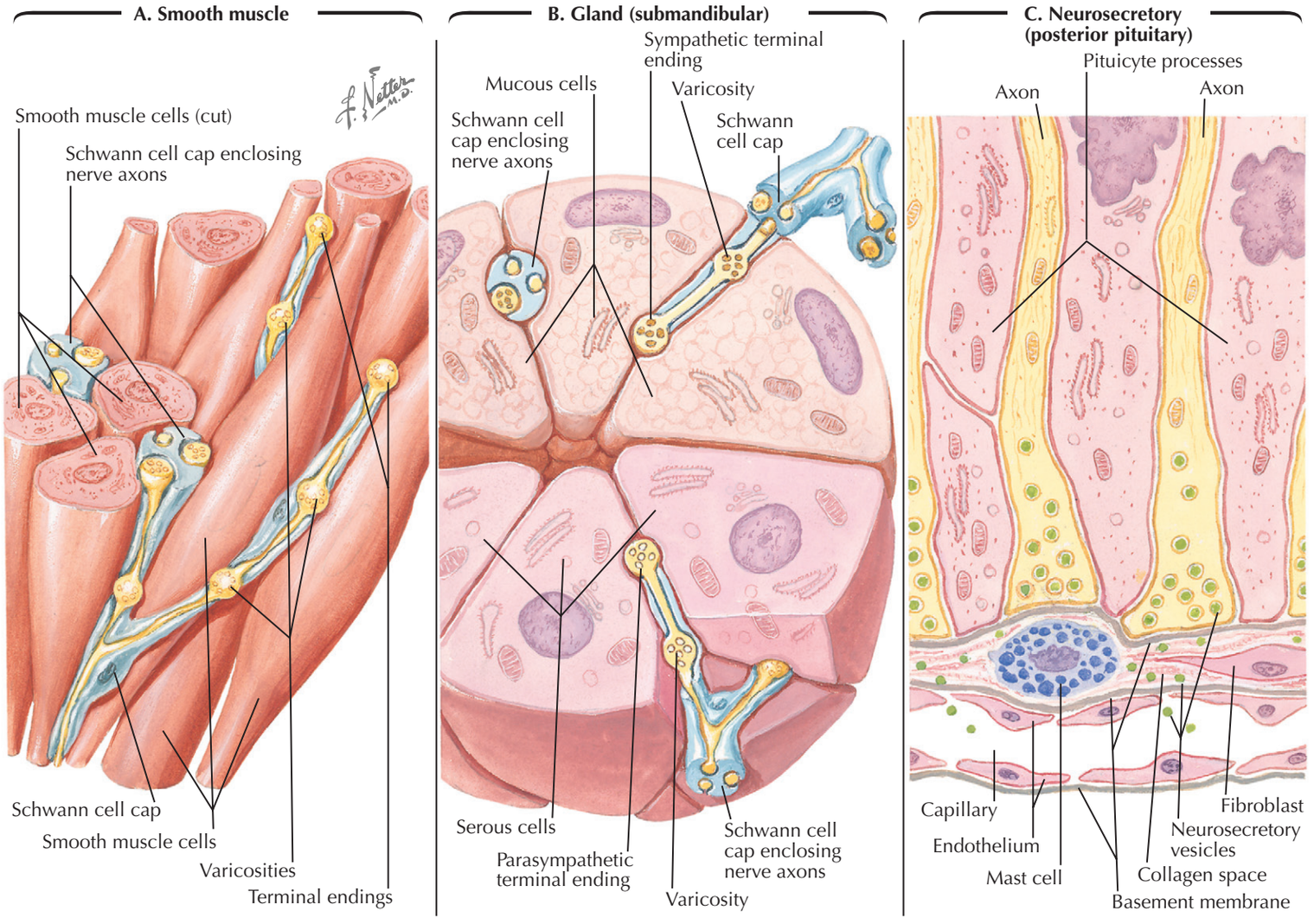
The resulting depolarization triggers an action potential at this node. Thus, unlike impulse propagation in an unmyelinated axon (part B), which proceeds continuously in very small steps, the impulse in a myelinated axon jumps from node to node and results in a much greater conduction velocity.

As shown in C, mammalian peripheral nerves contain myelinated fibers with diameters of 0.5 to 20 µm and conduction velocities of 3 to 120 m/sec, and unmyelinated fibers with diameters of less than 2 µm and conduction velocities of 0.5 to 2.0 m/sec. In 1930, Erlanger and Gasser published a classification of peripheral nerve fibers, based on conduction velocity. Three groups of fibers were defined according to descending conduction velocity, designated A (with subgroups α, β and γ), B, and C. A further subgroup, Aδ, was added later. This classification refers to both afferent (sensory) and efferent (motor) fibers, whereas a more recent classification of nerve fibers into groups I, II, III, and IV refers only to afferent fibers.

C. Classification of nerve fibers by size and conduction velocity



The properties and functions of the different classes of nerve fibers are summarized in part C. In the somatic efferent system, fibers supplying skeletal muscle fibers (alpha motor axons) have conduction velocities ranging from 50 to 100 m/sec (Aα and Aβ ranges), and fibers supplying the intrafusal muscle fibers of muscle spindles (gamma motor axons) have conduction velocities ranging from 10 to 40 m/sec (Aγ and Aδ ranges). Autonomic efferent fibers fall either into group B (preganglionic fibers) or group C (postganglionic fibers). In the afferent system, the larger myelinated fibers carry information from specialized receptors that respond to only one type of stimulus, whereas many smaller myelinated fibers carry information about noxious stimuli that give rise to the sensation of prickling pain. The function of unmyelinated sensory fibers (group IV, or C, fibers) is not entirely clear. Stimulation of these fibers as a group evokes only the sensation of burning pain, but experiments have shown that many of these fibers carry information about a specific type of stimulus (touch, pressure, temperature), and only a restricted group is specifically sensitive to noxious stimuli.



Visceral Efferent Endings

Efferent endings involved in the control of smooth muscle and glandular activity and in neurosecretion do not exhibit the discrete one-to-one type of relationship between presynaptic endings and postsynaptic cells characteristic of neuromuscular junction or central synapse. Instead, neural transmitter substances released by such efferent endings are discharged into the interstitial space or into the bloodstream, where they can influence the activity of numerous effector cells. Consistent with this functional difference, ultrastructural studies of visceral efferent endings have failed to demonstrate the type of close apposition of specialized presynaptic and postsynaptic membranes that characterizes other chemical synaptic junctions. A functional visceral efferent junction can be as wide as 2,000 Å.

Autonomic neuromuscular endings control such diverse functions as heart rate, intestinal and urogenital activity, pupillary size, and blood pressure. The morphologic features of this type of ending are shown in A, which illustrates a three-dimensional reconstruction of the smooth muscle lining the colon. Bundles of the unmyelinated postganglionic fibers that innervate intestinal muscle are enveloped by individual Schwann cells. As these bundles run between smooth muscle cells, each axon exhibits beadlike swellings filled with synaptic vesicles at various points along its length. At these *varicosities* ("boutons en passant"), the surrounding Schwann cell membranes are drawn back so that the released transmitter substance can diffuse into the interstitial space and act on nearby smooth muscle cells. After forming numerous varicosities, an individual axon loses its Schwann cell sheath; after a short distance, it forms a final terminal ending similar in structure to the earlier varicosities.

Autonomic nerve endings in exocrine glands are structurally similar to autonomic neuromuscular endings. In the case of the mandibular gland (B), bundles of unmyelinated postganglionic fibers in Schwann cell sheaths form varicosities and terminal endings in the spaces between secretory cells. In this gland, as in many structures innervated by autonomic fibers, two types of endings are seen. *Sympathetic endings*, which in this gland excite mucous cells to produce mucous saliva, are filled with densely staining vesicles indicating the presence of the transmitter norepinephrine. *Parasympathetic endings*, which act on serous cells to produce watery saliva, are filled with clear vesicles that contain acetylcholine.

The neurosecretory endings of the posterior pituitary gland (C) and adrenal medulla are adapted to allow the transmitter substance released by the arrival of an action potential in the nerve terminal to enter the bloodstream and be carried to target cells in other parts of the body. In the posterior pituitary, axons of neurons in the supraoptic and paraventricular nuclei of the hypothalamus run between supporting cells called pituicytes, to terminate directly on the basement membrane that delimits the collagen space around a capillary. Vesicles within the terminals contain one of the two posterior pituitary hormones, oxytocin and vasopressin (antidiuretic hormone). The morphology of the endings suggests that a hormone released by the arrival of action potentials in the terminals is able to diffuse through the collagen space and enter the capillary via pores between the endothelial cells. This diffusion process may be aided by mast cells, which are known to play a role in capillary permeability.

Cutaneous Receptors

Glabrous and hairy skin both contain a wide variety of receptors for the purpose of detecting mechanical, thermal, or painful stimuli applied to the body surface Because of the difficulty in visualizing these receptors and in stimulating an individual receptor in isolation, the identification of the function of different receptor types is still tentative in many cases. The situation is further complicated in that a receptor specialized to respond to one stimulus may also respond (usually more weakly) to another stimulus. How "crosstalk" of this kind is resolved by the central nervous system (CNS) is still unknown.

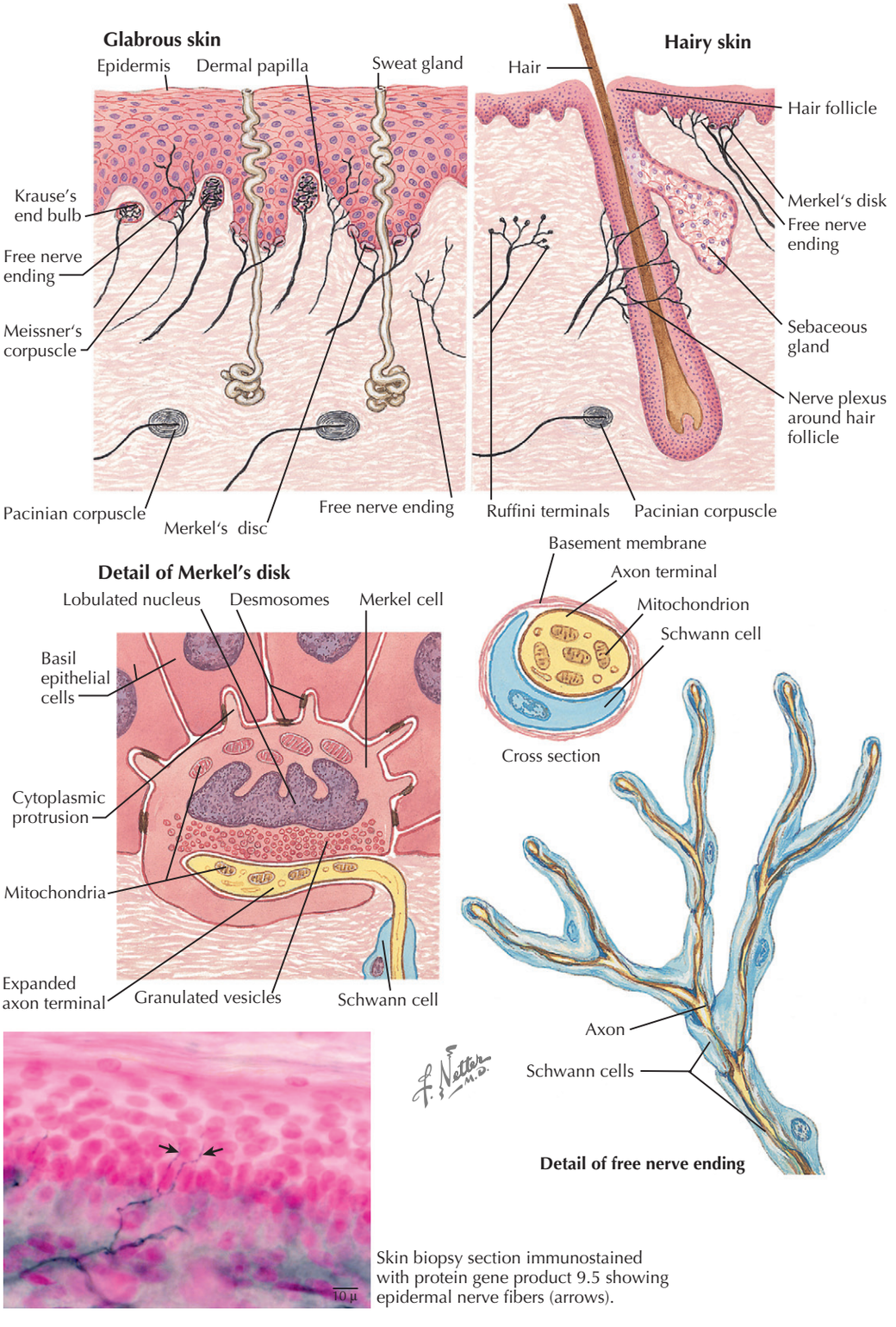
Three types of receptors are common to glabrous and hairy skin: pacinian (lamellated) corpuscles, Merkel disks, and free nerve endings. The *pacinian corpuscle* has been identified as a quickly adapting mechanoreceptor, and its mechanical transduction process has been extensively studied. The primary role of pacinian corpuscles appears to be the sensing of brief touch or vibration.

Merkel disks are slowly adapting mechanoreceptors structured to respond to maintaining deformation of the skin surface. Typically, one afferent fiber of large-to-medium diameter branches to form a cluster of Merkel disks situated at the base of a thickened region of epidermis. Each nerve terminal branch ends in a disk enclosed by a specialized accessory cell (Merkel cell). The distal surface of the Merkel cell is held to nearby epidermal cells by cytoplasmic protrusions and desmosomes, while the base of the cell is embedded in the underlying dermis. Thus movement of the epidermis relative to the dermis will exert a shearing force on the Merkel cell. The Merkel cell also contains numerous granulated vesicles, which suggests that some form of chemical synaptic transmission may occur, although attempts to demonstrate this have failed. Direct mechanical transduction by the nerve ending has not been ruled out as a possibility. However, whatever the transduction mechanism, the Merkel-cell/Merkel-disk ending appears to play a role in the sensing of both touch and pressure.

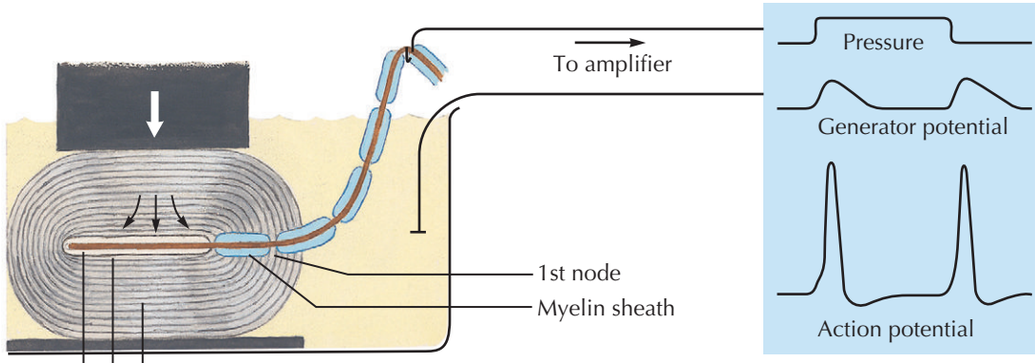
The so-called *free nerve ending* is made up of a branching nerve axon, which is entirely or partially surrounded by Schwann cells. The axon/Schwann-cell complex is further surrounded by a basement membrane. Free nerve endings originate from fine myelinated or unmyelinated fibers that branch extensively in the dermis and may penetrate into the epidermis. These endings respond to strong mechanical and thermal stimuli, and they are particularly activated by painful stimuli.

The other receptors found in glabrous skin are *Meissner corpuscles* (tactile corpuscles), in which the terminal branches of a myelinated axon intertwine in a basket-like array of accessory cells, and *Krause end bulbs*, in which a fine myelinated fiber forms a club-shaped ending. Meissner corpuscles have been tentatively identified as quickly adapting mechanoreceptors subserving the sense of touch, whereas Krause end bulbs may be thermoreceptors.

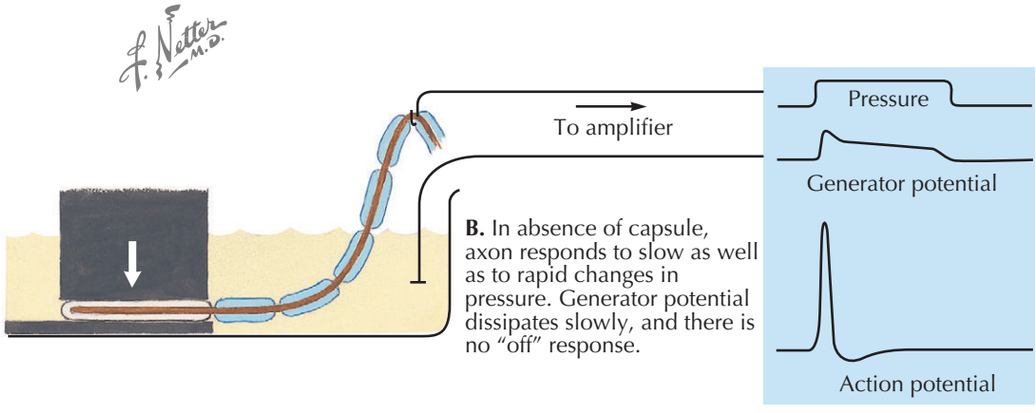
The most important receptors in hairy skin are the *hair follicle endings*, in which axon terminals of sensory nerve fibers wrap themselves around a hair follicle. These endings are quickly adapting mechanoreceptors that provide information about any force applied to the hair and, thus, to the skin. Hairy skin also contains the spraylike *Ruffini terminals*, which may be involved in the sensing of steady pressure applied to hairy skin.



Skin biopsy section immunostained with protein gene product 9.5 showing epidermal nerve fibers (arrows).



A. Sharp "on and off" changes in pressure at start and end of pulse applied to lamellated capsule are transmitted to central axon and provoke generator potentials, which in turn may trigger action potentials; there is no response to a slow change in pressure gradient. Pressure at central core and, accordingly, generator potentials are rapidly dissipated by viscoelastic properties of capsule. (Action potentials may be blocked by pressure at a node or by drugs.)



B. In absence of capsule, axon responds to slow as well as to rapid changes in pressure. Generator potential dissipates slowly, and there is no "off" response.

Pacinian Corpuscle

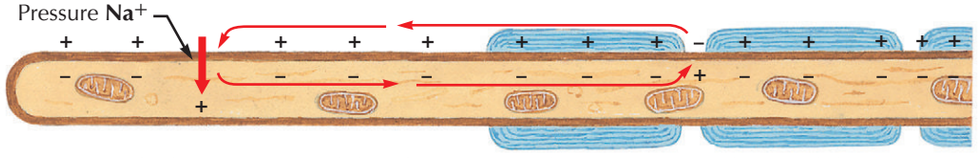
The pacinian corpuscle is one of a group of receptors, known as mechanoreceptors, which transform mechanical force, or displacement, into action potentials. In a simple mechanoreceptor, such as the pacinian corpuscle, transduction of the mechanical stimulus into action potentials occurs in three stages. First, the mechanical stimulus is modified by the viscoelastic properties of the receptor and the accessory cells surrounding it. Then, the modified mechanical stimulus acts on the mechanically sensitive membrane of the receptor cell to produce a change—a generator potential—in the transmembrane potential of the receptor cell. Finally, the generator potential acts to produce action potentials in the afferent nerve fiber linked to the mechanoreceptor.

The pacinian corpuscle consists of the unmyelinated terminal part of an afferent nerve fiber that is surrounded by concentric lamellae formed by the membranes of numerous supporting cells. The axon terminal membrane is adapted in such a way that its ionic permeability increases when it is deformed by applied pressure. Although the permeability change appears to be nonspecific, the principal ion flux that occurs is an inflow of sodium ions (Na^+) because of the great difference in the electrochemical potential of this ion on the two sides of the membrane. The Na^+ influx causes a depolarizing current to flow through the axon terminal and the nearby nodes of Ranvier of the afferent fiber. The depolarization caused by this current comprises the generator potential. If the depolarization is great enough, it will produce an action potential at the point of lowest threshold, in this case, at the first node. This action potential then propagates along the afferent fiber to the central nervous system (CNS).

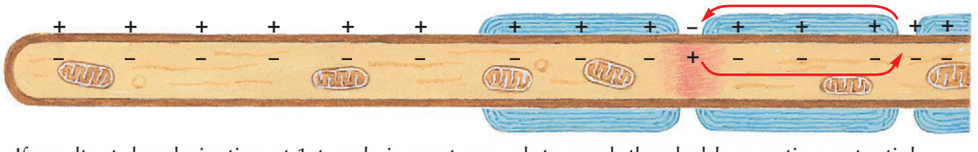
The pacinian corpuscle is specifically adapted to respond to rapidly changing mechanical stimulation. Experiments on isolated pacinian corpuscles have shown that this adaptation involves both the physical structure of the receptor and the properties of the action potential–generating mechanism.

When pressure is applied to an intact pacinian corpuscle, single-action potentials are evoked at the beginning and end of the pressure pulse. If action potentials are blocked by a drug such as tetrodotoxin, the generator potentials evoked by the pressure pulse can be recorded. In the intact pacinian corpuscle, these potentials consist of rapidly decaying depolarizations that occur at the beginning and end of the pulse.

If all the lamellae of the sheath, except the innermost, are dissected away, the response of the pacinian corpuscle to the pressure pulse is modified. The generator potential now decays slowly throughout the period of applied pressure, and no additional depolarization appears at the termination of the pulse. This finding indicates that the viscoelastic properties of the intact capsule dissipate applied pressure, which means that only sudden pressure changes can reach the membrane of the nerve terminal and produce a generator potential.



Pressure applied to axon terminal directly or via capsule causes increased permeability of membrane to Na^+, thus setting up ionic generator current through 1st node



If resultant depolarization at 1st node is great enough to reach threshold, an action potential appears, which is propagated along nerve fiber

Muscle and Joint Receptors

Several types of mechanoreceptors located in the joints and muscles (see Plate 6-12) provide the central nervous system (CNS) with vital proprioceptive information about the position of the parts of the body and the length and tension of various muscles.

Joint Receptors

Four types of receptors have been described in the joint capsule and ligaments. *Golgi-type* endings are located in ligaments but not in the capsule, and are innervated by large-diameter (Aα) fibers; they are slowly-adapting receptors that respond to joint position with changes in their tonic discharge rates. *Ruffini terminals* and *paciniform corpuscles*, which resemble pacinian corpuscles but are smaller, are found in the joint capsule and are innervated by medium-diameter (Aβ) fibers. Ruffini terminals respond to both movement and position, whereas paciniform corpuscles respond only to movement. *Free nerve endings*, supplied by small group III (Aδ) fibers and unmyelinated C fibers, are found in both ligaments and joint capsules; they are thought to respond to extreme, painful movement of the joint. The part played by these four receptor types in signaling joint position is not well understood. A particular difficulty arises from the fact that the most receptors respond only at maximum joint extension or flexion, whereas position sense is sensed throughout the entire range of a movement.

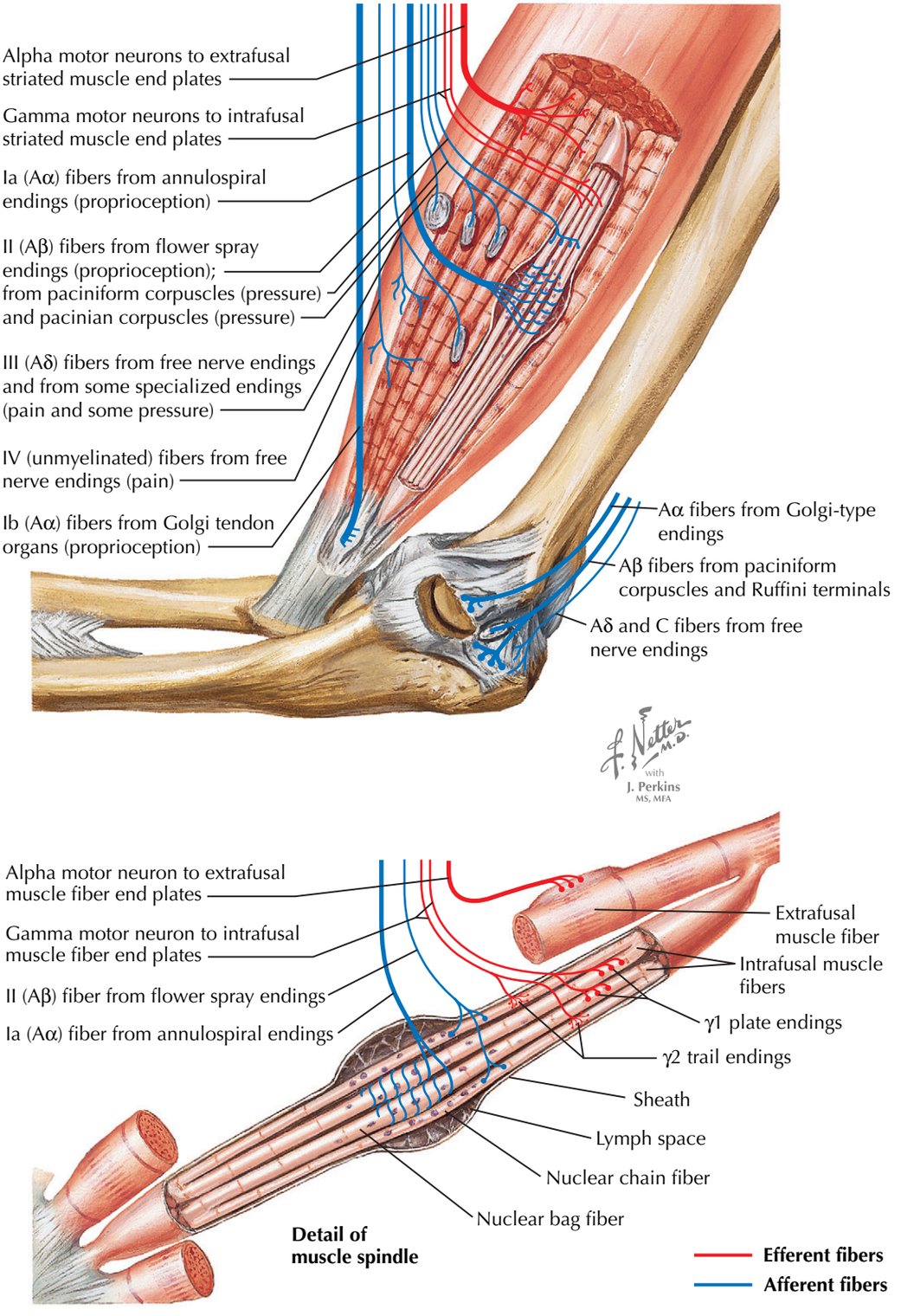
Muscle Receptors

Muscles also contain four types of receptors, two of which—Golgi tendon organs and muscle spindles—are specific to muscle and contribute to the proprioceptive control of reflexes.

Golgi tendon organs are encapsulated receptors located in a tendon, close to the junction of the tendon and the corresponding muscle. The tendon organ capsule surrounds a bundle of tendon fascicles, which are connected to 3 to 25 muscle fibers. Each tendon organ is innervated by a single group Ib (Aα) fiber that enters the capsule and forms spraylike endings in contact with the tendon fascicles. Because it is connected in series with the muscle fibers, the tendon organ is stretched and thereby excited when muscle tension increases. Tension produced by active muscle contraction has been shown to be more effective in exciting tendon organs than tension produced by passive muscle stretch.

The *muscle spindle* is a complex receptor consisting of *intrafusal fibers*, a bundle of small muscle fibers encased in a sheath. The fibers typically do not run the entire length of the muscle; instead, they insert into one or both ends of the sheath of a large extrafusal muscle fiber. The intrafusal fibers are of two types: smaller *nuclear chain fibers*, in which the cell nuclei lie in a line along the middle portion of the fiber, and larger *nuclear bag fibers*, in which the nuclei are more clustered. Both nuclear bag and nuclear chain fibers are innervated by small-diameter gamma motor fibers, which increase the sensitivity of the spindle by causing a contraction of the intrafusal muscle fibers. Each spindle receives afferent innervation from a single, large group Ia (Aα) fiber, which forms large *annulospiral* (primary) endings around both nuclear chain and nuclear bag fibers, and from one to five medium group II (Aα) fibers, which form *flower spray* (secondary) endings chiefly on nuclear chain fibers. Because these spindles lie parallel to the extrafusal muscle fibers, they are stretched when the muscle lengthens. The range of muscle stretch encountered during normal movement excites both kinds of afferent fibers but in somewhat different fashions. The group II fibers respond to lengthening with an increase in their tonic discharge rate, which remains constant as long as the muscle is stretched, whereas the group Ia fibers respond especially vigorously to the dynamic phase of muscle lengthening and, more weakly, to maintained stretch.

The remaining two classes of muscle receptors include *pacinian corpuscles*, which are innervated by group II (Aβ) fibers and respond to vibratory stimuli, and *free nerve endings*, which are innervated by group III (Aδ) or IV (C) fibers and respond to strong, noxious stimuli. Thus they resemble corresponding types of receptors found in other tissues.



Proprioceptive Reflex Control of Muscle Tension

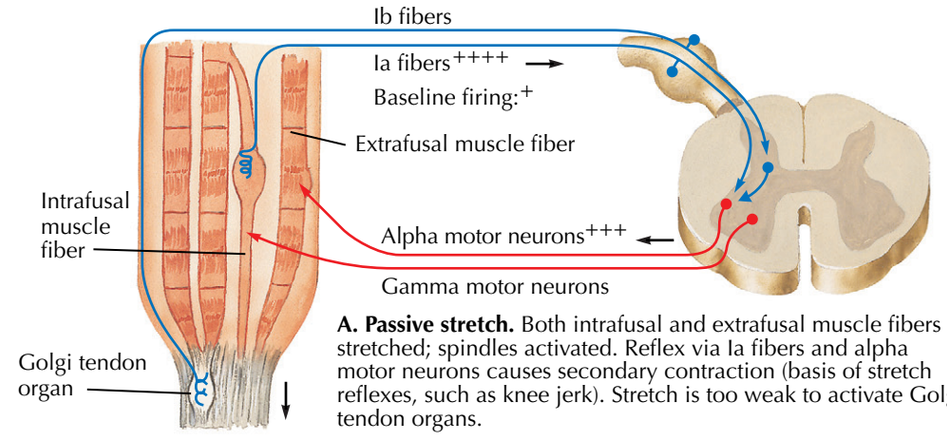
The higher motor control centers of the brain receive information from *muscle spindles* and *Golgi tendon organs* primarily via the group I fibers of the posterior spinal roots. The central processing of this proprioceptive information leads to the smoothness of normal muscle activity and coordinated movement. Even without the higher processing, however, muscle spindle and tendon organ activity can work directly at the spinal level via groups I and II collateral fibers and result in the reflexes that occur when there is a need to compensate for rapid changes in body position and orientation. This segmental processing in the sensorimotor system operates effectively even when there is a loss of connection with the brain centers, such as after spinal cord transection or in certain disease states.

When muscle spindles respond to stretching or to a change in the length of a given muscle, there is increased activity in the Ia afferent fibers, which then directly stimulates the alpha motor neurons supplying that particular muscle. (The same Ia fibers inhibit antagonist muscles through interneuron connections.) By contrast, activity in Ib afferent fibers caused by Golgi tendon organs, which respond to muscle tension, stimulates spinal interneurons to inhibit the alpha motor neurons supplying a particular muscle.

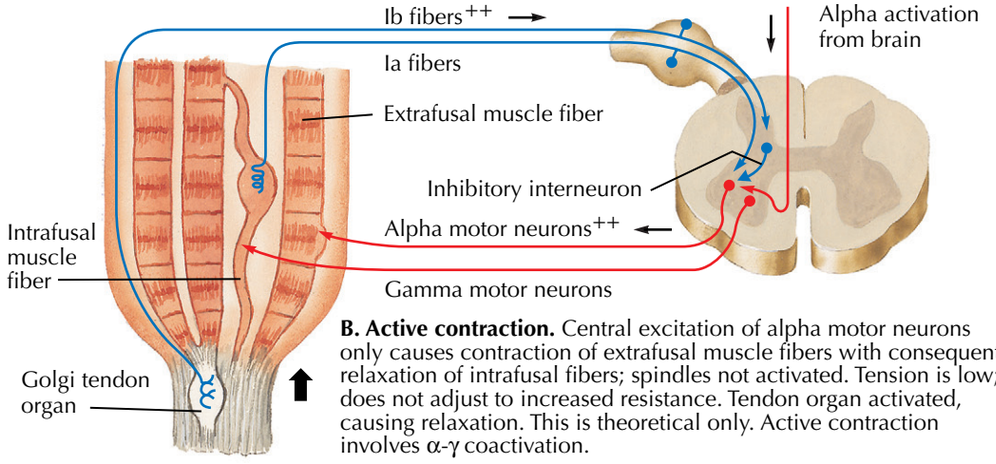
Passive Stretch. When the muscle is passively lengthened, both extrafusal and intrafusal fibers are stretched (A). The *muscle spindles* are activated, causing a volley of activity in group Ia and group II (not shown) fibers; this provokes reflex excitation of alpha motor neurons, thus stimulating the extrafusal fibers to contract and oppose the applied force. Golgi tendon organs, which respond poorly to passive stretch, do not discharge under these circumstances. The more rapid or intense the stretching and the change in length, the more rapid or intense the contraction, an example of which is the knee jerk. Thus the spinal stretch reflex enables the muscle to perform like a spring; if either the afferent or the efferent limb of the nerve supply is damaged, such action is not possible.

Active Contraction. The role of spinal reflexes during active contraction of a muscle is shown in B and C (see Plate 6-13). A situation in which there is *higher stimulation of alpha motor neurons only* (B), brings about the contraction of the extrafusal fibers, which leads to a shortening of the muscle overall and a slackening of the intrafusal fibers. This results in a termination of activity in the muscle spindles and Ia fibers. The increase in muscle tension, however, is sufficient to activate the *Golgi tendon organs* and the Ib afferent fibers that attempt to inhibit the alpha motor neurons via interneurons. Sufficient Ib inhibition will lead to relaxation or cessation of muscle contraction.

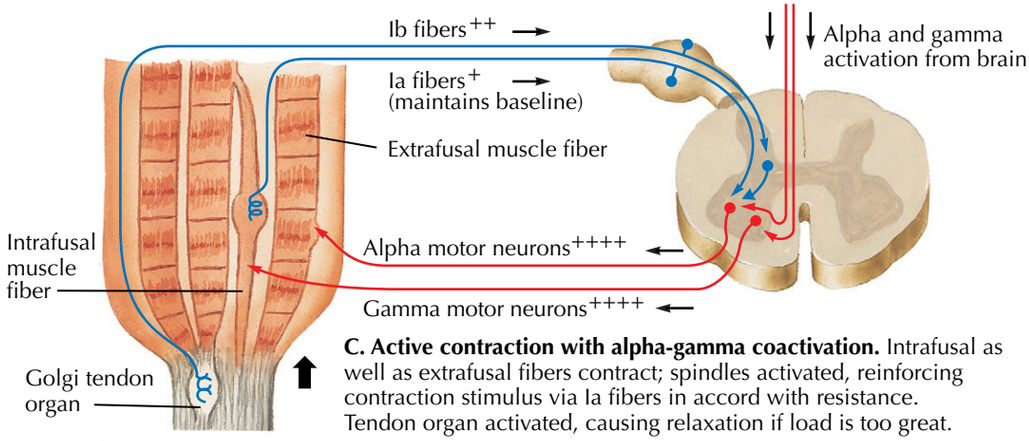
In a *normal situation during voluntary contraction of a muscle* (C), commands from the brain excite both alpha and gamma motor neurons, resulting in the stimulation and shortening of both extrafusal and intrafusal fibers. The *muscle spindles* are activated and produce a discharge of Ia fibers, which thus reinforce the higher stimulation of the alpha motor neurons. This reinforced motor neuron activity increases the springlike tension of the contracting muscle and helps it adjust to changes in the load. The activated Ib afferent fibers from the *Golgi tendon organs* oppose the alpha motor neurons through a feedback mechanism that reduces tension and causes relaxation if the load becomes too great. The role of this "force feedback" mechanism is not well understood.



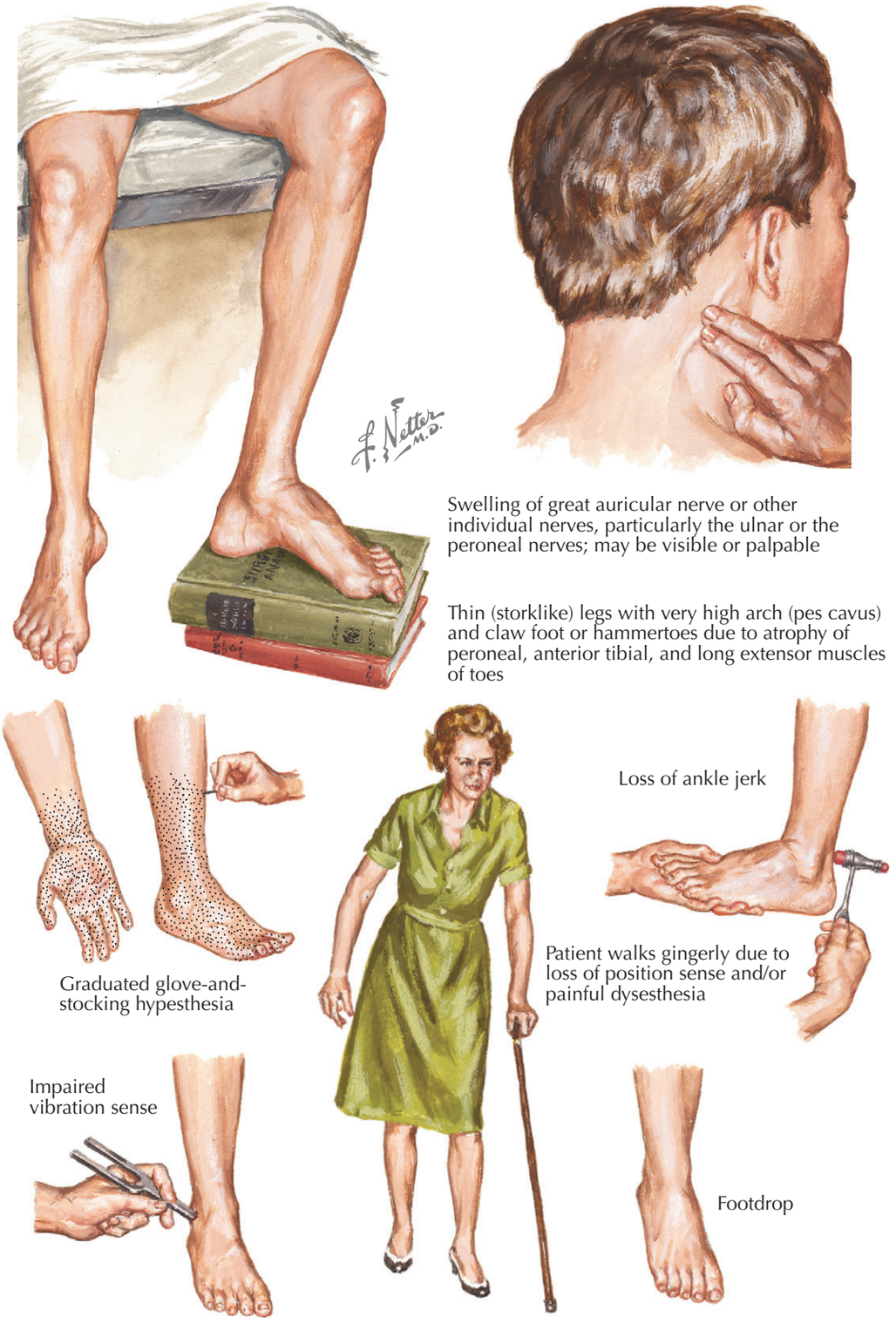
A. Passive stretch. Both intrafusal and extrafusal muscle fibers stretched; spindles activated. Reflex via Ia fibers and alpha motor neurons causes secondary contraction (basis of stretch reflexes, such as knee jerk). Stretch is too weak to activate Golgi tendon organs.



B. Active contraction. Central excitation of alpha motor neurons only causes contraction of extrafusal muscle fibers with consequent relaxation of intrafusal fibers; spindles not activated. Tension is low; does not adjust to increased resistance. Tendon organ activated, causing relaxation. This is theoretical only. Active contraction involves α-γ coactivation.



C. Active contraction with alpha-gamma coactivation. Intrafusal as well as extrafusal fibers contract; spindles activated, reinforcing contraction stimulus via Ia fibers in accord with resistance. Tendon organ activated, causing relaxation if load is too great.



Hereditary Motor and Sensory Neuropathies (HMSN, i.e., Charcot-Marie-Tooth Disease)

Approximately 30% to 40% of chronic polyneuropathies are on the basis of a genetic mutation. In some cases of polyneuropathy, a clear pattern of familial inheritance can be determined, and in others, careful description of neuropathic symptoms may reveal that there is a family history even in the absence of prior, formally diagnosed polyneuropathy. Autosomal dominant transmission is the most common mode of inheritance but X-linked recessive and autosomal recessive types also occur.

The classifications of the different types of hereditary polyneuropathy were initially based on clinical and electrophysiologic features. More recently, however, advances in genetics have led to identification of many specific genetic mutations known to produce polyneuropathy, and the classification of hereditary polyneuropathies has hence been modified.

Symptom onset of inherited polyneuropathies tends to be insidious. High arches of the feet, curling of the toes, gradually progressive weakness of the feet and ankles, and mild gait problems are often the initial manifestations, which may first be identified by the patient, a family member, or a health-care provider (in some cases, by a school nurse). On examination, both motor and sensory fibers are usually affected symmetrically and predominantly distally (e.g., ankle dorsiflexion weakness, reduced vibration sensation at the toes). In most cases, negative (e.g., sensory loss) sensory symptoms predominate over positive (e.g., pain, prickling, tingling) sensory symptoms, although these can occur as well. Autonomic features are uncommon. These disorders are chronic, lifelong, and slowly progressive.

Initial classifications of inherited neuropathies affecting motor and large fiber sensory modalities include Charcot-Marie-Tooth disease (CMT). CMT is a very common genetic disorder, affecting approximately 1 in 2,500 people. CMT is also often classified as hereditary motor and sensory neuropathy (HMSN). The most common types of HMSN are type I (demyelinating), type II (axonal), and HMSN X (demyelinating-axonal). Types I and II are both inherited as an autosomal dominant trait. Type III (Déjerine-Sottas disease) has historically been considered an autosomal recessive severe polyneuropathy, although more recently, Déjerine-Sottas disease has been linked to sporadic ("de novo") mutations in genes that more commonly cause dominant forms of CMT. Consequently, Déjerine-Sottas disease is now thought to be an autosomal dominant disease and is classified as a severe form of HMSN type 1. HMSN X is an X-linked neuropathy, usually with more severe clinical manifestations in males. Type IV usually presents early in life, and can have other associated abnormalities (e.g., deafness, vocal cord paralysis) depending on the subtype and affected gene. Refsum disease is a very rare disorder that causes a relative block in the degradation of phytanic acid and clinically mimics HMSN III in many respects.

Because of all of the advances in medical genetics, the classification of inherited neuropathies has become very complicated and is continually changing. A comprehensive review of these advances is beyond the scope of this book, but a review of some of the more common and more recognized forms is included later.

Hereditary Motor and Sensory Neuropathy Types I and II

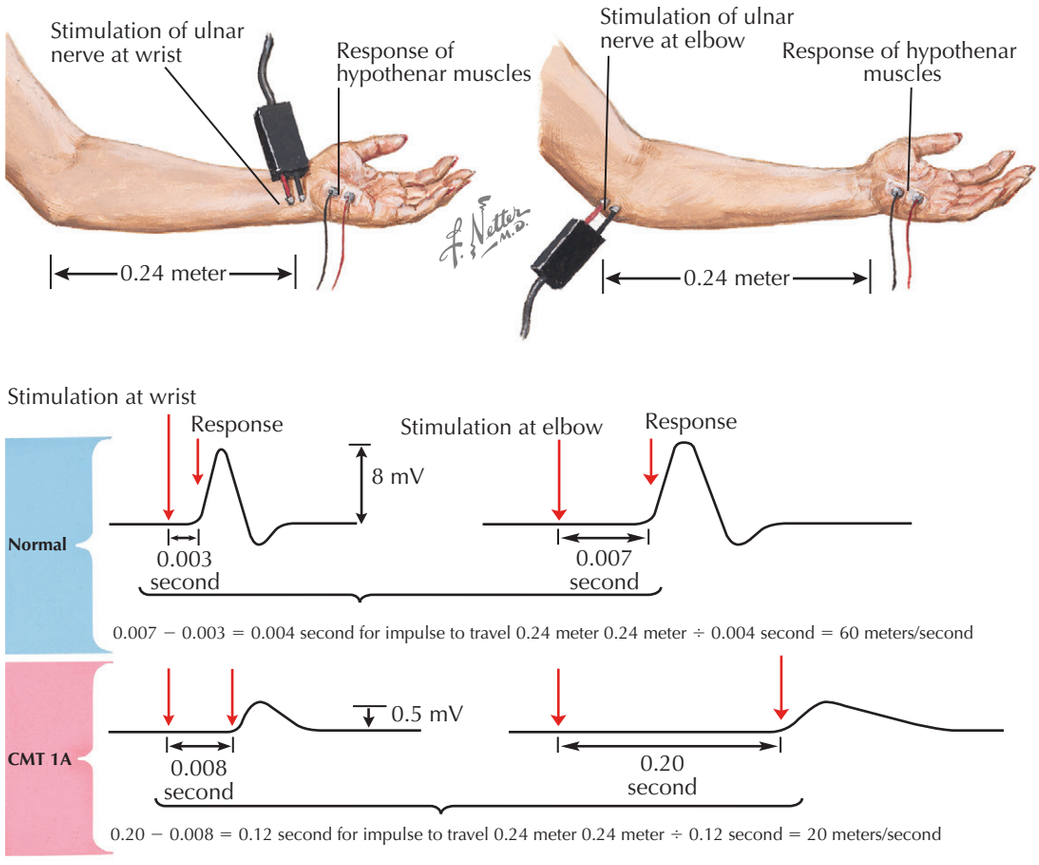
Charcot-Marie-Tooth diseases 1 and 2 (CMT1 and CMT2, i.e., HMSN I and HMSN II) cause motor and sensory dysfunction. Symptoms may not be evident early in life because the progression is slow, and patients are able to compensate for their physical limitations. Symptoms of inherited neuropathy are typically not reported until the second or third decade, or even later. Early symptoms include clumsiness when walking, difficulty running, a history of "weak ankles," with difficulty doing activities such as ice skating or roller skating; frequent tripping or ankle sprains are often reported. On examination, some degree of distal lower extremity weakness and atrophy is usually present. High arched feet and hammertoes (i.e., downward curling of toes) are common. Distal upper extremity weakness can also occur, usually later in the course of the disease. Sensory findings are present on examination, but are more often negative sensory signs, such as large fiber sensory loss; positive sensory symptoms, such as pain, prickling, and tingling, are less common and usually not a major feature of the disease.

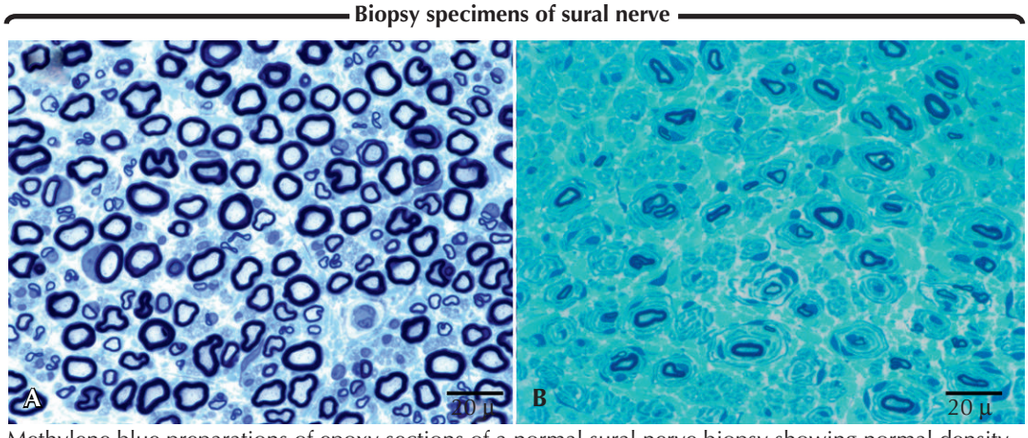
Nerve conduction studies (NCS) distinguish predominantly demyelinating diseases, such as CMT1, from axonal neuropathies. In demyelinating neuropathies (e.g., CMT1a), conduction velocities are generally less than 60% of normal and may be as low as 15% of normal. Slowing of nerve conduction can be used to identify affected family members before they are symptomatic. The degree of conduction slowing is relatively uniform across nerves. Distal latencies may be significantly prolonged, consistent with slowing along the entire course of the nerve. Temporal dispersion and conduction block are usually not present.

In contrast to CMT1, CMT2 (i.e., HMSN I) is predominantly an axonal neuropathy. NCS show low-amplitude motor and sensory responses, with relatively preserved conduction velocities and latencies. Needle electromyography in patients with CMT2 shows a greater degree of axonal changes, (e.g., fibrillations or positive sharp waves, long-duration motor units).

Nerve biopsies are usually not used diagnostically, but may be useful when genetic testing is negative and other etiologies need to be ruled out. In CMT1, nerve biopsy specimens may demonstrate a decrease in the number of myelinated nerve fibers associated with an increased fascicular area, producing onion bulbs (circumferentially arranged Schwann cell processes), which are caused by repeated episodes of demyelination and attempted remyelination. It is also common to see thinly myelinated nerve profiles as well as "naked axons" that have become denuded of myelin. Teased fiber preparations on the nerve biopsy will show areas of segmental demyelination and remyelination. Although both inherited and acquired forms of demyelinating polyradiculoneuropathy may show similar findings of demyelination and remyelination, acquired forms are more likely to show inflammatory changes. CMT2 nerve biopsies predominantly show axonal loss in a diffuse pattern, with degenerating profiles, and with teased fibers showing axonal degeneration in varying stages, consistent with an indolent process. Genetic testing has a progressively greater role in the diagnosis of inherited neuropathies. Early in research, duplication of the *PMP22* gene was found to be a cause of CMT1a, but subsequently, other genetic abnormalities were also found to produce an CMT1 phenotype, including defects in the genes myelin protein zero *(MPZ)*, *EGR2*, and *GJB1*. Similarly, several gene abnormalities have been found to cause CMT2, including *MFN2*, *MPZ*, *EGR2*, *PRX*, *NFL*, *LITAF*, and *GJB1*. Identification of a specific genetic abnormality is important, both for genetic counseling of the patient and family members, and for implicating potential targets for research in future therapeutics.

There is currently no curative treatment available for the underlying genetic processes at this time, and no treatment consistently found to be effective in slowing the progression of the disease process. Because the genetic defects are variable and new genes continue to be identified, it is unlikely a single treatment strategy will be effective for all these entities. The degree of disability acquired can vary dramatically, with some patients wheelchair-bound but others minimally affected, and many cases are only identified after a more affected family member has been diagnosed. Many patients with severe foot drop benefit from ankle-foot orthoses to avoid muscle fatigue and falls. Painless injury, particularly to the feet, is a risk in these patients, and care of the feet is important. In extreme cases, patients can develop a Charcot joint. In some cases, the use of a cane or other gait aid can markedly improve quality of life.





Methylene blue preparations of epoxy sections of a normal sural nerve biopsy showing normal density and size distribution of small and large myelinated fibers (**A**) and a sural nerve biopsy of a patient with CMTA (**B**) showing slight decrease in density with fewer large myelinated fibers and essentially all fibers surrounded by onion bulbs.

Other Hereditary Motor and Sensory Neuropathies (HMSN III, IV, and X)

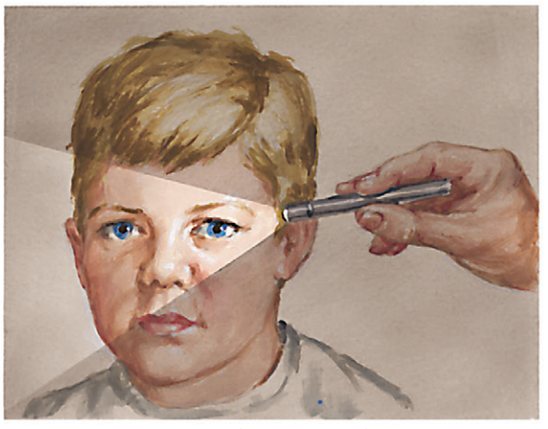
HMSN III, also known as Déjerine-Sottas disease, is a rather rare peripheral neuropathy with onset in infancy or childhood. Motor developmental milestones are typically delayed in affected children. They walk later than their unaffected siblings, some not until 4 years of age. Most acquire other motor skills slowly. The course may be insidiously progressive. In the past, the inheritance was assumed to be autosomal recessive because of the absence of a family history; however, with advances in genetics and genetic testing, we have learned that most cases occur on the basis of a sporadic ("de novo") mutation. They are likely autosomal dominant, but the individuals are generally too severely affected to have children. Because of this, many of the experts now believe that HMSN III is better classified as a severe form of HMSN I, rather than its own disease entity. Weakness of the distal musculature is noted mainly in the feet and legs early in the disease, later becoming evident in the upper extremities, manifesting as the child's difficulty with performing fine tasks, such as coloring, drawing, and manipulating small objects. Deep tendon reflexes are absent. Large fiber nerve sensation is also impaired but may be difficult to reliably assess at a young age. Miotic pupils unresponsive to light stimuli are seen in some patients. As in HMSN I, skeletal abnormalities, such as pes cavus (i.e., high arches) or kyphoscoliosis, develop in many patients. Careful examination may show thickened peripheral nerves, as can sometimes be seen in patients with HMSN I. The hypertrophic nerves are usually easier to palpate than to see. The course of this illness is progressive, and by their teenage years, most patients usually require significant assistance, including some need for a wheelchair.

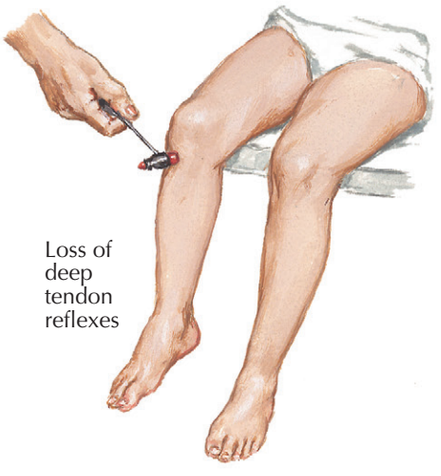
The cerebrospinal fluid (CSF) protein is often significantly increased. Nerve conduction studies may show absent sensory potentials and marked slowing of motor conduction velocity, with values in the range of 5 to 20 m/sec, characteristic of demyelinating process. Temporal dispersion and conduction block are not typically present. Nerve biopsy, which is usually not necessary for diagnosis, demonstrates a characteristic histologic picture of large onion bulbs (redundant Schwann cell processes from repetitive demyelination and attempts at remyelination) and very little intact myelin so that almost all of the axons are "naked." In general, these nerve biopsies do not have inflammatory changes. Genetic testing for *PMP22* and *MPZ* may show mutations.

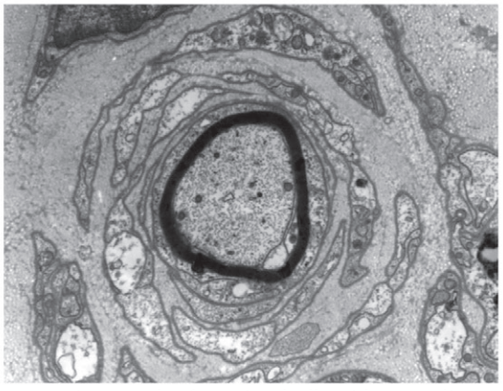
HMSN IV is a rare condition. The clinical course of HMSN IV is severe and generally found earlier in life, sometimes in infancy and often with marked weakness. These patients have an autosomal recessive inheritance pattern. Nerve conduction studies typically, but not always, show a demyelinating pattern. These may be associated with other abnormalities aside from the length-dependent neuropathy, such as vocal cord paralysis or deafness. Several genes have been implicated in the development of HMSN type IV.

HMSN X, an X-linked dominant disorder, is much more common than types III and IV. HMSN X is usually more severe in males owing to the X-linked dominant inheritance. It usually becomes symptomatic in early adulthood. Nerve conduction studies show varying degrees of conduction slowing, with velocities intermediate between the ranges for demyelinating and axonal processes. Some reports indicate more severe electrophysiologic findings in males. Nerve biopsy shows predominantly axonal loss. Genetic testing for *GJB1*, the gene producing connexin-32, may be helpful diagnostically.

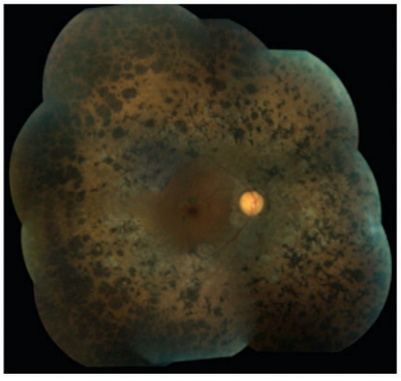
Refsum disease is a very rare autosomal recessive disorder characterized by abnormal fatty acid oxidation, leading to elevated levels of phytanic acid in the blood. Refsum disease usually begins in adolescence with a slowly evolving peripheral neuropathy, although it has a remitting-relapsing course in some patients. Most subjects have retinitis pigmentosa characterized by night blindness. Associated pupillary changes, nerve deafness, ataxia, cardiomyopathy, and ichthyosis may also be seen. In some patients, ataxia mimicking Friedreich ataxia is the initial complaint. Cerebrospinal fluid (CSF) findings and results of nerve conduction velocity studies are similar to those of Déjerine-Sottas disease. Although phytanic acid is a relatively ubiquitous compound found in many foods, a carefully controlled diet that excludes whole milk, all vegetables except potatoes, fat meats, chocolate, and nuts, can prevent further relapses and may improve the patient's clinical condition.

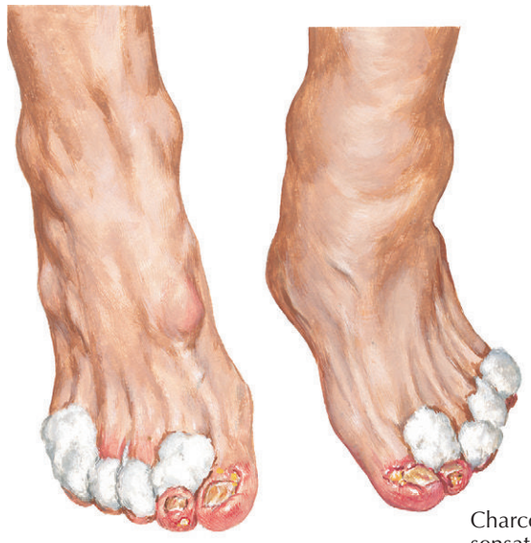

Loss of pupillary reflex

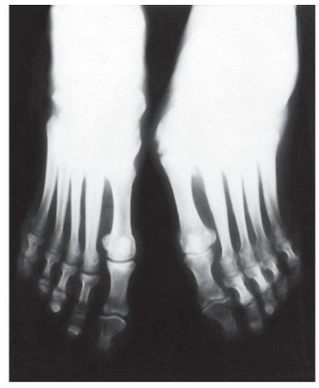



Electron micrograph of a onion bulb with a myelinated fiber in center surrounded by attenuated Schwann cell processes.

Refsum Disease

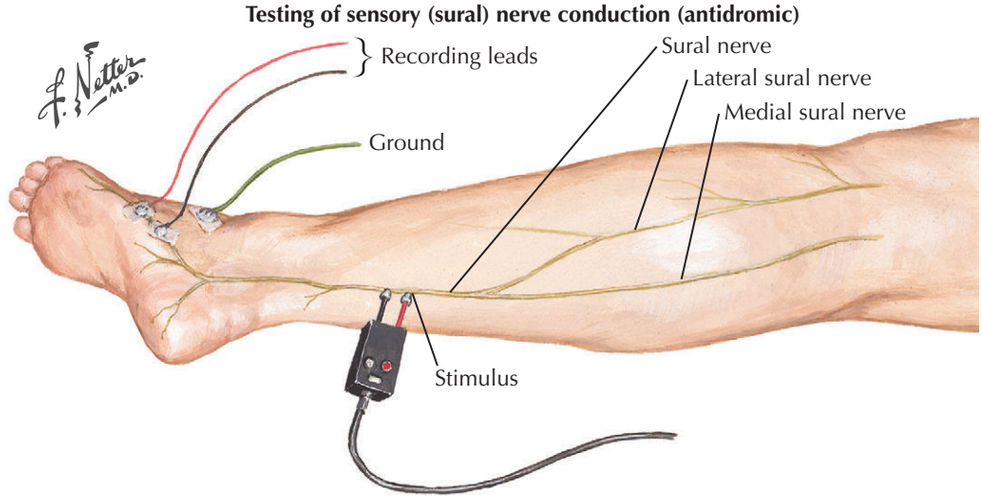

Retinitis pigmentosa is characteristic feature of Refsum disease, which may clinically resemble Déjerine-Sottas disease of Friedreich ataxia





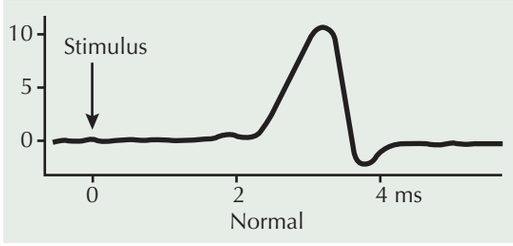
X-ray film showing dissolution of ankle joints

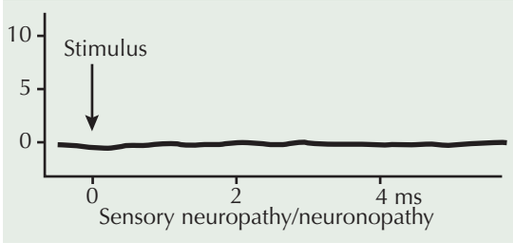
Charcot joints of both ankles, resulting from lack of pain sensation. Cotton pledgets protect ulcerated toes.



Hereditary Sensory and Autonomic Neuropathy

Hereditary sensory and autonomic neuropathy (HSAN) is a rare condition characterized primarily by loss of small fiber sensory modalities, often associated with pain. In many cases, inheritance is autosomal dominant. The clinical presentation of these patients generally reflects the major site of damage, which is most commonly to small unmyelinated or thinly myelinated sensory nerve fibers and autonomic fibers. As such, strength is mostly spared, as are large fiber sensory modalities (e.g., vibration, touch, and proprioception). Small fiber sensation of pain and temperature is disturbed. From a clinical standpoint, the main complication of this is the development of painless injuries, which can occur with repetitive trauma. Local ulcerations may not be detected unless there is visible blood or infection develops, risking the health of the limb. The development of a "Charcot joint" can occur, and sometimes amputations are necessary with severe enough tissue damage. Another typical presentation of HSAN is the development of burning feet in middle and old age. Physicians typically do not think of inherited causes for the neuropathy when adult patients present with burning feet but, in fact, inherited etiologies are among the most common causes of painful neuropathy presenting later in life. The family history is frequently not appreciated because family members often do not discuss their medical problems with each other as adults.





A careful history and neurologic examination is crucial in these patients. Family history is very important, particularly a history of painful feet and/or amputations. Neurologic examination should include testing of small fiber sensory modalities (pinprick sensations and temperature sensation). These findings mimic the dissociated sensory loss seen in syringomyelia. However, in contrast to a syrinx with primary involvement at the level of the central part of the spinal cord, the small neurons at the level of the dorsal root ganglion appear to be involved in hereditary sensory neuropathy.

Nerve conduction studies and electromyography are very useful for assessing large fiber sensory and motor nerve fibers and are a mainstay of diagnosis for HMSN but are usually not as revealing in HSAN. Dedicated small nerve fiber testing can help clarify the diagnosis, such as quantitative sensory testing, autonomic function testing, and thermoregulatory sweat test, which can show focal areas of sweat loss in these neuropathies. Skin biopsy to evaluate epidermal nerve fiber density can be a useful diagnostic tool. Nerve biopsies are not standard diagnostic tools in these cases, but if performed, may show a relative reduction in small nerve fibers. There is no specific treatment available to halt or slow the progression of the underlying disease process. However, good foot care will help to avoid secondary complications of the disease, such as poorly healing ulcers and amputations. Similar to the recommendations for HMSN, proper well-fitting footwear is essential as is avoidance of repetitive trauma.

GUILLAIN-BARRÉ SYNDROME

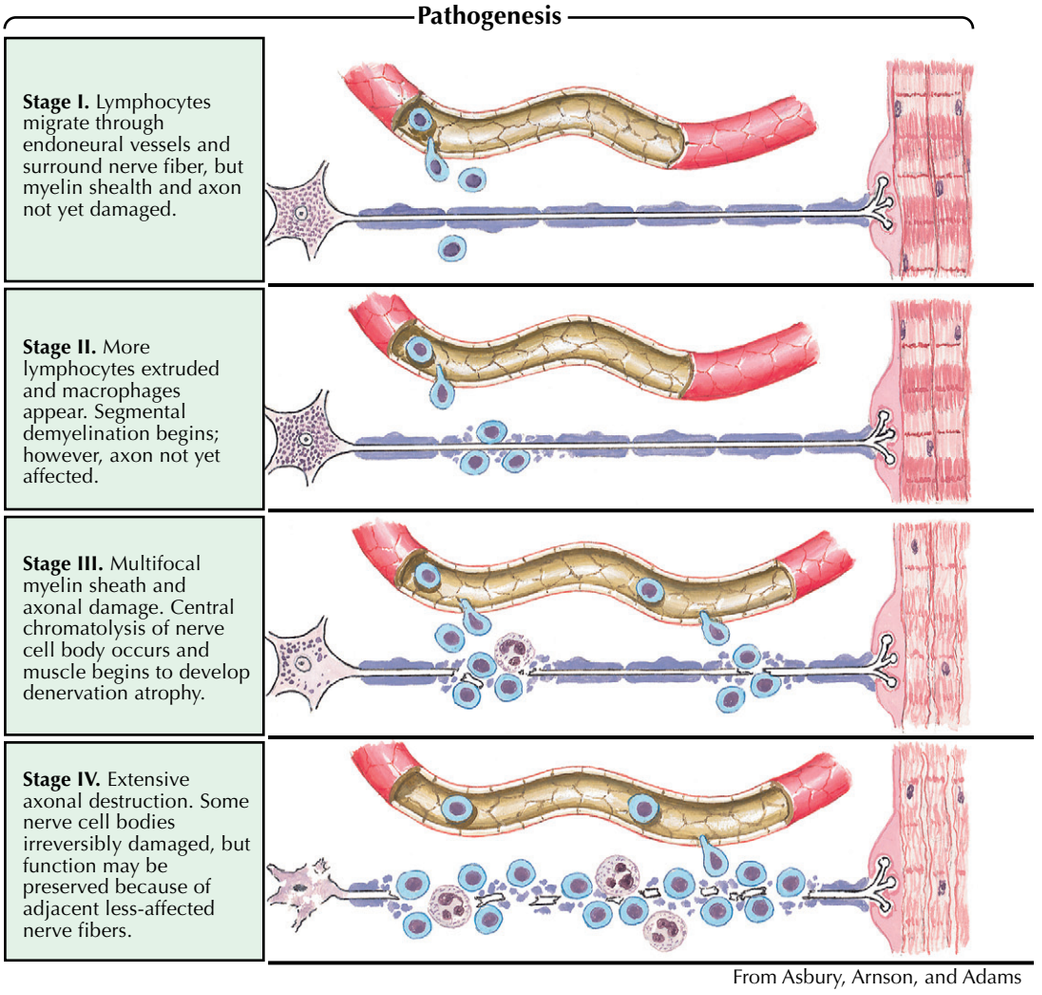
Guillain-Barré (GBS) syndrome, also known as acute inflammatory demyelinating polyradiculoneuropathy (AIDP), may vary in severity but typically manifests acutely as a demyelinating polyradiculoneuropathy with motor predominant findings. Associated features include total areflexia and elevated cerebrospinal fluid (CSF) protein. In about 60% of patients, an antecedent infection (e.g., virus or bacteria) precedes the syndrome by a few weeks. Rarely, GBS may be preceded by vaccination weeks earlier, although, in many of these instances, the prior vaccination is probably a coincidental event. Investigational studies suggest that the predominant lesion results from an attack on the myelin sheath by inflammatory cells, with concomitant myelin breakdown and, in severe cases, secondary axonal damage. The peripheral nerves may be affected at any level between the spinal nerve root and the distal ending of the nerve.

Mild cases of AIDP may never come to medical attention, but the typical presentation in those that seek medical assistance is one of acute ascending paralysis, which reaches its peak within 4 weeks. These motor findings are the most characteristic, although in some cases, paresthesias or pain may accompany the weakness. In severe cases, respiratory failure can occur, sometimes requiring intubation. Autonomic dysfunction may coexist, manifesting as hemodynamic instability with labile blood pressures, heart rates, and even cardiac arrhythmias, and patients may need hemodynamic support. Intensive care unit–level care is commonly required.

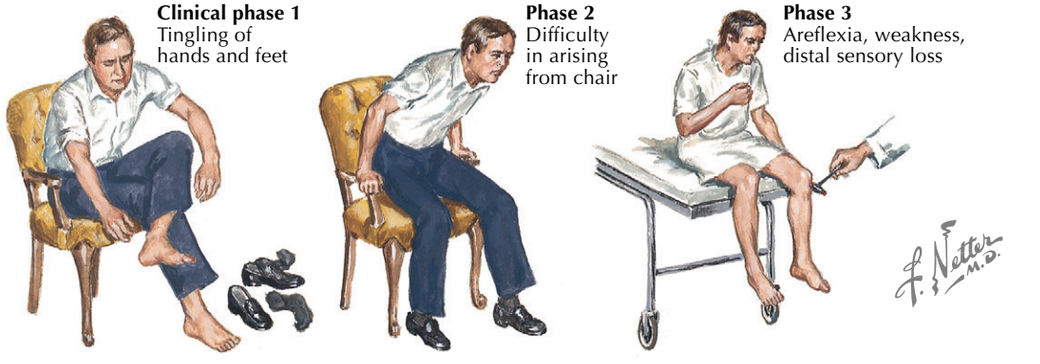
Physical examination generally reveals symmetric weakness, although some asymmetry can occur. The weakness can worsen rapidly in these patients and requires close monitoring. Significant sensory loss is atypical. Reduced or absent reflexes are common. Cranial nerve dysfunction is less common, although facial nerve palsy (sometimes asymmetric) is seen in up to 30% of patients, and extraocular muscles are affected in about 5%. Tongue and palate involvement is rare.

Variants of AIDP may present a diagnostic challenge; these include acute motor axonal neuropathy (AMAN), an axonal variant of AIDP with a worse long-term prognosis, an acute autonomic neuropathy, and Miller-Fisher syndrome (characterized by ataxia, areflexia, and ophthalmoplegia) in addition to the more typical AIDP presentation.

Nearly all patients with AIDP require hospitalization, even in mild cases, because progression of weakness is expected. The standard of care treatment is intravenous immunoglobulin or plasmapheresis. Supportive measures are necessary. Monitoring and management of respiratory and autonomic dysfunction has significantly reduced mortality. Other complications that should be prevented or treated include deep vein thrombosis, pulmonary emboli, pressure sores, and hyponatremia. Early involvement with physical therapy is important. AIDP is self-limiting in most patients. The maximum deficit is usually seen in 2 to 4 weeks, and improvement follows, with the course determined by the degree of axonal damage that accompanied demyelination. If axonal damage is severe, maximum recovery may take more than a year, and there may be significant residual weakness. Most patients eventually recover from AIDP, but the course is variable, and approximately 20% are left with some permanent disability.



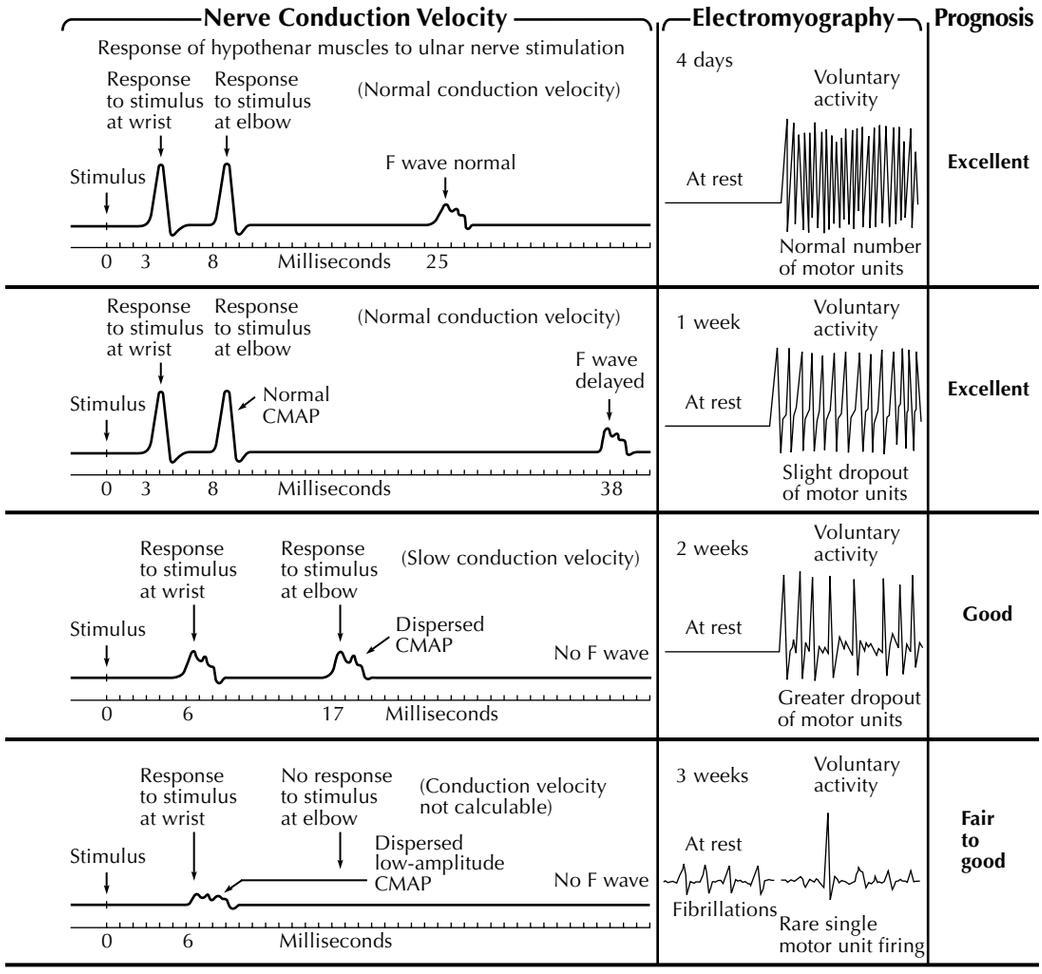
From Asbury, Arnson, and Adams

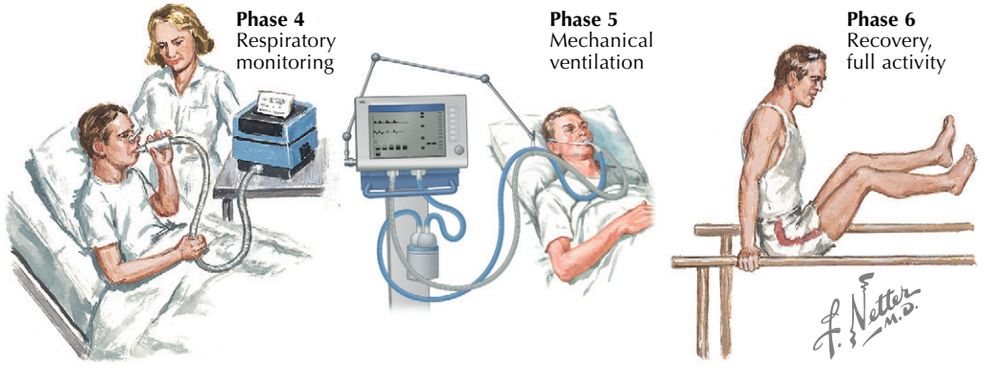


DIAGNOSIS OF AIDP

Electrodiagnostic studies can be extremely useful for evaluating patients with possible AIDP, but much of what are considered to be the most characteristic electrophysiologic features are often not present on studies done in the very early stages of the disease process. Among the earliest changes seen is loss of or prolongation of F-wave latencies or H reflexes. Over time, other features of demyelination, such as prolonged distal

GUILLAIN-BARRÉ SYNDROME
(Continued)



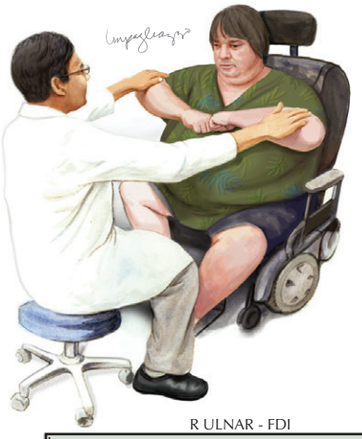


latencies, slowed conduction (usually measured along intermediate segments of nerve), and temporal dispersion, can be seen. Needle examination is usually not as revealing but may reflect neurogenic changes from axonal injury, which is secondary to the inciting inflammatory demyelinating process. These changes occur late in the disease process. The findings on electrodiagnostic studies mirror the degree of underlying pathologic changes in the four stages of the AIDP, as shown in the illustration.

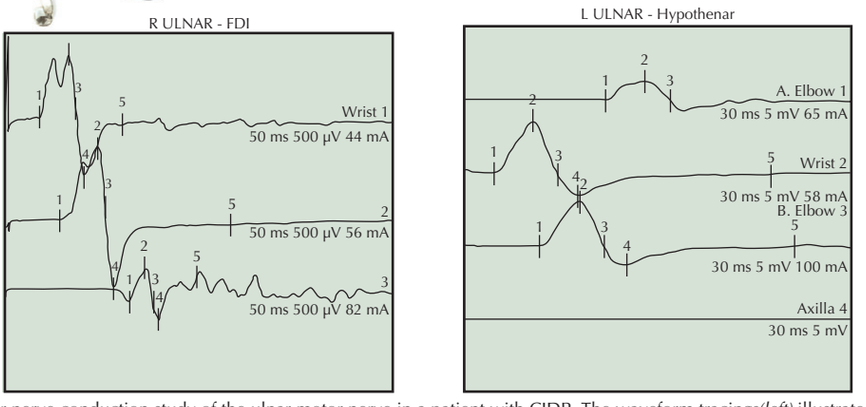
There are no classic serologic findings associated with AIDP. Spinal fluid evaluation is useful, with the typical pattern showing elevated spinal fluid protein in the absence of increased white blood cells. In the acute setting, with worsening weakness, treatment decisions are often made on clinical grounds, in association with a suggestive spinal fluid profile, and by carefully ruling out alternative etiologies by clinical evaluation and other studies. However, a normal CSF protein, particularly early in the disease process, does not rule out AIDP.

The differential diagnosis for AIDP needs to be carefully considered because the classic electrophysiologic features are often not present early in the disease process. Acute spinal cord lesions may be confused with AIDP. Spinal cord lesions may cause rapidly progressive paralysis, but sensory examination usually demonstrates a spinal cord level. In a process involving only anterior horn cells, flaccid paralysis can occur, but with more extensive spinal cord injury, hyperreflexia and spasticity are seen. These upper motor neuron signs are often very helpful in distinguishing a spinal cord lesion from AIDP. However, in the acute state, these other features (e.g., hyperreflexia) may not be present. Spinal cord lesions also typically cause early bowel and bladder dysfunction. Back pain may be a feature of either disorder. If there is high clinical suspicion for a primary spinal cord injury, magnetic resonance imaging can be diagnostically helpful. Clinical findings in a number of toxic, metabolic, or infectious processes, including arsenic poisoning, may be very similar to those in the AIDP but should generally be able to be differentiated and should be considered very rare causes of polyneuropathy. A carefully documented history and appropriate laboratory studies usually point to the specific mechanism. Infectious diseases that should be considered include poliomyelitis, diphtheria, Lyme disease, West Nile infection, and human immunodeficiency virus (HIV). CSF pleocytosis should be a strong clue that the underlying process is infectious. The presence of a "bulls-eye" rash or presence in an endemic area should prompt evaluation for Lyme disease; Lyme serology and spinal fluid evaluation can be performed. West Nile exposure can be evaluated in blood or spinal fluid. As is the case with Lyme disease, markers for acute infection should be sought. An AIDP clinical picture can also be associated with acute HIV infection, which should be considered. Pupillary abnormality points to either diphtheria or *botulism*, both of which also have predominant bulbar symptoms. Acute intermittent porphyria (AIP) may mimic classic AIDP, and the patient should be questioned about use of any medication that could precipitate a porphyric crisis. Clues to an attack of AIP include a personal or family history of similar events, coexisting acute neuropsychiatric symptoms, and severe abdominal pain. Severe weakness can occur as part of a porphyric attack; the pathology is primarily axonal rather than demyelinating, although this distinction is difficult to establish in the acute setting; urine porphyrins can be tested if the clinical suspicion is high. The scalp and skin should be carefully examined to exclude the presence of a tick that could produce tick paralysis. Associated facial palsy may suggest sarcoidosis, whereas bulbar symptoms may also be seen with myasthenia gravis and rarely could mimic AIDP.

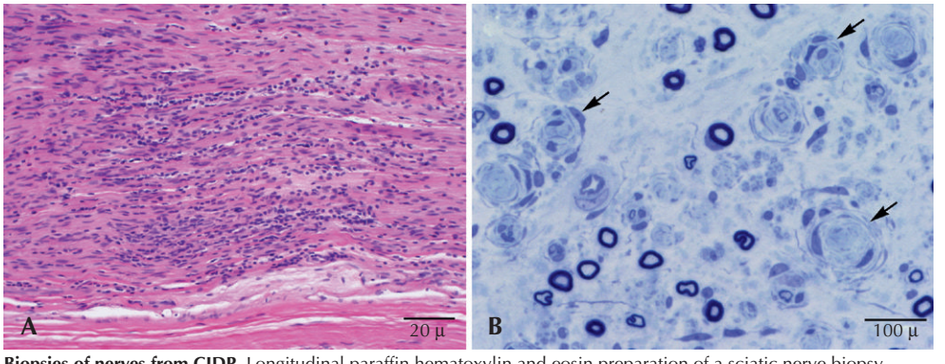
Chronic Inflammatory Demyelinating Polyradiculoneuropathy



Principal manifestation of CIDP is four-extremity weakness; paresthesias in the feet and hands are also noted. On examination, patient is weak (shoulder abduction testing), areflexic, and demonstrates sensory loss in the feet and hands. NCS/EMG demonstrated a predominantly demyelinating sensorimotor polyradiculoneuropathy.



Motor nerve conduction study of the ulnar motor nerve in a patient with CIDP. The waveform tracings*(left)* illustrate temporal dispersion. On proximal stimulation above the elbow *(lower tracing)*, there is a marked increase in the duration of the CMAP, as well as a significant drop in the amplitude, which is called temporal dispersion. The waveform tracings *(right)* illustrate conduction block. On proximal stimulation above the elbow *(top tracing)*, there is a significant drop in the amplitude compared with CMAPs elicited with more distal stimulation. Temporal dispersion and conduction block are both indicative of acquired demyelination, occurring somewhere in the nerve between the above-elbow and below-elbow stimulation sites.



Biopsies of nerves from CIDP. Longitudinal paraffin hematoxylin and eosin preparation of a sciatic nerve biopsy showing endoneurial inflammation (**A**). Methylene blue–stained epoxy section of a sural nerve biopsy showing some fibers with large onion bulbs without myelinated fibers at their centers (**B**, *arrows*), whereas other myelinated fibers do not have onion bulbs (a pattern typical of CIDP).

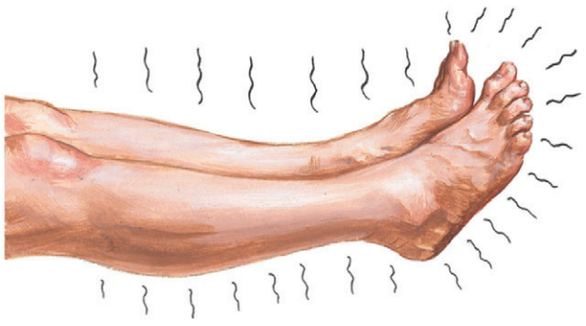
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), as indicated by the name, is also a type of demyelinating peripheral nerve disorder, which, unlike AIDP, is a chronic condition. CIDP is sometimes thought of as a long-term form of AIDP because of the similar electrophysiologic similarities and immune-mediated etiology. Similar to AIDP, CIDP tends to be motor predominant, with significant weakness causing disability, although the weakness of CIDP is usually not as severe as it is with AIDP. Sensory symptoms, such as paresthesias and pain, are frequent but tend to be relatively mild. Sensory ataxia is often present. The large myelinated fibers are most susceptible to demyelination in CIDP, and damage to them causes weakness and loss of joint position sense and vibration. The symptoms of CIDP tend to be more slowly progressive, and the maximum deficit generally occurs greater than 8 weeks after symptom onset. The course of disease can either be relapsing-remitting or chronic progressive. It is less common than in AIDP to be associated with an antecedent illness, vaccination, or other precipitating event. Respiratory and severe bulbar involvement is also less common than in AIDP but can occur. Clinically evident autonomic dysfunction is rare in CIDP, which is also different from AIDP, in which autonomic involvement is common.

The diagnosis of CIDP can be challenging. Patients generally have both proximal and distal weakness on examination. Deep tendon reflexes are markedly reduced or absent. Distal sensory loss is often found on clinical examination. Electrodiagnostic studies are extremely important and typically show clear signs of demyelination, with prolonged distal and F-wave latencies and slow conduction velocities on nerve conduction studies. Conduction block and temporal dispersion of compound motor action potentials are common. Cerebrospinal fluid examination generally reveals significantly elevated spinal fluid protein without an increased white blood cell count. Nerve biopsy is almost never needed for diagnosis but, if performed, may demonstrate segmental demyelination and endoneurial and epineurial inflammation. Teased nerve fiber preparation may show features of demyelination and remyelination along individual nerve strands, and routine studies may show the presence of onion bulbs and inflammatory exudates.

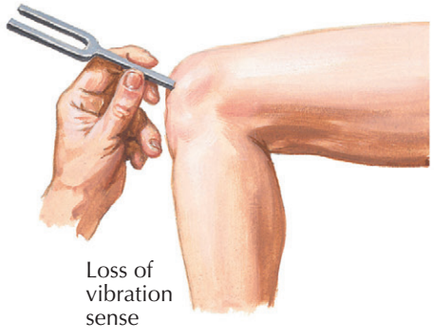
The differential diagnosis of CIDP can be broad, but in most cases, the clinical and laboratory features point to the diagnosis without need for a large differential diagnosis. Diagnosis of CIDP becomes more complex in cases of late-stage CIDP, when there may be significant axonal injury found on electrodiagnostic studies, making it difficult to assess if the demyelinating or axonal component is primary. Diabetic polyneuropathy often shows mixed axonal and demyelinating features electrodiagnostically; some authors have described a form of "diabetic CIDP." It remains controversial if diabetic CIDP is a true entity because epidemiologic studies have not found an increased rate of CIDP in diabetic patients. A rare condition called POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome can present with a demyelinating polyradiculoneuropathy; this is often diagnosed when suspected CIDP patients are refractory to immunotherapy. POEMS is discussed later under "Monoclonal Protein–Associated Neuropathies." Lymphoma can also manifest as a polyradiculoneuropathy and should be carefully considered if there are risk factors; CSF cytology and nerve biopsy can also be helpful diagnostically in cases where this is suspected. Immunoglobulin M (IgM) monoclonal gammopathy of undetermined significance (MGUS) neuropathy, another acquired demyelinating polyneuropathy, is discussed later under "Monoclonal Protein–Associated Neuropathies."

Variants of CIDP include focal or multifocal forms, which are described by various names in the literature, including CIDM (chronic inflammatory demyelinating mononeuropathy), MADSAM (multifocal acquired demyelinating sensory and motor neuropathy) and CISP (chronic inflammatory sensory polyradiculopathy). In these less classic forms, diagnosis is more difficult, and sometimes magnetic resonance imaging and fascicular nerve biopsy can be helpful.

The treatment of CIDP is varied, and large clinical trials are limited. Patients are generally treated with immunomodulatory agents. There are three first-line treatments: oral or intravenous corticosteroids, intravenous immunoglobulin, and plasma exchange. Controlled trials have shown these agents to be effective. Oral steroid-sparing immunomodulatory agents are often used, without good comparative data for their relative efficacy. The treatment of CIDP is very effective; without treatment many patients will need aids to walk or will be wheelchair confined. With treatment, many can lead essentially normal lives. In general, long-term treatment with some type of immunosuppressive drug is required, because this is a chronic condition.



Paresthesia, hyperalgesia, or hypesthesia



Loss of vibration sense

Diabetic Neuropathies

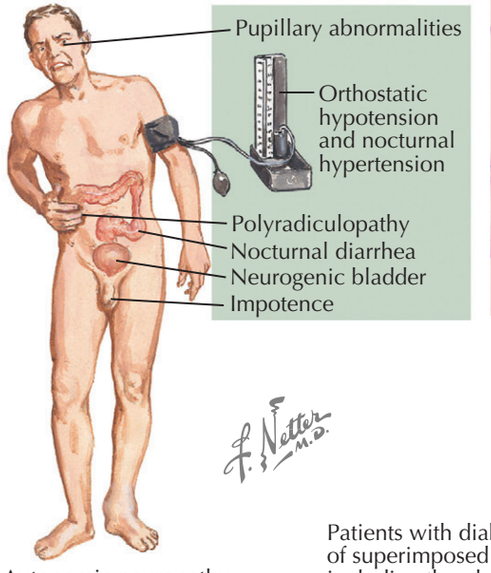
Diabetic neuropathies are varied, and can consist of a diabetic polyneuropathy, autonomic neuropathy, compression neuropathy, and can be as severe as diabetic lumbosacral radiculoplexus neuropathy. Most types of diabetic neuropathy occur in long-standing diabetics, but some subtypes can occur in early disease.

Clinical Manifestations

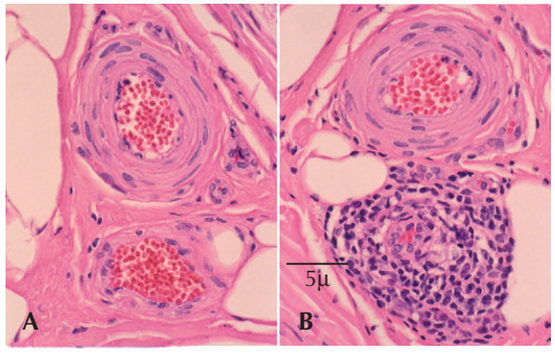
Diabetic polyneuropathy (DPN) is one of the most common neuropathies seen in clinical practices (see Plate 6-21). It is generally length dependent, with prominent sensory symptoms, and can include both sensory loss as well as painful paresthesias. Autonomic neuropathies can occur with DPN and other forms of diabetic neuropathy, or it can occur independently and can manifest with orthostatic hypotension, sweat loss, gastrointestinal dysmotility, and erectile dysfunction, as well as other symptoms. Compression neuropathies (see Plate 6-21), such as median neuropathy at the wrist (carpal tunnel syndrome) and ulnar neuropathies at the elbow, occur frequently in diabetic patients. Diabetic radiculoplexus neuropathy (DRPN) usually manifests as severe unilateral extremity pain, often with associated weight loss, followed by weakness and sensory loss in that same extremity; over time this can become bilateral. This is usually a monophasic illness but can sometimes recur. DRPN can occur in the lower limb (lumbosacral) segment (DLRPN), the trunk (thoracic) segment (DTPN), or the upper limb (cervical) segment (DCRPN); the lower limb syndrome (DLRPN) is most common.

The presence of the clinical history of diabetes mellitus is important, as is a compelling clinical history. DPN generally occurs in long-standing diabetes mellitus, usually in patients who already have nephropathy and retinopathy associated with their diabetes. In cases with large fiber sensory involvement or weakness, nerve conduction studies and electromyography can be helpful. In DPN, nerve conduction studies usually show a length-dependent predominantly axonal peripheral neuropathy. In DLRPN, there is evidence of involvement of nerve root, plexus, and distal nerve, typically asymmetric. Electrophysiologic studies are also sensitive for evaluating for focal neuropathies and identifying common sites of compression. Autonomic reflex screen and a thermoregulatory sweat test can be helpful to assess suspected autonomic neuropathy. Other testing, such as gastrointestinal motility and urodynamic studies, can be useful in some cases. Nerve biopsies are rarely performed in diabetic neuropathies, particularly in classic DPN cases, but, where performed, show axonal loss. In cases of DLRPN, pathologic changes of microvasculitis have been found.

Overall, the best treatment strategy for diabetic neuropathies is to attempt to prevent worsening of the underlying disease through tight glucose control. Similar to cases of HMSN, good foot care is important to prevent painless injuries and ulcerations. Management of neuropathic pain is very important in these patients to improve quality of life. Supportive treatments for autonomic neuropathy can be considered depending on the specific organ in which the symptoms manifest (e.g., for orthostatic hypotension, management of fluid and salt intake, consideration of medications to increase plasma volume). In DPN, the cause of the neuropathy is related to the length and severity of the exposure to hyperglycemia. Consequently, treatment is centered on optimizing diabetic control. In DLRPN, in contrast, the putative mechanism is ischemic injury from microvasculitis. A controlled trial with intravenous methylprednisolone did show some efficacy and immunomodulatory therapy can be considered. Usually, the treatment should be a short course because the disease is most frequently monophasic.

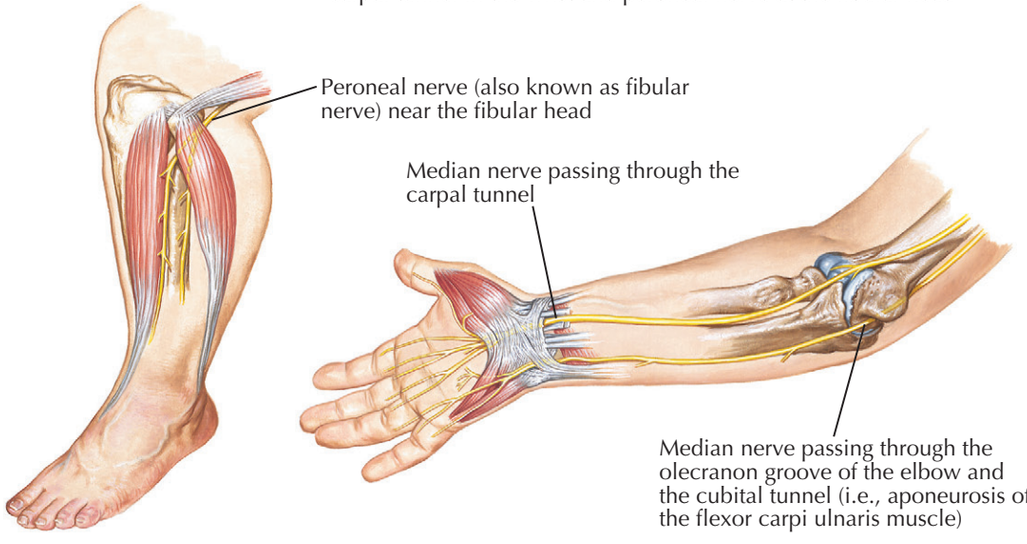


Autonomic neuropathy



Serial skip paraffin section of a microvessel above (**A**) and at (**B**) regions of microvasculitis in the superficial radial nerve of a patient with diabetic radiculoplexus neuropathy. Sections are stained with hematoxylin and eosin.

Patients with diabetic polyneuropathy are prone to the development of superimposed mononeuropathies at common sites of entrapment, including the ulnar nerve at the elbow segment, median nerve at the carpal tunnel in the wrist and peroneal nerve at the fibular head



Monoclonal Protein–Associated Neuropathies

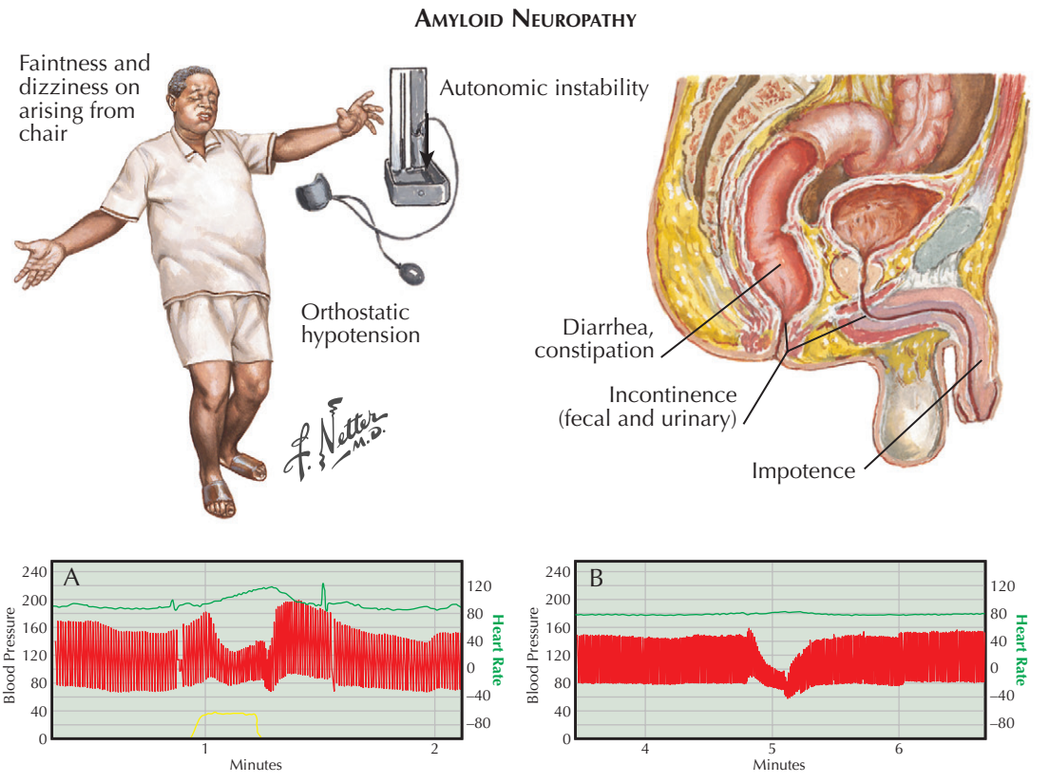
Many neuropathies can occur in patients with monoclonal proteins. However, in many cases, these may not be causative. Neuropathies are more common in older patients, as is the presence of a monoclonal protein, so the presence of a monoclonal protein should therefore not always be interpreted to reflect the etiology of neuropathy. Neuropathies have been reported with monoclonal gammopathy of undetermined significance (MGUS), with amyloidosis, as well as with malignancies such as osteosclerotic myeloma (POEMS syndrome—discussed further), lymphoma, Waldenström macroglobulinemia, and others, including patients with an immunoglobulin M (IgM) monoclonal gammopathy. In addition, it is important to remember that neuropathies can occur as side effects of some of the agents used to treat lymphoproliferative disorders.

IgM MGUS NEUROPATHY

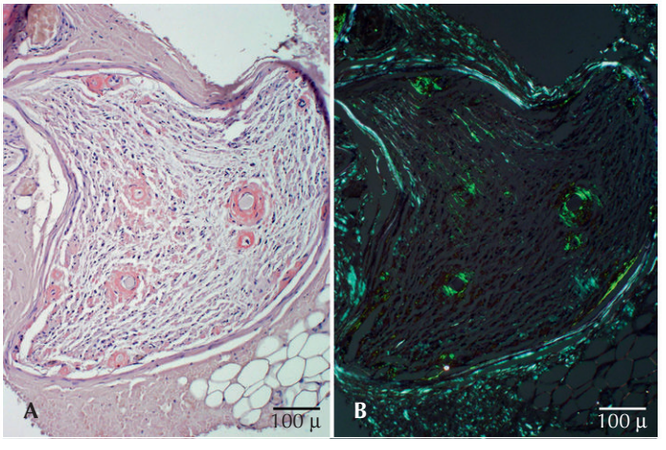
Although most patients who present with chronic distal sensory or sensorimotor symptoms and signs have an axonal polyneuropathy unrelated to a paraprotein, rarely, patients with distal clinical features have electrodiagnostic evidence of demyelination and are found to have an IgM monoclonal protein. These patients are often referred to as distal acquired demyelinating symmetric (DADS) neuropathy. The majority of patients with a DADS neuropathy phenotype will have a MGUS, which is almost exclusively IgM kappa. The IgM MGUS neuropathy (e.g., DADS neuropathy) patient presents with sensory-predominant polyneuropathies of insidious onset, particularly in men older than 50 years. Because of profound sensory involvement, gait unsteadiness (sensory ataxia) is a common complaint. When motor signs are present, they are confined to the distal (toes, ankles, fingers, wrists) musculature. Tremor is also a frequent finding. These patients are often found to have associated myelin-associated glycoprotein (MAG) autoantibodies. Motor nerve conduction studies demonstrate widespread symmetric slowing. In many cases, distal latencies are dramatically prolonged, resulting in a short terminal latency index (TLI). This finding implies that the motor conduction velocity slowing is more pronounced in distal nerve segments and is considered an electrodiagnostic hallmark of anti-MAG neuropathy. In neuropathies felt to have a clear association with anti-MAG antibodies or with other monoclonal proteins in the absence of a more severe hematologic disorder, some immunomodulatory treatments (e.g., rituximab) have been tried with varying degrees of success. Sensory or sensorimotor polyneuropathies are often seen in patients with Waldenstrom macroglobulinemia, an IgM-associated cancer of B cells.

AMYLOID NEUROPATHY

Amyloidosis that causes neuropathy can be separated into primary amyloidosis (associated with a bone marrow disorder) and inherited forms. Amyloid is an amorphous material that can deposit in nerve, causing significant neuropathy, but can also deposit in many other tissues including fat, gastrointestinal tissue, kidney, and heart, leading to multisystem damage, and in some cases to death. Primary amyloidosis occurs in patients with a serum monoclonal protein, with free light-chain deposition into tissues. There are inherited forms of amyloidosis, the most common being associated with mutations in transthyretin (which is largely made by the liver), but there are other subtypes.



Blood pressure (BP) and heart rate (HR) responses to the Valsalva maneuver showing a normal response in a male aged 80 years (**A**) and a patient with amyloid autonomic neuropathy (female aged 68 years) (**B**). In the normal recording (**A**), the maneuver induced fall in BP results in an increase in heart rate (vagal baroreflex response), and this BP fall is followed by a BP rise (late phase II), followed by a transient fall (phase III, resulting from cessation of the maneuver), a rapid BP recovery and a BP overshoot (phase IV). All the BP increments are the result of an increase in total peripheral resistance. In the amyloid recording (**B**), baroreflex failure is manifest as a failure of HR to rise, and a loss of late-phases II and IV and delayed BP recovery after phase III.



Sural nerve paraffin sections shows congophilic deposits surrounding endoneurial microvessels (Congo red stain, **A**) and apple green birefringence under polarized light (**B**). These changes are diagnostic of amyloidosis.

Monoclonal Protein–associated Neuropathies
(Continued)

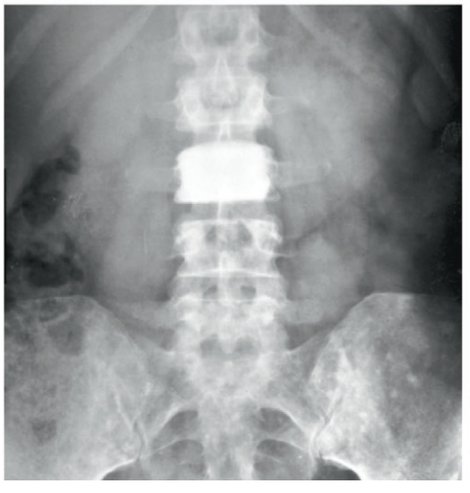
Approximately 15% of patients with primary amyloidosis will develop neuropathy. These neuropathies are usually diffuse, but lower limb predominant, and symmetric. Classically, there is significant small greater than large nerve fiber involvement, with prominent features of pain, sensory loss, orthostasis, and sweat loss. Clinical suspicion should be elevated for this diagnosis in those circumstances, and especially when there are associated systemic symptoms or evidence of multiorgan dysfunction. Diagnosis can be challenging, and requires a high clinical suspicion. In cases of primary amyloidosis, the presence of a monoclonal protein in the blood should prompt further evaluation. If there is a strong family history of peripheral neuropathy, particularly with associated cardiomyopathy and early demise, this should be considered. Assessment of kappa and lambda light chains in the blood, as well as urine monoclonal protein study, can be helpful. Genetic testing for transthyretin abnormalities is also available. Tissue biopsy can be helpful if amyloid can be demonstrated, potential sites of biopsy include subcutaneous fat, rectum, and peripheral nerve. Other tissues suspected to be affected can be biopsied as well. Treatment depends on the type of amyloid demonstrated. Treatments for primary amyloidosis include melphalan and peripheral blood stem cell transplant. Because the primary source of transthyretin is in the liver, liver transplantation can be considered in patients with transthyretin amyloidosis. In transthyretin amyloidosis, some newer agents that prevent the folding conformational changes may prevent the formation of new amyloid deposits.

POEMS Syndrome

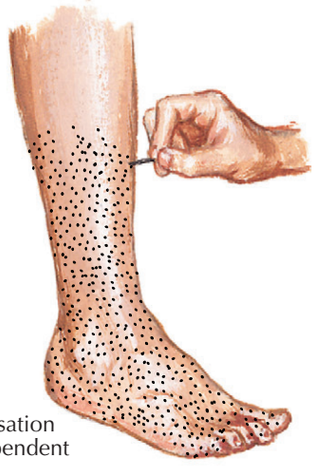
POEMS syndrome is an uncommon disorder that can produce a predominantly demyelinating peripheral neuropathy, with a clinical pattern very similar to that of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), with progressive weakness and sensory loss. This syndrome is occurs in conjunction with the presence of an osteosclerotic myeloma or Castleman disease. Clinical manifestations of POEMS syndrome are often dominated by the neurologic symptoms, which include progressive weakness, sensory loss, and sometimes pain. These patients are often misdiagnosed as having CIDP and only come to more specialized medical attention after they are found to have poor or limited response to standard immunomodulatory therapies. The other critical elements of POEMS syndrome should be assessed. These include organomegaly, which can be detected by a full medical examination and sometimes with the help of adjunctive imaging techniques. Endocrinopathies can be found by serologic screening for endocrine abnormalities. A monoclonal protein can generally be demonstrated by serum and/or urine monoclonal protein study. Skin changes may include discoloration or hypertrichosis among others. Thrombocytosis is also a common laboratory finding, as is the presence of elevated levels of vascular endothelial growth factor in the blood. Screening for osteosclerotic myeloma can be performed through skeletal radiographs, and Castleman disease can be identified through computed tomography (CT) imaging of the body and sometimes positron emission tomography (PET)/CT. Early referral to a hematologist is crucial for effective management of this disorder. Treatment strategies are dependent on the underlying etiology. If a single osteosclerotic myeloma is found, local irradiation can be helpful. If the disease process is more diffuse, peripheral blood stem cell transplantation could be considered.

Distal Acquired Demyelinating Symmetric (DADS) Neuropathy

Patient has an IgM-kappa monoclonal protein and antibodies to myelin-associated glycoprotein (MAG). Chief manifestation is gradually progressive sensory ataxia, resulting in the need to use a cane and frequently place hand on walls to maintain balance. NCS/EMG demonstrated a predominantly demyelinating sensorimotor polyneuropathy.

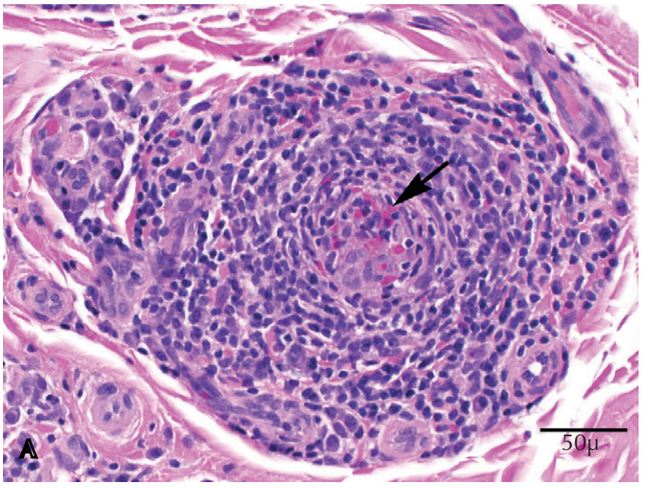


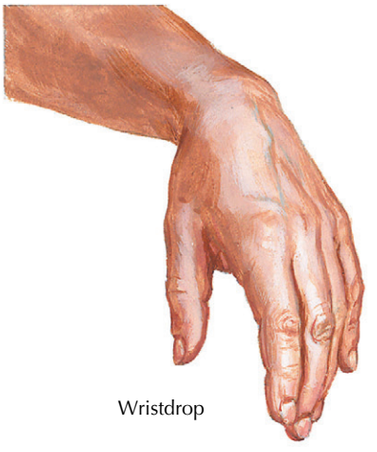
X-ray film showing osteosclerotic myeloma affecting isolated vertebra as seen in POEMS syndrome

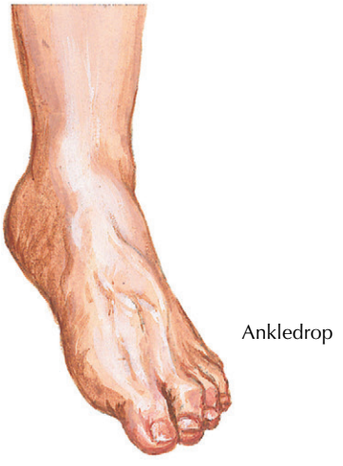


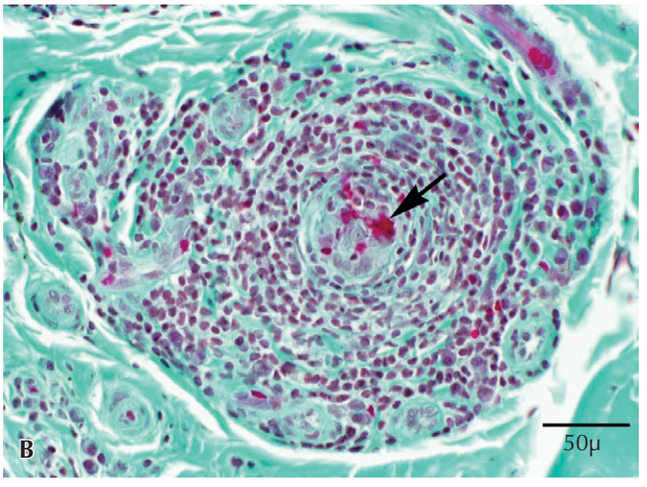
Decreased sensation in a length-dependent distribution

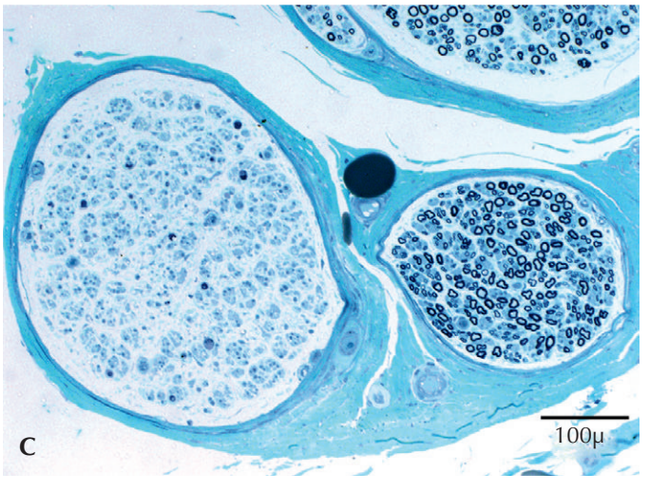
Fibrinoid Necrosis











Sural nerves from patients with large nerve vessel necrotizing vasculitis. Serial paraffin sections stained with **A**, hematoxylin and eosin and **B**, Masson trichrome shows fibrinoid necrosis *(arrows)*, luminal occlusion and transmural inflammation. These findings taken together are diagnostic of necrotizing vasculitis. Methylene blue–stained epoxy section, **C,** shows multifocal fiber loss, typical of ischemic nerve injury.

Vasculitic Neuropathy and Other Connective Tissue Disorders Associated with Neuropathy

Vasculitic neuropathies can occur in an isolated fashion, only affecting peripheral nerve, or can occur as part of a systemic vasculitic process, such as polyarteritis nodosa, Churg-Strauss syndrome, microscopic polyangiitis, and Wegener granulomatosis. Neuropathy can also be seen in other primary connective tissue diseases. Vasculitides associated with connective tissue disorders are predominantly small vessel vasculitides but can also involve larger nerve blood vessels (small arteries and large arterioles). Consequently, they are classified as nerve large arteriole vasculitis. In contrast, the radiculoplexus neuropathies (notably diabetic lumbosacral radiculoplexus neuropathy (DLRPN) as described earlier) and nonsystemic vasculitis involve microvessels and are described as nerve microvasculitis (see Plate 6-21).

Vasculitic neuropathies usually manifest with asymmetric nerve involvement, in a stepwise fashion often described as mononeuritis multiplex. They are often painful, in addition to clinically manifesting with signs of focal nerve dysfunction with weakness and sensory loss. In long-standing cases, many patients will appear to have a length-dependent symmetric peripheral neuropathy, if enough nerves are involved so that there is enough overlap for the process to appear diffuse. In systemic processes, fever and weight loss are often accompanying symptoms. In polyarteritis nodosa, there may also be vasculitic involvement of the skin, heart, and kidneys as well as other organ systems. The presence of asthma can be a clue for Churg-Strauss syndrome. Kidney involvement is common in microscopic polyangiitis.

A clinical examination that reveals significant asymmetry of neuropathic findings is a major clue to this diagnosis, as is a clinical history of stepwise involvement of different peripheral nerves, particularly when accompanied by pain. In DLRPN, there is typically lower limb pain and weakness with associated weight loss. Electrophysiologic studies show an asymmetric axonal-predominant neuropathy in most cases, although, as previously discussed, these findings can be symmetric, particularly in long-standing disease. Serologies including connective tissue markers, sedimentation rate, and C-reactive protein are often helpful diagnostically, as well as evidence of clinical involvement of other organ systems. In these cases, biopsy of a clinically affected nerve can be very useful, with findings of axonal degeneration and inflammatory changes, with prominent inflammatory changes involving and disrupting the layers of blood vessel walls. In some cases, necrotizing

Vasculitic Neuropathy and Other Connective Tissue Disorders Associated with Neuropathy *(Continued)*

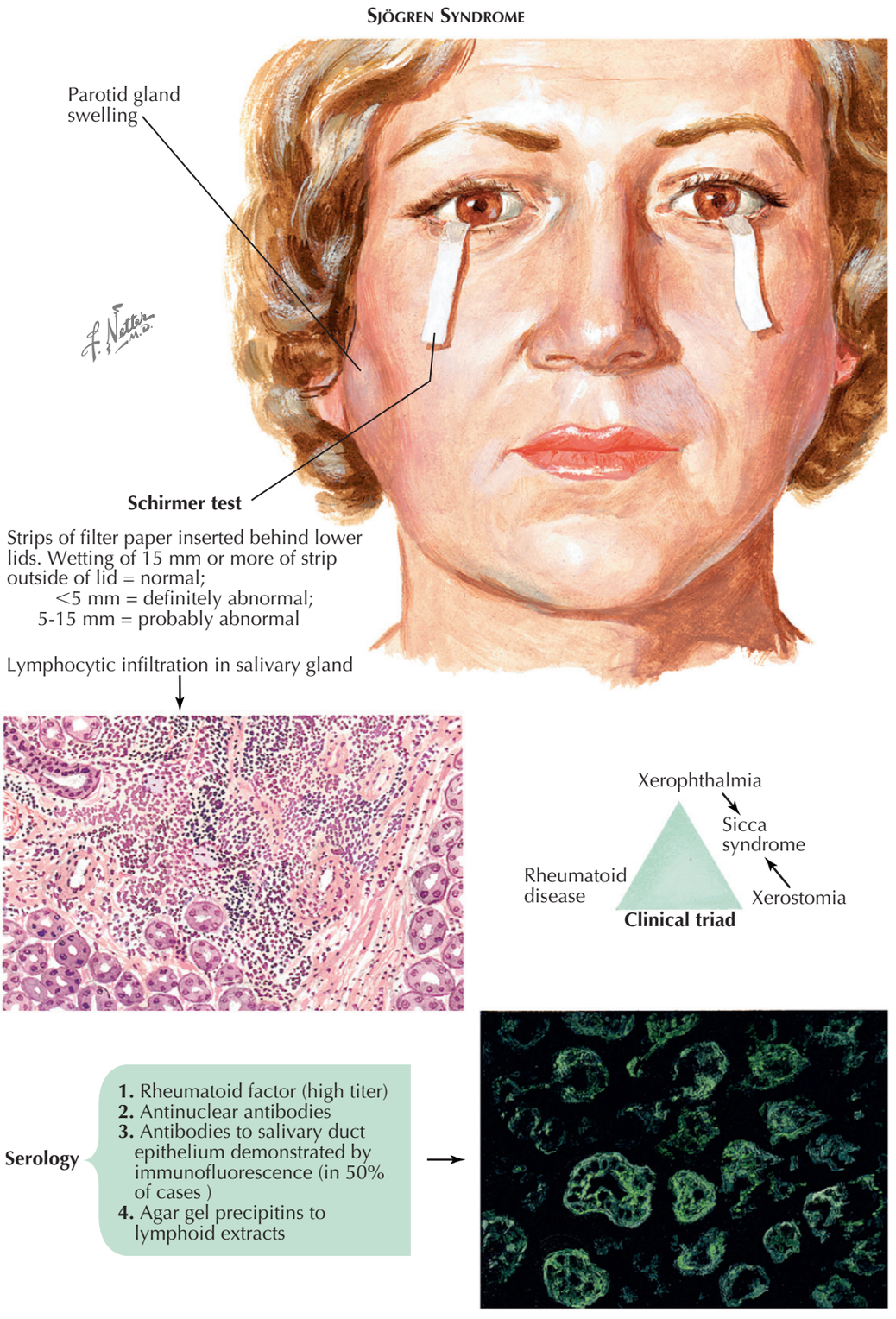
changes in blood vessel walls are noted, and these cases are referred to as necrotizing vasculitis. Treatment is generally with immunosuppressive agents. Some patients with isolated peripheral nerve microvasculitis are managed with corticosteroids. Patients with evidence of a more systemic condition or necrotizing vasculitis often need stronger degrees of immunosuppression for long-term management.

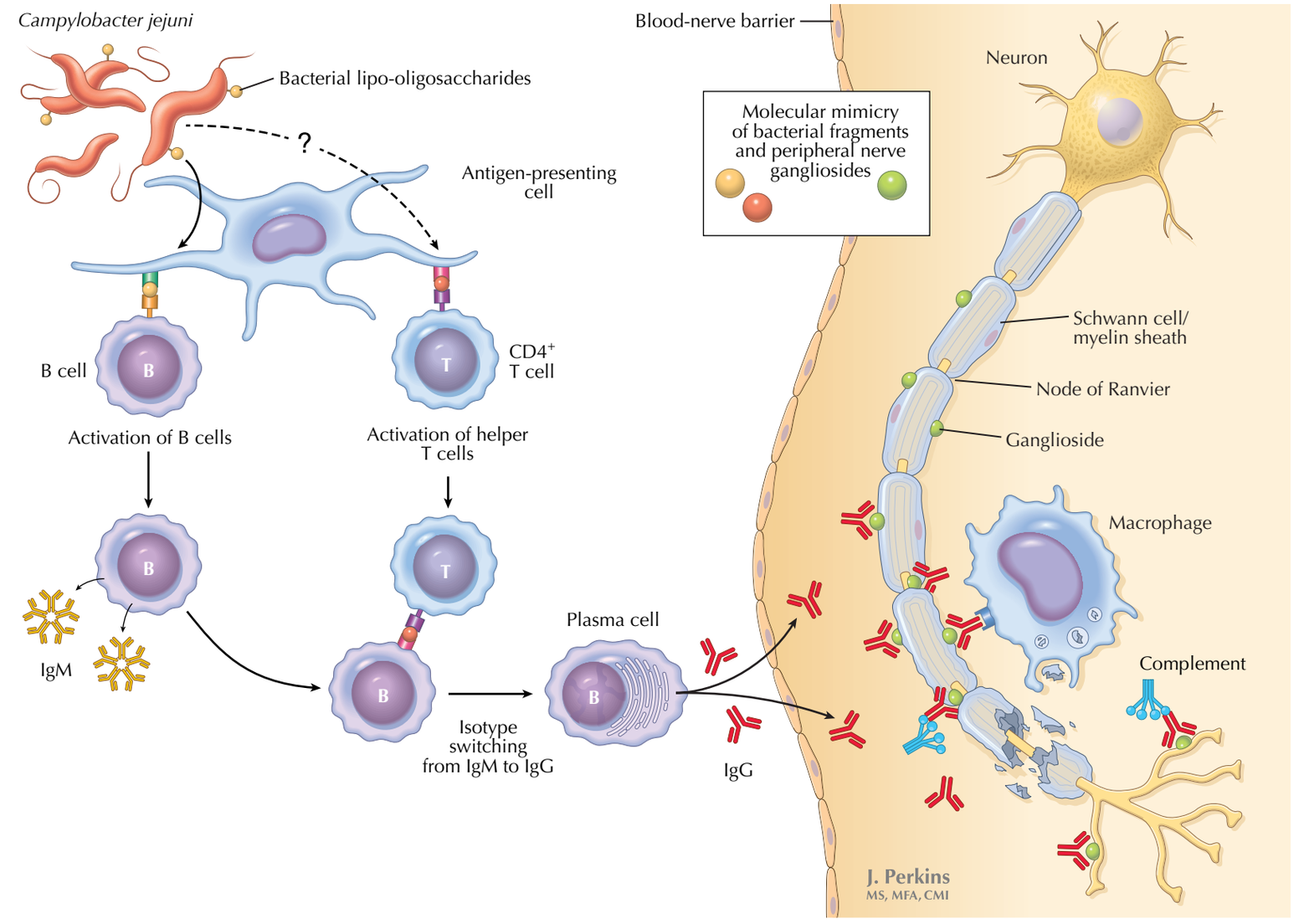
SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematous (SLE) is a multisystem disorder that can manifest with variable combinations of fever, rash, alopecia, arthritis, pleuritis, pericarditis, nephritis, anemia, leukopenia, thrombocytopenia, and nerve system disease. Neuropathy is reported in approximately 20% of patients with SLE. The most common neuropathy phenotype in SLE is the mild, gradually progressive, length-dependent, sensory, or sensorimotor neuropathy. Patients often note positive (prickling, tingling, pain) and negative (dead-type numbness) sensory symptoms. In less than 5% of SLE patients, the pattern is of multiple mononeuropathies, likely secondary to vasculitis. Less commonly, patients have a pure small-fiber neuropathy.

SJÖGREN SYNDROME

Sjögren syndrome (SS) is a systemic autoimmune disease that primarily affects middle-aged women. The criteria for diagnosis include sicca symptoms (dry eyes, dry mouth), objective evidence of keratoconjunctivitis, evidence of chronic lymphocytic sialoadenitis, and the presence of either anti–SS-A or anti–SS-B antibodies. Rash, arthralgias, and the Raynaud phenomenon are also common. Peripheral neuropathy is reported to occur in 10% to 30% of patients with SS. The neuropathy of SS is secondary to vasculitis in some cases and secondary to mononuclear cell infiltration without vasculitis (e.g., ganglionitis) in other cases. There may also be other mechanisms of neuropathy in these patients. For example, the etiology of the small fiber neuropathy seen in some cases of SS may be different. Several patterns of neuropathy are seen in association with SS: sensory ataxic neuropathy, painful sensory neuropathy without ataxia, multiple mononeuropathies, multiple cranial neuropathies, trigeminal sensory neuropathy, autonomic neuropathy with anhidrosis, and radiculoneuropathy. Abnormal pupils and orthostatic hypotension are relatively common accompaniments to many of these neuropathies and should be sought on examination.





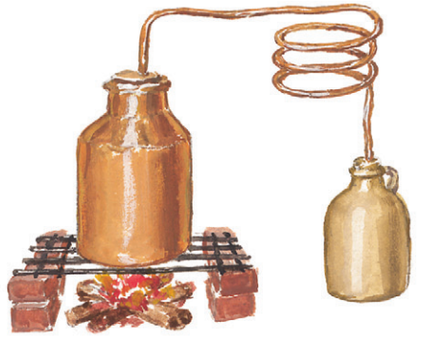
Immunopathogenesis of Guillain-Barré Syndrome

The pathophysiology of the immune-mediated polyneuropathies is complex and varies greatly. What follows is a simplified overview for three common immune-mediated polyneuropathies. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP), the most common form of GBS, is characterized pathologically by demyelination, lymphocytic infiltration, and macrophage-mediated clearance of myelin. Approximately two thirds of GBS cases occur weeks after an otherwise trivial infection, for example *Campylobacter jejuni*. The infectious agents have epitopes on their surface that are similar to epitopes on the surface of peripheral nerves (e.g., gangliosides, glycolipids), resulting in peripheral nerve elements acting as a "molecular mimic" of the infectious agent. During the infection, the complement-fixing IgG antibodies that arise to attack the infection also bind to peripheral nerve gangliosides, inducing autoimmune injury. Macrophage-mediated stripping of myelin also occurs in AIDP, mediated by antibody and complement deposition on Schwann cell and myelin membranes.

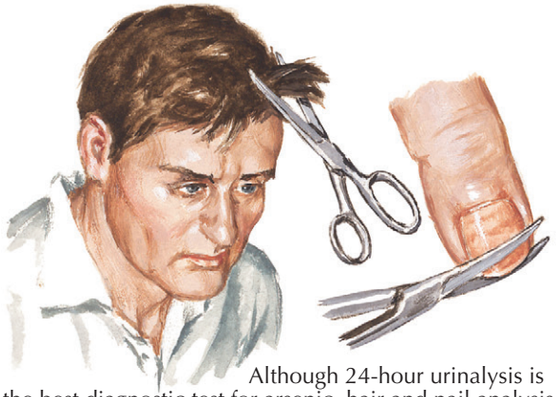
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) shares many similarities with GBS but also important differences. For example, the autoimmune attack of CIDP is chronic, not self-limiting as with GBS. Furthermore, CIDP does not seem to follow an otherwise trivial infection. In CIDP, similar to GBS, T cells, antibodies, macrophages, and complement work together to induce an immune attack on peripheral nerve elements. On nerve biopsy, macrophages are found around endoneurial vessels.

The pathophysiology of vasculitis, on the other hand, is much different than of GBS and CIDP, in large part because what are being attacked in vasculitis are not peripheral nerve epitopes but rather blood vessels, causing secondary ischemic injury to nerve in cases involving blood vessels of nerve. The inflammation of vasculitis may affect blood vessels of any size anywhere in the body, and many forms of vasculitis affect the peripheral nervous system. When peripheral nerve vasculitis occurs, nerve axons are principally damaged, resulting in an "axonal" neuropathy, in contrast to the demyelinating neuropathies of AIDP and CIDP. Vasculitis may occur as a primary process or as a secondary phenomenon that is related to a variety of disorders, ranging from rheumatologic disorders to viral infections. The pathologic changes of nerve large arteriole vasculitides are seen in epineurial and perineurial vessels measuring 75 to 200 microns in diameter. Examples of nerve large arteriole vasculitis include polyarteritis nodosa and Wegener granulomatosis. Nerve "microvasculitis" principally involves the smallest arterioles (<40 μm), microvessels, and venules of the epineurium, although there is some overlap in vessel size with the large nerve arteriole vasculitides. Nerve microvasculitis occurs in classic nonsystemic vasculitic neuropathy (classic NSVN), classic Sjögren syndrome, many virus-associated vasculitic neuropathies, and diabetic lumbosacral radiculoplexus neuropathy (DLRPN).

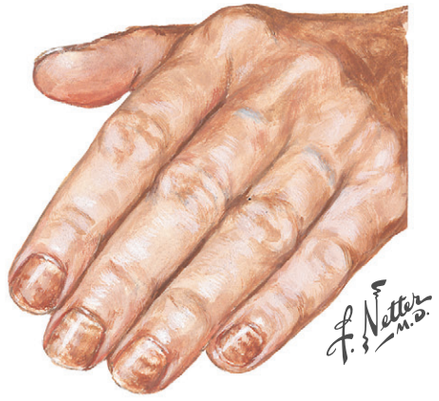
History of nausea and vomiting may suggest arsenic poisoning in patient with peripheral neuropathy



Antique copper utensils (e.g., still used for bootleg liquor) and runoff waste from copper smelting plant may be sources of arsenic poisoning



Although 24-hour urinalysis is the best diagnostic test for arsenic, hair and nail analysis may also be helpful



Mees lines on fingernails are characteristic of arsenic poisoning

Spotty alopecia associated with peripheral neuropathy characterizes thallium poisoning

Lead poisoning, now relatively rare, causes basophilic stippling of red blood cells. 24-hour urinalysis is diagnostic test

Peripheral Neuropathy Caused by Heavy Metal Poisoning

Peripheral neuropathy secondary to heavy metal exposure is rare, but should be considered in patients with risk factors, particularly through occupation and hobbies. Heavy metal ingestion can also occur through deliberate poisoning.

ARSENIC

Arsenic has a ubiquitous distribution in the environment, particularly as an impurity in copper ores. Although it is a means of notorious surreptitious homicide, the presence of excessive levels of arsenic in a patient should not immediately indicate a possible criminal cause. Arsenic contamination may be due to exposure to an agricultural environment or to an industrial environment, such as copper smelting. Other sources have included drinking water (e.g., when a well has been inadvertently drilled in a former storage location of arsenic insecticides). The clinical manifestations of arsenic poisoning may vary. Usually, the initial symptoms are gastrointestinal rather than neuropathic, and vomiting, diarrhea, and abdominal pain are common early signs of poisoning. The peripheral nerve manifestations ultimately follow, usually as length-dependent sensory symptoms with a prominent pain component, followed by weakness. These symptoms may continue to progress for a period of time after the source of exposure is gone. Central nervous system findings are often present, such as confusion and psychiatric symptoms. Skin changes may eventually occur with erythema or abnormal areas of pigmentation. Occasionally, if the amount ingested is sufficiently large, growth-arrest lines, so-called *Mees lines*, may be seen in the fingernails. The diagnosis is confirmed by analysis of a 24-hour urine sample, a more sensitive indicator than serum values, which can decrease rapidly after exposure has ceased. Differentiation between inorganic and organic arsenic is important, because some dietary sources (e.g., seafood) can result in elevations of urinary arsenic in a nontoxic form. Samples of hair and nails may provide supporting evidence of arsenic exposure, and may be useful to analyze long after the exposure has ceased. If electrophysiologic tests are performed, they will generally show an axonal peripheral neuropathy. The most important treatment components are removing the source of the arsenic and use of chelating agents.

NEUROPATHIES CAUSED BY OTHER METALS

Gold salts, which had been used in treating rheumatoid arthritis, have sometimes produced a distal sensorimotor peripheral neuropathy, although sometimes this can be difficult to separate clinically from neuropathy secondary to rheumatoid arthritis itself. Improvement in neuropathic symptoms after discontinuation of gold salts usually confirms an underlying toxic mechanism. Ingestion of thallium salts, occasionally used in rodenticides and insecticides, causes a potentially severe sensorimotor neuropathy associated with development of alopecia 10 to 30 days after ingestion. Exposure to lead, now seen infrequently, can cause a predominantly motor neuropathy, often initially involving wrist and finger extensors

Metabolic, Toxic, and Nutritional Peripheral Neuropathies

There are many metabolic, toxic, and nutritional causes of peripheral neuropathy, with alcohol abuse being the most common etiology in this category.

ALCOHOL

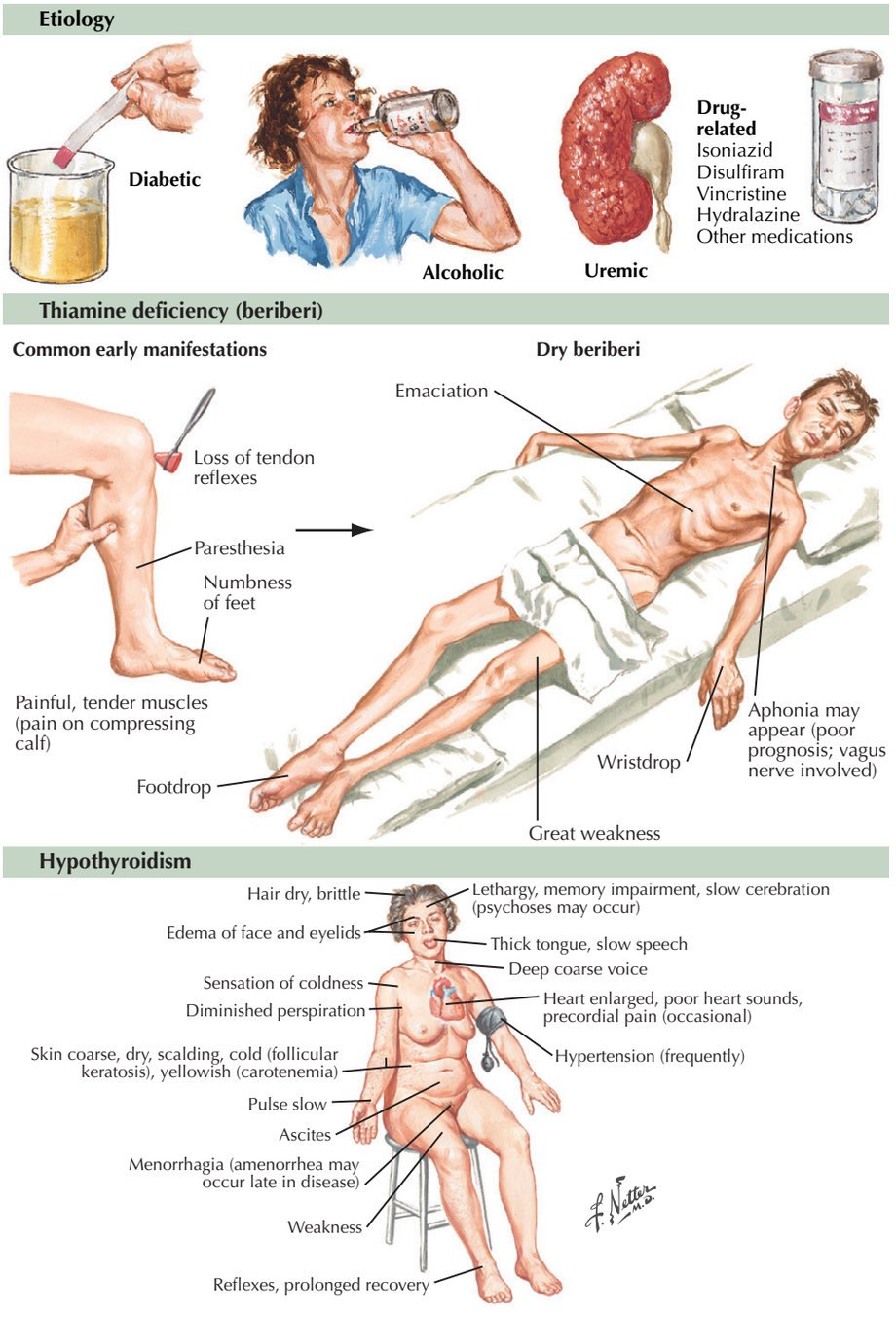
The prevalence of neuropathy in alcohol use is uncertain, but has been estimated to exist in approximately 50% of alcoholics. Incidence of neuropathy in alcoholics correlates with age of the patient and the duration of alcohol use. The pathophysiology is uncertain, but the direct toxic effect of alcohol on peripheral nerves seems to be the most important etiology. Alcoholic neuropathy has a similar phenotype to other metabolic neuropathies. The neuropathy is often distal, symmetric, pure sensory, or sensory predominant and slowly progressive. There are often positive neuropathic sensory symptoms, such as tingling and or burning, as well as loss of nociceptive sensation on examination. Patients should be evaluated for other vitamin deficiencies or causes of malnutrition, because alcohol neuropathy often coexists with neuropathy due to thiamine deficiency and sometimes vitamin B_{12} deficiency.

THIAMINE (VITAMIN B_1)

Thiamine (vitamin B_1) deficiency most commonly occurs in chronic alcohol abuse, chronic gastrointestinal problems (including recurrent vomiting), cancer patients, and after weight reduction surgery (i.e., bariatric surgery). Severe vitamin B_1 deficiency causes congestive heart failure (wet beriberi), peripheral neuropathy (dry beriberi), Wernicke encephalopathy, and Korsakoff syndrome. Neuropathy associated with thiamine deficiency may present with acute onset or insidiously with distal, symmetric, sensory, or sensorimotor neuropathy with positive neuropathic sensory symptoms (e.g., tingling) Thiamine-deficient patients may develop weakness, numbness, and loss of balance (ataxia). Evaluation of thiamine deficiency should include measurement of whole blood thiamine.

VITAMIN B_{12} DEFICIENCY

Multiple nutritional deficiencies can result in peripheral neuropathy, with vitamin B_{12} deficiency as one of the most recognized forms, which can lead to both a peripheral neuropathy as well as a myelopathy. Vitamin B_{12} deficiency can result from a number of factors, both related to poor diet as well as syndromes of malabsorption, including the presence of pernicious anemia, inflammatory bowel disease, and bowel resection surgery (including gastric bypass surgeries). The usual manifestation of vitamin B_{12} deficiency is distal numbness (large fiber sensory modalities) and paresthesias, with progressive gait unsteadiness. Vitamin B_{12} deficiency can also cause cognitive dysfunction and should be considered in this clinical setting. Serologic testing for vitamin B_{12} as well as methylmalonic acid is crucial for this diagnosis. Electrophysiologic studies show findings of an axonal sensorimotor peripheral neuropathy, and somatosensory evoked potentials may also show central conduction slowing, reflecting spinal cord involvement. Magnetic resonance imaging of the spinal cord may at times show abnormal T2 signal in the posterior columns of the spinal cord. Vitamin B_{12} supplementation should be instituted. Depending on whether the etiology of the deficiency is poor dietary intake or malabsorption, oral or intramuscular administration should be chosen. Follow-up serologic studies should be done to ensure normalization of vitamin B_{12} and methylmalonic acid levels after supplementation.



HYPOTHYROIDISM

Hypothyroidism is a common disorder most commonly affecting women. The diagnosis should be considered in patients with symptoms such as fatigue, weight gain, cold intolerance, coarse dry hair and skin, constipation, depression, and abnormal menstrual cycles. Neuropathic symptoms often include paresthesias, numbness, and pain. Patients often complain of subjective weakness but do not often have findings of weakness on examination.

UREMIA

Peripheral neuropathy due to uremia occurs in 10% to 80% of patients with chronic renal failure who are on dialysis but has become less frequent due to renal transplantation. The neuropathy in uremia is similar to other neuropathies due to a metabolic cause, being often distal, symmetric, sensory predominant, and slowly progressive. Patients often have symptoms of numbness and imbalance as well as paresthesias and burning. Other common symptoms include restless legs, cramps, and weakness. The diagnosis should be considered especially in patients with end-stage renal disease with a creatinine level of 5 mg/dL or higher or creatinine clearance less than 12 mL/min.

Leprosy and Other Infections Sometimes Causing Peripheral Neuropathy

Leprosy

Leprosy (Hansen disease) is probably the most common cause of peripheral neuropathy in the world and is caused by an infection with *Mycobacterium leprae*. This organism tends to involve only nerves close to the skin where the body is cooler. Most people are not susceptible to infection. Leprosy is most common in third-world countries, and its elimination from Europe correlates with improved standards of living. There are different forms of leprosy—tuberculoid, lepromatous, and borderline forms, and the type developed depends not on the organism but on the host's response to the bacilli. In tuberculoid leprosy, the spread of the bacilli are limited, and a focal, asymmetric disease results. The skin is often hypopigmented. In contrast, in lepromatous leprosy, spread of the leprae bacilli is widespread. The clinical manifestations are due to extensive involvement of regions of cooler body temperature. The hallmark clinical feature of leprosy is sensory loss. This sensory loss is frequently found when an affected person develops painless injury. Nerves involved by leprosy may become enlarged and hardened. Antileprosy treatment stops ongoing nerve damage and helps existing nerves to heal. However, leprosy is a chronic disease, and treatment needs to be long term.

Lyme

Lyme disease in the United States is caused by *Borrelia burgdorferi* infection transmitted by the *Ixodes* tick. In the majority of infected individuals, Lyme disease manifests first with erythema migrans, a painless and nonpruritic skin lesion that evolves over days to weeks. Patients typically have flulike symptoms and may have infection of large joints, meninges, heart, or peripheral nerve. Approximately 15% of patients develop neurologic complications days to weeks after untreated infection. The most typical neurologic manifestations are one or more elements of the triad of polyradiculoneuritis, lymphocytic meningitis, accompanied by cranial neuritis. The polyradiculopathy or polyradiculoneuropathy is typically sensorimotor, painful, asymmetric, and non–length-dependent due to involvement of nerve roots. Approximately 5% of untreated patients develop a chronic axonal neuropathy, with symptoms of relatively symmetric, distal paresthesias. Serologic testing may be negative early in the course and should be repeated if the clinical suspicion is high. Positive serologies should be confirmed by a Western blot. Cerebrospinal fluid (CSF) in acute disease typically shows modest lymphocytic pleocytosis and mild increase in protein. In chronic infection, the immunoglobulin G (IgG) synthesis rate should be increased, and oligoclonal bands may be present. CSF Lyme polymerase chain reaction (PCR) has 40% to 50% sensitivity and 97% specificity.

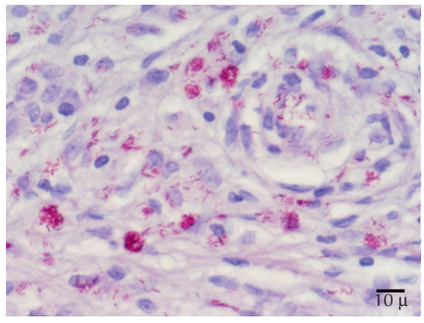
Human Immunodeficiency Virus (HIV)

Symptomatic neuropathies occur in approximately 10% to 15% of HIV-1–infected patients, and the incidence increases as the immunodeficiency worsens. Distal symmetric sensory polyneuropathy (DSPN) is the most common HIV neuropathy manifestation. DSPN presents with distal pain, paresthesias, and numbness in a symmetric length-dependent manner. It involves sensory or sensorimotor nerve fibers and is gradually progressive. The neuropathy is similar to that associated with nucleoside-analog reverse-transcriptase inhibitors (NRTIs: dideoxyinosine [ddI], dideoxycytodine [ddC], 2′-3′-didehydro-2′-3′-dideoxythymidine [d4T/Stavudine]), used in the treatment of HIV. Polyradiculopathy is a much less common presentation for neuropathy in an HIV-infected patient. Acute inflammatory demyelinating polyradiculopathy (AIDP) can rarely occur at the time of seroconversion (CD4 counts ≥ 500). Polyradiculopathy can also be seen in moderately advanced HIV (CD4 counts 200-500) as a CIDP phenotype. In both cases, cerebrospinal fluid (CSF) examination typically demonstrates lymphocytosis of 10 to 50 cells/mm^3. Mononeuritis multiplex is infrequent complication of HIV (0.1%-3% of patients). In advanced HIV (CD4 counts < 50), co-infection with cytomegalovirus (CMV) can cause painful mononeuritis multiplex, polyradiculoneuropathy, or polyradiculopathy. In these cases, CSF demonstrates polymorphonuclear pleocytosis in 5%; CMV PCR in CSF is positive in 90% of cases.

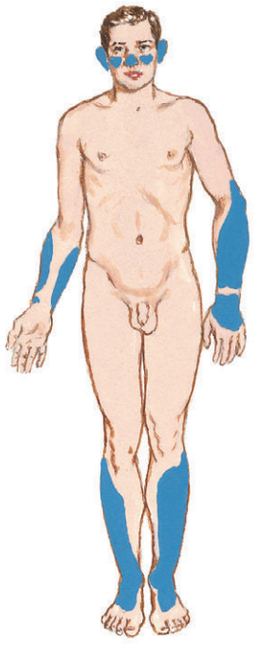
Hepatitis C Virus

Hepatitis C virus (HCV) is the most common chronic blood-borne viral infection in the United States. Neuropathy associated with HCV may affect approximately 10% of patients, with a higher prevalence (up to 30%) in those also positive for type II or type III cryoglobulins. Different pathophysiologic mechanisms have been suggested, including virus-triggered nerve microvasculitis and intravascular deposits of cryoglobulins, leading to disruption of the vasa nervorum microcirculation. The peripheral neuropathy may present as a distal, asymmetric sensory or sensorimotor polyneuropathy or as multiple mononeuropathies. Patients often have prominent symptoms of pricking, burning, or pain. Palpable purpura, for example, on the ankles, is common and should be looked for during the examination.

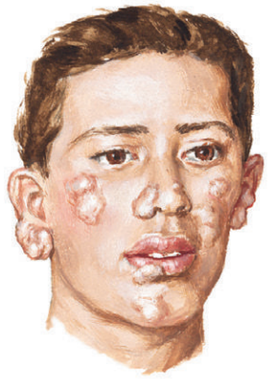
Leprosy (Hansen Disease)



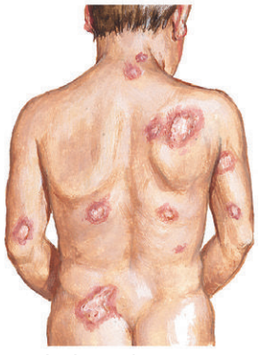
Sural nerve paraffin sections stained with Fite showing many acid-fast bacilli of a patient with leprosy



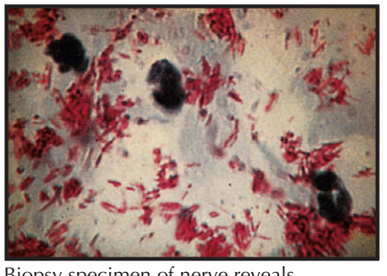
Typical early pattern of sensory loss in leprosy (Hansen disease) tends to affect cooler skin areas not following either segmental or nerve distribution; area kept warm by watchband not affected



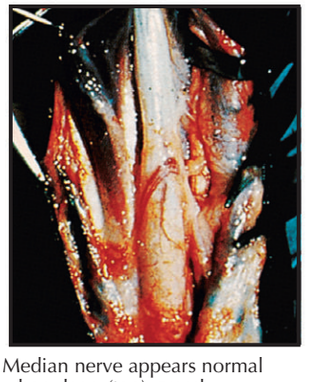
Patches and plaques on face and ears



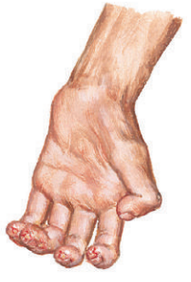
Multiple patches seen in lepromatous leprosy; central healed areas tend to be hypesthetic or anesthetic (dimorphous leprosy)



Biopsy specimen of nerve reveals abundant acid-fast bacilli (*M. leprae*).



Median nerve appears normal when deep *(top)*, grossly thickened and hyperemic when superficial (*bottom*).



Late-stage finger contractures with ulcerations due to sensory loss

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AUTONOMIC NERVOUS SYSTEM AND ITS DISORDERS

General Topography of Autonomic Nervous System

The nervous system is divided into somatic and autonomic divisions: the somatic division controls predominantly voluntary activities, while the autonomic system regulates involuntary functions. The two divisions develop from the same primordial cells; they comprise closely associated central and peripheral components and are both built up from afferent, efferent, and interneurons linked to produce ascending and descending nerve pathways and reflex arcs.

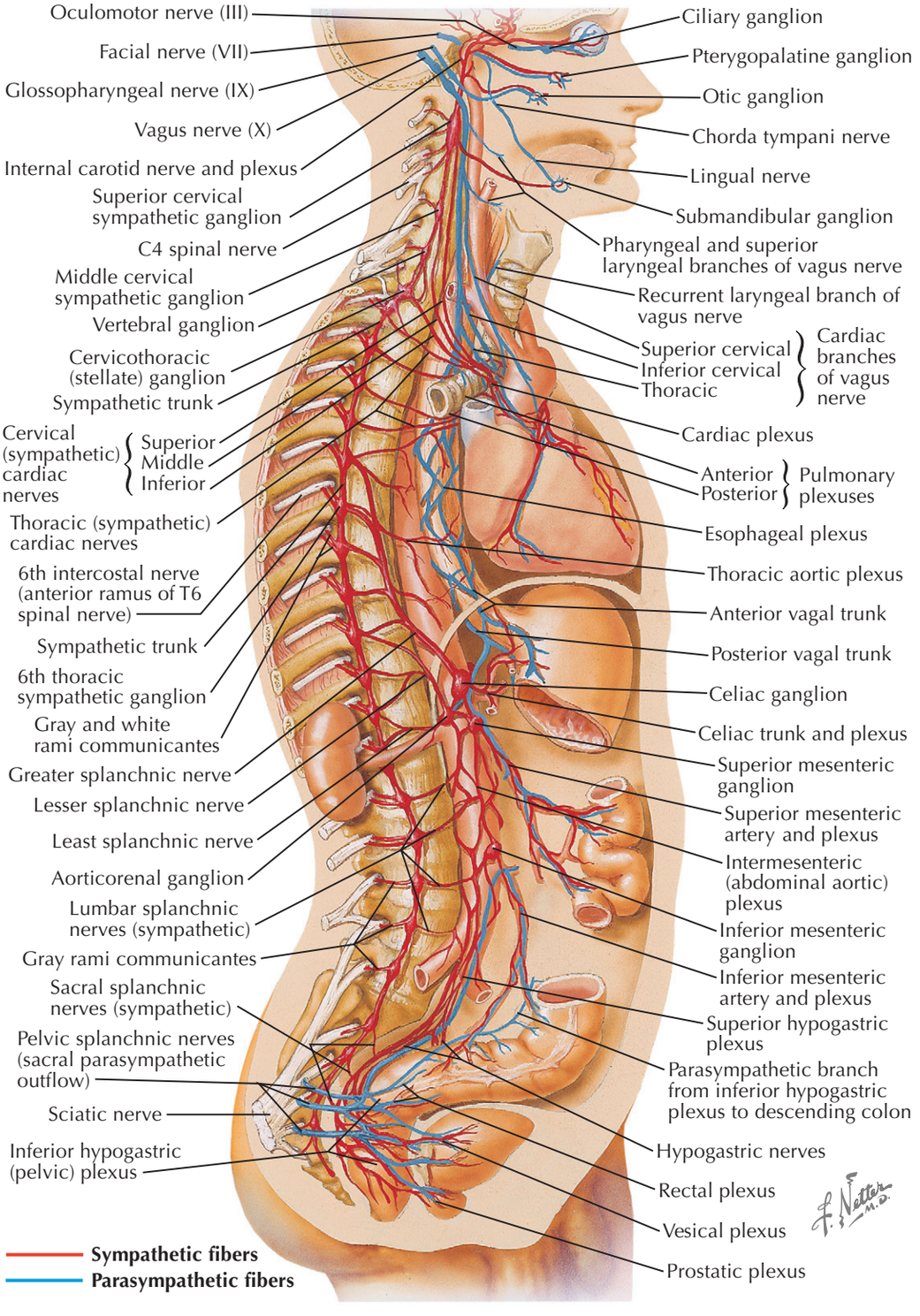
The central autonomic components include regions of the cerebral cortex, diencephalon, and brainstem. In the cerebral cortex, autonomic areas include the frontal premotor areas, telencephalic cortex in the hippocampus, insular cortex, anterior cingulate gyrus, and anteromedial prefrontal cortex. The central nucleus of the amygdala and the bed nucleus of the stria terminalis are known as the extended amygdala and modulate the autonomic responses to emotions.

The hypothalamus integrates autonomic and endocrine responses and includes nuclei in three functional zones: periventricular, lateral, and medial. Nuclei in the periventricular region control biologic rhythms; the suprachiasmatic nucleus, the pacemaker for the circadian rhythms, and the paraventricular nuclei are involved in endocrine responses by modulating the anterior pituitary. The lateral hypothalamic nuclei are involved in arousal and behavior, whereas the medial hypothalamic area, including the medial preoptic region, is involved in homeostatic functions such as thermoregulation. The periaqueductal gray nuclei of the midbrain integrate autonomic and behavioral response to nociceptive environmental stimuli. The parabrachial nucleus of the pons and the nucleus of tractus solitarius in the medulla are the principal relay nuclei in the control of cardiovascular, respiratory, and visceral function in response to environmental stimuli. The reticular formation of the anterolateral medulla contains the primary premotor neurons that control the respiratory motor neurons of the brainstem and cervical spinal cord as well as the sympathetic neurons in the intermediolateral column of the thoracic spinal cord.

These higher and lower levels of representation are interconnected by ascending and descending tracts, or pathways. For example, efferent autonomic inputs originating in the frontal premotor cortical areas descend through fasciculi, usually via synaptic relays in the thalamus, hypothalamus, and reticular formation, and end in certain cranial nerve nuclei and thus influence involuntary muscles, blood vessels, and exocrine and endocrine glands supplied by them. Other fibers descend still farther and form synapses with neurons in the intermediolateral columns in the thoracic and upper two lumbar spinal cord segments, and with neurons in the gray matter of the second to fourth sacral cord segments.

Afferents to the central autonomic area is conveyed by cranial and spinal pathways. Afferent innervation from baroreceptors, chemoreceptors, and pulmonary and gastrointestinal autonomic receptors is conveyed by

Autonomic Nervous System: General Topography



General Topography of Autonomic Nervous System *(Continued)*

the vagus and glossopharyngeal nerves to the nucleus of the tractus solitarius. The information is relayed from this nucleus to the more rostral autonomic centers; visceral input and taste are relayed to the anteromedial nucleus of thalamus and then to the insular cortex. Humoral signals are relayed to the central autonomic areas by the circumventricular organs that lack a blood-brain barrier, such as the subfornical organ, the lamina terminalis in the third ventricle, and the area postrema.

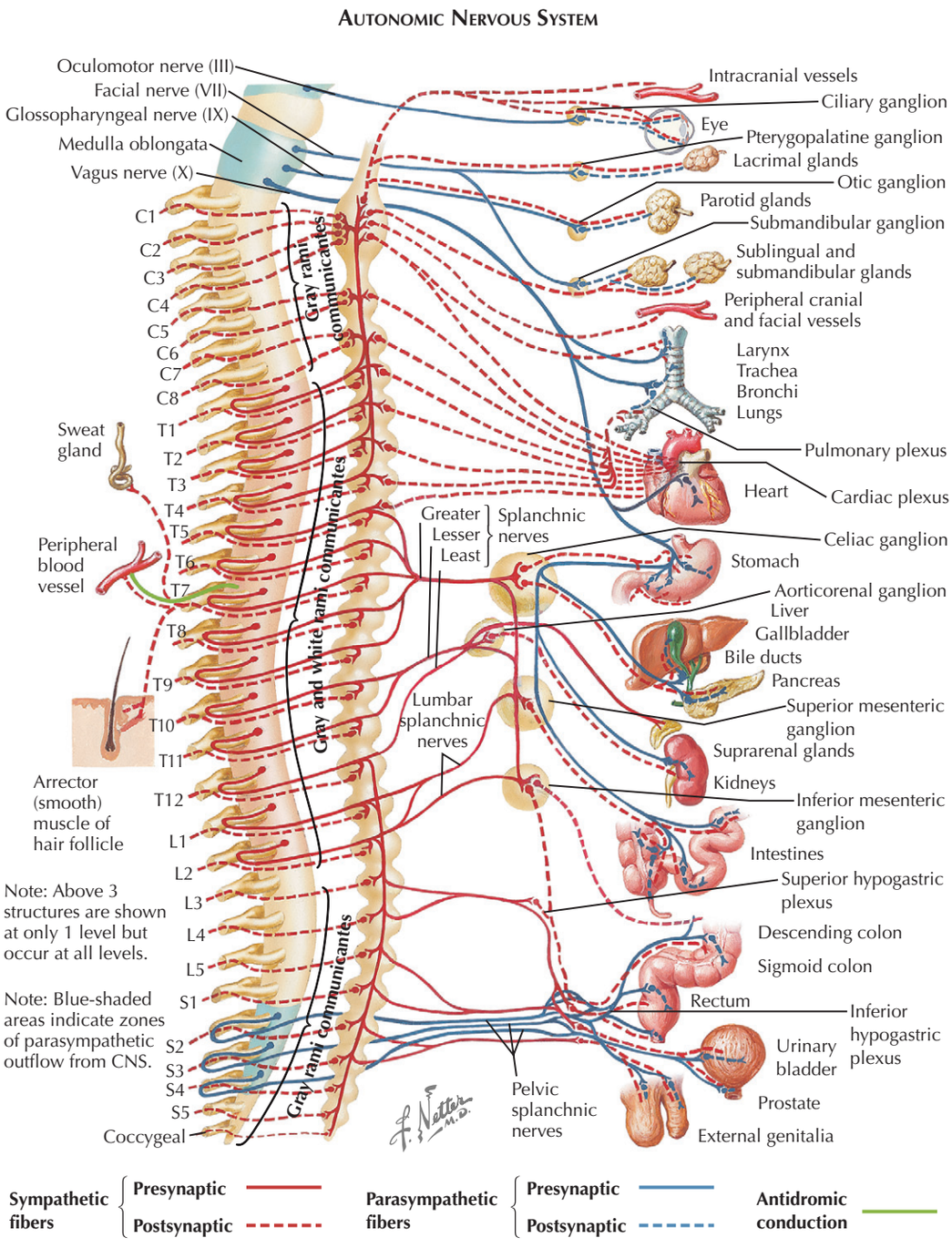
The peripheral parts of the autonomic nervous system include sympathetic ganglia and the paravertebral sympathetic trunks, which extend from the cranial base to the coccyx. Other sympathetic and parasympathetic ganglia include the ciliary, pterygopalatine, otic, submandibular, and carotid in the cranial region; prevertebral plexuses and ganglia, such as the cardiac, celiac, mesenteric, aortic, and hypogastric; plexuses located on or in the walls of viscera and vessels; and ganglia associated with the liver and adrenal gland.

The axons of autonomic neurons in the cranial nerve nuclei and sacral spinal segments usually produce effects opposite to those produced by the axons of neurons in the thoracolumbar intermediolateral cell columns. The cranial and sacral groups comprise the *parasympathetic system*, and the more numerous thoracolumbar groups, the *sympathetic system*. The neurons of sympathetic and parasympathetic systems are morphologically similar; they are smallish, ovoid, multipolar cells with myelinated axons and variable number of dendrites.

The axons of the autonomic nerve cells in the nuclei of the cranial nerves, in the thoracolumbar intermediolateral columns, and in the gray matter of the sacral spinal segments are termed preganglionic fibers and form synapses in peripheral ganglia. The axons of the ganglion cells are called postganglionic fibers; these unmyelinated axons convey efferent output to the viscera, vessels, and other structures.

The *cranial parasympathetic preganglionic fibers* form synapses in the ciliary, pterygopalatine, otic, submandibular, cardiac, and celiac ganglia, and in much smaller ganglia in the walls of the trachea, bronchi, and gastrointestinal tract. The corresponding sacral fibers form synapses in the inferior hypogastric (pelvic) plexuses, within the enteric plexuses of the distal colon and rectum, and in the walls of the urinary bladder and other pelvic viscera. Most of the *thoracolumbar sympathetic preganglionic fibers* synapse in sympathetic trunk ganglia, but some fibers pass through the sympathetic trunk ganglia to form synapses in other ganglia, such as the celiac, mesenteric, and renal.

Parasympathetic relay ganglia are located near the structures innervated or within the walls of hollow organs or solid viscera; therefore parasympathetic postganglionic fibers are relatively short. Sympathetic relay ganglia are generally more distant from the structures they innervate, so sympathetic postganglionic fibers are often much longer than their parasympathetic counterparts. Plate 7-2 illustrates the arrangement of the preganglionic and postganglionic fibers to all the important viscera, the positions of the ganglia in which the synaptic relays occur, and the consequent disparities in the lengths of the postganglionic fibers. For example, in the heart, sympathetic preganglionic fibers synapse with the neurons in the superior cervical to the fifth thoracic sympathetic ganglia; the relatively long postganglionic fibers are conveyed to the heart in the cervical and thoracic sympathetic cardiac nerves. The parasympathetic preganglionic fibers reach the heart in the cardiac branches of the vagus nerves and relay in ganglia of the cardiac plexus or in small subendocardial ganglia; their postganglionic fibers are relatively short.



AUTONOMIC REFLEX PATHWAYS

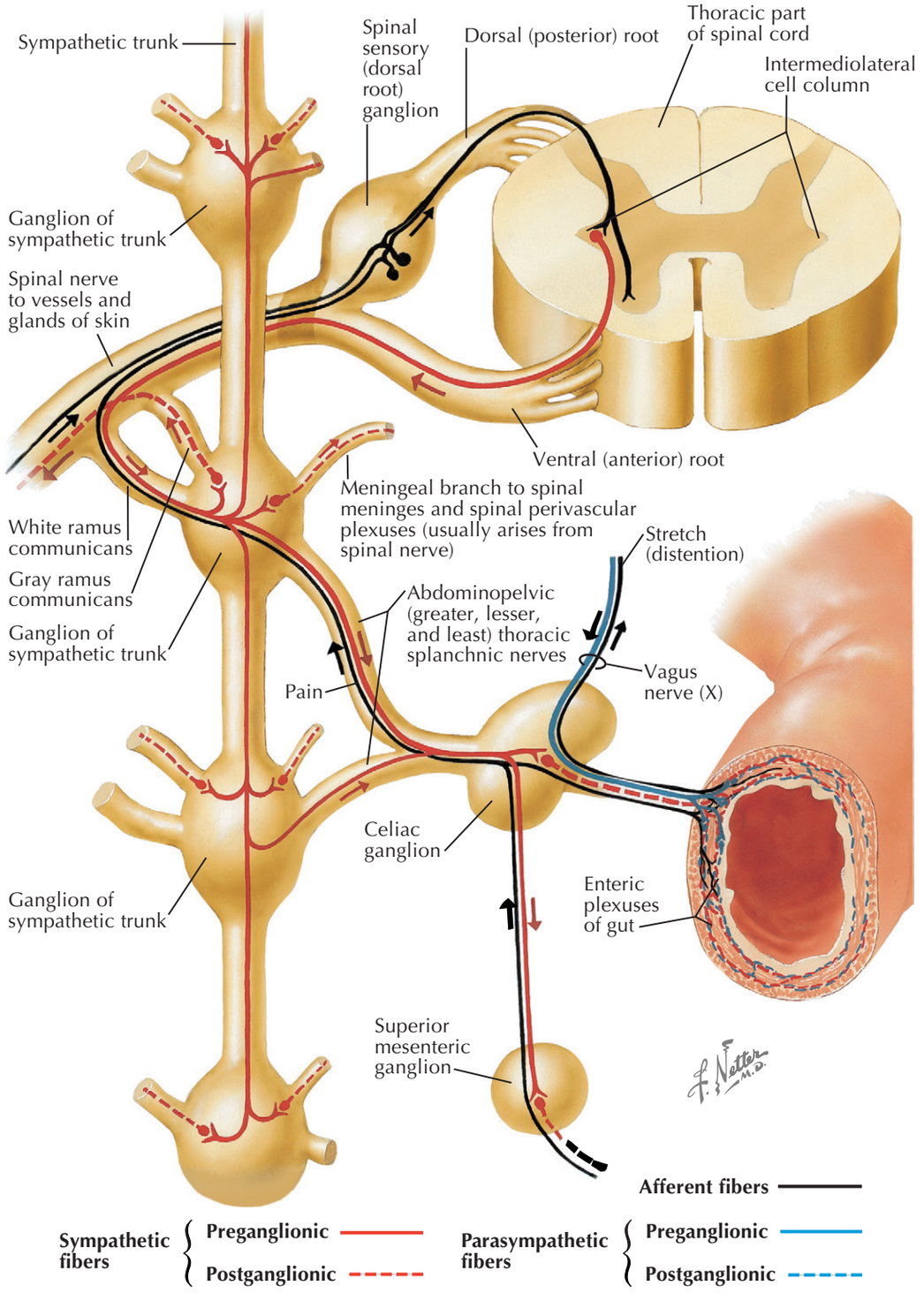
The illustration on the right shows the arrangement of a typical spinal autonomic reflex arc, in this example involving the enteric plexus in the gut. Similar reflex arcs exist in the brainstem.

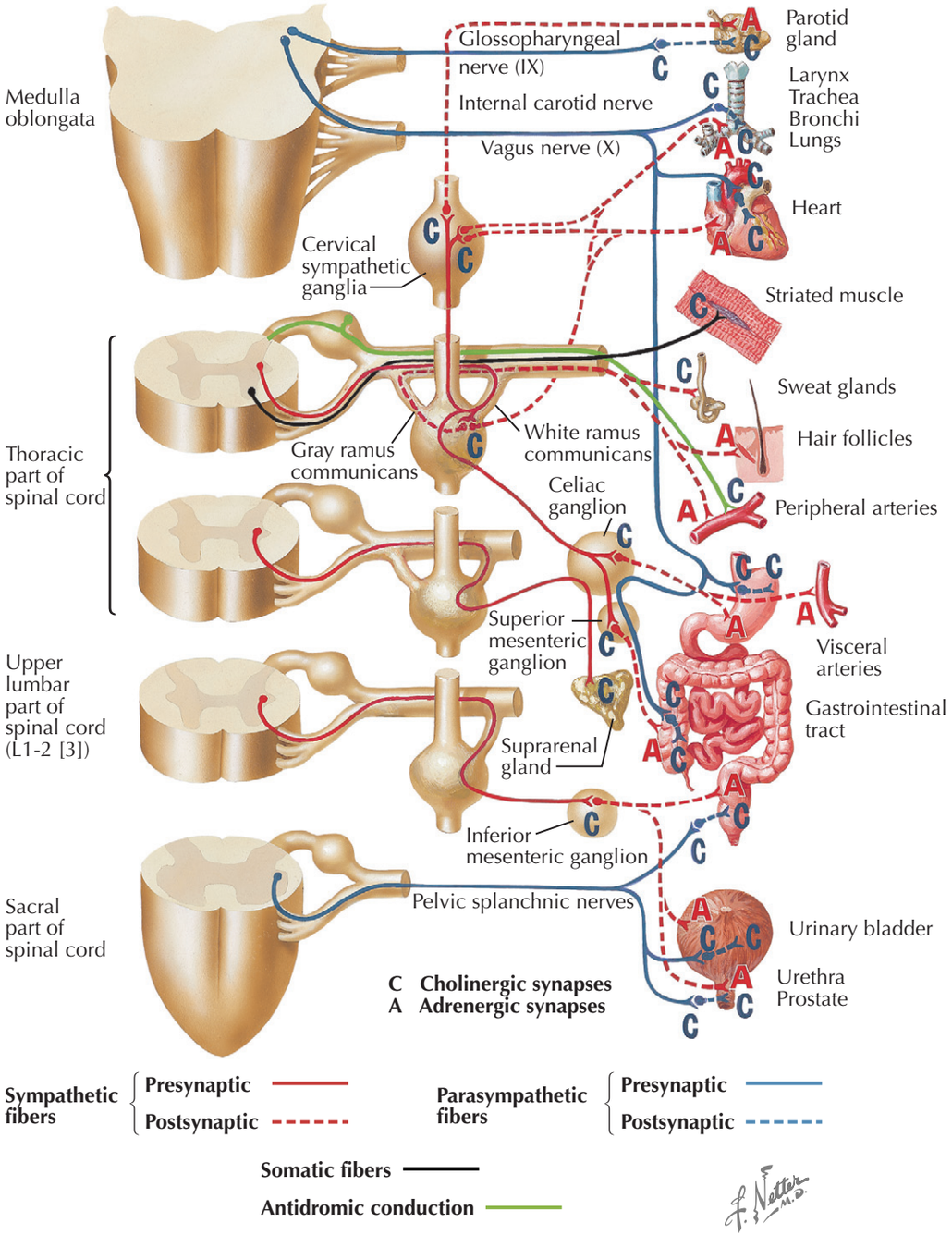
The autonomic reflex arc is similar to the somatic reflex arc, although, in the somatic arcs, the interneurons and their connections are entirely within the central nervous system (CNS). In the autonomic arcs, the interneurons are within the CNS, but their axons synapse outside the CNS to reach the ganglia in which they terminate. Initially, the autonomic and somatic components of the nervous system develop together, but during the embryonic and fetal phases, groups of nerve cells migrate outward along the spinal nerve roots and form ganglia, such as those of the sympathetic trunks, and more peripheral ganglia, such as the celiac and mesenteric (see Plate 7-13). These migrant cells are efferent autonomic neurons, and in order to maintain their synaptic relationships, the axons of the interneurons must follow them, to reach the autonomic ganglion cells with which they form synapses. These axons are termed *preganglionic fibers*, whereas the axons of ganglionic neurons lie beyond the ganglia and are called *postganglionic* fibers.

The preganglionic fibers are myelinated, and when seen together, as in the large groups of sympathetic preganglionic fibers passing from all the thoracic and the upper two lumbar spinal nerves to nearby sympathetic trunk ganglia, they are almost white in color and constitute the *white rami communicantes*. Afferent myelinated fibers pass through these rami to the spinal nerves and contribute to their whitish appearance. The postganglionic fibers are unmyelinated and appear grayish pink in color when seen in mass. They form the *gray rami communicantes* connecting each sympathetic trunk ganglion to the adjoining spinal nerves.

One part of a *parasympathetic arc (vagal)* is illustrated; the efferent preganglionic fibers arise from the dorsal vagal nucleus and reach the walls of the intestine by vagal branches that are part of, and synapse with cells in the ganglia forming the enteric plexus; postganglionic fibers innervate the intestines. The cell bodies of the afferent pseudounipolar neurons are also located in afferent ganglia of the enteric plexus and their central axonal processes travel to the brainstem in the vagal nerve to synapse with the neurons in the dorsal vagal nuclei.

The illustration also shows that sympathetic preganglionic fibers emerge through the anterior root of the thoracic or upper lumbar spinal nerves. They all pass through white rami communicantes to the adjacent sympathetic trunk ganglia. Many of these preganglionic fibers synapse with the cells of the ganglia; others pass upward or downward in the sympathetic trunks to form synapses with neurons in other cervical, lumbar, and sacral ganglia. Still other preganglionic fibers pass through the sympathetic trunk ganglia without relaying and run in splanchnic nerves to end in ganglia, such as the celiac and mesenteric or the adrenal medulla. The postganglionic axons all pass to adjacent spinal nerves as gray rami communicantes; this explains why all spinal nerves have gray rami communicantes, whereas white rami communicantes are limited to the thoracolumbar region. Also shown is the recurrent meningeal sympathetic branch carrying postganglionic fibers to the spinal meninges and the spinal perivascular plexuses.





Cholinergic and Adrenergic Nerves

The terms "adrenergic" and "cholinergic," introduced by Dale in 1933, are based on the concept that synaptic transmission between autonomic nerve fibers, and between the postganglionic axon and the structures they innervate, is effected by adrenergic or cholinergic chemicals.

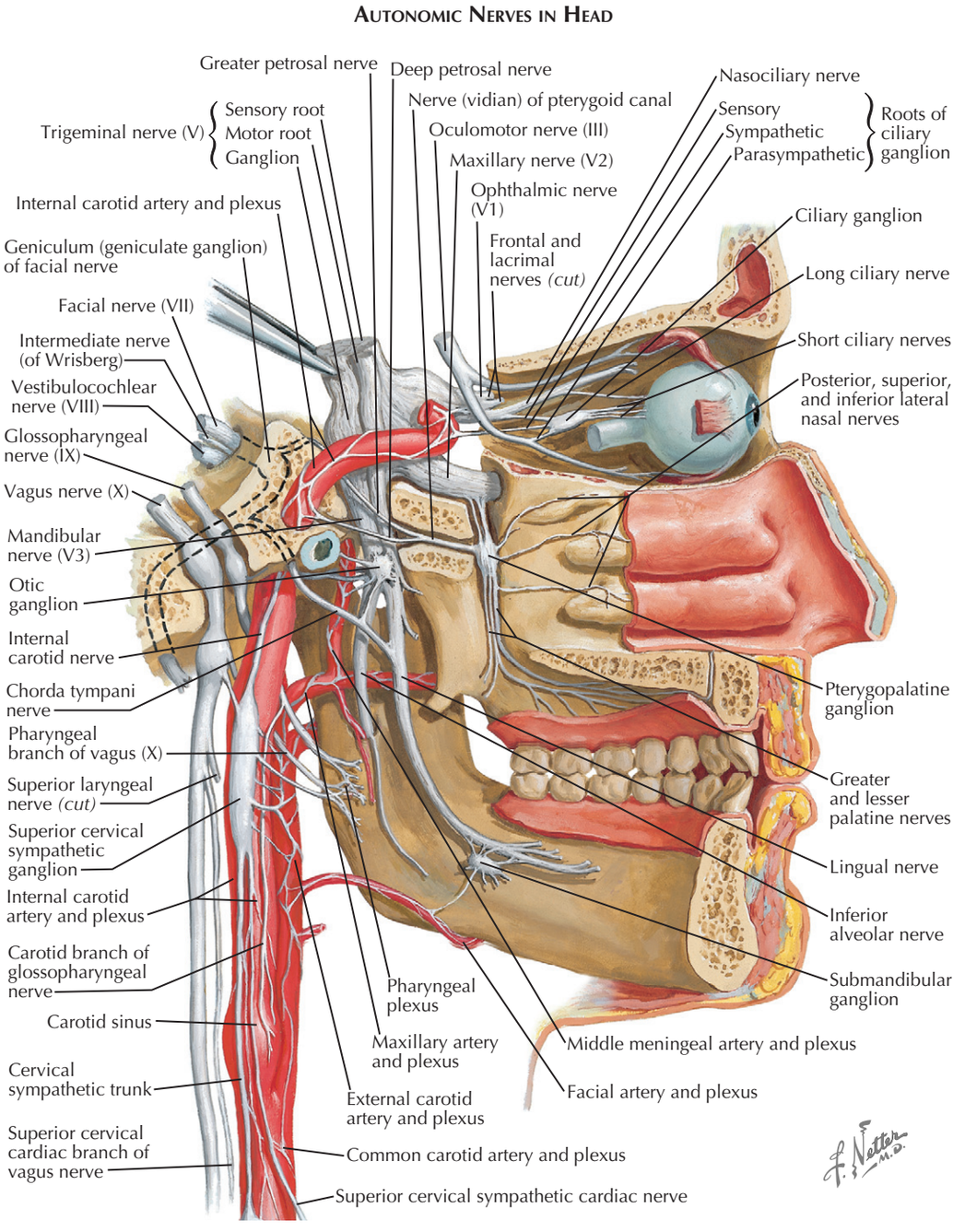
Epinephrine (adrenaline), and the closely related *norepinephrine* (noradrenaline), are the chief neurotransmitters at peripheral sympathetic or *adrenergic* terminations, whereas *acetylcholine* is generally associated with parasympathetic, or *cholinergic* effects. However, in reality, acetylcholine is an important neurotransmitter at synapses in both sympathetic and parasympathetic pathways. Dale's terms were initially applied only to *postganglionic fibers*; acetylcholine, in fact, is the chief neurotransmitter at synapses between *preganglionic fibers* and ganglionic neurons of both the sympathetic and parasympathetic systems.

The illustration shows the sites at which acetylcholine (C) and norepinephrine (A) are the chief neurotransmitters. Other chemical substances, such as adenosine triphosphate (ATP), gamma-aminobutyric acid (GABA), a polypeptide called substance P, histamine, glutamic acid, and prostaglandins have also been implicated as neurotransmitters.

Sympathetic or adrenergic efferent nerve fibers usually elicit active reactions in effector structures, such as smooth (unstriated) muscle or glands, which are the reverse of the diminished activity produced by parasympathetic, or cholinergic, fibers. Thus stimulation of the sympathetic and parasympathetic cardiac nerves produces cardiac acceleration and deceleration. However, these effects are not universal. For example, activity of the alimentary adrenergic nerves produces slowing of gastrointestinal motility; conversely, activity in the cholinergic supply results in acceleration of gastric and intestinal movements. Similar reactions occur in other structures. Thus in the urinary tract, the sympathetic nerves produce relaxation of the bladder wall, and the parasympathetic nerves cause contraction, so the former have been aptly described as "filling" and the latter as "emptying" nerves.

Sweat glands are classified as apocrine or eccrine glands. The apocrine glands open into the lumen of the sweat glands in the axilla, perineum, and periareolar region and are innervated by adrenergic fibers and probably respond to humoral epinephrine. The eccrine sweat glands open directly into the skin and are innervated by sympathetic postganglionic fibers that are cholinergic. Eccrine glands are one of the most important skin appendages and play a vital role in temperature regulation.

Autonomic Nerves in Head and Neck



The cervical part of each sympathetic trunk generally has four ganglia: *superior* and *middle cervical*, *vertebral*, and *cervicothoracic*. The superior and middle cervical ganglia are usually connected by a single cord, but the middle cervical, vertebral, and cervicothoracic ganglia are connected by several cords, one or more of which form a loop, the ansa subclavia, around the subclavian artery and sometimes also around the vertebral artery. A true inferior cervical ganglion is present only in about 20% of individuals; in the majority, the lowest cervical and uppermost thoracic ganglia are fused to form the cervicothoracic (stellate) ganglion.

The superior cervical ganglion is fusiform in shape. It is produced by the coalescence of the upper three or four cervical ganglia. The preganglionic fibers emerge through the uppermost thoracic spinal nerves and ascend to it as the cervical sympathetic trunk; a relatively small number of these fibers are from adjacent cervical nerve roots. A small proportion of the preganglionic fibers pass through it without interruption and relay at higher levels in the internal carotid ganglia.

The superior cervical ganglion receives and supplies communicating, visceral, vascular, muscular, osseous, and articular rami. It communicates with the last four cranial nerves or their branches, with the vertebral arterial plexus and, occasionally, with the phrenic nerve. It supplies gray rami to the upper three or four cervical spinal nerves, and the contained postganglionic fibers are distributed with the branches of the cervical nerves. *Visceral fibers* pass to the larynx, pharynx, and heart, and other fibers are carried in vascular plexuses to the salivary, lacrimal, pituitary, pineal, thyroid, and other glands. *Vascular fibers* are supplied to the internal and external carotid arteries and form plexuses around them; nerve continuations from these plexuses form subsidiary plexuses around all their branches. From the internal carotid plexus, minute caroticotympanic offshoots join the tympanic branch of the glossopharyngeal nerve and thus reach the tympanic plexus. A deep petrosal branch unites with the greater petrosal nerve to form the *nerve of the pterygoid canal*, which constitutes the *sympathetic root of the pterygopalatine ganglion*. The sympathetic fibers are postganglionic and run through the ganglion without relaying, to be distributed to vessels and glands in the nose, palate, nasopharynx, and orbit. The *sympathetic root of the ciliary ganglion* arises from the cranial end of the ipsilateral internal carotid nerves or plexus; its fibers are postganglionic, having relayed in the superior cervical or internal carotid ganglia; they pass through the ganglion and run onward in the ciliary nerves to supply the ocular vessels and the dilator pupillae. In addition to postganglionic efferent fibers, many *visceral efferent* and *afferent fibers* are also present in the vascular plexuses. They convey sympathetic efferent output to the pituitary, lacrimal, salivary, thyroid, and other smaller glands in the territories supplied by the carotid arteries, and they also transmit sensory information from the same structures. In a similar fashion, sympathetic fibers are carried to adjacent *osseous*, *articular*, and *muscular* structures.

The middle cervical ganglion is much smaller than the superior ganglion and usually represents fused fifth and sixth cervical ganglia. It contributes gray rami communicantes to the fifth and sixth cervical nerves and sends fibers to the vertebral periarterial plexus. Inconstant strands form interconnections with the vagus, phrenic, and recurrent laryngeal nerves, and *visceral branches* are supplied to the thyroid and parathyroid glands. The ganglion may give off the middle cervical sympathetic cardiac nerve and contributes several twigs

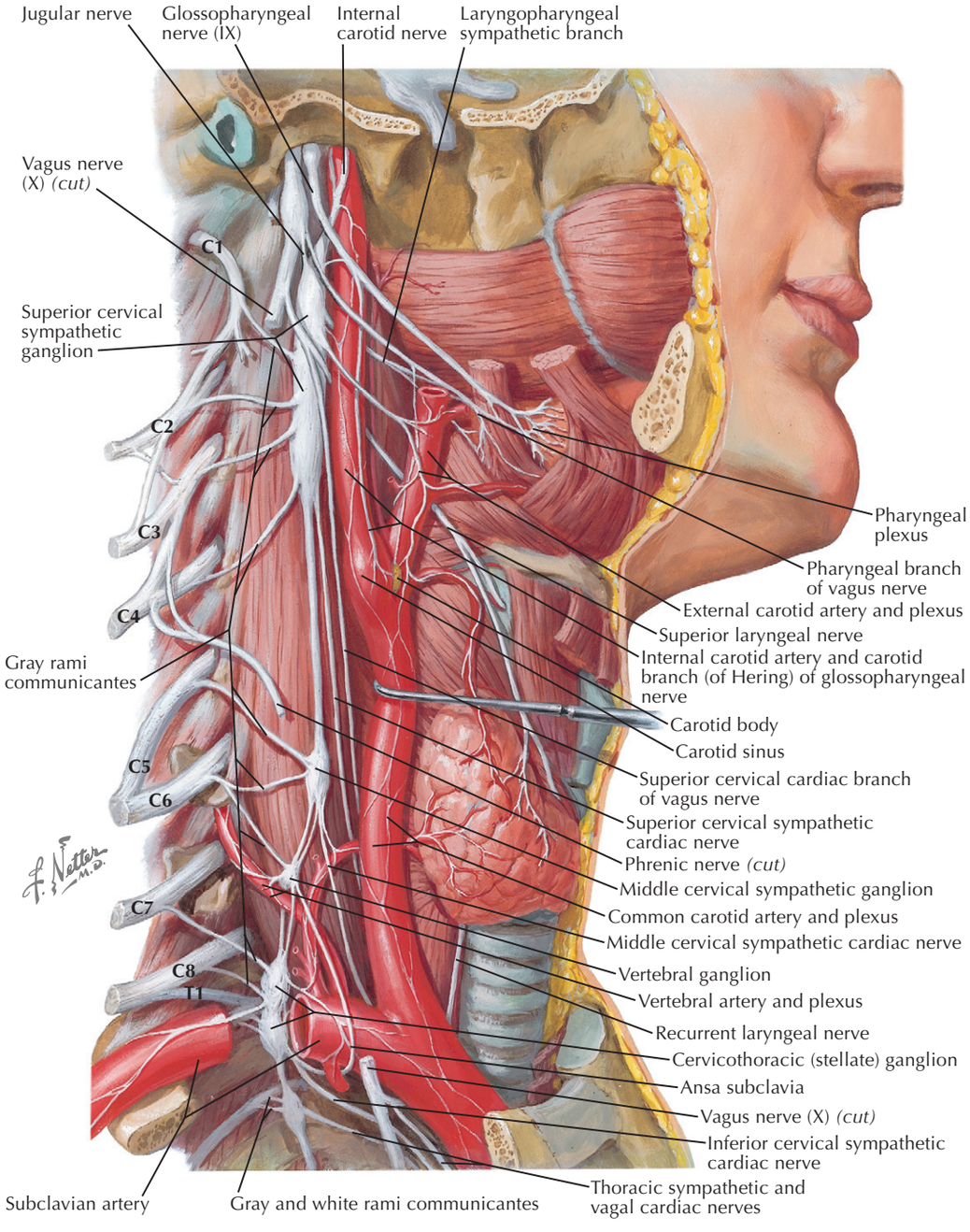
Autonomic Nerves in Head and Neck *(Continued)*

to the esophagus and trachea. *Vascular branches* help in the innervation of the common carotid, inferior thyroid and vertebral arteries and the jugular veins. Fibers pass to adjacent muscular, osseous, and articular structures, usually alongside the arteries supplying them.

The vertebral ganglion is small and is located anterior to the vertebral artery, near its point of entry into the transverse foramen of the sixth cervical vertebra. It may receive gray rami communicantes from the sixth and/or seventh cervical nerves, and thus may represent a detached element of the middle cervical ganglion or the cervicothoracic ganglion. It gives off *vascular branches* that accompany the vertebral artery; it may be connected by fibers to the vagus and phrenic nerves; and it supplies tiny *visceral branches* to the thyroid gland, trachea, and esophagus.

The cervicothoracic (stellate) ganglion is formed by the fusion of the seventh and eighth cervical ganglia with the first and/or second thoracic ganglia. It is an irregularly fusiform structure with many radiating branches. The cervicothoracic ganglion is situated posterior to the first part of the subclavian artery, the origin of the vertebral artery, the vertebral vein, and the apex of the lung. It lies anterior to the last cervical transverse process, the neck of the first rib, and the anterior primary ramus of the eighth cervical nerve as it passes outward to unite with the corresponding ramus of the first thoracic nerve to form the inferior trunk of the brachial plexus. The vertebral vessels run over the upper pole of the ganglion, and the superior intercostal vessels run lateral to it at the level of the neck of the first rib. An aponeurotic slip from the scalene muscles spreads out to become attached to the suprapleural membrane and may veil the ganglion during the anterior operative approach. If a scalenus minimus is present, it may also obscure the ganglion.

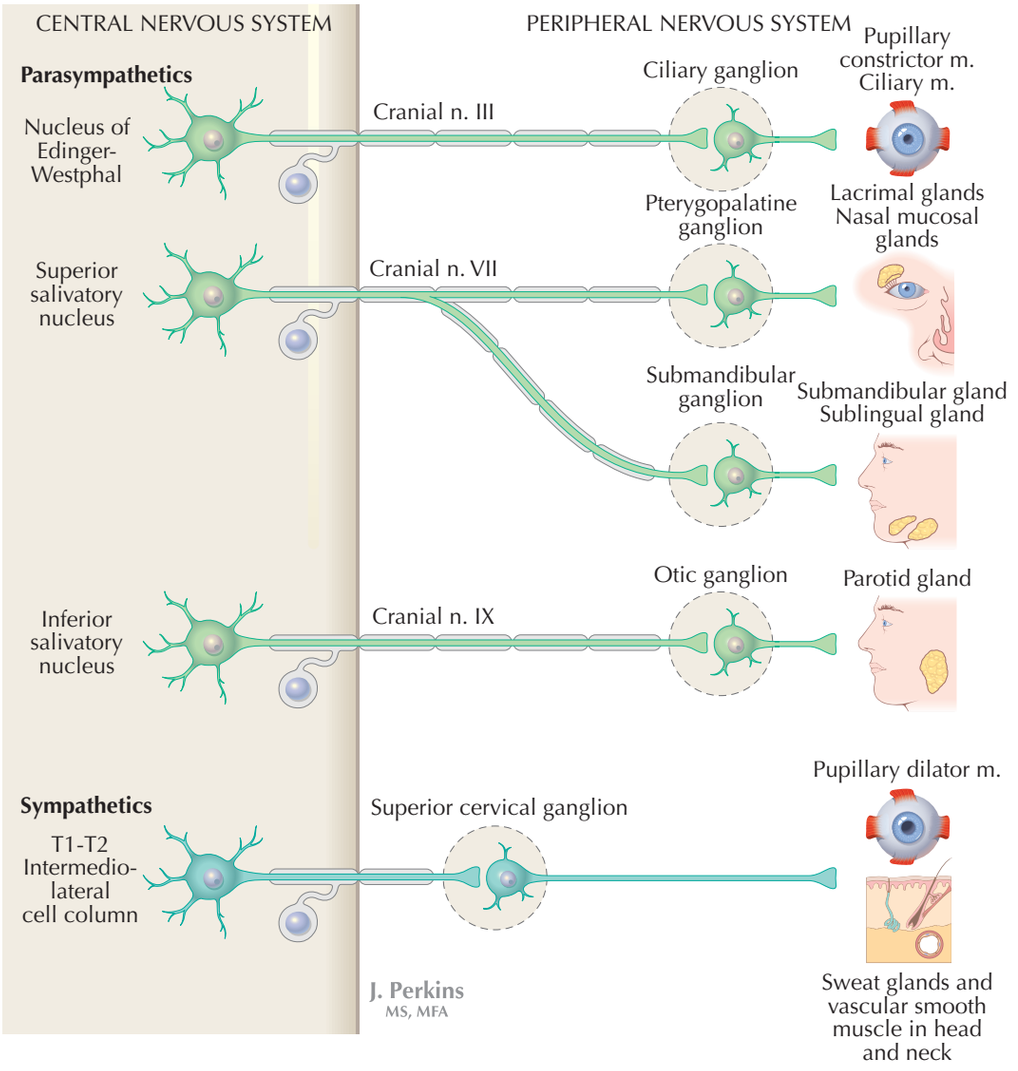
Autonomic Nerves in Neck



The cervicothoracic ganglion receives white rami communicantes from the first and second thoracic nerves and sends gray rami communicantes to the eighth cervical and first thoracic nerves and, occasionally, to the seventh cervical and second thoracic nerves. These rami carry efferent and afferent sympathetic fibers to and from the brachial plexus and the uppermost intercostal nerves, thus helping to innervate *vessels*, *sweat glands*, *arrectores pilorum*, *bones*, and *joints* in the upper limbs and superior parts of the chest wall. The ganglion or the ansa subclavia invariably communicate with the ipsilateral phrenic nerve, and almost constantly with the vagus or the recurrent laryngeal nerve. Fibers are supplied to the heart, esophagus, trachea, and thymus. Some vascular fibers from the ganglion pass directly to the large vessels in the cervicothoracic inlet, but most of the sympathetic fibers for the upper limb structures enter the inferior trunk of the brachial plexus. They pass mainly into the medial cord of the plexus and then into the median and ulnar nerves and, to a lesser extent, into the axillary, radial, musculocutaneous, and other branches of the plexus. Vasomotor and sudomotor disturbances, or causalgia, are therefore most likely to follow irritation or injury to the inferior trunk of the brachial plexus or to the ulnar or median nerves.

Most of the preganglionic fibers for the upper limbs emerge through the anterior rami of the second to sixth or seventh thoracic nerves, and the second and third nerves probably contain the majority of the fibers.

Autonomic Distribution to the Head and the Neck



Autonomic Innervation of Eye

The eye receives a rich innervation by the sympathetic and parasympathetic systems.

Sympathetic Fibers

The sympathetic *preganglionic fibers* for the eye arise from the intermediolateral column of the thoracic cord and travel in the ipsilateral first, second, and, occasionally, in the third thoracic spinal nerves. They pass through white rami communicantes to the sympathetic trunks; the fibers ascend to the superior cervical ganglion where they relay, although a few synapse higher in the internal carotid ganglia. The *postganglionic fibers* run either in the internal carotid plexus and enter the orbit through its superior fissure, or else they run alongside the ophthalmic artery in its periarterial plexus. Some of the ocular sympathetic fibers may make a detour through the caroticotympanic nerves and tympanic plexus before rejoining the cavernous part of the internal carotid plexus by means of a branch that emerges from the anterior surface of the petrous part of the temporal bone near the greater petrosal nerve; thereafter, they accompany the other ocular fibers.

Some of the branches passing through the superior orbital fissure form the *sympathetic root of the ciliary ganglion*; their contained fibers pass through it without relaying to become incorporated in the 8 to 10 *short ciliary nerves*. Other branches join the ophthalmic nerve or its nasociliary branch and reach the eye in the two to three *long ciliary nerves* that supply the radial musculature in the iris (dilator pupillae). Both long and short ciliary nerves also contain afferent fibers from the cornea, iris, and choroid. Fibers conveyed in the short ciliary nerves pass through a communicating ramus from the ciliary ganglion to the nasociliary nerve; this ramus is called the *sensory root of the ciliary ganglion*. The parent cells of these sensory fibers are located in the trigeminal (semilunar) ganglion, and their central processes end in the *sensory trigeminal nuclei* in the brainstem. The sensory trigeminal nuclei have multiple interconnections with other somatic and autonomic centers and thus influence many reflex reactions. Other sympathetic fibers from the internal carotid plexus reach the eye through the ophthalmic periarterial plexus and its subsidiary plexuses around the central retinal, ciliary, scleral and conjunctival arteries (see Plate 7-5).

Parasympathetic Fibers

The parasympathetic preganglionic fibers for the eye are the axons of cells in the *autonomic, (Edinger-Westphal) oculomotor nucleus*. They run in the third cranial nerve and exit in the *motor root of the ciliary ganglion*, where they relay. The axons of these ganglionic cells are postganglionic parasympathetic fibers, which reach the eye in the *short ciliary nerves* and are distributed to the constrictor fibers of the iris (sphincter pupillae), to the ciliary muscle, and to the blood vessels in the eyeball.

Visual Centers

The visual reflex centers are located in the tectal and pretectal areas of the mesencephalon. They are connected to the lateral geniculate bodies (lower visual centers) and to the superior colliculi in which the *tectospinal tracts* originate; these connections provide the anatomic basis for the reflex movements of the head and eyes in response to visual stimuli. The light and accommodation reflexes are affected through pretectal

Autonomic Innervation of Eye *(Continued)*

connections. Fibers from the lateral geniculate bodies are connected through synapses in pretectal nuclei to the accessory oculomotor nucleus (Edinger-Westphal nuclei), which controls the sphincter pupillae and the ciliary muscle.

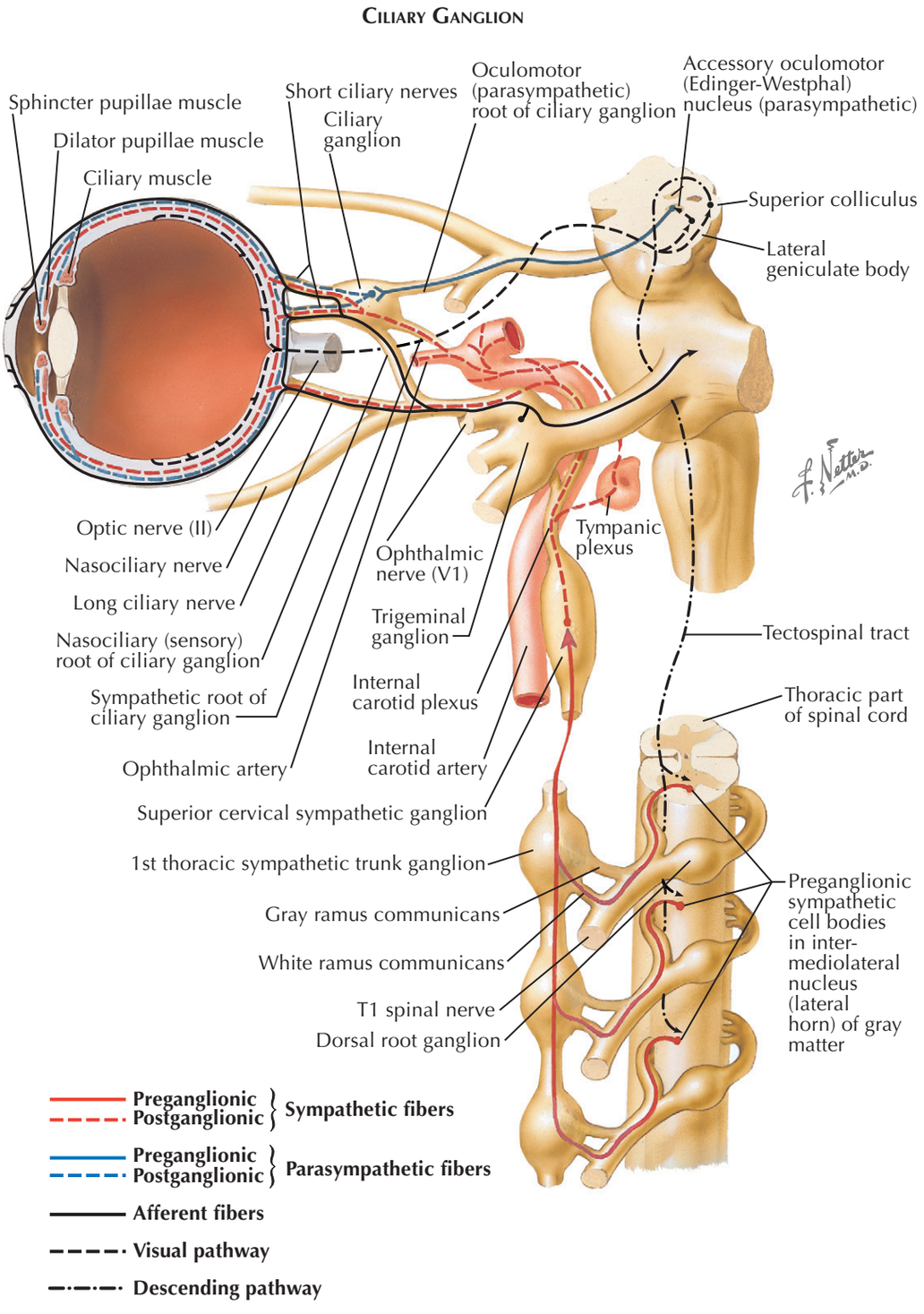
PUPILLARY LIGHT REFLEX

Light causes pupillary constriction, miosis. The impulse generated by the light travels from the retina by the optic nerve and optic tract to bilateral pretectal nuclei in the midbrain, decussating in the posterior commissure. The axons from the pretectal nuclei terminate in the accessory oculomotor nuclei. Preganglionic parasympathetic information travels via the oculomotor nerve to the ciliary ganglion. Postganglionic fibers from the ciliary ganglion traverse the short ciliary nerves to innervate the sphincter pupillae muscle of the iris. If one eye is stimulated by light, both pupils will react; ipsilateral (direct response) and contralateral (consensual response) pupils both respond because of the termination of the fibers of the optic tract in the pretectal nuclei bilaterally.

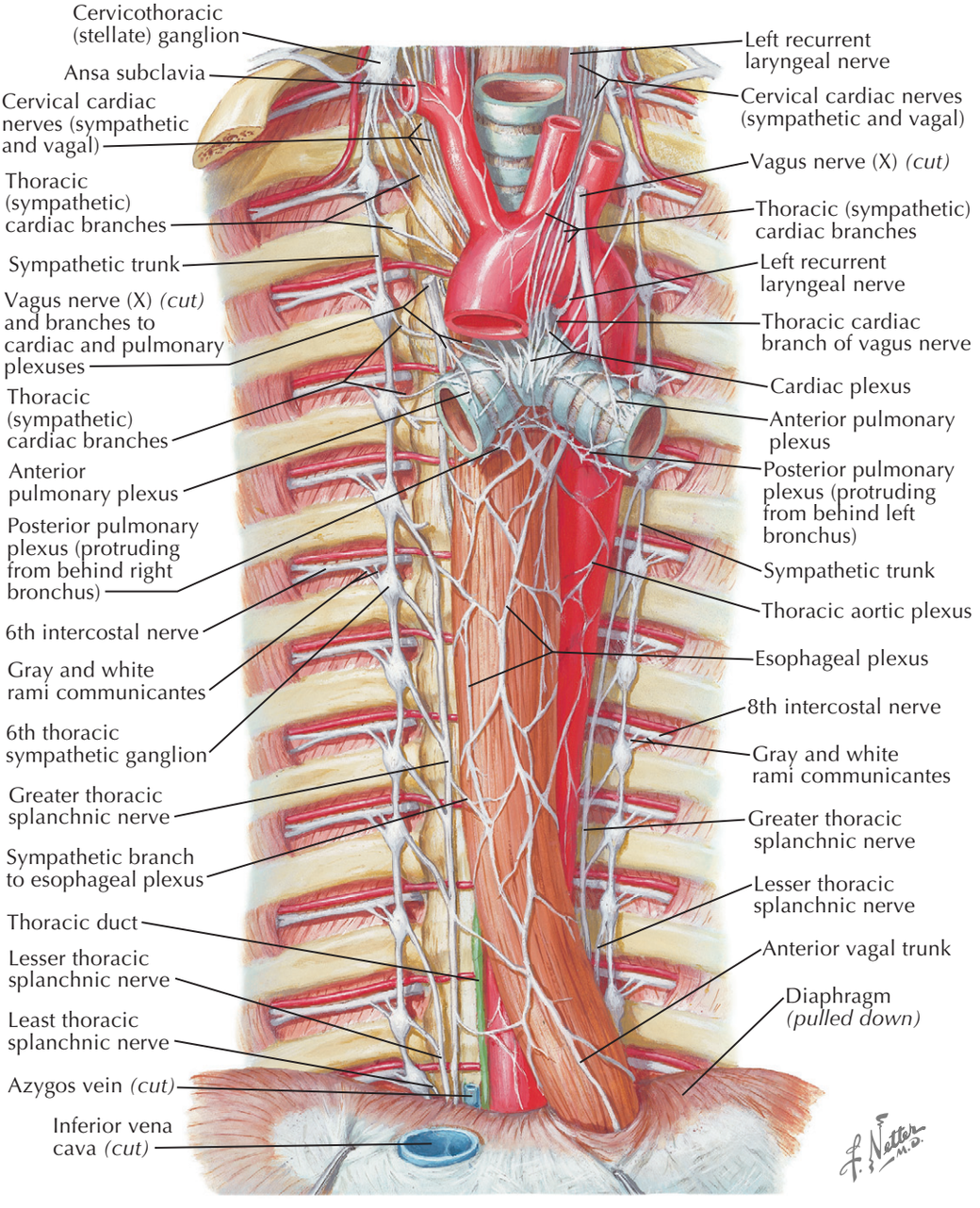
Dilation of the pupil, mydriasis, occurs due to postganglionic sympathetic innervation from the superior cervical ganglion. Preganglionic fibers arise from the neurons first and second thoracic intermediolateral column and by the upper thoracic spinal nerves, and white rami communicantes reach the superior cervical ganglion. From there, they traverse the long ciliary nerves to the dilator pupillae. Pupils also dilate in response to pain, presumably due to fibers from the sensory system reaching the preganglionic neurons (pupillary skin reflex).

ACCOMMODATION REFLEX

In viewing objects that are near, the pupils constrict, the eyes move medially, and the lens changes shape to become more convex. The reflex for this begins in the retina, and then involves the optic nerve, optic tract, lateral geniculate bodies, optic radiations, and visual cortical centers. From there, the impulse is thought to reach the "near response neurons" in the pretectal nuclei by corticotectal fibers. From the pretectal nuclei, the information reaches the oculomotor nuclei. The parasympathetic fibers reach the sphincter pupillae via the ciliary ganglion and short ciliary nerves. The parasympathetic fibers cause stimulation of the ciliary muscles, which causes relaxation of the zonule, and the lens becomes more spheric; the medial recti are activated by the ventral oculomotor nuclei, causing the eyes to converge.



Thoracic Sympathetic Chain and Splanchnic Nerves



Autonomic Nerves in Thorax

The thoracic parts of the sympathetic trunks lie anterior to the junctions between the heads and necks of the ribs and posterior to the pleura. There are usually 10 or 11 ganglia on each side; the first is often incorporated into the cervicothoracic (stellate) ganglion (see Plate 7-6), and the last thoracic and first lumbar ganglia may also be united. The interganglionic cords are usually single, but double or triple cords between some adjacent ganglia are not uncommon. The thoracic trunks supply or receive communicating, visceral, vascular, muscular, osseous, and articular branches.

Each ganglion receives at least one white ramus communicans and contributes at least one gray ramus to the adjacent spinal nerve, although several white and gray rami communicantes may be attached to each ganglion. Visceral branches are supplied to the heart and pericardium, lungs, trachea and bronchi, esophagus, and thymus.

Sympathetic Cardiac Nerves. Three pairs of sympathetic cardiac nerves arise from the cervical trunk ganglia, and the others emerge from the upper thoracic ganglia.

The *superior cervical sympathetic cardiac nerves* originate from the corresponding trunk ganglia. On the right, the nerve passes posterolateral to the brachiocephalic artery and aortic arch; on the left, it curves downward over the left side of the aortic arch to reach the cardiac plexus.

The *middle cervical sympathetic cardiac nerves* are usually larger than the corresponding superior and inferior nerves. They arise from the middle cervical and vertebral ganglia of the sympathetic trunks and usually run independently to the cardiac plexus.

The *inferior cervical sympathetic cardiac nerves* consist of fibers arising from the cervicothoracic ganglia and subclavian ansae.

The *thoracic sympathetic cardiac nerves* are four or five slender branches, which run forward and medially from the thoracic trunk ganglia to the cardiac plexus.

Parasympathetic Cardiac Nerves. Three pairs of parasympathetic (vagal) cardiac nerves are usually present. The *superior cervical vagal cardiac branches* leave the vagus nerves in the upper part of the neck. The *inferior cervical vagal cardiac branches* arise in the lower third of the neck and descend posterolateral to the brachiocephalic artery and aortic arch on the right side; on the left side, they descend lateral to the left common carotid artery and aortic arch. The *thoracic vagal cardiac branches* arise at or below the level of the thoracic inlet.

Multiple interconnections exist between all the sympathetic and parasympathetic cardiac nerves and between the cardiac and other visceral branches of the sympathetic trunks.

Other thoracic sympathetic branches supply the thoracic viscera from the paired greater, lesser, and lowest thoracic splanchnic nerves, although these are mainly destined to supply abdominal structures and contain a mixture of preganglionic, postganglionic, and afferent fibers. The *greater (major) splanchnic nerve* lies medial to the ipsilateral sympathetic trunk and enters the abdomen by piercing the crus of the diaphragm. The *lesser (minor) splanchnic nerve* lies slightly lateral to the greater splanchnic nerve and also usually pierces the diaphragmatic crus. The *lowest (imus) splanchnic nerve* is inconstant.

Minute twigs from the sympathetic trunks join and innervate the intercostal arteries. Other sympathetic postganglionic fibers reach these vessels in fascicles from adjacent intercostal nerves or their branches, and these also carry sudomotor and pilomotor fibers.

The muscular, osseous, and articular fibers from the thoracic sympathetic trunks and their branches supply the adjacent structures concerned; their exact functions are uncertain.

Innervation of Heart

The heart is supplied by sympathetic nerves arising mainly in the neck because the heart develops initially

Autonomic Nerves in Thorax
(Continued)

in the cervical region and later migrates into the thorax, taking its nerves down with it. The parasympathetic supply is conveyed in cardiac branches of the vagus nerves.

The *sympathetic preganglionic cardiac fibers* leave the spinal cord in the anterior roots of the upper four to five thoracic spinal nerves and enter the white or mixed rami communicantes passing to adjacent thoracic sympathetic trunk ganglia. Some of the fibers relay here; others ascend in the trunks to form synapses in the cervical ganglia, giving rise to the *cardiac nerves* (see earlier discussion). Most cardiac fibers are postganglionic and pass through the cardiac plexus without relaying, to be distributed to the heart wall and its vessels via the *coronary plexuses*.

The *parasympathetic preganglionic (vagal) fibers* are the axons of cells in the dorsal vagal nucleus. From the vagal cardiac nerves, they relay in ganglia of the *cardiac plexus* or in *intrinsic cardiac ganglia*, which are located mainly in the atrial subepicardial tissue along the coronary sulcus and around the roots of the great vessels. The sinoatrial node and the atrioventricular node and bundle have a rich supply of parasympathetic innervation. Ventricular ganglia are scanty, but enough of them exist to cast doubts on the hypothesis that ventricular innervation is purely sympathetic.

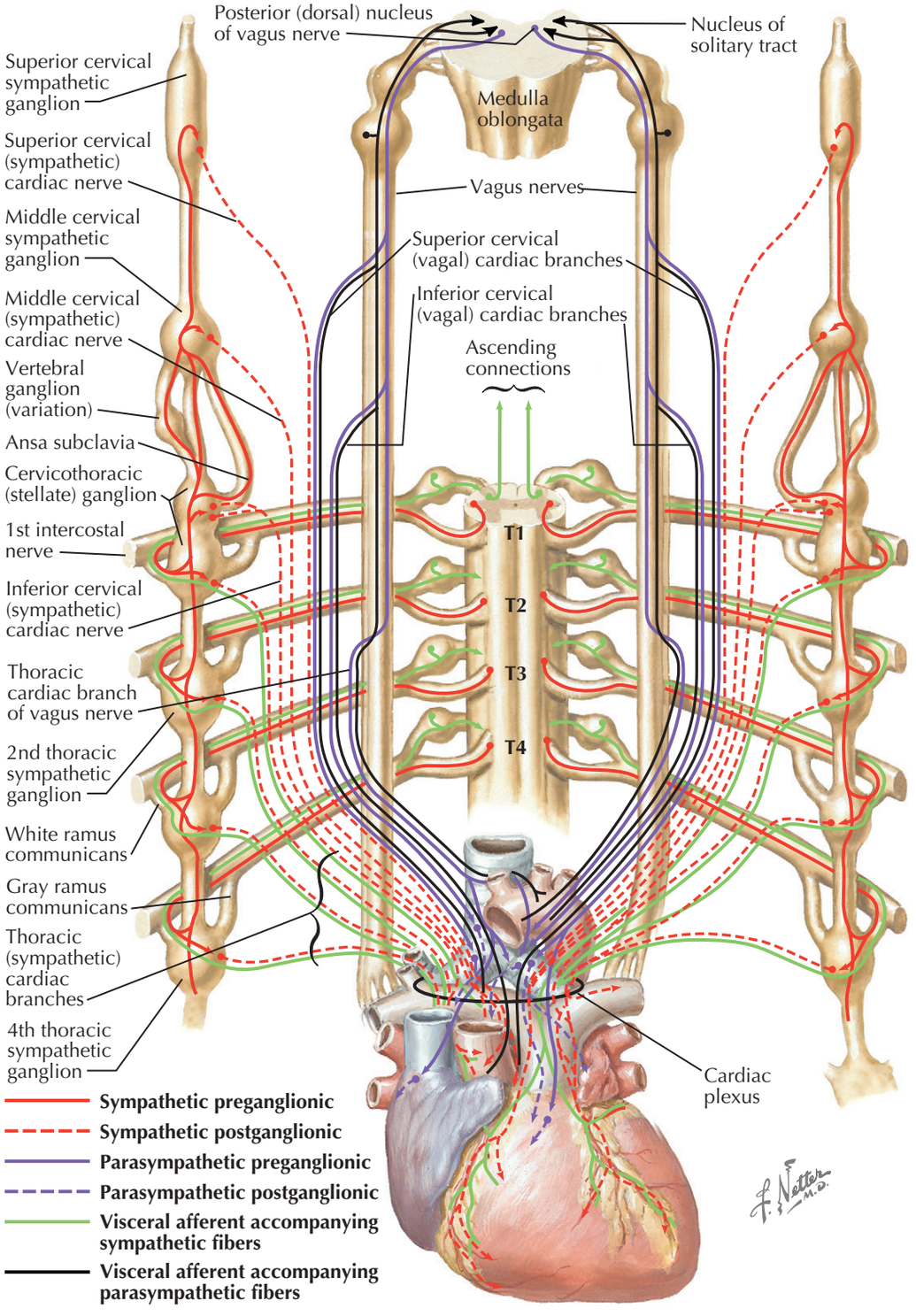
The more important afferent and efferent pathways in cardiac innervation are shown in the illustration. The peripheral processes of the afferent pseudounipolar neurons in the posterior root ganglia transmit input from cardiac receptors of various types and from terminal nerve networks in reflexogenic zones, such as those in and around the large cardiac venous openings, the interatrial septum, and the ascending aorta. Some of their central processes are implicated in spinal reflex arcs, whereas others ascend to the dorsal vagal nuclei in the medulla oblongata, the nearby reticular formation, or the hypothalamus and frontal cortex.

The thoracic sympathetic cardiac nerves carry many *afferent pain fibers* from the heart and great vessels, and this endows them with a clinical interest disproportionate to their small size, because their surgical destruction produces alleviation of angina pectoris. Other cardiac pain afferents run in the middle and inferior cervical sympathetic cardiac nerves; however, after entering the corresponding cervical ganglia, they descend within the sympathetic trunks to the thoracic region before passing through rami communicantes to the upper four or five thoracic spinal nerves.

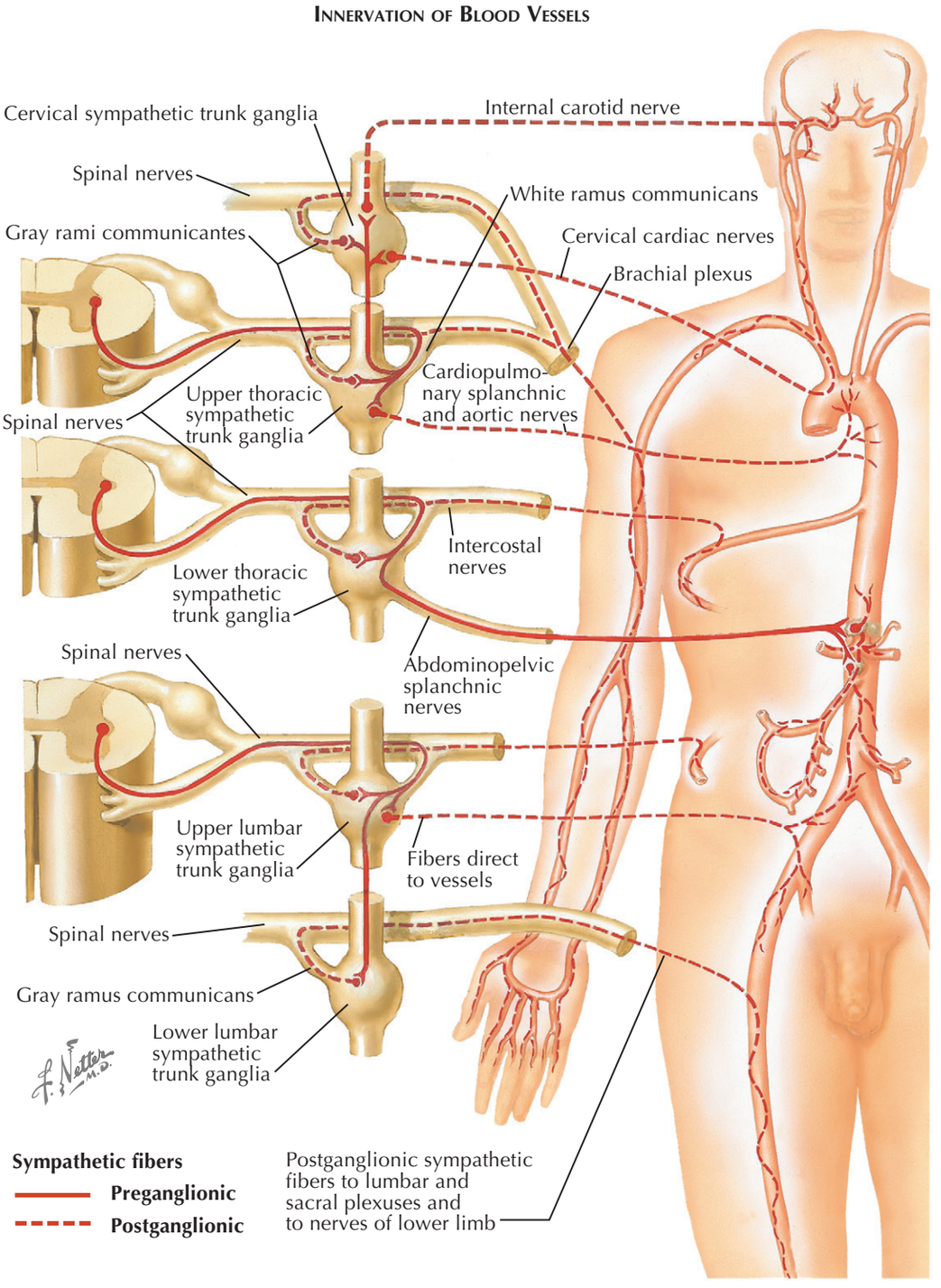
Afferent vagal fibers from the heart and vessels play an important role in modifying efferent output that adjusts the rate and strength of the heartbeat; usually, they depress cardiac activity. In humans, the afferent vagal information pass through cardiac branches of the recurrent laryngeal nerves to the main vagus nerves, and thus to the brainstem.

Afferent pericardial fibers from the fibrous and parietal serous pericardium are carried mainly in the phrenic nerves, but those from the visceral serous pericardium join the coronary arterial plexuses.

Innervation of Heart



Innervation of Blood Vessels

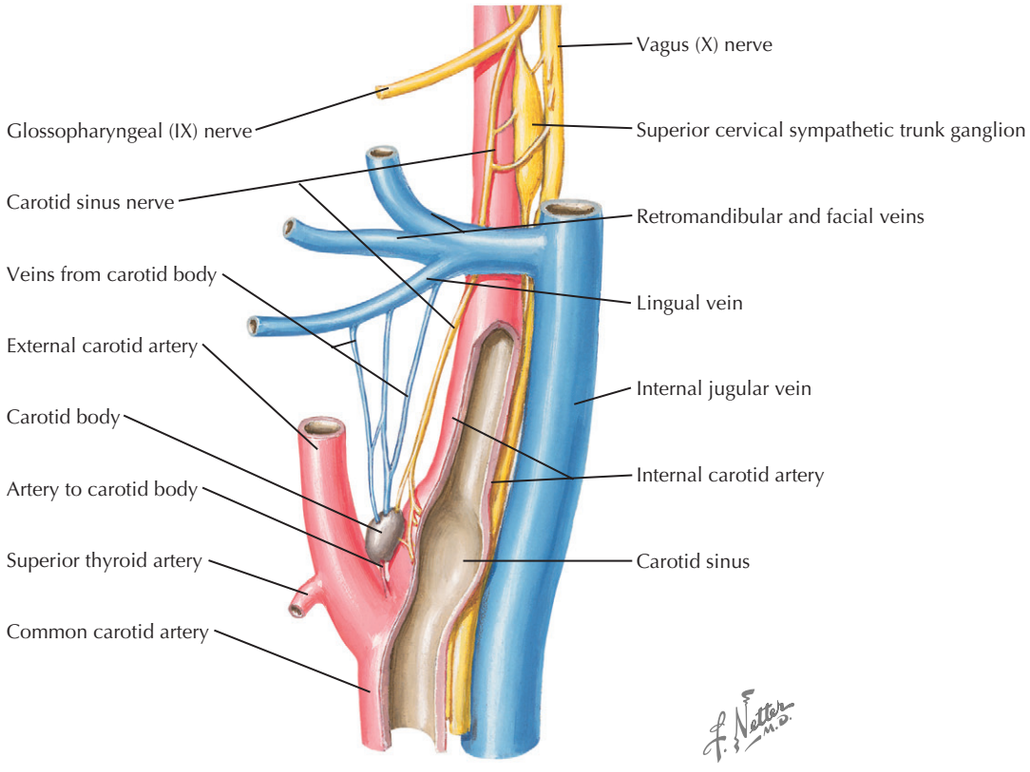


Blood vessels are innervated by afferent and efferent autonomic nerves. All receive sympathetic fibers, but some may not have a parasympathetic supply. The great vessels near the midline in the neck and body cavities receive direct innervation from adjacent parts of the sympathetic trunks. Some of these vessels and their branches also obtain supplies from nearby autonomic plexuses, which contain both sympathetic and parasympathetic elements. Thus the ascending aorta, the aortic arch and its branches, and the superior vena cava receive offshoots from the cardiac plexus; the pulmonary vessels, from the pulmonary plexuses; the celiac, hepatic, gastric, splenic, superior mesenteric, renal, and adrenal vessels and the portal and inferior caval veins, from the celiac and superior mesenteric plexuses; the inferior mesenteric vessels, from the corresponding plexus; and the pelvic vessels, from the superior and inferior hypogastric plexuses.

The chief outflow of sympathetic preganglionic fibers is through the anterior roots of spinal nerves T1 to L2. The fibers pass in white rami communicantes to adjacent sympathetic trunk ganglia, where many relay. The axons of these ganglionic cells (postganglionic fibers) may pass in nerves to nearby structures, such as midline vessels and prevertebral plexuses (cardiac, celiac, mesenteric), or they may join the lowest cervical, thoracic, and upper lumbar spinal nerves through gray rami communicantes, to be distributed with them to vessels and glands in the thoracic and abdominal cavities and limbs.

Other preganglionic fibers, however, do not relay in adjacent trunk ganglia, but ascend or descend in the sympathetic trunks to form synapses in the cervical or lower lumbar and sacral ganglia. The axons (postganglionic fibers) of the cervical ganglionic cells supply the vessels and glands in the head and neck, while others contribute to the sympathetic cervical cardiac nerves. Some of the postganglionic fibers arising in the lumbar and sacral ganglia run in lumbar and sacral splanchnic nerves to the mesenteric and hypogastric plexuses, but others pass through gray rami communicantes to the lumbar, sacral, and coccygeal spinal nerves to be distributed with them and their branches to vessels, sweat glands, and arrectores pilorum muscles in the loin, lower abdominal wall, buttocks, perineum, and lower limbs.

Carotid Body and Carotid Sinus



Innervation of Blood Vessels
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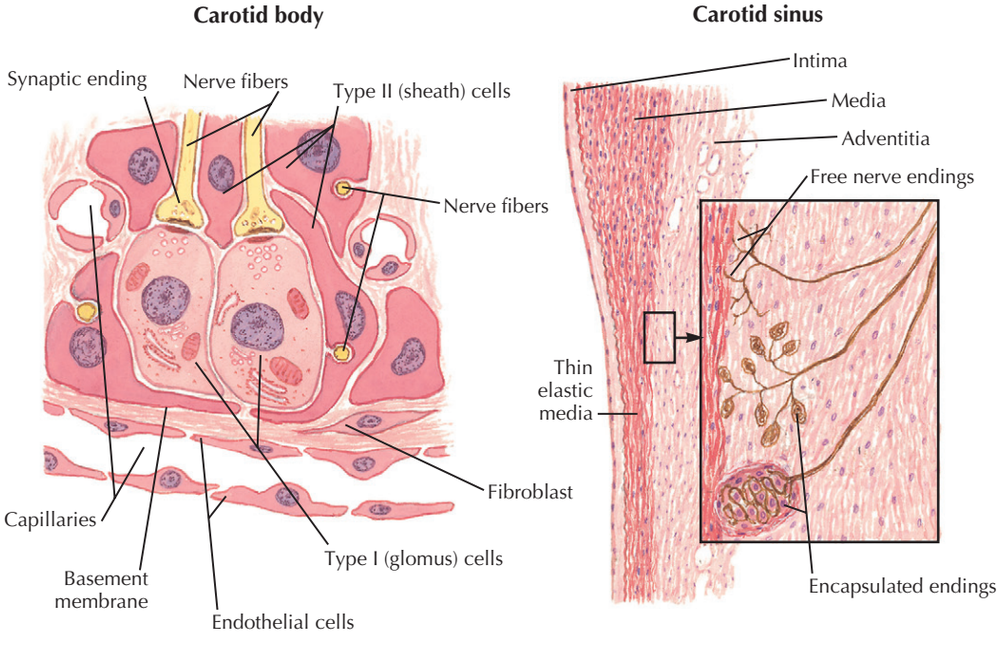
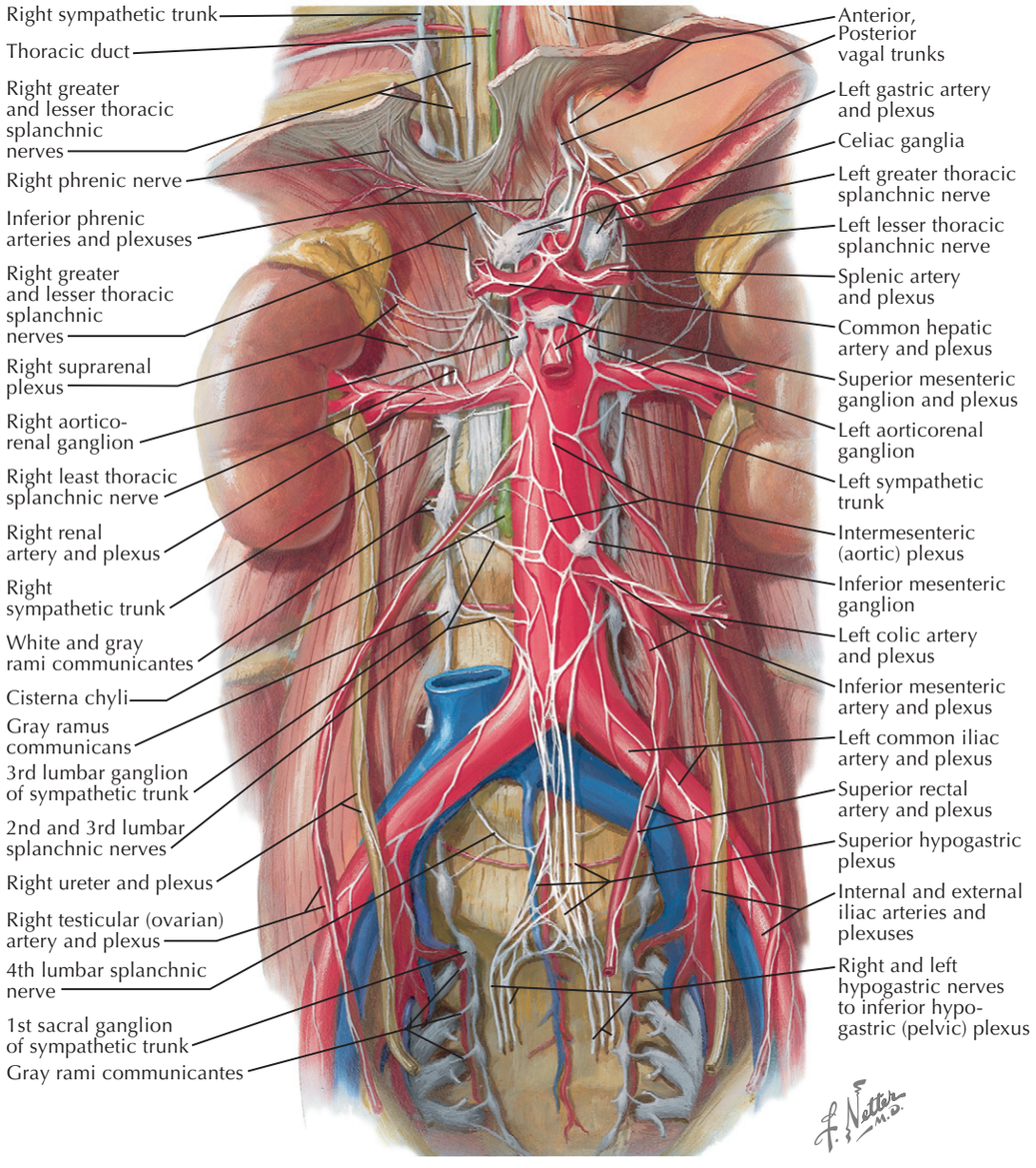


The vascular nerves from the diverse sources unite around individual vessels in wide-meshed *perivascular adventitial plexuses*. Fascicles arising from these sink inward to form more delicate plexuses between the adventitial and medial coats, from which nerve fibers originate to ramify in the media and in the zone between the media and intima. Subsidiary perivascular plexuses extend along the vessel branches and are augmented at intervals by branchlets from nearby cranial or spinal nerves, which contain autonomic fibers. Thus innervation is segmental rather than longitudinal, and only relatively short lengths of arteries can be denervated by the removal of adventitial cuffs.

Most cranial and spinal nerves contain efferent and afferent vascular fibers. The oculomotor (III), trigeminal (V), facial (VII), vagus (X), glossopharyngeal (XI), phrenic, ulnar, median, pudendal, and tibial nerves contain relatively large numbers of vascular fibers. Accordingly, lesions involving these nerves are more likely to produce vasomotor and other autonomic disturbances. Vascular disorders are usually more evident in peripheral arteries and arterioles (like those in the fingers and toes) and in arteriovenous anastomoses because they have thicker muscular layers and a richer innervation than larger arteries, which have more elastic tissue in their walls. Arteries supplying erectile tissues and the skin are also richly innervated, whereas the nerve supply to veins and venules is comparatively sparse. Nerve fibers are often associated with capillaries, but their functions are unknown.

Carotid Sinus and Carotid Body. The carotid sinus is a dilation in at the beginning of the internal carotid artery; the tunica media is thin, and adventia are thicker with multiple terminations of the glossopharyngeal nerve. The carotid sinus serves as a baroreceptor and plays an important role in the control of intracranial blood pressure. The carotid body is a small reddish brown structure behind the bifurcation of the common carotid artery and is a chemoreceptor.



Autonomic Nerves and Ganglia in Abdomen

There are more sympathetic nerves in the abdomen and pelvis than anywhere else because these cavities contain the major parts of the digestive and urogenital systems, the adrenal glands, and the extensive peritoneum.

The abdominal sympathetic nerves include the lumbar parts of the sympathetic trunks and their branches and contribute to the celiac, mesenteric, intermesenteric (abdominal aortic), hepatic, renal, adrenal, superior hypogastric, and other plexuses, including all subsidiary plexuses. Apart from the lumbar sympathetic trunks and branches, however, all the autonomic plexuses mentioned contain both sympathetic and parasympathetic elements.

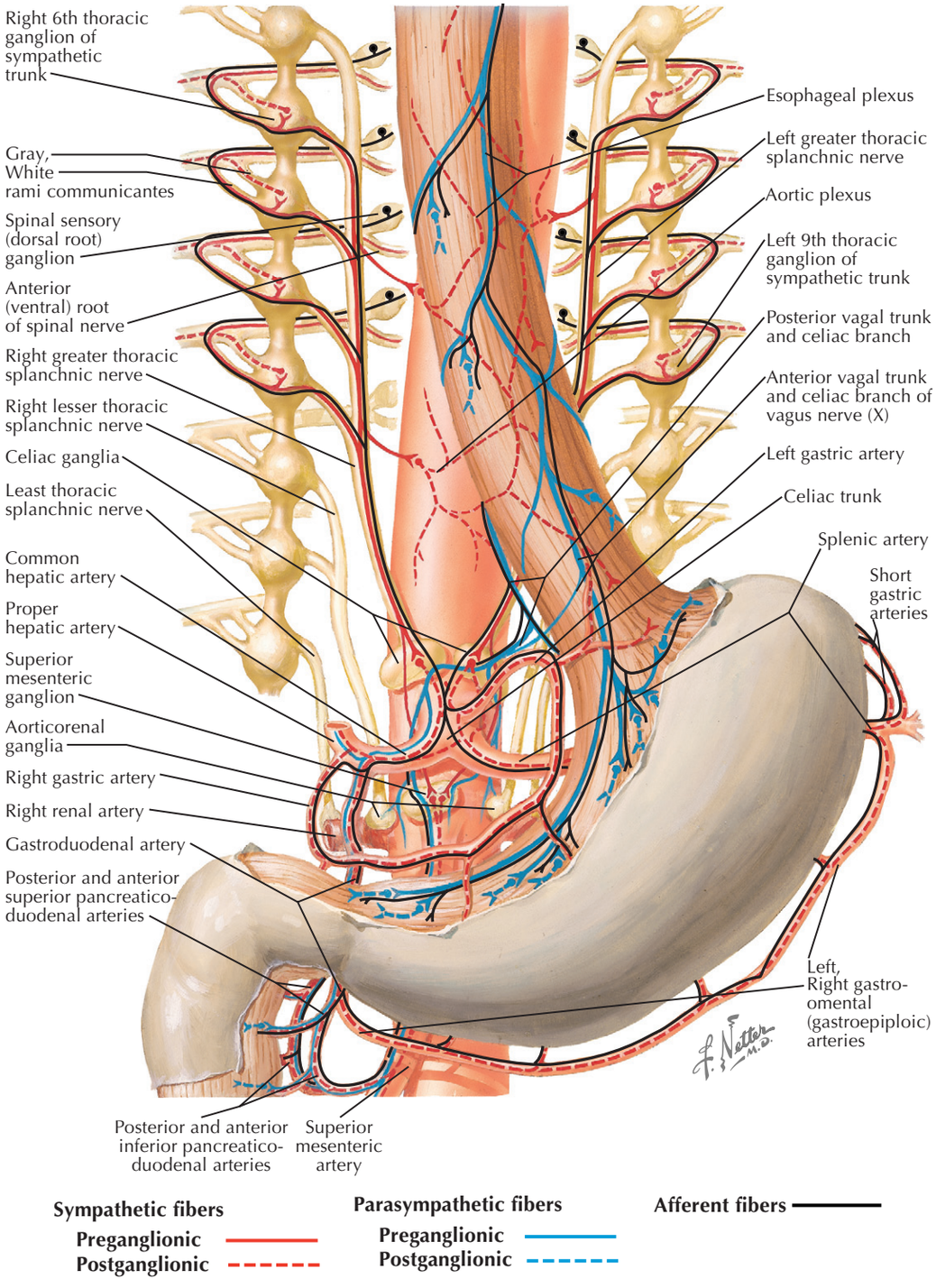
The lumbar parts of the sympathetic trunks are directly continuous above with their thoracic counterparts behind the medial arcuate ligaments, whereas below, they pass over the pelvic brim and behind the common iliac vessels to become the sacral parts of the sympathetic trunks. The trunks lie in the retroperitoneal connective tissue on the anterolateral aspect of the lumbar vertebrae, along the medial margins of the psoas muscles; the right trunk is partly overlapped by the inferior vena cava and the cisterna chyli, and the left trunk is just lateral to the abdominal aorta. There are usually four lumbar ganglia on each side; the intervening cords may be single or split into two or even three strands. Each trunk supplies or receives communicating, visceral, vascular, muscular, osseous, and articular branches.

Only the upper two or, occasionally, three lumbar spinal nerves contribute white rami communicantes to the adjacent lumbar trunk ganglia, but every lumbar spinal nerve receives one or more gray communicating rami from adjacent trunk ganglia. White rami contain preganglionic and visceral afferent fibers, whereas gray rami contain vasomotor, sudomotor, and pilomotor fibers, which are distributed with the lumbar spinal nerves.

Three or four lumbar splanchnic nerves arise on each side and are seldom arranged symmetrically. The *first lumbar splanchnic nerve* arises from the first lumbar ganglion and ends in the renal, celiac, and/or intermesenteric plexuses, but some fibers may end directly in the duodenum, pancreas, and gastroesophageal junction. The *second lumbar splanchnic nerve* arises from the second lumbar ganglion and ends mainly in the intermesenteric plexus, although it may give direct contributions to the renal plexus, duodenum, and pancreas. The *third lumbar splanchnic nerve* usually originates from the third and fourth ganglia and ends in the upper part of the superior hypogastric plexus. The *fourth lumbar splanchnic nerve*, when present, arises from the fourth and/or the inconstant fifth lumbar ganglion and joins the lower part of the superior hypogastric plexus or the homolateral hypogastric nerve; it communicates with the ureteric and testicular plexuses.

Vascular fibers from the lumbar sympathetic trunks and their lumbar splanchnic branches pass to the abdominal aorta and the inferior vena cava, where they form the delicate intermesenteric and caval plexuses. All the aortic branches and vena caval tributaries are surrounded by subsidiary plexuses continuous with those around the parent vessels. Twigs from the right sympathetic trunk also supply the cisterna chyli and the commencement of the thoracic duct. Nerve fibers from the renal plexus, sometimes reinforced by fascicles from the second and third lumbar splanchnic nerves, usually join the plexus around the common or external iliac arteries.

Muscular, osseous and articular fibers supply the adjacent muscles, vertebrae, and joints in the lumbar region. They contain postganglionic (efferent) fibers, which are possibly vasomotor, and afferent fibers conveying impulses from meningeal, bony, and articular structures.



Innervation of Stomach and Proximal Duodenum

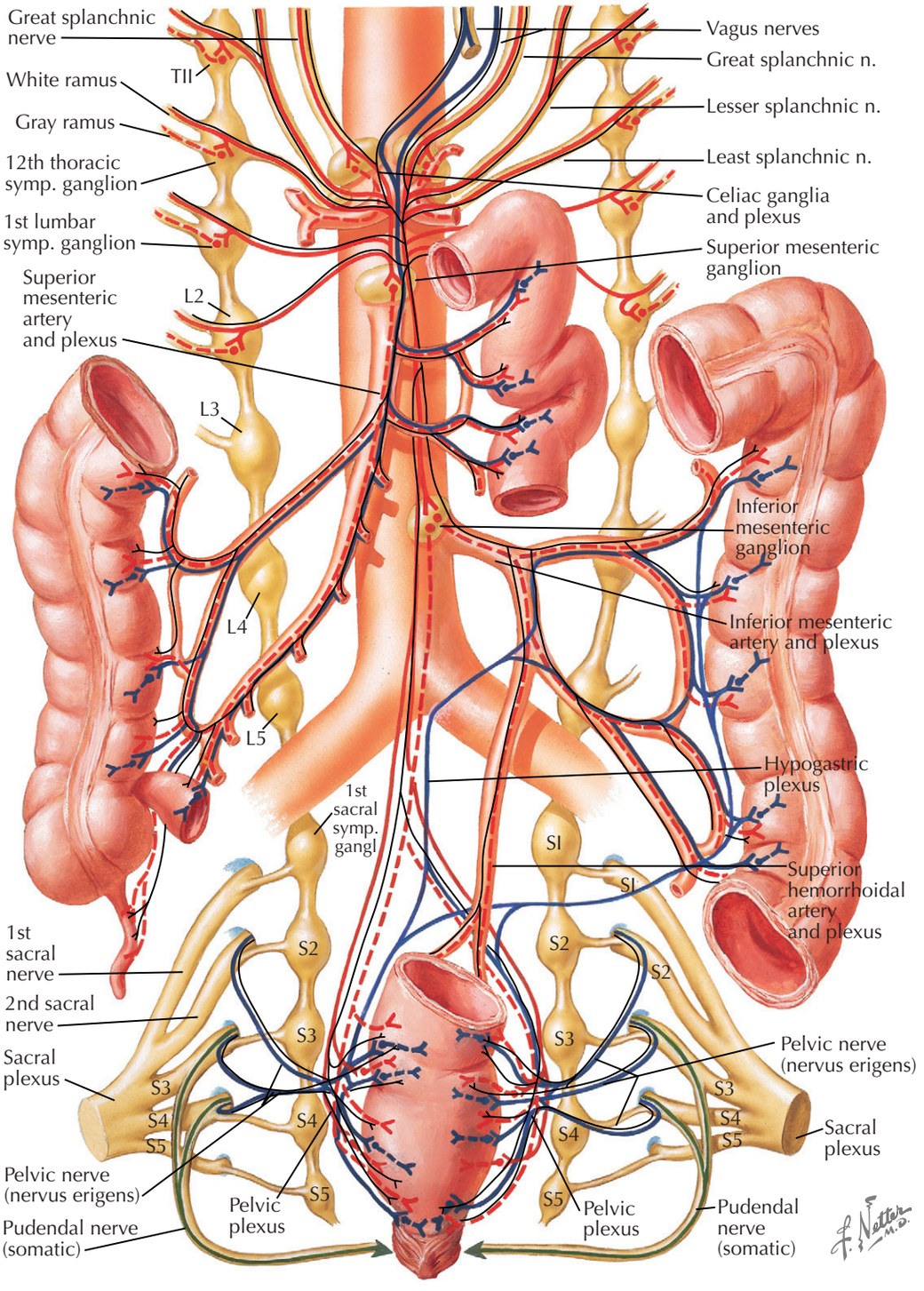
Sympathetic Fibers. The gastric sympathetic preganglionic fibers are the axons of cells located in the intermediolateral cell columns of the sixth to ninth or tenth thoracic spinal segments. They reach the celiac plexus via the *sympathetic trunk ganglia* and the *greater (major)* and *lesser (minor) thoracic splanchnic nerves*. Some of the fibers form synapses in trunk ganglia, but most continue through them to end in synapses within the *celiac* and *superior mesenteric ganglia*. The resulting postganglionic fibers may run in fascicles ending directly in the stomach and duodenum, but the majority are conveyed to their destinations in the *perivascular plexuses* along the various branches of the celiac trunk. These plexuses are composed mainly of sympathetic fibers, but they also contain parasympathetic fibers derived from the celiac branches of the vagal trunks. The sympathetic postganglionic fibers traverse the intramural enteric ganglia without relaying, and are distributed mainly to the gastric musculature and blood vessels.

Parasympathetic Fibers. The two *vagus nerves* form an *esophageal plexus* around the lower esophagus, which is reinforced by twigs from the *thoracic parts* of the *sympathetic trunks* and from the *greater (major)* and *lesser (minor) thoracic splanchnic nerves*. Before reaching the diaphragm, the meshes of the esophageal plexus are reconstituted to form *anterior* and *posterior vagal trunks*. In general, more fibers from the left vagus enter the anterior trunk, whereas the posterior trunk contains more fibers from the right vagus, although the anatomic relationships are highly variable. The vagal trunks give off gastric, pyloric, hepatic, and celiac branches.

Anterior and *posterior gastric branches* supply the corresponding surfaces of the stomach. They run between the layers of the lesser omentum and give off branches that radiate over the surfaces of the stomach and can be traced for some distance in the subperitoneal tissue before they sink into muscle coats; no definite anterior or posterior gastric plexuses exist. Often, one branch on both the anterior and posterior aspects is larger than the others—the *greater anterior* and *greater posterior gastric nerves. Pyloric branches* arise from the anterior vagal trunk or its greater anterior gastric branch and supply the pyloric antrum, pylorus, and superior (first) part of the duodenum. *Hepatic branches* are provided by both vagal trunks; that from the anterior trunk arises near the gastric cardiac ostium and is called the *hepatogastric nerve* because it supplies offshoots to the hepatic plexus and stomach (there may be more than one hepatogastric nerve). The hepatic contribution from the posterior vagal trunk usually reaches the hepatic plexus through its celiac branch. Both vagal trunks give off *celiac branches*, and the posterior branch is larger than the anterior. All efferent (preganglionic) vagal fibers ending in the stomach make synaptic contacts with ganglionic neurons in the gastric parts of the *myenteric* and *submucous plexuses*; the resulting postganglionic fibers are distributed to the gastric musculature, glands, and vessels, where they exert both motor and secretory effects (see Plate 7-17).

Afferent Fibers. Afferent parasympathetic and sympathetic fibers pursue reverse routes to those described for vagal and sympathetic efferent fibers.

Innervation of the Intestine



Innervation of Intestines

Sympathetic Fibers

The preganglionic sympathetic fibers to the intestines are the axons of intermediolateral cells located in the lowest four or five thoracic and upper two lumbar spinal segments. Some form synapses in the *sympathetic trunk ganglia*, but most are conveyed in the *thoracic*, *lumbar*, and *sacral splanchnic nerves* to the celiac, mesenteric, and hypogastric plexuses, where they relay. From the celiac and superior mesenteric plexuses, an unknown proportion of fibers descend in the *intermesenteric* and *hypogastric nerves* to the inferior mesenteric and hypogastric plexuses. Postganglionic fibers from ganglionic synapses, along with afferent and preganglionic parasympathetic fibers, are carried to the intestines in branches of the various plexuses.

The parasympathetic supply to the intestines is derived from the vagus and pelvic splanchnic nerves. The *vagal* contributions pass to the celiac plexus in the *larger* and *smaller celiac branches* arising, respectively, from the *posterior* and *anterior vagal trunks*. Some fibers are distributed with branches of the *celiac plexus* to the stomach and duodenum (see Plate 7-14), but others descend to the *superior mesenteric plexus*. They comprise efferent (preganglionic) and afferent fibers, and innervate the small intestines and the colon almost to the left colic flexure. Parasympathetic fibers follow the same routes to the intestines as sympathetic postganglionic fibers but are still preganglionic and end by forming synapses in the enteric plexuses (see Plate 7-17).

The *pelvic splanchnic nerves* arise from the second, third, and fourth sacral nerves. They contain parasympathetic preganglionic and afferent fibers, which include those supplying the distal end of the transverse colon and left colic flexure, the descending and sigmoid colons, and the rectum. They join the *inferior hypogastric (pelvic) plexuses* and are distributed with their branches. The preganglionic intestinal fibers pass through the ganglia in these plexuses without relaying; like their vagal counterparts, they end by making synaptic contacts in the *enteric plexuses*. Some branches pass directly to the rectum and lower end of the sigmoid colon, others accompany rectal and colic vessels, and still others may ascend in the *hypogastric nerves* to the *superior hypogastric plexus* and thence to the *inferior*

Innervation of Intestines
(Continued)

mesenteric plexus, to be distributed with its branches to the distal parts of the colon. However, the majority of the parasympathetic fibers for these parts of the colon pursue a different course: they arise by several filaments from the *pelvic splanchnic nerves* or the *inferior hypogastric plexuses* and run upward across the sigmoid and left colic vessels. They can be traced as far as the left colic flexure, and they supply offshoots to the adjacent parts of the sigmoid and descending colons and communicate with branches of the inferior mesenteric plexus.

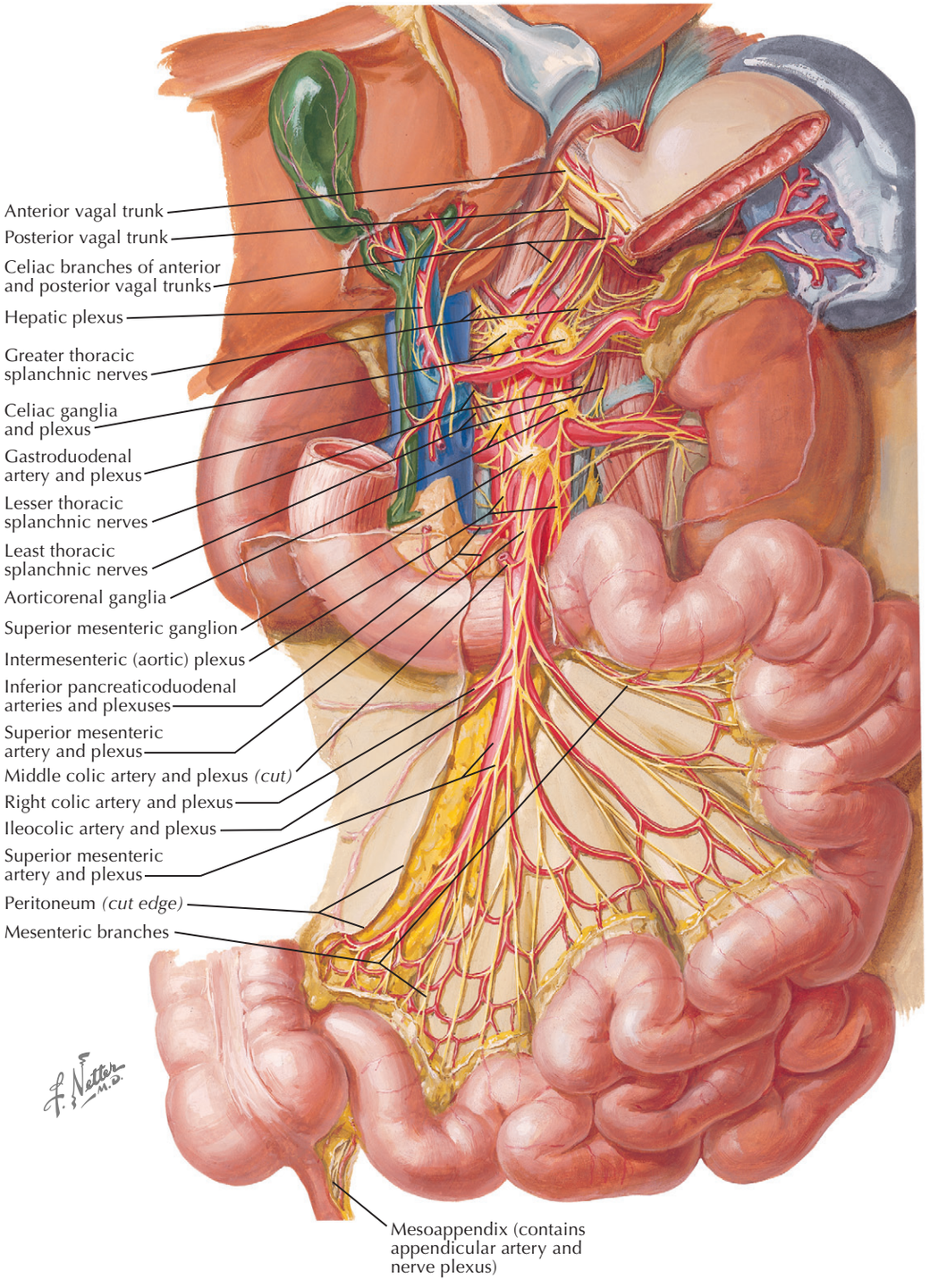
Afferent pathways, in general, follow (in reverse direction) both the sympathetic and the parasympathetic supplies to the small and large bowel. The afferent components of the vagus and pelvic nerves and of the sympathetic pathways subserve reflex activity, but most localized sensations referable to the gastrointestinal tract appear to be mediated through the sympathetic afferents.

At the anorectal junction, the autonomic innervation gives way to somatic innervation.

Autonomic Nervous System Role in Gut Motility

The enteric nervous system (ENS) is a complex network of neurons and nerve fibers located within the gut wall and consist of the two ganglionic strata: the myenteric, or Auerbach plexus between the two layers of the external muscle, and the submucosal Meissners plexus, which extends from the esophagus to the anal canal and is responsible for peristaltic activity, secretion of mucosal glands, vasoconstriction and vasodilation, water absorption, and electrolyte balance. The parasympathetic and sympathetic exert external regulatory influences on the ENS. The cholinergic terminals of the parasympathetic system, acting on the smooth muscles of the small and large intestine and also via the enteric plexuses, cause increased motility of the intestine and increased secretory activity of the glands. Postganglionic fibers of the sympathetic nervous system release norepinephrine, causing decreased motility.

Autonomic Innervation of Small Intestine



Enteric Plexuses

Enteric plexuses exist within the walls of the alimentary tract, from the esophagus to the rectum. They form microscopic networks and consist of bundles of nerve fibers (axons) and dendrites, which link ganglia located chiefly at nodal points in the meshes. These networks are most evident between the layers of the muscle coats (myenteric, or Auerbach, plexus) and in the submucosa (submucous, or Meissner, plexus). Tenuous subserous plexuses with sparsely disposed nerve cells are present in those parts of the gastrointestinal tract that possess peritoneal coverings.

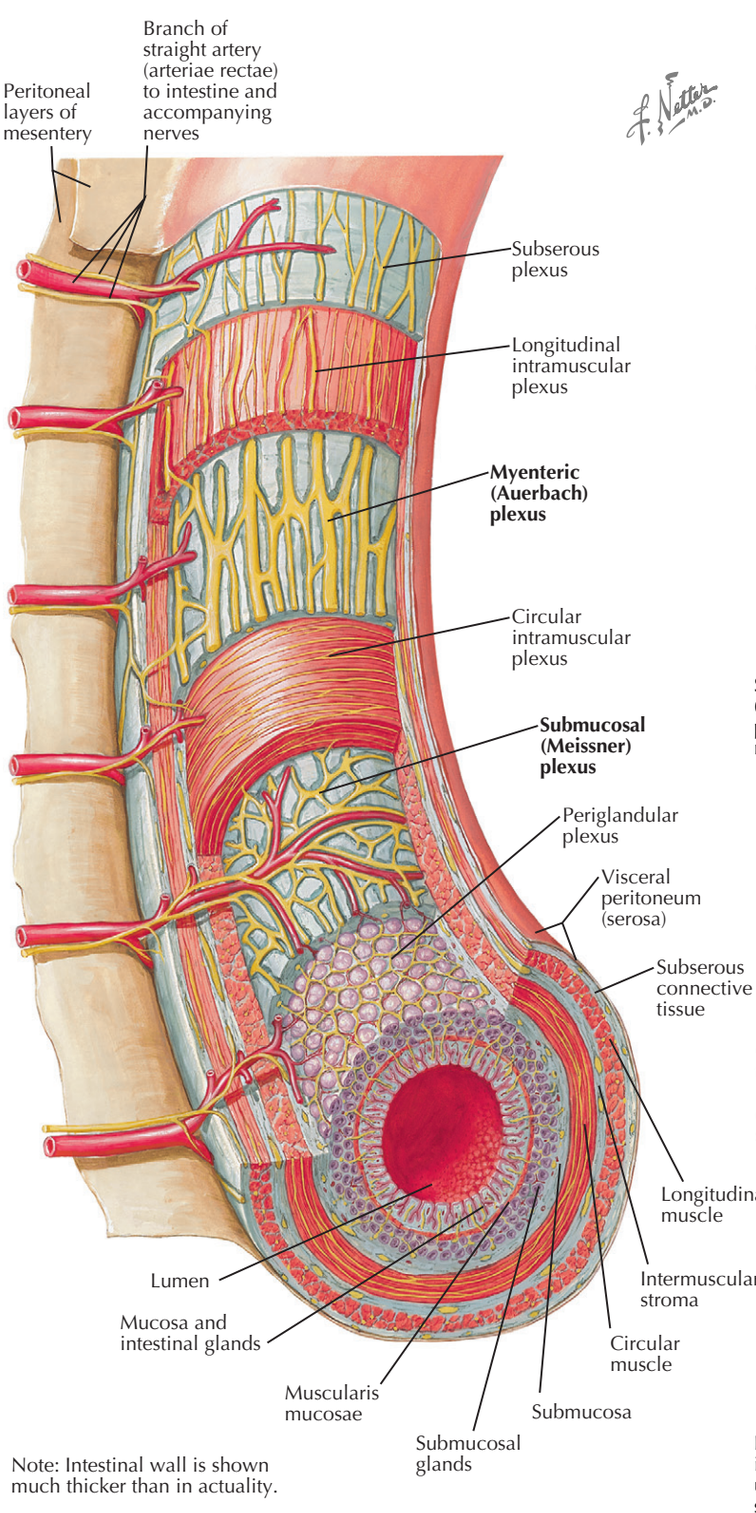
The *myenteric (Auerbach) plexus* is relatively coarse, with thicker meshes and larger ganglia. The main, or primary, meshes give off fascicles that form secondary networks in the interstices of the primary networks. These, in turn, split into minute bundles of fibers that ramify between the muscle tunics and supply them. The *submucous (Meissner) plexus* is more delicate and its meshes are more irregular. Its delicate offshoots mostly end in relation to cells forming the muscularis mucosae or form rarefied periglandular plexuses, while other offshoots end in almost invisible subepithelial plexuses.

The patterns and densities of these plexuses vary in different parts of the alimentary tract. They are less well defined in the upper part of the esophagus but are well developed from the stomach to the lower end of the rectum. The ganglia are not uniformly distributed. The density of ganglionic cells in the plexuses is lowest in the esophagus, rises steeply in the stomach until it reaches a peak at the pylorus, falls to an intermediate level throughout the small intestines, and gradually increases along the colon to reach another, lesser peak in the rectum.

The extrinsic nerves involved contain *efferent* and *afferent sympathetic* and *parasympathetic fibers* derived from thoracic, lumbar, and sacral branches of the sympathetic trunks and from the vagus and pelvic splanchnic nerves. Most of the sympathetic efferent fibers entering the enteric plexuses are postganglionic, while parasympathetic efferent fibers are still preganglionic. The vagal fibers form synapses with ganglion cells located in the enteric plexuses, from the esophagus to the distal third of the transverse colon; below this level, the preganglionic parasympathetic fibers are carried in branches of the pelvic splanchnic nerves. Thus in this as in other situations, the parasympathetic postganglionic fibers are very much shorter than their sympathetic counterparts.

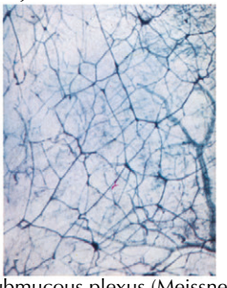
Many interconnections exist between the myenteric and submucous plexuses. In general, the former are mainly concerned with the innervation of the muscle layers in the visceral walls, whereas the latter are chiefly involved with supplying the glands and muscularis mucosae and in forming delicate subepithelial plexuses. The enteric plexuses and their subdivisions are also responsible for supplying adjacent vessels and transmitting sensory impulses. The sympathetic innervation is primarily inhibitory to peristalsis and stimulatory to the sphincters, while the parasympathetic innervation is the opposite.

Afferent fibers from the alimentary tract are conveyed to the central nervous system (CNS) through the same sympathetic and parasympathetic nerves that carry the corresponding efferent fibers. There is also evidence that local reflex arcs exist.

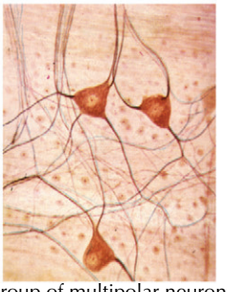


Note: Intestinal wall is shown much thicker than in actuality.

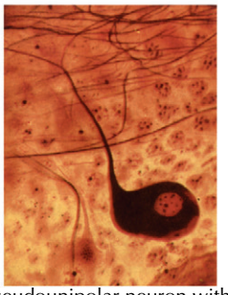
Myenteric plexus (Auerbach) lying on longitudinal muscle coat. Fine tertiary bundles crossing meshes (duodenum of guinea pig, Champy-Coujard, osmic stain, x20).



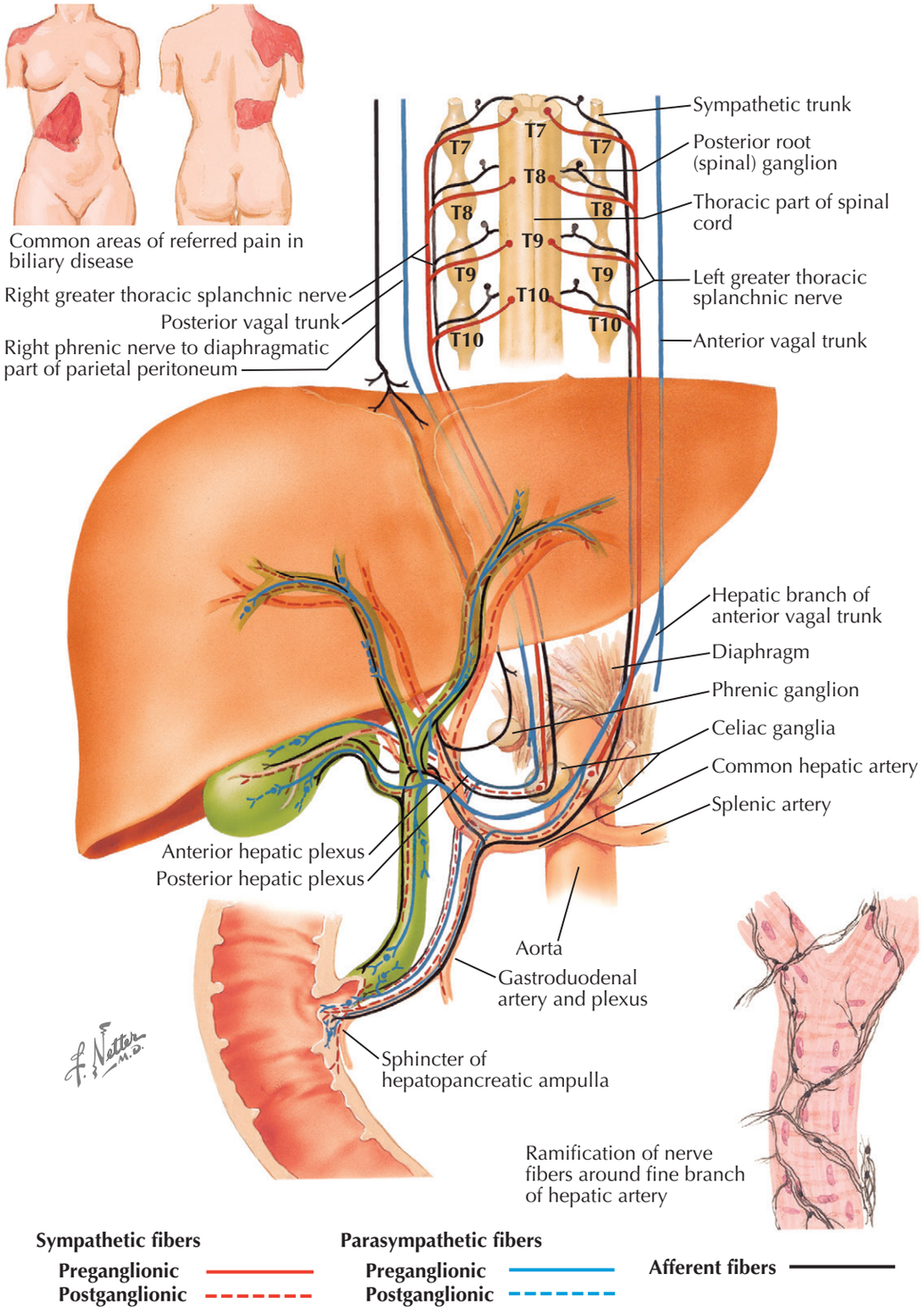
Submucous plexus (Meissner) (ascending colon of guinea pig. Stained by gold impregnation, x20).



Group of multipolar neurons, type II, in ganglion of myenteric (Auerbach) plexus (ileum of cat; Bielschowsky, silver stain, x200)



Pseudounipolar neuron within ganglion of myenteric plexus (ileum of cat; Bielschowsky, silver stain x375)



Innervation of Liver and Biliary Tract

The liver, biliary tract, and gallbladder receive their nerve supplies from sympathetic and parasympathetic sources. The *preganglionic sympathetic fibers* originate mainly in the seventh to tenth thoracic segments and pass to the celiac plexus via the sympathetic trunk ganglia and the greater and lesser thoracic splanchnic nerves (see Plates 7-13 and 7-14). Most of the fibers form synapses in the celiac ganglia, although some may relay in small ganglia located in the porta hepatis. The *postganglionic sympathetic fibers* reach the liver in the hepatic plexuses, which also contain parasympathetic and afferent fibers. The *parasympathetic supply* is provided by branches of the vagal trunks.

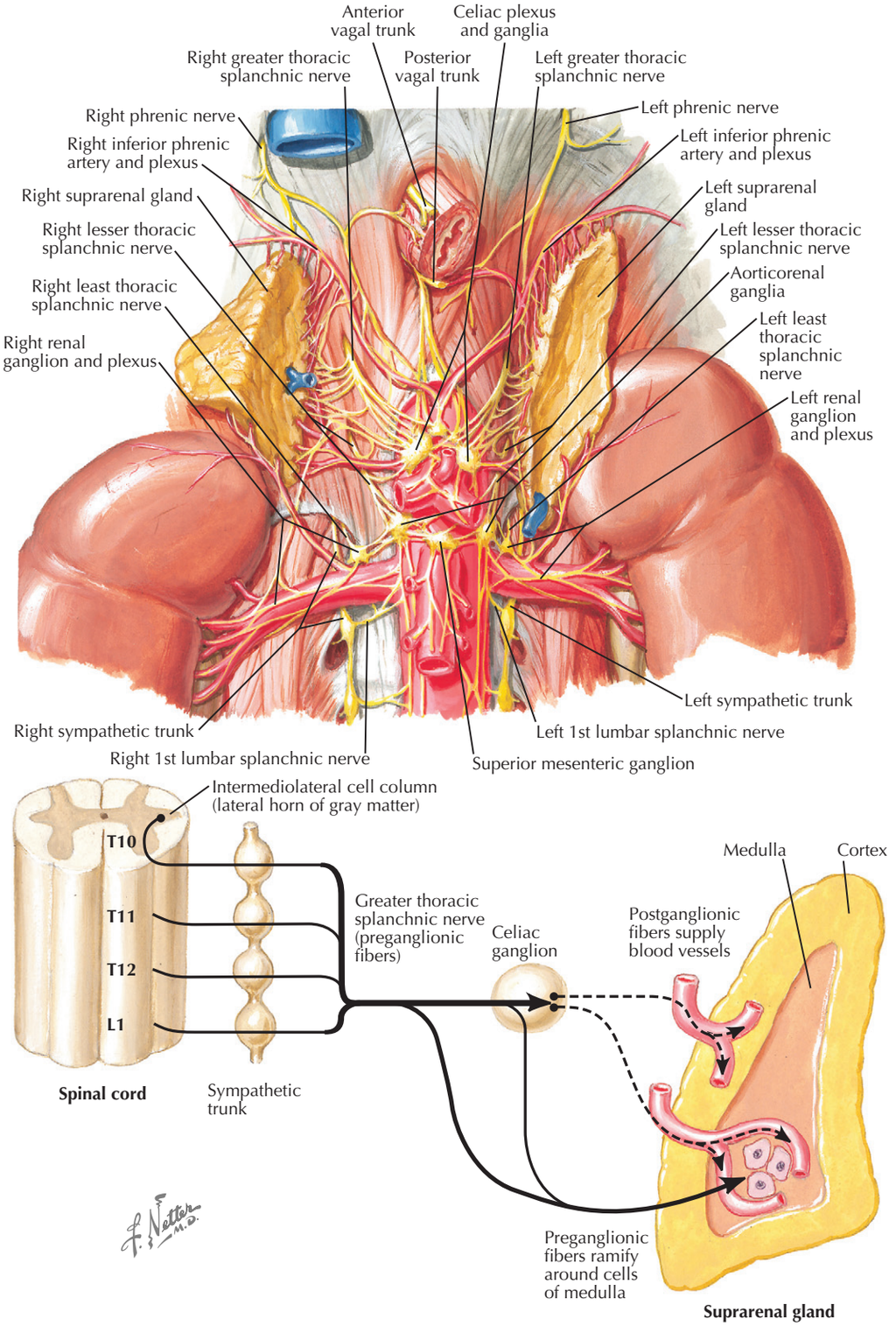
Afferent fibers from the liver and biliary tract are conveyed through the hepatic and celiac plexuses to the *thoracic splanchnic nerves* or to branches of the *vagus nerves*. The sympathetic afferents reach the seventh to twelfth thoracic spinal cord segments through the corresponding posterior spinal nerve roots, whereas the vagal afferents are carried upward to the brainstem. The right, and possibly the left, phrenic nerve also conveys afferents from receptors in the peritoneal lining over the liver and biliary tract, which can be stimulated by stretching—as by acute hepatic enlargement or distention of the gallbladder. The resultant pain in the right shoulder region associated with liver and biliary tract disorders is an example of referred pain.

Liver. The *hepatic plexuses* lie in the right free margin of the lesser omentum anterior to the epiploic (omental) foramen. They are formed mainly by offshoots from the *celiac plexus*, which contain sympathetic and parasympathetic efferent and afferent fibers, supplemented by direct contributions from the *anterior vagal trunk* and by indirect contributions from the *right phrenic nerve*. They are arranged in two interconnected groups, one of which lies along the anterior and lateral sides of the hepatic artery, and the other, posterior to the common bile duct and portal vein.

Subsidiary plexuses surround and accompany the branches of the hepatic artery, portal vein, and right and left hepatic ducts as they enter and ramify within the liver; their offshoots penetrate between the cells of the liver lobules to form a widespread *parenchymal plexus*. Histochemical studies reveal that the nerve fibers in relation to the hepatocytes and sinusoids are parasympathetic, whereas sympathetic fibers remain mainly or entirely associated with vessels in the interlobular spaces. Direct contacts between the terminations of nerve fibers and liver cells have been observed in electron micrographs.

Gallbladder. The gallbladder is supplied by perivascular nerve fibers accompanying the right hepatic and cystic arteries from the *anterior hepatic plexus* and by other nerve fibers extending along the cystic duct from the *posterior hepatic plexus*. The common bile duct (choledochal duct) is supplied by twigs from both anterior and posterior hepatic plexuses and by offshoots from the plexus around the gastroduodenal artery and its retroduodenal branches. The arrangement of the nerves within the walls of these structures resembles that in the enteric plexuses.

Both the sphincter ampullae and the sphincter of the choledochal duct are supplied by sympathetic and parasympathetic fibers. The former normally cause contraction of the sphincters and dilation of the gallbladder, while the latter produce the opposite effects.



Innervation of Adrenal Glands

The adrenal (suprarenal) glands show a high degree of species variation, and this also applies to their nerve supplies. The cortex and medulla differ in their development. The *medullary (chromaffin) cells* are modified migrant neuroblasts from the neural crest and are homologous with ganglion cells in the sympathetic trunks. Accordingly, they are innervated directly by preganglionic fibers. Relative to their size, the adrenal medullae are more richly innervated than any other viscus.

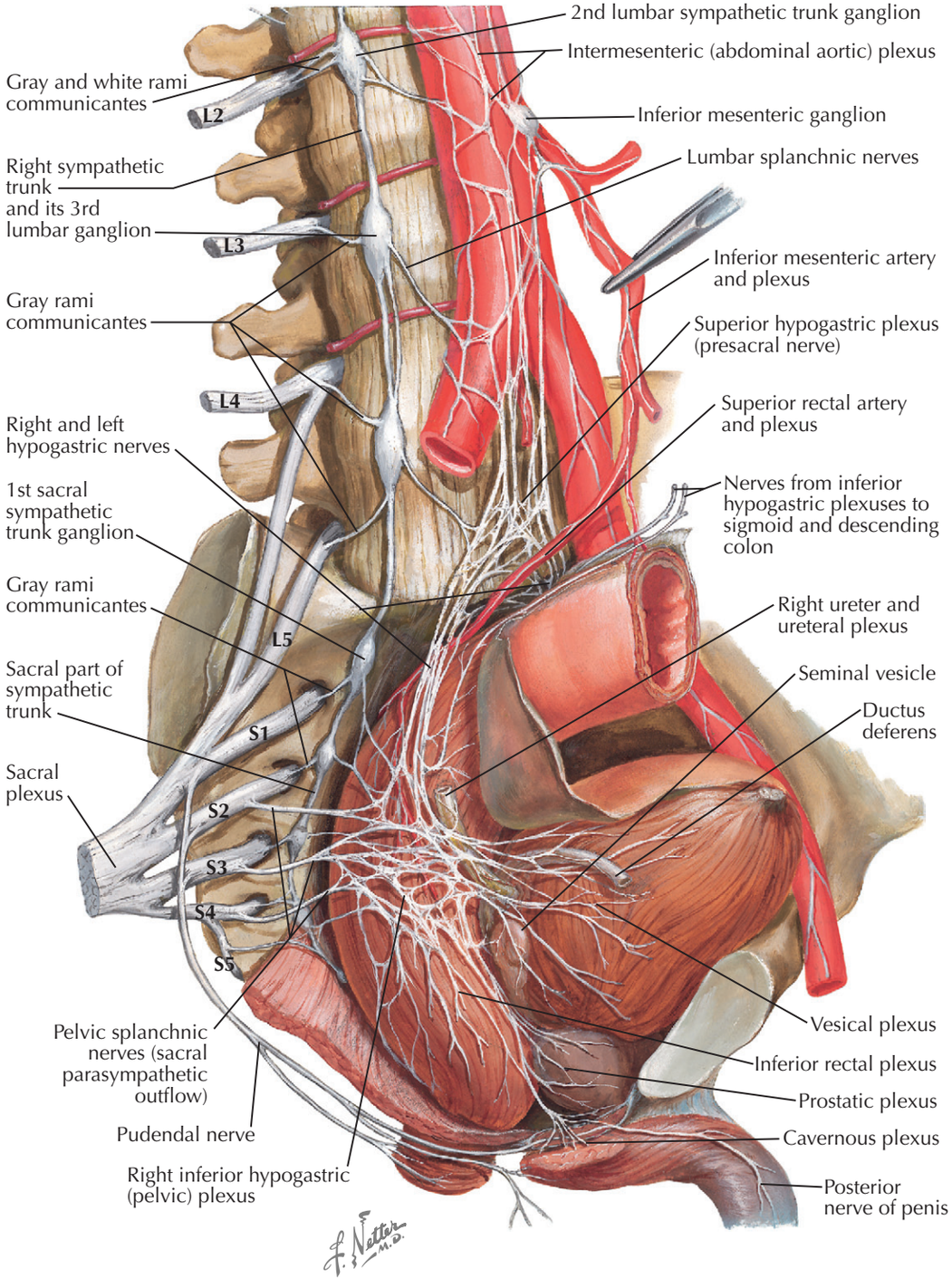
The *preganglionic sympathetic fibers* are the axons of cells located in the intermediolateral gray columns of mainly the lower three or four thoracic and upper one or two lumbar segments of the spinal cord. They emerge in the anterior rootlets of the corresponding spinal nerves, pass in white rami communicantes to the sympathetic trunks, and leave them in the thoracic and first lumbar splanchnic nerves that run to the celiac, aorticorenal, and renal ganglia. Some of the fibers conveying impulses for the adrenal vessels may relay in these ganglia, but the majority continue onward to enter the adrenal branches of the celiac plexus.

Some of the *parasympathetic fibers* reaching the celiac plexus through the vagal trunks may be concerned with adrenal innervation and may relay in small ganglia near or in the glands, but as yet, no definite proof of this hypothesis exists. The adrenal parasympathetic supply may well emerge via posterior spinal nerve root efferents, which enter the thoracic splanchnic nerves and thereafter follow the same routes as the sympathetic preganglionic fibers; however, the existence of such posterior root efferents is still unproven. A proportion of the fibers in the adrenal nerves may be afferent and enter the spinal cord through the ninth to eleventh thoracic spinal nerves.

Adrenal Nerves. Numerous fine nerves pass outward to each gland from the *celiac plexus* and *ganglia*. They are joined by contributions from the terminations of the *greater* and *lesser thoracic splanchnic nerves*, and they communicate with the ipsilateral *phrenic nerve* and *renal plexus*.

Many nerve fibers from the adrenal nerves enter the gland through its hilus and medial margin. Other nerve fibers spread out over the gland to form a delicate *subcapsular plexus* from which fascicles penetrate the cortex to run alongside arterioles in the trabeculae to the medulla. The majority of nerve fibers entering the gland end in the medulla, where they ramify profusely and give off fibers that mostly terminate in synaptic-type contacts with the chromaffin cells. As already stated, these are the homologues of ganglion cells in the sympathetic trunks. Some fibers invaginate the cell membranes deeply but do not penetrate them. A minority of fibers innervate the medullary arterioles and the central vein, which has an unusually thick muscle coat.

Multipolar or bipolar neurons, singly or in small groups, have been noted within the adrenal medullae. Their significance and the destinations of their axons have not yet been determined, although it is assumed that the cells are the final relay stations in the parasympathetic pathways.



Autonomic Nerves and Ganglia in Pelvis

Sympathetic fibers reach the pelvis through the sympathetic trunks and the superior hypogastric plexus, and in visceral and vascular nerves accompanying and supplying such structures as the colon, ureters, and the inferior mesenteric and common iliac vessels. *Parasympathetic fibers* emerge in the anterior roots of the second, third, and sometimes, fourth sacral spinal nerves and leave them in the slender bilateral pelvic splanchnic nerves (nervi erigentes) that join the corresponding inferior hypogastric (pelvic) plexuses and are distributed with their branches.

Sympathetic Fibers. The lumbar and sacral parts of the sympathetic trunks are directly continuous at the level of the pelvic brim. The sacral trunks lie in the pelvic fascia behind the parietal peritoneum and rectum, and on the anterior surface of the sacrum, just medial to its anterior foramina and the nerves and vessels passing through them. Below, they converge and unite in a single tiny "ganglion impar" anterior to the coccyx. In general, four, or sometimes, three sacral trunk ganglia exist on each side. No white rami communicantes are present in this region, but each ganglion supplies one or more gray rami communicantes containing postganglionic sympathetic fibers to the adjoining sacral and coccygeal spinal nerves; these fibers are conveyed in branches of the sacral and coccygeal plexuses to vessels, sweat glands, arrectores pilorum muscles, striated muscles, bones, and joints.

The pelvic sympathetic trunk ganglia also supply slender rami, the *sacral splanchnic nerves*, which pass to the inferior hypogastric plexuses. The majority of sympathetic fibers, however, reach these plexuses through the *right* and *left hypogastric nerves*, formed just below the level of the lumbosacral junction by the splitting of the median superior hypogastric plexus (often misleadingly referred to as the "presacral nerve"—a single nerve is very rare). Similarly, the right and left hypogastric nerves are more often elongated plexuses consisting of several nerves interconnected by oblique strands, which incline downward on each side, behind the peritoneum and lateral to the sigmoid colon and rectosigmoid junction, to end in the upper parts of the homolateral inferior hypogastric plexus.

The *inferior hypogastric plexuses* are situated on each side of the rectum, lower part of the bladder, prostate, and seminal vesicles. In females, the cervix of the uterus and vaginal fornices replace the prostate gland and seminal vesicles as medial relations. The plexuses supply branches to the pelvic viscera and genitalia and often form subsidiary plexuses (such as the rectal, prostatic, and vesical). The branches contain visceral, glandular, vascular, and afferent fibers, often combined in the nerve fascicles supplying the various structures concerned (see Plates 7-21 to 7-24). The *sympathetic efferent fibers* in these branches, like those in the gray rami communicantes connecting the ganglia of the pelvic sympathetic trunks to the sacral and coccygeal spinal nerves, are almost entirely postganglionic because most or all of the sympathetic preganglionic fibers involved in the supply of pelvic, perineal, gluteal, and lower limb structures relay in lumbar and sacral trunk ganglia; a minority may form synapses in ganglia within the inferior hypogastric plexuses.

The parasympathetic fibers in the *pelvic splanchnic nerves*, which arise from the sacral nerves and end in the *inferior hypogastric plexuses*, are preganglionic. Some relay in ganglia within the plexuses, but many more form synapses in ganglia located near or within the walls of the viscera and vessels innervated.

Other branches from the inferior hypogastric plexuses ascend to assist in the innervation of the distal colon and the renal pelvises.

Innervation of Kidneys, Ureters, and Urinary Bladder

Kidney and Upper Ureter. The *preganglionic sympathetic fibers* for the kidneys and upper ureters emerge from the spinal cord through the anterior nerve roots of the eleventh and twelfth thoracic spinal nerves, and often, the tenth thoracic and first lumbar spinal nerves as well. The fibers then pass in white rami communicantes to adjacent ganglia in the sympathetic trunks. They leave the ganglia in the splanchnic nerves: the lesser, lowest thoracic, first lumbar, and second lumbar. The lesser thoracic splanchnic nerve usually ends in the ipsilateral celiac or aorticorenal ganglia, and the other nerves mentioned may do the same, although they usually end directly in the renal plexus or in the small renal ganglion lying posterior or posterosuperior to the renal artery. Most of the preganglionic fibers form synaptic relays in the aorticorenal or posterior renal ganglia or in smaller ganglia incorporated into the renal plexuses. The *postganglionic sympathetic fibers* form fascicles that surround and accompany the upper ureteric, renal, pelvic, calyceal, and segmental branches of the renal vessels.

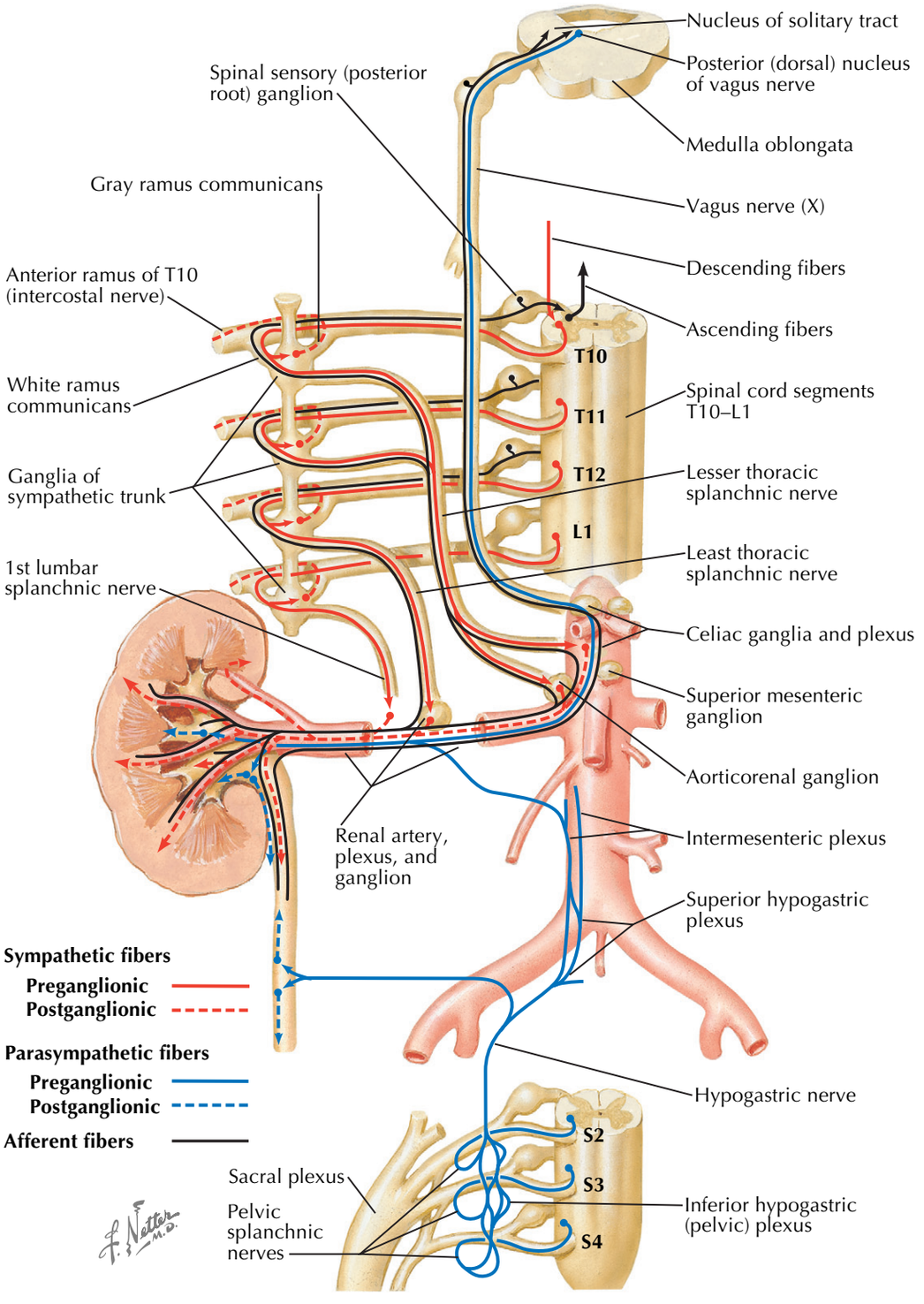
Some *parasympathetic fibers* are carried through the vagal contributions to the celiac plexus and are conveyed onward to the kidneys in the renal branches of this plexus; others emerge through the pelvic splanchnic nerves and may reach the renal collecting tubules, renal calyces and renal pelvis and upper ureter by a more indirect route. Such an arrangement is understandable on embryologic grounds because the structures mentioned are all derived from buds developed from the cloacal ends of the mesonephric (wolffian) ducts. These pelvic parasympathetic fibers join the inferior hypogastric plexuses, ascend in the hypogastric nerves to the superior hypogastric plexus, and exit in fine branches that ascend retroperitoneally to enter the inferolateral parts of the homolateral renal plexus.

Afferent fibers from the kidneys and upper ureter follow similar routes in the reverse direction, but they do not form relays in peripheral ganglia; their cell bodies are located in posterior spinal nerve root ganglia. The central processes of these ganglion cells enter the spinal cord mainly through the posterior nerve roots of the tenth to twelfth thoracic spinal nerves and then ascend in or alongside the spinothalamic tracts and also in the posterior white columns of the cord.

Within the renal hilus and sinus, the *renal plexus* supplies nerve fibers to the renal pelvis, calyces, and upper ureter. Other nerve fibers form rich plexuses around the renal vessels and their branches and accompany them into the kidney. They contain mostly unmyelinated fibers, and relatively few of the myelinated type. The *sympathetic fibers* are distributed to the smooth muscle in the renal pelvis and calyces, to the vascular musculature, and possibly to the juxtaglomerular cells and glomeruli. The *parasympathetic fibers* supply the muscle in the pelvis, calyces, and upper ureter, but it is uncertain whether they supply the vessels and tubules. *Sensory nerve endings* have reputedly been detected in the pelvis and ureter, in the adventitia of the larger vessels, and near the glomeruli.

Urinary Bladder and Lower Ureter. The *preganglionic sympathetic cells* concerned with vesical innervation are located in the upper two lumbar segments and perhaps also in the lowest thoracic segment of the spinal cord. The sites where the preganglionic fibers form synapses with the ganglionic neurons that give off the postganglionic fibers have not been determined accurately. The *preganglionic parasympathetic cells* are located

Autonomic Innervation of Kidneys and Upper Ureters



Innervation of Kidneys, Ureters, and Urinary Bladder *(Continued)*

in the second to fourth sacral segments of the spinal cord, and their axons (nervi erigentes) relay in ganglia close to or within the wall of the urinary bladder. The neurons in the anterior gray matter of the sacral spinal cord S1 to S3, *Onuf* nucleus, provide the motor supply to the external urethral sphincter through the motor branches of the pudendal nerve. *Afferent fibers* pursue similar pathways, but in the reverse direction; thus some vesical sensory impulses enter the cord through the upper lumbar and last thoracic posterior nerve roots, while others from the neck of the bladder and the lowest parts of the ureters reach the cord via the pelvic splanchnic nerves and the posterior nerve roots of the second to fourth sacral nerve segments.

Many fascicles from the *extrinsic vesical plexuses* enter the bladder wall, mainly alongside its blood vessels. They divide and subdivide and are ultimately carried to all parts, forming a widespread *intramural*, or *intrinsic, vesical plexus*. The nerve fasciculi are most conspicuous in the trigonal and neighboring regions, becoming more scattered and attenuated toward the fundus. Many small ganglia are present on the surface or are buried more deeply between the muscular bundles, and these are more numerous in the trigonal region. Many fibers enter the submucosa and penetrate between the mucosal cells, where they apparently end in small boutons.

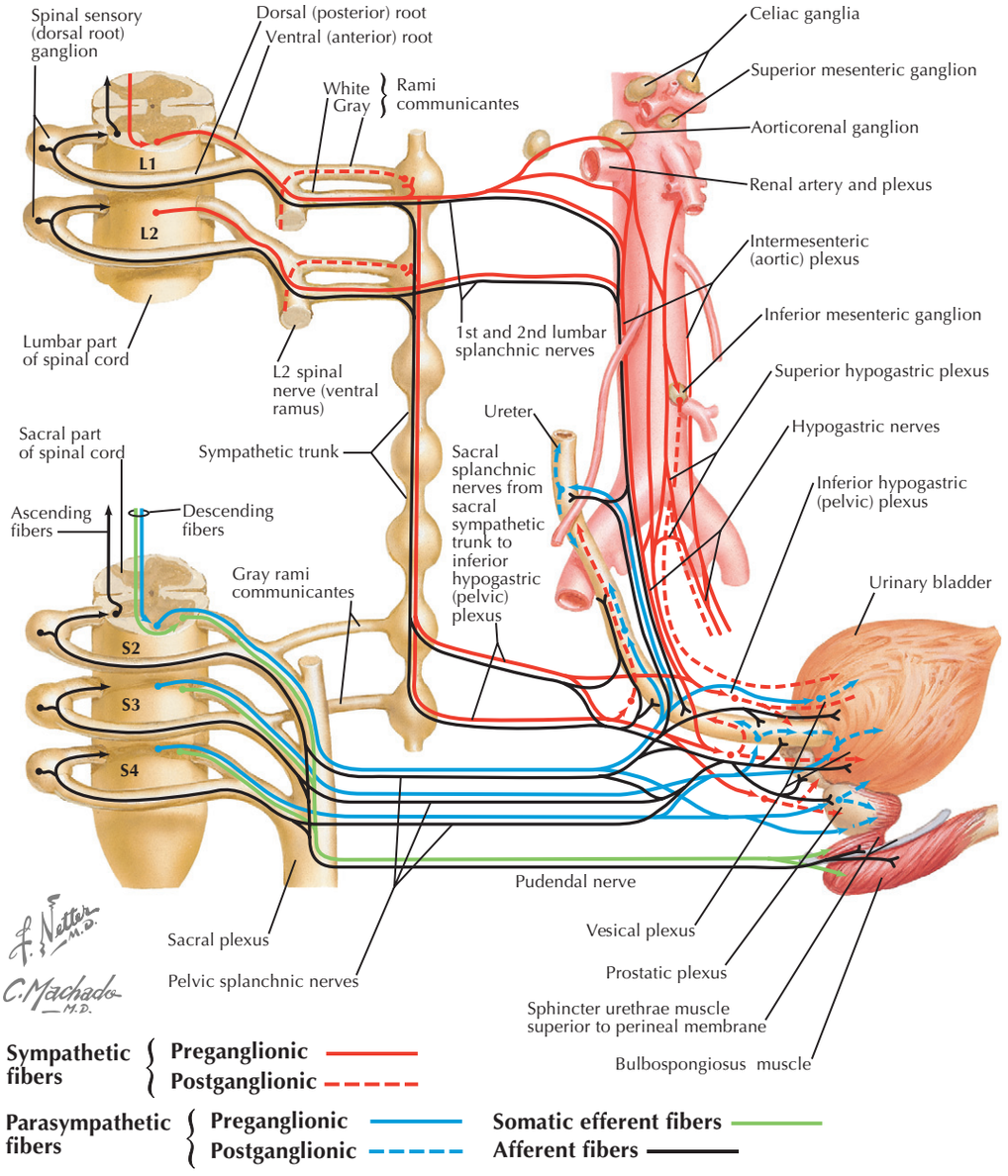
Most of the nerve fasciculi in the urinary bladder wall contain unmyelinated or finely myelinated fibers. A small proportion of larger myelinated and, presumably, sensory fibers are connected with terminal arborizations regarded as stretch receptors. Many other putative sensory endings have been described in the submucosa and mucous membrane. The parasympathetic nerves may transmit many or most of the afferent fibers from the trigonal area of the urinary bladder and from the lowest parts of the ureters, including those conveying painful impulses. However, some afferents from the neck of the bladder and prostatic urethra may reach the spinal cord via the pudendal nerves.

Sensations associated with vesical distention may be mediated through sympathetic pathways because vague discomfort may still be experienced by patients with transverse lesions of the cord below the level of the uppermost lumbar segments. This suggests that there is an afferent inflow from the bladder through the upper lumbar or lowest thoracic posterior spinal nerve roots. Alternatively, such sensations may be produced by the stimulation of nerve endings in the peritoneum over a distended bladder. However, "presacral neurectomy" (removal of the superior hypogastric plexus) rarely completely alleviates discomfort in patients with painful and intractable cystitis because only a proportion of the vesical afferent fibers traverse the hypogastric nerves and superior hypogastric plexus. Other afferent fibers traveling in the perivascular plexuses of the vesical and iliac arteries may also reach the superior hypogastric plexus. Beyond the plexus, the fibers run in lumbar splanchnic nerves to the sympathetic trunks, pass through rami communicantes to the upper lumbar and lowest thoracic spinal nerves, and enter the spinal cord through the posterior roots of these nerves.

The parasympathetic supply to the bladder produces contraction of the walls and relaxation of the sphincteric mechanism and is thus actively involved in micturition. Many credit the sympathetic supply with opposing effects, such as relaxation of the detrusor muscles of the vesical wall by activation of beta-adrenergic receptors and contraction of the internal sphincter by activation of alpha-adrenergic receptors. However, the sympathetic nervous system may play a minor role in bladder function, and the preponderance of evidence suggests that human bladder function depends on the integrity of the parasympathetic and somatic motor innervation of the bladder.

There are multiple interactive reflex arcs that are important in the volitional control of the bladder. The first is a connection between the posteromedial frontal lobe to the pontine nuclei via the basal ganglia. Lesions of this loop result in detrusor hyperreflexia and failure of volitional suppression of the detrusor reflex. The second reflex arc extends from the pontine nuclei to the motor neurons of the sacral region that innervate the bladder; again interruption results in detrusor hyperreflexia. The third reflex arc includes afferents from the detrusor muscle to the motor neurons of the bladder and the fourth involves afferents from the external urethral sphincter to the motor nuclei; loss of these reflex arcs results in distention of the bladder with failure to empty.

Innervation of Urinary Bladder and Lower Ureter



Innervation of Reproductive Organs

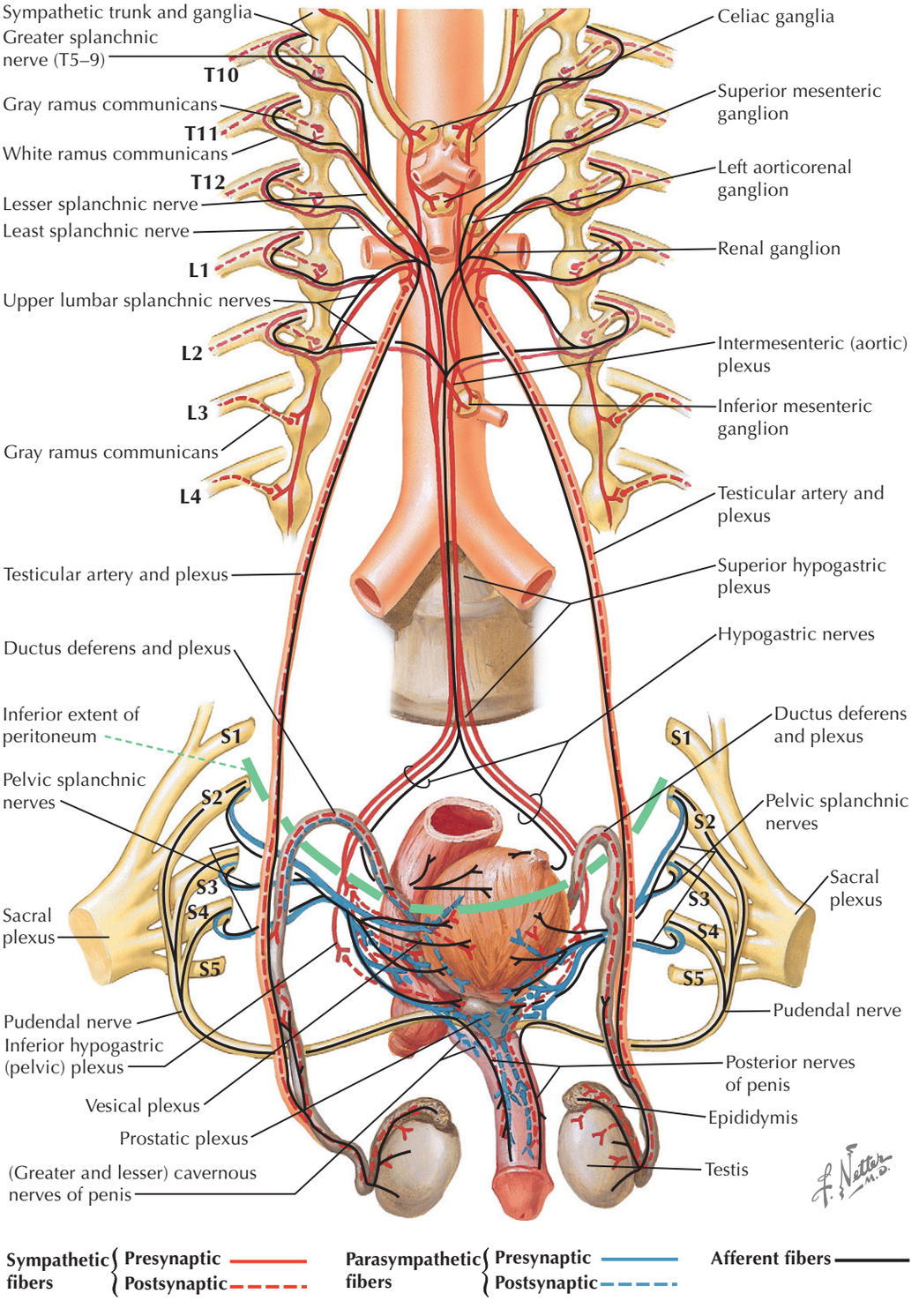
The nerves supplying the male and female genital organs contain sympathetic and parasympathetic efferent and afferent fibers; their origins are similar in both sexes.

Sympathetic preganglionic fibers are the axons of intermediolateral column cells located in the lowest two or three thoracic and upper one or two lumbar segments of the spinal cord. They emerge in the anterior nerve roots of the corresponding spinal nerves and leave them in white rami communicantes passing to adjacent sympathetic trunk ganglia. They course via the thoracic and the upper lumbar splanchnic nerve, the celiac, intermesenteric (aortic) and superior hypogastric plexuses, and the hypogastric nerves to the *inferior hypogastric (pelvic) plexuses*. Many of these fibers relay in the lowest thoracic and upper lumbar sympathetic trunk ganglia or within the celiac plexus, but others do not relay until they reach ganglia in the inferior hypogastric plexuses. Consequently, the postganglionic fibers to the pelvic organs may be either long or relatively short. A minority of the sympathetic fibers for the pelvic viscera descend in the sympathetic trunks to emerge in the tiny *sacral splanchnic nerves* and thus join the inferior hypogastric plexuses.

Preganglionic parasympathetic fibers reach the inferior hypogastric plexuses in *pelvic splanchnic nerves* arising from the second, third, and fourth sacral spinal nerves. Nerve fibers from the *inferior hypogastric plexuses* supply the genital organs, and most of them relay in ganglia close to the prostate gland, neck of the bladder, cervix of the uterus, and upper vagina. Others relay in microscopic ganglia in or near the walls of seminal vesicles, deferent ducts, epididymis, and uterine tubes. There are no ganglia within the substance of the testes and ovaries. Inconclusive evidence suggests that parasympathetic fibers reach the outer parts of the uterine tubes by passing through the celiac plexus into the superior ovarian nerves that help to supply the oviducts. Histochemical studies indicate that parasympathetic innervation of the genital systems in both sexes is less abundant than sympathetic innervation.

Afferent fibers exist in both the sympathetic and parasympathetic pathways and follow the same routes as the efferent fibers, but in the reverse direction. Their parent pseudounipolar cells are situated in the posterior root ganglia of the lower thoracic, upper lumbar, and midsacral spinal nerves. The peripheral processes of these cells transmit impulses from the genital organs, ducts, and vessels. Their central processes carry the impulses into the cord, where many are carried to the brain in ascending pathways in the lateral and posterior white columns, whereas others form synapses with lateral cornual cells in the related cord segments and are thus involved in spinal reflex arcs.

Male Reproductive Organs



Male Reproductive Organs

The nerves supplying the testis, epididymis, and ductus (vas) deferens are derived from three bilateral sources.

A superior group arises by rootlets from the *renal* and *intermesenteric plexuses*, with inconstant contributions from the *lumbar splanchnic nerves* and the origin of the *superior mesenteric plexus*. One or two small ganglia are associated with these rootlets. They communicate with the superior ureteric nerves and, on the right side, with branches supplying the duodenum and pancreas. The rootlets coalesce to form two or three slender nerves, which descend on the testicular artery to the *testis*.

Innervation of Reproductive Organs *(Continued)*

A middle group arises by rootlets from the *superior hypogastric plexus* and from the ipsilateral *hypogastric nerve*, and often communicates with the *middle ureteric* and *genitofemoral nerves*. The resultant nerves are mostly or entirely distributed to the *epididymis* and the *ampulla* of the *ductus deferens*.

An inferior group of a few small nerves arises from the *inferior hypogastric plexus* and from the nerve loops around the *lower end of the ureter* (see page 195). This third group is closely associated with small nerves given off from the anterior part of the inferior hypogastric plexus to the seminal vesicles, prostate gland, ejaculatory ducts, and the base of the urinary bladder. The *prostatic* and *urethral nerve fibers* communicate with branchlets of the *pudendal nerves*, and offshoots from these united nervelets innervate the corpora cavernosa, the corpus spongiosum and the part of the urethra within it, and the bulbourethral glands. The nerve fibers supplying the cavernous structures and their vessels are termed the *penile cavernous nerves*, whereas their ramifications are often called the *cavernous plexuses*.

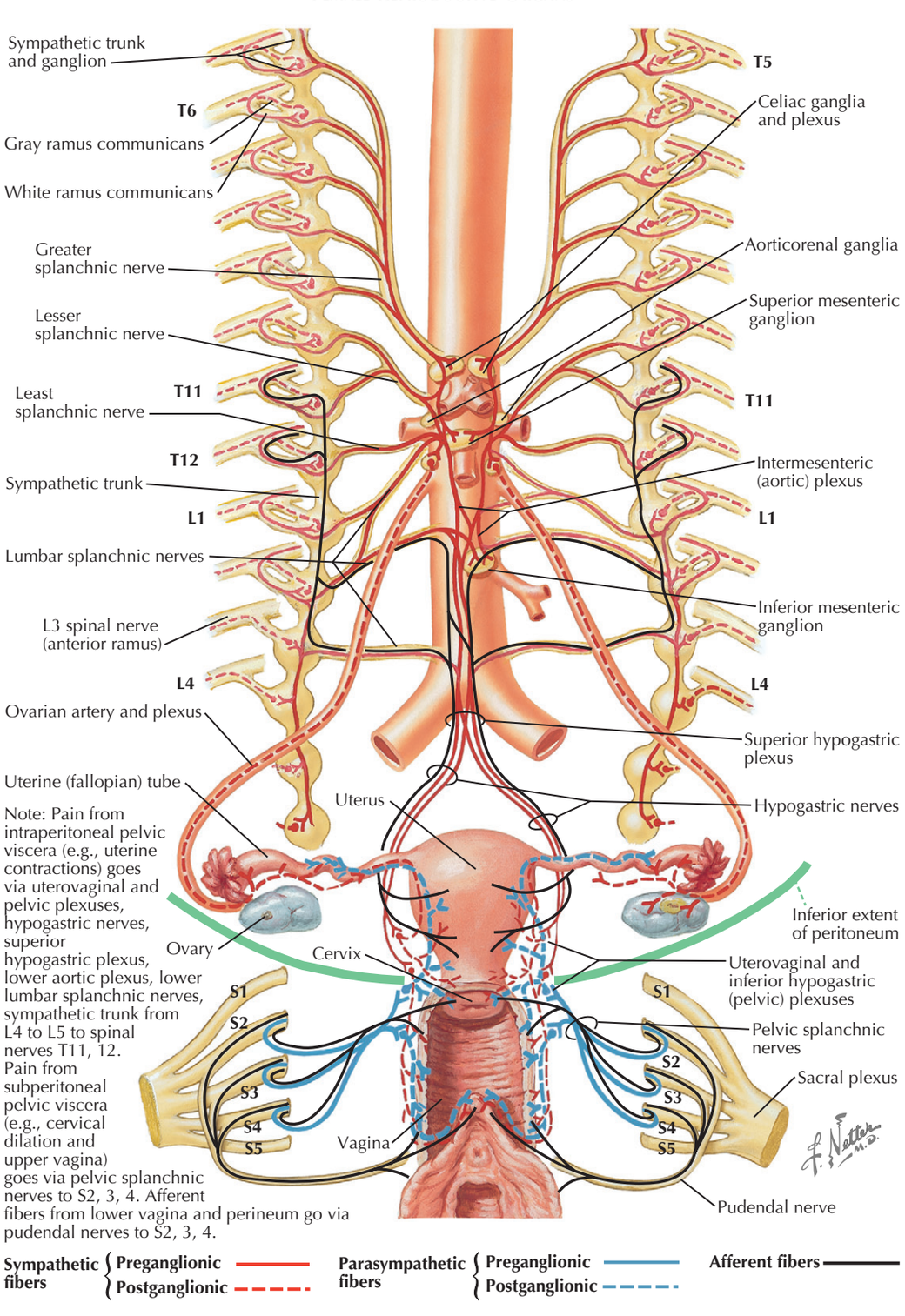
Female Reproductive Organs

The autonomic nerves supplying the female genital organs have similar origins to those supplying the male genital organs.

The superior group coalesces to form two or three slender nerves, which accompany the ovarian artery and supply nerve fibers to it and to the *ovary* and outer parts of the *uterine tube*. Their terminal fibers communicate with *uterine fibers* innervating the inner end of the uterine tube. Most of the afferent fibers in these nerves enter the spinal cord through the posterior roots of the tenth and the eleventh thoracic nerve, although a number may enter through the ninth or twelfth nerves.

The middle group helps to supply the *ovaries* and the *uterine tube* and vessels and gives off fascicles to the common and external iliac arteries.

The inferior group consists of nerves that enter the *cervix* of the *uterus* and the *vagina* directly, often alongside branches of the uterine and vaginal vessels, and other nerves that ascend with or near the uterine artery, supplying nerve fibers to the *body* and *fundus* of the *uterus*, as well as to the artery and its branches. The terminal nerve fibers supply the uterine end and isthmus of the *uterine tube*, where they communicate with corresponding nerve fibers from the superior and middle groups of nerves.



The *uterine nerves* ramify throughout the myometrium. The fibers, which are predominantly unmyelinated and adrenergic in type, are most plentiful around the uterine end of the uterine tube, in the cervix, and near the arterial branches.

The nerves entering the upper part of the *vagina* contain tiny ganglia. They break up into nerve fibers that supply the vaginal arteries and give off fascicles to the muscular and mucous coats of the vagina and urethra, the erectile tissue of the vestibular bulb and corpora cavernosa clitoridis, and the greater and lesser vestibular glands. These nerves contain a mixture of sympathetic and parasympathetic efferent and afferent fibers.

Autonomic Testing

Tests are performed to assess both the sympathetic and parasympathetic systems.

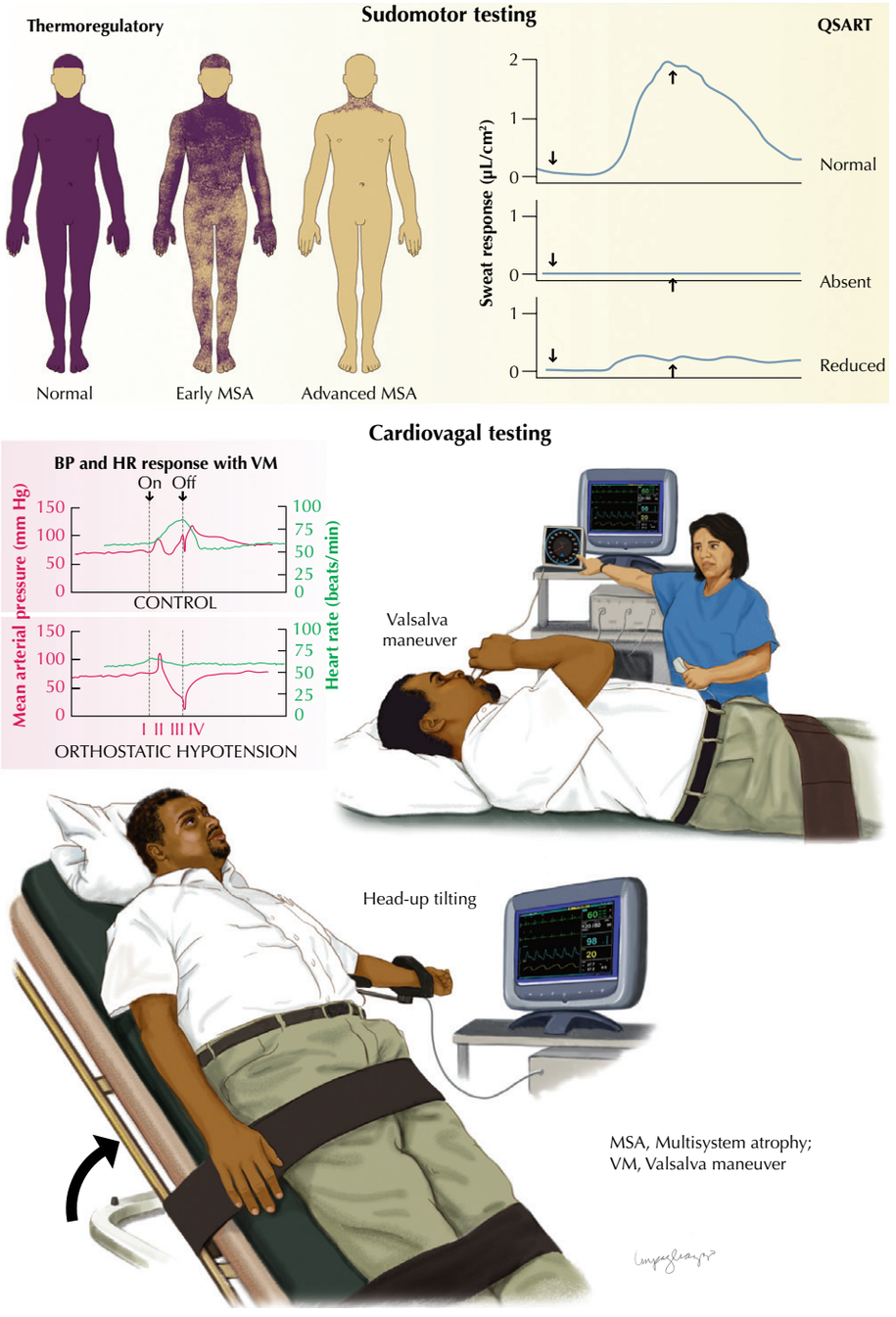
SWEAT TESTING

The thermoregulatory sweat test consists of the visual detection of skin humidity in response to warm external temperature. A dye that changes color when moist is painted or sprinkled onto the patient's skin, and the ambient temperature is raised by 1°C by a heat cradle over the torso. As the patient starts to sweat, the dye changes to a dark purple color. This test measures abnormalities in the sweat pathways at all levels (afferent, central, and efferent). The quantitative sudomotor axon reflex test (QSART) evaluates postganglionic sudomotor cholinergic fibers more objectively. It involves the iontophoresis of acetylcholine, resulting in an axon reflex: an impulse travels antidromically to reach a branch point and then orthodromically to the sweat gland, stimulating the release of acetylcholine from the nerve terminal to evoke the sweat response. A multicompartment sweat capsule is attached to the skin to measure the sweat response at standardized sites. Abnormality indicates that postganglionic sudomotor sympathetic axons are dysfunctional. QSART is usually normal in preganglionic lesions. The sympathetic skin response (a voltage change at the skin surface after an electrical stimulus) also reflects postganglionic sudomotor function, with results correlating with those of other sweat tests.

CARDIOVAGAL TESTING

Cardiovagal function is assessed by measuring the heart rate response to deep breathing, the Valsalva maneuver (VM), and standing. For the heart rate response to deep breathing, the patient inspires and expires deeply at six breaths per minute, and the difference between the maximum and minimum heart rate response is calculated. For VM, the subject makes a forced expiration to maintain a column of mercury at 30 to 40 mm for 15 seconds, and the ratio of the maximum heart rate during the maneuver to the lowest rate occurring within 30 seconds of its conclusion is determined. Concurrent measurement of beat-to-beat blood pressure (BP) enables quantification of baroflex sensitivity. There are four main phases to the response to the VM; during phase I, there is a transient rise in BP due to increased intrathoracic and intraabdominal pressure. In early phase II (II_e), the reduced venous return results in a fall in BP followed by a compensatory increase in heart rate and peripheral resistance, resulting in an increase in BP in the late phase II (II_L). During phase III, there is a transient decline in BP from a reduction in intrathoracic pressure, and in phase IV, the BP overshoots due to normalized venous return and cardiac output in the presence of persistently increased peripheral resistance. Late-phase II (II_L) is a function of alpha-adrenergic and phase IV of beta-adrenergic responses; they can be used to assess sympathetic adrenergic integrity. Abnormality may lead to an excessive decline in blood pressure in phase II, with no BP overshoot in phase IV.

On standing, the heart rate increases, peaking at about the 15th beat after standing, and then declines to reach a stable state at about the 30th beat. The ratio of the R-R interval at the 15th and 30th beats after standing provides a test of parasympathetic (vagal) function. It is age dependent, but in young adults, a ratio of less than 1.04 is abnormal. The biphasic response that occurs on standing is not present with passive tilt.



HEAD-UP TILTING

Patients with sympathetic dysfunction have a progressive decline in blood pressure during head-up tilt to 70 degrees. The heart rate response is also usually attenuated and does not compensate fully for the fall in blood pressure. If the patient is being evaluated for neurocardiogenic syncope or delayed orthostatic hypotension, prolonged tilting beyond 10 minutes, often for about 45 minutes, is needed.

ISOMETRIC HANDGRIP

During sustained handgrip, sympathetic outflow increases due to muscle contraction, increasing the BP. For testing purposes, a 30% maximal contraction for 3 to 5 minutes is required; diastolic BP usually increases by more than 15 mm Hg.

NEUROCHEMICAL TESTING

Measurement of supine and upright plasma norepinephrine levels provides a measure of postganglionic release of norepinephrine; levels usually double on standing. With preganglionic lesions, supine levels are normal, but there is a limited rise or no change in the standing level. In postganglionic lesions of the sympathetic system, both supine and standing values are low.

^{131}I-labeled metaiodobenzylguanidine (MIBG) scintigraphy is useful in evaluating cardiac sympathetic innervation.

Abnormal Pupillary Conditions

Adie's Tonic Pupil

The tonic pupil, or Adie's pupil, results from parasympathetic denervation. The tonically dilated pupil does not usually respond to light but responds to accommodation with slow constriction and then remains constricted for longer than normal (light-near dissociation). There is degeneration of the ciliary ganglion and the short ciliary nerves, sometimes with aberrant reinnervation. Most cases are idiopathic, but other causes include inflammation, ischemia, tumor, trauma, and paraneoplastic and autonomic neuropathies. When idiopathic, it is seen usually in young women, but it may occur in men and manifest at any age. It is commonly associated with reduced or absent muscle stretch reflexes in the lower limbs and sometimes with abnormalities of thermoregulatory sweating. The pupillary abnormality is commonly unilateral but may become bilateral.

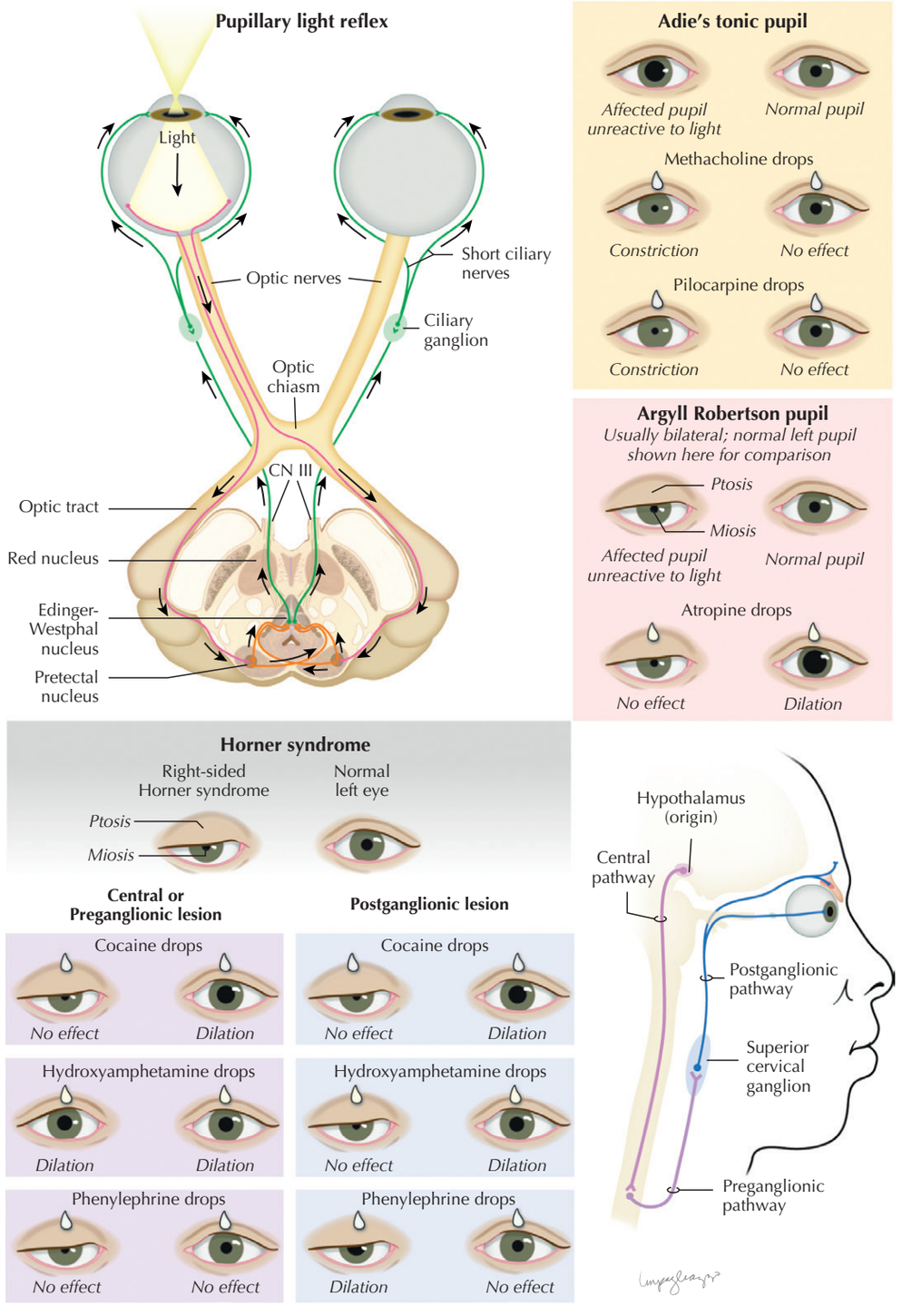
Although initially the affected pupil is larger than the contralateral pupil, with time it can become smaller. The pupil is very sensitive to acetylcholine (probably due to denervation supersensitivity), with strong, tonic constriction; this can be demonstrated by the vigorous miotic response to methacholine chloride and 0.1% pilocarpine. The intact sympathetic innervation is demonstrated by the normal response to cocaine.

Argyll Robertson Pupil

This was initially described in neurosyphilis or tabes dorsalis. The classic findings include a normal near or convergence reflex with normal pupillary responses to accommodation and an abnormal pupillary response to light. In addition, the pupils are small, irregular, and constrict with physostigmine and dilate variably with atropine and cocaine. The location of the lesion in the brain that causes the abnormal response is thought to be the rostral midbrain, near the periaqueductal gray. Although previously thought to be pathognomonic of neurosyphilis, it is now recognized in diabetes, viral encephalitis, multiple sclerosis, and other inflammatory and degenerative diseases of the brain.

Horner Syndrome

Horner syndrome results from loss of sympathetic innervation to the eye and is characterized by ptosis (droopy eyelid), miosis (constricted pupil), and facial anhidrosis (impaired facial sweating). Additional findings may include pigmentary changes in the iris. Pupillary reactions to light and accommodation are normal. The anisocoria (inequality in pupil size) is accentuated in dim light. The ptosis is due to paralysis of the Muller muscle; this is the sympathetically innervated smooth muscle of the upper eye lid. Acquired Horner syndrome may be central, preganglionic, or postganglionic. A central lesion may involve the first-order neuron at any point from the cell origin in the hypothalamus to its termination in the intermediolateral column of the spinal cord. Causes include brainstem infarction, tumor, and syringomyelia (cavitation in the spinal cord). Preganglionic Horner syndrome is due to involvement of the second-order neuron from its origin in the intermediolateral column to its termination in the superior cervical ganglion; causes include trauma or tumor of the cervical or upper thoracic spinal cord and lesion of the lower trunk of the brachial plexus, such as by tumors of the lung apex, jugular vein puncture, and thyroid surgery. Postganglionic Horner syndrome results from lesions of the third-order neuron in the sympathetic ganglion and the pathway leading to its termination in the face and eye, such as by extracranial carotid artery dissection, intracranial lesion in the carotid canal, or cavernous sinus pathology. Use of cocaine eye drops (which block the reuptake of norepinephrine) will help distinguish true Horner syndrome from physiologic anisocoria; 1 hour after instillation of 4% to 10% cocaine drops, a normal pupil will have dilated more than a pupil with sympathetic dysfunction (irrespective of site of lesion), increasing the baseline anisocoria. Apraclonidine, an alpha-adrenergic receptor agonist will cause the affected pupil to dilate (due to alpha-adrenergic supersensitivity), whereas the normal pupil will constrict. Pharmacologic testing will also differentiate between central, preganglionic, and postganglionic lesions. Hydroxyamphetamine (1%) drops instilled into the eye do not affect the pupil of Horner syndrome resulting from a lesion of the third-order postganglionic neuron, whereas a dilation occurs of normal pupils and in Horner syndrome with an intact third-order neuron due to release of norepinephrine. Similarly, 1% solution of phenylephrine hydrochloride will dilate the pupil in postganglionic lesions (third-order neurons) but not normal pupils.



ABNORMAL PUPILLARY CONDITIONS *(Continued)*

CLINICAL PRESENTATION OF AUTONOMIC DISORDERS

Patients usually have combinations of parasympathetic and sympathetic dysfunction. The former is characterized by dry mucous membranes, particularly the eyes and mouth, with gastrointestinal and urogenital symptoms: early satiety, nausea, vomiting, constipation, diarrhea, urinary bladder dysmotility, and erectile dysfunction. Feelings of light-headedness or syncope, when assuming an upright posture, and alteration of sweating are symptoms of impaired sympathetic function. Sexual dysfunction is due to combined parasympathetic and sympathetic disorders. Signs of autonomic dysfunction include fixed heart rates, orthostatic hypotension, and tonic pupils, with normal strength and sensation unless somatic nerves are also affected.

Autonomic disorders may be classified as peripheral or central and acute or chronic disorders.

ACUTE PERIPHERAL AUTONOMIC DISORDERS

Acute/subacute autonomic neuropathies are usually due to toxic, metabolic, autoimmune, or paraneoplastic causes. Primary autonomic polyneuropathies represent an uncommon subgroup. However, many length-dependent polyneuropathies have associated autonomic fiber involvement. Impotence is such an example in diabetic polyneuropathies.

Antecedent viral infections may occur in patients with *autoimmune autonomic neuropathy*, suggesting that it may be a variant of Guillain-Barré syndrome. They usually have severe generalized disorders, but restricted milder forms also occur. Orthostatic intolerance and gastrointestinal dysmotility are common presentations. Autonomic tests are abnormal. Recovery is slow and incomplete. High titers of ganglionic nicotinic acetylcholine receptor antibodies are reported, supporting an autoimmune basis.

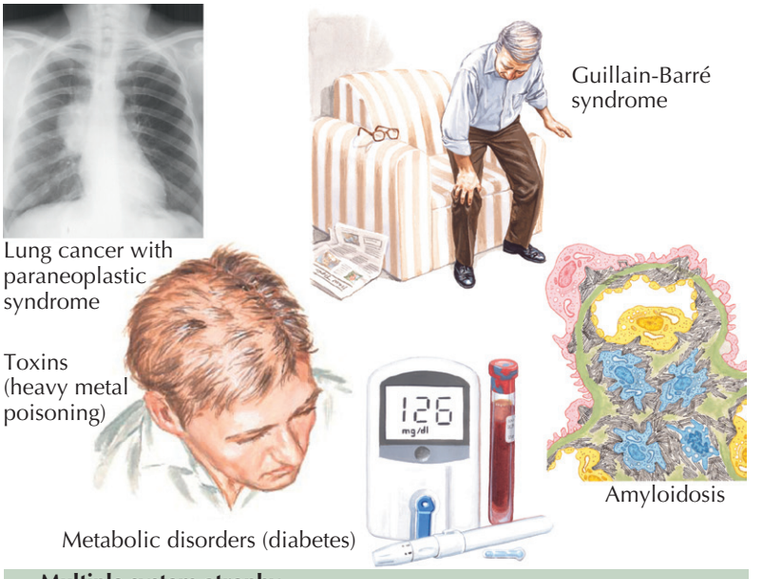
Guillain-Barré syndrome preferentially involves somatic fibers but causes dysautonomia in two thirds of cases, especially affecting the cardiovascular and gastrointestinal systems. Bladder dysfunction is less common. Autonomic complications may be life-threatening; patients must be monitored in the intensive care unit.

Paraneoplastic autonomic neuropathy is indistinguishable from autoimmune autonomic neuropathy. Gastrointestinal dysmotility is a common manifestation. Antineuronal nuclear antibody type 1 is associated with small cell lung cancer. In the Lambert-Eaton myasthenic syndrome, which is associated with presynaptic voltage-gated calcium channel antibody (P/Q type), significant dysautonomia may occur.

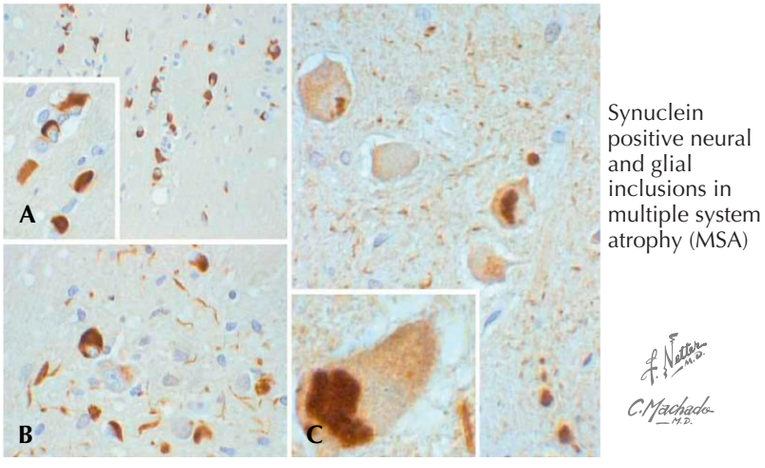
Hereditary porphyria manifests with acute attacks of dysautonomic symptoms (abdominal pain, vomiting, constipation, hypertension, and tachycardia) in addition to motor polyneuropathies. Diagnosis requires demonstration of increased urinary excretion of porphobilinogen.

Toxins, including medications (particularly cisplatinum and vinca alkaloids) may cause peripheral neuropathies with autonomic features. Other autonomic nerve toxins include organophosphates, thallium, arsenic, hexacarbons, and acrylamide.

Causes of dysautonomia



Multiple system atrophy



CHRONIC PERIPHERAL AUTONOMIC DISORDERS

Autonomic neuropathies are common accompaniments of diabetic peripheral neuropathies and correlate with duration and control of diabetes. Autonomic testing reveals evidence of cardiovagal dysfunction manifested by impairment of heart rate response to Valsalva maneuver or to deep breathing.

Postural orthostatic tachycardia syndrome (POTS) is seen predominantly in young women. It is characterized by orthostatic symptoms associated with significant rise in heart rate on standing, without orthostatic hypotension or other clinical or laboratory evidence of autonomic neuropathy, except for distal loss of sweating.

Amyloidosis is a multisystem disorder that may be sporadic or familial. Autonomic neuropathy often occurs and presents with symptoms of somatic small fiber dysfunction, orthostatic intolerance, and constipation alternating with diarrhea.

Pure autonomic failure is also known as idiopathic orthostatic hypotension. It is an insidious process with typical signs of disordered autonomic function. The absence of parkinsonian features helps differentiate this disorder from multiple systems atrophy. It results from postganglionic sympathetic neuron degeneration.

Hereditary autonomic neuropathies are rare disorders. Hereditary sensory and autonomic neuropathy type III, also known as Riley-Day syndrome, is an autosomal recessive disorder with defective control of blood pressure, sweating, temperature, and lacrimation in children. Dysautonomic manifestations are less pronounced in other hereditary sensory and autonomic neuropathies.

CENTRAL DISORDERS

Parkinson disease is associated with significant autonomic dysfunction, particularly in long-standing disease. There is loss of pigmented dopaminergic cells in substantia nigra; other pigmented nuclei, including locus ceruleus and dorsal vagal nucleus are affected; this may explain the dysautonomia. Peripheral sympathetic denervation of the heart is common, resulting in orthostatic hypotension in severe cases.

Multiple systems atrophy, a degenerative disorder, is characterized by parkinsonian features with autonomic, cerebellar, and corticospinal involvement. When autonomic symptoms predominate, the disorder is called *Shy-Drager syndrome*.

Spinal cord disorders may also cause autonomic symptoms. Common disorders include trauma, syringomyelia, and multiple sclerosis. They usually manifest with arrhythmias, blood pressure lability, and bladder atony.

PAIN

Pain Pathways Anatomy
Ascending Pathways
Endorphin System

Pain propagation is initiated with activation of nociceptors, distributed within skin, muscle, joints, and viscera. These receptors include small-diameter Aδ and C-fiber free nerve endings representing distal primary afferent neurons. Cutaneous *Aδ fibers (myelinated)* mediate sharp sensation of first-phase or acute pain known to trigger withdrawal responses. These include two fiber groups; first are high-threshold *mechanoreceptors fibers*, responding to mechanical stimuli of high intensity and, after sensitization, to noxious heat. *Mechanothermal receptors* for extreme (i.e., noxious) heat and cold sensation comprise the second group of fibers. Once sensitized, these receptors are activated by mechanical stimuli at non-noxious thresholds.

C-type fibers (unmyelinated) slowly propagate dull, burning (secondary) pain sensation information. Some C fibers are modality-specific and respond only to thermal, mechanical, or chemical noxious stimuli. However, the majority of C fibers are polymodal, which means that they respond to both thermal and mechanical noxious stimuli, as well as to chemical algesiogenic substances (e.g., potassium ions, prostaglandins, substance P, and histamine). A unique C-fiber subtype responds to high-intensity thermal stimuli and also mediates flare responses after tissue damage. Some C-type nociceptors, designated *silent receptors*, are primarily activated by inflammation.

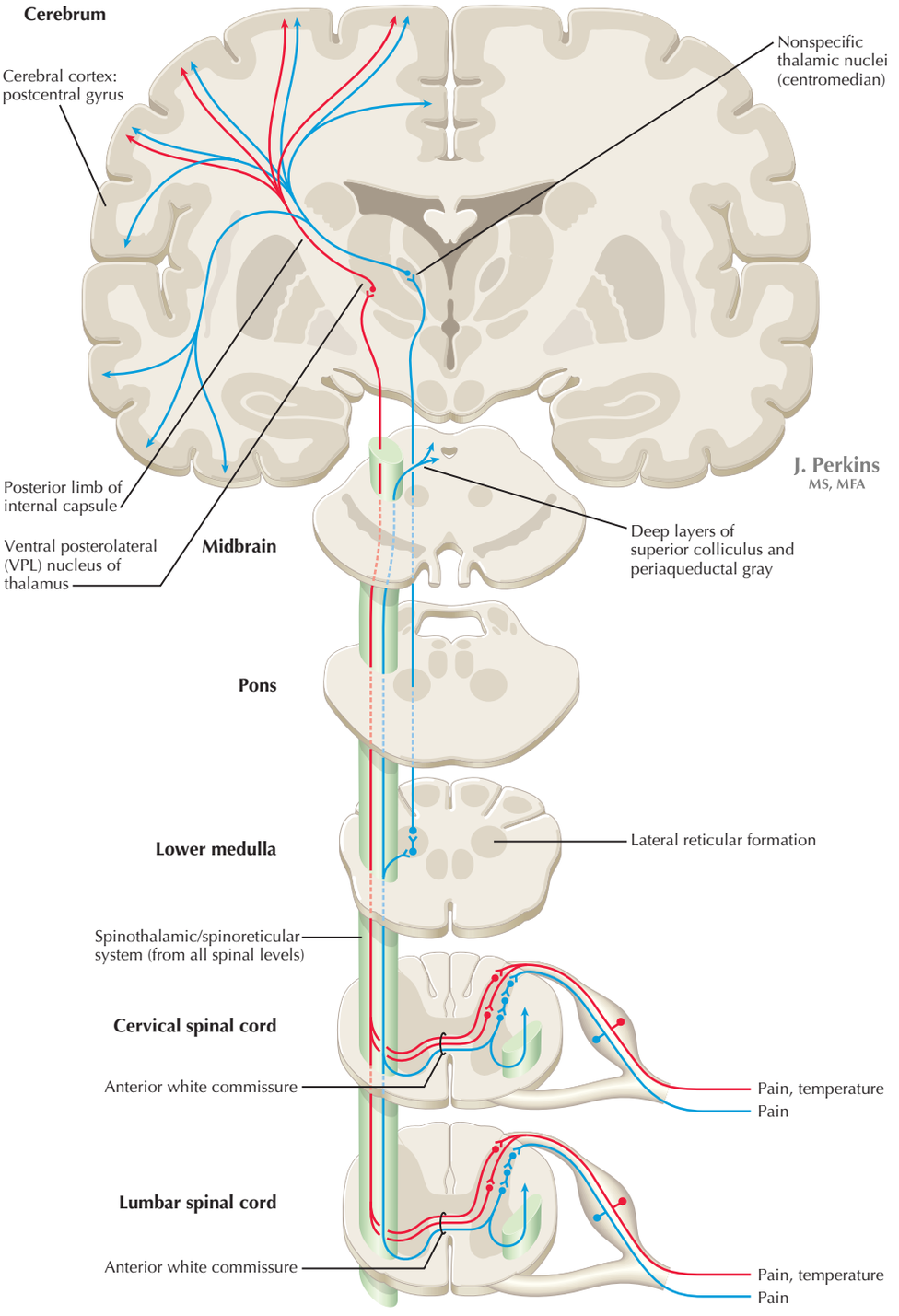
The primary afferent fibers travel through dorsal nerve roots entering the dorsal horn of the spinal cord, where they divide in a "T" pattern traveling two to three spinal segments within the Lissauer tract in both rostral and caudal directions, and sending collateral projections to the gray matter along the entire four- to six-segment length, thus transmitting pain signals over a broad spinal cord area.

Both myelinated and unmyelinated primary afferent fibers project predominantly to the superficial laminae of the dorsal horn. Although there is considerable overlap in the projection of fibers, signaling innocuous and noxious stimuli, there exists some degree of functional segregation at the postsynaptic level in the superficial laminae. Dorsal horn neurons are classified into three distinct groups. The specific nociceptive neurons that respond exclusively to noxious stimuli are found in Rexed laminae I, II, V, and VI. Their receptive fields in lamina I are punctiform and display somatotopic organization.

Lamina I neurons are classified into several modality-selective classes, relaying information from particular subsets of small-diameter fibers and relating the current physiologic status of body tissues. The two nociceptive cell types, *nociceptive-specific (NS)* and *polymodal nociceptive (HPC, for heat, pinch, and cold)* have different characteristics. *NS neurons* receive mainly *Aδ inputs* associated with first-pain, and relay information about noxious stimuli localization and physical quality. *HPC cells* receive *polymodal C-nociceptor* information and are associated with second pain. *Lamina I cells* relate current physiologic conditions of all body tissues and regulate spinal cord excitability, and therefore pain behavior, through the activation of descending inhibitory and excitatory pathways from the brainstem.

Lamina V neurons are large cells with dendrites extending across the dorsal horn, receiving myelinated primary afferent input from Aβ, Aδ, and C fibers. According to *gate control theory*, this fiber group is important for segmental suppression of pain; however, their inhibitory role is not yet confirmed. Almost all of lamina V consists of *wide dynamic range (WDR)* cells, which have large receptive fields and high-frequency ongoing discharges. WDR neurons demonstrate graded responses to pressure and noxious stimuli, including heat, cold, and deep and visceral stimulation. Their activity represents integration of all dorsal horn afferent inputs. In contrast to lamina I neurons, WDR cells are not somatotopically organized; their complex excitatory and inhibitory receptive fields are musculotopically organized. Their main characteristic is to code stimulus intensity; they demonstrate increasing frequencies of response from innocuous to noxious stimulation.

Intrinsic dorsal horn neurons promote interaction of afferent and efferent nociceptive stimuli and are also responsible for their transfer to supraspinal structures. These are classified as (1) *projection neurons* directly transmitting information to supraspinal centers, (2) *intersegmental propriospinal neurons* integrating several spinal levels, and (3) *interneurons* having inhibitory or excitatory features. Nociceptive projection neurons relay information to various brainstem and diencephalon regions, including the thalamus, periaqueductal gray, bulbar reticular formation, and limbic structures within the hypothalamus, amygdala, and other sites. There is also a visceral nociceptive pathway within the postsynaptic posterior column pathway.



Pain Pathways Anatomy
Ascending Pathways
Endorphin System *(Continued)*

The spinothalamic tract (STT) mediates sensations of pain, cold, warmth, and touch. This pathway originates from WDR, SN, and non-nociceptive dorsal horn neurons in laminae I, II, and deeper lamina V. Most spinothalamic tract axons decussate transversely through the anterior white commissure of the spinal cord and ascend through the contralateral anterolateral funiculus. Passing through the brainstem, the spinothalamic tract sends collateral projections to the medullary, pontine, and midbrain reticular formation, including gigantocellularis and paragigantocellularis nuclei and periaqueductal gray matter. These are probably responsible for descending suppressor system activation, as well as behavioral and neurovegetative responses to pain. Three spinothalamic tract afferent forms are recognized, including a *monosynaptic neospinothalamic pathway* (anterior spinothalamic tract) that directly projects to lateral complex thalamic nuclei involved in sensory-discriminative pain components. Another is a *multisynaptic paleospinothalamic pathway*, (dorsal spinothalamic tract) projecting to posterior medial and intralaminar complex thalamic nuclei involved in the motivational-affective aspects of pain. Lastly, there is a monosynaptic spinothalamic pathway projecting directly to thalamic medial central nucleus that is related to affective components of pain sensation.

The thalamus is the main relay structure for sensory information destined for the cortex; it is involved in reception, integration, and transfer of nociceptive potentials. WDR neurons project to the *ventroposterolateral (VPL) and ventroposteromedial (VPM) nuclei*. SN neurons project to the *ventroposteroinferior (VPI) nucleus*, considered the main somatosensory relay. It receives both noxious and innocuous information of cutaneous, muscular, and articular origin. This nucleus has numerous interconnections with the primary somatosensory (SI) cortex. The VPI participates in the processing of visceral pain, occurring through the postsynaptic dorsal column pathway with nucleus gracilis projections.

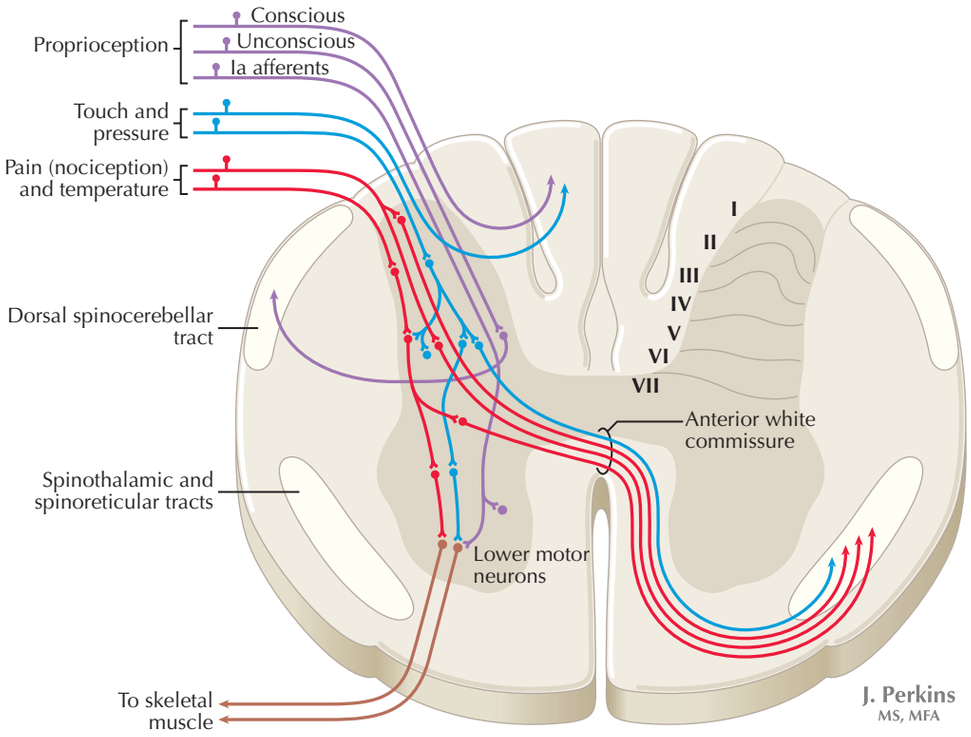
The *VPM nucleus* is likewise involved in sensory-discriminative aspects of thermal, mechanical, and tactile information. Owing to its projections to the prefrontal cortex, the convergence of fibers arising from the parabrachial region within the lateral pons at the locus ceruleus level, as well as to amygdala, hypothalamic, and periaqueductal gray interconnections, the VPM nucleus is likely involved with emotional pain, as well as psychomotor and autonomic reactions to painful stimuli. Posterior division of the *ventromedial nucleus (VmPO)* and posterior nucleus (PO) are essential parts of the medial nociceptive system establishing insular and cingular cortex connections involved in affective-cognitive aspects of pain. Specific spinothalamic tract projections, originating from lamina I, suggest that these nuclei are noxious information integration centers, especially for cases of freezing and visceral sensations.

The *thalamus medial complex* receives afferent input from laminae I and V of the spinothalamic tract, interconnecting with the striatum and the cerebellum. This is responsible for the control of attention and motor responses, suggesting that this area may be involved in escape behavior in the presence of harmful stimuli.

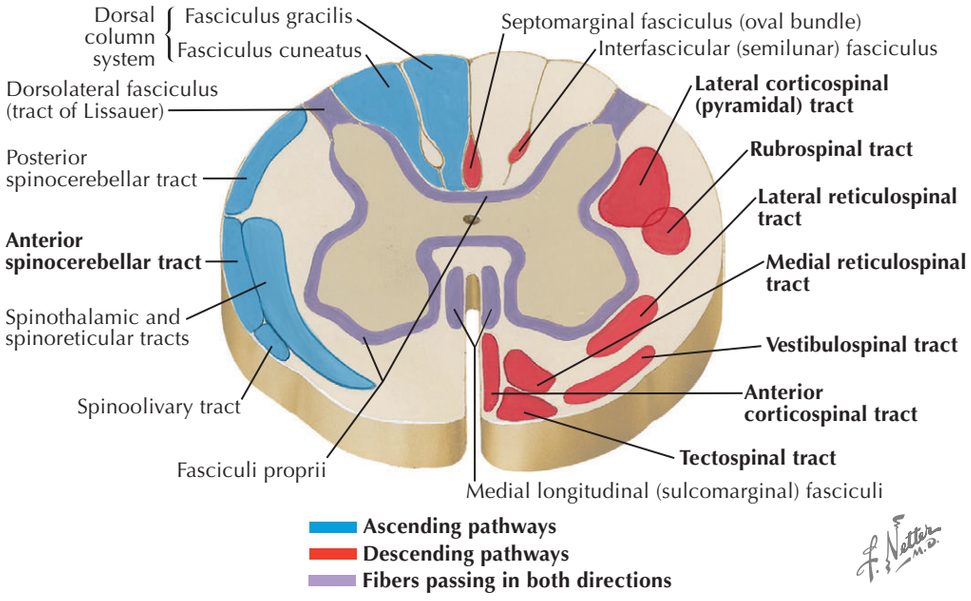
Ultimately the nociceptive signal is relayed from the thalamus to a variety of cortical regions. *Two systems of nociceptive cortical projection* are commonly distinguished: the lateral and medial systems. There are three important cortical regions: primary somatosensory cortex (SI), secondary somatosensory cortex (SII), and the anterior cingulate cortex. The *lateral nociceptive system* participates directly in the sensory-discriminative ascription of nociception involving specific thalamic nuclei, projecting to SN and WDR neurons of the SI and SII cortices. *SN neurons* are associated with topographic localization of peripheral stimuli, whereas *WDR neurons* code the intensity of these stimuli. Nociceptive neurons in the SII cortex code the painful stimulus in temporal terms. Both SI and SII cortices have connections with the posteroparietal area and the insula, responsible for somatosensory input association with learning and memory. This pathway is crucial to assessment of the stimuli features and behavioral decisions in relation to the prefrontal cortex functions. Conversely, the *medial nociceptive system* has more diffuse projections from the medial thalamus to SI and SII, and limbic structures, such as the insula and the anterior cingulate cortex. Accordingly, it is predominantly responsible for the motivational-affective component of pain.

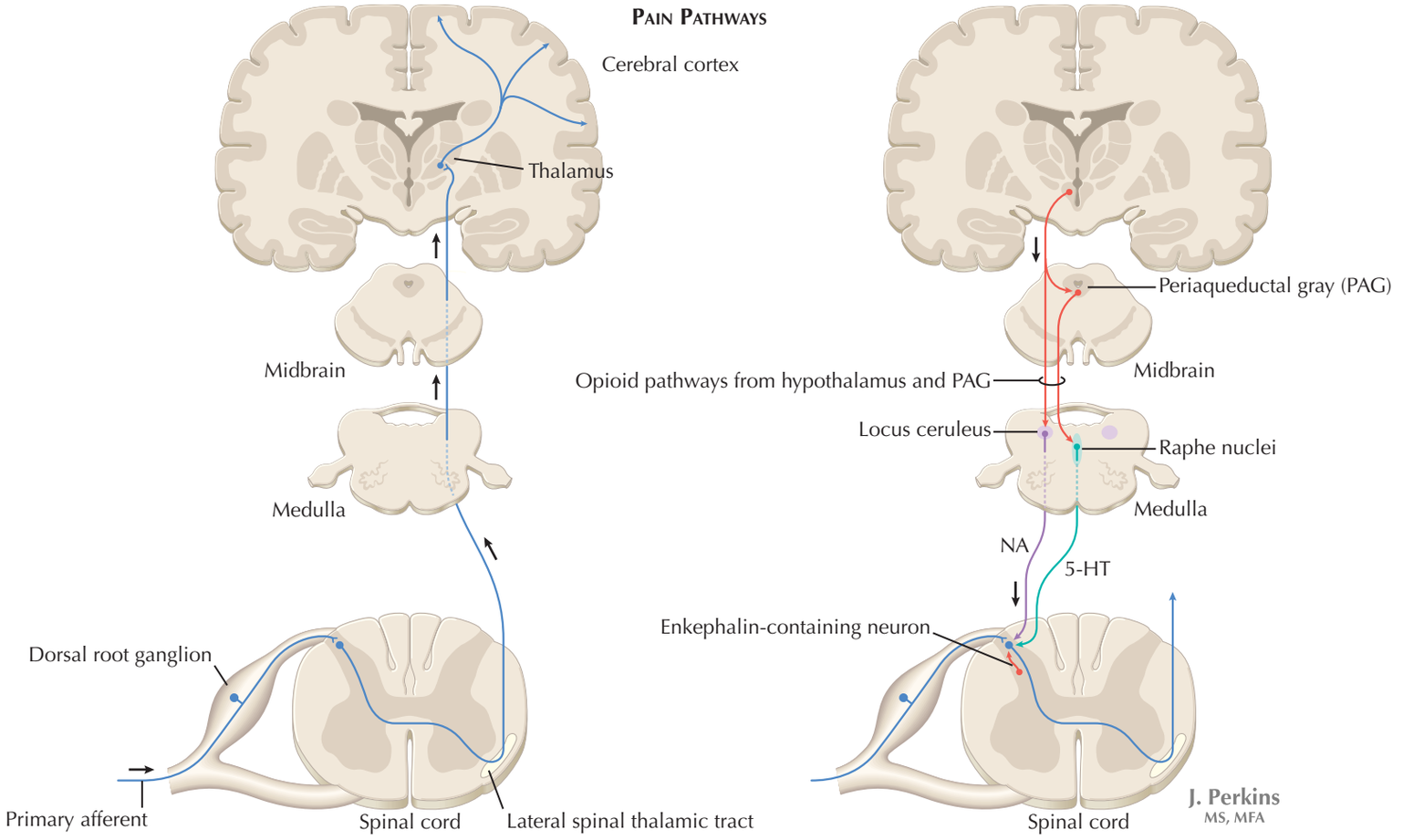
The insula relays information from the *lateral nociceptive system* to the limbic system, mainly via the amygdala and prefrontal cortex associated with the emotional and affective component and with memory integral to the painful experience. The anterior cingulate cortex coordinates inputs from parietal areas with frontal cortical regions, integrating the perception of threat with the appropriate pain behavior.

Somatosensory afferents to the spinal cord



Principal fiber tracts of spinal cord





Descending Nociceptive Pathways and Neurochemical Foundations of Descending Pain Modulation

Descending Nociceptive Pathways

Descending control of spinal nociception arises from various brain areas and is pivotal in determining the experience of pain, both acute and chronic. Several central nervous system areas exert a top-down modulation of nociceptive processing. Projections from prefrontal, anterior cingulate, and insular cortices, as well as hypothalamus and amygdala to the brainstem pain modulatory system, support the notion of emotional and affective regulation of pain transmission. Attention, anticipation, control over pain, and religious beliefs affect pain perception, supporting the importance of the anterior cingulate cortex and frontal lobes in modulation of nociceptive processing.

The current model of descending pain modulation involves both inhibitory and facilitatory influences on spinal nociceptive transmission. The balance between inhibition and facilitation is dependent on different behavioral, emotional, and pathologic conditions. Intense stress or fear is associated with decreased response to pain, whereas inflammation, nerve injury, or sickness is associated with hyperalgesia that partially can be ascribed to descending facilitatory mechanisms. Several studies suggest that descending facilitatory systems are also activated by safety signals that follow an aversive event. In addition, descending facilitation of spinal nociception contributes to central sensitization and development of secondary hyperalgesia. Finally, hyperalgesia encountered during acute opioid abstinence also entails descending nociceptive facilitation from the rostral ventromedial medulla.

A number of supraspinal sites activated by nociceptive input contribute to central modulation of pain. The most prominent ones include *periaqueductal gray (PAG)* and rostral ventromedial medulla (RVM). The effects of descending modulation are exerted in the spinal dorsal horn on the synapse between the primary afferent and projection neurons or on interneurons that synapse with projection neurons, by inhibiting the release of neurotransmitter from primary afferent fibers or by inhibiting the function of neurotransmitter receptors on the postsynaptic neuron.

In awake, behaving animals, *anterolateral periaqueductal gray (PAG)* stimulation leads to immobility, sympathoinhibition, and analgesia as well as inhibition of nociceptive dorsal horn neurons, including spinothalamic tract cells. The PAG contains a large number of neurons. Local injection of opioids, nonspecific *enkephalin*, *substance P, and gamma-aminobutyric acid (GABA) ergic* excitants or neuropeptides into the PAG produces analgesia in animals. Excitatory pathways projecting from the PAG to the brainstem are subject to inhibitory control by GABAergic inhibitory neurons within the PAG. Analgesic opioids and cannabinoids relieve GABAergic control and thus induce analgesia. The PAG is significantly interconnected with the hypothalamus and limbic forebrain structures, including the amygdala. This suggests that cognitive and emotional aspects influence ascending nociceptive input, further modulating the resultant experience of pain.

Major brainstem inputs to the PAG originate from the *nucleus cuneiformis*, *the locus ceruleus*, *the pontomedullary reticular formation*, and other *catecholaminergic nuclei*.

Major descending projections from the anterolateral PAG are to the rostral ventromedial medulla, including the *nucleus raphe magnus* and adjacent *reticular formation*. The PAG pain-modulating action is relayed almost exclusively through the RVM that, in turn, sends bilateral descending projections through posterolateral spinal funiculi terminating within the spinal dorsal horn. The *RVM* is a functional term describing the *midline pontomedullary area* in which opioid injection or electrical stimulation produces *antinociception*, that is, analgesia. It *includes* the *nucleus raphe magnus* and *adjacent reticular formation* and projects diffusely to dorsal horn laminae important in nociceptive processing, including superficial layers and deep dorsal horn.

With increasing understanding of RVM neuronal physiology, it is recognized that this area is central to the mediation of the bidirectional control of nociception. It receives projections from serotonin-containing neurons of the dorsal raphe, neurotensinergic neurons of the PAG, and limbic and prelimbic cortex, including the anterior insula. Nonselective stimulation or inactivation of RVM neurons can either suppress or facilitate nociception, depending on the functional background. This suggests that there are parallel inhibitory and facilitatory output pathways from the RVM to the spinal cord. Adjacent neurons are simultaneously under facilitatory and inhibitory control from supraspinal structures. The equilibrium between inhibition and facilitation determines the net effect of descending modulation on nociceptive transmission.

The RVM includes three distinct types of neurons: (1) neurons that begin discharging just before the withdrawal from noxious heat, entering a period of activity

Descending Nociceptive Pathways and Neurochemical Foundations of Descending Pain Modulation *(Continued)*

("*ON-cells*"), (2) neurons that stop discharging before the withdrawal reflex, entering a period of silence ("OFF-cells"), and (3) neurons that do not demonstrate consistent changes in activity when withdrawal reflex occurs *("neutral cells")*. *ON and OFF cells* send projections specifically to laminae I, II, and V of the dorsal horn. Activation of *OFF cells* produces behavioral antinociception, and is required for the analgesic opioid effect. In contrast, direct, selective activation of *ON cells* produces hyperalgesia; their discharge is associated with enhanced nociception. Thus *OFF cells* exert a net inhibitory effect on nociception, whereas the *ON cells* play a facilitatory role in the descending modulation of pain.

Neutral cells' role in pain modulation is unexplained. One theory is that neutral cells are recruited to become ON or OFF cells during development of chronic pain states, which is supported by wide variations of ON and OFF cells excitability under basal conditions. At least some neutral cells are *serotonergic.* Considering the importance of serotonin in nociceptive modulation, this suggests that *neutral cells* may be involved in the descending control of pain transmission.

The *locus ceruleus* and the *A5 and A7 noradrenergic cell groups* of the *posterolateral pons* are the main source of noradrenergic input to the dorsal horn. These regions send bilateral projections that primarily descend to contralateral laminae I, II, and V of the spinal dorsal horn, exerting an antinociceptive effect. The PAG sends input to the locus ceruleus and the A7 region. RVM neurons containing substance P or enkephalin also send input to A7. Consequently, the *posterolateral pontine tegmentum* provides a corresponding pathway for the PAG and RVM to provide descending nociception control over the spinal dorsal horn. *Posterolateral pontine systems* may also provide cortical control of spinal pain transmission. The anterior insular cortex has locus coeruleus and RVM connections, suggesting that inhibition of the insular outflow disinhibits noradrenergic neurons of the locus ceruleus.

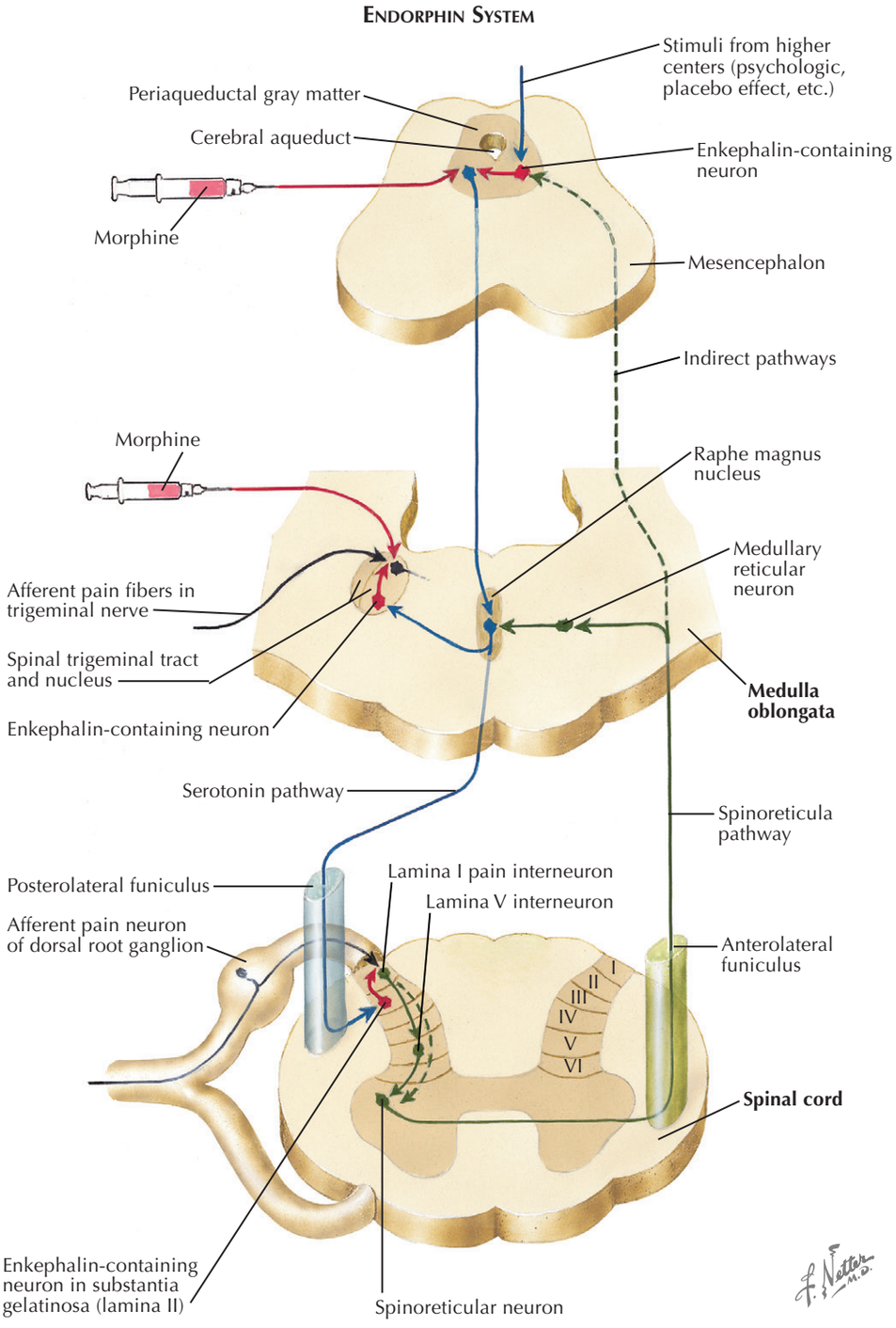
Neurochemical Foundations of Descending Pain Modulation

Opioids have long been considered the archetypical analgesics, with endogenous opioids ("enkephalins") believed to play a pivotal role in the modulation of pain transmission. Recently, however, it has been shown that the monoaminergic pathways mediate modulation of nociceptive processing. Monoaminergic systems include *serotonergic*, *noradrenergic*, *and dopaminergic neurons* that elicit either *antinociceptive* or *pronociceptive* effects, depending on the type of receptor involved and its location. Monoaminergic modulation entails complex interplay between primary nociceptive afferents, dorsal horn projection neurons, local interneurons, and glial cells.

The RVM is the major source of *serotonergic input* to the dorsal horn; it is the final common output for descending influences from rostral brain regions projecting to the superficial and deep dorsal horn. The *PAG-RVM serotonergic pathway* is considered to be the major endogenous pain modulatory system and the main target of supraspinal opioid analgesia. *Serotonergic neurons* can exert *antinociceptive action* (in response to chemical stimuli and neurogenic inflammation) as well as *pronociceptive action* (in response to mechanical stimuli), depending on the activation of different serotonergic receptors.

Noradrenergic neurons originating from locus ceruleus and A5 and A7 pontine tegmentum groups provide inhibition of nociceptive input via *presynaptic alpha-2 receptors*. In this case, noradrenergic modulation relies upon volume transmission, in contrast to the serotonergic system mediating punctate synaptic transmission. The effect of this noradrenergic system is essentially an extrasynaptic spread of neuroactive substances that may be involved in late and long-lasting changes of a group of neurons. The analgesic effects mediated through presynaptic alpha-2 receptors involve presynaptic inhibition in primary afferents, postsynaptic inhibition of projection neurons, as well as a complex interplay with opioid and adenosine antinociceptive systems.

Dopaminergic pathways originate mainly from A11 neurons of the *periventricular posterior thalamus*. Their activation results in *diminished response to noxious stimuli* mediated by *D2 receptors*, with concomitant inhibition of neurotransmitter release from primary afferents. Possibly, endogenous opioids provide potentiating effects that develop from. Conversely, *D1 receptor* activation engenders *facilitated nociception transmission*, both directly and by opioid antagonism. The possible *mechanism of action for dopamine* may rely on local dopamine concentration; low levels activate antinociceptive D2 receptors, and high levels elicit pronociceptive effects via D1 receptors.



Nociceptive Processing and Central Nervous System Correlates of Pain

Neuropathic Pain

The International Association for the Study of Pain defines this as *pain initiated or caused by a primary lesion or dysfunction within the nervous system*. The term "dysfunction" may be rather vague, and perhaps using a lesion-based definition is more accurate. Peripheral neuropathic pain results from a diverse array of insults to the peripheral nervous system (PNS) variously caused by mechanical trauma, metabolic diseases (i.e., diabetes mellitus), infection (i.e., herpes zoster), tumor invasion, or neurotoxic chemicals. Among the associated risk factors for neuropathic pain, gender, age, anatomic site of the injury, and even the severity of acute postoperative pain are cited. Epidemiologic studies identify the prevalence of neuropathic pain to be as high as 5%.

Neural injury triggers a range of processes affecting primary afferent receptors, their axons and cell bodies, as well as unleashing a complex immune response in central neurons and glial cells. Some of these processes facilitate healing and normative repair, for example, removal of cell and myelin debris, recruitment of antiapoptotic strategies, induction of axonal growth and sprouting, synaptic remodeling, and remyelination. In contrast, animal neurophysiologic studies demonstrate that some of these secondary effects have a maladaptive effect. Other well-characterized effects leading to chronic pain include central sensitization, ectopic impulse generation, reduced central inhibition, neuronal loss, and glial scarring.

Peripheral Sensitization

Various signaling molecules, including cytokines, chemokines, neurotransmitters, neurotrophic factors, and excess protons released due to tissue injury and inflammation, directly activate or sensitize nociceptors. Increased expression of ion channels involved in pain transmission is an important mechanism leading to development of peripheral sensitization. Peripheral nerve injury leads to increased expression of specific *voltage-gated sodium (Nav)* channels and *transient receptor potential vanilloid receptor 1 (TRPV1)* cation channels in the primary afferent terminals, in axonal sprouts at the lesion site, demyelinated areas, and adjacent unharmed nociceptors in the site of injury. These channel changes are significant for the expression of neuropathic pain.

Peripheral sensitization has several important ramifications. It reduces the threshold for nociceptor activation, causes primary hyperalgesia (augmentation of normally noxious stimuli), and elicits spontaneous depolarization in primary afferent fibers (ectopic activity). Concomitantly, the peripheral injury enables these neurotrophic factors to migrate in a retrograde direction, thus affecting dorsal root ganglion and dorsal horn cells.

Ectopic Impulse Generation

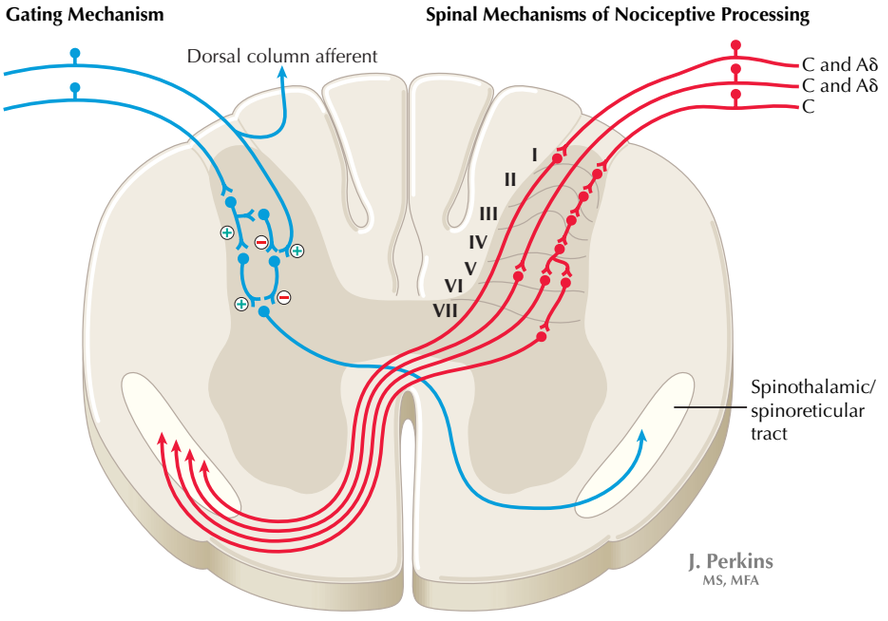
The persistence of an unpleasant sensory and emotional experience in the absence of an identifiable ongoing stimulus is a characteristic feature of neuropathic pain. This spontaneous pain occurs as a result of ectopic action potential generation in primary afferent neurons. It may originate both from ectopic activity in nociceptors and from low-threshold large myelinated afferents due to central sensitization and altered connectivity in the spinal cord. Ectopic discharges originating in the cell body of injured primary afferents may cause antidromic stimulation, the release of mediators, and neurogenic inflammation at the periphery. Ectopic impulses can also generate along neuromas and from the sprouting of sympathetic efferents, forming "baskets" around dorsal root ganglion (DRG) cells. Sympathetic sensory coupling is believed to play an important role in the pathophysiology of inflammatory pain, complex regional pain syndrome (CRPS), diabetic neuropathy, postherpetic neuralgia, phantom limb sensations, and other conditions. Also deafferentation (loss of normal afferent input) can lead to sensitization and ectopic discharges in spinal cord or thalamic neurons.

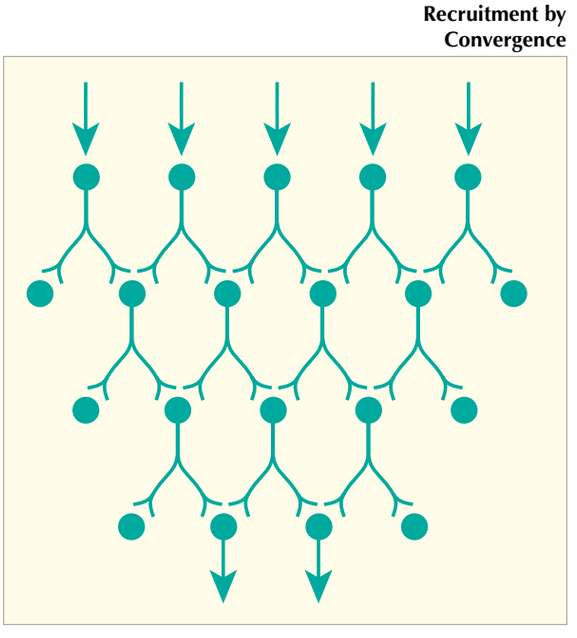
Voltage-gated sodium channels are important influences on the generation of ectopic activity; their role in the pathogenesis of neuropathic pain is supported by the reversal of nociceptive effects by nonselective sodium channel blockers such as local anesthetics. Dorsal root ganglion neurons express several types of sodium channels that are either sensitive or resistant to tetrodotoxin.

Central Sensitization

This is a form of *activity-dependent synaptic plasticity* that also has a pivotal role in the pathophysiology of neuropathic pain. It is responsible for *secondary hyperalgesia* characterized as increased pain intensity to noxious stimuli experienced beyond the distribution of the inciting area of injury, and *tactile allodynia*, defined as pain due to a normally innocuous stimulus. *Central sensitization* represents amplification in the functional status of neurons and nociceptive circuits, caused by reduced inhibition, increased membrane excitability, and enhanced synaptic efficacy. Because these changes appear in the central nervous system (CNS) neurons, the perceived pain does not reflect the presence,

Spinothalamic and Spinoreticular Nociceptive Processing in the Spinal Cord





Nociceptive Processing and Central Nervous System Correlates of Pain *(Continued)*

intensity, or duration of peripheral stimuli. On the contrary, it corresponds to a pathologic state of responsiveness or increased activity of the nociceptive system.

The development of central sensitization often requires high-intensity, repetitive, and continuous noxious input. Induction and maintenance of central sensitization is dependent on *N*-methyl-D-aspartate receptors (NMDARs) that are ubiquitous within the superficial laminae synapses of the dorsal horn. Normally, the voltage-dependent NMDAR pore is blocked by a magnesium ion (Mg^{2+}). Continuous release of glutamate, substance P, and calcitonin gene–related peptide (CGRP) leads to sufficient membrane depolarization to force Mg^{2+} to leave the NMDAR channel, allowing glutamate to bind to the receptor and generate an inward current. This allows entry of calcium ion (Ca^{2+}) into the neuron, activating various intracellular pathways that contribute to the maintenance of central sensitization. This early, acute phase of central sensitization results in activation of intracellular kinases that phosphorylate NMDA subunits and other receptors, enhancing their activity and density and leading to *postsynaptic hyperexcitability*. Alterations in transcription in the dorsal horn contribute to the delayed or late phase of central sensitization. Increased synthesis of transmitters and neuromodulators, such as glutamate, substance P, CGRP, brain-derived neurotrophic factor (BDNF), or nitric oxide (NO), results in presynaptic functional changes in the dorsal horn. All of these processes can increase membrane excitability, facilitate synaptic strength, and decrease inhibitory influences on dorsal horn neurons. Of note, these alterations are not necessarily restricted to the activated synapse (*homosynaptic facilitation*) but can easily spread to adjacent synapses (*hetero-synaptic facilitation*). Consequently, *these modulatory processes lead to enhanced responsiveness of nociceptive neurons*, which lasts longer than the initiating stimuli, or results in activation of nociceptive networks by stimuli that are subthreshold compared with the preinjury baseline.

DISINHIBITION

Several local inhibitory circuits and descending inhibitory pathways serve to modulate the perception of pain. However, after peripheral nerve injury, primary afferents, dorsal horn neurons, and gamma-aminobutyric acid (GABA)ergic inhibitory neurons undergo a number of maladaptive changes. Primary afferents express fewer opioid receptors, and dorsal horn neurons are less susceptible to inhibition by mu opioid agonists. Activation of GABAergic receptors may provoke paradoxic excitation and spontaneous activity. This loss of local inhibition promotes pain transmission, especially the Aβ-fiber–mediated pain.

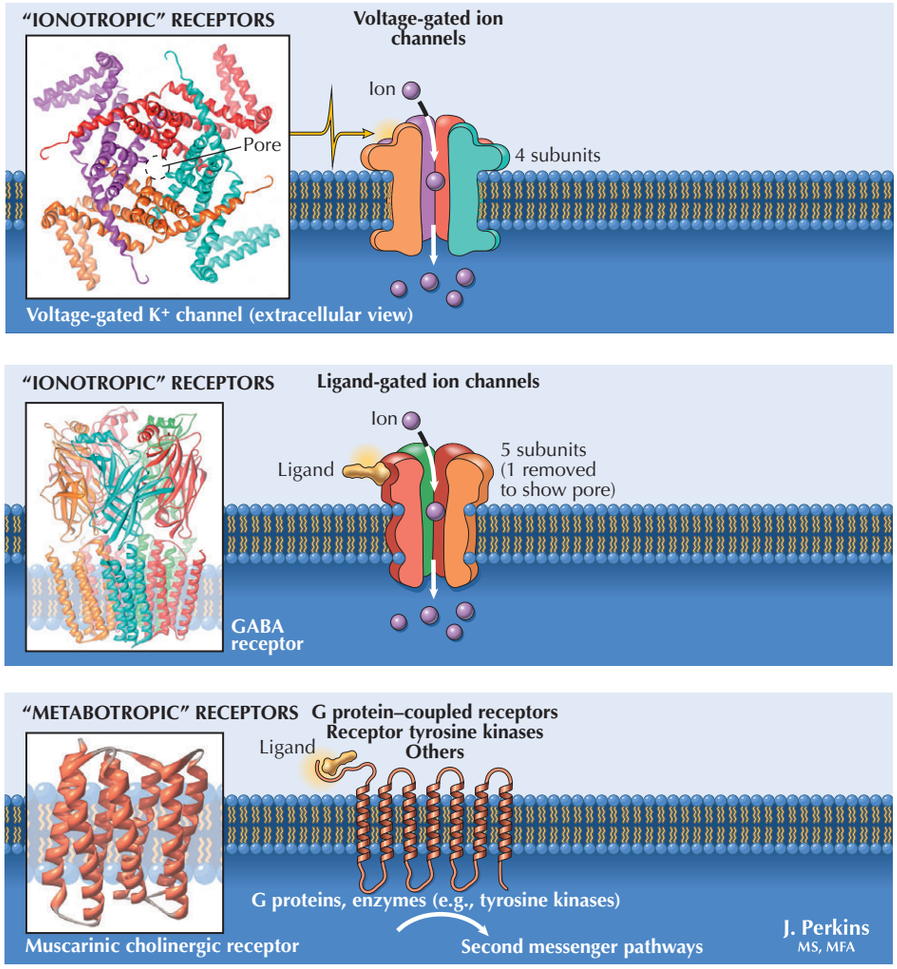
LOW-THRESHOLD Aβ-FIBER–MEDIATED PAIN

These fibers mediate not only touch, pressure, vibratory, and joint movement sensation but also, and very importantly, the suppression of nociceptive pain caused by rubbing the affected area. However, after neural lesions, Aβ fibers begin to activate superficial dorsal horn nociceptive projection neurons. Peripheral injury induces regenerative responses to help damaged neurons in reconnecting with their targets. These gene-activated growth stimuli may cause sprouting of Aβ fibers into the superficial layers of dorsal horn. Regenerative sprouts may demonstrate ectopic activity or be activated by otherwise subthreshold stimuli. Along with central sensitization, these changes *manifest clinically as the ability to generate pain in areas outside of injured nerve territories*, and is usually coupled with a loss of C-fiber terminals.

NEUROIMMUNE INTERACTIONS

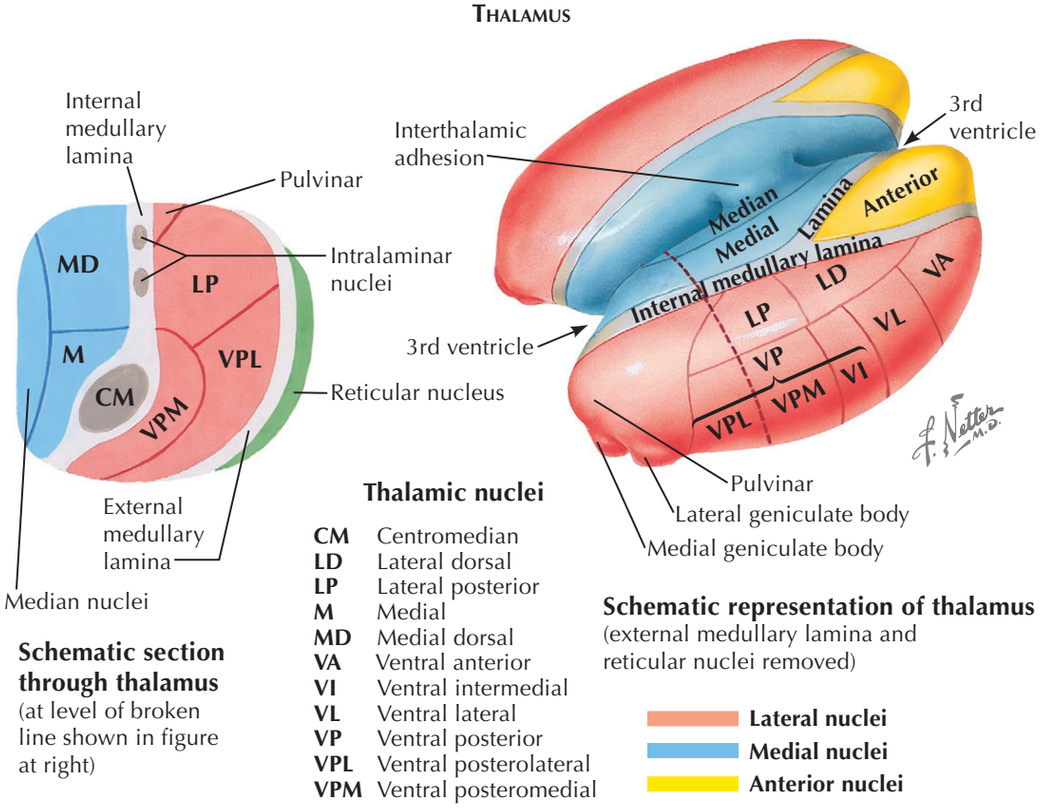
Macrophages have a central role in the immune surveillance of the peripheral nervous system. They clear cellular debris and serve as antigen-presenting cells to activate T lymphocytes. Both macrophages and T cells use cytokines and chemokines as means of communication with neurons, oligodendrocytes, Schwann cells, and spinal microglia. Peripheral nerve injury unleashes *microglial activation* in the dorsal horn; this occurs in close proximity to the injured afferent. The activated spinal microglia *express chemokine receptors* and *release immune mediators* (interleukin [IL]-1B, IL-6, tumor necrosis factor-alpha [TNF-alpha], BDNF), inducing and maintaining maladaptive pain conditions. Mediators released by microglia and astrocytes, as well as cytokines/chemokines produced by DRG cells directly activate nociceptors, cause peripheral sensitization by increasing the excitability of primary afferents, and stimulate adjacent chemokine-expressing neurons. Changes in the expression and function of the transient receptor potential channels and increases in sodium and calcium currents contribute to induction of action potentials. TNF-alpha also has been shown to stimulate DRG neurons and enhance the expression of chemokines, and its antagonists abolish neuropathic pain behavior in animal models.

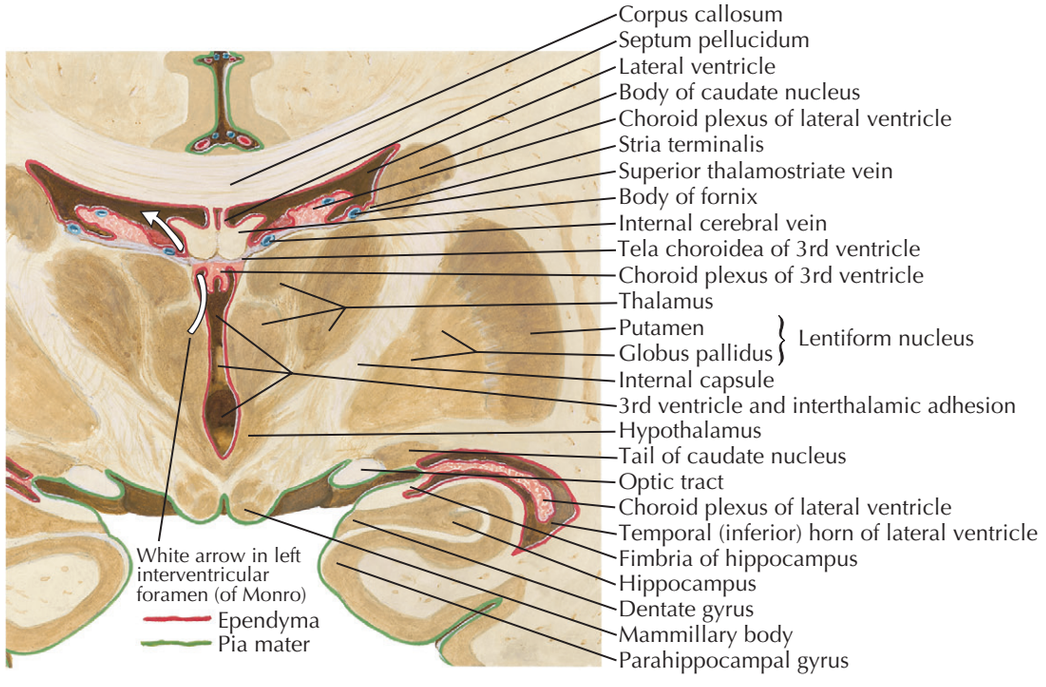
Central Nervous System Neurotransmitters, Receptors, and Drug Targets



Select CNS Neurotransmitters and Neuromodulators

Acetylcholine	Dopamine	Glycine	Oxytocin
Adenosine	Eicosanoids	Histamine	Somatostatin
AMP, ADP, ATP	Endothelins	Neuropeptide Y	Substance P (tachykinins)
Anandamide	Epinephrine	Neurosteroids	Taurine
Aspartate	FMRF-amide-related peptides	Neurotensin	Vasoactive intestinal polypeptide (VIP)
Bombesin	GABA	NO (nitric oxide)	Vasopressin
Bradykinin	Galanin	Norepinephrine	
Calcitonin gene–related peptide (CGRP)	Gastrin	Opioid peptides (endorphins, enkephalins, dynorphins)	
Cholecystokinin	Glutamate		
Cytokines	Glutamine		





Coronal section of brain: posterior view

THALAMIC PAIN SYNDROME

Thalamic pain syndrome (TPS), first described by Déjerine and Roussy in 1906, is a central neuropathic pain disorder primarily resulting from a thalamic infarct or hemorrhage referred to as *central poststroke pain (CPSP)*. Other nonthalamic central nervous system lesions occasionally have similar symptoms, broadening the central *pain syndrome* perspective. The defining clinical features include an initial contralateral feeling of numbness or tingling with compromised tactile sensation, sometimes with hemiparesis if the adjacent internal capsule is affected. Subsequently, as these symptoms gradually dissipate, a persistent, extremely uncomfortable allodynia develops, that is, hypersensitivity to stimuli that normally do not cause pain, particularly to the least degree of mechanical or thermal stimuli. CPSP usually develops within a few months or, rarely, years later after the inciting stroke, occurring in a small percentage of stroke patients, particularly so in senior citizens. There is a broad spectrum of severity; an annoying numbness to a debilitating condition, severely impacting quality of life while undercutting rehabilitation efforts. The patient is often unable to sit still only a short time, may wear a glove to avoid touching anything, often pleading—almost crying out—for help, and eventually experiences psychologic disturbances, bringing the previously self-sufficient, stalwart patient to tears, with eventual concern for potential suicide risk. Treatment options are typically ineffective; the pain severity varies from an annoyance to almost overwhelming, something most individuals have never previously experienced.

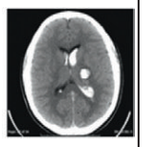
PAIN CHARACTERISTICS

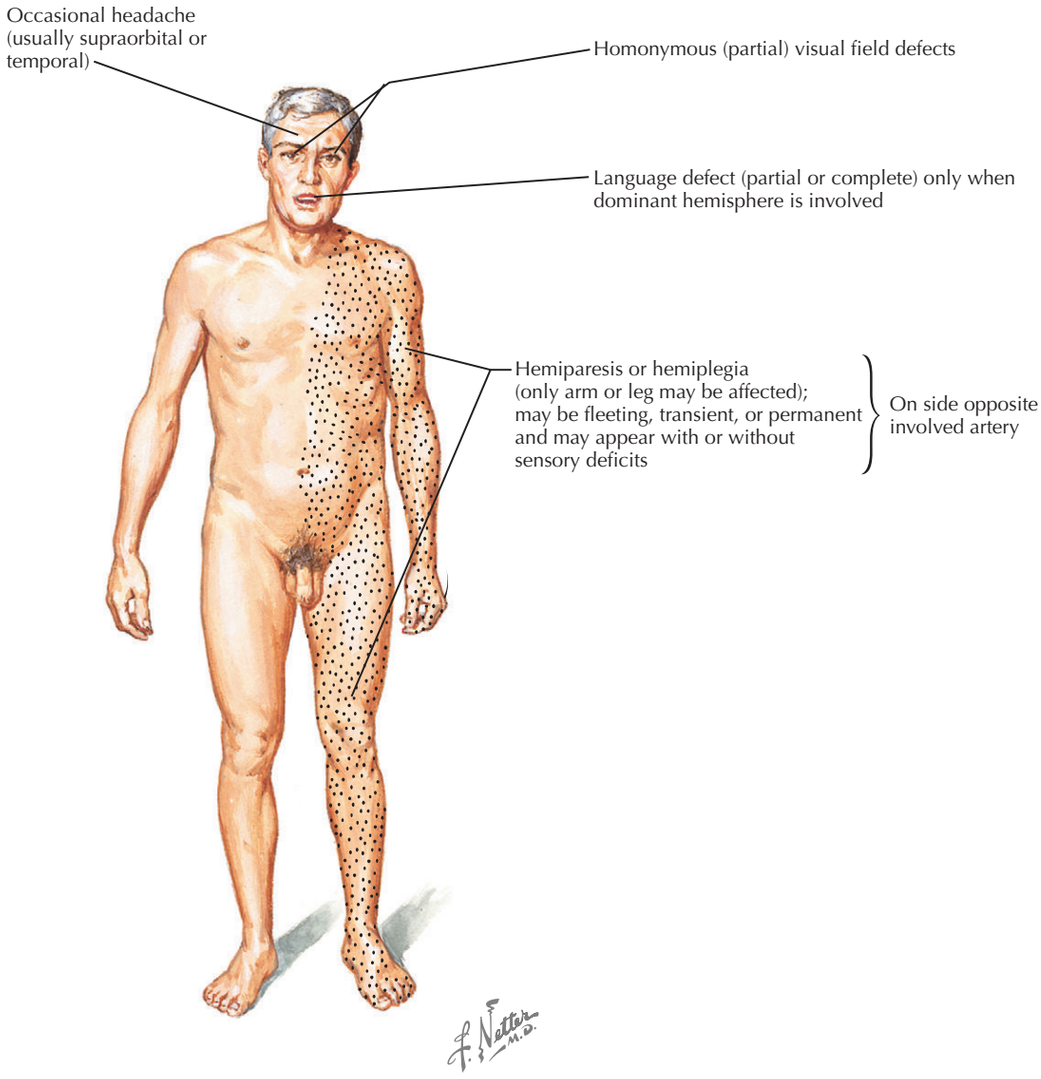
The patient typically reports a burning, stinging, stabbing, or shooting pain; hyperalgesia to temperature and touch are often noted. Pain may travel unilaterally from the extremities to sometimes being accompanied by facial paresthesias; anesthesia may also occur in regions affected by the stroke. CPSP is more common in right-sided strokes. Primarily, this is a very persistent syndrome with daily intermittent pain lasting seconds to minutes. The occasional relief is limited to a few hours; however; the hypersensitivity, hyperpathia, or allodynia continue in response to various stimuli.

PATHOPHYSIOLOGY

The thalamus plays a central role in modulation of sensory information between the periphery and cerebral cortex. There are various hypothesized mechanisms underlying the pathophysiology of CPSP, including central imbalance, central disinhibition, and central sensitization. *Central imbalance* is associated with the clinical finding of dissociated sensory loss

Clinical Manifestations Related to Thalamus Site in Intracerebral Hemorrhage

Pathology	CT scan	Pupils	Eye movements	Motor and sensory deficits	Other
Thalamus 		Constricted, poorly reactive to light bilaterally	Both lids retracted; eyes positioned downward and medially; cannot look upward	Slight contralateral hemiparesis, but greater hemisensory loss	Aphasia (if lesion on left side)



Thalamic Pain Syndrome
(Continued)

characterized by hypersensitivity to thermal and noxious stimuli, with preserved sensory perception to touch and vibration. It is speculated that this symptom pattern is attributable to an imbalance of inputs among spinothalamic tracts and spared dorsal column/medial lemniscus activity. *Central disinhibition* may account for abnormal thermal sensation with burning pain and cold allodynia related to the medial thalamus and anterior cingulate cortex. The concept of *central sensitization* postulates that changes in electrophysiologic properties of nociceptive neurons lead to hyperexcitability through multiple mechanisms. There is still no acceptable precise clinical correlation with a specific underlying pathophysiologic mechanism.

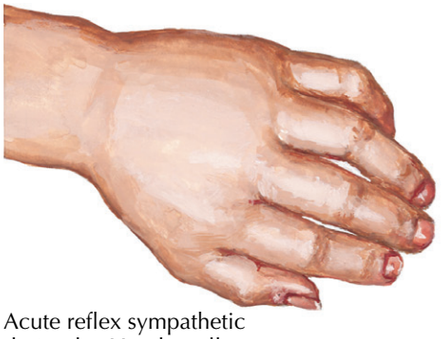
TREATMENT

Management of CPSP remains a major therapeutic challenge due to the severity and quality of the pain, the associated unilateral spasticity, and psychologic distress. Each area must be addressed. There are few class I randomized controlled therapeutic (RCT) trials. Lately, new pharmacologic treatments are emerging. One randomized controlled study of pregabalin demonstrated significant reduction in pain intensity as well as improvements in sleep and global patient status. There is evidence for the dose-dependent analgesic benefit of opioids in these syndromes. A recent duloxetine study demonstrated that despite some advantageous biologic effects, this is no more effective in controlling neuropathic pain than placebo.

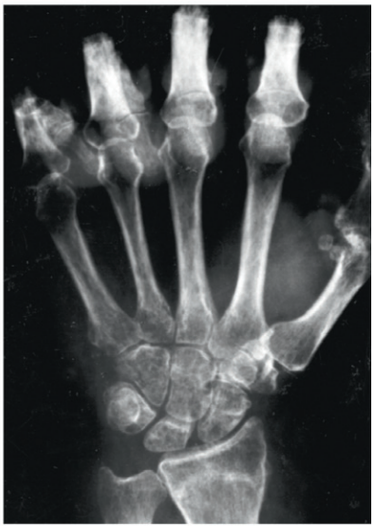
Currently, a multistep pharmacologic approach is endorsed by some experts specializing in CPSP treatment; however, no trials are yet published, supporting a polypharmacy algorithm. Some pain physicians advocate tricyclic antidepressants and gabapentin as first-line treatment. If improvement in pain intensity is not seen and the pain has a shooting characteristic, then anticonvulsants, such as carbamazepine, are added to the medication regimen. The timing of incorporation of opioids must be tailored to individual patient risk factors for drug-dependent behavior.

Invasive procedures include deep brain, spinal cord, motor cortex stimulation, and various ablative approaches are reported in small series with modest and, unfortunately, often short-lived therapeutic benefit. Patients with CPSP sometimes also benefit from psychologic treatment addressing chronic pain behaviors, and the poststroke rehabilitation seems to be of utmost importance in this group of patients.

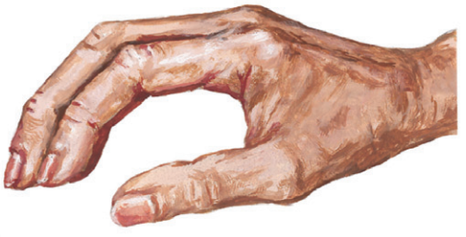
Complex Regional Pain



Acute reflex sympathetic dystrophy. Hand swollen, red, and painful.



Associated severe disuse osteoporosis



Chronic reflex sympathetic dystrophy. Hand atrophic, cold, and painful, with slight clawing of fingers.

In chronic reflex sympathetic dystrophy, right upper limb atrophic, stiffened. Arm held at rest protectively to avoid pain.

Complex regional pain syndrome (CRPS), previously known as reflex sympathetic dystrophy, is an important chronic neuropathic pain syndrome with a distinctive clinical phenomenology. The epidemiology of CRPS is difficult to estimate due to the spectrum of symptom severity and frequent paucity of clinical signs. Studies maximizing diagnostic sensitivity suggest a postsurgical incidence as high as 30% and 20% to 25% in extremity fractures; chronic "severe" CRPS occurs in less than 2% of these patients. The ratio of CRPS occurrence in women versus men is 2:1 to 3:1, and more frequently affects the arm in adults and leg in children.

PATHOPHYSIOLOGY

This is enigmatic; one CRPS theory suggests that cutaneous innervation is altered post-traumatically. Human pathologic studies demonstrate reduced local nociceptive fiber density with aberrant hair follicles and sweat glands innervation. However, it is not clear whether this is the primary pathology or a reaction to the painful symptoms.

Other studies propose that some central and peripheral sensitization leads to CRPS. Hyperalgesia and allodynia encountered after initial tissue trauma are attributed to local release of pronociceptive neuropeptides, leading to enhanced nociceptor responsiveness with lowered thresholds for innocuous thermal and mechanical stimuli. Higher preoperative pain intensity may predict postoperative CRPS invoking a central sensitization theory. Neuropeptides and proinflammatory cytokines released from injured nociceptive fibers are implicated in experimental neurogenic inflammation. Neuropeptides, such as calcitonin gene–related peptide (CGRP), substance P, and bradykinin, cause vasodilation, increase vessel permeability, hyperhidrosis, and hair growth in the affected area, leading to characteristic CRPS features.

Sympathetic nervous system dysfunction (SNSD) may account for common autonomic CRPS features. Reduced SNS-induced vasoconstriction predicts CRPS and explains the warm, red extremity in acute CRPS. Concomitantly, SNSD may contribute to post-traumatic nociceptive excitation through adrenergic receptors expressed on nociceptive fibers.

In addition, the central nervous system (CNS) may have a CRPS pathophysiologic role. The region of somatosensory cortex representing the affected limb is considerably reduced. Such brain plasticity is associated with greater pain intensity, hyperalgesia, and impaired tactile discrimination. Motor dysfunction accompanying CRPS may be linked to significant reorganization of central motor circuits.

CLINICAL FEATURES AND DIAGNOSIS

CRPS occurs predominantly with fractures and various surgeries, including total knee replacement, hip arthroplasty, carpal tunnel release, and numerous arthroscopic procedures. Major clinical CRPS features include spontaneous pain, allodynia, hyperalgesia, edema, vasomotor instability, autonomic dysfunction, and progressive trophic changes. CRPS pain occurs in a distribution beyond an initially affected nerve(s); eventually, this may involve the entire affected limb, and rarely, the contralateral limb. Weakness and tremor may occur, leading to profound functional loss. CRPS occurs as two subtypes: type I CRPS has no identifiable focal nerve lesion, often developing after minor fracture or trauma, whereas type II CRPS has specific nerve damage.

CRPS is diagnosed by clinical evaluation; there are no specific widely recognized diagnostic tests. Various diagnostic tools have their advocates, but the diagnosis remains clinical. Sympathetic nerve blocks at various levels of the neuraxis are sometimes used to support the presence of an autonomic component. If successful (>50% reduction in pain intensity), a more durable blockade with phenol or a radiofrequency ablation procedure may be performed.

TREATMENT

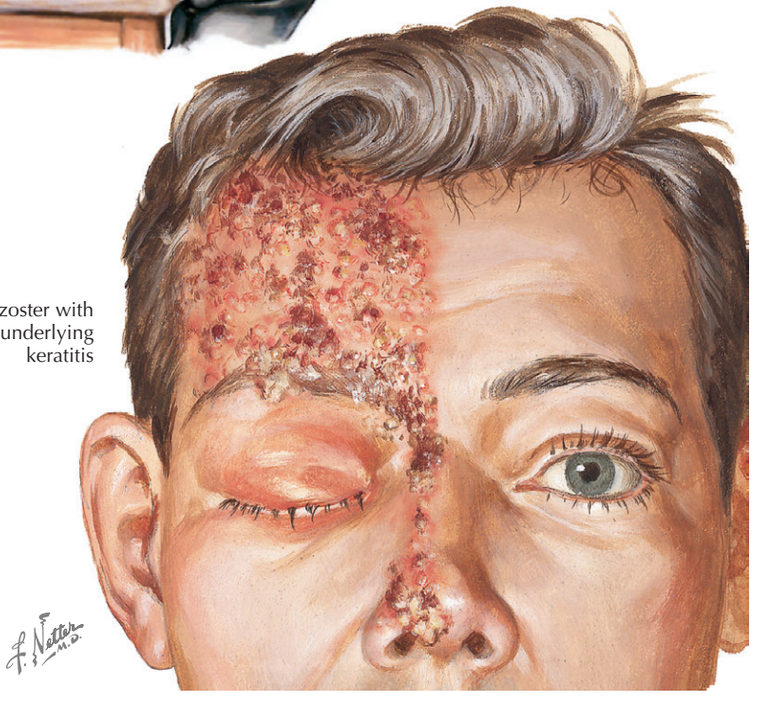
A multidisciplinary approach is used. Early diagnosis and prompt treatment favorably influence prognosis. Symptom management is based on pain severity. Physiotherapy, including range-of-motion exercise, desensitization, and isometric strengthening, is a first-line treatment.

Pharmacotherapy may begin with tricyclic antidepressants and antiepileptics; although these are effective in treating neuropathic pain, their usefulness in CRPS patients is not precisely defined. Anti-inflammatory drugs, including nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are sometimes effective. Topical analgesic using capsaicin and lidocaine transdermal patches is sometimes effective. Opioids are sometimes valuable when tolerated because these analgesics have demonstrated efficacy for neuropathic pain, but adverse consequences, such as tolerance, abuse, and misuse, may become problematic.

A number of interventional modalities exist. Those used include regional anesthetic blocks (i.e., sympathetic blockade), sympathectomy, and somatic blockade when moderate-to-severe pain does not respond to physiotherapy or pharmacotherapy. Neuromodulation, such as transcutaneous electrical nerve stimulation (TENS) at the site of the pain and spinal cord stimulation (SCS), has also shown promise in the treatment of CRPS, and a subpopulation of patients may experience a durable robust response. These modalities are demanding to perform and require a pain medicine specialist.

Herpes Zoster

Herpes zoster dermatomal vesicles



Varicella-zoster with presumed underlying keratitis

Known to the layman as "shingles," herpes zoster (HZ) is an acute neuralgia typically confined to the distribution of a specific spinal nerve root or cranial nerve. It is the most common peripheral nervous system infection. The annual U.S. incidence is 0.5%. After causing primary infection, known as "chickenpox," the varicella-zoster virus (VZV) becomes latent in trigeminal, autonomic, and dorsal root ganglia due to acquired cell-mediated immunity. The virus reactivates later in life, causing an extremely painful vesicular skin rash. Age and immunosuppression are important VZV reactivation factors; others include stress, trauma, surgery, and a family history of HZ.

Herpes zoster complicates 10% of lymphomas, particularly Hodgkin disease. One in 25 active shingles patients harbor undetected carcinomas, lymphomas, or other diminished T-cell immunity pathophysiology, particularly immunosuppression with corticosteroid or medication for transplants or human immunodeficiency virus (HIV) infection.

Postherpetic neuralgia (PHN), characterized by severe and relentless pain highly refractory to treatment, is an important HZ complication. PHN risk factors include age older than 50 years, female gender, severe disseminated rash, initially severe pain, and polymerase chain reaction (PCR)-detectable viremia. VZV is associated with other neurologic complications, including cerebral arteriopathies, particularly with ophthalmic trigeminal zoster. Other potential issues include cranial nerve palsies, myelitis, segmental motor weakness, and herpetic neuralgia without the zoster rash (zoster sine herpete)—a difficult diagnosis.

Pathology

The dorsal root ganglion (DRG) is the primary infectious site. VZV, a DNA-type virus similar to herpes simplex virus, also causes childhood chickenpox. Subsequently, the VZV probably migrates up the peripheral/sensory nerve to the DRG, remaining dormant for years until immunocompromise potentiates reactivation. Here an acute inflammatory reaction leads to DRG destruction. Concomitantly, the VZV spreads peripherally to the skin, producing the rash. The neuropathic pain component of zoster, independent of pain associated with the actual lesions, occurs with intraneuronal virus replication, leading to neuronal lytic damage, inflammation, and hemorrhage with virus eruption from the neurons.

Clinical Manifestation

The rash, reminiscent of chickenpox is confined to a radicular or cranial nerve distribution. Its onset is often heralded by a few days of either severe localized pain or nonspecific discomfort in the affected area. The vesicles appear 72 to 96 hours later. They have an erythematous base with a tight, clear bubble that eventually becomes opaque and dries and crusts over after 5 to 10 days; scarring and hypopigmentation may occur. Typically, the pain ceases in 1 to 4 weeks.

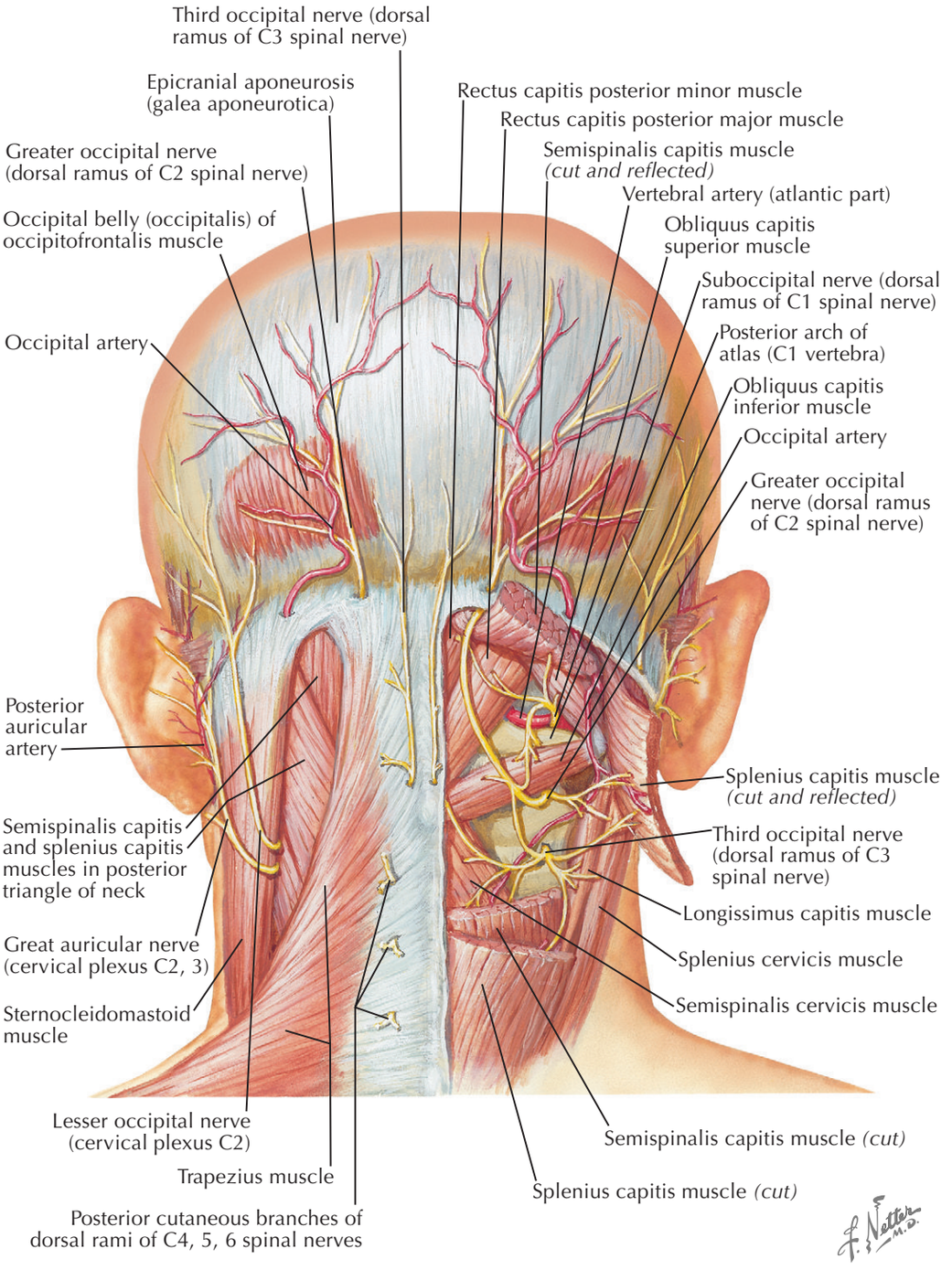
More than half of patients are affected in the thoracic region as with varicella. Ophthalmic trigeminal herpes zoster is fairly common and carries the risk of corneal anesthesia and consequent scarring, along with conjunctivitis, keratitis, and iridocyclitis. This also has the uncommon potential for middle cerebral artery infarction from viral arterial wall invasion. Common motor deficits result from infections of the facial nerve when the geniculate ganglion is affected. This infection, also referred to as Ramsay Hunt syndrome, is usually associated with vesicles in the external ear and sometimes leads to tinnitus, vertigo, and deafness.

A serious primary complication of acute herpes zoster (AHZ) is postherpetic neuralgia (PHN), or chronic neuropathic pain in the affected nerve territory that persists after the skin eruptions and acute inflammatory response have subsided. Although PHN may improve over time, the incidence and severity of symptoms directly correlate with advanced age at rash onset and the degree of rash severity. Once the initial lesions of HZ have healed, the scarred regions have decreased sensation and numbness, although the surrounding skin is marked by allodynia, hyperalgesia, and hyperesthesia. The pain may either be characterized as persistent burning or lancinating pain precipitated by friction of the skin, intense itching and formication can be present as well.

Treatment

A live attenuated vaccine (Zostavax; Merck, Whitehouse Station, NJ) is approved by the U.S. Food and Drug Administration (FDA) for the HZ prevention in patients older than 50 years. Protection against HZ begins around 4 to 6 weeks postvaccination. This is not for treatment of herpes zoster or PHN per se. Antiviral agents, including acyclovir, valacyclovir, and famciclovir reduce the acute and symptomatic period if administered within 3 days of rash appearance. The latter two drugs also decrease the incidence and severity of PHN, although not preventing its occurrence.

For treatment of PHN per se, oxycodone has demonstrated analgesic benefit in the acute and subacute phase after acute herpes zoster reactivation. Tricyclic antidepressants, adjuvants such as gabapentin and pregabalin, topical lidocaine (5%), topical high-dose (8%) capsaicin, and opioid medications are all efficacious for PHN pain relief.



Occipital Neuralgia

Occipital neuralgia (ON), as defined by the International Headache Society, is a paroxysmal shooting pain within the distribution of the greater, lesser, and third occipital nerves. The pain involves occipital and periauricular areas and may radiate to the lateral scalp and retro-orbital area. Episodes of ON may be provoked with palpation of the occipital nerves, especially at the anatomic landmark of the occipital notch. Stress and tension may also modulate pain intensity in the distribution of the occipital nerve. Although there is no definitive localizing test, multiple studies indicate that the greater occipital nerve accounts for the majority (90%) of cases. One study found that, in roughly 8.7% of cases, both the greater and lesser nerves were involved.

PATHOLOGY

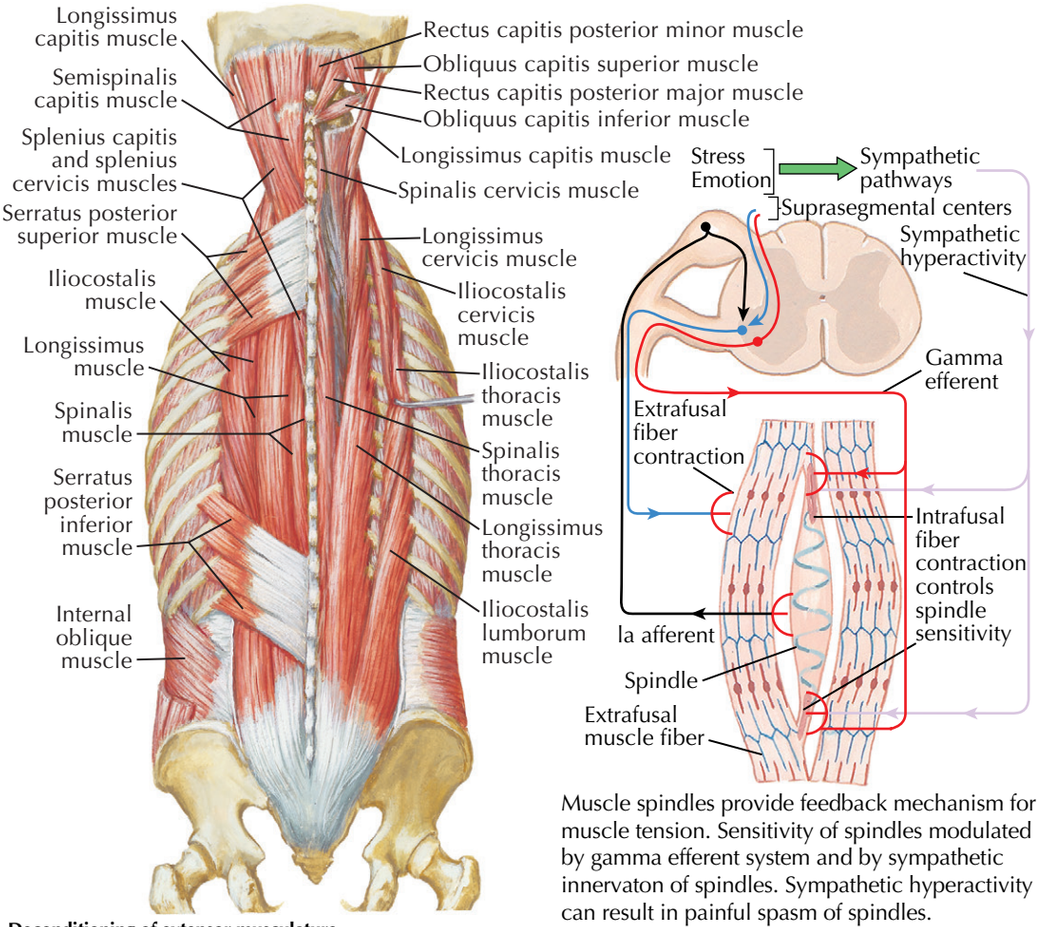
This uncommon neuralgia has various etiologies, primarily categorized as neurogenic, vascular, muscular, or osteogenic. Parenthetically, it is important to note that the C1 root, suboccipital nerve, is entirely motor in function, having no sensory component in contrast to all other nerve roots. Trauma to the C2 root due to traction injury or secondary to the arthritic changes at the atlantoaxial joint are the primary causes of occipital neuralgia. Another postulated but unproven mechanical cause includes nerve entrapment with sustained contraction or spasm of the posterior neck muscles. Osteogenic origins include osteoarthritis and arthritic degeneration of the spine leading to nerve entrapment by hypertrophied atlantoaxial ligaments. Instances of vascular etiology include irritation of C1/C2 nerve roots by diverging branches of the posterior inferior cerebellar artery and extremely rare dural arteriovenous fistulas in the cervical regions. Tumors of the second and third cervical dorsal roots and multiple sclerosis account for more uncommon, neurogenic causes. Most often, however, the inciting factor is not identified with clinical evaluation, and the neuropathic changes in greater or lesser occipital nerve are considered idiopathic. Perhaps these pathophysiologic mechanisms will be more easily identified with the increased availability of 3-tesla magnetic resonance imaging (MRI), providing more accurate detail.

CLINICAL MANIFESTATION

Occipital neuralgia is typically described as stabbing pain with periods of aching pain between the paroxysmal episodes. Retro-orbital pain may be explained by the convergence of nociceptive pathways in the dorsal root of C2 and the pars caudalis division of the spinal trigeminal nucleus. In addition, visual deficits, ringing in the ears, dizziness, and nasal congestion may accompany painful periods due to the involvement of cranial nerves (CNs) VIII, IX, and X and the cervical sympathetic trunk. Stress-induced muscle tension headaches may also occur. On physical examination, dysesthesia is elicited along the greater and lesser occipital nerve, as well as tenderness to palpation. Diagnosis is confirmed via diagnostic nerve block of the occipital nerve, along with imaging scans to identify any suspected lesions.

TREATMENT

Effective management depends on whether an identifiable entrapment mechanism is identified. If so, surgical intervention or decompression is a viable option. Occipital nerve blocks are often effective at attenuating pain intensity in this region. Most treatments, however, are aimed at symptom reduction and relief of any accompanying muscle tension. Empiric use of drugs based on efficacy data from other neuropathic syndromes is common. These agents include adjuvants, such as tricyclic antidepressants, and anticonvulsants, such as carbamazepine or gabapentin. Botulinum toxin type A injections are also used. Local anesthetic and corticosteroid injections to the greater occipital nerve are variably effective. Pulsed radio frequency of the C2 or C3 dorsal root ganglion is currently being evaluated in small preliminary studies. There is an emerging body of evidence to support the use of subcutaneous peripheral nerve stimulation in intractable, severe cases of occipital neuralgia.



Muscle spindles provide feedback mechanism for muscle tension. Sensitivity of spindles modulated by gamma efferent system and by sympathetic innervaton of spindles. Sympathetic hyperactivity can result in painful spasm of spindles.

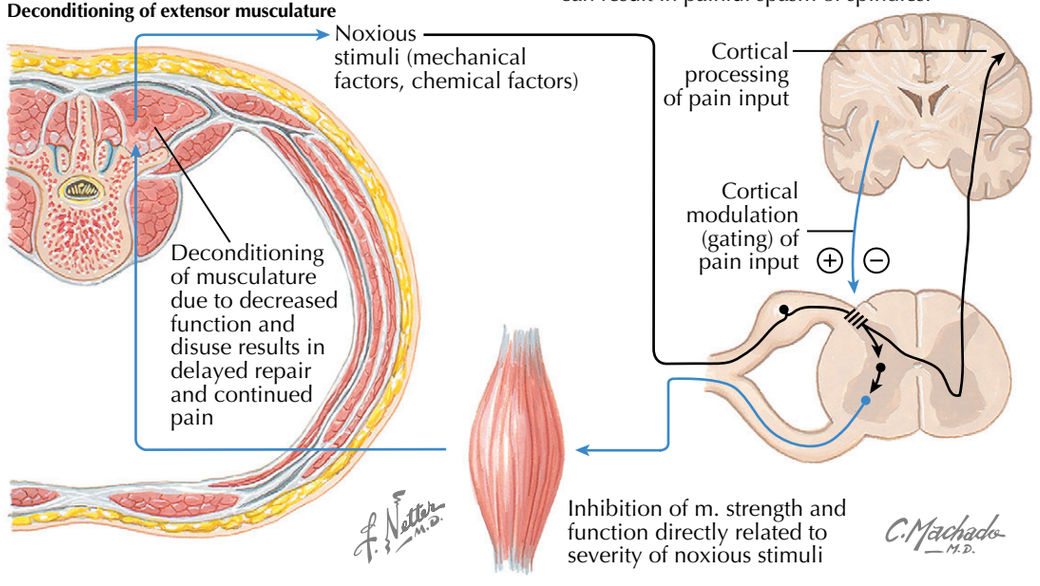
Myofascial Factors in Low Back Pain

Myofascial structures are implicated in virtually all acute and chronic low back pain syndromes. Myofascial pain syndrome (MPS) is strictly defined by the presence of local and referred pain that originates from a myofascial trigger point (MTrP). This symptom pattern overlaps clinically with pain referred from diverse somatic structures, such as ligaments, periosteum, scar tissue, skin, and tendons. *Trigger points*, defined as a zone of intense pain associated with a hardened muscle band, may be identified on physical examination; however, it is not uncommon that syndromes with a myofascial component lack a discrete TrP when somatic pain is referred pain from deeper muscles, such as the psoas, into the inguinal region. The prevalence varies from 30% of general medical clinic patients with regional pain to as high as 85% to 93% of patients presenting to specialty pain management centers. Women are much more likely to suffer from MTrPs.

PATHOPHYSIOLOGY

The development of MPS is often associated with postural derangements, such as muscle overload, dystonia, and fatigue. Postural abnormality (e.g., scoliosis) may reflect asymmetric extensor or flexor tone in a group of paraspinal muscles. Secondary causes of myofascial pain are extremely common, including painful spasm with spondylolisthesis or increases in tone with emotional stress. The most common cause of myofascial trigger point (MTrP) formation is repetitive stress on individual muscles or muscle groups. In the low back, a small hemipelvis or short leg may lead to MPS.

An MTrP is a hyperirritable spot within skeletal muscle associated with a hypersensitive palpable nodule in a taut band. Here the key pathophysiologic abnormalities are principally located at the muscle center near its motor end-plate zone. Precipitating factors may facilitate acetylcholine release at motor end plates, causing sustained muscle fiber contractions, release of vascular and neuroactive substances, and muscle pain perpetuating the muscle spasm. The abundance of the nociceptors in muscle, joints, skin, and blood vessels explains the pain severity and exquisite muscle tenderness upon palpation. Possibly, the chronicity of MPSs is attributable to altered sensory processing as characterized by central sensitization with alteration in supraspinal inhibitory descending pain-control pathways.



Inhibition of m. strength and function directly related to severity of noxious stimuli

CLINICAL MANIFESTATIONS

Characteristic MPS symptoms begin after discrete trauma or insidiously. Patients note varying degrees of regional deep aching sensations. Functional complaints include decreased work tolerance, impaired muscle coordination, stiff joints, fatigue, and weakness, leading to sleep disturbances, mood changes, and stress. The most reliable physical signs of trigger points are pain

Myofascial Factors in Low Back Pain *(Continued)*

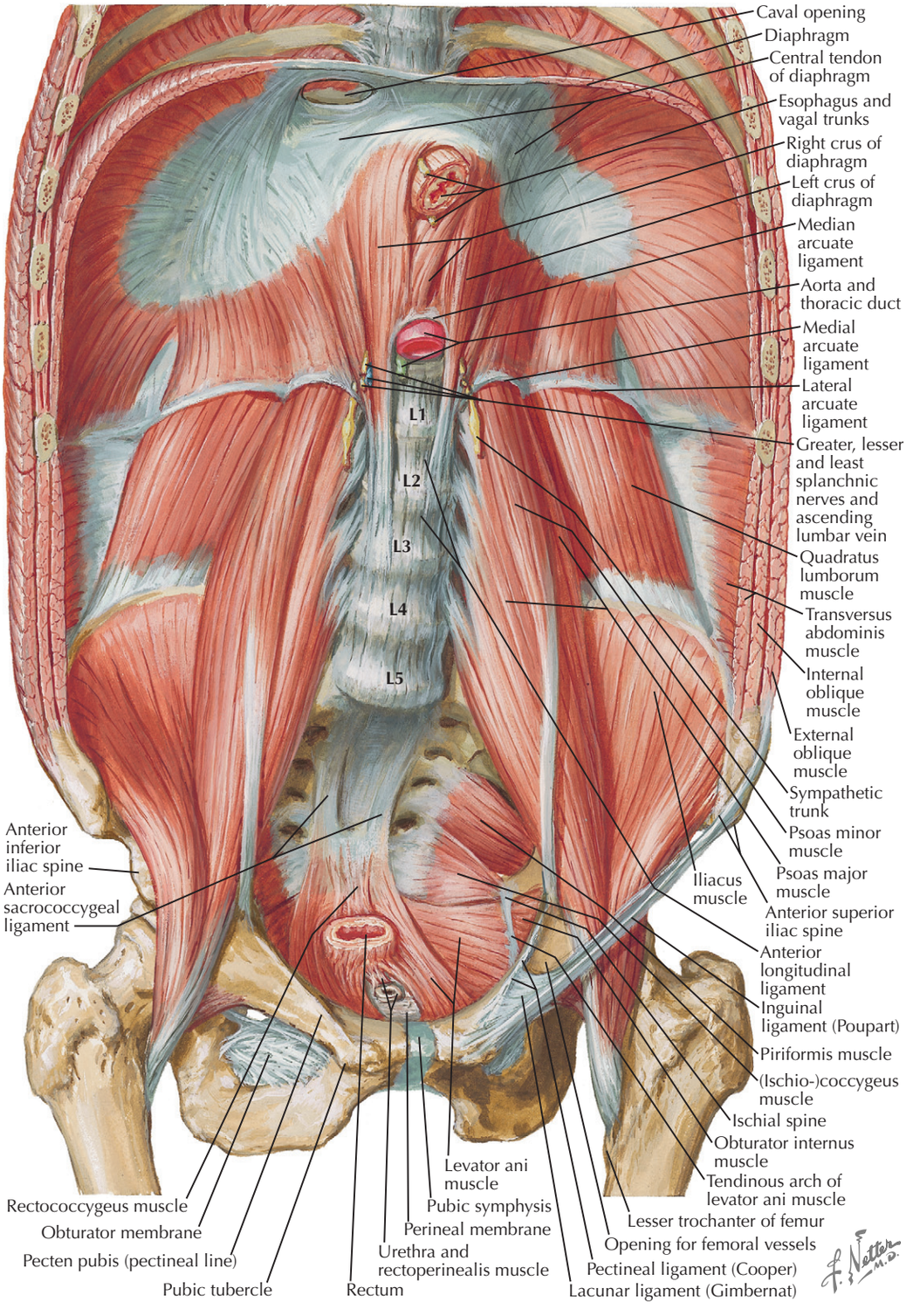
recognition, taut band, tender point, referred pain, and local twitch response. MTrPs usually appear in muscular structures used for posture maintenance, including quadratus lumborum, gluteus maximus, gluteus medius, iliocostalis, iliopsoas, levator ani, longissimus thoracis, lower rectus abdominis, multifidi, piriformis, and hip rotators. With low back pain, quadratus lumborum, used for trunk stabilization and posture, is the most common source of MTrP. Palpation of MTrP will reproduce or increase regional pain, possibly eliciting referred, radiating pain patterns. Sometimes MTrP activation may evoke autonomic phenomenon, including dermal flushing, lacrimation, sweating, and temperature changes. Chronic MTrP patients require evaluation for postural abnormalities, ergonomic factors, and hypothyroidism.

TREATMENT

This requires a comprehensive rehabilitation, medication approach, sometimes including local interventions. One attempts to abolish MTrPs and tender spots. Overall flexibility needs to be restored to the muscle, while associated precipitating factors require modification. Medications, including acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs), are initially used with local inflammation. Adjuvant analgesics, antidepressants, or anticonvulsants are added for neuropathic components.

Rehabilitation approaches for MPS, including neuromuscular relaxation techniques, heat, or electrical therapy may also help. Physical treatments can also be used in the management of MPS. The "stretch and spray" technique is popular, utilizing a vapocoolant spray applied just before stretching the involved muscle. Other physical therapies include massage therapy or low-level laser therapy. More unusual treatments include mud baths and magnetic fields.

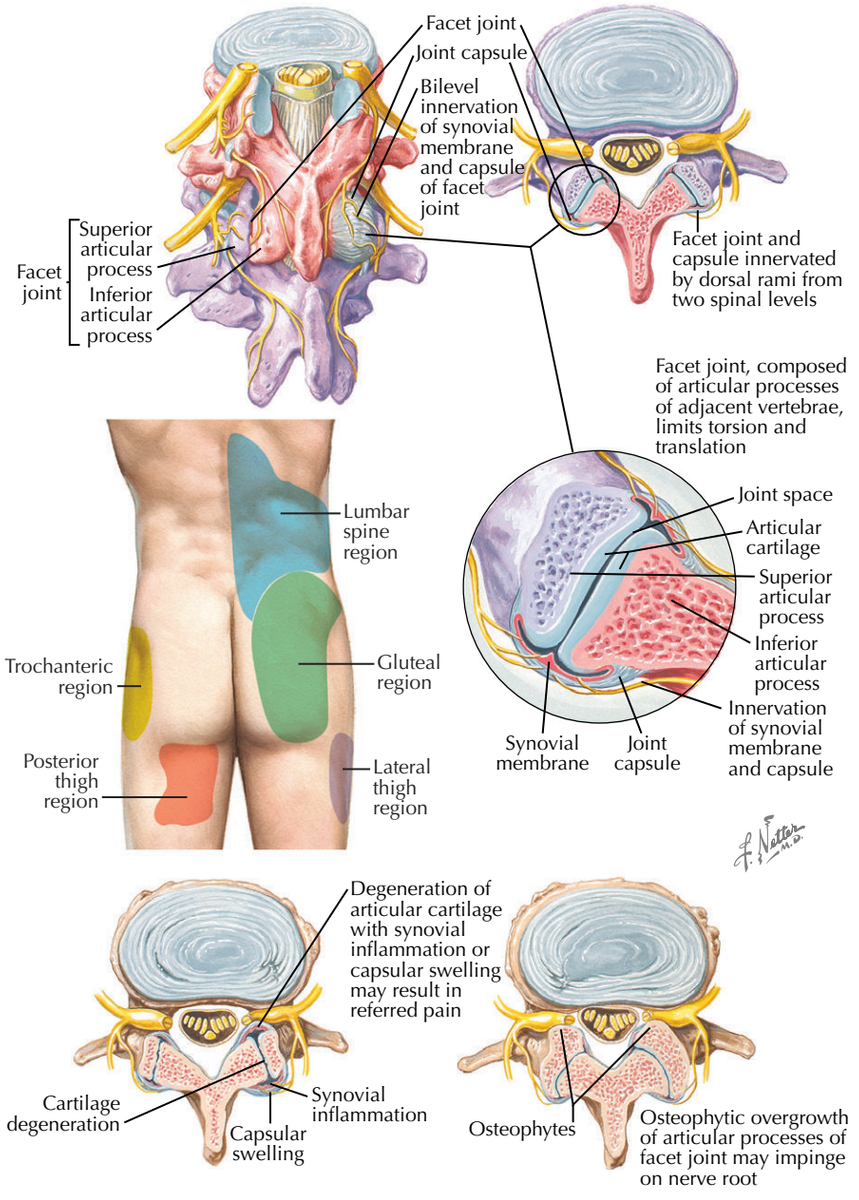
Posterior Abdominal Wall: Internal View



Needling of myofascial trigger points is a common MPS treatment. However, no causal relationship between direct needling of MTrPs and improvement in symptoms is established. A systematic 2001 review discussing randomized controlled trials (RCTs) failed to conclusively demonstrate any therapeutic benefit in wet (injection with botulinum or local anesthetic) versus dry needling. The authors of this meta-analysis concluded that any effect resulting from these therapies is derived from the direct needle insertion into the MTrP. Recent interest in using the 5-hydroxytryptamine 3 (5-HT3) receptor antagonist tropisetron for injection into MTrPs associated with MPS has not been tested with an RCT.

Lumbar Zygapophyseal Joint Back Pain

Lumbar zygapophyseal (facet) joint degeneration (ZfJD) is a leading cause of axial predominant chronic low back pain (LBP). Facet-mediated pain is a multifactorial process intimately related to intervertebral disk degeneration. These syndromes originate from any structure integral to function and configuration of lumbar zygapophyseal (LZ) joints, including the fibrous capsule, synovial membrane, hyaline cartilage surfaces, and bony articulations. Controversy exists regarding the relative contribution of these structures to the back pain process. Recent evidence, based on the Kirkaldy-Willis tripod theory of the spinal motion segment, identifies LZ joints as primary sources for pain. Epidemiologic studies identify ZfJD as the primary diagnosis in 6% of chronic LBP patients.



PATHOPHYSIOLOGY

LZ joint pain primarily results from repetitive load-bearing strain accumulated over a lifetime; rarely, LZ joint arthropathy is traced to one inciting event. During midlife, cartilaginous changes accelerate, and subchondral sclerosis and osteophytes growth are commonly observed phenomena. Intervertebral disk disease is the initial site of spinal degeneration; facet joint deterioration subsequently develops secondary to biomechanical effects. Mechanical consequences of disk degeneration include reduced disk height and segmental microinstability leading to increased facet load. This provokes joint subluxation and cartilage alteration with subsequent facet joint degeneration.

Rheumatoid arthritis, ankylosing spondylitis, synovial impingement, chondromalacia facetae, pseudogout, meniscoid entrapment, and capsular/synovial inflammation also predispose to chronic facet joint strain.

Lumbar facet joints are richly innervated with encapsulated, unencapsulated, and free nerve endings, and contain substance P, calcitonin gene–related peptide (CGRP), as well as neuropeptide Y. Nerve fibers occur within subchondral bone and intra-articular inclusions of lumbar zygapophyseal joints, thus signifying that facet-mediated pain may originate beyond the joint capsule. In models of degenerative lumbar spinal disorders, inflammatory mediators, such as prostaglandins and the inflammatory cytokines (interleukin [IL]-1beta, IL-6, and tumor necrosis factor-alpha [TNF]-alpha), occur within facet joint cartilage and synovial tissue.

PAIN-REFERRAL PATTERNS

Lumbar facet joints produce pain referred into the groin. Pain emanating from upper facet joints tends to extend into the flank, hip, and upper lateral thigh, whereas pain from the lower facet joints penetrates deeper into the posterolateral thigh.

CLINICAL PICTURE

Clinically, LZ joint–mediated back pain overlaps considerably with multiple other LBP etiologies. Although LZ joint pain is not associated with anatomically specific neurologic deficits, patients experiencing this referred somatic pain may demonstrate a pain-inhibited non-myotomal weakness. Similarly, these individuals also report a nondermatomal referred extremity sensory-loss–type complaints reaching as far distal as the foot.

There are no specific radiographic computed tomography (CT) facet joint abnormalities identified to provide firm diagnosis of facet-mediated LZ pain. Single photon emission–computed tomography (SPECT) bone scintigraphy may sometimes help identify active inflammation with some facet-mediated sources in low back pain individuals.

LZ joint–mediated pain is a diagnosis made primarily by exclusion of other possible etiologies (see Plate 8-13). This is difficult to confirm, however; positive results with controlled analgesic injections may be supportive of this diagnosis. These nerve blocks are accomplished in two ways. The more reliable method targets the small nerve fibers branching from the dorsal spinal root known to innervate the facet joints, with the so-named medial branch block. Intra-articular anesthetic injection is also performed after an appropriate arthrogram. However, these injections have never been tested for validity.

MANAGEMENT

Controlled prospective studies comparing varied LZ joint pain treatments are limited despite increasing number of interventional therapies targeted at these joints. Conservative treatments, including medications, physical therapy, or manual therapy, lack specific analgesic efficacy for the joint pain per se. Nevertheless these modalities provide standard first-line treatment for acute-onset LBP.

Intra-articular steroid injection for treatment of LZ joint pain is a somewhat controversial subject. However, in general, it is concluded that intra-articular steroid injections may provide intermediate-term relief to LZ joint pain patients who appear to have active inflammation.

Lumbar medial branch neurotomy (LMBN) has the most evidence-based support. The thermal coagulation probe used for a medial branch neurotomy denaturates nerve proteins; therefore this provides a more superior clinical effect than medial branch anesthetic block. Several clinical trials have demonstrated LMBN efficiency in the treatment of LZ joint pain.

Low Back Pain and Effects of Lumbar Hyperlordosis and Flexion on Spinal Nerves

Hyperlordosis, also known as saddleback or swayback, is an excessive vertebral curvature (lordosis). The lumbosacral region plays a pivotal role in terms of mobility and weight-bearing potential; any postural aberrations affecting the lumbosacral angle may lead to low back pain (LBP). Hyperlordotic posture is a common contributor to chronic nonspecific LBP syndromes. Common causes include pregnancy, tight low back muscles, obesity, or congenital disorder.

Lumbar hyperlordosis is 50% more accentuated with standing rather than sitting. This may cause nonspecific LBP localizing to somatic tissues (e.g., paraspinal muscles, facet joints) mediated by inflammatory mechanisms. In extreme hyperlordosis, exiting nerve root entrapment secondary to intervertebral foramen narrowing with this posture may cause radicular irritation or a frank radiculopathy with sensorimotor deficits. Patients with lumbar spinal stenosis (LSS) have reduced anteroposterior central canal and lateral recess dimensions with hyperlordosis. Associated compromise of microvascular perfusion of the cauda equina possibly accounts for posture-precipitated pain while standing and walking, known as neurogenic claudication (NC). LSS nerve root injury may cause radicular pain characterized by sharp, lateralized pain conforming to dermatomal distributions, a radiculopathy, or NC. Straight-leg raising stretches the sciatic nerve, simulating radicular traction that provokes pain in an inflamed or otherwise sensitized nerve root.

In the lumbar spine, the primary motion is flexion/extension with very little segmental rotation. Lumbar flexion opens the foramen more widely, reducing nerve root compression. The amount of compressive force and tension on the nerve root decreases with spinal flexion and increases with spine extension.

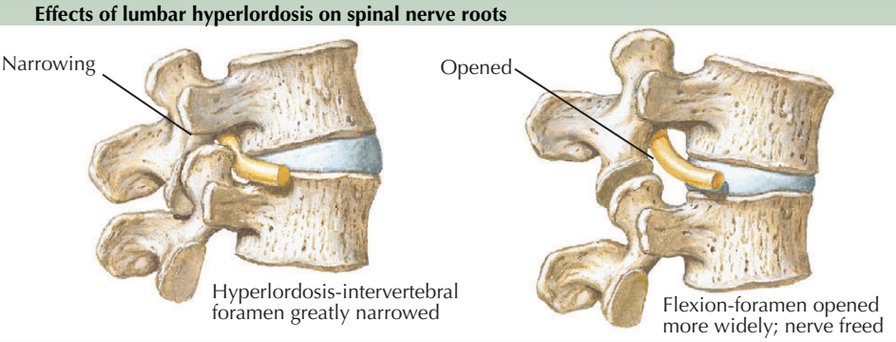
Lordosis typically occurs maximally at L4-S1. A simple radiographic image to determine the postural status may capture the extent of lordosis. The normal range of lumbar lordosis is 20 degrees to 50 degrees, whereas hyperlordosis is defined as greater than 60 degrees. LSS patients have physical examination findings denoting loss of lumbar lordosis. Another test for NC is the stoop test; here the patient walks with an exaggerated lumbar lordosis until NC symptoms appear or are worsened. The patient is then instructed to lean forward at the waist; reduction in symptom intensity is considered suggestive of NC.

A radiographic study of sagittal lumbar spine measurements of 552 asymptomatic subjects with lordosis found that, in pain-free subjects, 65% of lordosis occurs between L4-5, and 35% occurs above L4. This study also demonstrated that hyperlordotic patients tended to have acute low back pain, whereas chronic low back pain patients were hypolordotic, emphasizing the importance of hyperlordosis in chronic LBP individuals.

A systematic review of randomized clinical trials of conservative treatment for acute and chronic low back pain (CLBP) supports the use of muscle relaxants, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, manipulation, and active exercise therapy in the treatment of acute LBP. Hyperlordosis is not always associated with painful symptoms, and this, per se, is not an indication for treatment. Analysis of chronic LBP therapies have shown stronger evidence of the effectiveness of exercise and manipulation therapy as compared with behavior therapy. NSAIDs may accelerate the process of returning to usual activities or work. Of interest, other popular treatment options, including transcutaneous electrical nerve stimulation (TENS), electromyographic biofeedback, acupuncture, and orthoses are not proved to be useful.

Conservative treatment, such as physical therapy, is recommended for patients with LSS or hyperlordosis. Lumbar extension exercises should be avoided in these patients because spinal extension and increased lumbar lordosis are known to worsen LSS. Flexion exercises for the lumbar spine are emphasized because these methods increase the spinal canal dimension and decrease stress on the spine, thereby reducing lumbar lordosis. Strengthening exercises include back hyperextensions, hip flexor, and gluteus and hamstring stretches, along with abdominal exercises. Avoiding sedentary lifestyle, such as sitting for long periods of time, or wearing a lumbar brace may also be helpful. Short-term pain relief can be achieved with the use of NSAIDs. A study published in 2005 demonstrated the greater benefit of Iyengar yoga (significant reduction in self-reported disability and pain, and reduced use of pain medication) than educational programs in the management of CLBP patients. For CLBP, positions that include twists and inversions may alleviate hyperlordotic pain. Twisting motions involve the deeper layer of back muscles and reduce the pain symptoms by realigning the vertebra, increasing intervertebral disk space, and decreasing possible impingement of nerve roots, whereas inversions reverse the compressive effects of gravity on the intervertebral disk space.

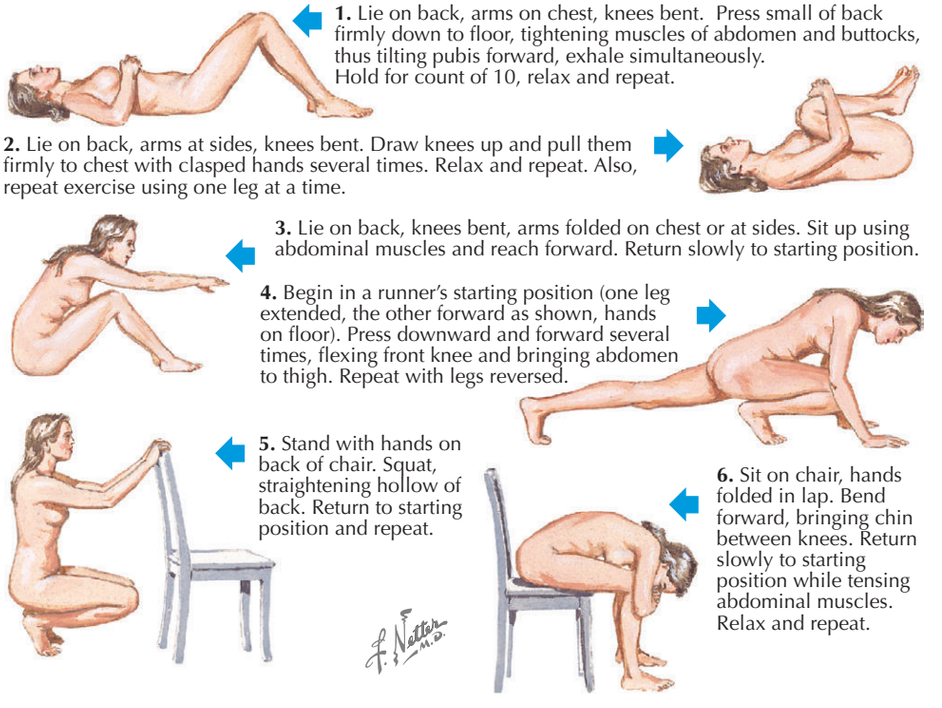
Effects of lumbar hyperlordosis on spinal nerve roots



Treatment of lumbar strain

Acute	Chronic and prophylactic
Absolute bed rest	Reduction of weight
Warm tub baths, heat pad, hydrocollator	Correction of posture
Sedation	Firm mattress, bed board
Firm mattress, bed board	Daily low back exercises
Diathermy, massage	Regular sports activity compatible with age and physique
Local anesthetic infiltration to trigger zones	
Occasionally corset, brace, or strapping	

Exercises for chronic lumbar strain (starting positions in outline)



Exercises are best done on hard, padded surface like carpeted floor. Start slowly. Do each only once or twice a day, then progressively to 10 or more times within limits of comfort. Pain, but not mild discomfort, is indication to stop.

Examination of the Low Back Pain Patient

Low back pain (LBP) is defined as pain localized between the 12th rib and the inferior gluteal folds, with or without leg pain. Although it is the fifth leading reason for doctor visits, up to 85% of patients in some population-based studies have nonspecific low back pain, even without specific spinal anomalies or disease. Many low back pain patients are regarded as being of nonspecific character because no evaluation (radiographic or otherwise) is carried out to identify an underlying structural lesion. This finding primarily relates to the fact that most acute LBP episodes, without radicular symptoms, resolve spontaneously within 6 weeks; routine imaging is not sensitive or specific for initial evaluation in this setting. Often, LBP may be a result of a multitude of pathologic processes, including degenerative diseases, inflammatory conditions, systemic or local infection, neoplasms, metabolic bone disease, referred pain, trauma, and congenital disorders. Because of this wide array of etiologies, clinical assessment of patient's condition is essential to establishing the correct diagnosis.

Clinical Evaluation

Focused history and physical examinations are fundamental elements in the assessment of low back pain. They are especially helpful in the preliminary classification of acute LBP into one of three groups: (1) *nonspecific low back pain*, (2) LBP potentially associated with *radiculopathy or spinal stenosis*, or (3) LBP potentially associated with *systemic disease*. The third category is most important to recognize early; it includes the small proportion of LBP patients with serious or progressive neurologic deficits or underlying medical conditions requiring prompt evaluation (such as tumor, infection, or the cauda equine syndrome), as well as patients with other conditions that may respond to specific treatments (such as ankylosing spondylitis or vertebral compression fracture). The vast majority of these patients experience nociceptive pain referred from somatic structures. The clinical picture associated with this syndrome is one of axial pain predominance, whereas radicular impingement or irritation typically involves leg symptoms in a unilateral or, less commonly, bilateral distribution.

The *physical examination* of a low back pain patient involves assessment of motor, sensory, and reflex function, as well as strength, range of motion, and neurologic impairments. It must begin with the assessment of vital signs and a systemic survey aimed at identifying evidence of nonmechanical and visceral causes of low back pain, including primarily bony malignancies—such as multiple myeloma—or metastatic malignancies, particularly of the lung, breast, and prostate; disk space infection; nephrolithiasis; pyelonephritis; pancreatitis; aortic aneurysm; or metabolic bone disease. A thorough inspection and palpation of the affected area follow, with careful attention to the presence of deformities or radiation of pain. All patients require evaluation for the certain important "red flags" that may indicate serious disorders.

Neurologic findings, such as saddle anesthesia, bilateral radiculopathy, bilateral leg weakness, urinary retention, and fecal incontinence, are consistent with the diagnosis of *cauda equina syndrome* and require immediate emergent attention. Malignancy should be suspected in patients with severe low back pain after minor trauma, unrelenting night or rest pain, unexplained weight loss, and progressive neurologic deficit.

Chronic steroid use, immunosuppression, intravenous drug abuse, recent urinary infection, or skin infection near the spine should direct the differential diagnosis toward infectious etiology, particularly epidural abscesses. Fracture is a possible diagnosis in the setting of trauma, osteoporosis, or chronic steroid use.

When there is no neurologic deficit present and LBP is localized to the lumbar spine and buttocks, lumbar strain related to soft tissues, or inflammatory processes at the level of disk, facet joints, or bony end plates are likely considerations.

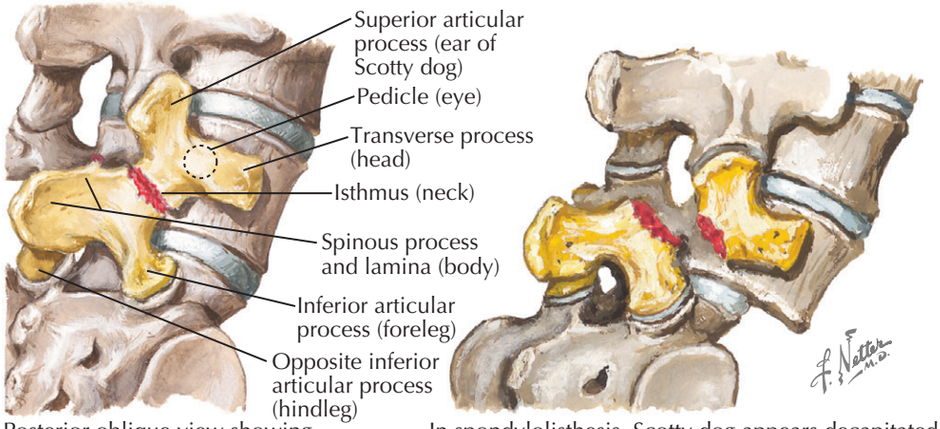
Range of Motion

Range of motion in the lumbar spine is dependent on the resistance to movement of the intervertebral disks and the size of the articular surfaces. The most significant degree of motion is in the thickest disks and largest joint surfaces, mostly between L5-S1. Tests for range of motion include flexion, extension, lateral bending, and rotation. The clinician should bear in mind, however, that limitation of spinal range of motion is a nonspecific finding that is not strongly associated with any particular diagnosis.

Flexion. While standing, have the patient fold forward with the knees straight and touch his toes. Measure the distance from the fingertips to the floor. Lumbar pain may prevent full range of motion.

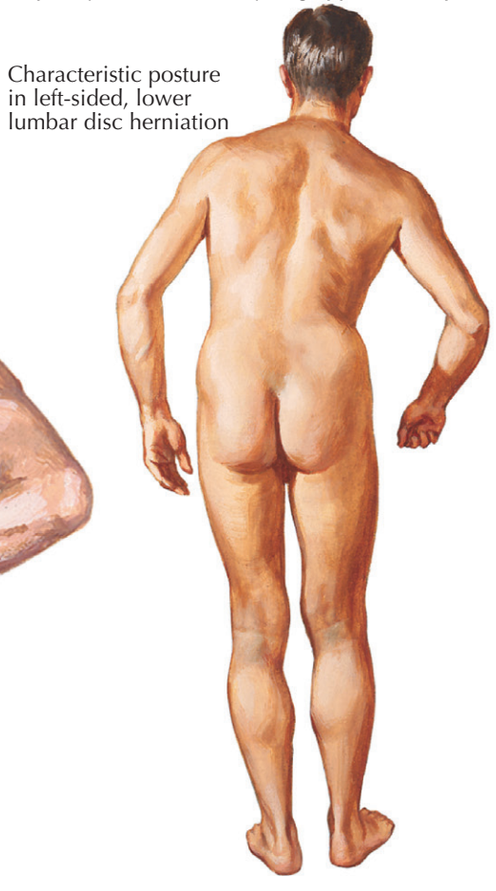
Extension. With the patient standing, place your palm on the patient's posterosuperior iliac spine and have the patient bend backward as far as possible. Assess the degree of extension. This motion aggravates the pain experienced by patients with spondylolisthesis, whereas flexion results in pain relief.

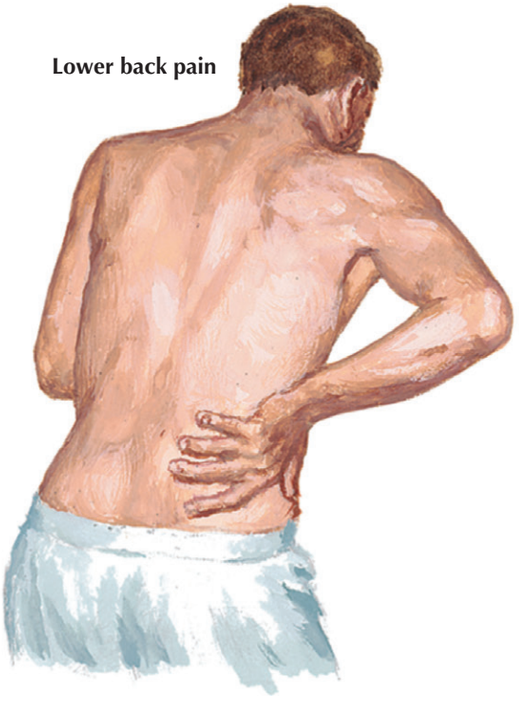
Spondylolysis and Spondylolisthesis



Posterior oblique view showing radiographic Scotty dog. In simple spondylolysis, dog appears to be wearing a collar

In spondylolisthesis, Scotty dog appears decapitated





Examination of the Low Back Pain Patient *(Continued)*

Lateral Bending. Support the iliac crest and have the patient lean as far left and right as possible. To test for passive bending, perform this motion on the patient by leaning him or her to the left and right by placing a hand on his or her shoulder.

Rotation. Place one hand on the pelvis and the other on the opposite shoulder. Rotate the pelvis and shoulder posteriorly and repeat on the other side; note any asymmetry in motion.

SPECIFIC TESTS

Two specific tests include the straight-leg raise test and the crossed straight-leg raise test. These are valuable diagnostic tools for disk herniation and lumbosacral radiculopathy.

Straight-Leg Raise Test. To perform, have the patient lie supine with legs relaxed. Lift the patient's leg upward by supporting the heel with one hand and ensuring the knee remains straight with the other hand; when the patient experiences pain, lower the leg slightly and dorsiflex the foot to stretch the sciatic nerve. Note the degree of elevation, description and location of pain, and effect of dorsiflexion. The test is positive if pain is felt in the low back or along the sciatic nerve. A positive test is indicative of lumbosacral radicular inflammation.

Crossed Straight-Leg Raise Test. To perform, place the patient in supine position, raise the unaffected leg. If back or sciatic pain is felt in the opposite leg, this is suggestive of a lesion, such as a herniated disk, in the lumbar region.

REFLEX TESTING

Patellar muscle stretch reflex arises predominantly from L4 nerve roots, although innervation is also supplied by L2 and L3 segments of the spinal cord. Damage to the L4 nerve will elicit a significantly decreased patellar reflex due to L2 and L3 involvement.

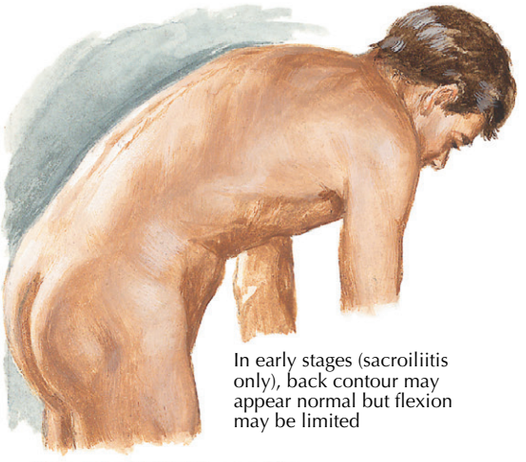
Achilles muscle stretch reflex typically involves the S1 nerve root. Dorsiflex the foot and strike the tendon to elicit plantar flexion of the foot.

IMPORTANT FINDINGS

Mechanical low back pain characterized by aching pain in the lumbosacral region presents with paraspinal muscle or facet tenderness but no evidence of motor, sensory, or reflex deficits.

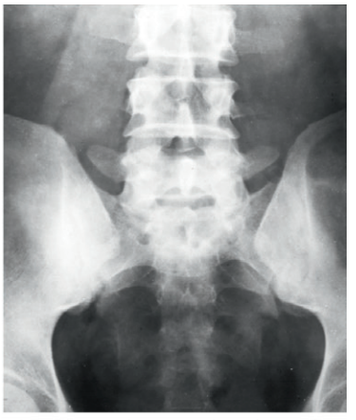
Radicular low back pain is typified by pain that extends below the buttocks into the posterior thigh and often below the knee into the lateral leg or back of the calf. Clinical findings in sciatica due to disk herniation include decreased ankle dorsiflexion, tibialis anterior and tibialis posterior (L5) or gastrocnemius (S1) weakness, no ankle jerk (S1), and positive crossed straight-leg test.

Lumbar spinal stenosis findings are variable. Classically, patients complain of pain with standing or walking, particularly with hyperextension such as walking downhill; this is relieved with rest or flexion. Anterior thigh paresthesias are common. Often, there are no significant abnormal findings; however, there may be mild proximal, quadriceps, and iliopsoas (L3-4), weakness with a decreased patellar reflex. Straight-leg raising is normal.

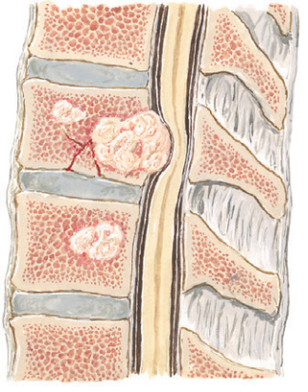


In early stages (sacroiliitis only), back contour may appear normal but flexion may be limited

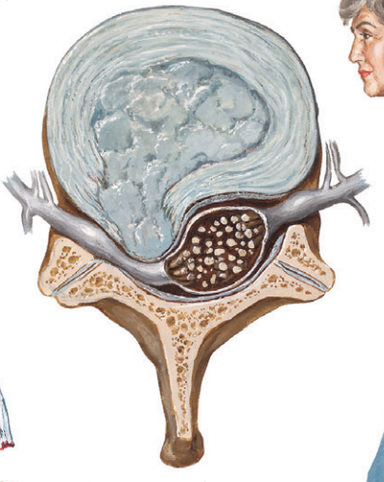
Osteoporosis



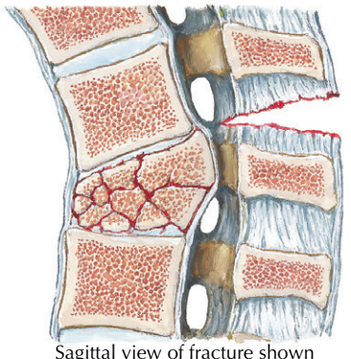
Bilateral sacroiliitis is early radiographic sign. Thinning of cartilage and bone condensation on both sides of sacroiliac joints.



Cancer within the vertebral body



Cross section showing compression of nerve root



Sagittal view of fracture shown in radiograph at left

Progressive thoracic kyphosis, or dowager's hump, with loss of height and abdominal protrusion

DIAGNOSTIC IMAGING

Although imaging or other diagnostic tests need not be obtained routinely in patients early in the course of acute or subacute nonspecific LBP, they are irreplaceable in the management of patients with severe or progressive neurologic deficits or with other serious underlying conditions.

Plain radiography is of limited use, as it fails to depict a detailed picture of the disease; however, it has been recommended for initial evaluation of possible vertebral compression fracture in patients with a history of osteoporosis or steroid use.

Magnetic resonance imaging (MRI) provides superior soft tissue detail compared with computed tomography (CT) and plain radiography. It is the method of choice for visualization of intrathecal nerve roots, detecting intraspinal malignancy and infection within the spine, as well as bone marrow evaluation. MR imaging is less useful for detecting acute spinal fractures.

CT scans are particularly valuable for detecting traumatic and degenerative changes in cortical bone and have a good sensitivity for detecting herniated disks. It can also demonstrate foraminal and extraforaminal nerve root impingement. CT is superior to plain films for detecting infection and neoplasm.

LABORATORY EVALUATION

This is primarily useful in the clinical setting suggestive of visceral or other nonmechanical causes for the pain. Initial studies of value are complete blood count, erythrocyte sedimentation rate, and C-reactive protein, whereas urinalysis, prostate-specific antigen, alkaline phosphatase, and protein immunophoresis are valuable when there are clinical clues suggesting urinary infection and malignant or metabolic disease.

Diagnosis of Low back, Buttock, and Hip Pain

Discriminating among patterns of referred and neurogenic pain from the lumbar region is a common clinical challenge. In the context of concomitant hip and spine pathology, identifying the cause of pain is especially difficult. These patients may present with radiating pain below the knee, back pain, or symptoms evoked by internal rotation of the hip. Certain combinations of signs and symptoms favor one localization over another. Reported odds ratios in one study suggest that signs and symptoms of a limp, groin pain, and limited internal rotation of the hip are all much more likely to be present in a patient with a hip disorder. Similarly, in a comparison of patients diagnosed with a hip disorder versus those with a spine disorder or both, patients with a positive femoral stretch test are 4.76 times more likely to have a spine disorder or a hip and spine disorder.

In general, true hip pain manifests as groin pain that sometimes radiates to the knee. Thigh pain, buttock pain, and pain radiating below the knee are more often attributable to disorders of the lumbar spine or buttock and proximal thigh musculature.

Low Back Pain

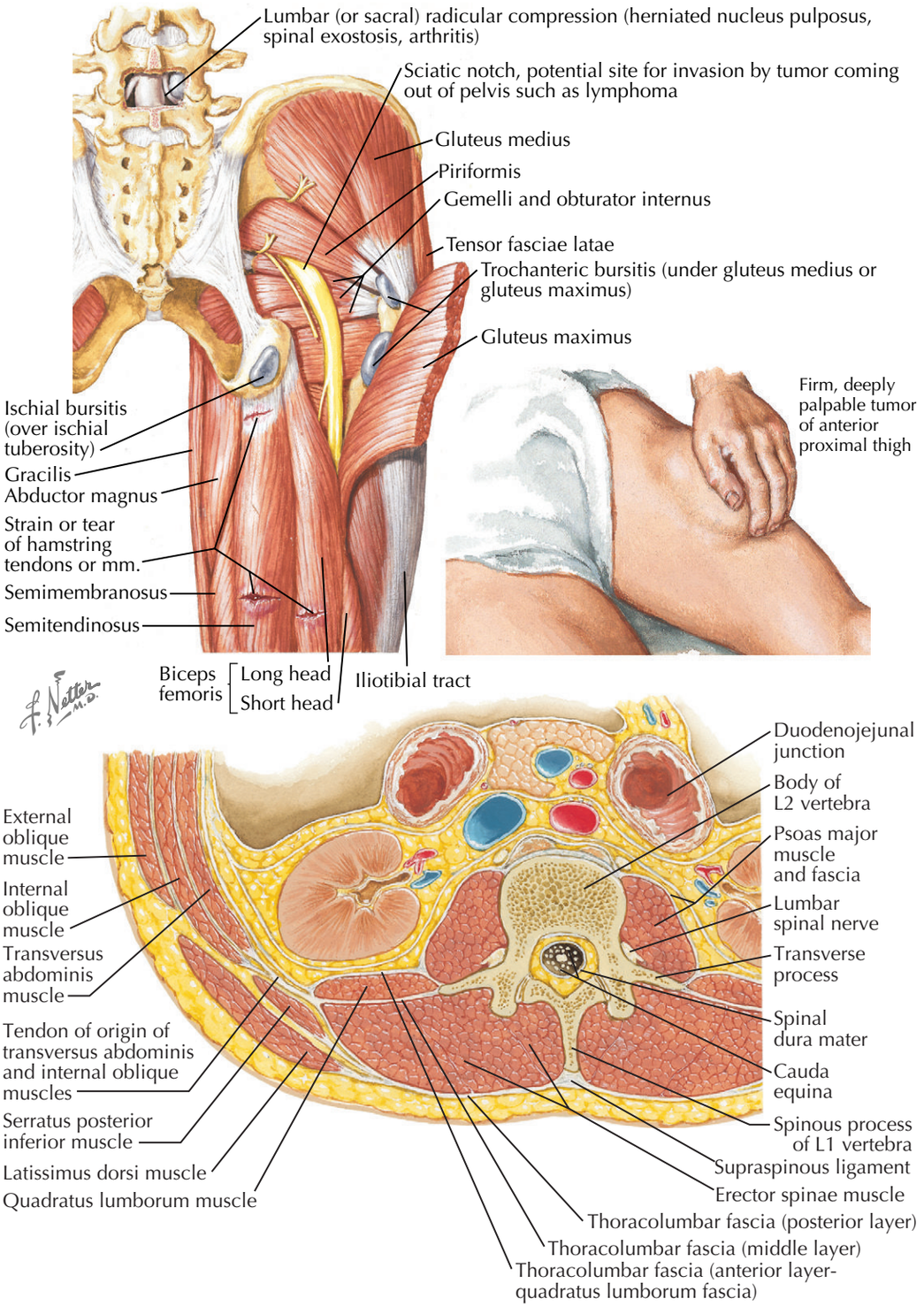
Chronic nonspecific low back pain may result from peripheral injury to various neural and non-neural anatomic structures in the lumbar region. Pain generators may include the vertebral column, surrounding muscles, tendons, ligaments, and fascia, or the neural structures such as the lumbosacral roots. Hip osteoarthritis, trochanteric bursitis, ischial bursitis, sacroiliac dysfunction, piriformis syndrome, and osteitis condensans ilii are examples of somatic conditions that will refer pain to and from the low back. Hip-joint pathology and bursitis of the greater trochanter can mimic mechanical or radicular LBP, both in its onset and symptoms.

It is crucial to distinguish radicular pain from somatic referred pain because their management is significantly different. Somatic referred pain is the result of noxious stimulation of structures in the lumbar spine, such as intervertebral disks, facet joints, or sacroiliac joints, and never of the nerve roots. It has a dull, gnawing quality, and is difficult to localize. Conversely, radicular pain is elicited by ectopic discharges from a dorsal root. The most common cause of such pain is disk herniation complicated by the inflammation of the affected nerve. It is described as lancinating or shocking, and it can involve allodynia in case of nerve damage and neuropathy. Finally, radiculopathy is a condition characterized by motor and sensory loss in dermatomal distribution due to conduction block along the nerve, and it often accompanies radicular pain.

LBP associated with lumbosacral radiculitis is classically characterized by unilateral lower extremity pain and paresthesias. The onset of pain or paresthesias is typically abrupt and often reported as more severe in the leg versus the low back region. The patient may exhibit decreased truncal range of motion.

Lumbar spinal stenosis is a distinctive syndrome in which the cauda equine and exiting nerve roots are compromised due to degenerative changes. The distinctive experience of pain evoked with standing and walking is known as neurogenic claudication. In contrast to radiculitis, this pain typically remits in the seated (and recumbent) posture or with forward flexion at the waist. This symptom pattern is the leading indication for spine surgery in older adults.

Diagnosis of Hip, Buttock, and Back Pain



Spondylolisthesis is a common, painful condition that exists when there is disruption of the normal segmental alignment of a vertebral body in relation to the adjacent level, usually from failure (e.g., fracture of the pars interarticularis) of the posterior vertebral elements. Patients may present with dull, achy back pain that radiates posteriorly to or below the knees. Lumbosacral tenderness, reduced lateral bending, and hamstring tightness are also common findings.

Vertebral compression fractures are also a common cause of LBP, especially in the elderly. Point tenderness is common in early fractures and often is associated with muscle spasm.

Buttock Pain

In the low back, referral pain patterns commonly manifest with hip or leg symptoms. A classic example

Diagnosis of Low back, Buttock, and Hip Pain
(Continued)

of a referral pain pattern in the lumbosacral spine is low back pain associated with aching buttock pain. The lumbosacral region and buttocks are both innervated by L4-S1. However, the buttock is innervated by the ventral rami of these nerve roots (the superior and inferior gluteal nerves), and the lumbosacral region is innervated by the dorsal rami.

Spinal causes for buttock symptoms include facet joint injury and lateral fissure in the lumbar disk. In older patients, lateral recess stenosis and degenerative spondylolisthesis may cause buttock pain.

Muscular or myofascial syndromes can arise in gluteus maximus and medius, quadratus lumborum, and the soleus muscle, all producing strong referral patterns of pain in the region of the sacroiliac joint. This diagnosis may be supported by injecting local anesthetic into a trigger point at which myofascial palpation reproduces the primary symptom pattern.

HIP PAIN

Limited internal rotation of the hip, antalgic gait, and groin pain have been identified as the best predictors of identifying hip disorders. Pain in the groin or hip with single-leg stance, Patrick's test (also known as the FABER test [hip *f*lexion, *ab*duction, and *e*xternal *r*otation]), along with the presence of a leg-length discrepancy, are useful for detecting an underlying hip disorder, sacroiliac dysfunction, or greater trochanteric bursitis. Hip internal rotation also can cause increased LBP in patients with piriformis syndrome by placing this muscle on stretch. The pain is often ameliorated by external rotation of the hip in this condition, along with abductor weakness. The groin should be examined for femoral or inguinal hernias. Osteitis pubis, athletic pubalgia, and adductor tendonitis can produce groin pain that mimics pain associated with disorders of the hip. Persistent hip pain can originate from intra-articular disorders, such as avascular necrosis, osteoarthritis, loose bodies, labral tears, or pyarthrosis. It can also be secondary to lumbar spine disorder. Nerve entrapment syndromes involving the ilioinguinal, genitofemoral, and lateral femoral cutaneous nerve of the thigh may manifest as hip pain or paresthesias.

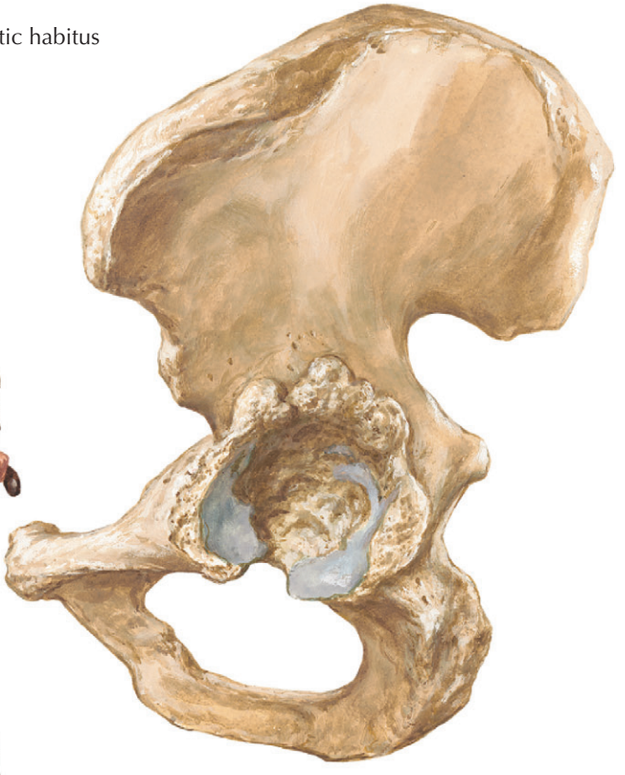
Osteoarthritis is a common condition affecting the hip in adults. Motion in the hip becomes progressively restricted because of synovitis, soft tissue contractures, and loss of joint congruency. Patients complain of pain in the groin, buttock, anterior thigh, or knee and often have an antalgic gait. Examination of the hip shows limited range of motion and a flexion contracture.

The so-called piriformis syndrome has been attributed to compression of the sciatic nerve as it exits the pelvis under the piriformis muscle. Patients are said to complain of a dull ache in the low back and midbuttock region, pain with walking up stairs, prolonged sitting, or walking. There are no sensitive or specific imaging correlates of this putative site of entrapment. As such, this syndrome remains a controversial clinical diagnosis.

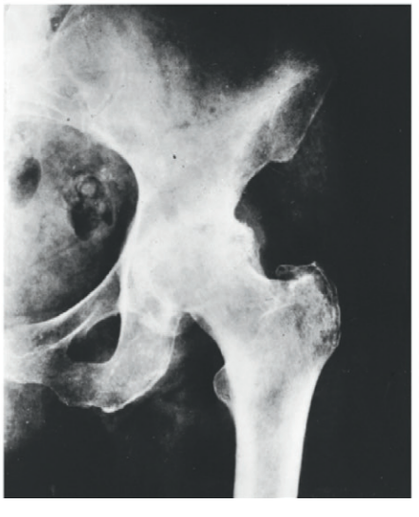
Hamstring syndrome is a pain radiating from the ischial tuberosity down the posterior aspect of the thigh into the popliteal fossa. Physical examination reveals tenderness over the ischial tuberosity and pain with resisted leg extension.

Hip Joint Involvement in Osteoarthritis

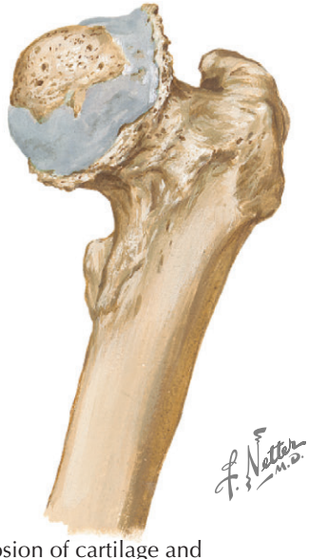
Characteristic habitus and gait



Advanced degenerative changes in acetabulum



Radiograph of hip shows typical degeneration of cartilage and secondary bone changes with spurs at margins of acetabulum



Erosion of cartilage and deformity of femoral head

Bursitis is a common cause of hip pain related to inflammation of one of the three main bursae of the hip. It may be caused by overuse or degenerative changes in the bursae. Patients with trochanteric bursitis present with pain over the greater trochanter that is exacerbated by hip adduction. Ischiogluteal bursitis is often associated with sitting for long periods.

Osteitis condensans ilii is a benign cause of LBP usually found in postpartum women and is thought to develop as a result of mechanical strain placed on the sacroiliac joint during pregnancy. The physical examination is unrevealing, except for localized pain in the low back.

Painful Polyneuropathies

The most common causes of painful peripheral neuropathy (PPN) include diabetes, human immunodeficiency virus (HIV) infection, toxin exposure, alcohol abuse, and certain medications; however, in at least one third of patients, the precise etiology is enigmatic. Painful neuropathies are typically characterized by progressive pain and paresthesia predominantly affecting distal nerve fibers, usually beginning symmetrically in the feet. The prevalence of PPN in persons older than 40 years is nearly 15%, with the incidence being significantly higher in diabetics, where the onset of this neuropathy sometimes leads to the first diagnosis of diabetes mellitus.

Peripheral nerve degeneration is the underlying pathophysiologic mechanism. Axons require their neuronal cell bodies to remain healthy to maintain appropriate nerve activity and function; however, when neuronal damage occurs, the part of the axon most distal from the lesion is the first to degenerate. This is known as "*dying back.*" (It is comparable to a tree dying where its top, most distal part, loses its leaves first because this area is most remote from its roots.) The cell body remains intact and begins a process to redirect growth of the remaining axon to reestablish connection or form new ones. In addition, sometimes loss of blood supply from disorders, such as polyarteritis nodosa, affecting the vasa nervorum, results in peripheral nerve ischemia, leading to similar injury.

Pathophysiology of Diabetic Peripheral Neuropathy (DPN)

The pathogenesis of DPN is attributed to increased oxidative stress, accumulation of sorbitol, and decreased nitric oxide, leading to microvascular damage. Oxidative stress results from hyperactivity of the polyol pathway, causing the intracellular accumulation of polyol. Nerve cells are permeable to glucose independent of insulin. Aldose reductase converts the glucose into sorbitol and polyol within the cell. Because polyol cannot diffuse out of the cell, it accumulates within the neuron, making the cell osmotically active, leading to excess salt and water influx. In turn, sorbitol is converted to fructose, and its increased levels lead to advanced glycosylation end-product (AGE) precursors. AGEs, in turn, accumulate on neurovascular proteins and damage tissues. These two pathways lead to a reduction in the cell's Na^+/K^+ adenosine triphosphatase (ATPase) activity, further impairing endothelial function. In addition, nitric oxide is also a key modulator of Na^+/K^+ ATPase, and endothelial superoxide radicals from the excess glucose reduce nitric oxide's stimulation of the ion pump via decreased nitric oxide synthase activity.

Other cellular changes include *protein kinase C activation*, and *alterations in fatty acid metabolism*, which also contribute to vascular damage.

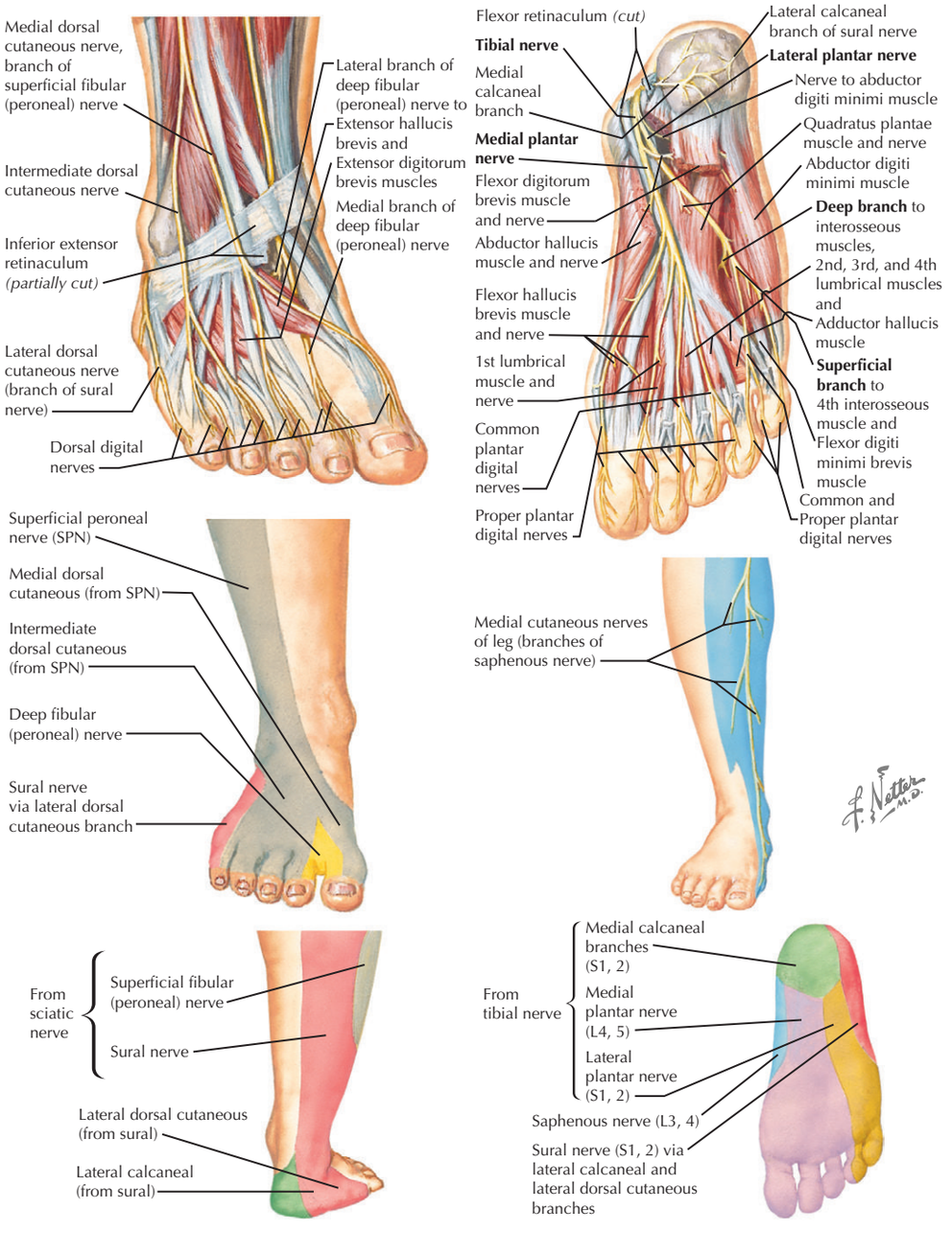
Decreased perfusion of the peripheral nerve per se is another possible cause for the development of PPN. Hyalinization and hyperplasia of the vasa nervorum impairs nerve fiber function. This is particularly true with *unmyelinated fibers* that *innervate arterioles* needed to shunt arterial and venous supply within the nerve. This leads to *damage by hypoxia and ischemic insult*. These metabolic changes, oxidative stressors, and hypoperfusion are responsible for the endothelial and nerve damage observed in DPN.

Although the degree of hyperglycemia affects the overall severity of a polyneuropathy, this may not be specifically causative in its development. There is a trend toward more *active degeneration of unmyelinated fibers* in patients with *peripheral diabetic neuropathy* when making comparative morphometric parameter evaluations between diabetic patients with and without peripheral neuropathy. However, there is no significant difference in the degree of myelinated nerve fiber loss. Skin biopsy studies evaluating *intraepidermal nerve fiber (IENF)* density demonstrate more severe loss of IENF in patients with neuropathic pain, suggesting that IENF damage may partially explain pain in this condition. IENF density measurement from skin biopsy can be used to evaluate small fiber involvement and is useful for detection of early changes in patients with diabetes.

Clinical Manifestations

The characteristic historical features of chronic painful neuropathy include burning, shooting, or stabbing sensations (with or without "pins and needles") that are particularly prominent in the evening and while trying to get to sleep, sometimes frequently awakening patients from their sleep. The pain can be severe, compromising the patient's ability to walk. that is, an *antalgic gait*. These individuals walk gingerly, trying to avoid pressure-induced painful feet. A thorough history to define other potential etiologies is essential to the diagnostic process. Neurologic examination demonstrates reduced or absent muscle stretch reflexes with diminished or absent sensation, particularly for modalities subserved by the small unmyelinated nerve fibers transmitting temperature and pain modalities as well as touch pressure and vibration. This occurs maximally in a distal superficial sensory distribution, leading to a *stocking-glove distribution*. A distal symmetric polyneuropathy, the commonest form of diabetic PN, is characterized by numbness and paresthesias beginning in the toes and spreading upward to the legs. In the most severe instances, involvement of the fingers and hands

Peripheral Nerves of Feet, Most Common Site of Painful Peripheral Neuropathies



Painful Polyneuropathies
(Continued)

develops in a "glovelike" pattern. Typically, DPN has a predilection for the most distal nerves fibers. Ataxia, motor, and autonomic deficits may also be present in later stages of the disease.

Acute painful neuropathy, which may follow initiation of insulin treatment in poorly controlled diabetes, features severe pain symptoms, accompanied by hyperesthesias; however, no alterations to the motor or sensory modalities are present. Painful neuropathy related to human immunodeficiency virus (HIV) infection will usually present with pain mostly on the soles and dorsum of the feet, decreased primary sensory modalities in the feet, decreased ankle reflexes, and minimal intrinsic foot weakness.

TREATMENT

The therapy for neuropathic pain is largely dependent on the primary condition. Novel therapeutic strategies aim to address the underlying neurophysiologic alterations because many recent studies have demonstrated that differences in drug efficacy depend on the cause of the neuropathy. Diabetic painful neuropathy requires a polymodal therapeutic approach.

Several open-labeled uncontrolled studies have suggested that achieving stable normoglycemic state is helpful in the management of the symptoms, and according to general recommendations, intensive diabetes therapy to control blood sugars and hemoglobin A1C are important initial steps in the treatment of any form of diabetic neuropathy.

Medications, such as tricyclics, gabapentin, and pregabalin, are widely used to treat neuropathic symptoms. Large clinical trials confirm their utility in the treatment of DPN because they influence not only pain, but also sleep patterns, mood disturbances, and overall quality of life. A recent Practice Guideline of the American Academy of Neurology concludes that "Pregabalin is established as effective and should be offered for relief of PDN (Level A). Venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, opioids (morphine sulfate, tramadol, and oxycodone controlled-release), and capsaicin are probably effective and should be considered for treatment of PDN (Level B). Other treatments have less robust evidence or the evidence is negative. Effective treatments for PDN are available, but many have side effects that limit their usefulness, and few studies have sufficient information on treatment effects on function and quality of life."

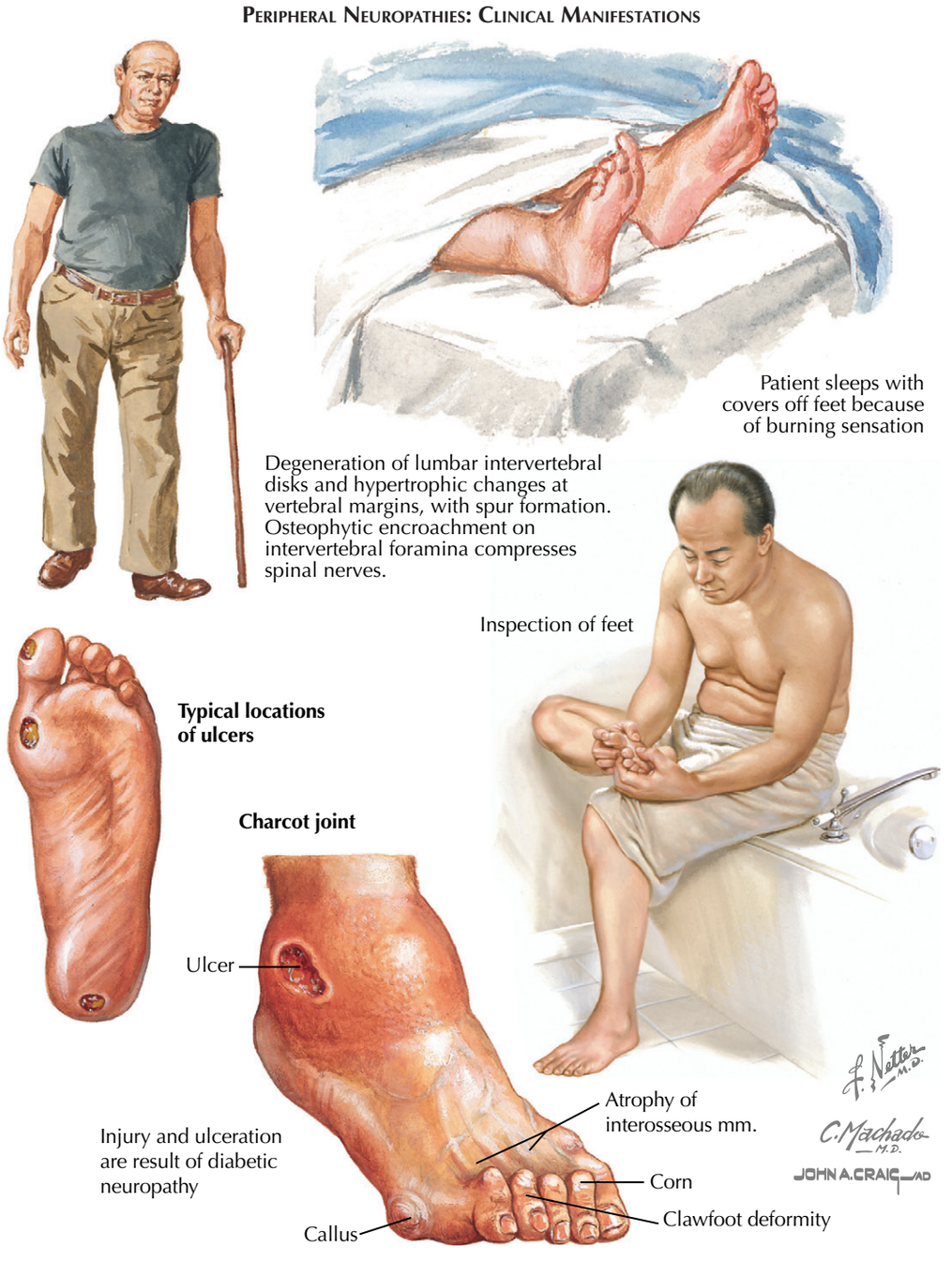
Topical capsaicin is effective for pain relief in recent randomized, controlled studies. Long-term application of capsaicin leads to depletion of axonal substance P, a primary C-fiber neurotransmitter, and thus reduces the transmission of painful stimuli. Lidocaine, targeting the hyperexcitable superficial, free nerve endings, is successful for self-limited forms of neuropathy.

Newer research focuses on norepinephrine and/or selective serotonin norepinephrine reuptake inhibitors (SSNRIs) as the first line of DPN treatment. Duloxetine, approved by the U.S. Food and Drug Administration (FDA) in the treatment of painful neuropathies, is efficacious for treatment of DPN. Venlafaxine, another recently studied SSNRI, also improves pain, mood, and quality of life when added to gabapentin treatment. Tricyclics, such as amitriptyline and imipramine, possibly alleviate pain through inhibition of norepinephrine and/or serotonin reuptake and the antagonism of *N*-methyl-D-aspartate (NMDA) receptors (responsible for hyperalgesia and allodynia). An alternative treatment commonly used in Europe is alpha-lipoic acid, which is thought to stabilize nitric oxide metabolites to increase neuronal perfusion.

Because diabetic neuropathy affects pain fibers, the patient experiencing discomfort may paradoxically not appreciate the pain associated with skin breakdown or joint damage. In these individuals, one of the most important issues is to avoid skin ulceration and breakdown because these can lead to infection, ulceration, and osteomyelitis that may become resistant to treatment and eventually necessitate amputation; thus it is imperative for the diabetic patient to inspect her or his feet on a daily basis, searching for even the most minute sign of infection and, when found, to immediately institute treatment. Similarly, joint pain may not be appreciated, and consequently persistent joint damage occurs, eventually leading to a severely damaged joint referred to as a Charcot joint (see Plate 8-21).

Treatment of HIV-related painful neuropathy poses more problems for the clinicians. So far, there are no positive studies in patients with HIV-related neuropathy. The most recent randomized double-blind clinical trial on the effectiveness of amitriptyline and mexiletine, successfully used in other types of neuropathic pain, has no significant benefit in pain relief in these patients. Similarly, a recent trial of pregabalin found that this therapy did not significantly reduce pain intensity in this population compared with placebo.

For etiologies such as alcoholism and chemotoxic side effects, the mainstay of treatment is discontinuation, dose reduction, or change in the offending agent causing the PPN, and replenishment of vitamin B complex and folate, which are deficient in alcohol-induced PPN.



Neurologic Evaluation of the Somatoform Patient

Chronic pain patients often present with symptoms mimicking a number of neurologic illnesses; one of the most challenging clinical scenarios is to distinguish genuine organic neurologic disorders from primary somatoform disorders, particularly conversion disorders that were previously referred to as *hysterical*. **These patients require the clinician to dedicate the utmost diligence to their evaluation.** Many fine neurologists can recount a number of patients who were previously assigned a diagnosis of hysteria elsewhere before a careful history and examination, sometimes with a period of ongoing observation within a different practice venue, led to an organic diagnosis.

Somatoform diagnoses encompass disorders of somatization, conversion, pain, body dysmorphic disorder, and hypochondriasis, according to *Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV)* criteria (American Psychiatric Association). Each is characterized by symptoms affecting voluntary motor or sensory function, having a resemblance to neurologic or medical diseases, concomitant involvement of psychologic factors, and unintentional, unfeigned symptoms. In contrast to most acute pain syndromes, chronic pain states often lack a clear pathoanatomic or pathophysiologic correlate. Our limited understanding of pain mechanisms tends to invite the clinician to suggest psychogenic origins or motives when an immediate organic cause is not confirmed. A *dualistic model of chronic pain*, perceived as either wholly organic or psychogenic, is not supported by prevailing basic or clinical understanding of pain pathophysiology. Thus diagnostic constructs including *conversion disorder* are less commonly applied now.

The *biopsychosocial model of pain* is the most widely utilized heuristic means to characterize the experience of chronic pain. Viewed as a complex interplay of biologic, psychologic, and social factors, this model embraces concepts of both disease and illness. *Disease* is defined as an objective biologic event involving the disruption of specific bodily organ systems, whereas *illness* refers to the *subjective experience* or self-attribution that a disease is present. Accordingly, the biopsychosocial model distinguishes between nociception and pain. *Nociception* is defined as the stimulation of *nerves that relay information about potential tissue damage* to the brain. Conversely, *pain is the subjective perception* resulting from transduction, transmission, and modulation of sensory information. This model incorporates concepts of suffering, including fear and apprehension about the future, triggered by nociception and pain behaviors that provide a means to communicate pain and distress.

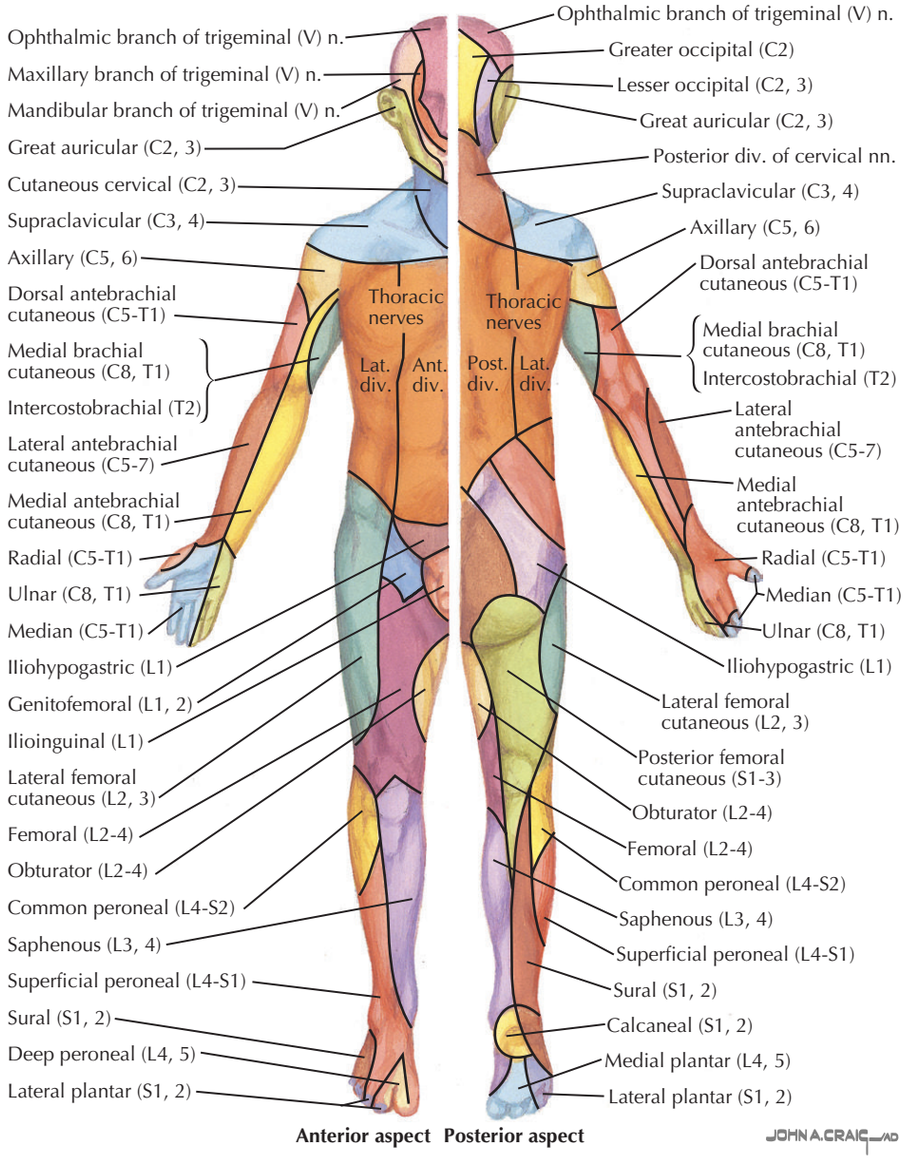
Psychologic Formulations of Pain Behavior and "Conversion" Disorders

Pain behaviors serve not only to gain attention, or avoid undesirable consequences, but may also be considered as pain-reducing strategies or as protective strategies to diminish exacerbation of pain. So-called "*abnormal illness behavior*" describes patients who present with symptom complaints in the absence of physical pathology or who present with exaggerated illness behavior. It is considered a social mechanism that exempts a patient from certain responsibilities, concurrently establishing an obligation to seek treatment and cooperate in the healing process. In other words, pain behavior may offer a more socially legitimate way to express distress or anxiety. In contrast, psychoanalytic explanations of *conversion* emphasize unconscious drives, including sexuality, aggression, or dependency, and the internalized prohibition against their expression. Other psychoanalytic explanations focus on the need to suffer or identification with a lost object.

Other theories emphasize the role of *fear-avoidance beliefs* and *catastrophizing* (tendency to engage in negative thinking and worry about pain) as the catalysts of persistent pain and disability. *Catastrophizing* is a strong risk factor for increased pain, increased illness behavior, and the development of both physical and psychologic disability. *Fear-avoidance beliefs* stem from a conviction that pain is synonymous with harm and that any pain-provoking activity should thus be avoided; such beliefs are likely to be predictive of pain chronicity and disability.

The *neuromatrix model of pain* proposes that pain experience results from the integration of outputs from perceptual, behavioral, and homeostatic systems in response to injury and chronic stress. It is considered the output of the diffuse brain neural networks rather than a direct response to sensory information. Neuroimaging studies are beginning to delineate the neural processes implicated in the somatoform disorders. The cortical correlates of the touch and pain pathways include the primary and secondary somatosensory cortex (S1, S2), insula, and anterior cingulate cortex (ACC). However, additional cortical regions associated with attention, such as posterior parietal cortex (PPC), prefrontal cortex, and the temporoparietal junction, can also impact on or be influenced by somatosensory processing.

Cutaneous Distribution of Peripheral Nerves (After Dejone)



Loss of sensory modalities is based on the anatomic location of the inciting lesion. The pattern of loss may follow either a spinal dermatome pattern or one based on peripheral nerve damage. Because exact peripheral nerve distribution varies among individuals, patterns may differ.

Note that isolated islands of anesthesia (e.g., axillary and deep peroneal) can exist on an anatomic basis.

Neurologic Evaluation of the Somatoform Patient
(Continued)

Furthermore, attentional state can modulate sensory-evoked responses. There are also somatosensory inputs to circuits involved in the processing of emotional or other aspects of psychosocial behavior that may then feed back to somatosensory or motor circuits. Functional magnetic resonance imaging (fMRI) during stimulation of the symptomatic limb reveals prominent abnormalities in somatosensory areas—namely, lack of activations, novel activations, and stimulus-related deactivations in the S1, S2, and PPC cortices. One notable activation study performed during unperceived noxious stimulation demonstrated activity in the rostral and pregenual ACC, suggesting these areas are involved more generally in cognitive processes and emotion.

DIAGNOSIS

Pain behavior in the context of chronic pain has a wide differential diagnosis, requiring clinicians to incorporate historical and examination findings into an unbiased patient-centered global assessment. However, sensory findings, including midline pain/touch sensation splitting, vibration sense splitting, and *inconsistencies* in symptom reporting and examination responses on clinical examination, offer useful contexts for the clinician to carefully assess the role of psychosocial factors that may be contributing to reported pain intensity. Sometimes somatoform patients report an unequivocal sensory loss exactly to the midline for all sensory modalities. Testing of vibration perception is sometimes a good means to differentiate the organic from the somatoform patient. If the clinician places the tuning fork on a midline position, such as the skull or sternum, and then tilts the double end of the instrument to the "affected side," the somatoform patient will report lack of any vibratory appreciation. In contrast, with the base unchanged and the fork then tilted to normal, this patient will appropriately report normal perception. However, the clinician evaluating such symptoms must recognize that certain painful symptom patterns related to a thalamic stroke or postherpetic neuralgia may precisely respect the midline.

The concept of *la belle indifference*, as it was initially described, also applied to patients who were unaware of sensory loss found on examination. The term has also been used to describe a certain indifference of patients to the symptoms they are presenting with; however, this finding performs poorly as a discriminator of organic disease.

TREATMENT

The biopsychosocial model of pain stresses the multitude of factors that influence a person's perception of pain and response to it. In accord with this conception, it is theorized that a multidimensional approach to chronic pain syndromes and abnormal pain behaviors is most effective at reducing symptoms and associated loss of function. Medical and surgical treatments may address the biologic underpinnings of pain experience, although their utility in the treatment of abnormal pain behaviors is controversial. As yet, there is no firm evidence that antidepressants or any other pharmaceutical agent can be regarded as the best approach for treating somatoform disorders. There is also no information on the optimum dose, duration of treatment, or long-term outcome in patients treated with such medication for this indication.

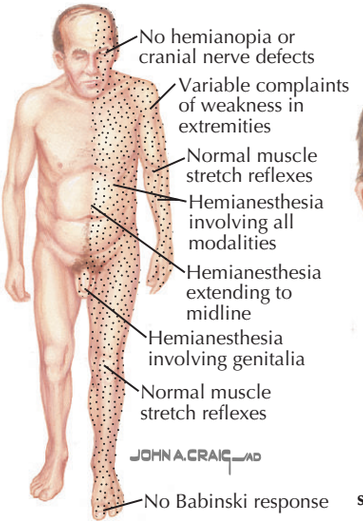
Psychologic and social factors that play a pivotal role in the development of abnormal pain behaviors need to be addressed through various interventions. Comorbid conditions, such as depression, anxiety, and sleeping disorders, not only reinforce the undesirable effects of pain, but these psychologic factors may interfere with successful rehabilitation. There is growing evidence that *cognitive-behavioral therapy* (CBT) improves long-term rehabilitation success for patients with chronic pain symptoms. The primary aim of such interventions is to improve daily functioning, self-efficacy, and quality of life. In case of abnormal pain behaviors, CBT also helps to diminish fear-avoidance beliefs, catastrophizing, and other behavioral responses to pain, thus modifying the pain experience. Family therapy or psychodynamic psychotherapy may prove effective as well, because they address the social aspect of pain behaviors. However, there are no systematic reviews assessing efficacy of these methods.

Conversion symptoms, especially when acute, may undergo spontaneous resolution after explanation and suggestion. Some patients may benefit from education about the patterns of sensorimotor disturbance associated with alteration in neurotransmission, as in the case of major depression, thereby providing a cognitive framework for treatment. Hypnosis is also a potential intervention in the management of this disorder; its goals are to enhance symptom reduction and exploration. This can sometimes also be used to evoke memories of a traumatic event having a positive link with the symptoms. Although there are many anecdotal accounts of the efficacy of hypnosis in conversion disorder, a recent randomized controlled trial found that hypnosis had no additional effect on treatment outcome.

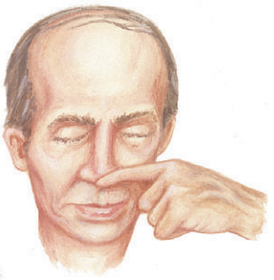
Somatoform Conversion Reactions

Hysterical hemianesthesia

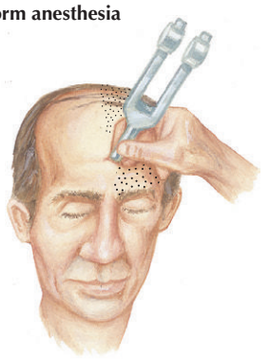
Clinical picture



Tests for somatoform anesthesia



Finger-to-nose test: if successfully performed, demonstrates intact proprioception and thus somatoform hemianesthesia of extremity

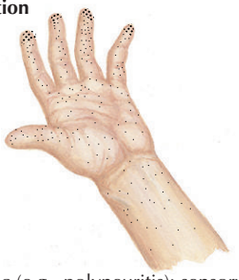


Vibration test: unilateral loss of vibration sensation indicates hysteria because sensation is bilateral if bony skeleton is intact

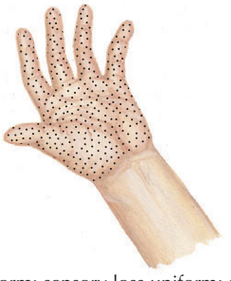
Features of somatoform hemianesthesia:
- involves all modalities
- extends to midline
- involves genitalia

Stocking-glove anesthesia

Demarcation

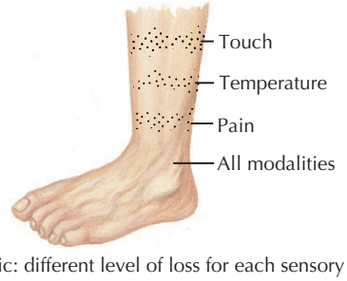


A. Organic (e.g., polyneuritis): sensory loss more profound distally; gradual transition to area of normal sensation

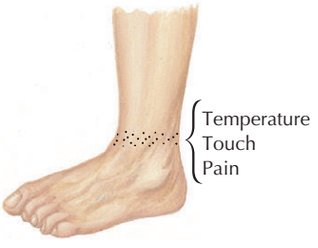


B. Somatoform: sensory loss uniform; sharp demarcation from area of normal sensation, usually at external anatomic landmark (e.g., joint, skin fold) rather than along a nerve distribution

Dissociation



A. Organic: different level of loss for each sensory modality



B. Somatoform: single level of loss for all sensory modalities

FLOPPY INFANT

Neonatal Hypotonia

Neonatal hypotonia, often referred to as the "floppy infant," is the main presenting clinical feature of most neuromuscular diseases of early life. However, disorders of the central nervous system may also manifest with hypotonia.

Two types of muscle tone can be assessed clinically: postural and phasic. *Postural* (antigravity) tone is a sustained, low-intensity muscle contraction in response to gravity. It is mediated by both gamma and alpha motor neuron systems in the spinal cord, and it is assessed clinically by passive manipulation of the limbs. *Phasic* tone is a brief contraction in response to a high-intensity stretch. It is mediated by the alpha motor neuron system only, and is examined clinically by eliciting the muscle stretch reflexes. Hypotonia is defined as reduction in postural tone, with or without a change in phasic tone. When postural tone is depressed, the trunk and limbs cannot overcome gravity, and the child appears hypotonic or floppy.

Physical Examination and Assessment of a Hypotonic Child

After a careful general physical examination, the neurologic assessment needs to include an evaluation of primary neonatal reflexes, a sensory examination, and, most importantly, a motor examination. Muscle tone is assessed by passive manipulation of the infant's limbs.

Muscle tone can be evaluated further by performing the traction response, vertical suspension, and horizontal suspension maneuvers. A floppy infant exhibits "head lag," "slips through" the examiner's hands on vertical suspension, and "drapes over" the examiner's hand on horizontal suspension.

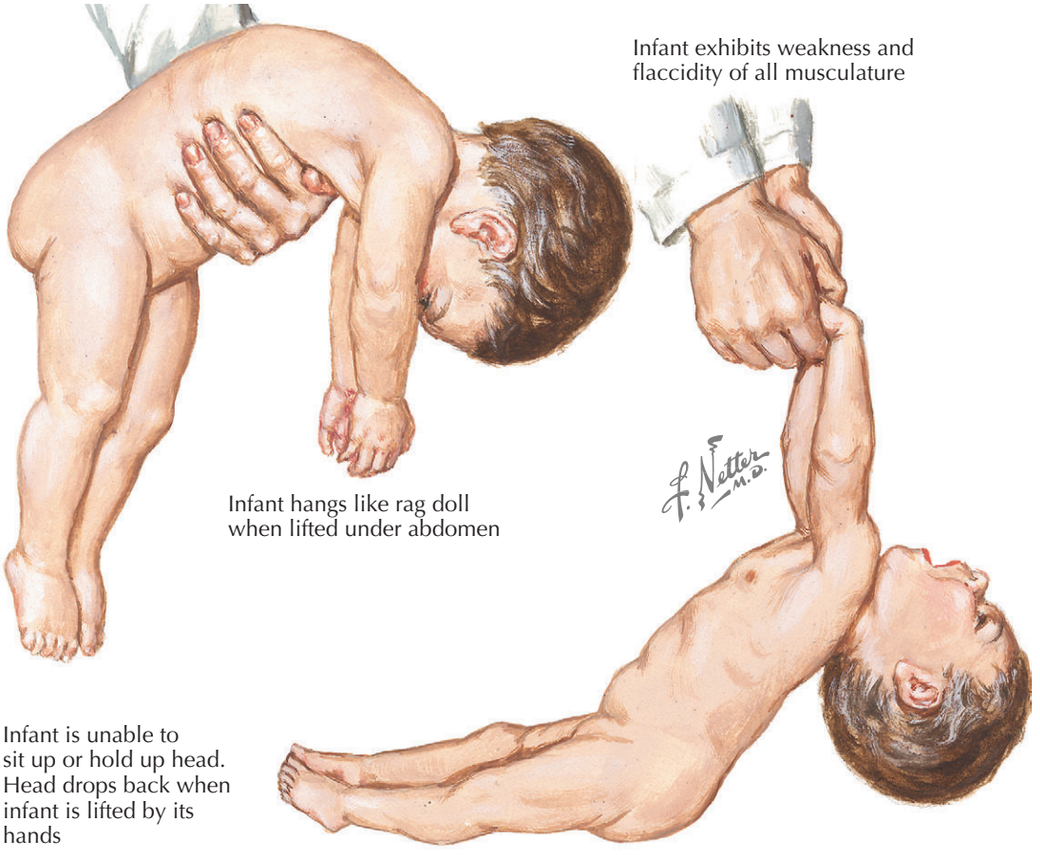
Differential Anatomic Diagnosis

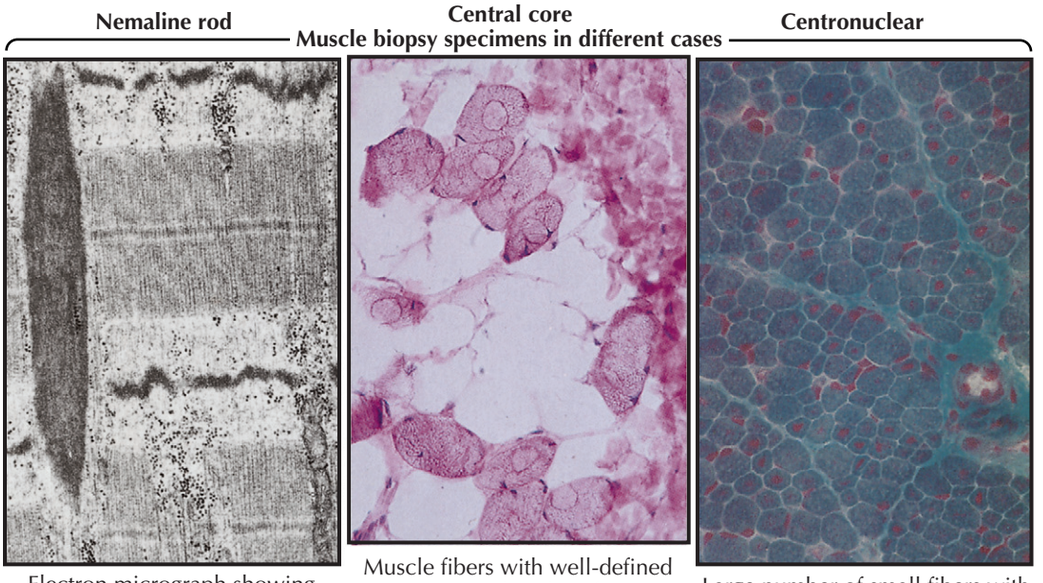
Neonatal hypotonia may be the manifestation of pathology involving the central nervous system (CNS), the peripheral nervous system (i.e., lower motor unit), or both. In infants with *cerebral or central hypotonia* (nearly two thirds of these cases), the perinatal or prenatal history may suggest a CNS insult. There may also be associated global (rather than an isolated gross-motor) developmental delay, occasionally seizures, microcephaly, dysmorphic features, and/or malformation of the brain and/or other organs. Central hypotonia may be associated with brisk and/or persistent primitive reflexes and normal-brisk muscle stretch reflexes. The degree of weakness noted in these infants is usually less than the degree of hypotonia (*"nonparalytic" hypotonia)*.

In *lower motor unit hypotonia or peripheral hypotonia*, developmental delay is primarily gross-motor and is associated with absent or depressed muscle stretch reflexes and/or muscle atrophy and fasciculations of the tongue. In general, antigravity limb movements are decreased and cannot be elicited via postural reflexes. In these infants, the degree of weakness is proportional or in excess of the degree of hypotonia *("paralytic" hypotonia*). Trauma to the high cervical cord due to traction in breech or cervical presentation may also initially manifest itself as flaccid paralysis, which may be asymmetric, and initially muscle stretch reflexes are absent; later on, however, upper motor neuron signs develop.

Because muscle tone is also determined by the viscoelastic properties of muscle and joints, connective tissue disorders, such as *Marfan* and *Ehlers-Danlos* syndromes, osteogenesis imperfecta, and also benign ligamental laxity, can present with hypotonia. In addition, a *combined cerebral and lower motor unit hypotonia* occurs in infants and older children as a presenting manifestation of congenital myotonic dystrophy, some congenital muscular dystrophies, peroxisomal disorders, mitochondrial encephalomyopathies, neuroaxonal dystrophy, leukodystrophies (e.g., globoid cell leukodystrophy), familial dysautonomia, and asphyxia secondary to motor unit disease. Further, hypotonia without significant weakness may be a feature of systemic diseases, such as sepsis, congenital heart disease, hypothyroidism, rickets, renal tubular acidosis, and others.

Neuromuscular diseases in infancy manifest primarily with *hypotonia* and *weakness*; however, infants with severe hypotonia but only marginal weakness usually do not have a disorder of the lower motor unit (anterior horn cell, peripheral and cranial nerves, neuromuscular junction, and muscle). These infants may have genetic conditions, metabolic disturbances, or as discussed above, systemic disorders (e.g., congenital heart disease, renal failure, etc.).





Electron micrograph showing nemaline body continuous with Z band (×30,000)

Muscle fibers with well-defined "cores." Muscle is largely replaced by adipose tissue (PAS stain).

Large number of small fibers with abnormally located central nuclei (trichrome stain)

Spinal Muscular Atrophy Type I (Werdnig-Hoffmann Disease)

Spinal muscular atrophy (SMA) is an autosomal recessive hereditary illness. Rarely, variant forms exist, including X-linked and dominant forms. It is one of the two most common causes for a floppy infant secondary to lesions of the peripheral motor unit. The most common form of SMA is the proximal recessive type, which includes a broad range of subtypes, ranging from the severe infantile variant (depicted here) to ambulatory forms with adult onset.

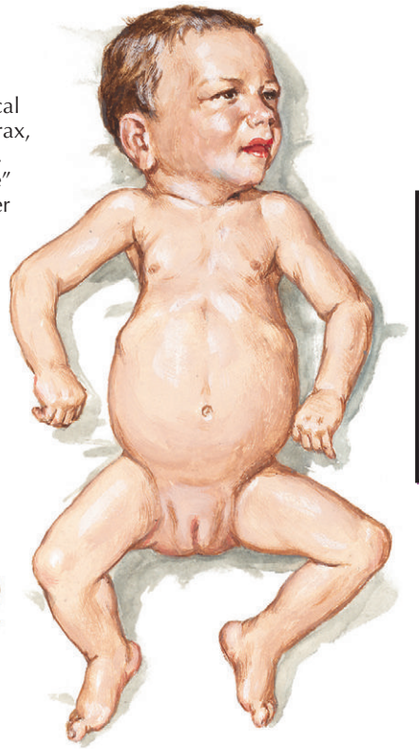
In the healthy newborn infant, purposeless extremity movements have a well-defined muscular tone, despite the lack of coordinated motor function. Concomitantly, full-term newborns have well-developed suck and swallow function. At birth, many SMA type I infants appear normal; however, within a few weeks to months, generalized hypotonia and neuromuscular weakness develop. A classic hypotonic posture characterized by abducted hips, internal rotation of the forearms, and frog-legged and jug-handle habitus is typical. Their respiratory pattern is characterized by paradoxic chest and abdomen movement resulting from selective intercostal muscle weakness with preserved diaphragm function. Without supportive treatment, such infants subsequently develop characteristic bell-shaped deformities of the thorax. Progressive bulbar and respiratory insufficiency results in a vulnerability to both aspiration and infectious pneumonias.

Extraocular and facial movements are preserved; these infants typically have a bright, attentive countenance. Careful evaluation of the tongue reveals tongue fasciculations. In contrast to adult motor neuron disorders, fasciculations in limbs are difficult to appreciate due to excessive subcutaneous infantile fat. Abnormal motor milestones with poor head control, inability to roll and to achieve independent sitting, as expected during the first few months, leads to investigation and eventual diagnosis of SMA type I. In a most severe subset, reduced fetal movements occurs prenatally; these infants are born with generalized hypotonia, weakness, respiratory insufficiency, bulbar dysfunction, and proximal joint contractures.

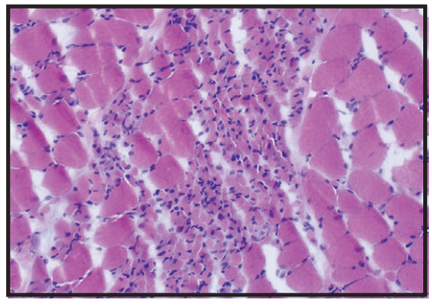
Spinal muscular atrophy with respiratory distress (SMARD) is distinguished by early respiratory failure due to diaphragm involvement, especially in association with more distal presentation of limb weakness. X-linked SMA manifests as a severe infantile SMA variant predominantly affecting males.

SMA II infants initially can sit but never become able to walk and are diagnosed at ages 6 to 24 months. Kugelberg-Welander disease, SMA III, typically occurs between ages 2 and 14 years with symptoms of proximal weakness. These children may have mild elevations of creatinine kinase (CK, <1000 IU/L).

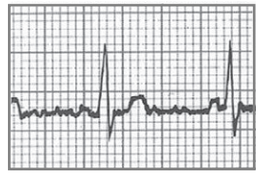
More than 95% of SMA I infants have a homozygous deletion/mutation of exon 7 of the survival motor neuron 1 gene (*SMN1* gene) on chromosome 5q11-13. Infants who do not have this deletion identified may have a non–chromosome 5 SMA or a mutation(s) in the survival motor neuron gene not detectable with the currently used polymerase chain reaction (PCR)-based methods. Both SMA II and SMA III have exactly the same genetic defects as those with type I. When a child with proximal muscle weakness, shown by electromyography (EMG), demonstrates neurogenic changes, deoxyribonucleic acid (DNA) testing for *SMN1* gene is the diagnostic tool of choice.



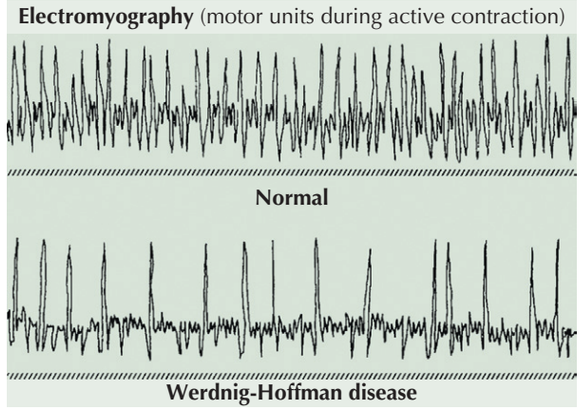
Infant with typical bell-shaped thorax, frog-leg posture, and "jug-handle" position of upper limbs

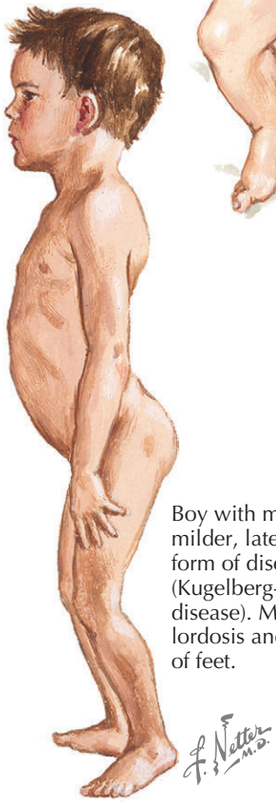


Muscle biopsy specimen showing groups of small atrophic muscle fibers and areas of normal or enlarged fibers (group atrophy) (trichrome stain)



Baseline tremor in otherwise normal electrocardiogram





Boy with much milder, late-onset form of disease (Kugelberg-Welander disease). Marked lordosis and eversion of feet.

Electromyography is a very sensitive primary diagnostic tool; however, it has been largely supplanted by DNA analysis. However, when DNA testing is normal and significant weakness is manifest, the EMG findings are distinct in type I SMA, demonstrating diffuse fibrillations in virtually all muscles in association with markedly reduced recruitment of small motor units in the absence of the typical large complex motor units characteristic of reinnervation in milder, more chronic forms of the disorder. Muscle biopsy demonstrates findings typical of neurogenic atrophy, although the reduced reinnervation capacity in SMA type I often results in a predominance of small rounded fibers within entirely denervated fascicles.

Other lesions in the motor unit can mimic Werdnig-Hoffmann disease (WHD), but, as a rule, can be differentiated by clinical and electromyographic findings and examination of muscle biopsy specimens if genetic and/or neurophysiologic testing are not definitive. Differential diagnosis includes the very rare recessive inherited peripheral neuropathy variants, such as congenital hypomyelinating neuropathy that may clinically mimic WHD, even to the point of tongue fasciculations. More distally within the motor unit, neuromuscular junction disorders, including transient neonatal myasthenia gravis and infantile botulism, as well as the various congenital myopathies and dystrophies, may present as a floppy baby.

Treatment for Werdnig-Hoffmann disease remains largely supportive. The prognosis is generally poor, with onset is in the neonatal period. Many of these infants do not survive until their first birthday. However, even in the absence of extensive supportive care, historically, up to 30% of infants with SMA type I survive beyond 2 years of age, some into adolescence or beyond.

Infantile Neuromuscular Junction (NMJ) Disorders

Infants rarely develop acute NMJ disorders, including transient neonatal myasthenia gravis, infantile botulism, and congenital myasthenic syndromes (CMS). Magnesium sulfate treatment for eclampsia is a theoretical possibility but not one that is presented to the child neurologist.

TRANSIENT NEONATAL MYASTHENIA GRAVIS (TNMG)

Mothers with autoimmune MG have a 15% incidence of having babies with TNMG despite the finding that all infants born to seropositive mothers have circulating acetylcholine receptor (AChR) antibodies. These normally cross the placenta, entering the fetal circulation to bind at fetal NMJs. Once an affected mother has one TNMG infant, her subsequent babies are likely to be affected.

TNMG infants sometimes have weak fetal movements, display fetal distress during delivery, or severe hypotonia shortly after birth. Other manifestations include facial diplegia, poor suck/feeding, a weak cry, intermittent cyanosis (especially during feeding), and respiratory weakness and/or failure. Muscle stretch reflexes, sphincter function, and sensation are preserved. Ptosis and external ophthalmoplegia are paradoxically less frequent than in juvenile MG. Typically, symptoms are transient, lasting 3 to 12 weeks.

Transient improvement after injection of 0.1 mg/kg of edrophonium supports this diagnosis; however, this is often difficult to assess with a ventilated neonate; not all affected infants respond, and a response does not distinguish TNMG from some forms of CMS. The presence of AChR antibodies provides the definitive diagnostic study when the clinical setting fits. Once delivered, the maternal AChR antibodies are no longer pathogenic even within breast milk. Supportive treatment is the primary therapeutic modality and is necessary until symptoms clear. Acetylcholinesterase inhibitors such as pyridostigmine or neostigmine methylsulfate may be helpful. Both intervenous immune globulin (IVIG) and exchange transfusion provide other therapeutic alternatives.

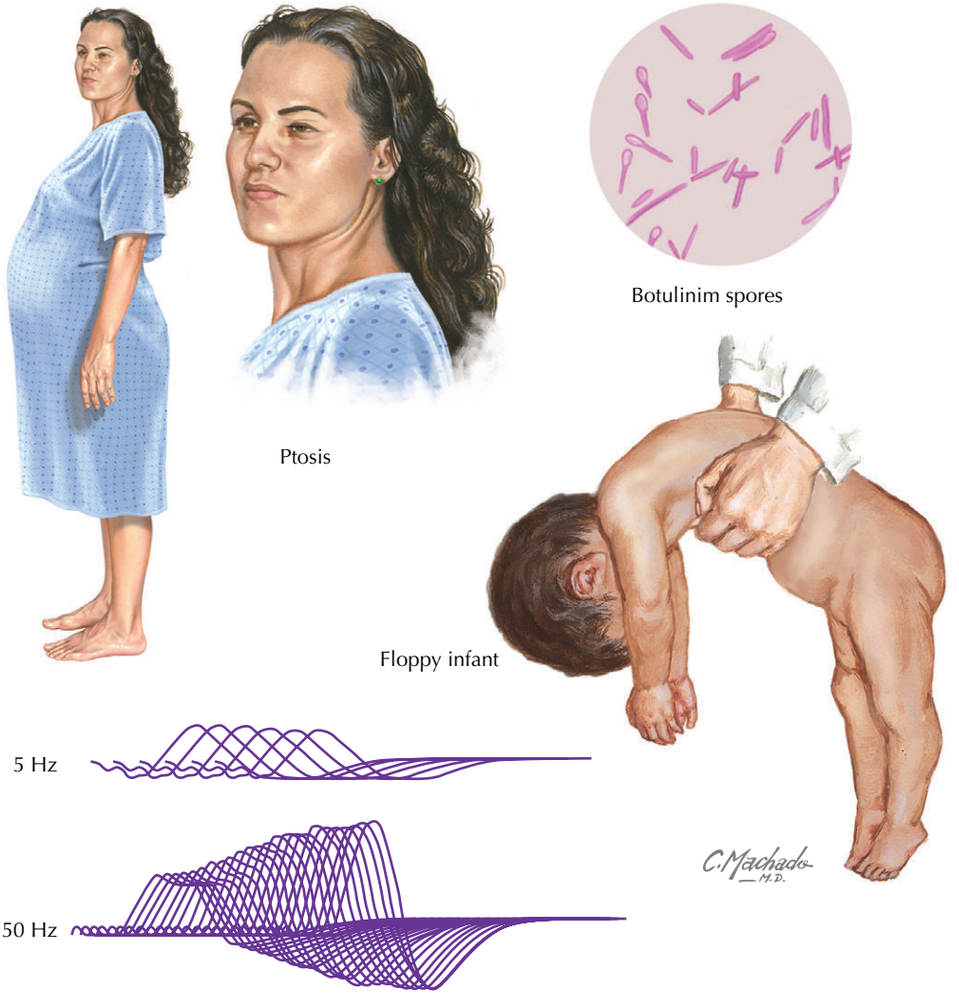
INFANTILE BOTULISM (IB)

This rare disorder typically occurs in previously healthy infants between the third and sixth months of life, particularly in the Mid-Atlantic states, Utah, and California, although it is occasionally seen in other regions. *Clostridium botulinum* is an obligatory anaerobic gram-positive spore-forming rod-shaped bacterium that is ubiquitous within the immature gut. It releases a toxin affecting presynaptic ACh release from the NMJ. In economically developed settings, this is the most common form of human botulism. The normal intestinal microflora changes when formula, sometimes honey, and/or solid foods are introduced into the diet. Sometimes this may enhance the ability of *C. botulinum* to colonize the infant's colon. This is not a contagious disease.

Infantile botulism usually has a fairly stereotyped clinical presentation. Typically, a previously healthy infant, between ages 10 days and 6 months develops acute hypotonia, generalized weakness, poor feeding secondary to bulbar dysphagia, and poor suck that impairs nursing; also, there sometimes is a potentially life-threatening respiratory crisis. Aspiration often leads to hospitalization of an alert, afebrile, nonirritable infant with poorly reactive pupillary light reflexes, ophthalmoparesis, symmetric facial bulbar weakness, and generalized hypotonia. The mother often notes in retrospect that her baby is constipated—has not "stooled" with normal frequency. The face is typically expressionless, drooling, and there may be a high-pitched, mewing cry. Infantile botulism needs consideration in the differential diagnosis of unexplained respiratory distress in any baby up to 6 months old.

Electromyography is the diagnostic study of choice; rapid repetitive motor nerve stimulation (20 or 50 Hz) of infants with IB demonstrates significant incremental responses (23%-313%). This is in keeping with a presynaptic defect in neuromuscular transmission, with the area that the toxin specifically affects essentially blocking the release of acetylcholine. The botulinum *toxin* and the *Clostridium organism* are recoverable from stool.

Treatment primarily is supportive, often with acute intubation. Human-derived botulinum immune globulin (BIG) is beneficial when administered within the first 3 days. Antitoxin per se is not used for infantile botulism because of the possible risk of anaphylaxis. Early aggressive supportive care will ensure that these children all have an excellent outcome.



Repetitive stimulation at 5 Hz of a hypotonic baby's ulnar nerve; recording at the hypothenar eminence demonstrates no facilitation or decrement in the response, whereas 50-Hz stimuli promotes an almost 100% facilitation in the eventual size of the recorded response. Facilitation on 50-Hz stimulation is the characteristic and diagnostic finding of a presynaptic defect in neuromuscular transmission as occurs with infantile botulism.

CONGENITAL MYASTHENIA SYNDROMES (CMS)

CMSs are a group of widely differing, rare familial NMTDs, each characterized by compromised NMT safety margins leading to fatigable weakness.

These genetically determined "*myasthenic*" disorders usually manifest during the first years of life. Clinically, ptosis and extraocular weakness are often more subtle than in juvenile myasthenia gravis (JMG). In addition, bulbar, neck, and extremity weakness occur sometimes with a restricted distribution.

Respiratory distress leading to sudden death occurs rarely in one CMS, namely end-plate choline acetyltransferase deficiency. These infants develop unexpected episodic attacks of apnea associated with bulbar paralysis occurring precipitously during excitement, exertion, febrile events, or without a known precipitating factor. Some babies have fluctuating ptosis, poor suck and cry, feeding difficulty, and secondary respiratory infections.

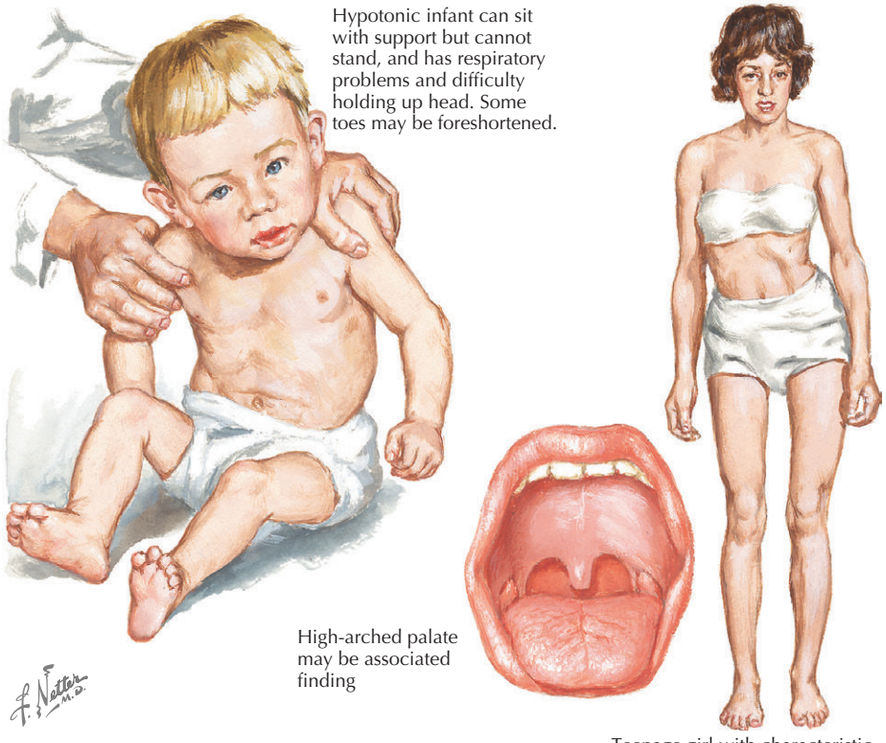
EMGs demonstrate a decremental response similar to JMG; this may be restricted to certain muscles and present intermittently.

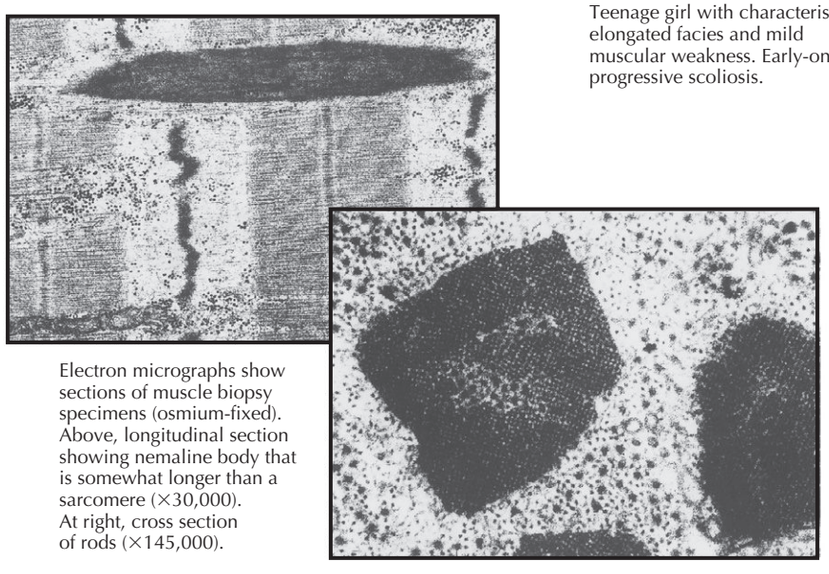
Cholinesterase inhibitors provide a primary treatment option and may be lifesaving.

Congenital Myopathies

Shy and Magee introduced the term "congenital myopathy" to describe central core disease and myopathy present at birth, excluding muscular dystrophy. Clinical distinction from the muscular dystrophies is blurred by conditions such as nemaline and centronuclear myopathies, but these are distinct at a pathologic level. The muscle biopsy findings in congenital myopathies show distinct myopathologic features without significant fibrosis, muscle fiber degeneration, or replacement with adipose tissue. Recently, the specificity of distinguishing pathologic features in congenital myopathies has declined with the inclusion of conditions with similar but not identical histologic features, such as multicore or minicore disease.

Hypotonia and weakness are the major clinical features. Other characteristic features such as scoliosis, ptosis, and ophthalmoplegia may not be apparent at birth, and diagnosis may be delayed until gross-motor developmental delay and associated weakness develop in late infancy or early childhood. The creatine phosphokinase (CPK) level is usually normal or slightly elevated, and diagnosis is heavily dependent on the muscle biopsy.




Electron micrographs show sections of muscle biopsy specimens (osmium-fixed). Above, longitudinal section showing nemaline body that is somewhat longer than a sarcomere (×30,000). At right, cross section of rods (×145,000).

Nemaline Myopathy

The term nemaline (Greek *nema*, thread) characterizes the presence of rods or threadlike structures seen in the muscle biopsies of patients with this type of congenital myopathy. The neonatal type is the most severe, presenting with hypotonia, diminished spontaneous activity, history of poor fetal movements, and early respiratory distress. More commonly, presentation is delayed until after the newborn period when gross-motor delay with proximal weakness develops.

The nemaline bodies on muscle biopsy originate from the Z disks and tend to cluster under the sarcolemma. To date, six genes have been involved in the pathogenesis of nemaline myopathy (gene products α-tropomyosin-3, nebulin, α-actin, β-tropomyosin, troponin T type I, and cofilin-2). It is transmitted by autosomal dominant or recessive inheritance.

Central Core Disease

Most patients with central core disease (CCD) present with hypotonia in early infancy and childhood and a subsequent delay in motor milestones. Rarely, severe hypotonia and marked contractures are present at birth. Skeletal abnormalities are present, also. The clinical course varies from nonprogressive to slowly progressive. An association between CCD and malignant hyperthermia has been observed. On muscle biopsy, central cores appear to be packed with myofiber material and depleted of organelles.

CCD is an autosomal dominant condition. Mutations of the ryanodine receptor-1 have been detected in families with susceptibility to malignant hyperthermia and patients with CCD.

Centronuclear/Myotubular Myopathy

The mode of inheritance of centronuclear/myotubular myopathy can be X-linked recessive, autosomal dominant, or recessive. Early-onset cases are the most common form and present with severe hypotonia, weakness, and respiratory distress. Affected infants are very weak and have major feeding difficulties, facial diplegia, bilateral ptosis, and limitation of eye movements (external ophthalmoplegia). Despite intensive respiratory support, infants rarely survive or improve their motor function. The muscle biopsy shows central nuclei present in many muscle fibers and type I fiber predominance. The gene product in the X-linked recessive variety (*MTM1*) was designated myotubularin. Dynamin-2, amphiphysin (*B1N1*), and also *RYR1* mutations have also been described in patients with centronuclear myopathy.

Congenital Fiber-Type Disproportion

Congenital fiber-type disproportion (CFTD) typically presents with hypotonia and weakness at birth or in the neonatal period. There is delay in acquisition of motor milestones. CPK is normal, and electromyography (EMG) may be normal or myopathic. The muscle biopsy shows type I fiber predominance but also nonspecific type I fiber atrophy seen in other, clinically diverse conditions. Therefore the existence of CFTD as an entity has been debated. α-Actin (*ACTA1*), *RYR1*, α-tropomyosin, and selenoprotein N (*SEPN1*) mutations have been described in patients with CFTD.

Other Congenital Myopathies

In addition to the four most common congenital myopathies described above, there are uncommon types with similar clinical characteristics but less well-defined patterns of inheritance. Their names reflect their myopathologic features and include (1) actin myopathy (non-nemaline), (2) fingerprint body myopathy, (3) sarcotubular myopathy, (4) hyaline body myopathy, (5) reducing body myopathy, (6) cytoplasmic body myopathy, (7) myopathy with myotubular aggregates, (8) zebra body myopathy, and (9) trilaminar myopathy. The mutated genes are known in some of them, but diagnosis is made by muscle biopsy.

Arthrogryposis Multiplex Congenita

Arthrogryposis is defined as the presence of a congenital joint contracture. Arthrogryposis multiplex congenita (AMC) is, by extension, a syndrome in which an infant is born with congenital contractures at two or more major joints. The incidence is estimated to range from 1 in 3000 to 1 in 12,000 live births. Approximately 150 causes of AMC are defined, including maternal factors and genetic disorders. A prolonged period of fetal immobility provides the final common pathway shared by all the pathologic processes that lead to the clinical phenotype of AMC. Vigorous and frequent fetal movements are needed to maintain a normal range of motion across joints.

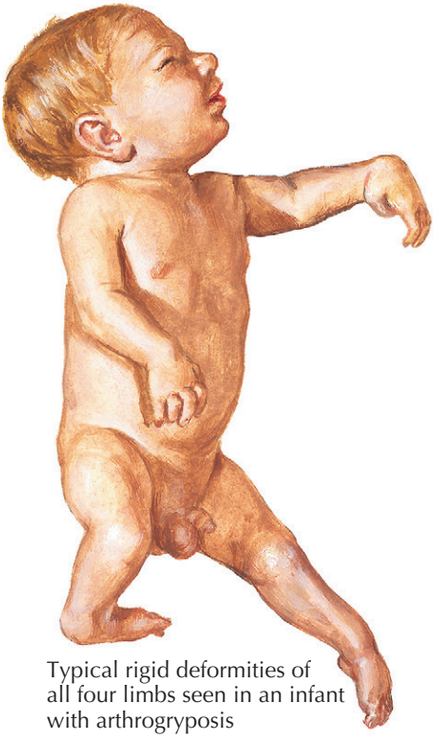
The maternal conditions that put an infant at risk for AMC are those that restrict fetal movements. They include oligohydramnios, placental insufficiency, and structural abnormalities such as bicornate uterus. Medical conditions, such as maternal myasthenia gravis, may also cause prolonged prenatal weakness. A wide variety of genetic disorders also can lead to AMC; some of these affect the central nervous system and lead to decreased fetal motor abilities. Chromosomal aneuploidies are occasionally associated with AMC but account for a small fraction of cases. Inherited peripheral nervous system disorders cause AMC if they prevent a fetus from moving normally, and they account for a significant proportion of cases. These include motor neuron disease (variants of spinal muscular atrophy), congenital myasthenic syndrome, congenital myopathy, congenital muscular dystrophy, and congenital myotonic dystrophy. Among the neuromuscular etiologies, a form of motor neuron disease is the most common; these cases are less consistently associated with deletions in *SMN1* than the traditional forms of spinal muscular atrophy.

The diagnostic evaluation of AMC starts with a thorough history, including details of gestation. If a maternal issue, such as oligohydramnios or uterine structural abnormalities, is identified and no findings in the infant suggest an endogenous disease process, the infant may not require an extensive evaluation. If no clear maternal factor is defined, then a diagnostic evaluation for an endogenous disease should be initiated. Certain findings on history and examination, such as cognitive delays, dysmorphic features, and microcephaly, may suggest a central nervous system localization or generalized genetic syndrome. In such cases, basic screening tests that may be useful include karyotype and brain magnetic resonance imaging (MRI). Additional studies may be indicated depending on the individual presentation.

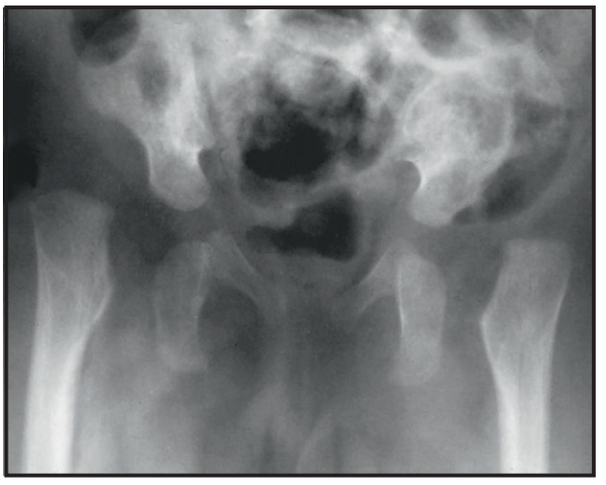
The presence of muscle weakness, taking into account the limitations in range of motion, is strongly suggestive of a peripheral nervous system etiology. The presence or absence of muscle stretch reflexes may in some cases help differentiate between central and peripheral motor unit disorders; however, reflexes are not as accurate as the presence or absence of weakness in making this distinction. In cases where a peripheral motor unit process is suspected, a serum creatine phosphokinase (CPK) level should be obtained, although it should be noted that these levels are sometimes artifactually elevated in the first several days of life.

Whenever possible, both an electromyography (EMG) study and muscle biopsy should be obtained because these tests are most accurate when they are concordant with each other. There are some conditions, such as certain subtypes of congenital muscular dystrophy, in which both the central and peripheral nervous systems are affected, and thus the infant may have clinical features suggestive of both. Some endogenous causes are not neurologic in origin; these may include connective tissue disorders such as multiple pterygium syndrome, developmental disorders such as amyoplasia, and genetic arthrogryposis syndromes such as Pena-Shokeir syndrome. In some cases, a specific etiology cannot be identified after a reasonably thorough evaluation.

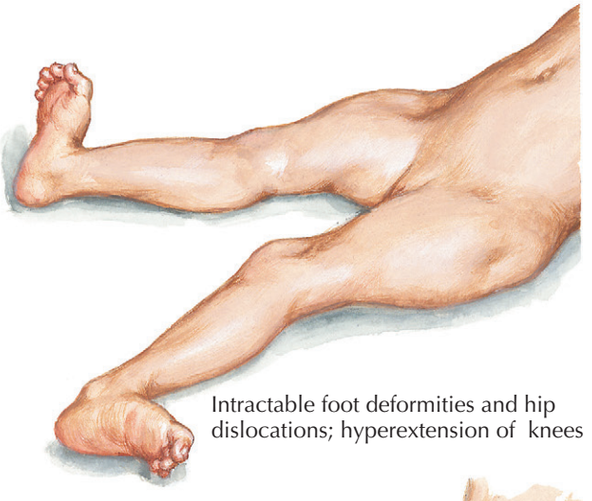
The treatment of AMC is largely supportive because the injuries to the affected joints occur prenatally and are difficult to reverse. Physical therapy is needed on a long-term basis. A skilled orthopedic surgeon familiar with arthrogryposis, or at least contractures in children, will need to be involved for a prolonged period because these patients often need multiple surgeries to help alleviate some of the joint limitations.



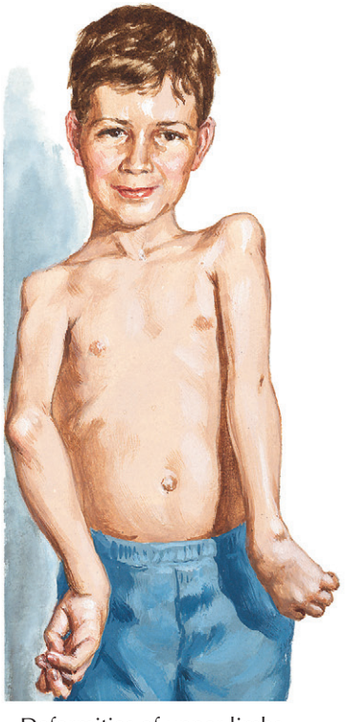
Typical rigid deformities of all four limbs seen in an infant with arthrogryposis



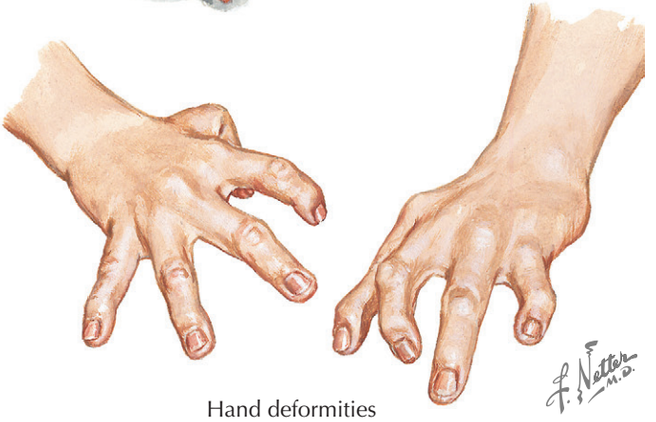
Radiograph of pelvis and hips of 2-week-old infant shows advanced changes typical of teratologic dislocation of hips



Intractable foot deformities and hip dislocations; hyperextension of knees



Deformities of upper limbs in older child



Hand deformities

MOTOR NEURON AND ITS DISORDERS

Peripheral Nervous System: Overview

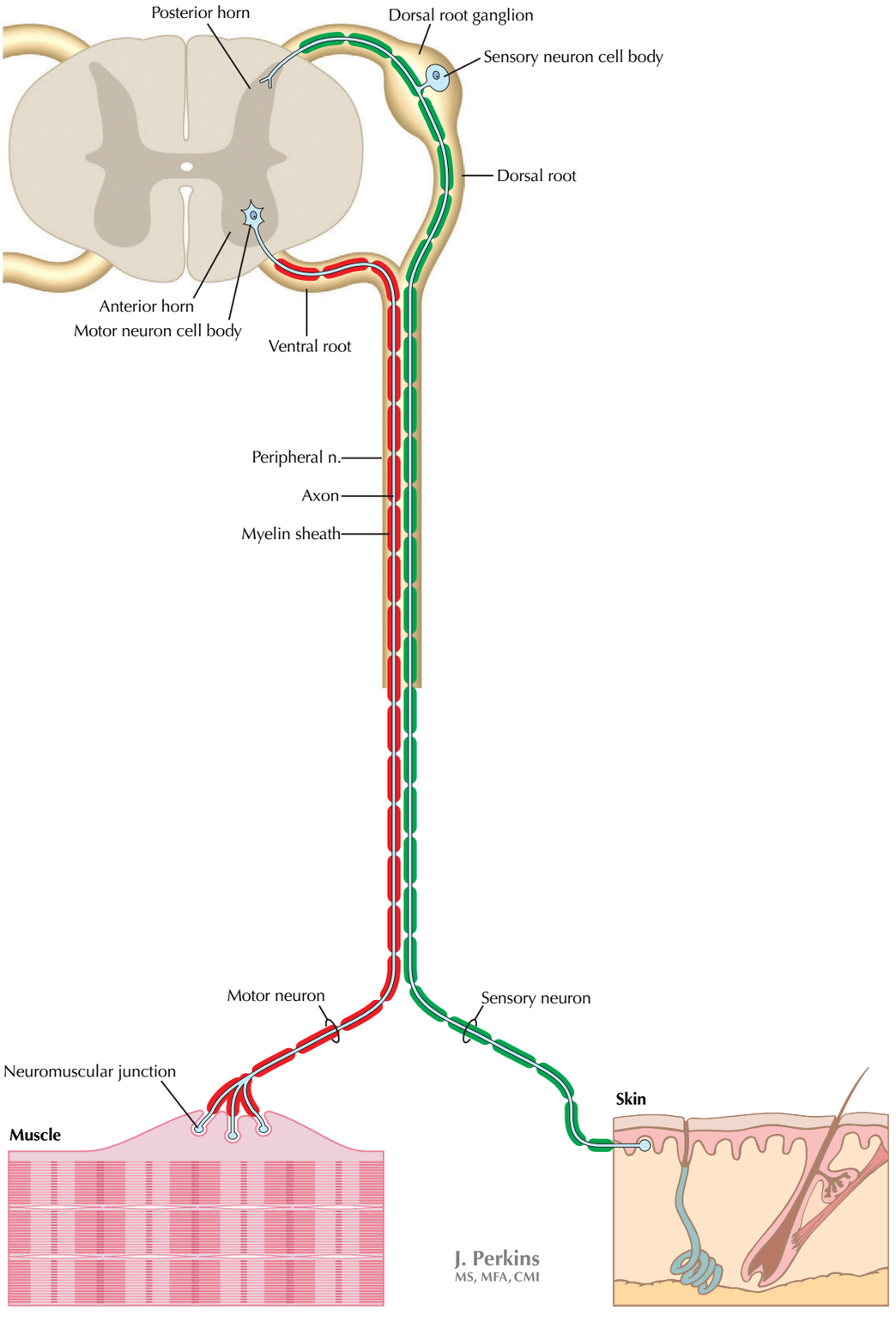
The major function of the nervous system is the transmission and processing of information. This relies on propagation of electrical signals between the peripheral nervous system and the central nervous system. The somatic peripheral nervous system is composed of afferent (sensory) neurons (green in the figure) and efferent (motor) neurons (red in the figure). The first-order somatic sensory neurons transmit the initial electrical signals generated by a sensory stimulus. For example, a sensory stimulus to the skin initiates sensory processing by activating the local sensory receptors within the skin. A sensory nerve action potential (electrical signal) is generated and propagates along the afferent sensory axons within a peripheral nerve, toward the spinal cord. The final-order somatic motor neurons generate a signal within the anterior horn cells in the spinal cord, after depolarization of the anterior horn cells from a central activation. The action potentials propagate away from the spinal cord through the motor axon, generating a cascade of reactions at the neuromuscular junction and muscle, ultimately leading to muscle contraction. The somatic sensory and motor neurons have several morphologic differences.

The *peripheral somatic sensory neurons* are bipolar neurons. The sensory neuron cell bodies reside in the dorsal root ganglion, that is, situated posterolateral to the spinal cord, usually at or near the intervertebral foramen. Extending out from the cell body are two axon extensions; one extending distally to the skin or other organs and one extending proximally through the dorsal root into the posterior horn of the spinal cord. The relationship between the sensory neuron cell bodies within the dorsal root ganglion and the sensory axons is important; when the axon branch (either the distal or proximal branch) is separated from the cell body, the separated axonal component undergoes axonal (wallerian) degeneration. As a result, an injury at the proximal nerve root ("pre-" or proximal to the ganglion) will lead to sensory deficits even though the distal sensory axon remains intact. The clinical implications of this occur during electrophysiologic testing with nerve conduction studies in which a distal sensory nerve is studied. In the presence of sensory loss in an extremity, a preserved or normal sensory nerve conduction study response suggests that the sensory loss is caused by a disorder involving the sensory pathway, either in the proximal root (proximal to the ganglion) or the central somatosensory conduction pathways in the spinal cord or brain and not the peripheral nerves per se.

Several structurally different types of sensory neurons exist within a somatic nerve. The largest sensory neurons are type IAα and Ib fibers, which are large, myelinated fibers whose function is to transmit proprioceptive signals from muscle spindle endings, Golgi tendon organs, and proprioceptive sensory receptors. Type II (Aβ) fibers are smaller myelinated fibers that transmit signals from the muscle spindles and skin receptors controlling touch and pressure. Type III (Aδ) fibers are small myelinated fibers that play a role in sharp pain, temperature, touch and pressure, and visceral sensations. In addition, small unmyelinated fibers, type IV (C), contribute to sensation of somatic and visceral pain.

Somatic motor neurons are unipolar neurons. The motor neuron cell bodies reside in the anterior gray matter (anterior horns) of the spinal cord. A single axon extends distally from each anterior horn cell, through the ventral root, and joins the peripheral nerve that innervates individual muscles. The motor conduction pathway continues along the nerve to the nerve terminal. At this site, an action potential traveling through the motor axon to the nerve terminal leads to a cascade of reactions at the neuromuscular junction, where the nerve terminal is adjacent to the muscle fiber. Through these reactions, an action potential is generated along the muscle fibers, resulting in muscle fiber contraction. The integrity of the motor unit (an anterior horn cell and its axon, nerve terminal, neuromuscular junction, and innervated muscle fibers) can be tested during electrophysiologic testing with motor nerve conduction studies.

Motor neurons are typically large in diameter and myelinated. The major type of motor neuron, the alpha motor neuron, innervates the *extrafusal striated muscle fibers* and, primarily, is responsible for muscle fiber contraction. Smaller, myelinated gamma motor neurons innervate the *intrafusal fibers of muscle spindles.*



Spinal Cord and Neuronal Cell Body with Motor, Sensory, and Autonomic Components of the Peripheral Nerve

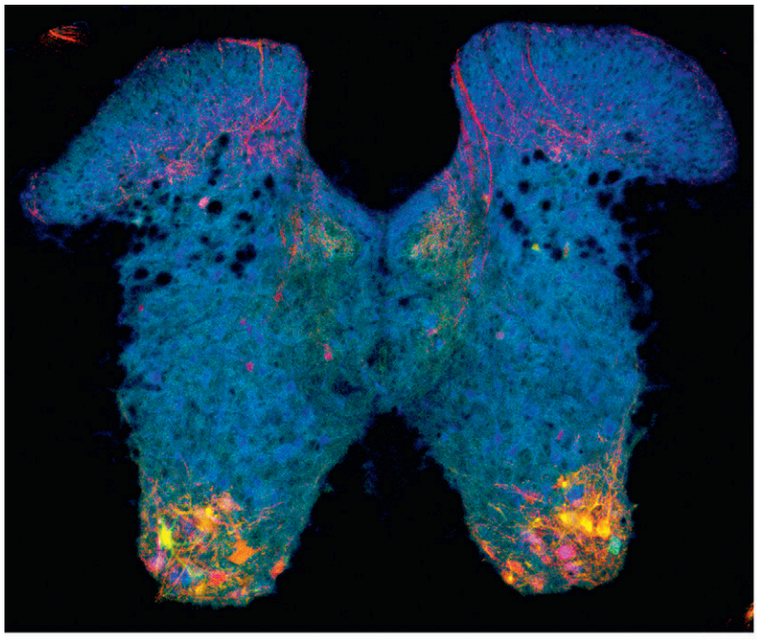
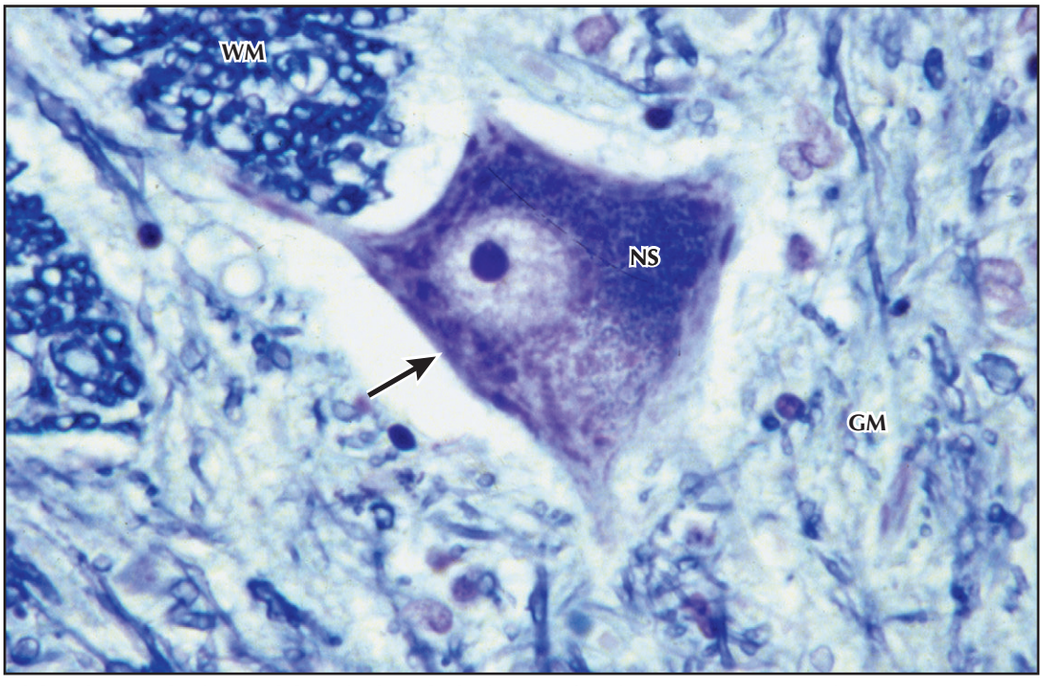


Image of the upper thoracic spinal cord of a Brainbow transgenic mouse. Individual motor neurons in the ventral spinal cord express randomized amounts of a red, green, and blue fluorescent protein. The colors are generated by genetic recombination using a recombinase enzyme that is specifically activated in motor neurons but in few other spinal neurons. This method allows researchers to track the connections of individual neurons by tracing the nerve cell's processes through multiple serial sections of brain and spinal cord tissue.
Image courtesy of Dawen Cai, Joshua Sanes and Jeff Lichtman, Harvard University.



Light micrograph of part of the spinal cord. The large multipolar neuron *(arrow)* in the gray matter *(GM)* has an irregularly shaped soma with dispersed Nissl substance *(NS),* which makes the cytoplasm basophilic. A lightly stained, spheric nucleus is eccentrically placed and contains a prominent, dark nucleolus. The neuron is close to the white matter *(WM),* consisting of bundles of myelinated nerve fibers. Small round nuclei in the gray matter are those of glial cells. 750×. Luxol fast blue and cresyl violet.
Reprinted with permission from Ovalle W, Nahirney P. Netter's essential histology. Philadelphia: Saunders; 2008.

The cell body (soma) is the major structural component that maintains the neuron. The motor neuron cell body resides in the ventral horn of the spinal cord as an "anterior horn cell" or in the cranial nerve nuclei within the brainstem. The cell body is the metabolic center of the neuron and performs numerous functions necessary to maintain the health and function of the neuron. Within the cell body are numerous organelles, each of which serves a particular role for the neuron. The nucleus and nucleolus contain the cell's deoxyribonucleic acid (DNA). The mitochondria play the important role of energy metabolism within the neuron and produce adenosine triphosphate (ATP), which is necessary for other metabolic processes within the cell to occur. The rough endoplasmic reticulum, along with the Nissl substance and its associated ribosomes, synthesize proteins that are then secreted through the smooth endoplasmic reticulum and Golgi apparatus. In these latter organelles, the proteins undergo certain modifications. The proteins are subsequently packaged into vesicles that store and transport proteins throughout the cell. Lysosomes are organelles that are responsible for degradation of molecules within the cell.

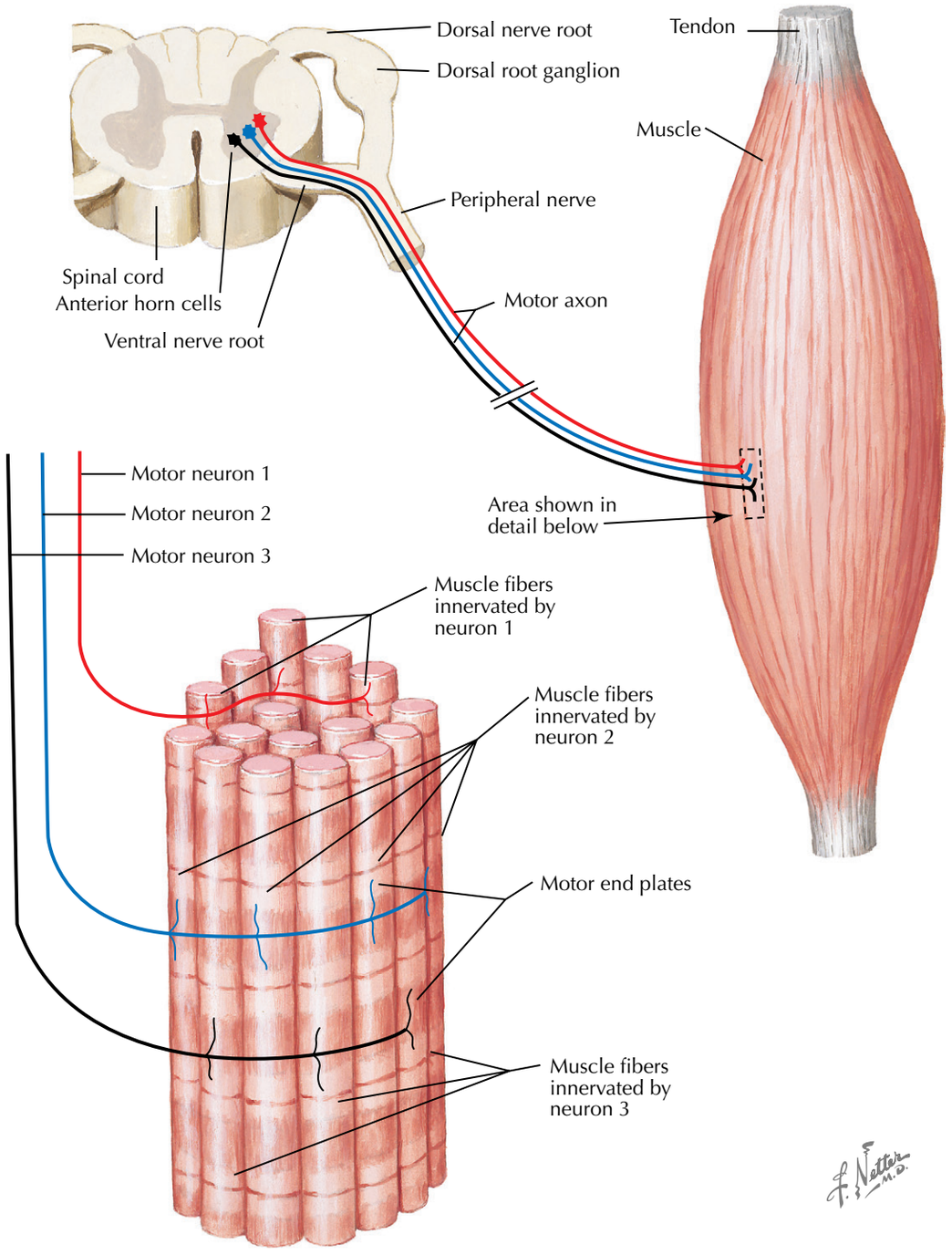
Each neuronal cell body contains many dendrites, which are peripheral extensions from the cell body that, along with the smaller dendritic spines (gemmules), receive the input from other neurons. Each dendrite receives *excitatory or inhibitory potentials* from the nerve terminals of neighboring neurons at the *axodendritic synapses*. The dendrites and the cell body of a single neuron may have hundreds of synapses from many different neurons. Each of the postsynaptic excitatory or inhibitory potentials are summated to determine whether an action potential will or will not be initiated within the neuron. When initiated, an action potential originates at the axon hillock, the region of the cell body at which the axon originates. Distal to the axon hillock is the axon, which is the structure that conducts the electrical activity and trophic factors away from the cell body toward other neurons or organs. The course of the axons and route of conduction of the electrical signals varies according to the type of neuron and its function.

The somas of the somatic sensory neurons are located in the dorsal root ganglion, just lateral to the spinal cord and typically within the intervertebral foramen. The somatic sensory neurons are bipolar neurons with two axonal extensions, one conducting impulses from the sensory receptors, including free nerve endings and pacinian corpuscles, toward the dorsal root ganglion through the peripheral nerves and dorsal rami, and the other extending from the dorsal root ganglion through the dorsal root into the dorsal column of the spinal cord.

The cell bodies (anterior horn cells) of the somatic motor neurons are located in the anterior gray matter of the spinal cord. The motor neurons are unipolar neurons, and each neuron has an axon that extends through the ventral root and then through either the dorsal ramus (innervating paraspinal skeletal muscles) or the ventral ramus (innervating limb and peripheral skeletal muscles) and into individual nerves.

The cell bodies of the sympathetic autonomic peripheral neurons are located in spinal cord. The preganglionic sympathetic neurons extend through the ventral root and through the white ramus communicans, and they synapse in peripherally located ganglia—either the sympathetic chain adjacent to the spinal cord or the collateral sympathetic ganglia near the organs that the neurons supply. After synapsing at either site, the postganglionic sympathetic neurons course to the end organs, including vascular smooth muscle, sweat glands, and arrector pili muscles in the skin or the smooth muscles and glands of other organs.

Motor Unit



The outflow of nearly all behavior depends upon the neuromuscular system where nerves emanating from the spinal cord and brainstem connect with skeletal muscles, allowing us to move, stand, and express ourselves. The numbers of skeletal muscles in the human body is daunting, between 500 and 1000. Our face has enormous numbers of muscles, allowing us to express emotions, communicate, and eat our food. Our hands are the second most "muscular" parts of our anatomy. These provide humans with the finesse to write and speak, for a surgeon to perform the most intricate finger movements, to form sign language, to play musical instruments, and occasional individuals to sing in the most beautiful fashion. The "motor unit" is the *"final efferent pathway"* of the peripheral somatic motor pathway. A motor unit is defined as a single anterior horn cell or brainstem motor neuron, its axon, and all of the muscle fibers innervated by that axon.

Some muscles are huge. The gluteus maximus has many thousands of muscle fibers essential to walking. Miniscule muscles are designed to produce the slightest movements of the eardrum or the larynx; these often have fewer than 100 muscle fibers. The set of muscle fibers innervated by a single axon, a *motor unit*, is very small for muscles that require very fine control, such as the extraocular and finger muscles. All of the muscle fibers within a single motor unit are of the same fiber type. Some motor units are even smaller than 10, that is, 1 motor axon innervating only 10 muscle fibers (e.g., in the extraocular muscles). In contrast, other motor units, not requiring fine control, are very large, hundreds to thousands, these innervate very massive postural (back musculature) as well as girdle and extremity muscles (gluteus maximus and gastrocnemius muscles). Because an action potential impulse heading out an axon in a peripheral nerve will enter all the branches of the axon, *the motor unit is the unitary muscle contraction from a single axon*. When muscles are activated, *motor units are recruited in a fixed order*. Typically, the *weakest motor units* causing the smallest muscle twitches are *recruited first*. If insufficient numbers are recruited for the task, additional motor units are activated, each progressively producing larger amounts of muscle tension. In this way, there is fine control of small muscle contractions and less control as muscle contraction force is increased. All muscle fibers within a single motor unit have similar contraction properties because they have similar subtypes of the contraction protein myosin.

Within a small section of muscle, the fibers of several (up to 10 or more) different motor units are interspersed with each other. (bottom part of Plate 10-3). This figure illustrates the anatomy of three different "*motor units*" forming the final peripheral components of the descending motor pathway that emanates from a single anterior horn motor neuron cell body and all axons and muscle fibers innervated by that single neuron. The cell bodies of the motor units lay within the brainstem for motor cranial nuclei, serving the somatic cranial muscles, such as the extraocular, facial, and pharyngeal muscles, and within the anterior horn cells of the spinal cord for the motor neurons serving somatic motor function to the noncranial muscles.

The upper left illustration demonstrates that cells bodies of each of three motor units originate within spinal cord anterior horn gray matter. The peripheral axon arising from each *anterior horn cell* leaves the spinal cord through the ventral nerve root to course as a peripheral nerve component until reaching the muscle. Here the nerve terminals of different motor units are positioned in a relatively confined intramuscular area named the "*end-plate zone*" or "*motor point.*" At this site, there are high concentrations of acetylcholine receptors attached within the muscle fibers. It is here, usually toward the middle of a muscle, that muscle fiber action potentials are generated after acetylcholine is released and bound to the receptors.

The *first motor units* recruited comprise muscle fibers having "*slow*" *fatigue-resistant myosin* that cause slow contractions. The *last motor units* to be recruited activate muscle fibers that have *fast contractions* thanks to fast myosin but are *highly fatigable*. It is possible to see positions of all muscle fibers within each of the motor units in one muscle. Such descriptions reveal "*connectomes*" that are complete maps of all the positions of all the motor axons and their connections within a muscle.

Motor Unit Potentials

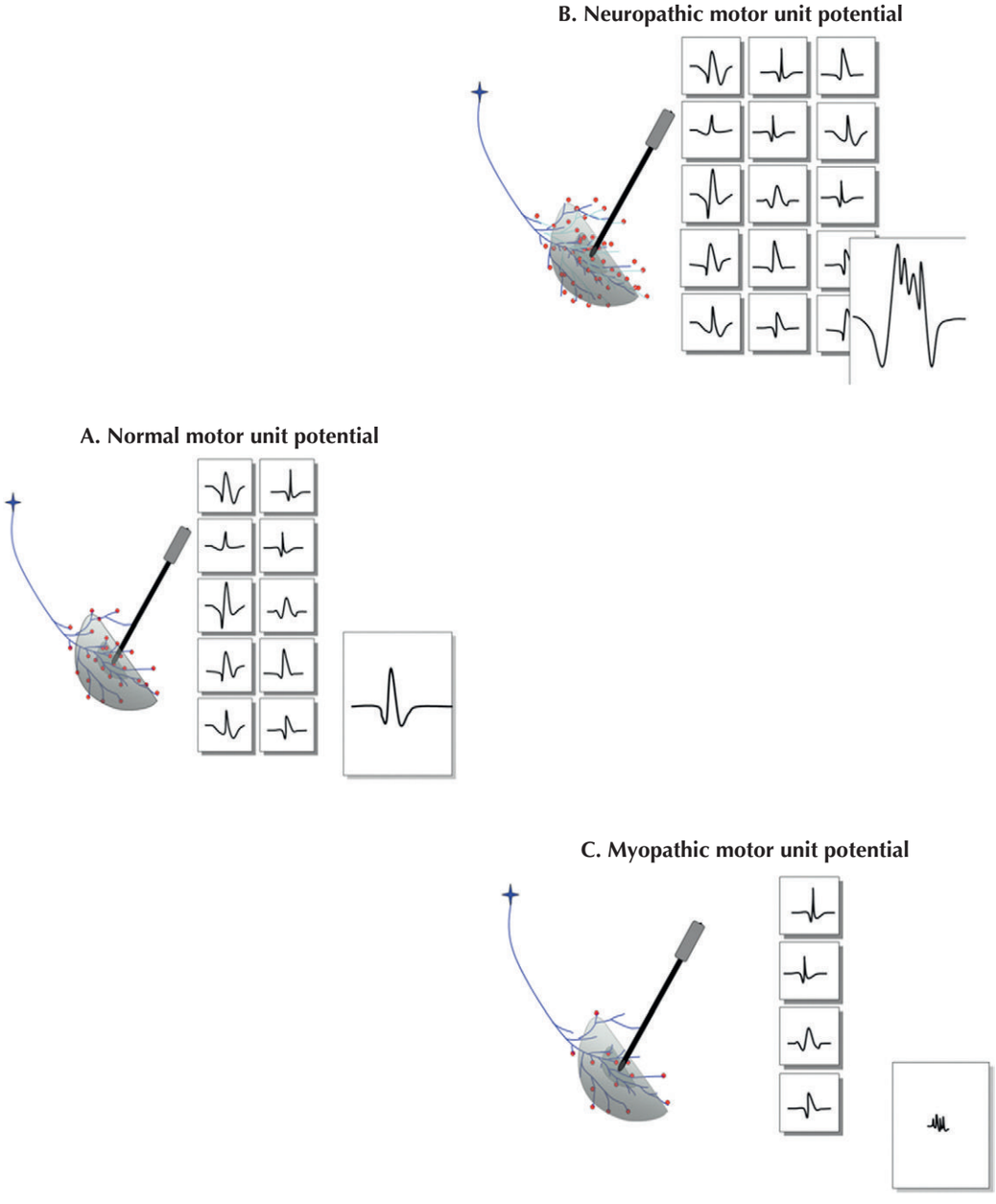
Needle electromyography (EMG) assesses the electrical signals from muscle fibers within a muscle. This is one of the two major parts of the clinical electromyography evaluation; nerve conduction studies are complementary. During voluntary activation, when an anterior horn cell fires from within the spinal cord, an action potential is generated and propagates along the main axon, and its terminal branches to the neuromuscular junction (NMJ), releasing acetylcholine that, at the postsynaptic NMJ, leads to depolarization of all of the muscle fibers innervated by that specific anterior horn cell. When a recording needle electrode is placed within the muscle in the region of an activated motor unit potential, the action potentials of each of the muscle fibers in the recording range of the electrode (usually 1-2 mm) are recorded and summated to record the *motor unit potential* (MUP). In a normal individual, the axon branches of each motor unit conduct the action potential at a similar rate; therefore the firing of the individual muscle fiber action potentials is relatively synchronous. Because all of the muscle fiber action potentials fire at a similar time, the MUP is of relatively short duration (usually 8-12 msec) and has a summated amplitude that typically varies between 400 to 1000 msec *(part A)*.

When a patient presents with diseases of the nerve or muscle, these pathologies lead to rather classic morphologic changes within the motor unit. These changes, which are recorded with a needle electrode, are reflected in the MUP. *Neuropathic disorders* are associated with specific changes in the MUP character that develop temporally in several stages. Initially, as loss of anterior horn cells or axons occurs, there is a reduction in the number of functioning motor units innervating an individual muscle. In this *acute stage*, characterized by the loss of motor units, the MUP recorded during needle EMG appear morphologically normal, although fewer MUPs are activated with increasing effort. This reduction in recruitment of motor unit potentials with effort can be recognized by an increased firing rate of seemingly healthy motor unit potentials relative to the number of MUPs activated within the region of the recording electrode.

As *recovery* begins, newly formed collateral axons derived from the remaining healthy anterior horn cells reinnervate those affected muscle fibers that have lost their normal innervation. The reinnervated motor unit consists of an increased number and density of muscle fibers within a region of the muscle compared with the original motor unit. Because the collateral nerve sprouts may not be adequately or completely myelinated, and as a result of the wider distribution of innervated fibers within the muscle, the synchrony of firing of the individual muscle fibers is reduced. The resultant effect of these changes is a recorded MUP that is of higher amplitude, longer duration, and may have multiple phases leading to a polyphasic appearance. In attempt to compensate, these fire more rapidly *(part B)*.

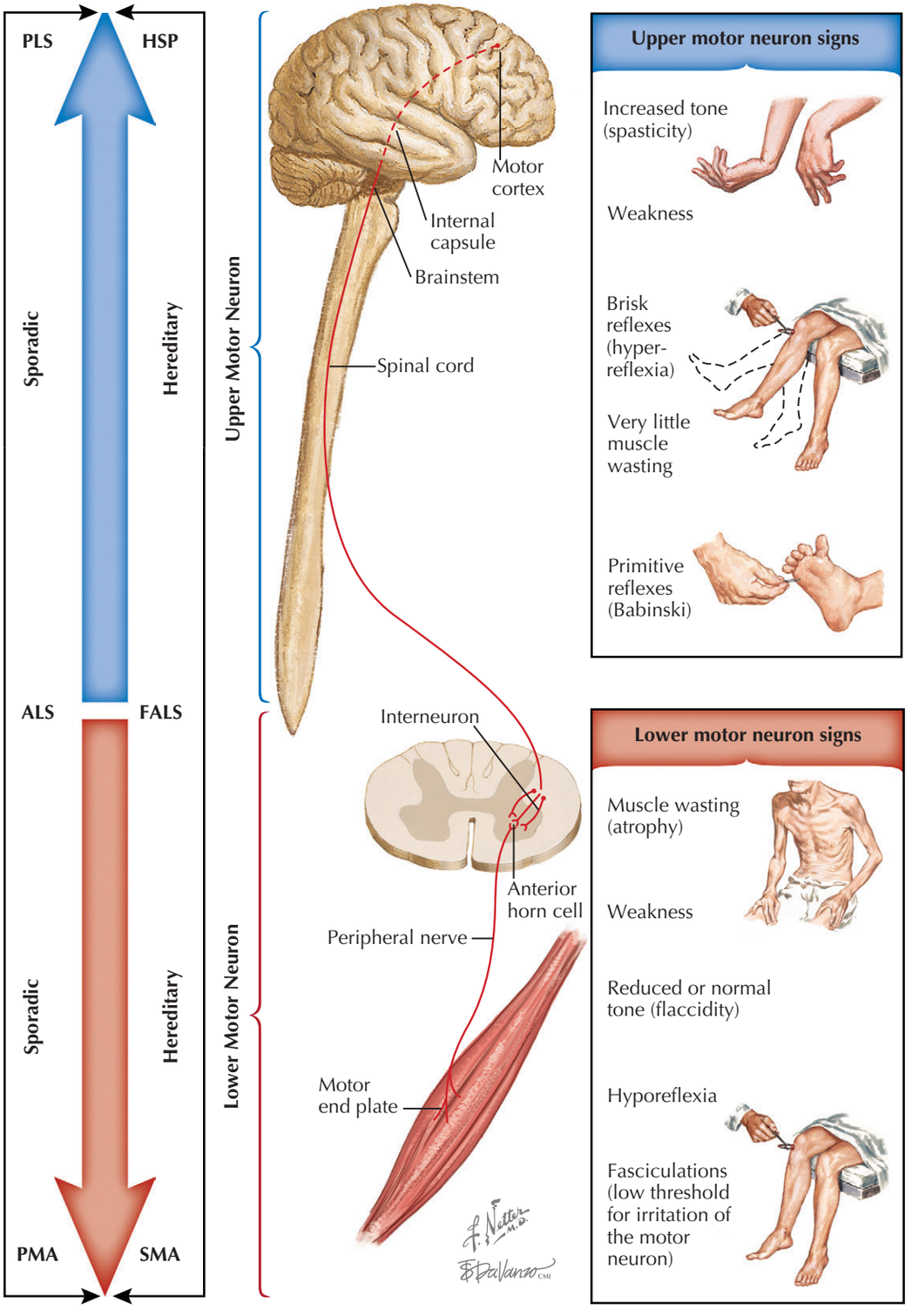
The classic examples are patients having poliomyelitis with significant paralysis as young persons. The surviving anterior horn cells provided a means to develop collateral reinnervation and thus partial recovery. In this instance, needle EMG demonstrates just a few remaining MUPs. However, these fire at very high amplitude at much greater rates, to provide compensation and ability to move the limb once again. Today amyotrophic lateral sclerosis, that is, motor neuron disease (also known as Lou Gehrig disease), provides a different example of this process. Here, although there is an initial consistent attempt to provide collateral reinnervation, the continued decrease in numbers of healthy anterior horn cells can no longer provide compensatory reinnervation, and the patient becomes progressively paralyzed.

In contrast, myopathies are disorders characterized by a reduction in functioning muscle fibers within a motor unit. The muscular dystrophies and inflammatory myopathies are typical disorders. Here there are diminished numbers of healthy muscle fibers within a motor unit. Therefore fewer MUPs remain within in the region of the recording needle electrode, leading to a summation of fewer muscle fiber action potentials. In addition, those small remaining MUPs need to have their anterior horn cells fire in increased numbers. The resultant myopathic motor unit potential is of shorter duration, lower amplitude, and polyphasic secondary to asynchronous activation *(part C)*. To compensate, an increased firing of anterior horn cells occurs in an attempt to generate required forces. Thus patients with myopathies characteristically demonstrate many low-amplitude short-duration polyphasic MUPs.



Three different motor unit potentials recorded from needle EMG (normal, neurogenic, myopathic). Each image illustrates the schematic of a single motor unit — the anterior horn cell, an axon, and a group or muscle fibers (in red) innervated by the axon. The gray area is the recording area from the needle electrode. Each small box contains the representation of a single muscle fiber action potential. The larger box illustrates the summation of all of the single muscle fiber action potentials in the needle recording area. In a chronic, neurogenic process, where collateral sprouting and reinnervation has occurred, there are more muscle fibers in the needle recording area, resulting in a large, motor unit potential (MUP). In a myopathic process, with loss of muscle fibers, there are fewer fibers in the needle recording area, resulting in a smaller MUP. Both the neurogenic and myopathic processes also result in asynchronous firing of the muscle fiber action potentials, which manifests on the needle examination as increased phases of the MUPs (i.e., polyphasic MUPs).

Clinical Spectrum of Upper and Lower Motor Neuron Involvement



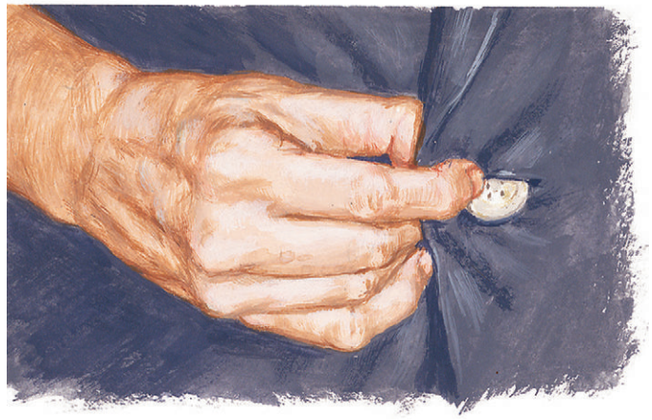
Primary Motor Neuron Disease

Primary motor neuron diseases (MND) have protean clinical manifestations. The pathology involves the motor neurons of the spinal cord, cerebral cortex and brainstem (with the exception of brainstem nuclei subserving eye movements), and the associated corticospinal and corticobulbar tracts. Classically, these diseases are grouped into several categories, according to the predominant clinical manifestations at onset and whether the disorder is inherited or sporadic: (1) sporadic lower motor neuron disorders, such as progressive muscular atrophy (PMA); (2) sporadic upper motor neuron disorders, such as primary lateral sclerosis (PLS); (3) hereditary lower motor neuron disorders, such as spinal muscular atrophy (SMA) or spinal bulbar muscular atrophy; (4) hereditary upper motor neuron processes, such as hereditary spastic paraparesis (HSP); and (5) amyotrophic lateral sclerosis (ALS), the most common MND, which manifests with various degrees of degeneration of the upper motor neurons in the cortex associated with corticospinal tract involvement superimposed on degeneration of the lower motor neurons within the spinal cord. Familial ALS (FALS) represents 10% of cases of ALS, whereas the majority of ALS is considered sporadic.

The signs and symptoms characteristic of many of these diseases (e.g., PMA, PLS) eventually evolve in most patients to demonstrate mixed upper and lower motor neuron involvement and thus a diagnosis of ALS. Notable exceptions include HSP, SMA, and spinal bulbar muscular atrophy.

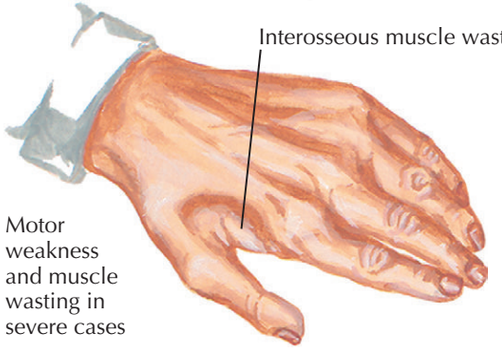
Amyotrophic lateral sclerosis (known as "Lou Gehrig disease" in the nonmedical literature in the United States) characteristically involves a mixture of lower motor neuron findings (weakness, atrophy, fasciculations) and upper motor neuron features (spasticity, brisk reflexes, upgoing toes). Estimates suggest that this disease affects 3 to 6 of every 100,000 persons, with a male to female ratio of about 1.6:1. Onset is insidious and usually in middle to late life, although symptoms rarely begin in the second or third decade. About 10% of cases in adults are hereditary, primarily of dominant inheritance.

Clinical Manifestations of Amyotrophic Lateral Sclerosis



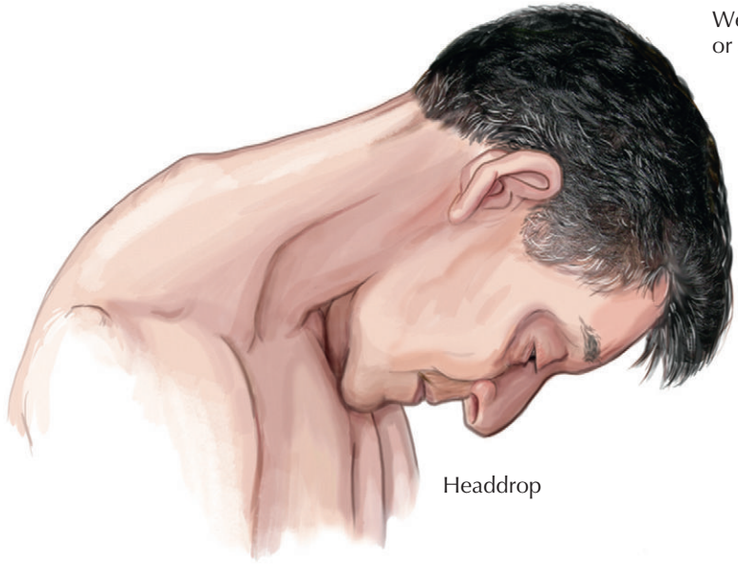
Fine movements of hand impaired; prominent metacarpal bones indicate atrophy of interossei muscles

Clinical signs



Motor weakness and muscle wasting in severe cases

Weak, dragging gait; footdrop or early fatigue on walking



Headdrop

Amyotrophic Lateral Sclerosis

The most common presentation of ALS is painless progressive weakness of a limb in the absence of sensory disturbance. In approximately 25% of patients, symptoms may be initially confined to the motor nuclei of the brainstem, with the exception of the nuclei that supply the extraocular muscles. Progressive difficulty with articulation, inability to move the tongue, and failure of the palate to rise on phonation results in stiff, breathy speech that is characteristic of ALS (a mixed spastic/flaccid dysarthria). Early pharyngeal involvement makes swallowing difficult. The term *progressive bulbar palsy* has been used to describe these patients. Some patients initially develop regional variants, such as the bibrachial amyotrophic diplegia phenotype characterized by a predominantly lower motor neuron syndrome affecting both arms, often remaining confined to the arms for several years before advancing to more typical ALS. A lower-extremity diplegia phenotype has also been described.

Cognitive dysfunction is present in up to 60% of patients with ALS and can range from mild impairment of word fluency to frontotemporal lobe dementia. This discovery has led to the recognition of ALS as a multisystem disorder extending beyond the motor neurons.

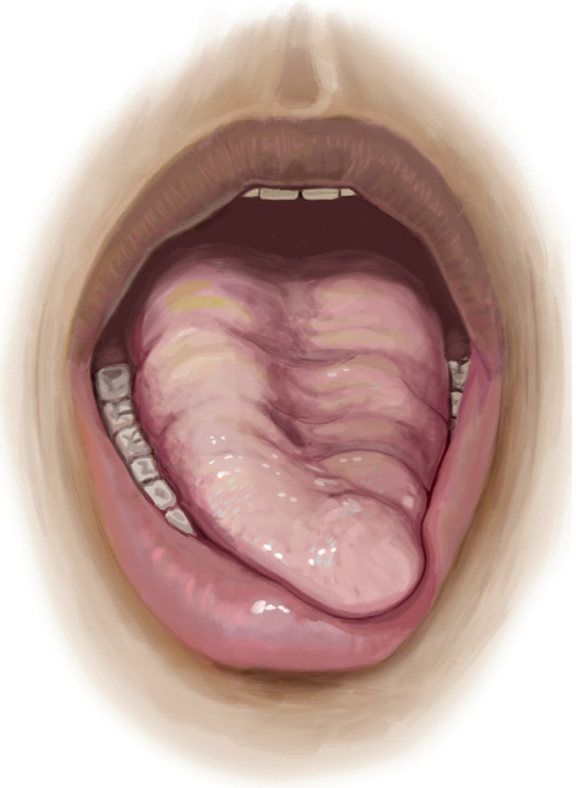
The pathophysiologic basis underlying the progressive degeneration of motor neurons in these disorders is incompletely understood. Defects in glutamate clearance, ubiquitin-proteosome pathways, ribonucleic acid (RNA) processing, mitochondrial function, axonal transport, apoptosis, and several other mechanisms have been advanced.

Progressive muscular atrophy (PMA) is a MND variant that accounts for approximately 5% of adult-onset acquired MND. Patients with PMA initially report symptoms of weakness and muscle atrophy, sometimes associated with cramping. Most commonly, onset is asymmetric and in the distal musculature, beginning in either the upper or the lower extremity. Fine movements of the hands may be impaired, or a foot may become weak. Sensory symptoms and pain are absent. Patients may also note spontaneous twitching (fasciculations) of muscles at rest. Some patients with apparent PMA develop upper motor neuron (UMN) symptoms over time, requiring reclassification as ALS. Even in the absence of clinical UMN signs, approximately half of the patients diagnosed with PMA have autopsy evidence of corticospinal tract involvement, again implying ALS. Whether these disorders represent distinct entities or points on a continuum is unclear.

Primary lateral sclerosis (PLS) is a syndrome of progressive upper motor neuron dysfunction. It is an uncommon diagnosis and accounts for less than 5% of patients with MND. PLS is pathologically characterized by corticospinal degeneration, with sparing of the anterior horns that distinguishes it from ALS. The typical clinical presentation is characterized by leg

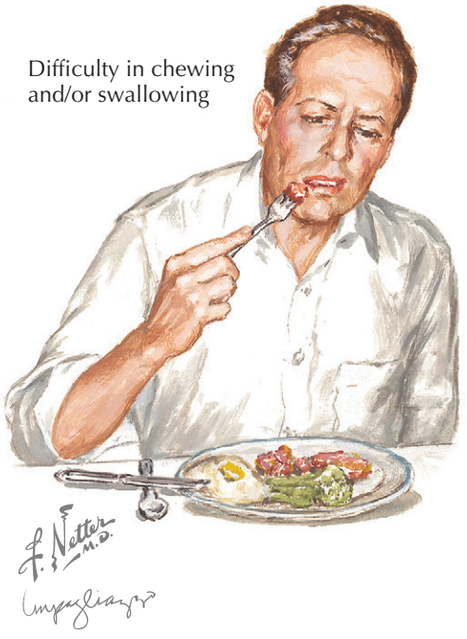
CLINICAL MANIFESTATIONS OF AMYOTROPHIC LATERAL SCLEROSIS (CONTINUED)

Salivary drooling due to impaired swallowing and poor facial muscle tone



Asymmetric (left greater than right); atrophy, weakness, and fasciculations of the tongue, with deviation to the left on protrusion

Difficulty in chewing and/or swallowing



Variable speech impairment due to weakness of tongue, soft palate, and/or larynx or respiratory muscles. Patient may resort to writing (often also impaired) to communicate.

AMYOTROPHIC LATERAL SCLEROSIS *(Continued)*

weakness and spasticity or predominant bulbar involvement, with an upper extremity presentation less common. Symptoms usually start unilaterally and tend to spread to the contralateral side first, before involving a new region. Stiffness, clumsiness, and poor coordination are prominent complaints. A patient with a MND who presents with idiopathic spasticity and does not develop wasting and other clinical or electrophysiologic evidence of lower motor neuron (LMN) involvement within 4 years likely has PLS; before 4 years has elapsed, it is more uncertain whether such a patient will or will not eventually evolve to a diagnosis of ALS (i.e., a diagnosis of upper motor neuron–predominant ALS). The course of PLS is very slowly progressive, with average disease duration of 8 years or more, in contrast to a shorter average life span for patients with ALS.

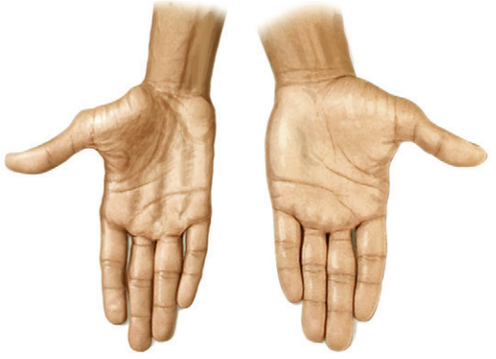
MIMICS OF AMYOTROPHIC LATERAL SCLEROSIS

The differential diagnosis for a patient with possible ALS varies depending on the particular clinical characteristics of the patient. Common considerations include inclusion body myositis (IBM), cervical myelopathy plus radiculopathy, multifocal motor neuropathy (MMN), hereditary spastic paraparesis and juvenile monomelic amyotrophy (JMA). Recognition of the specific clinical features and appropriate diagnostic testing almost always allows for a focused differential diagnosis and efficient diagnosis. Hereditary spastic paraparesis and JMA are discussed below. Other mimics, IBM and MMN, are discussed in Sections 12 and 6, respectively.

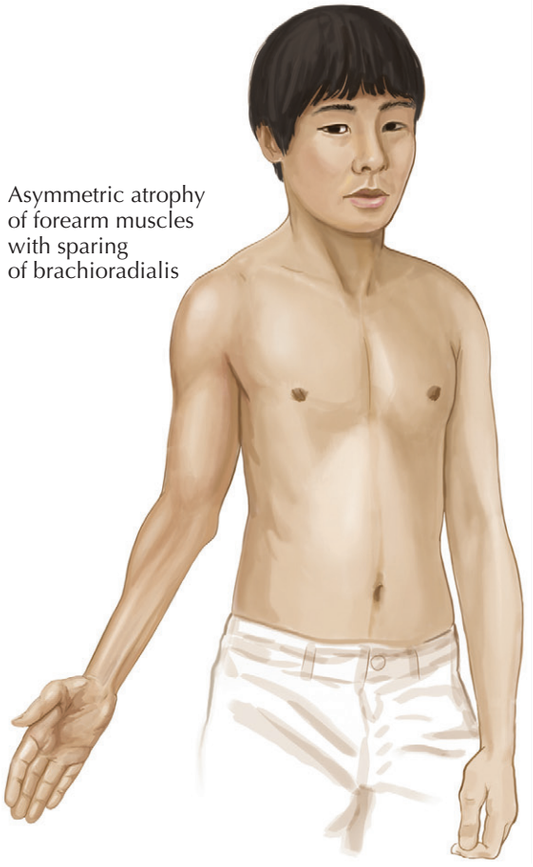
Juvenile monomelic amyotrophy (JMA) is characterized by insidious onset of unilateral or asymmetric muscular atrophy and weakness of the hand and forearm in the absence of sensory or pyramidal signs. JMA predominantly affects young men between 15 and 25 years of age. The manifestations are often unilateral, although bilateral, asymmetric involvement may occur. The clinical course is initially progressive for a few years, followed by spontaneous stabilization. Although disputed, some specialists believe that the pathophysiology of JMA may be related to abnormal movement of the lower cervical spinal cord during neck flexion, which somehow damages the anterior horn cells of the lower cervical spinal cord, leading to a focal motor neuronopathy manifesting as weakness and atrophy of lower cervical segment–innervated muscles. Treatment options for JMA may include patient education to avoid neck flexion, wearing a soft cervical collar, and surgical decompression. The majority of patients show spontaneous arrest of progression within 3 to 5 years. However, hand weakness and atrophy are permanent.

Mimics of Amyotrophic Lateral Sclerosis

Hirayama disease

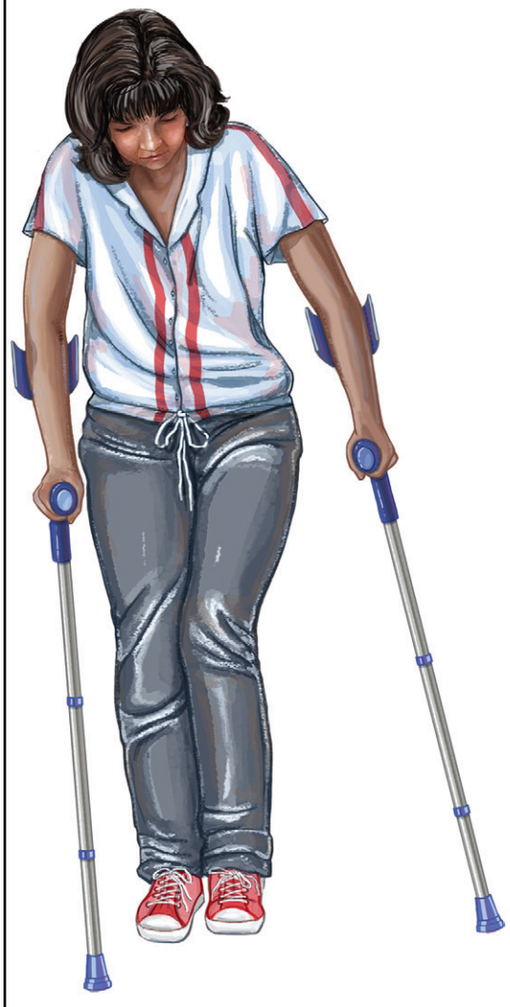


Asymmetric atrophy of intrinsic hand muscles



Asymmetric atrophy of forearm muscles with sparing of brachioradialis

Hereditary spastic paraparesis



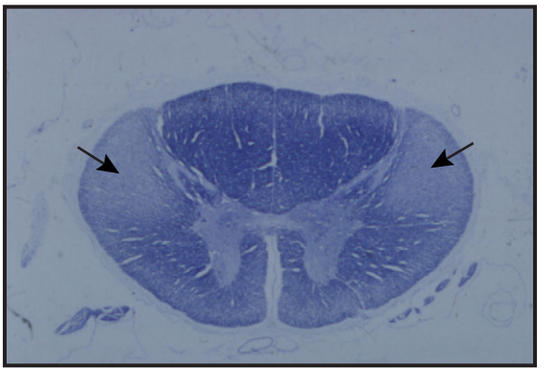
Amyotrophic Lateral Sclerosis *(Continued)*

Hereditary spastic paraparesis (HSP), also known as familial spastic paraparesis, is a genetic disorder that may mimic PLS. HSP symptom onset can occur from infancy to late adulthood. Clinical features include relatively symmetric, progressive limb spasticity, progressive gait disturbance, and variable bladder disturbances. Clinical examination demonstrates spasticity and pathologically brisk reflexes. Lower extremity spasticity progresses very gradually over time and sometimes spreads to the arms and, rarely, the bulbar region (e.g., spastic dysarthria). Other features may include mild impairment of vibratory and joint position sense and pes cavus malformation. Less common accompaniments for some forms of complicated HSP include optic atrophy, mental retardation, peripheral neuropathy, dementia, and deafness. It is sometimes difficult to confidently differentiate apparently sporadic HSP from PLS based on clinical characteristics alone. HSP usually does not cause early bulbar manifestations, whereas this is common in PLS. HSP is also relatively symmetric, with manifestations beginning first in the lower extremities; PLS, on the other hand, may manifest first in any limb and is usually asymmetric. HSP tends to progress more slowly than PLS. A detailed family history is necessary, and genetic testing can be helpful. The pattern of inheritance can be autosomal dominant, autosomal recessive, X-linked, or apparently sporadic. There are currently more than 40 different genetic mutations or loci identified for various families with HSP. Cerebral and spinal magnetic resonance imaging (MRI) help exclude nongenetic causes of spasticity.

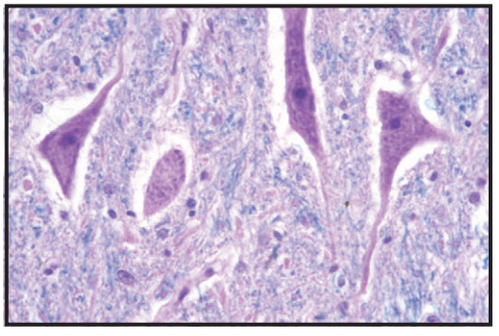
DIAGNOSIS

In a patient with symptoms of footdrop or an atrophied hand, the diagnosis usually considered is an isolated lesion of a peripheral nerve or nerve root. If such a lesion is the initial sign of early motor neuron disease, careful testing of other muscles often reveals more diffuse motor weakness, typically in a myotomal pattern. Fasciculations and widespread evidence of atrophy on examination are useful additional diagnostic signs. Atrophy and fasciculations of the tongue may be the first sign of cranial nerve involvement. Reflexes may vary from depressed to brisk. The Babinski sign may be extensor or plantar, depending on whether lower or upper motor neuron involvement predominates. Sensory examination must be thorough and detailed, and results should be normal if motor neuron disease is present. The coexistence of both upper (increased tone, brisk reflexes) and lower motor neuron (atrophy, fasciculations) signs in the same limb is strongly suggestive of ALS.

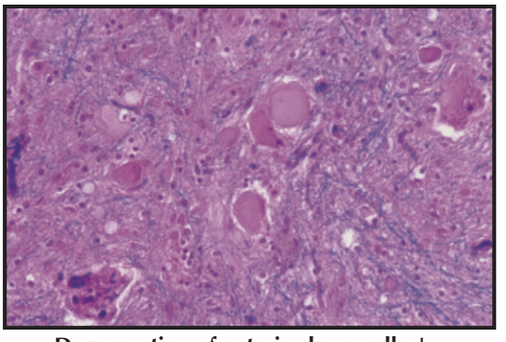
Diagnosis of Amyotrophic Lateral Sclerosis



Cross-section of spinal cord. From patient with amyotrophic lateral sclerosis showing bilateral degeneration of corticospinal tracts *(arrows)*.

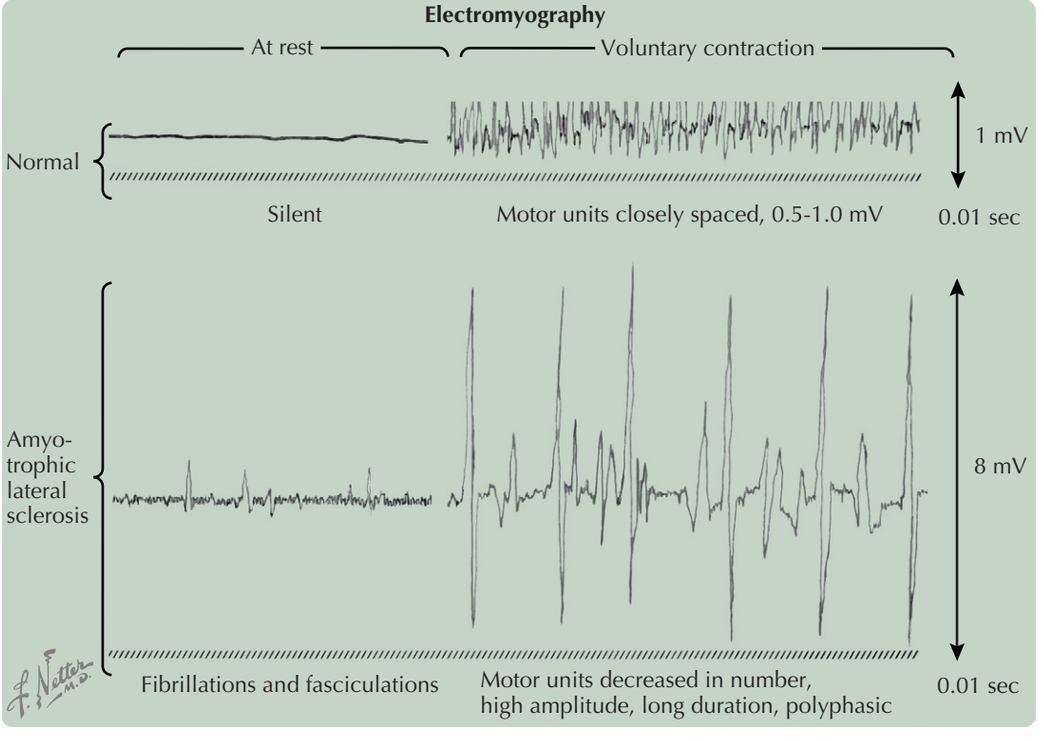


Anterior horn of spinal cord. With normal motor neurons (Luxol fast blue with H and E stain).



Degeneration of anterior horn cells. In amyotrophic lateral sclerosis (same stain).

Amyotrophic Lateral Sclerosis *(Continued)*



Electromyography and nerve conduction studies (collectively known as "EMG") are the most useful diagnostic techniques for confirming the diagnosis of motor neuron disease and excluding potential mimics, such as inclusion body myositis and multifocal motor neuropathy. In ALS, motor conduction studies may demonstrate no more than minimal slowing of conduction velocity and a mild-to-moderate decrease in the compound action potential amplitude. Sensory conduction studies are normal. Signs of active (fibrillation potentials and positive sharp waves) and chronic (high-amplitude, long-duration motor units) neurogenic changes should be demonstrated in at least two of four neuroanatomic segments (bulbar, cervical, thoracic, lumbosacral) on the needle EMG study. When bulbar symptoms predominate, checking for the presence of acetylcholine receptor binding antibodies or performing repetitive nerve stimulation or single fiber EMG should sometimes be done to exclude the possibility of myasthenia gravis. Occasionally, cervical spine imaging may be indicated to exclude a structural cervical myeloradiculopathy. Rarely, a muscle biopsy specimen is taken to exclude an inflammatory myopathy in the patient who has weakness of the proximal musculature, although electromyography is also helpful in differentiating this disorder.

TREATMENT

To date, riluzole is the sole Food and Drug Administration (FDA)-approved drug for the treatment of ALS. Several randomized trials have demonstrated that riluzole prolongs the life of ALS patients by 2 to 3 months. Until more effective drug therapies are discovered, symptomatic control and emotional support are the primary therapeutic goals because these diseases usually progress relentlessly to death in 2 to 10 years. Fortunately, there have been significant advances in the realm of supportive therapy for ALS.

Feeding difficulties are frequently related to an inability to move food about in the mouth and to swallow effectively. Some patients may manage food prepared in a blender. Instructing the patient in chin tuck and other mechanical maneuvers can facilitate safe swallowing. When oral intake becomes unsafe or ineffective at maintaining weight, a feeding gastrostomy tube can be placed.

Numerous adaptive devices and machines can facilitate functional independence. Mobility can be maintained with scooters and motorized wheelchairs. Transfers can be facilitated with ramps, lifts, and boards. Grab bars, commodes, and structural adjustments to

Amyotrophic Lateral Sclerosis *(Continued)*

the home environment can improve access. Several adaptive devices, including strategic foot bracing, arm boards and foam grips can enhance function (see Plate F). Physical therapy regimens can maintain flexibility and avoid frozen joints.

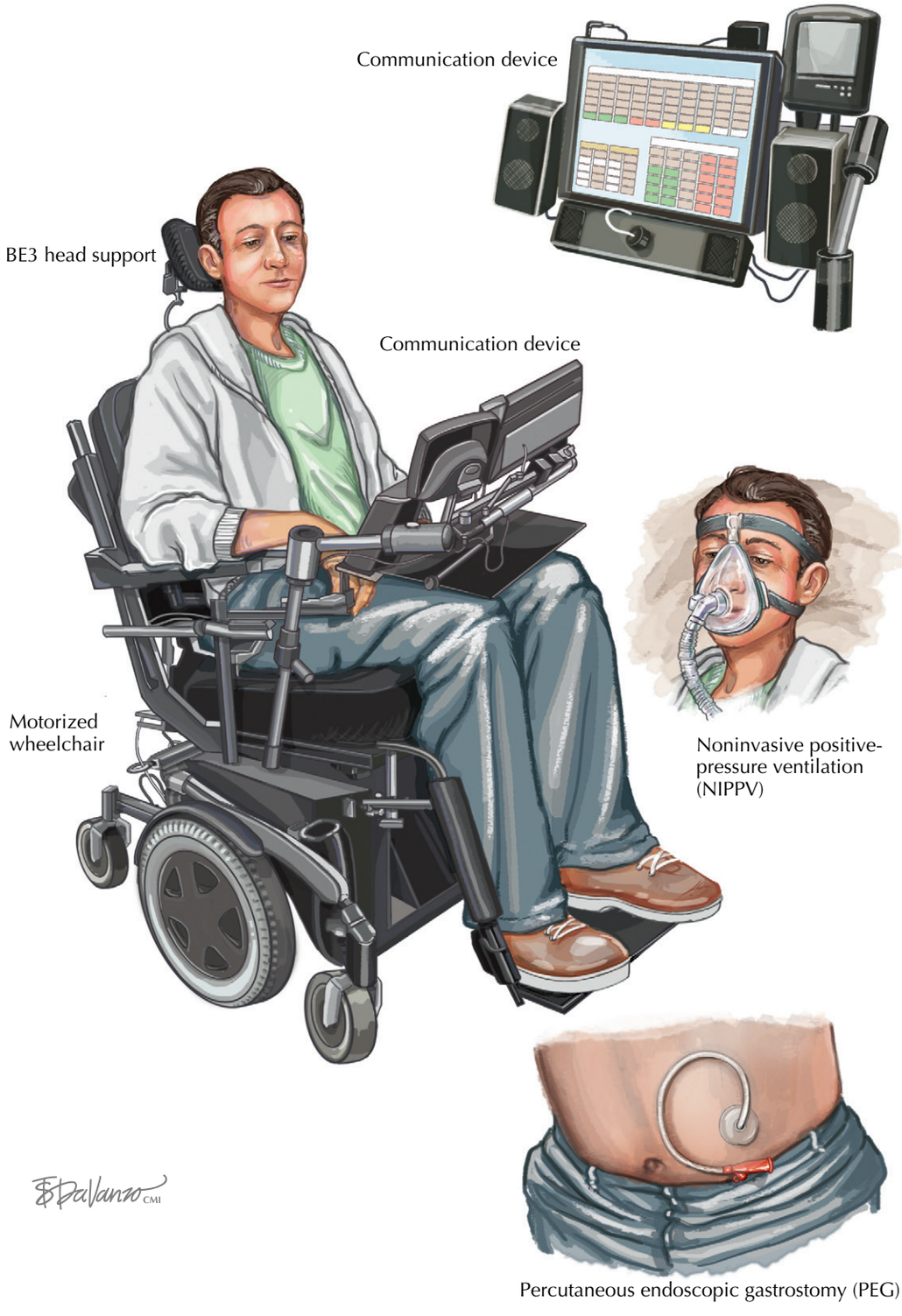
One of the many tragic consequences of MND is the patient's loss of ability to speak understandably. Numerous augmentative devices utilizing digital technology can maintain effective communication, no matter how impaired the patient. Such devices can be controlled with slight finger movements, eye movements, or minimal head movements.

Respiratory failure is the cause of death in most patients. Early in the course of the illness, the patient should be warned against the use of respiratory depressants such as sedatives, particularly in combination with alcohol. The patient should be prophylactically immunized against influenza and pneumococcal infections. Pulmonary function testing should be regularly assessed at each clinic visit. When the patient develops symptoms of early respiratory failure (excessive daytime fatigue, orthopnea, early-morning headaches, dyspnea on exertion or at rest) or the forced vital capacity (FVC) falls below 50% of predicted, noninvasive positive-pressure ventilation (NIPPV) should be considered. NIPPV has been shown to prolong life and improve quality of life in ALS patients. Initially, NIPPV can be confined to nighttime use during sleep but can eventually be extended to daytime use as needed. Ultimately, some patients opt for tracheostomy and mechanical ventilation.

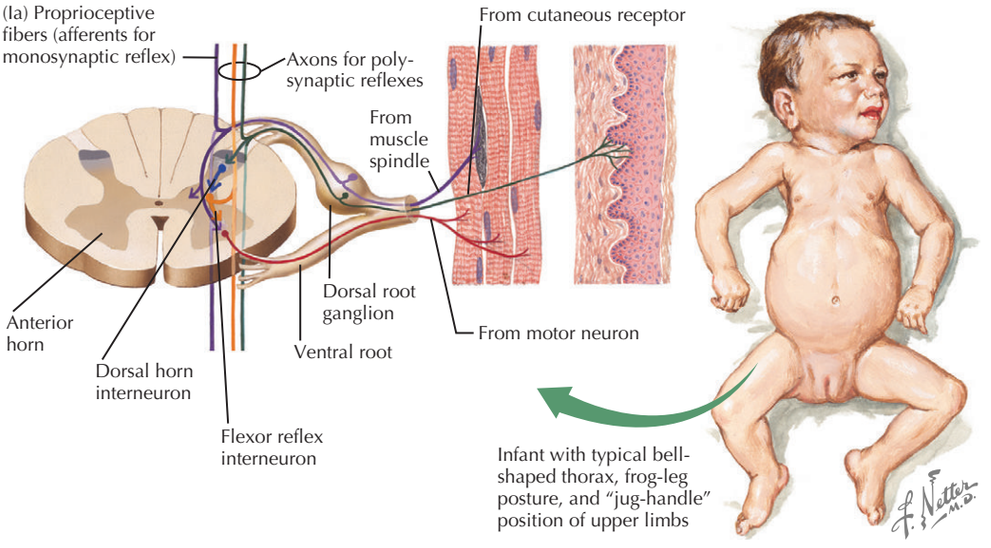
Pseudobulbar affect, characterized by unexpected outbursts of laughing and crying, can be managed with a combination of dextromethorphan and quinidine, tricyclics, or selective serotonin reuptake inhibitors. Troubling sialorrhea can be treated with numerous oral anticholinergic agents (e.g., atropine, nortriptyline), scopolamine patches or botulinum toxin injections. Portable suction devices and cough-assist machines can also assist in secretion management. Depression and anxiety can be successfully managed pharmacologically.

Most important is the providers' honest and compassionate approach to the total patient and the caregivers. Care is best delivered by a multidisciplinary team. The care team should never destroy the patient's hope but should provide optimal symptomatic treatment and family- and patient-centered counseling throughout the disease process.

Treatment of Amyotrophic Lateral Sclerosis



Spinal Muscular Atrophy and Spinal Bulbar Muscular Atrophy



Spinal bulbar muscular atrophy (SBMA, or Kennedy disease) is produced by a trinucleotide repeat mutation disrupting the gene for the androgen receptor. Inheritance is X-linked and thus affects men only. Onset is typically in the 40s, with a nasal lower motor neuron (LMN) dysarthria, dysphagia, and proximally predominant weakness. Reflexes are depressed or absent and fasciculations common; perioral fasciculations are characteristic. Gynecomastia, diabetes, and testicular atrophy may be seen. Creatine kinase (CK) is elevated. Electrodiagnostic studies demonstrate findings consistent with motor neuron diseases (MND), including reduced compound muscle action potentials (CMAPs) with preserved latencies and velocities, and signs of active (fibrillation potentials and positive sharp waves at rest) and chronic (high-amplitude, long-duration motor unit potentials) denervation on needle electromyography (EMG). However, unlike other MNDs, the EMG in SBMA reveals an associated sensory neuronopathy manifested as a global reduction or absence of sensory nerve conduction responses. Differentiating SBMA from amyotrophic lateral sclerosis (ALS) is important for reasons of family counseling as well as prognosis (SBMA has a much slower progression). Gene testing is diagnostic.

Spinal Muscular Atrophy Type I (Werdnig-Hoffmann Disease). In the healthy newborn infant, the purposeless movements of the extremities are associated with a well-defined muscular tone, despite the lack of coordinated motor function. In addition, the full-term newborn has a well-developed suck and swallow. Most infants with SMA type I demonstrate normal muscular tone, motor function, and bulbar function at birth. However, within the first few weeks to months postbirth, they develop generalized hypotonia and weakness. In addition, they manifest a respiratory pattern characterized by paradoxic chest and abdomen movement that results from the selective weakness of intercostal muscles in the setting of preserved diaphragm function. Without supportive treatment, infants subsequently develop the characteristic bell-shaped deformity of the thorax. In addition, they manifest a hypotonic posture characterized by abducted hips and internal rotation of the forearms (frog-legged and jug-handle habitus). Progressive bulbar and respiratory insufficiency results in a vulnerability to both aspiration and infectious pneumonias. Extraocular movements and facial movement are preserved until late. Careful evaluation of the tongue reveals evident tongue fasciculations. In contrast to adults, fasciculations in limbs are difficult to appreciate due to excessive subcutaneous fat in infants. In milder cases, normal motor milestones, such as head control and ability to roll and sit, are simply not acquired as expected during the first few months. Ultimately, however, SMA type I is defined clinically by the inability of all such infants to achieve independent sitting. In a subset of the most severe cases, reduced fetal movement occurs before birth, and the infant is born with generalized hypotonia, neuromuscular weakness, respiratory insufficiency, bulbar dysfunction, and proximal joint contractures.

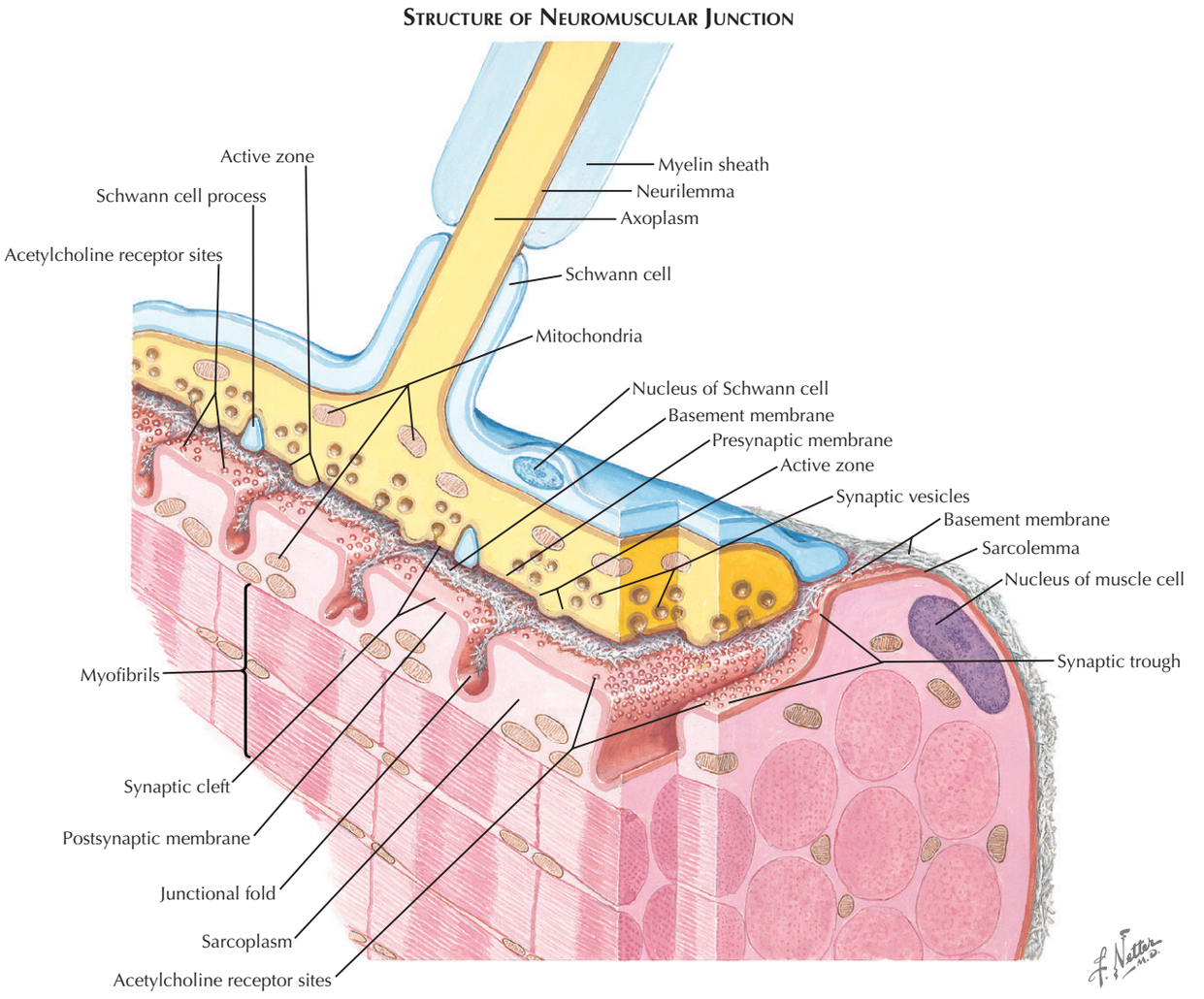
Spinal muscular atrophy is a hereditary illness, most often of autosomal recessive inheritance, although other variant forms exist, including X-linked and dominant forms. The most common form of SMA is the proximal recessive type, which includes a broad range of subtypes ranging from the severe infantile variant (depicted here) to ambulatory forms with adult-onset.

Spectrum of phenotypic manifestations in proximal spinal muscular atrophy

SMA Type	Typical age of onset	Typical life span	Also called	Clinical characteristics Maximum milestones achieved
0	Prenatal	<6 months	SMA-arthrogryposis multiplex congenita type	Congenital hypotonia, weakness, respiratory failure, proximal joint contractures Unable to breathe unsupported
I	Birth 6 months	~32% survival probability >2 years	Werdnig-Hoffman disease	Infantile onset of generalized hypotonia weakness, impaired bulbar function, respiratory insufficiency Unable to sit unsupported
II	6-12 months	~70% survival to adulthood[A]	SMA, Dubowitz type	Able to sit independently Onset of limb weakness as infants or toddlers Progressive weakness, respiratory insufficiency, scoliosis , joint contractures in childhood
IIIa IIIb	After 12 months After 3 years	Normal	Kugelberg-Welander disease	Onset of proximal muscle weakness in childhood Able to walk independently, although 50% with type IIIa lose independent ambulation by 12 years of age
IV	Adulthood	Normal		Onset of proximal leg weakness in adulthood, able to walk independently

Electromyography as a primary diagnostic tool has been largely replaced by genetic testing in most cases because more than 95% of such infants have a homozygous deletion/mutation of exon 7 of the survival motor neuron 1 gene (*SMN1* gene). Once significant weakness is manifest, the EMG findings are distinct in type I, demonstrating diffuse fibrillations in virtually all muscles in association with markedly reduced recruitment of small motor units in the absence of the typical large complex motor units characteristic of reinnervation in milder, more chronic forms of the disorder. Muscle biopsy shows findings typical of neurogenic atrophy. Other lesions in the motor unit can mimic Werdnig-Hoffmann disease but, as a rule, can be differentiated by clinical and electromyographic findings and examination of muscle biopsy specimens if genetic and/or neurophysiologic testing is not definitive. Differential diagnosis for presentation in infancy includes spinal muscular atrophy with respiratory distress (SMARD), which is distinguished by early respiratory failure due to diaphragm involvement, especially in association with more distal presentation of limb weakness. X-linked SMA manifests as a severe infantile SMA variant predominantly affecting males. Diseases of the neuromuscular junction, such as transient neonatal myasthenia gravis and infantile botulism, and rare recessive inherited peripheral neuropathy variants, such as congenital hypomyelinating neuropathy, should be considered in the differential diagnosis. Treatment for Werdnig-Hoffmann disease remains largely supportive. The prognosis is generally poor, with onset is in the neonatal period. Many of these infants do not survive until their first birthday. However, even in the absence of extensive supportive care, historically, up to 30% of infants with SMA type I survive beyond 2 years of age, some into adolescence or beyond.

NEUROMUSCULAR JUNCTION AND ITS DISORDERS



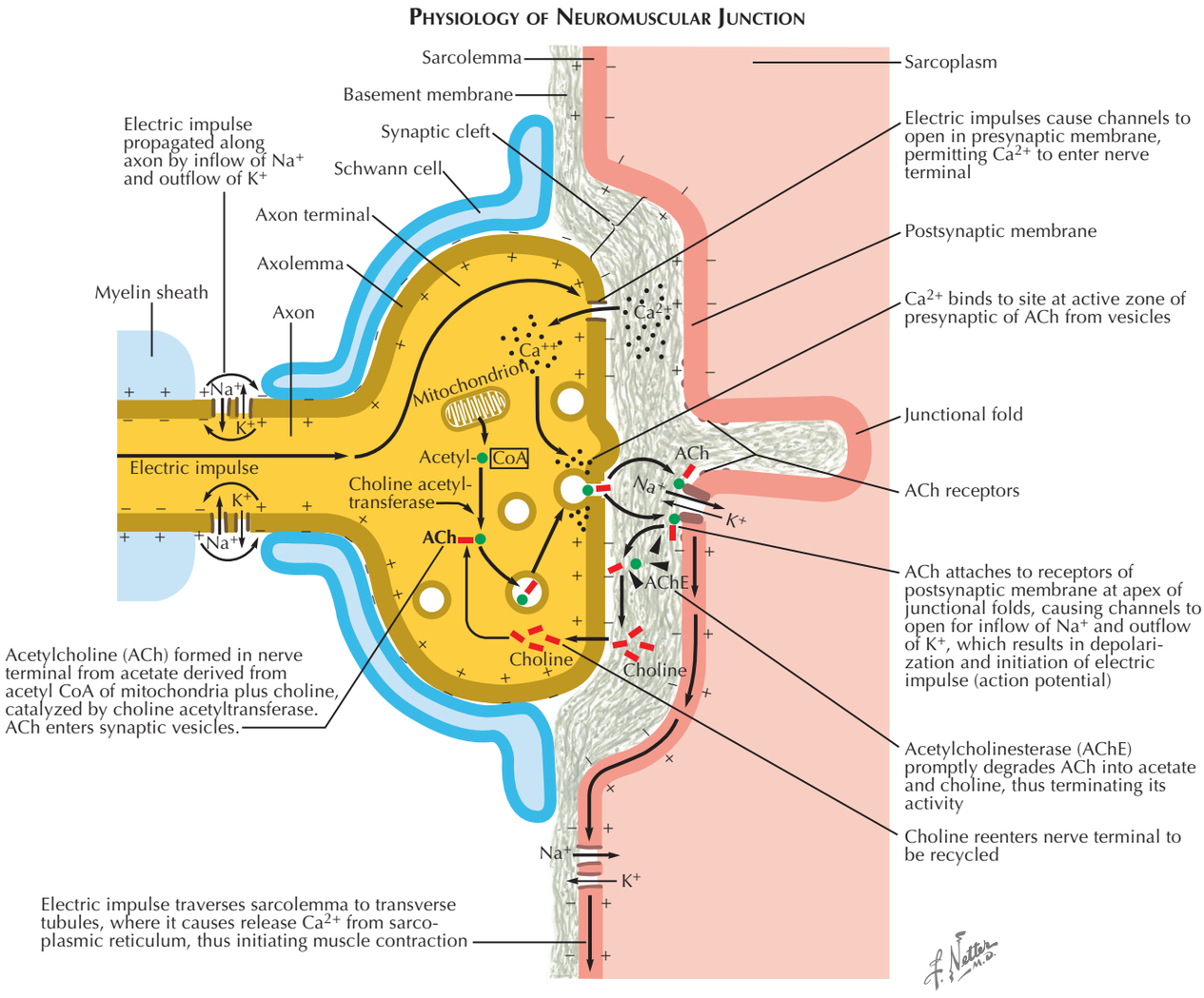
Neuromuscular Junction

The outflow of nearly all behavior depends upon the neuromuscular system, where nerves emanating from the spinal cord and brainstem make connections with skeletal muscles that allow us to move, stand, and express ourselves. The numbers of skeletal muscles in the human body is daunting: somewhere between 500 and 1000. The face alone has enormous numbers of muscles that allow us to express our emotions, articulate our words, and eat our food. Our hands are the second most "muscular" parts, giving us the finesse to play musical instruments, communicate with sign language, and write. Some muscles are huge. The gluteus maximus, for example, has many thousands of muscle fibers and is essential for walking. Other muscles are miniscule, designed to cause the slightest movements of the eardrum or the larynx and have a few hundred muscle fibers or fewer. The set of muscle fibers innervated by an axon (a motor unit) is very small in muscles that require very fine control, such as the extraocular and finger muscles, where motor units can be fewer than 10, or very large (100s or 1000s) in postural (back musculature) and girdle muscles (gluteus maximus). Despite the functional and structural diversity of muscles, however, the communication between the nervous system and muscles is much the same throughout the body. In humans and other mammals, muscles are composed of many muscle fibers, and each muscle fiber is typically innervated by only one motor neuron, with innervation focused on a small region of the muscle fiber known as the *neuromuscular junction* (NMJ). A NMJ may occupy less than 0.1% of the muscle fiber's surface area and yet is sufficient, without fail, to cause the muscle fiber to twitch each time an electrical impulse travels from the motor neuron cell body in the central nervous system to the muscle via the peripheral nerve. Thus the NMJ is among the most reliable and powerful synapses within the body.

The structure of the neuromuscular junction explains why it is so powerful. An axonal branch terminates in a branched structure that is laden with mitochondria, synaptic vesicles, and a number of special features that ensure that when an action potential invades the terminal a sequence of events is set in motion, leading to the near-synchronous release of neurotransmitter as hundreds of synaptic vesicles fuse with the nerve's plasma membrane and release their contents into the synaptic cleft. The main constituent of these synaptic vesicles is acetylcholine (ACh), the neurotransmitter at all skeletal muscle neuromuscular junctions. The released acetylcholine diffuses across the synaptic cleft, which is a mere 10 to 20 nm wide. It takes roughly 1 µsec for an ACh molecule to traverse the cleft and reach the synaptically specialized membrane of the muscle fiber, known as the postsynaptic membrane.

However, at least half of the released neurotransmitter never reaches the postsynaptic membrane because there is a high concentration of an enzyme on the cleft that enzymatically inactivates the neurotransmitter, cleaving it into acetate and choline. It may seem strange that this enzyme, known as *acetylcholinesterase*, should be juxtaposed between the nerve's release site and the muscle fiber's receptive site. However, the large amount of ACh released from hundreds of synaptic vesicles means that there is far more ACh available than is normally required to cause the muscle fiber to twitch when an electrical impulse from the axon invades the nerve terminal. This "*safety factor*" means that, in normal use, it is very unlikely that the available neurotransmitter will fail to cause the muscle to contract. The muscle contraction is initiated by the binding of ACh to the acetylcholine receptors (AChR) in the postsynaptic membrane. The AChRs are packed into the postsynaptic membrane at as high a concentration as their size permits, about 10,000 receptors per square micron of membrane, guaranteeing that any ACh molecule that makes it through this gauntlet of esterases will find a receptor.

The AChR is a typical *ligand-gated ion channel*. Thus, when ACh (the ligand) binds to the AChR, the receptor becomes an ion channel that allows cations to pass through a central pore. The main cations are *sodium (Na^+) and potassium (K^+)*. The high concentration of Na^+ outside and the negative resting membrane potential drives Na^+ into the muscle fiber. The *positive charges* that enter the muscle fiber *depolarize the muscle's membrane potential* from a negative value to a much less negative



NEUROMUSCULAR JUNCTION
(Continued)

value. This depolarization *initiates a muscle fiber action potential* that propagates away from the NMJ in both directions, rapidly causing the muscle fiber to contract.

The esterase in the synaptic cleft prevents the same ACh from rebinding multiple times to the receptors so that *each single nerve impulse in the axon leads to exactly one action potential* in the muscle fiber. The esterase plays a second essential role: the *choline* it creates from ACh is taken back *(reuptaken)* by the nerve terminal to make additional ACh via an intracellular enzyme (choline acetyltransferase). The NMJ is thus a highly regulated site where a nerve terminal, muscle fiber, and several supporting glial cells are juxtaposed. A wide range of pharmacologic agents, natural toxins, and electrolyte imbalances associated with disease have profound effects on the function of this synapse. For example, *NMJ function can be blocked* by agents that affect the muscle's AChRs, the nerve terminal vesicle release machinery, or even the synaptic cleft. Venom from certain poisonous snakes has a component (alpha bungarotoxin) that blocks the ability of ACh to bind to the AChR and is thus paralytic. Anaerobic *Clostridia* bacteria make a factor (botulinum toxin) that is also paralytic, by blocking the ability of synaptic vesicles to fuse with the nerve terminal membrane. Insecticides can block the function of the acetylcholinesterase, causing abnormally large amounts of neurotransmitter to reach the muscle fiber. Muscles protect themselves from excessive depolarization by inactivating their receptors, which also has the effect of paralysis.

Alpha bungarotoxin has another use. Because it binds to tightly to the AChR, it provides a means of seeing each muscle fiber's postsynaptic site. This is accomplished by tagging bungarotoxin with a small organic fluorescent dye so that the alpha bungarotoxin (red in the figure) clearly delineates the postsynaptic site. Over the last several years, the ability to visualize nerves has become much easier thanks to the Nobel Prize–winning discovery (2003 chemistry prize) of the green fluorescent protein (GFP). This gene for a jellyfish protein that gives certain jellyfish their green bioluminescent glow has been modified so that it can be inserted into the genome of mammals, especially mice. The transgenic mice are engineered by molecular biologists to express the GFP in neurons selectively. In this way, a transgenic mouse can express GFP in its motor nerves, while the AChRs are labeled with red alpha bungarotoxin. The two distinct colors in the nerve (green) and the muscle membrane (red) show the remarkably precise alignment of the nerve's release sites and the muscle's AChRs. The fluorescent protein expression also allows visualization and identification of all the muscle fibers innervated by a single axon. The motor axon and all the muscle fibers it innervates are called a *motor unit*, and this is a critical aspect of neuromuscular function. Because an action potential impulse heading out an axon in a peripheral nerve will enter all the branches of the axon, *the motor unit is the unitary muscle contraction from a single axon*.

Motor units are recruited in a fixed order when muscles are used. Typically, the *weakest motor units* that cause the smallest muscle twitches are *recruited first*. If these are insufficient for the task, additional motor units are recruited so that each gives rise to progressively larger amounts of muscle tension. In this way, there is fine control of small muscle contractions and less control as the force of muscle contraction is increased. All the muscle fibers within a single motor unit have very similar contraction properties because they have the same subtype of the contraction protein myosin.

The *first motor units* recruited comprise muscle fibers having "*slow*" *fatigue-resistant myosin* that causes slow contractions. The *last motor units* to be recruited activate muscle fibers that have *fast contractions*, thanks to fast myosin, but are *highly fatigable*. It is possible to see positions of all muscle fibers in each of the motor units in one muscle. Such descriptions reveal "*connectomes*," which are complete maps of all the positions of all the motor axons and their connections within a muscle.

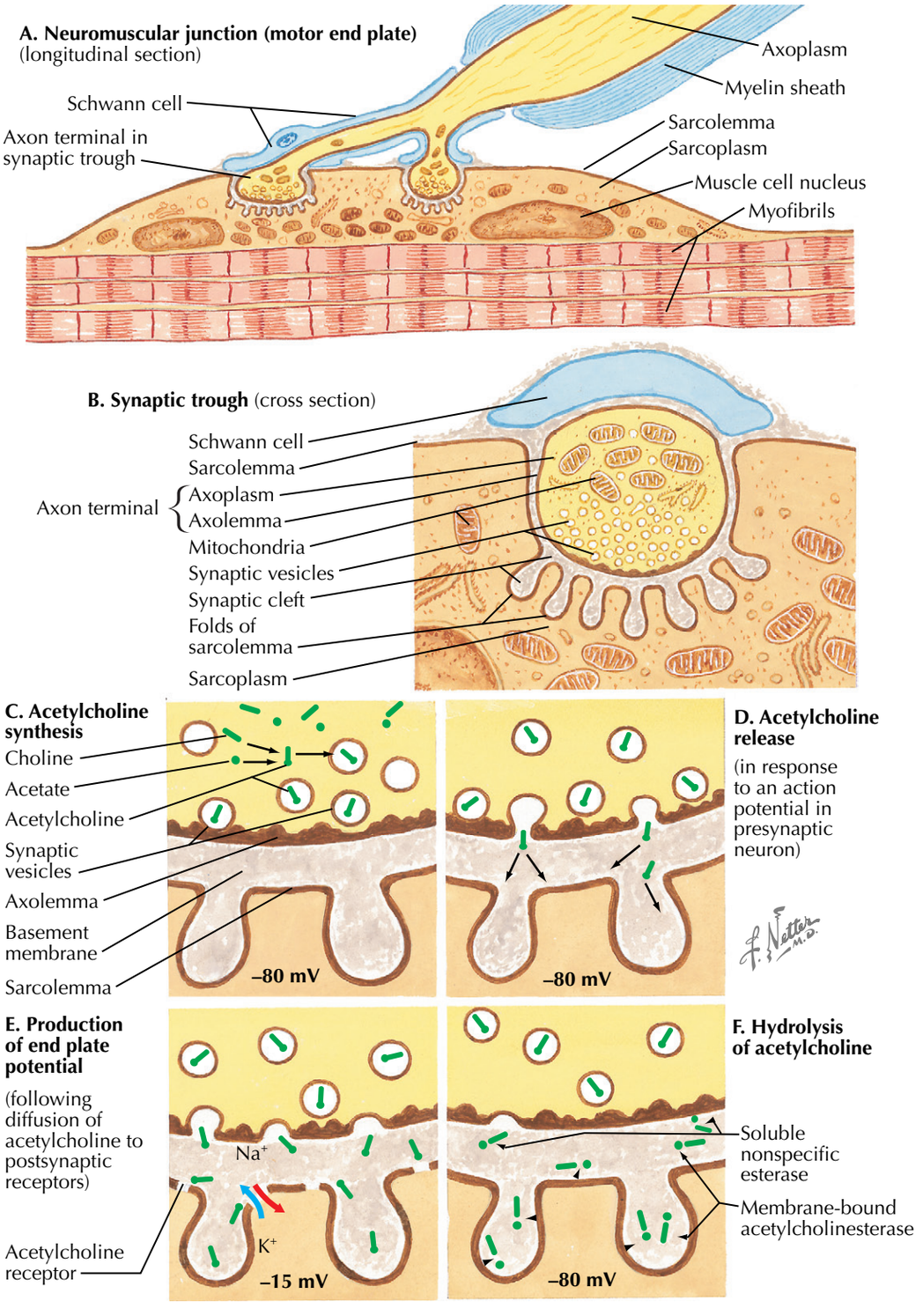
Synaptic Transmission

Normal somatic motor nervous system function requires rapid and efficient electrical impulse transmission. These initially propagate along peripheral nerves, releasing acetylcholine through a complex series of electrochemical processes at the nerve terminal to immediately bind at the postsynaptic neuromuscular junction (NMJ), generating electrical impulses that propagate along the muscle fiber. The subsequent muscle fiber action potentials couple with the muscle cell's inherent contractile mechanism, producing muscle contraction. The physiologic steps of synaptic transmission are divided into those that occur in the (1) presynaptic nerve terminal, (2) the synaptic cleft, and (3) the postsynaptic muscle membrane.

The presynaptic nerve terminal is the site of synthesis, release, and reuptake of the neurotransmitter acetylcholine (ACh), the chemical responsible for neuromuscular transmission. Acetylcholine is synthesized in the peripheral nerve terminal when acetate derived from acetyl CoA within the mitochondria and choline that has been recycled and taken up from the synaptic cleft is catalyzed by the enzyme choline acetyltransferase. The newly formed acetylcholine is then packaged into synaptic vesicles within the nerve terminal. Some ACh vesicles are located immediately adjacent to the nerve terminal membrane and are available for immediate release, whereas others are localized a short distance from the terminal nerve membrane and mobilized for rapid release.

ACh release is triggered by calcium influx into the nerve terminal. As a propagating nerve action potential reaches the nerve terminal, the depolarization activates voltage-gated calcium channels in the active zones of the terminal membrane, resulting in an influx of calcium (Ca^{2+}) ions into the axon terminal. The Ca^{2+} binds to active zones within the nerve terminal lying in juxtaposition to the muscle postsynaptic ACh receptors. This allows for synaptic vesicle membrane fusion to the nerve terminal membrane, with ACh release into the synaptic cleft.

Somatic Neuromuscular Transmission



The synaptic cleft is the neuromuscular junction site where ACh released from the nerve terminal crosses and eventually binds to postsynaptic muscle membrane ACh receptors. The time required for ACh to move across the synaptic cleft is slower than electrical impulse transmission along the axon or muscle fiber membrane. Unlike action potential transmission, movement of ACh across the cleft is unidirectional. ACh remaining within the cleft, either before or after attachment to the ACh receptors, is rapidly degraded within the synaptic cleft into acetate and choline by acetylcholinesterase (AChE), thus terminating its activity. Subsequently, choline is redirected into the nerve terminal and recycled to form new ACh transmitters.

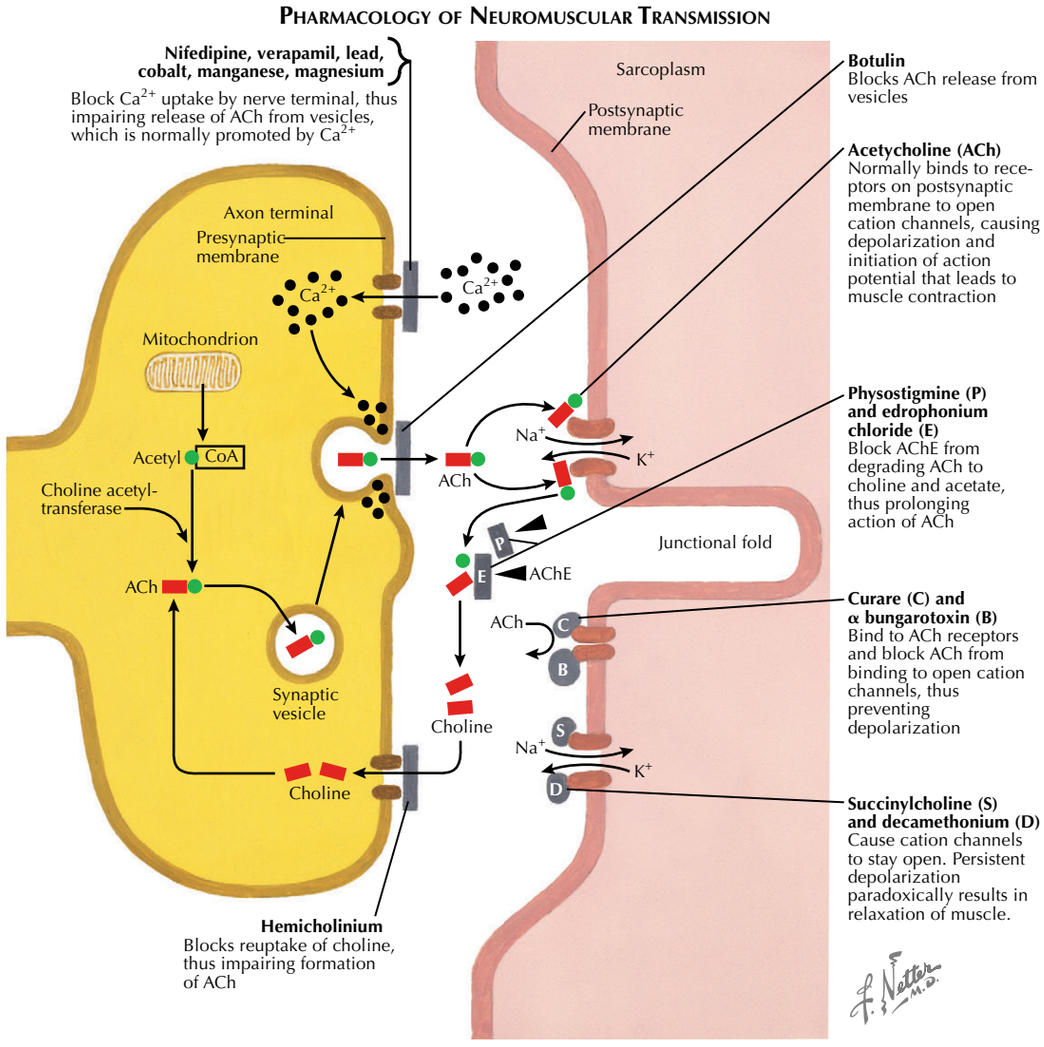
Synaptic Transmission
(Continued)

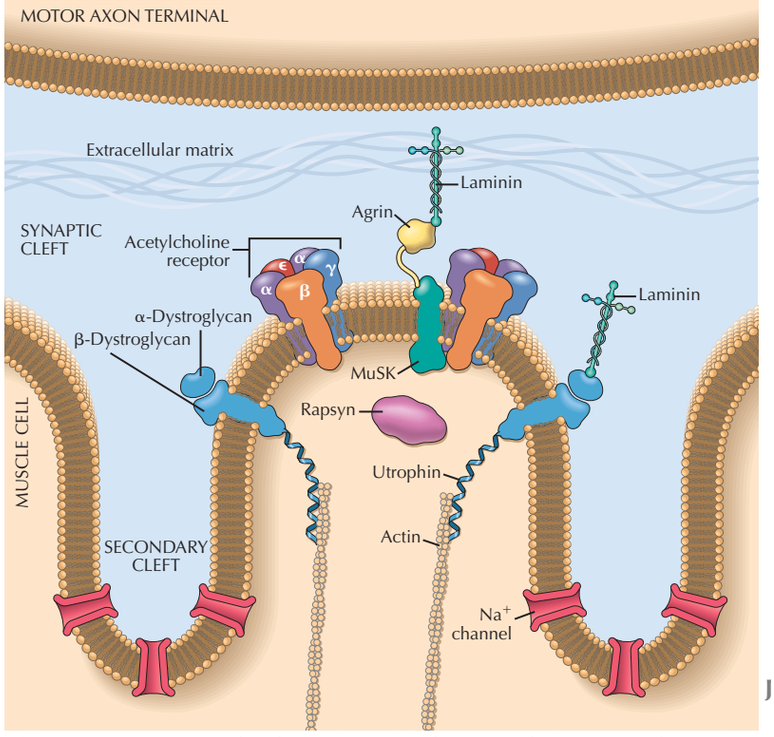
The final step of neuromuscular transmission occurs at the postsynaptic muscle fiber membrane, composed of junctional folds within the membrane; AChRs are concentrated at the apex of the folds. When ACh is released from the nerve terminal and crosses the synaptic cleft binding to ACh receptors, muscle fiber membrane sodium channels open, resulting in Na^+ influx into the muscle fiber with generation of muscle fiber action potentials.

The nicotinic AChR contains five subunits arranged radially around a transmembrane ion channel. Antibodies generated in myasthenia gravis are primarily directed against the AChR alpha subunit. These antibodies may bind at or near the acetylcholine binding site, directly preventing acetylcholine binding, or may alter receptor function through other mechanisms, such as increased receptor degradation or complement-mediated receptor lysis. The receptor that is required for NMJ formation is called the MuSK receptor (muscle-specific kinase). MuSK, agrin, and rapsyn are important for clustering of acetylcholine receptors during neuromuscular junction development by allowing binding to the receptor's skeletal muscle cytoplasmic domain. Agrin binds several other proteins on the surface of muscle, including dystroglycan and laminin. Rapsyn anchors or stabilizes the AChR at synaptic sites linking the receptor to the underlying postsynaptic cytoskeleton.

Acquired MG develops as a result of formation of antibodies primarily to the alpha-1 postsynaptic NMJ immunogenic regions (epitopes). AChR antibodies trigger immune-mediated AChR degradation. The loss of large numbers of functional AChRs decreases the pool of muscle fibers available for depolarization during motor nerve terminal activation. This results in decreased generation of muscle fiber action potentials and subsequent muscle contraction, leading to clinical weakness if large numbers of NMJs are affected.

Many medications have their pharmacologic site of action at the NMJ, subsequently affecting neuromuscular transmission. Several block Ca^{2+} uptake by the nerve terminal, resulting in impaired mobilization of the ACh vesicles and subsequent ACh release. These include calcium channel blockers and heavy metals. Although these agents do not often produce clinically evident NMJ failure in healthy persons, exposure to these medications in patients with a NMJ disease (i.e., myasthenia gravis or Lambert Eaton myasthenic syndrome) may cause clinical exacerbations.





Representation of the normal neuromuscular junction, adult acetylcholine receptor in the postsynaptic muscle membrane and other important associated proteins

Repetitive Motor Nerve Stimulation

The integrity of neuromuscular transmission can be assessed by repetitive nerve stimulation studies during clinical neurophysiologic testing. When an action potential propagates along the nerve and reaches the nerve terminal, multiple quanta of ACh are released from the presynaptic nerve ending. When the ACh binds to the AChR, an *end-plate potential (EPP)* is generated. When the difference between the actual end-plate potential and the threshold for muscle fiber action potential (known as the *safety factor*) is large, small reductions in the EPP do not have a significant effect on neuromuscular transmission, and a muscle fiber action potential is generated; however, when there is either a presynaptic or postsynaptic NMJ disorder, this safety factor is no longer operational, and clinical symptoms occur. Repetitive motor nerve stimulation (RMNS) provides a neurophysiologic means to assess neuromuscular transmission.

This technique is performed to specifically stress the safety factor by rapidly mobilizing and releasing multiple stores of ACh. With a 2-to 5-Hz RMNS, fewer stores of ACh are released, and less ACh is available to bind to the AchR with each stimulus, up to approximately 5 to 6 stimuli. By assessing the change in the recorded compound muscle action potential (CMAP) after depolarization of all of the axons, and therefore all of the muscle fibers within a muscle, defects of neuromuscular transmission can be identified.

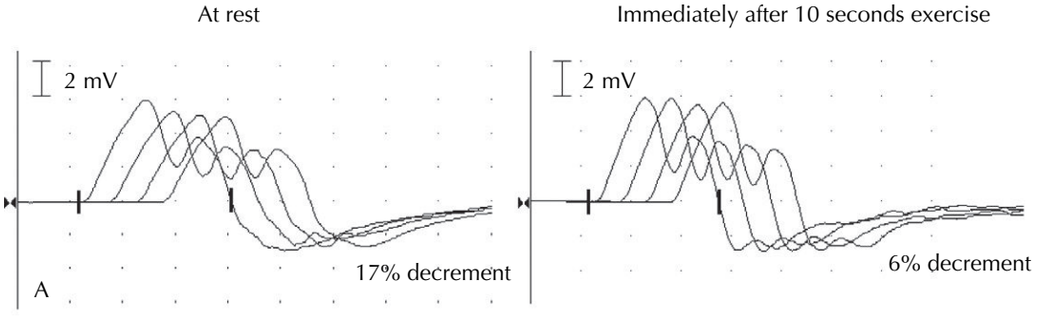
When evaluating normal neuromuscular junctions (NMJs), the EPP is much larger than the threshold required to initiate an action potential along the muscle fiber. As a result, the reduction in ACh release after repetitive stimulation at slow rates does not reduce the EPP below the threshold for depolarization, and action potentials are initiated in all muscle fibers innervated by the nerve. The resulting CMAP amplitude and area after each stimulus is therefore identical, and no reduction (decrement) of the responses occur.

When patients have a *presynaptic dysfunction*, such as in Lambert-Eaton myasthenic syndrome (LEMS) or infantile botulism, the resting EPP is markedly reduced as a result of a reduction in release of ACh from the presynaptic nerve. The ACh release is diminished at the peripheral nerve terminal at the NMJ because of either an autoimmune disorder blocking presynaptic uptake of calcium (Ca^{2+}) ions or a specific effect of the botulinum toxin having a similar effect. This EPP is often lower than the threshold for depolarization of the muscle fiber, and therefore a single stimulus will not produce a muscle fiber action potential in many fibers. With standard motor nerve conduction studies, the CMAP amplitude is often low as a result. With slow rates of stimulation during RNS, there is an additional reduction in the release of ACh stores with each stimulus and a decrement in the CMAP amplitude and area (similar to that occurring in a postsynaptic neuromuscular junction disorder) is seen. However, after brief isometric exercise for 10 seconds, the influx of Ca^{2+} and mobilization and release of additional ACh stores results in a significant increase (increment or facilitation) of the CMAP amplitude (Plate 11-5, upper panel). This facilitation is a characteristic and diagnostic finding in Lambert-Eaton myasthenic syndrome.

In patients with a much more common *postsynaptic dysfunction*, as is typical in myasthenia gravis (MG), there is an autoimmune disorder leading to accelerated breakdown of the ACh receptors at the muscle side of the NMJ as well as a blockade of the ACh at the postsynaptic end plate. This affects the ability of ACh to produce a normal EPP. Therefore the resting EPP may be lower than normal as the safety factor for neuromuscular transmission is reduced.

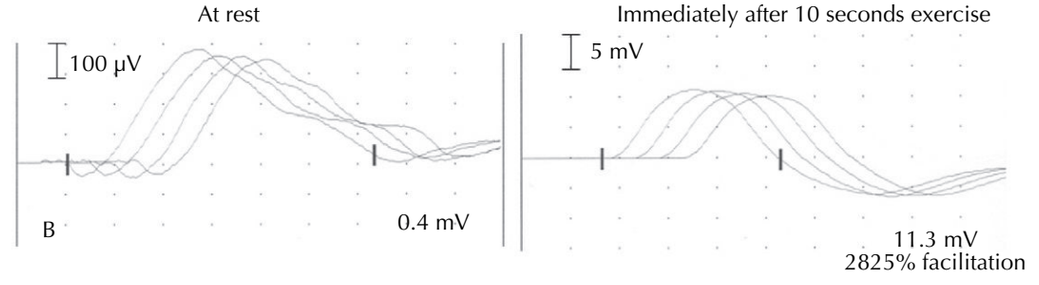
Therefore RMNS results in a reduction of both the recorded CMAP amplitude and area with each stimulus for the first 5 to 6 stimuli (Plate 11-5, lower panel). This decrement results from a loss of summated muscle fiber action potentials from those fibers in which the EPP does not reach the threshold for depolarization. Brief isometric exercise for 10 seconds leads to increased Ca^{2+} permeability in the presynaptic nerve terminal, causing mobilization and a release of additional stores of ACh. As a result, the degree of decrement immediately after brief exercise is less than at rest. However, with repeat testing between 1 to 4 minutes later, there is progressive NMJ fatigue, and the degree of deficit defined with RMNS increases up to a maximum at this time and then begins to improve with sequential testing.

Patient with myasthenia gravis



Two Hz repetitive nerve stimulation at rest *(left)* demonstrates a 17% decrement in amplitude in a patient with myasthenia gravis, which repairs slightly immediately after brief exercise *(right)*.

Patient with Lambert-Eaton myasthenic syndrome



In a patient with Lambert-Eaton myasthenic syndrome, there is a markedly low amplitude with mild decrement at rest *(left)*. After brief exercise, the amplitude increases from 0.4 mV to 11.3 mV, producing 2825% faciliation *(right)*.

Myasthenia Gravis

Demographics

Myasthenia gravis is a well-characterized and understood autoimmune disorder. It is the most common disorder of neuromuscular transmission resulting from an antibody-mediated, immunologic attack upon the acetylcholine receptor in the postsynaptic membrane of the neuromuscular junction. The hallmark of the disease is fluctuating weakness of ocular, bulbar, neck, limb, and respiratory muscles.

Myasthenia gravis is seen in all age groups, with a bimodal distribution, affecting younger adults in their 20s and 30s (with a female predominance) and older adults in their 60s and 70s (slight male predominance). The annual incidence is 10 to 20 new cases per million, and the prevalence is 150 to 200 per million.

The two major clinical forms of autoimmune myasthenia gravis are ocular and generalized. Transitory myasthenia gravis may also occur in infants born to myasthenic mothers—so-called neonatal myasthenia (a cause of the floppy baby syndrome) brought about by transplacental maternal antibodies. Myasthenia may also be congenital and nonimmune in character, presenting in infancy and childhood with ocular weakness, and resulting from a genetically determined defect at the neuromuscular junction (see Plate 11-11).

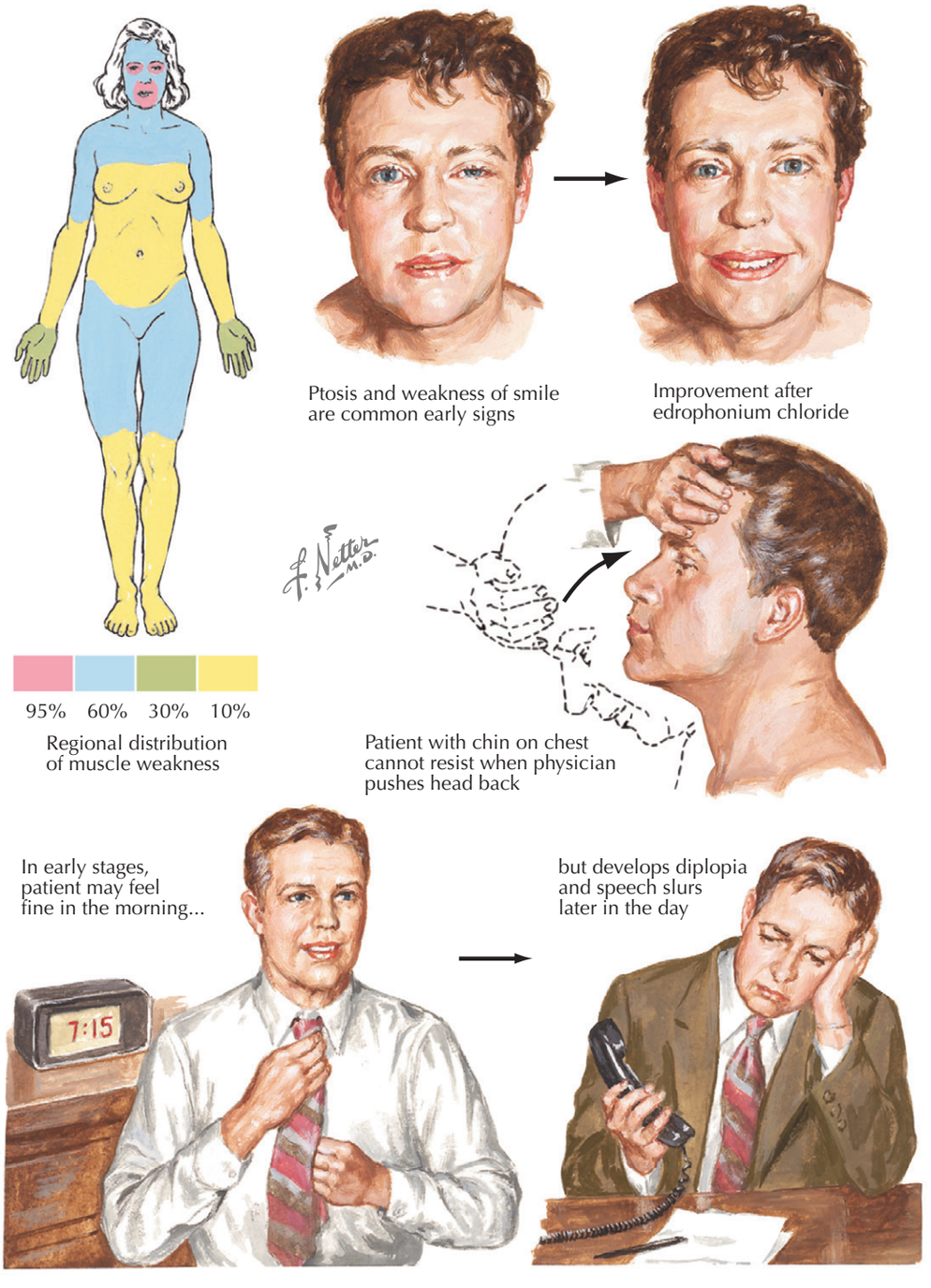
Clinical Picture

The cardinal feature of myasthenia gravis—the one that helps distinguish it from other neuromuscular disorders—is fluctuating weakness. The degree of weakness often varies throughout the day, typically most pronounced later in the day or evening and often mild in the morning after a period of rest, that is, diurnal.

More than 50% of patients initially present with ocular weakness, with complaints of double vision and lid droop. If there is bulbar and facial muscle involvement, patients experience difficulty chewing, speaking, swallowing, and effecting facial expressions. Neck extensors and flexors often become involved, causing head-drop. Limb weakness has a predilection for the shoulder and hip girdle muscles and the proximal muscles of the arms and legs so that difficulties washing and drying hair or climbing stairs are commonly reported complaints. Shortness of breath is a sign of diaphragmatic weakness and may herald respiratory insufficiency, leading to respiratory failure, and ultimately the life-threatening situation of "myasthenic crisis" that requires mechanical ventilation.

On physical examination, ocular involvement is revealed by (1) ptosis, which may be unilateral or bilateral and may worsen (or be unmasked) during the course of sustained (>60 seconds) upgaze, and (2) extraocular muscle weakness (sparing the pupil), the patient noting binocular diplopia or blurry vision. Facial weakness is typically characterized by both an inability to bury the eyelashes with forced eye closure and the "myasthenic snarl." In the latter, there is weakness of the orbicularis oris and inability to turn the corners of the mouth upward when the patient is asked to smile. This manifestation leads to a "*smile*" that is transverse and appears almost angry. Patients may also develop jaw weakness (with difficulty in keeping the jaw closed); changes in speech (nasal quality from palatal weakness or low quality/hypophonic); neck extensor weakness, causing the head to be propped up using the hand under the chin; and proximally predominant arm and leg weakness.

Myasthenia Gravis: Clinical Manifestations



Differential Diagnosis

Disorders that may be confused with ocular myasthenia gravis, which cause ptosis and/or diplopia, include thyroid ophthalmopathy, myotonic dystrophy, oculopharyngeal muscular dystrophy, chronic progressive external ophthalmoplegia, and brainstem pathology. Conditions that mimic generalized myasthenia gravis include motor neuron disease, myopathy, and Lambert-Eaton myasthenic syndrome. In most instances, however, these disorders are recognized by their distinctive clinical and laboratory features, and unlike myasthenia gravis, these do not demonstrate true fatigability with diurnal fluctuating weakness.

Diagnosis

Testing for autoantibodies specifically directed against the acetylcholine receptor (AChR) and muscle-specific tyrosine kinase (MuSK) are the MG diagnostic studies of choice; when positive, none of the other studies subsequently mentioned are usually required. The one drawback to these studies is that they are not immediately available in the acutely ill patient. Acetylcholine receptor antibodies (AChRAbs) are found in 90% of patients with generalized myasthenia gravis and 50% of patients with purely ocular involvement. These antibodies, which are able to fix complement, originate in hyperplasic germinal centers of the thymus gland and

MYASTHENIA GRAVIS *(Continued)*

bind to the acetylcholine receptors. The binding of antibody to receptors—each divalent immunoglobulin G (IgG) antibody cross-linking two receptor molecules—triggers a cascade of events resulting in loss of skeletal muscle postsynaptic ACh receptors. This is related to the effects of the terminal portion, that is, membrane attack complex of the complement cascade, leading to loss and simplification (marked reduction of surface area) of the postsynaptic membrane.

Approximately 40% of those occasional AChR antibody–negative patients harbor antibodies directed against a protein MuSK. MuSK plays a role in the clustering of acetylcholine receptors during neuromuscular junction development. MuSK antibodies have a deleterious effect on neuromuscular transmission and are responsible for myasthenic weakness. Clinical differences are noted in this subgroup of patients; in particular, these individuals may have tongue atrophy mimicking a lower motor neuron cranial neuropathy as seen with motor neuron disease.

Early in the disease course, a presumptive diagnosis of myasthenia gravis is supported by a test dose of edrophonium chloride (Tensilon), an acetylcholinesterase inhibitor characterized by very rapid onset (30-45 seconds) and short duration (5-10 minutes). This increases the availability of acetylcholine by briefly blocking the inherent neuromuscular junction postsynaptic acetylcholinesterase that normally leads to ACh breakdown. Thus ACh has a longer postsynaptic half-life, resulting in improvement in the strength of weak muscles. A test dose of 2 mg of Tensilon is given intravenously (to assess for any adverse affects), followed by 2to 10 mg to assess for improvement. It is prudent to have atropine at the bedside, to ameliorate a bradycardia associated with hypotension. One should be very cautious and possibly not utilize this test in senior citizens with a proclivity for heart block. A faster and easier, but very non-specific bedside test, involves placing a bag filled with ice over a ptotic eyelid for 1 to 2 minutes (cold pack test), which is sometimes useful to evaluate for immediate improvement in ptosis (a positive test result).

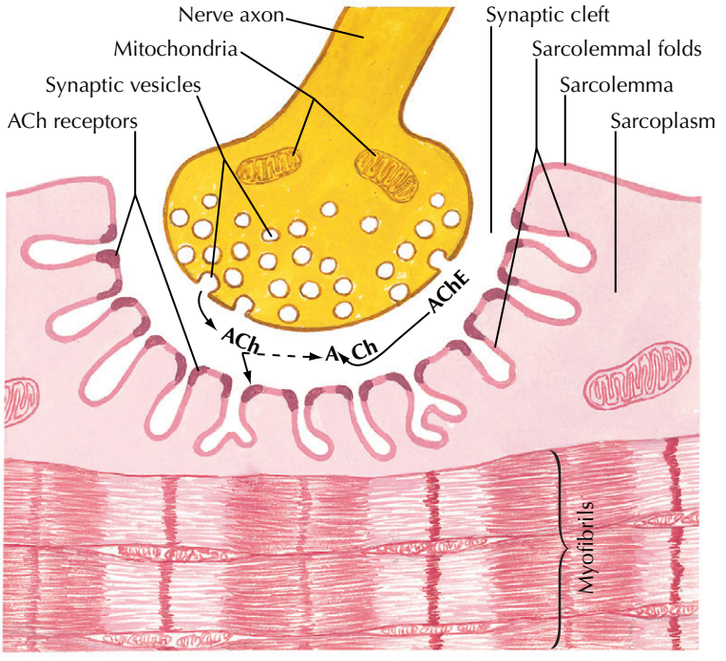
Traditionally, electromyography (EMG) has been utilized to provide confirmation of an MG diagnosis. Today EMG is most useful in the acutely ill MG patient when AChRAb results are not immediately available. Repetitive motor nerve stimulation (RMNS) and single fiber EMG (SFEMG) are designed to provide evidence for a postsynaptic defect in neuromuscular transmission and are sensitive (75% and 95%, respectively) in generalized MG. RMNS is performed by stimulating a motor nerve 6 to 10 times at low rates (2-3 Hz) and recording the amplitude of the response from the muscle that the nerve supplies. In the normal neuromuscular junction, RMNS elicits responses with identical amplitudes from stimulus to stimulus. In myasthenia gravis, however, a decrement (>10%) in the amplitude may be seen from the first to the subsequent stimuli, especially if the muscle is weak. Single fiber EMG is technically challenging, but highly sensitive, and uses a needle electrode to measure the variability in time of one action potential to reach threshold relative to another action potential from different muscle fibers innervated by the same axon. This variability, or "jitter," is increased when the transmission at the neuromuscular junction is compromised.

Patients with MG have an increased incidence of thymoma; although usually benign, a small percentage of these tumors are malignant. Therefore evaluation for the presence of thymoma should be done in all myasthenic patients by imaging the mediastinum with computed tomography (CT) or magnetic resonance imaging (MRI).

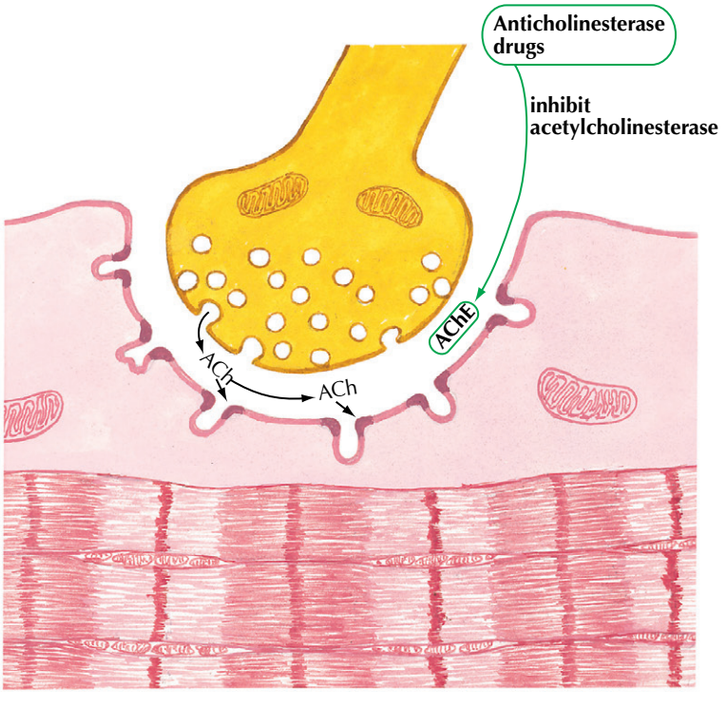
Treatment of myasthenia gravis consists of symptomatic control, immunosuppressive and/or immunomodulating therapy, and, in selected patients, thymectomy. For patients with mild symptoms, for example, isolated ptosis, anticholinesterase inhibitors (pyridostigmine) are used with good response. For patients with bulbar or limb involvement, corticosteroids and other immunosuppressive agents (azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, rituximab, etc.) are necessary.

For the most severely affected patients—those with bulbar and respiratory muscle weakness and who are in or close to developing myasthenic crisis—immediate transfer to the intensive care unit (ICU) and treatment with immunomodulating agents, such as intravenous immune globulin (IVIg) or plasmapheresis, is necessary. Thymectomy is an absolute indication for myasthenic patients with thymoma; however, in those patients without thymoma, who are younger than 60 years, thymectomy is considered an "option to increase the probability of remission." Prospective, randomized controlled trials are underway for more definitive evidence of benefit.

MYASTHENIA GRAVIS: ETIOLOGIC AND PATHOPHYSIOLOGIC CONCEPTS

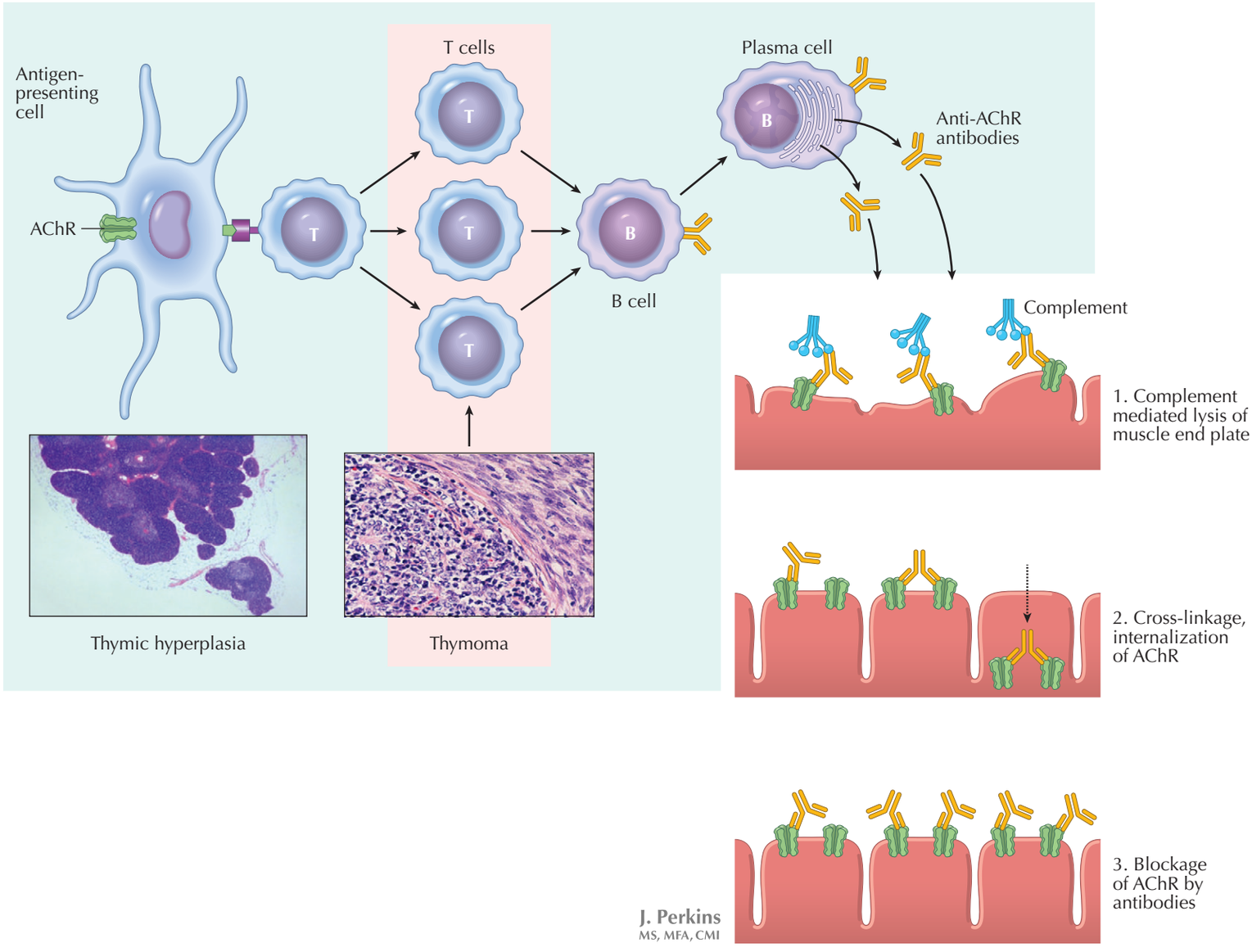


Normal neuromuscular junction
Synaptic vesicles containing acetylcholine (ACh) form in nerve terminal. In response to nerve impulse, vesicles discharge ACh into synaptic cleft. ACh binds to receptor sites on muscle sarcolemma to initiate muscle contraction. Acetylcholinesterase (AChE) hydrolyzes ACh, thus limiting effect and duration of its action.



Myasthenia gravis
Marked reduction in number and length of subneural sarcolemmal folds indicates that underlying defect lies in neuromuscular junction. Anticholinesterase drugs increase effectiveness and duration of ACh action by slowing its destruction by AChE.

F. Netter M.D.



Immunopathology of Myasthenia Gravis

Myasthenia gravis (MG) is a chronic, autoimmune disorder at the postsynaptic neuromuscular junction. Approximately 85% of patients with generalized MG have autoantibodies to the acetylcholine receptor (AChR). In most patients with MG, anti-AChR antibodies, usually of the immunoglobulin (Ig)G1 or IgG3 isotype, bind to the extracellular domain of the AChR molecule, activating complement and causing destruction to the muscle end plate. Complement-mediated lysis of the muscle end plate causes morphologic damage to the end plate, resulting in simplification of what was previously a highly folded muscle end plate. The morphologic changes to the end plate result in a reduction in the number and function of AChR channels, impairing the end-plate potential (EPP) amplitudes generated during neuromuscular transmission, thereby lessening the probability that the EPP amplitude generated will be sufficient to activate an all-or-nothing muscle fiber action potential. The morphologic changes at the end plate also result in a reduction of the voltage-gated sodium channels, which results in an increase in the muscle fiber action potential. In addition to the anti-AChR antibodies causing simplification of the muscle end plate, cross-linkage of AChRs by divalent antibodies causes internalization and degradation of AChRs. Furthermore, direct blockage of the AChRs by antibodies directed at the AChR binding sites likely contributes to functional loss of AChR, at least in some patients. The autoimmune events of MG are also influenced by T cells, with CD4 T cells facilitating B cells in the production of pathogenic antibodies. Approximately 7% of generalized MG patients have autoantibodies to muscle-specific tyrosine kinase (MuSK) and not to AChR. Although less is currently known about the specific role of anti–MuSK antibodies, such antibodies appear to impair the maintenance of clustering of AChR at the muscle end plate. Anti-MuSK antibodies are mainly the IgG4 isotype and do not activate complement.

The thymus gland plays a central role in the development of AChR-antibody MG, particularly for early-onset cases of MG (e.g., patients younger than 50 years). Hyperplastic thymus glands of patients with MG contain T cells, B cells, plasma cells, and muscle-like ("myoid") cells that express AChR. It is generally believed that the autoimmune response begins in the thymus and is subsequently exported to the periphery, where damage to the postsynaptic muscle end plate occurs, as described above. In early-onset MG, most patients have hyperplastic thymus glands (i.e., lymphofollicular thymic hyperplasia). In late-onset MG, patients often do not have thymic abnormalities, and the role of the thymus in late-onset MG is less clear. Approximately 10% to 15% of generalized MG patients are found to have thymomas, which are found to have an abundance of autoreactive T cells. These autoreactive T cells are exported to the periphery and facilitate pathogenic B cells and their autoantibodies. MuSK-antibody MG patients tend to lack thymus pathology, and the role, if any, of the thymus in MuSK-antibody MG is unknown.

Presynaptic Neuromuscular Junction Transmission Disorders: Lambert-Eaton Myasthenic Syndrome and Infantile Botulism

Presynaptic neuromuscular transmission disorders (NMTD) are very uncommon. Lambert-Eaton myasthenic syndrome (LEMS) is the most frequent adult presynaptic NMTD. It is the pathoanatomic mirror image of postsynaptic myasthenia gravis (MG). Infantile botulism is the pediatric acquired presynaptic NMTD.

Approximately 50% of LEMS patients have a small cell lung cancer (SCLC), often not clinically evident at the inception of neuromuscular symptoms. Presumably, the immune response leading to LEMS begins early in tumor evolution. SCLC is more likely in patients with weight loss greater than or equal to 5%, bulbar involvement, erectile dysfunction, in those older than 50 years, and in active smokers. Primary autoimmune, nonparaneoplastic LEMS occurs in younger adults and very rarely in children.

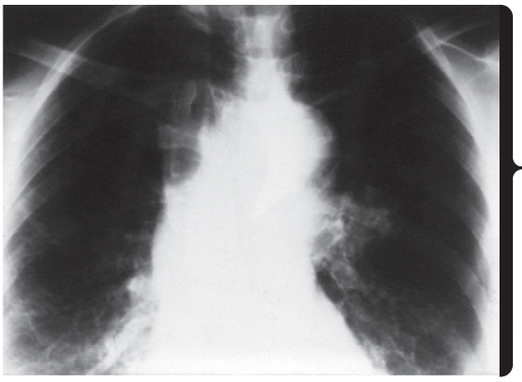
The initial LEMS clinical manifestations often begin months to a few years before SCLC is recognized. Sometimes, however, the cancer precedes LEMS. Classic symptoms include fatigue, proximal muscle weakness, dry mouth sometimes presenting as increased thirst, and, in men, erectile dysfunction. The motor components relate to autoimmune blockage of the nicotinic presynaptic NMJ calcium channels and muscarinic symptoms from similar effects on the acetylcholine-dependent autonomic nervous system receptors. Sometimes fatigue per se suggests to the unwary clinician that the younger patient most likely has emotional issues, particularly depression, or possibly is "hysterical." Occasional patients observe their symptoms improve after brief exercise, as exemplified by experiencing increased strength near the top of stairs. Additional more subtle symptoms of LEMS patients mimic myasthenia gravis: mild diplopia, ptosis, difficulty chewing, dysphagia, and dysarthria secondary to oropharyngeal weakness.

Neurologic examination demonstrates proximal weakness; sometimes initially noted by the examining physician when the patient arises to greet her or him. Sometimes the weakness has a "give way component;" however, when LEMS patients are asked to contract the weakened muscle a few times, their initial weakness may totally, albeit briefly, improve, only to weaken once again. Similarly, muscle stretch reflexes (MSR) are initially diminished or absent. However, if the biceps or quadriceps muscle strength is tested and then immediately reexamined for their respective MSR, the examiner may detect facilitation and a normal reflex for a limited time. This is the clinical representation of postexercise facilitation typical for presynaptic NMTD disorders and representative of the classic electromyographic (EMG) facilitation. Some LEMS patients present with, or develop, a gait ataxia over and above their degree of weakness. Sometimes, this is the primary LEMS manifestation and may be secondary to severe most proximal muscle weakness, particularly the paraspinal muscles necessary to stabilize the spine. Ataxic gait may also suggest a primary cerebellar degeneration from a concomitant paraneoplastic disorder.

EMG provides a means to confirm a clinical diagnosis of LEMS. Motor nerve conduction demonstrates low-amplitude compound muscle action potentials (CMAPs) that demonstrate postexercise facilitation after 10 seconds voluntary exercise. With LEMS, the CMAP at least doubles in amplitude. There is also a significant decrement on repetitive motor nerve stimulation (RMNS) similar to MG.

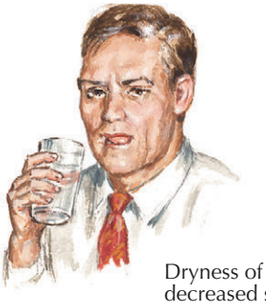
Voltage-gated calcium channel antibodies are detected in 90% of patients with either paraneoplastic or primary autoimmune LEMS. Because SCLC is found in 50% of LEMS patients, chest computed tomography (CT) is required to search for an occult tumor, particularly in older adults who smoke cigarettes. A tumor is often not immediately apparent; therefore repeat studies are required biannually.

Primary treatment for LEMS-associated lung cancer may eventually lead to muscle strength improvement, presumably by removing the antigenic stimulus. Symptomatic treatment of LEMS per se aims to improve neuromuscular transmission (NMT). 3,4-Diaminopyridine promotes presynaptic ACh release. In addition, the anticholinesterase medication pyridostigmine can sometimes also improve NMT. Immunemodulating agents, such as prednisone or azathioprine, are indicated in primary autoimmune LEMS. Despite improvement in muscle strength, sometimes the gait ataxia does not improve.

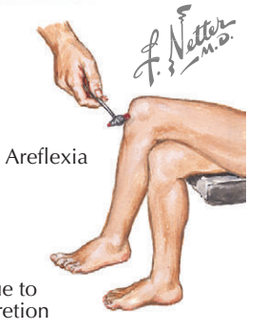


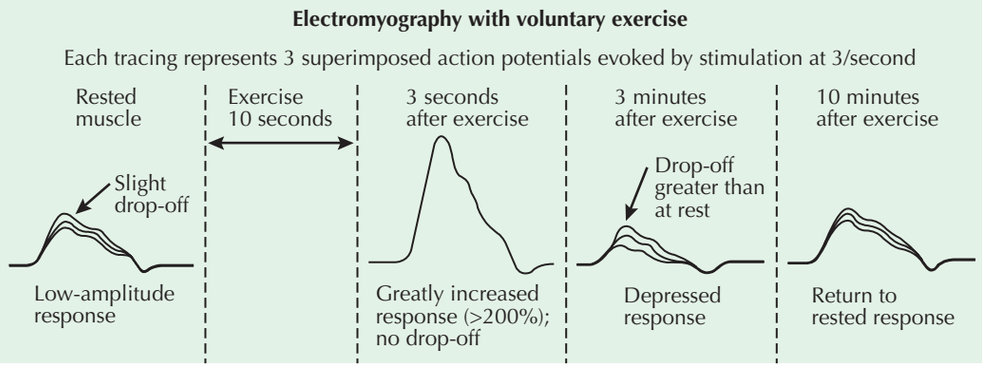
X-ray film showing large tumor in hilum of lung

Difficulty in climbing stairs or arising from chair often early symptoms due to weakness of pelvic girdle muscles



Dryness of mouth due to decreased saliva secretion





Congenital Myasthenic Syndromes

Congenital myasthenic syndromes (CMSs) are rare hereditary neuromuscular junction disorders. These conditions are usually present at birth or in the first 2 years of life with varying degrees of fluctuating and fatigable weakness, involving ocular, bulbar, and limb/trunk muscles. Important diagnostic tools are repetitive nerve stimulation (RNS) and single fiber electromyography (EMG). They are not immune mediated, and therefore antibodies to the acetylcholine receptor are absent. Weakness often improves after treatment with acetylcholinesterase inhibitors (AChEi), such as pyridostigmine, although there are forms that worsen with AChEi.

CMSs are caused by defects affecting the presynaptic, synaptic basal lamina–associated, and postsynaptic regions of the neuromuscular junction. Inheritance is autosomal recessive, except in the dominantly inherited slow-channel CMS. While clinical profile alone cannot distinguish among different forms of CMS, elegant morphologic and in vitro electrophysiologic studies have made it possible to distinguish among most of the CMSs and identify their associated genetic defects. In a small number of cases, however, a specific genetic diagnosis remains elusive.

Most mutations underlying the CMSs are in genes coding for proteins localized to the postsynaptic portion of the neuromuscular junction. When the abnormality involves the acetylcholine receptors (AChRs), mutations are concentrated in the gene encoding the epsilon subunit of the AChR (*CHRNE*). The most frequent CMS, caused by AChR deficiency due to *CHRNE* mutations, is usually benign, with prominent ophthalmoparesis and mild or no diplopia. Onset is usually at birth or infancy, with poor cry/suck and fluctuating ptosis. Bulbar symptoms regress with time, but fatigue and ptosis persist. There is partial response to AChEi and 3,4-diaminopyridine (3,4-DAP). Fast-channel CMS is similar regarding phenotype and treatment, but unlike AChR deficiency, acute respiratory crises occur frequently in childhood.

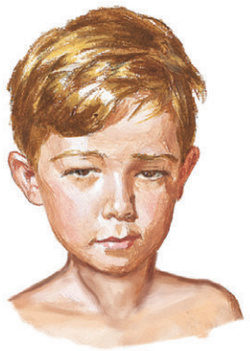
Almost all the proteins in the muscle-specific kinase (MuSK)/rapsyn signaling pathways have been associated with CMSs. Among them, postsynaptic rapsyn and DOK-7 deficiencies are major causes of CMS. In both, extraocular muscle involvement is mild or absent, while ptosis is common. Rapsyn deficiency causes a form of CMS characterized by mild arthrogryposis, strabismus, and frequent respiratory crises. Symptoms usually start at birth and rarely in adulthood. Patients improve with age and respond well to AChEi and 3,4-DAP.

DOK-7 mutations are responsible for some cases of limb girdle myasthenia. Proximal weakness, generally accompanied by ptosis and facial weakness, usually begins in early childhood. The severity of weakness may fluctuate over weeks. Respiratory problems may occur. AChEi are harmful, but the response to ephedrine or albuterol/salbutamol is generally favorable. Another subset of CMS patients with a limb girdle pattern of weakness and normal eye movements has a molecular defect mapped to the glutamine-fructose-6-phosphate transaminase 1 gene (*GFPT1*). These patients have tubular aggregates on muscle biopsy. They respond well to AChEi.

Two CMS syndromes with phenotypic similarities are postsynaptic slow-channel CMS and synaptic AChE deficiency. In both, the postsynaptic membrane is exposed to excessive acetylcholine, explaining the presence of repetitive compound muscle action potentials and the lack of response to AChEi. The clinical findings include variable ophthalmoparesis, neck muscle and upper extremity muscle weakness/atrophy, and respiratory insufficiency. The structural abnormalities of the end plate lead to clinical features resembling a myopathy. In slow-channel CMS, onset is in childhood or adult life and open channel blockers, such as quinidine and fluoxetine, are helpful. In synaptic AChE deficiency, onset is at birth or infancy, slow pupillary responses may be present, and strength and functional capacity are improved markedly by ephedrine or albuterol/salbutamol, their effect increasing over months.

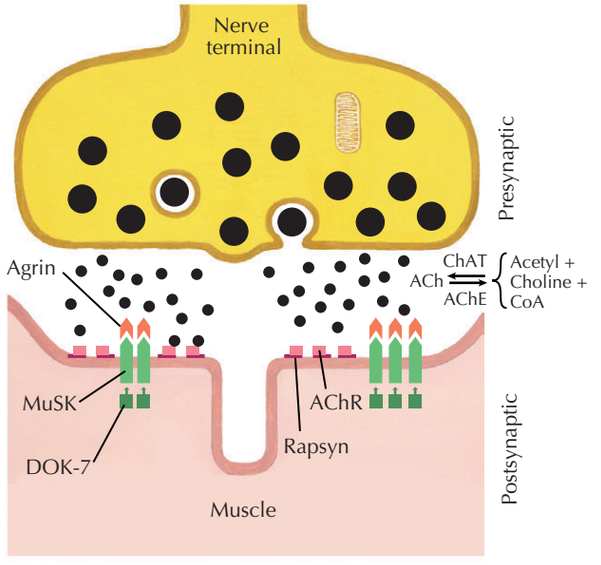
A very rare presynaptic CMS syndrome, choline acetyltransferase (ChAT) deficiency, causes episodic apnea, presenting with sudden respiratory insufficiency in infancy or childhood, particularly during the course of infections. Some patients have mild myasthenic symptoms in the interim, others become severely disabled. RNS may be normal at rest, with a decrement appearing after prolonged high-frequency stimulation or activity. Prophylactic AChEi may have a salutary effect.

The diagnosis of the CMSs is challenging, in part because patients with congenital disorders of the neuromuscular junction often have clinical features traditionally associated with congenital myopathies, such as a high arched palate, joint contractures, kyphoscoliosis, mild creatine kinase (CK) elevation, myopathic electromyography (EMG), and mild myopathic histopathologic changes. Once the clinical diagnosis is established, molecular genetic studies are important because therapeutic options will depend upon which specific mutation is identified. Although a small subset of patients with CMS experience pronounced weakness (requiring a wheelchair) and respiratory insufficiency (requiring noninvasive ventilatory support), with appropriate treatment, many individuals have a good prognosis and fare well through adolescence and adulthood.

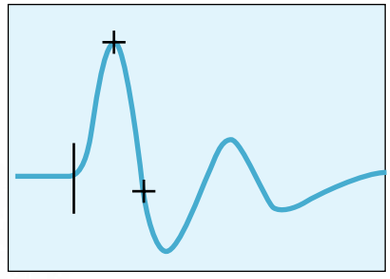


Marked bilateral ptosis and ophthalmoparesis in a patient with AChR deficiency due to mutation in the epsilon subunit of AChR

Unilateral ptosis in a patient with myasthenia gravis (MG). Note the asymmetry in MG in contrast to the symmetry in CMS.



Muscle-specific tyrosine kinase (MuSK), activated neurally by the presynaptic protein agrin (through LRP4, which is not shown in the picture) and aneurally by the postsynaptic protein DOK-7, associates with rapsyn leading to the clustering of AChRs, and the formation of the neuromuscular junction. ACh, Acetylcholine; AChE, acetylcholinesterase; ChAT, choline acetyltransferase.



Repetitive compound muscle action potentials in the motor nerves of patients with slow-channel CMS and endplate acetylcholinesterase deficiency

Slow-channel CMS with distal weakness and atrophy. Patient is unable to extend the wrist and the fingers.

Foodborne Neurotoxins

Diagnosis of a *foodborne neurotoxicity* requires consideration whenever patients suddenly present with nausea, vomiting, abdominal pain, diarrhea and fever with concomitant headache, paresthesias, and muscle weakness. Careful history is essential to a foodborne disease diagnosis, that is, which foods and what time interval occurred between ingestion and symptom onset, and whether symptoms and signs are specific. We review three foodborne neurotoxins—botulinum, ciguatera, and saxitoxin—and one infectious disease—trichinosis—causing distinctive neuromuscular disorders.

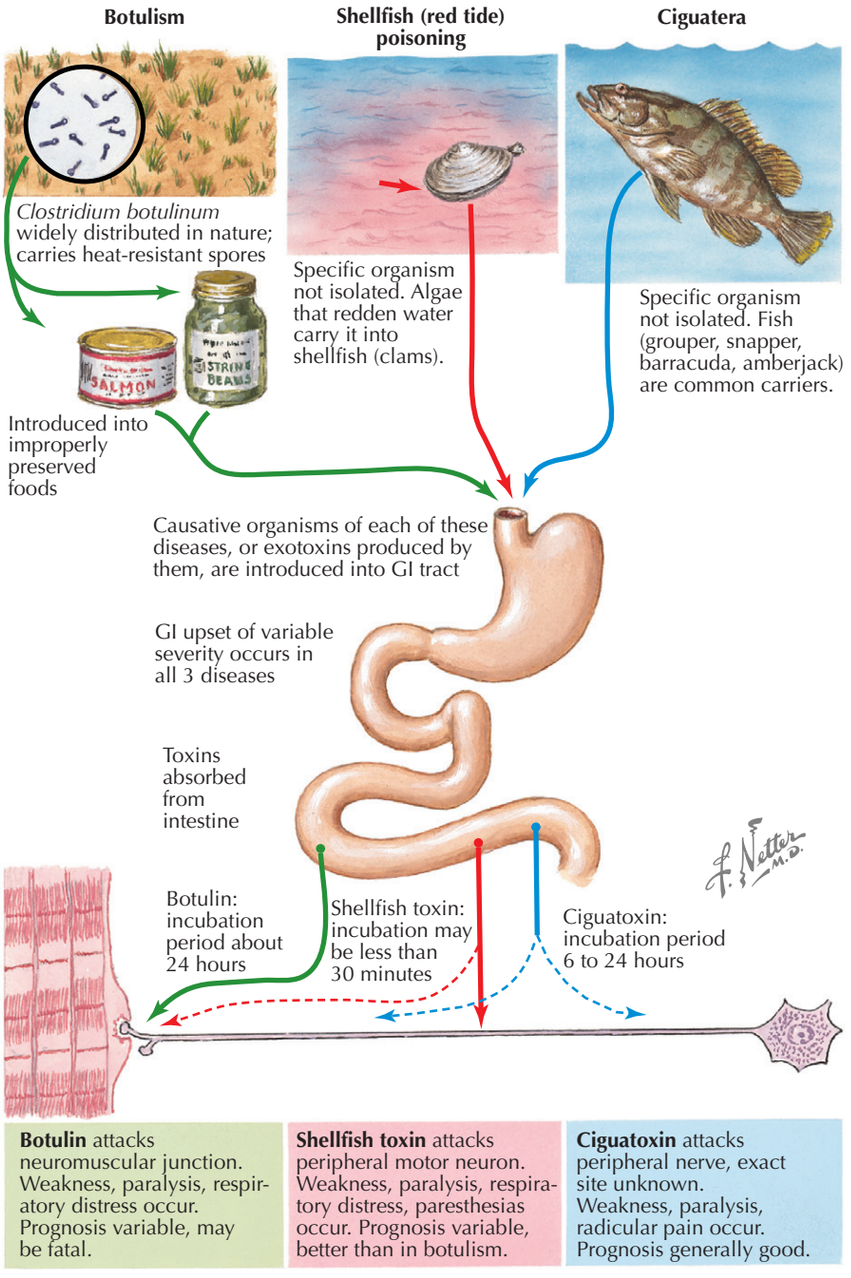
Botulism is a rare life-threatening neuroparalytic syndrome caused by an anaerobic organism, *Clostridium botulinum*, that produces an extremely potent neurotoxin. *C. botulinum* spores are heat resistant; when they germinate, these spores become toxin-producing bacilli. The spores are extremely hardy; in contrast, their toxins are denatured at greater than 80° C. The heat-resistant properties of *Clostridium botulinum* permit home-processed foods to provide a culture medium for spore growth and subsequent neurotoxin production. There are eight distinct *C. botulinum* toxin types (A, B, C1, C2, D, E, F, and G); only types A, B, and E may lead to clinical botulism. There are five acquired forms of botulism, namely foodborne, infantile, wound, adult enteric infectious, and inhalational. In the United States infantile botulism is the most common form (72%); the foodborne form comprises 25% of cases. Wound and adult infectious botulism are very uncommon (comprising 3% of cases).

Symptom onset in foodborne botulism begins 12 to 36 hours after toxin ingestion, characterized by nausea, vomiting, abdominal pain, diarrhea, and dry mouth. Neurologic manifestations develop rapidly, with pronounced cranial nerve paresis and extremity weakness. Pupils are sluggish or fixed. Ptosis, diplopia, dysphagia, dysarthria, and facial weakness develop. A descending muscle paralysis occurs; this initially affects arms, then legs, and subsequently there is diaphragmatic involvement.

Diagnosis is primarily a clinical, later confirmed by demonstration of toxin in the serum. This is a mouse bioassay performed by specialized laboratories. The toxin sometimes occurs in stool, vomitus, and contaminated food. This finding is diagnostic, with a classic clinical presentation. Electromyography/nerve conduction studies (EMG/NCS) demonstrate a classic presynaptic neuromuscular junction (NMJ) disorder with low-amplitude motor responses and postactivation facilitation.

When the clinical setting is highly suspicious, emergent antitoxin therapy is indicated. Equine serum heptavalent antitoxin, available through the Centers for Disease Control and Prevention (CDC, Atlanta), contains antibodies to botulism types (A through G). Utilizing expert respiratory/supportive care keeps mortality very low. Most patients have excellent recoveries within 3 months.

Trichinosis is an acute parasitic infection acquired by ingesting undercooked pork infested with roundworm *Trichinella spiralis* larvae. Typically, acute systemic infectious symptoms develop, that is, fever, headache, and severe muscle pain/tenderness; periorbital edema occurs early and is a good clue to diagnosis. Other manifestations include encephalitis, myocarditis, and subconjunctival hemorrhages. Leukocytosis with marked eosinophilia is present. Serum creatine kinase is elevated. Cerebrospinal fluid analysis demonstrates a lymphocyte pleocytosis and increased protein. Primary treatment is with mebendazole or albendazole; prednisone will blunt systemic responses to dying trichinella.



Ciguatera is the most common fish food poisoning in tropical coastal regions, accounting for the majority of fish-related foodborne disease outbreaks in the United States. There are several distinct *ciguatera toxins*; ciguatoxin is the best known. It is a heat-stable neurotoxin that opens voltage-dependent cell membrane sodium channels triggering depolarization. Dinoflagellates, algae-like organisms, form these toxins. These are later consumed by large reef fish, including grouper, red snapper, amberjack, and barracuda, which, when ingested by humans, leads to clinical poisoning.

Gastrointestinal symptoms develop acutely (3-6 hours) after eating contaminated fish. Neurologic symptoms may begin within 3 to 72 hours. These include paresthesias, nerve palsies, weakness, and hot/cold temperature reversal. Cardiovascular abnormalities occur within 2 to 5 days, including hypotension, bradycardia, and heart block.

There is no commercially available serum test for ciguatera toxin; diagnosis depends on clinical suspicion. Supportive care is the primary treatment modality when available; mortality is low. After an attack of ciguatoxin, patients are instructed to avoid all fish for at least 6 months because a second attack of ciguatera on the heels of the first may be much worse than the initial episode.

Shellfish poisoning relates to blooms of algae known as "red tides." There are several toxins, with saxitoxin the best known. Bivalve mollusks, including clams, mussels, scallops, oysters, crabs, and snails preferentially take up saxitoxin. In humans, saxitoxin blocks sodium ion channels, leading to rapid evolution of neurologic symptoms, ranging from mild perioral tingling to severe paralysis with respiratory failure that leads to death within hours when ventilatory support is lacking. Treatment is supportive—primarily mechanical ventilation for severely affected patients. Patients improve gradually over 12 to 72 hours.

MUSCLE AND ITS DISORDERS

Muscle Fiber Anatomy: Basic Sarcomere Subdivisions

The basic function of skeletal muscle is to move various parts of the body via muscle contraction. Muscle structure is specifically related to its function. Muscles are composed of numerous multinucleated muscle cells called muscle fibers, or myofibers. Muscle fibers insert into tendons at their ends, at what on the microscopic level is referred to as the myotendinous junction. The tendons attach to bones at the origin and insertion points for each particular muscle. Whole muscles are encased in a connective tissue covering, the epimysium. Each muscle is subdivided into smaller bundles of muscle fibers called fascicles. The perimysium is the connective tissue within the muscle that separates one fascicle from another. Within a fascicle, individual muscle fibers are separated by yet another thin layer of connective tissue, the endomysium.

Each muscle fiber is also surrounded by a basal lamina, or basement membrane. Lying under the basement membrane are specialized cells referred to as satellite cells. Satellite cells are derived from embryonic cells called myoblasts. They are likely important in muscle fiber regeneration and are thought to fuse with the muscle fiber during this process. The muscle fiber itself is surrounded by its cell membrane, the sarcolemma. It forms the membrane under which the multiple muscle fiber nuclei reside. Within the boundaries of the sarcolemma, the contractile myofibrils are contained. They are surrounded by the cytoplasm of the muscle fiber, called the sarcoplasm.

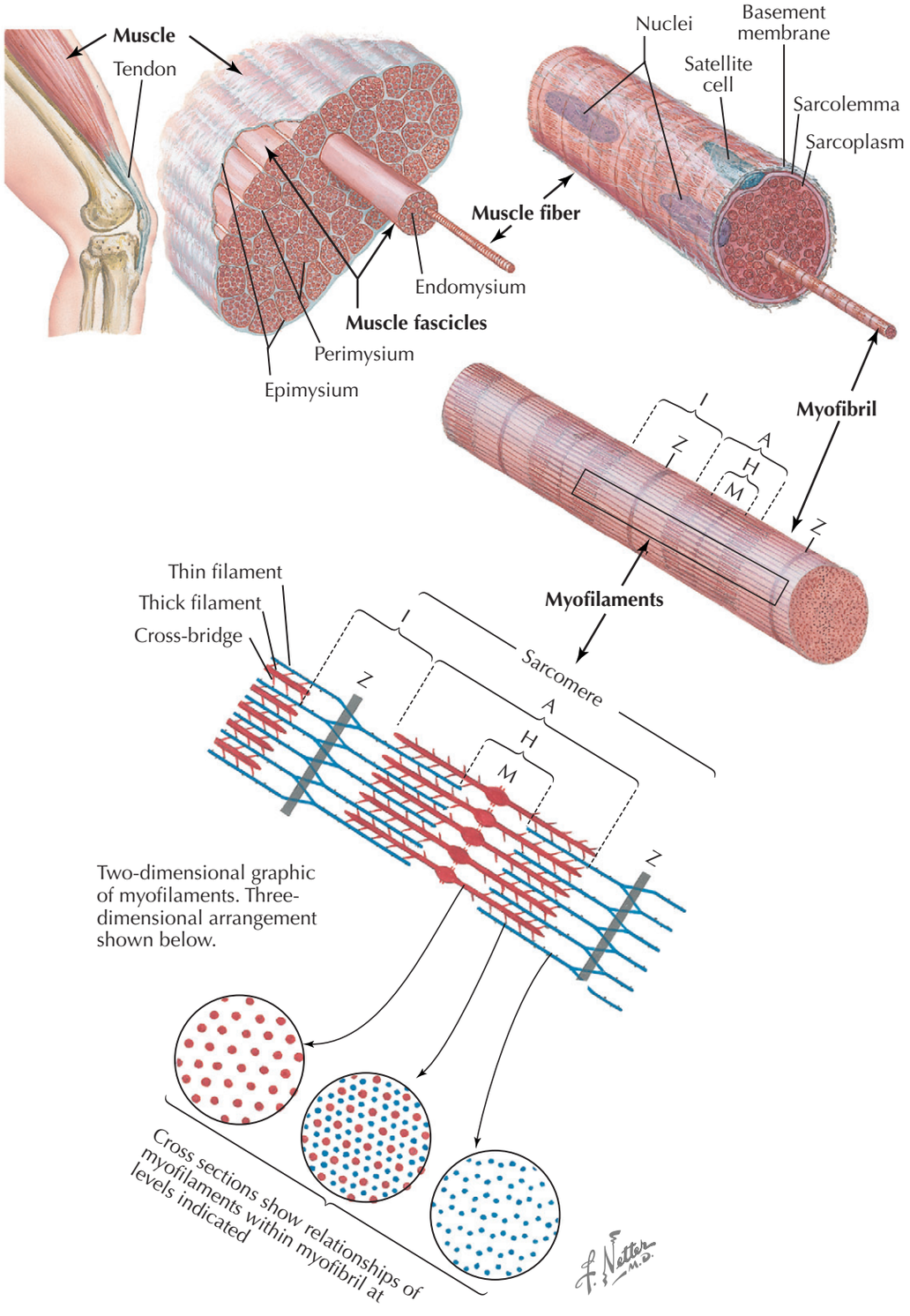
Just as a muscle contraction is dependent upon numerous muscle fiber contractions, muscle fiber contraction is dependent upon the action of the numerous muscle fiber subunits, the myofibrils that run longitudinally along the length of the muscle fiber. They are collections of thin and thick filaments—actin and myosin. The contractile unit of the muscle is the sarcomere. Each sarcomere is bound on either end by the Z disk, a proteinaceous structure that is oriented across the myofibril perpendicular to the filaments, and when the fibril is viewed longitudinally, it is apparent as the Z band. Z bands are seen with regular periodicity along the myofibril, defining the several sarcomeres lined up at their ends. The thin filaments, actin, anchor into the Z disk and do not extend along the length of the sarcomere but reside only at the ends.

In contrast, the thick filaments, myosin, are situated at the middle of the sarcomere at the area seen as the A band. A slight enlargement at the middle of the thick filaments, in the midline of the sarcomere, leads to the appearance of the M band, or M line. The thick filaments overlap the ends of the thin filaments not anchored into the Z disk. The thick filaments, however, also do not run the length of sarcomere.

Thus there are two additional areas seen within the sarcomere. On either side of the Z band, there are only thin filaments, and this region straddling the Z disk is the I band. Likewise, in the middle of the sarcomere at rest, there are only thick filaments, which appear as the H zone. Therefore, traveling from the Z disks to the midsarcomere, one sees the Z band, the I band, the A band, the H zone, and the M band.

When seen in cross section, the thick filaments are regularly dispersed throughout the myofibril. Hexagonally arranged around them are the thin filaments. Therefore each thin filament is equally near to three thick filaments. The thick filaments have outwardly oriented heads that are directed toward the thin filaments and that run along the length of the thick filaments, with the exception of the midline. At rest, the heads of the thick filaments are tilted slightly toward their nearest Z disk. During contraction, these thick filaments bind neighboring thin filaments, pulling these toward the sarcomeric midline. The alternating thick and thin filaments develop the contractile force as these thick filaments pull the thin filaments past it. Therefore, when a sarcomere contracts, the Z disks are drawn toward each other, shortening the sarcomere. When all the sarcomeres in a muscle shorten, the muscle contracts.

Organization of Skeletal Muscle

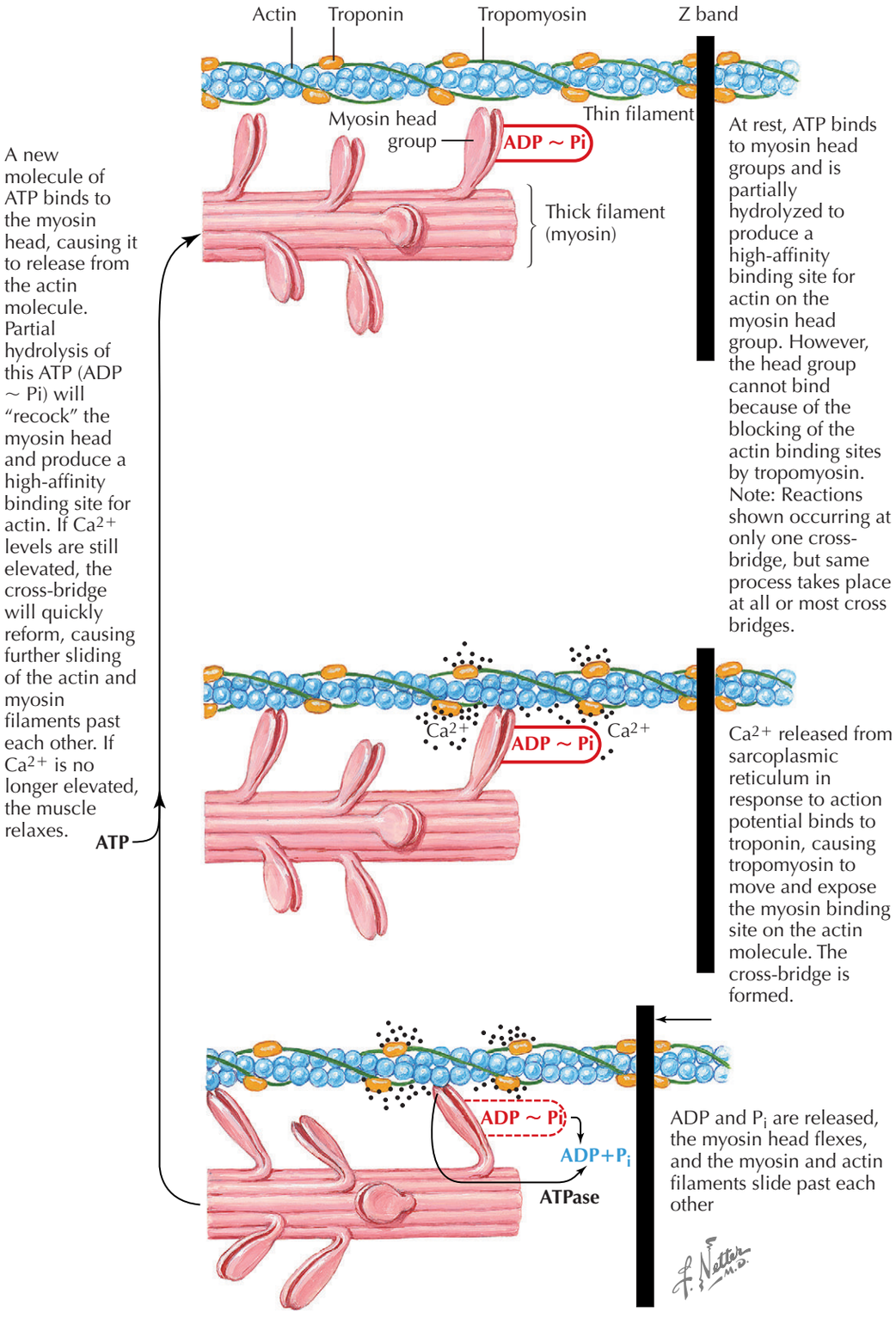


Muscle Fiber Anatomy: Biochemical Mechanics of Contraction

The *sarcomere* is the fundamental contractile element of skeletal muscle. Multiple sarcomeres align end-to-end along a muscle fiber, are defined by the *Z disk* at each end of the sarcomere, and give skeletal muscle its striated appearance. *Thin filaments* have a polymeric filamentous *actin* core and anchor to the Z disk. They are not continuous throughout the sarcomere, and only one end of each actin filament is associated with the Z disk. Multiple molecules of *globular actin* self-associate to form *filamentous actin*. Globular actin harbors a *myosin binding site* that is blocked at rest by *tropomyosin* molecules running the length of the thin filament.

Troponin molecules also run the course of the thin filament but occur as complexes bound at regular intervals. Three components comprise troponin: TnI, TnT, and TnC. *TnI* is an inhibitory molecule that *binds actin* itself and the other two troponin elements. *TnT binds tropomyosin*. *TnC binds the calcium ion (Ca^{2+})*, which then leads to a conformational change, ultimately rotating tropomyosin off and unblocking the myosin binding site on actin. Thick filaments are also a polymer but comprising numerous myosin molecules. Myosin is a hexamer of two heavy chains and two pairs of light chains. The heavy chain tails also self-associate to form the backbone of the thick filament. The heads of the heavy chains form the myosin heads, which, after self-assembly, protrude in all directions from the thick filament backbone toward the thin filaments that surround the thick filament in a hexagonal arrangement. One segment of the myosin head binds actin and hydrolyzes adenosine triphosphate (ATP), ultimately leading to a conformational change and "power stroke," thus flexing the myosin head and sliding the bound actin filament toward the middle of the sarcomere.

The cross-bridge cycle describes the steps by which myosin, actin, ATP, and Ca^{2+} interact to lead to sarcomere shortening and muscle contraction on an elemental level. At rest, ATP is bound to the myosin head and is partially hydrolyzed to adenosine diphosphate (ADP) and phosphate (P_i), the myosin head is "cocked" and available to form a high-affinity bond with actin, but the myosin binding site on actin is obstructed by tropomyosin. After depolarization of the muscle membrane and generation of a muscle fiber action potential, large amounts of Ca^{2+} are released from the sarcoplasmic reticulum. Ca^{2+} binds TnC, causing tropomyosin to "unblock" the myosin binding site on actin. The myosin head then binds actin, forming the "cross-bridge." ADP and P_i are released from the myosin head. The myosin head flexes on its backbone (the "power stroke"), pulling the bound actin toward the middle of the sarcomere. ATP again binds to the myosin head, which dissociates from actin. ATP is hydrolyzed again to ADP and P_i, the myosin head "recocks," and the actin binding site on the myosin head is again produced. If Ca^{2+} continues to be available, the sequence of events repeats, and actin is pulled further toward the middle of the sarcomere. When this happens multiple times over multiple "cross-bridges" between multiple myosin-actin molecules in multiple thick and thin filaments, the sarcomere shortens. As this occurs along several sarcomeres in the muscle fiber, the muscle fiber shortens. When multiple muscle fibers shorten within a muscle, the muscle contracts. If Ca^{2+} is no longer available, however, myosin binding sites on actin become blocked by tropomyosin, myosin cannot bind actin, and the muscle relaxes.



Muscle Membrane, T Tubules, and Sarcoplasmic Reticulum

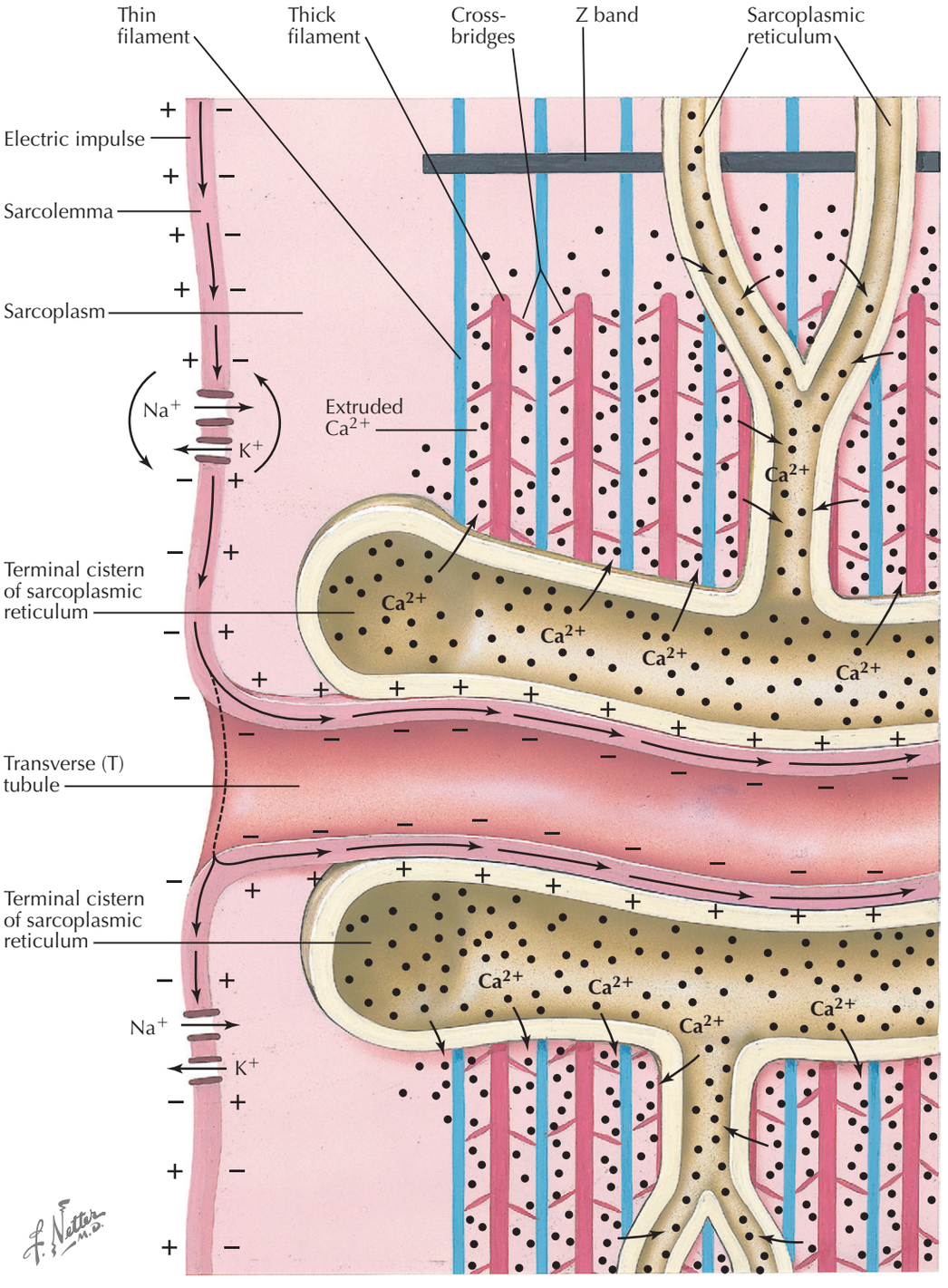
The muscle membrane system includes external (*sarcolemma*, *transverse (T) tubules*) and internal (*sarcoplasmic reticulum*) components. Although separate, the T tubules and sarcoplasmic reticulum are related in function. The membrane system is specially adapted to propagate the muscle membrane action potential and couple it to calcium ion (Ca^{2+}) release into the *sarcoplasm*, leading to excitation-contraction coupling. These components meet at *junctional triads* where a *T tubule* is flanked by two *terminal cisternae* of the sarcoplasmic reticulum. Triads recur at predictable intervals that mimic the cross striations of the sarcomeres. In mammals, the triads are situated at the junction of the A band and the I band. This periodicity and proximity to the myofibrils signifies the intricate role the triads have in control of muscle contraction. They are intimately involved in Ca^{2+} control—sequestration, release, and reuptake.

T tubules are specialized invaginations of the sarcolemma, with which it is continuous at multiple points. T tubules run transverse to the muscle fibers themselves and the sarcolemma and encircle individual muscle fibrils. T tubules form deep invaginations into the sarcolemma. This provides not only more rapid dispersal of muscle membrane depolarization along the muscle fiber, but it allows for propagation along both the surface of the sarcolemma and into the muscle fiber, where it can interact with deep sarcoplasmic reticulum. T tubules interact directly with components of the sarcoplasmic reticulum, leading to Ca^{2+} release into the sarcoplasm. They also harbor voltage-gated Ca^{2+} channels, L-type Ca^{2+} channels. These Ca^{2+} channels do not contribute to depolarization or the muscle fiber action potential but, rather, act as voltage sensors of muscle membrane depolarization. The sarcoplasmic reticulum forms a network of tubules surrounding muscle fibrils inside the sarcolemma.

Junctional sarcoplasmic reticulum (the *terminal cisternae*) stores Ca^{2+} and is the site of Ca^{2+} release in response to a muscle fiber action potential. Junctional sarcoplasmic reticulum contains high amounts of *calsequestrin*, which binds to Ca^{2+} and accounts for the high Ca^{2+} storage of the sarcoplasmic reticulum. The sarcoplasmic reticulum is so efficient in this role that the muscle fiber loses very little Ca^{2+} even after repeated muscle contractions. Junctional sarcoplasmic reticulum is also the site of the Ca^{2+} channel responsible for releasing large stores of calcium into the sarcoplasm, the *ryanodine receptor*, so named for its binding to the plant alkaloid ryanodine.

Sarcoplasmic reticulum voltage-gated Ca^{2+} channels sense the depolarization of the T tubule, interact directly with the ryanodine receptor and induce it to release Ca^{2+} from the sarcoplasmic reticulum. Free sarcoplasmic reticulum constitutes the remainder of the intrafiber sarcoplasmic reticulum membrane system. It is not associated with the T tubule system and functions in Ca^{2+} reuptake into the sarcoplasmic reticulum. It has a large number of Ca^{2+} adenosine triphosphatase (ATPase) pumps on its surface that function in the energy-dependent reuptake of sarcoplasmic Ca^{2+} and therefore plays a role in muscle relaxation rather than excitation and contraction.

A motor nerve action potential propagates down the motor nerve axon to the nerve terminal, causing release of acetylcholine (ACh) into the synaptic cleft of the neuromuscular junction. After binding of acetylcholine to the postsynaptic muscle membrane acetylcholine receptor (AChR), there is generation of an *end-plate potential*. Suprathreshold end-plate potentials generate *muscle fiber action potentials*. These propagate along the sarcolemma, depolarizing the muscle membrane sequentially as it travels along the membrane. The action potential continues down the T tubules. Depolarization of the T tubule membrane activates the voltage-gated Ca^{2+} channel, thus activating the ryanodine receptor, releasing large amounts of Ca^{2+} from the sarcoplasmic reticulum into the sarcoplasm. This leads to *cross-bridge formation* between thin and thick filaments, activation of the cross-bridge cycle, *sliding of the thick and thin filaments* past one another, *sarcomere shortening*, and eventually *muscle contraction*. Energy-dependent Ca^{2+} reuptake into the sarcoplasmic reticulum assists in relaxation and replenishes the supply of Ca^{2+} ready for release after the next depolarization.



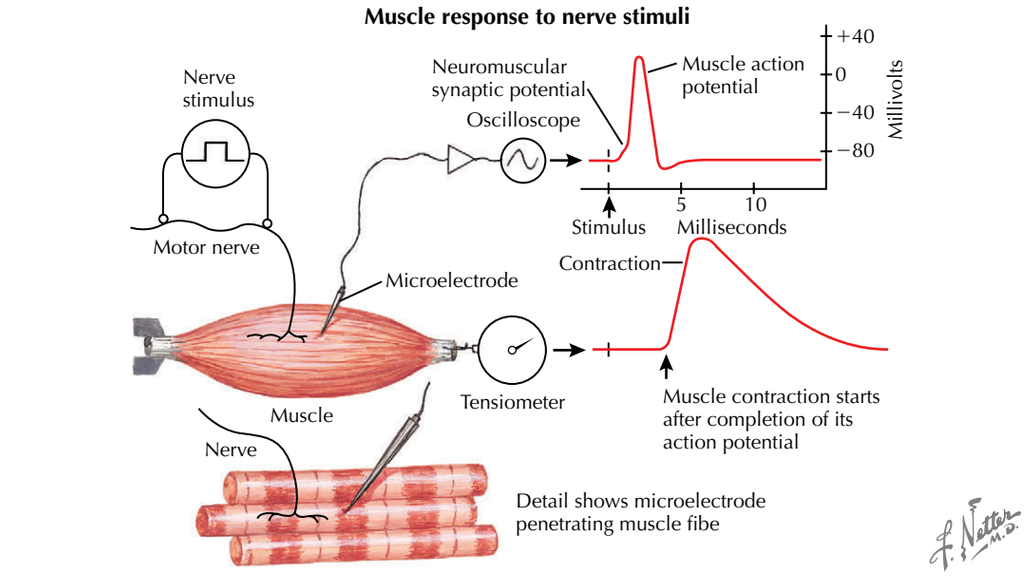
Electric impulse traveling along muscle cell membrane (sarcolemma) from motor end plate (neuromuscular junction) and then along transverse tubules affects sarcoplasmic reticulum, causing extrusion of Ca^{2+} to initiate contraction by "rowing" action of cross-bridges, sliding filaments past one another

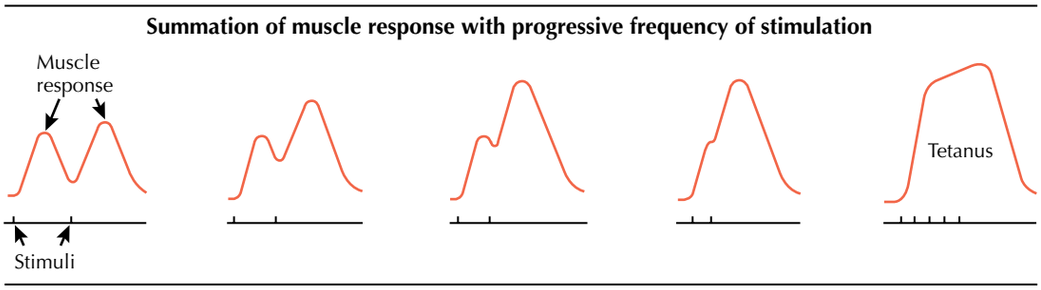
Muscle Response to Nerve Stimulation

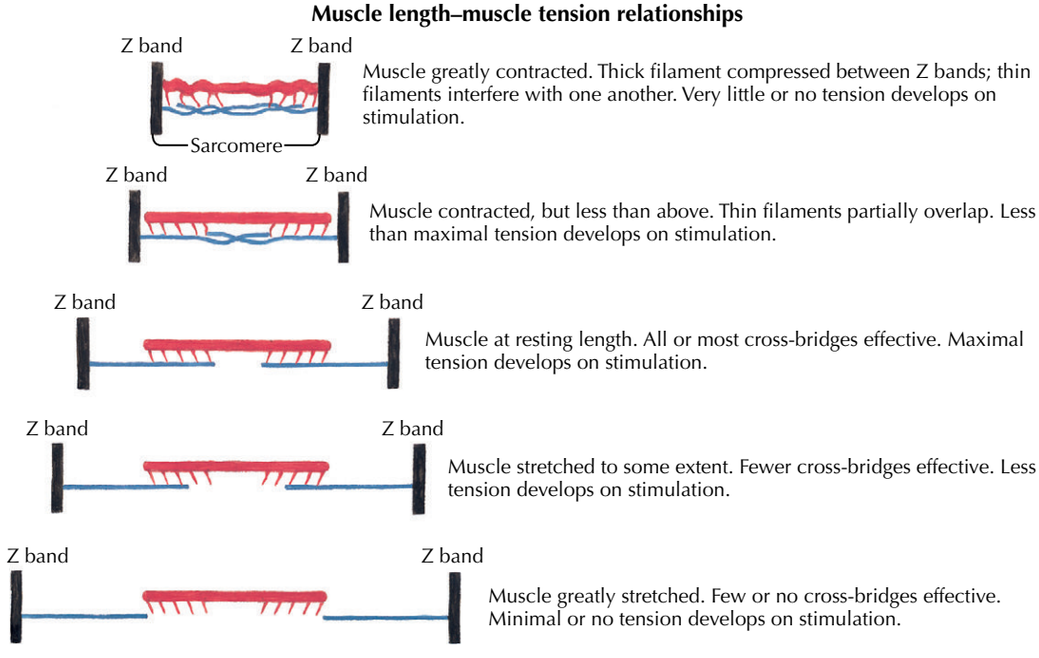
Stimulation applied to a motor nerve produces a motor nerve action potential. This propagates down the motor nerve axon to the nerve terminal. Acetylcholine is released from the nerve terminal, binds the acetylcholine receptor on the postsynaptic sarcolemma, and leads to an end-plate potential. The end-plate potential is an excitatory postsynaptic potential that, in normal conditions, reaches the threshold to generate a muscle fiber action potential that ultimately causes a muscle twitch, or contraction. These potentials are measurable by an intramuscular microelectrode that records the excitatory postsynaptic end-plate potential as a small initial deflection immediately preceding the larger muscle fiber action potential. The small delay from the initial stimulus to the initial deflection represents the time it takes to conduct the action potential down the motor nerve axon, release acetylcholine, bind acetylcholine to the postsynaptic membrane receptor, and generate the end-plate potential. In addition, the muscle fiber action potential continues along the sarcolemma, down the transverse tubules, leading to massive release of Ca^{2+} from the sarcoplasmic reticulum into the sarcoplasm, initiating the cross-bridge cycle, and eliciting a muscle twitch. This is measureable by a tensiometer during an isometric contraction (with the muscle held at a constant length so it cannot shorten). The time taken for muscle fiber action potential propagation, calcium release, and initiation of the cross-bridge cycle explains the latent period between the muscle fiber action potential and the measureable muscle contraction.

Measurement of the effects of stimulation frequency is possible under similar conditions of isometric contraction. Given that there is all-or-nothing activation and contraction of fibers within a motor unit after stimulation of a single motor neuron, single stimuli produce identical twitch responses with identical tension created. If a second stimulus is given after full relaxation of the muscle, this second twitch intensity will be the same as the first. If, however, the second stimulus is given before full relaxation (i.e., while the muscle is still at least partially contracted) the tension created by the second stimulus will surpass that created by the first. As the frequency of stimulation is increased, this phenomenon, called *summation*, is enhanced. At high enough stimulation frequencies, muscle fibers are unable to relax between stimuli, and they produce a prolonged single-peaked contraction, known as tetanus. This is one mechanism by which muscles generate varying degrees of force.

Isometric contractions also allow for the measurement of the effect of sarcomere length on the development of force generation, that is, the muscle length-tension relationship. Maximum tensile force results when the greatest number of cross-bridges forms. This occurs when the muscle is at its resting length and all or most of the cross-bridges are available (i.e., there is maximum overlap of myosin heads with actin), and stimulation will produce maximum tension. If the sarcomere is shortened, actin filaments begin to overlap or repulse each other and interfere with cross-bridge formation. As a result, there fewer cross-bridges form, resulting in less tension. Conversely, when the sarcomere is stretched, actin filaments are pulled laterally and myosin heads at the middle of the sarcomere no longer overlap with actin. Therefore fewer cross-bridges can form, also resulting in less tension. At the extreme, there is no actin-myosin overlap, and no tension develops after stimulation.







METABOLISM OF MUSCLE CELL

Muscle fiber contraction and relaxation is an energy-dependent process. The source of this energy is adenosine triphosphate (ATP). The muscle fiber requires an ongoing supply of ATP to maintain its function. Most ATP is generated in the muscle via utilization of local glycogen stores, free glucose, and free fatty acids.

CARBOHYDRATE METABOLISM

Blood glucose enters the muscle fiber through a specialized muscle-specific glucose transporter. It is then phosphorylated to glucose-6-phosphate and undergoes *glycolysis*. Glucose-6-phosphate is also derived from degradative phosphorylation of muscle glycogen stores. Phosphorylase b kinase activates *myophosphorylase* that initiates *glycogen breakdown*, and a debranching enzyme completes the process by which glucose-1-phosphate is produced. This is also converted to glucose-6-phosphate and enters glycolysis.

The *rate-limiting step* in glycolysis is the conversion of fructose-1-phosphate to fructose-1,6-diphosphate by *phosphofructokinase*. Ultimately, one molecule of glucose is broken down into two molecules of pyruvate, and three molecules of ATP are generated. Under *anaerobic conditions*, pyruvate is converted to lactate. Under *aerobic conditions*, pyruvate is instead converted to acetyl-coenzyme A (acetyl-CoA) and enters the tricarboxylic acid (TCA), or Krebs, cycle. Within the mitochondria, this cycle generates carbon dioxide and water, as well as the reduced forms of nicotinamide and flavin adenine dinucleotide (NADH and $FADH_2$, respectively) and guanosine triphosphate (GTP) (which can transfer phosphate to ADP to produce ATP). NADH and $FADH_2$ then undergo oxidative phosphorylation in the inner mitochondrial membrane, generating additional ATP molecules. Therefore *aerobic glycogen and glucose metabolism produces much more ATP* than anaerobic glycolysis.

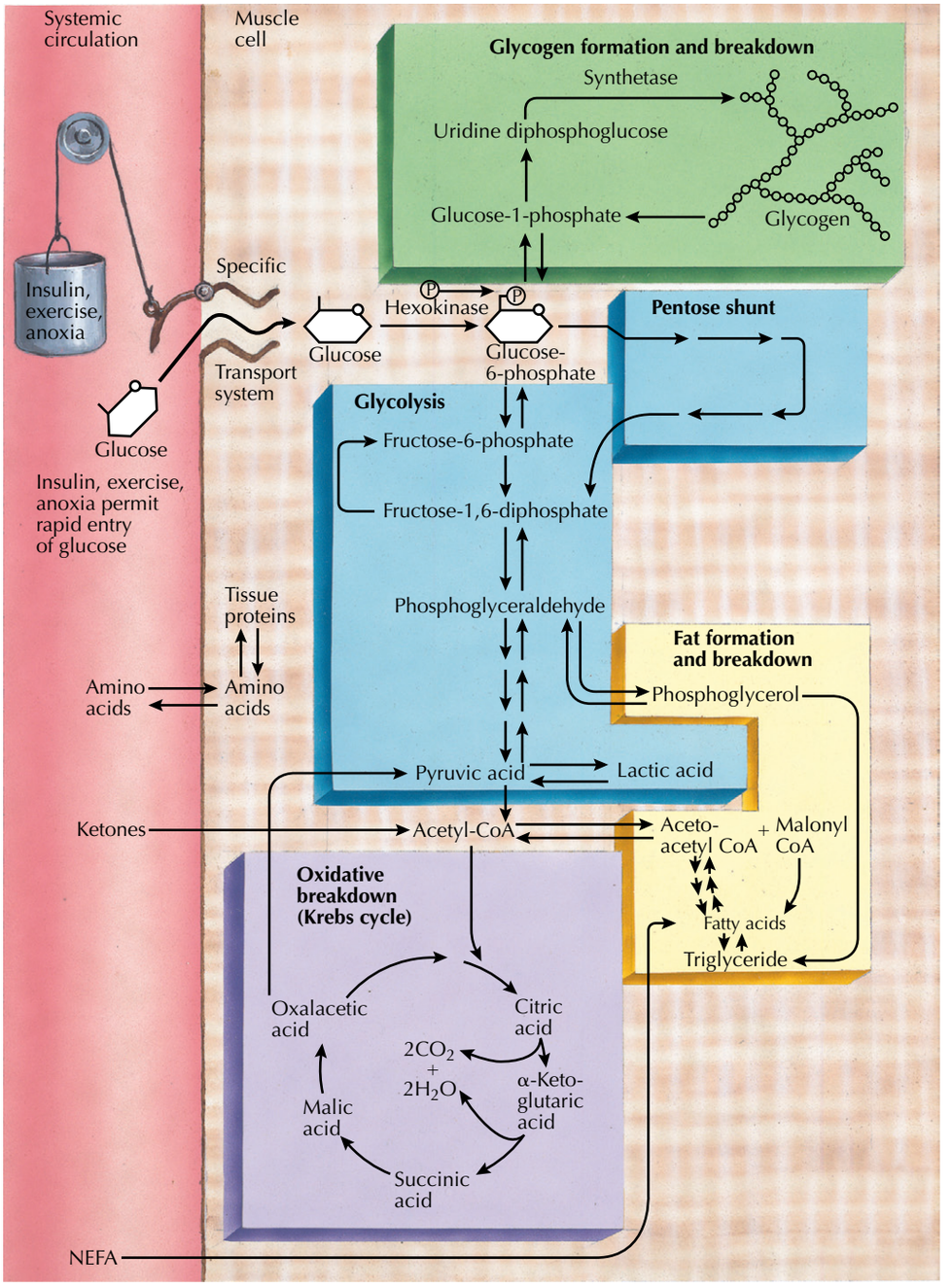
LIPID METABOLISM

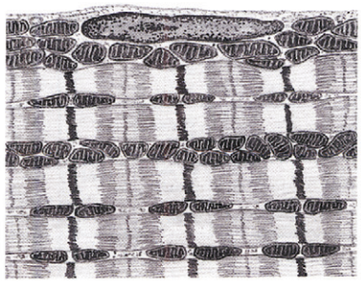
Nonesterified fatty acids (NEFAs) enter the muscle fiber from the bloodstream, derived from circulating *very-low-density lipoproteins and triglycerides* stored in adipocytes. *Free fatty acids* are first activated to their acyl-coenzyme A (acyl-CoA) thioesters. *Short- and medium-chain fatty acyl-CoAs* can cross the mitochondrial membranes, where they undergo *beta oxidation*. *Long-chain fatty acyl-CoAs* cannot undergo beta oxidation and require *esterification with carnitine* by carnitine palmitoyltransferase I (*CPT I*). The resultant palmitoylcarnitine is then transferred across the inner mitochondrial membrane and converted back into the long-chain fatty acyl-CoA by *CPT II*. The long-chain fatty acyl-CoA derivative *then can enter the beta-oxidation pathway*. Beta oxidation occurs via fatty acid chain length–specific enzymes, producing acetyl-CoA that can then enter the Krebs cycle.

Energy utilization in muscle is activity dependent; that is, the specific energy source is *dependent upon the level and intensity* of activity, type of activity, duration of activity, conditioning, and diet. *At rest, the predominant energy source is fatty acids*, particularly long-chain fatty acids. During low level, low-intensity exercise, the muscle primarily utilizes glucose and fatty acids. With *increasing intensity, glucose utilization* is increased, and muscle glycogen becomes a principle energy source. With maximal, isometric exercise, anaerobic glycolysis is the primary source. Also, during *long-duration low-level exercise, lipid metabolism* becomes the main source of energy.

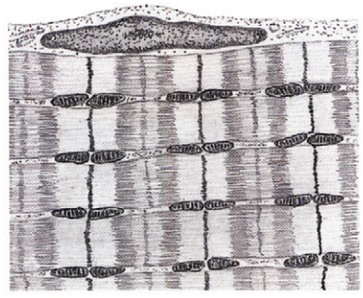
A classic example of a defect of carbohydrate metabolism is McArdle syndrome, or *myophosphorylase deficiency*. Here the deficiency in activity of myophosphorylase leads to the *inability to initiate glycogen breakdown*. This leads to *accumulation of glycogen* in the muscle. Because there is no ability to utilize glycogen as an energy source, there is a reduction in the production of pyruvate. As a result, less acetyl-CoA is available to go through the Krebs cycle, and less NADH and $FADH_2$ undergo oxidative phosphorylation. *Patients develop exercise intolerance* with myalgia, fatigability, and exertional weakness, and potentially *rhabdomyolysis*. This is more common *with isometric or sustained moderate-intensity exercise*. Patients typically experience a "*second wind*," whereby a brief rest or reduction in activity leads to improved exercise tolerance. This correlates to increased availability of blood glucose and free fatty acids.

The most common disorder of lipid metabolism is *CPT II deficiency*. CPT II deficiency causes an *inability to convert long-chain palmitoylcarnitines back into long-chain fatty acyl-CoAs* on the inner mitochondrial membrane. Therefore the long-chain fatty acyl-CoAs cannot enter the beta-oxidation pathway, and cannot produce acetyl-CoA to enter the Krebs cycle. Patients develop *exercise intolerance* and *exertional rhabdomyolysis* after *prolonged exercise*, rather than brief, intense exercise, and experience no "second-wind" phenomenon.





Type I: Dark or red fiber. Large profuse mitochondria beneath sarcolemma and in rows as well as paired in interfibrillar regions. Z lines wider than in type II.



Type II: Light or white skeletal muscle fiber in longitudinal section on electron microscopy. Small, relatively sparse mitochondria, chiefly paired in interfibrillar spaces at Z lines.

Muscle Fiber Types

Muscle fiber types differ regarding twitch speed, fatigability, and preferential use of glycolytic versus oxidative pathways for energy production. They also differ in muscle color, being white or red. Fiber typing involves differentiating between type I and type II fibers. In addition, type II fibers are further subdivided into type IIa and type IIb fibers.

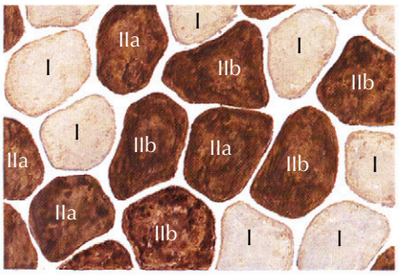
Type I fibers are adept at utilizing the *aerobic oxidative pathway* for long periods of time. As shown by electron microscopy, they contain *large numbers of mitochondria*, which confer a red color to the muscle itself. They react darkly for oxidative enzymes, such as reduced nicotinamide adenosine dinucleotide (NADH) dehydrogenase, succinate dehydrogenase, and cytochrome c oxidase. They have *low glycolytic activity*, and react weakly for the glycolytic enzyme myophosphorylase. Accordingly, type I fibers have *high lipid* but low glycogen content. The myofibrillar adenosine triphosphatase (ATPase) in type I fibers is acid stable and alkaline labile; thus they react darkly for ATPase activity after acid preincubation but do not react for ATPase activity after alkaline preincubation. These are *slow-twitch fibers*, generating low maximum tension. They are, however, *fatigue resistant* and can maintain activation for longer periods of time. Due to this quality, they are referred to as slow-twitch, fatigue-resistant fibers. They are relatively small compared with type II fibers. *Type I fibers activate before type II fibers* at low levels of muscle contraction, and their *motor unit potentials* are those that *electromyography assesses*.

Type IIa fibers are *fast-twitch* fibers with *both glycolytic and oxidative metabolic* activity. They also contain a *large number of mitochondria* and react somewhat darkly for oxidative enzymes. Unlike Type I fibers, however, they have high glycogen content and stain darkly for glycolytic enzymes. Type IIa myofibrillar ATPase is acid labile and alkaline stable; thus these fibers stain darkly for ATPase activity after alkaline preincubation but not after acid preincubation. As fast-twitch fibers, they are able to *generate an intermediate level of maximum tension quickly*, but they also fatigue slowly. They are therefore referred to as *fast-twitch, fatigue-resistant* fibers. They are larger than type I fibers and activate later as sustained contractions are required.

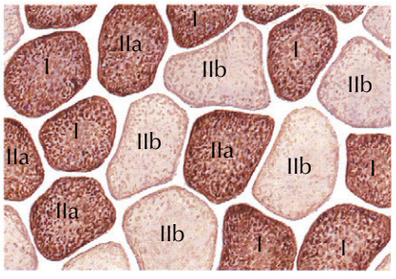
Type IIb fibers lie on the opposite end of the spectrum from type I fibers. They harbor *few mitochondria* and have a white appearance. As a result, they react faintly for oxidative enzymes. They have *high glycolytic activity*, however, and react darkly for glycolytic enzymes. They have *high glycogen* and low lipid content. Their myofibrillar ATPase is acid labile and alkaline stable, similar to type IIa fibers, but they show intermediate reactivity after preincubation at more moderate acidity levels (pH 4.6), unlike type IIa fibers, which have no reactivity under similar conditions. These are *fast-twitch fibers but fatigue easily.* They are accordingly referred to as fast-twitch, fatigable fibers. They reach high maximal force very quickly but only for short periods of time.

Muscle fiber–type predominance is reflective of certain types of activity typical for a particular muscle. Short bursts of anaerobic activity (such as sprinting) are especially suited to type IIb fast-twitch, fatigable fibers. Longer, aerobic exercise, however, is more suited to type IIa and type I fatigue-resistant fibers. There is evidence to suggest that consistent activity mimicking motor nerve activity of neurons that innervate fatigue-resistant fibers can slow contraction and increase fatigue resistance, suggesting that muscle fiber types can change in response to activity type.

Histochemical classification		
Fiber type	**ATPase stain**	**SDH stain**
1. Fast-twitch, fatigable (IIb) Stain deeply for ATPase, poorly for succinic acid dehydrogenase (SDH), a mitochondrial enzyme active in citric acid cycle. Therefore fibers rapidly release energy from ATP but poorly regenerate it, thus becoming fatigued.		
2. Fast-twitch, fatigue-resistant (IIa) Stain deeply for both ATPase and SDH. Therefore fibers rapidly release energy from ATP and also rapidly regenerate ATP in citric acid cycle, thus resisting fatigue.		
3. Slow-twitch, fatigue-resistant (I) Stain poorly for ATPase but deeply for SDH. Therefore fibers only slowly release energy from ATP but regenerate ATP rapidly, thus resisting fatigue.		



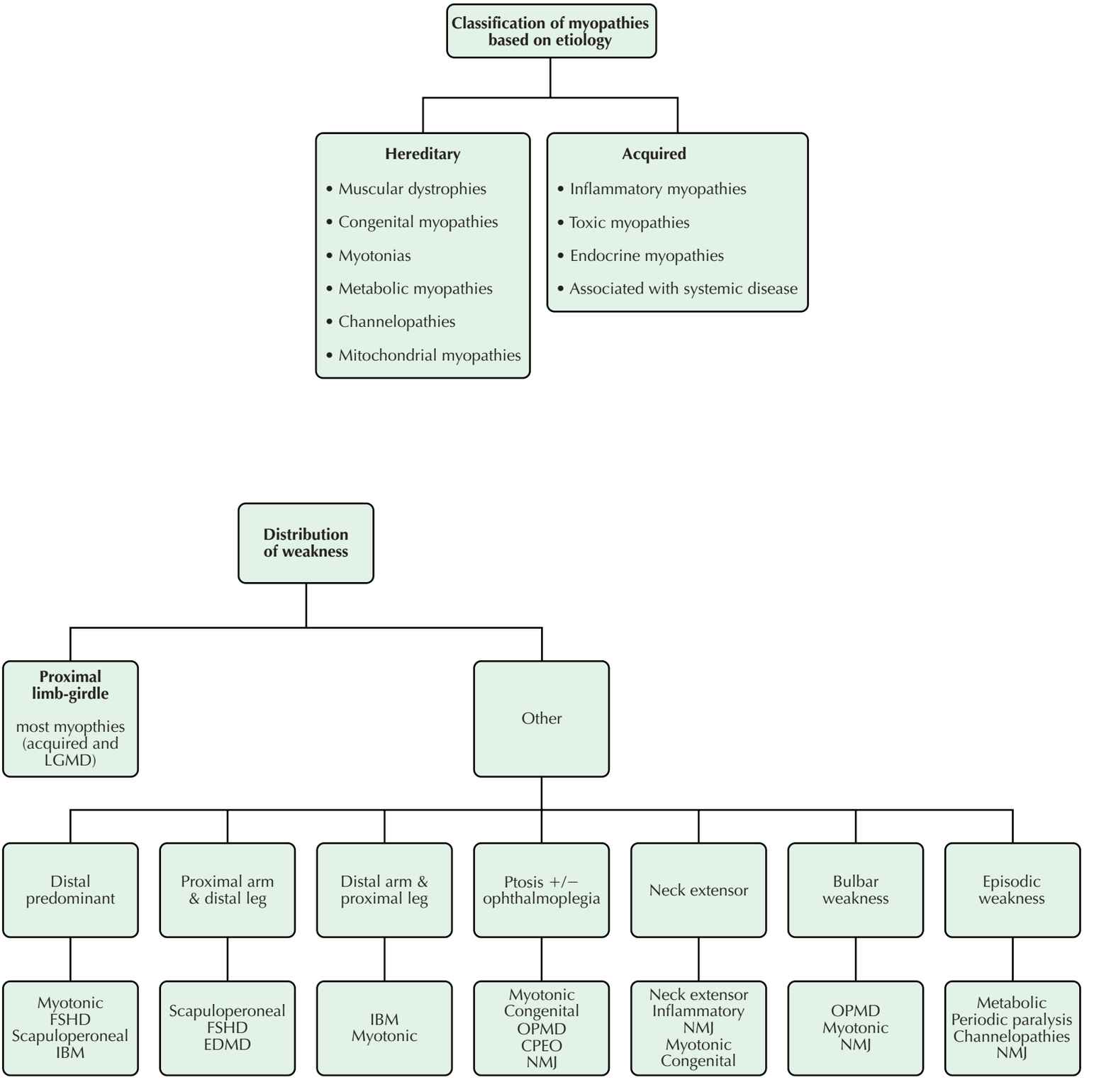
Cross section of skeletal muscle fibers stained for ATPase



Identical section stained for SDH

Sprinter
Training induces a greater proportion of type IIb fibers relative to type IIa

Marathon runner
Type IIa fiber is increased relative to type IIb



Overview of Myopathies: Clinical Approach

In approaching a patient with weakness, the first task of the clinician is "lesion localization": to determine by comprehensive clinical evaluation which one of the four organs of the motor unit—motor neuron, peripheral nerve, neuromuscular junction (NMJ), and muscle—is the site of the "lesion." Once localized to the muscle, a thorough history often helps clinicians determine whether the disorder of muscle (the myopathy) is inherited or acquired. By characterizing the distribution of muscle weakness, the physical examination may then provide additional diagnostic clues that help to identify correctly specific muscle disorders. Finally, the results of laboratory studies help to confirm and refine the diagnosis.

The history provides clinical clues. In most myopathies, weakness is proximal, affecting movements of the hips, thighs, shoulders, and upper arms. Typically, these patients have difficulty climbing stairs, arising from low chairs, and carrying out tasks above their head, such as

Overview of Myopathies: Clinical Approach *(Continued)*

placing a book on a high shelf or brushing their hair. Less commonly, weakness is distal (affecting movements of the feet/toes and hands/fingers), manifested by tripping over uneven terrain because of footdrop or difficulty opening jars. Much less commonly, weakness affects the cranial muscles so that patients report ocular symptoms (lid drooping, or ptosis), difficulty swallowing (dysphagia), effortful speech (dysarthria), and sometimes inability to keep the neck straight up, leading to a head-drop.

Associated "negative" symptoms of muscle disease include fatigue, exercise intolerance, and muscle atrophy. "Positive" symptoms often point in the direction of a specific myopathy. For example, myalgias tend to be associated with a toxic or infectious myopathy, with certain forms of inflammatory myopathy (associated with connective tissue disease) and with some myotonic myopathies. Cramps suggest metabolic or endocrine myopathies; stiffness or impaired relaxation of muscle points to the possibility of myotonia, as seen in the myotonic disorders; episodic tea-colored urine or myoglobinuria is strongly suggestive of a metabolic myopathy; and complaints of muscle enlargement, deemed muscle hypertrophy by the clinician, is often associated with muscular dystrophy, notably the dystrophinopathies.

Determining onset, duration, and evolution of muscle disease enhances the effectiveness of the diagnostic process. For example, weakness presenting at birth suggests some forms of congenital myopathy and infantile myotonic dystrophy; weakness emerging in childhood is typical of most types of muscular dystrophy, congenital myopathy, metabolic and mitochondrial myopathy, and rarely, inflammatory myopathy; and later-onset weakness, coming on in adulthood, is often seen in inflammatory, toxic and endocrine myopathies, and less commonly, is a first manifestation of muscular dystrophy and metabolic and mitochondrial myopathies.

In the vast majority of myopathies, weakness, once established, is fairly stable or constant over the course of a 24-hour period and is relatively uninfluenced by physiologic state (for example, active or resting, or fasting or postprandial). There are certain muscle diseases, however, such as the periodic paralyses and the metabolic myopathies, that are characterized by episodic weakness of varying intervals and intensity, and with or without concomitant metabolic derangements such as myoglobinuria. Disorders of neuromuscular transmission, particularly myasthenia gravis, have a diurnal variation that is worse in the evening.

The rate of the progression of weakness over time offers a clue to the character of the myopathy. Acute to subacute progression (that is, weakness evolving over weeks to several months) is typically seen in inflammatory myopathies (polymyositis/dermatomyositis). Chronic progression (with weakness developing over many months to years) is typical of most muscular dystrophies and the inclusion body myositis (IBM) form of inflammatory myopathy. Nonprogressive or mildly progressive weakness over the course of decades is characteristic of most forms of congenital myopathy, which explains why, in some rare instances of mild congenital myopathy, diagnosis is not established until adulthood.

Obtaining a detailed family history in any patient with a suspected myopathy is crucial to unlocking an underlying inherited disorder and identifying its pattern of inheritance. Patients are asked to reflect on certain details of their relatives' medical history, such as overall strength, functional capacity, ability to walk and run, whether there was a need for assistive devices or orthoses to walk, need for a wheelchair or scooter, history of cardiac disease, whether the patient's (i.e., proband's) symptoms were shared by males and females or were gender specific. Armed with such information, the clinician may have a heightened index of suspicion for an inherited muscle disease. This places the physician in the position to hypothesize the pattern of inheritance (autosomal dominant, autosomal recessive, X-linked, or mitochondrial) and thereby improve the ability to provide genetic counseling.

Clues to the diagnostic process are often found in exploring the patient's medication list, exercise experience, dietary preferences, and motor function in a cool or cold environment. For example, subacute myopathies in adulthood may have a toxic etiology, caused by a cholesterol-lowering agent (statin), colchicine use for gout, or chronic alcohol use. Corticosteroids prescribed for a wide spectrum of medical disorders may be responsible for a subacute or chronic myopathy. In susceptible individuals with a *glycolytic* pathway defect, *short bursts of intense activity* sometimes lead to muscle cramping, weakness, and myoglobinuria. In contrast, patients having *lipid oxidation* disorders generally require *longer periods of low-intensity exercise* to predispose to muscle weakness and myoglobinuria. In individuals with a genetic predisposition to periodic paralysis, a high-carbohydrate meal is sometimes the trigger for an attack of severe muscle weakness. Muscle stiffness worsening with cold exposure is typical of paramyotonia congenita.

The physical examination provides additional important clues that help in the diagnostic process. Some myopathies affect t*issues other than skeletal muscle* per se, because they are multisystem disorders, such as myotonic dystrophy. In this instance, extramuscular involvement may be truly multiorgan and multisystem, including cataracts, arrhythmia, cognitive impairment, and glucose intolerance. In others, concomitant *cardiac muscle* skeletal muscle involvement occurs as in the dystrophinopathies, Emery-Dreifuss muscular dystrophy (EDMD), and polymyositis/dermatomyositis, and there may be a serious concomitant cardiomyopathy, with a clinical course punctuated by arrhythmia and congestive heart failure. Although the *diaphragm* is a striated muscle, it is infrequently involved in muscle disease, with notable exceptions, including myotonic dystrophy type I, centronuclear myopathy, nemaline myopathy, and acid maltase deficiency.

Muscle thinning, or *hypertrophy*, especially enlarged calves, are important clinical signs that often suggest a dystrophinopathy or congenital myopathy. *Dysmorphic features* may be associated with congenital myopathies; nemaline myopathy is a good example, especially exhibiting an elongated facies, high-arched palate, and foreshortened toes. *Skin* changes, especially a rash over the face and hands, are typical of dermatomyositis. *Musculoskeletal contractures* indicate long-standing, usually inherited myopathies: Emery-Dreifuss muscular dystrophy and Bethlem myopathy. Myopathies presenting within the context of pronounced *multiorgan involvement* suggest sarcoidosis, amyloidosis, endocrinopathies, connective tissue, infectious disorders, and mitochondrial cytopathies.

Distribution of muscle weakness provides a clue to the diagnostic process. In most myopathic disorders, the proximal and limb-girdle muscles bear the brunt of involvement; but there are important exceptions. *Distal muscle* involvement is quite characteristic of classic *myotonic dystrophy type I* and *dysferlinopathy*. *Ocular* weakness is often an early manifestation of mitochondrial myopathy and *oculopharyngeal* muscular dystrophy (OPMD).

Laboratory tests often provide diagnostic confirmation in the clinical context of a patient with suspected myopathy. These tests include *serum creatine kinase (CK)* levels, which are elevated in myopathic disorders marked by muscle fiber necrosis and normal in muscle disorders with little injury to the muscle fiber membrane. Electrodiagnostic studies will show early recruitment of short-duration, low-amplitude motor unit potentials in weak muscles, irrespective of the cause of the myopathy. However, fibrillation potentials and positive sharp waves primarily occur in aggressive myopathies, including inflammatory, toxic, or dystrophic types. These potentials are less commonly seen in most congenital and endocrine myopathies.

Muscle biopsy analysis by light microscopy usually provides information that helps corroborate the classification into inherited and acquired myopathy and often provides further diagnostic specificity (for example, acquired myopathy that is inflammatory with features of dermatomyositis). *Immunohistochemical analysis* of frozen muscle tissue sections identifies specific muscle proteins when muscular dystrophy is suspected. In cases where muscular dystrophy is suspected but cannot be confirmed by immunohistochemical studies, *molecular genetic testing by deoxyribonucleic acid (DNA) analysis* of *leukocytes* can sometimes confirm the diagnosis of a muscular dystrophy by identifying a specific known mutation. In selected cases, when metabolic myopathy is suspected, *biochemical analysis* of frozen muscle tissue for analysis of the *glycolytic*, *oxidative*, *or mitochondrial metabolic pathways* can be performed.

Dystrophinopathies

Muscular dystrophies are inherited primary diseases of muscle. Progressive muscle weakness and muscle fiber degeneration are the primary clinical and pathologic characteristics, respectively. A number of distinctive pathologic, clinical, and genetic features provide the means to further classify this diverse group of diseases.

Duchenne muscular dystrophy (DMD) is the most common form of muscular dystrophy (incidence is 1 in 3917 live male births [Norway] to 1 in 4700 [Nova Scotia]). Becker muscular dystrophy (BMD) has a relatively milder clinical course (incidence from about 1 in 18,000 to 1 in 31,000 male births). Both DMD and BMD are inherited as X-linked recessive traits and present similarly. A third allelic type of muscular dystrophy, of intermediate severity, is recognized in patients known as "outliers." All three types result from dystrophin deficiency caused by mutations of the *DMD* gene.

Other dystrophinopathies occur at significantly lower incidences. These include carrier females who manifest DMD/BMD, DMD-associated dilated cardiomyopathy (DCM), and muscle cramps with myoglobinuria.

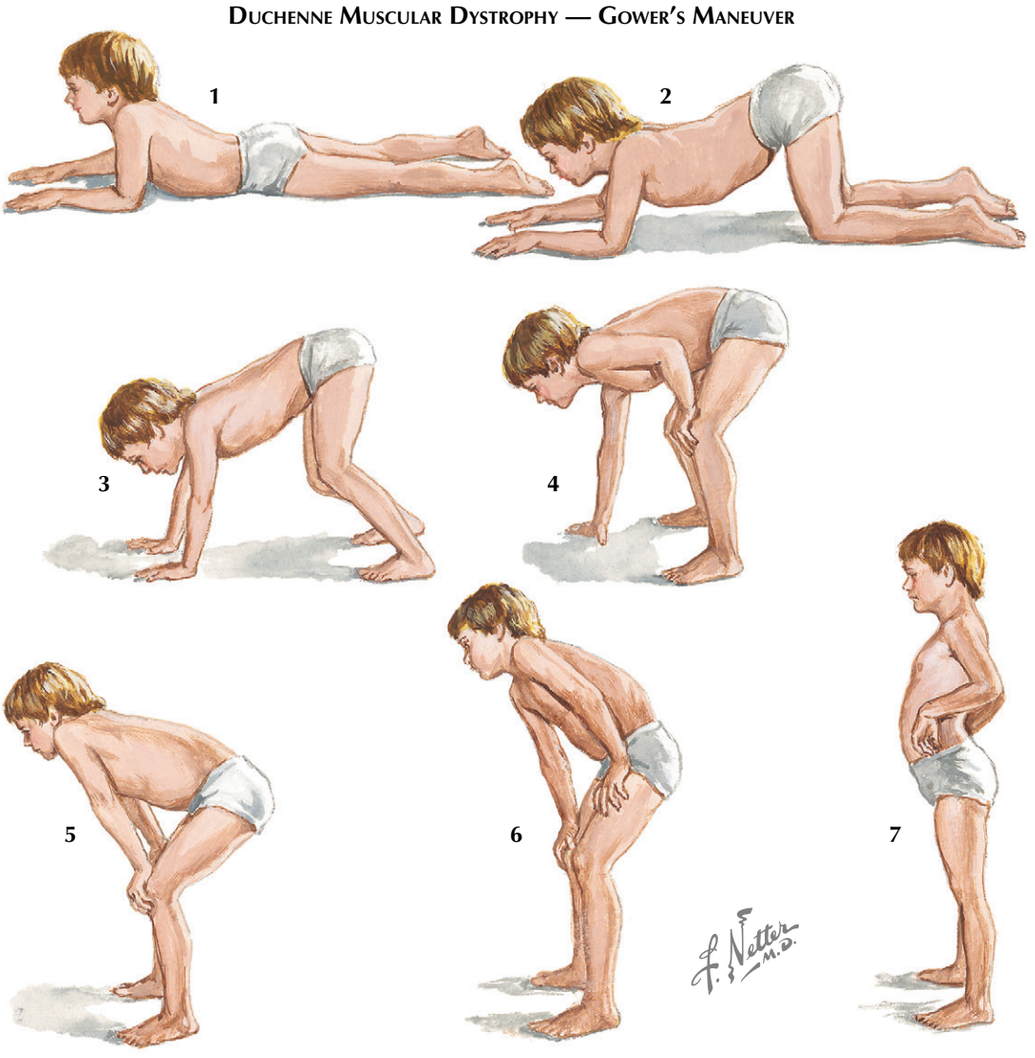
Clinical Aspects

The clinical features and course of the various dystrophinopathies vary across a wide spectrum. DMD, BMD, and the "outliers" (intermediate phenotype) have the most severe skeletal muscle involvement, and DCM has the most severe heart muscle involvement. DMD/BMD carrier females may be asymptomatic or manifest mild-to-severe symptoms. The age of wheelchair confinement distinguishes DMD and BMD clinically and is less than 13 years in DMD, more than 16 years in BMD, and between 13 and 16 years in outliers.

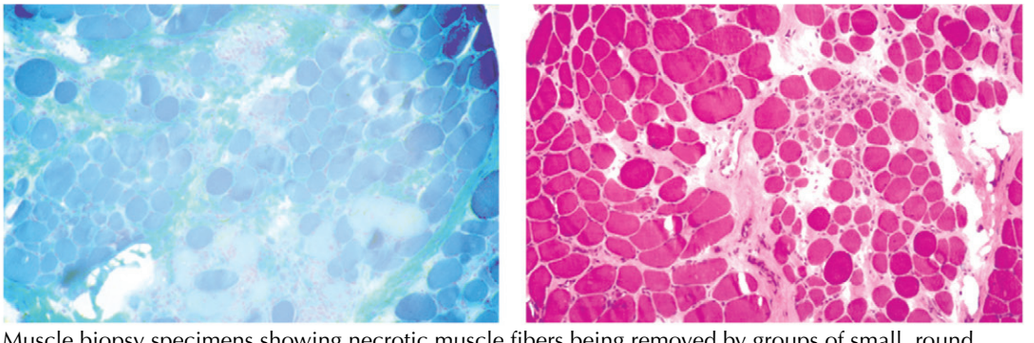
Duchenne Muscular Dystrophy

The onset of weakness in children with DMD usually occurs between 2 and 3 years of age and nearly always before age 5 years. Clinical signs include difficulty with running, jumping, going up steps, and other similar activities; an unusual waddling gait; lumbar lordosis; and calf enlargement. Symmetric muscular weakness affects proximal before distal limb muscles and the lower before upper extremities. Affected boys may complain of leg pains and display Gower's sign (using hand support to push themselves from the floor to an upright position). Neck flexor weakness distinguishes boys with DMD from those with milder presentations. Cardiac muscle is also affected. Cognitive function may rarely be average or above average but is usually impaired to a varying degree. Physical examination shows pseudohypertrophy of the calf muscles; possible pseudohypertrophy of quadriceps, gluteal, deltoid, and other muscles; lumbar lordosis; waddling gait; shortening of the Achilles tendons, leading to toe walking; and hyporeflexia or areflexia.

Although transient clinical improvement may be seen between 3 and 6 years of age, because normal maturation initially exceeds the early dystrophic process, relentless deterioration gradually follows, leading to wheelchair confinement. Contractures, scoliosis, and deterioration of pulmonary function follow wheelchair confinement. Cardiomyopathy affects about one third of patients by age 14 years, one half by age 18 years, and all patients after age 18 years. Intestinal hypomotility, also known as intestinal pseudo-obstruction, can be a life-threatening complication in patients with DMD. Cause of death is usually respiratory insufficiency or cardiac failure; most patients with DMD die in their late teens or twenties. Assisted ventilation can prolong



Characteristically, the child arises from prone position by pushing himself up with hands successively on floor, knees, and thighs, because of weakness in gluteal and spine muscles. He stands in lordic posture.



Muscle biopsy specimens showing necrotic muscle fibers being removed by groups of small, round phagocytic cells (*left,* trichrome stain) and replaced by fibrous and fatty tissue (*right,* H & E stain)

DYSTROPHINOPATHIES *(Continued)*

a patient's life expectancy but does not improve the patient's ability to perform activities of daily living.

BECKER MUSCULAR DYSTROPHY

Symptoms of BMD usually appear between ages 5 and 15 years but, on occasion, do not appear until the third or fourth decade or later. The degree of clinical involvement is milder, and cardiac disease and cognitive impairment are not as severe. Gastrointestinal symptoms, contractures, and scoliosis are not as likely to develop in BMD. Neck flexor muscle strength is relatively preserved. Patients with BMD typically remain ambulatory into adult life; they usually survive beyond the age of 30 years. Death occurs from respiratory failure or cardiomyopathy/cor pulmonale between 30 and 60 years of age.

MANIFESTING DMD/BMD CARRIER FEMALES

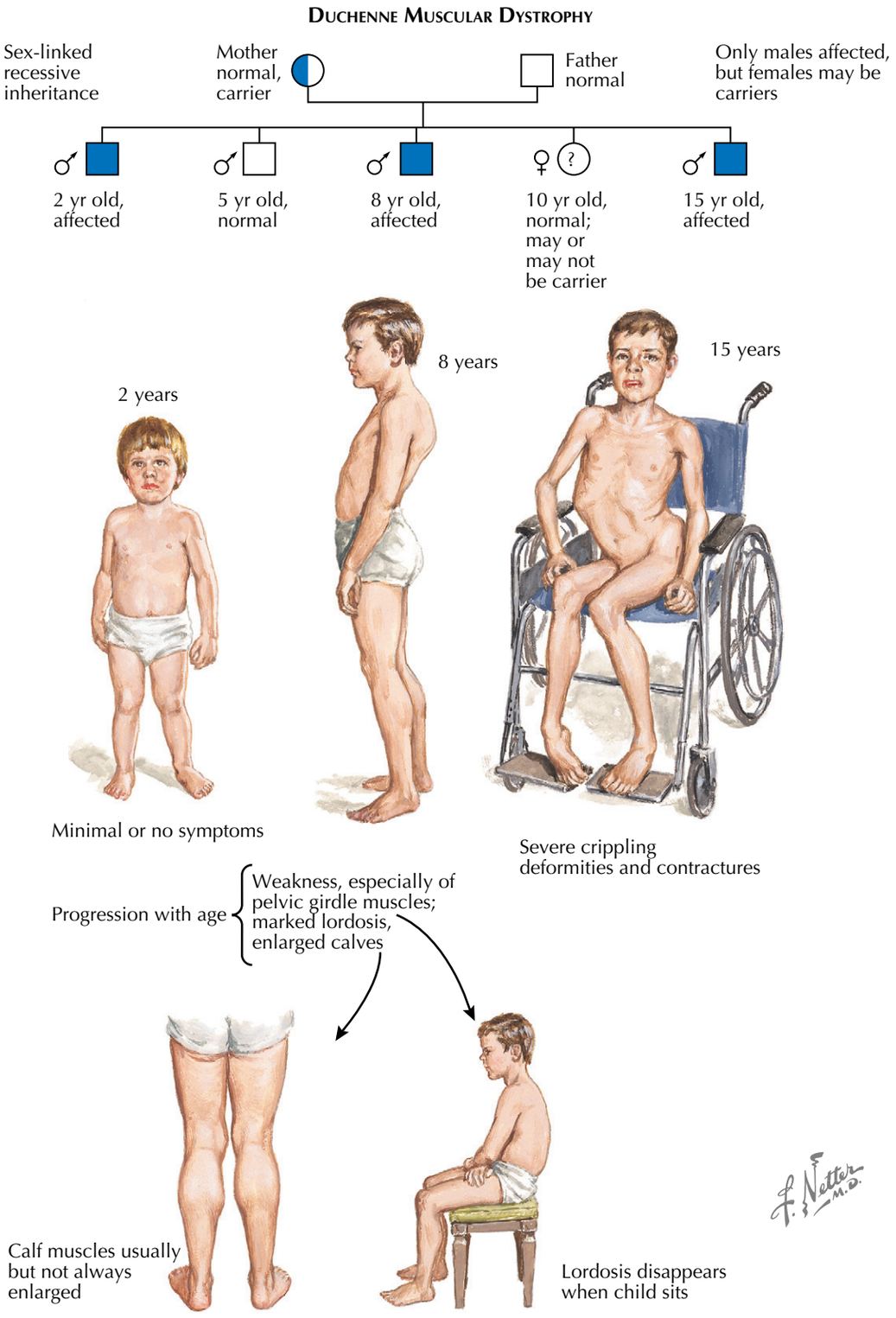
The vast majority of DMD/BMD carriers, 76% and 81%, respectively, are usually free of symptoms. Mild calf hypertrophy may be seen. However, approximately 8% to 19% of carriers present with mild-to-moderate and, occasionally, severe muscle weakness of the limb-girdle type or even with DMD/BMD.

GENETICS

DMD Gene. The *DMD* gene is the largest gene yet identified in humans, spanning approximately 2.3 megabases on the short arm of the X chromosome at Xp21. The protein product dystrophin is identified on Western blots of human skeletal muscle proteins using anti-dystrophin antibodies. The dystrophin-associated protein (DAP) complex also contains many other proteins that are tightly associated. The DAP complex appears to be stabilized and protected from degradation by dystrophin in normal cells; the complex becomes unstable when dystrophin is absent. The muscle tissue of patients with DMD usually shows secondary reduction in the amount of other proteins of the DAP complex.

DMD Gene Mutations. Most *DMD* gene mutations identified so far are *deletions* (about 5%-20%). Patients without detectable deletions or duplications are identified as having small insertions/deletions, point mutations, or splicing errors.

No apparent correlation has yet been found between the size of *DMD* gene deletions and the severity and progression of the DMD/BMD phenotype. In most patients, the molecular differentiation of Duchenne versus Becker muscular dystrophy appears related to the disruption or preservation of the amino acid reading frame by deletion or duplication mutations. The latter either disrupt (DMD) or preserve (BMD) the reading frame in most cases (in-frame, out-of-frame hypothesis).



Dystrophin. In greater than 99% of DMD patients, skeletal muscle biopsy specimens display complete or almost complete absence of dystrophin (0-5% of normal). The intermediate phenotype (mild DMD or severe BMD) appears to develop in patients with dystrophin levels between 5% to 20% of normal, regardless of protein size. Patients with mild-to-moderate BMD usually have dystrophin levels greater than 20% of either normal or abnormal molecular weight. In contrast, patients with neuromuscular diseases other than DMD/BMD have normal dystrophin concentrations.

DIAGNOSIS

Creatine kinase (CK) values varying between 1,000 to 50,000 IU/L are not unusual in DMD/BMD. If serum CK concentration is less than that, the diagnosis should

DYSTROPHINOPATHIES *(Continued)*

be questioned. From birth through 3 years, serum CK concentration in a child with DMD is always more than 10 times the upper limit of normal (ULN), and in a child with BMD is usually more than 5 times the ULN. However, CK values do not differentiate reliably between the two types of dystrophy. Serum CK may be mildly increased in manifest carriers.

Muscle biopsy features include

- Degeneration and regeneration.
- Isolated "opaque" hypertrophic fibers.
- Significant replacement of muscle by fat and connective tissue.
- Complete or almost complete absence of staining with anti-dystrophin antibodies in DMD.
- Normal or reduced ± patchy staining of the sarcolemma in BMD. In patients with other neuromuscular diseases, there is homogeneous staining of the plasma membrane.

TREATMENT

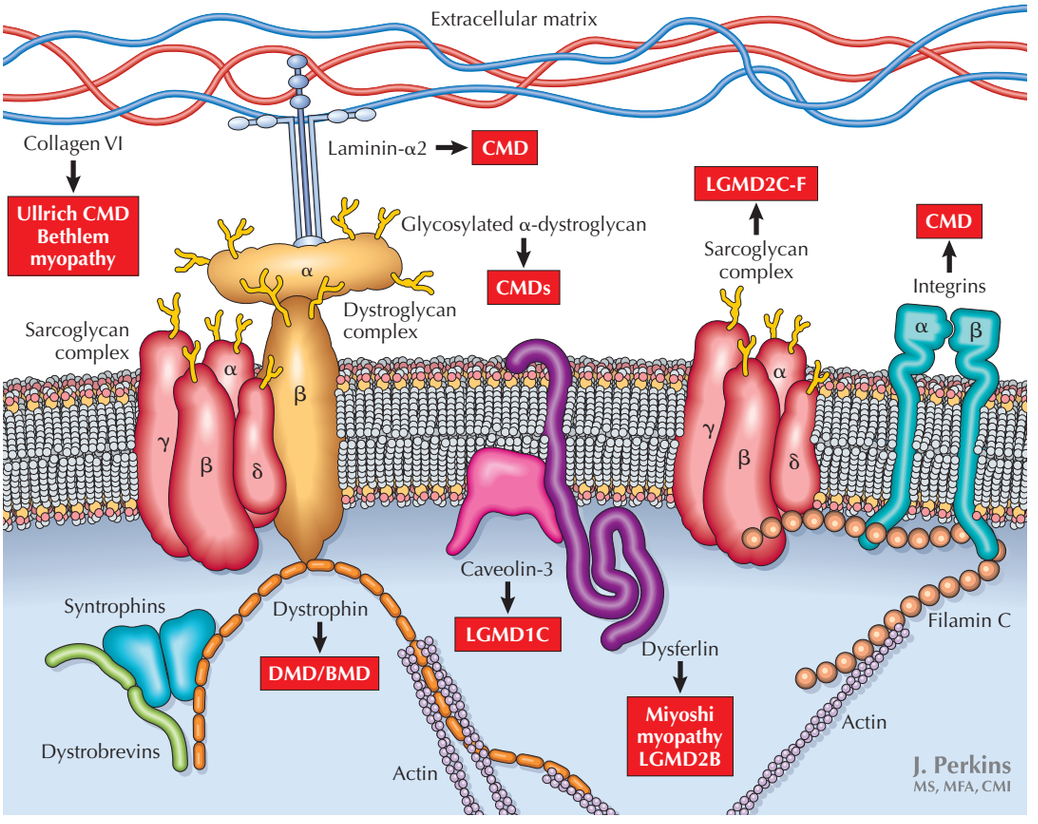
Goals of therapy in DMD/BMD are to maintain function, prevent contractures, and provide psychologic support. Physical therapy utilizes passive stretching exercises to prevent contractures of the iliotibial band, the Achilles tendons, and flexors of the hip; contractures may be addressed through orthopedic surgery and bracing. Standing and/or walking, which seem to prevent scoliosis, can be maintained by using long-leg braces. A cardiac evaluation is recommended upon diagnosis or by the age of 6 years. Annual pulmonary function studies, electrocardiography, and echocardiography should be performed after the age of 10 years. Symptomatic nocturnal hypoventilation may be treated with overnight mouth intermittent positive pressure. Respiratory assistance may be advisable during periods of respiratory infection.

Medications for Duchenne Muscular Dystrophy. Clinical studies demonstrate that prednisone improves the strength and function of patients with DMD. Deflazacort, a synthetic derivative of prednisolone, has been suggested to have fewer side effects than prednisone, particularly regarding weight gain. Deflazacort is used in Europe and Canada but is unavailable in the United States.

Practice parameters for the use of corticosteroid therapy have been published by the American Academy of Neurology and the Child Neurology Society. Some of the following recommendations are in accordance with those parameters.

- Boys with DMD, who are older than 5 years, may be treated with prednisone (0.75 mg/kg/day). Patient and family need to be made aware of potential benefits and risks of corticosteroid therapy before initiating therapy.
- Assess the potential benefits of corticosteroid therapy.
- Continue optimal maintenance dose of prednisone (0.75 mg/kg/day) if side effects are not severe. Improvement may remain significant but less robust with gradual tapering (as low as 0.4 mg/kg/day).
- Deflazacort (0.9 mg/kg/day) may be used to treat DMD with careful monitoring of side effects (weight gain, asymptomatic cataracts).

Therapies under Investigation. Experimental gene therapies as well as ribosomal read-through and exon skipping are currently under investigation. Stem cell therapy is under investigation but remains experimental. Myoblast transfer has been inefficient.



Molecular Genetic Testing Used in the Dystrophinopathies

Test Method	Mutations Detected	Males with DMD	Males with BMD
Targeted mutation analysis (multiplex PCR, MLPA, Southern blotting)	Deletion of one or more exons of DMD gene	~50-65%	~65-70%
Targeted mutation analysis (quantitative PCR, MLPA, Southern blotting)	Duplication of one or more exons of DMD gene	~5-10%	~10-20%
Mutation scanning and/or sequence analysis	Small insertions/deletions/point mutations/splicing mutations of DMD gene	~25-35%	~10-20%

BMD, Becker muscular dystrophy; CMD, congenital muscular dystrophy; DMD, Duchenne muscular dystrophy; LGMD, limb-girdle muscular dystrophy; MLPA, multiplex ligation probe amplification; PCR: polymerase chain reaction. (From Darras BT, Miller DT, Urion DK, Dystrophinopathies. In: Pagon RA, Bird TD, Dolan CR, et al, editors: *GeneReviews at GeneTests: Medical Genetics Information Resource* (online database,). Seattle: University of Washington; 1997-2011. Available at http://www.genetests.org. (updated November 23, 2011).

Myotonic Dystrophy and Other Myotonic Disorders

Myotonic dystrophy (DM) is a clinically and genetically heterogeneous disorder characterized by myotonia, namely the phenomenon of slowed relaxation after a normal muscle contraction. There are two major forms: DM1 and a phenotypically different, milder version designated DM2. The prevalence of DM is 1 in 8000 in the general population, but the relative proportions of myotonic dystrophy caused by DM1 and DM2 are unknown. These autosomal dominant conditions are among the most common forms of adult-onset muscular dystrophy.

Both DM1 and DM2 are characterized by skeletal muscle weakness and myotonia with additional multisystem involvement. DM1 commonly presents in adolescence and early adult life, as well as a severe congenital form. DM2 typically begins in adulthood. In contrast to DM1, there is no congenital form of DM2. These two genetically determined myotonic disorders occur in relation to expanded repeats in the noncoding regions of *DMPK* (DM1) and *ZNF9* (DM2) genes.

The onset of *DM1* is insidious; patients initially notice distal weakness of the feet and hands, along with myotonia, described by patients as muscle "stiffness," manifested by difficulty in relaxing muscles after strong contractions. Weakness slowly progresses, ultimately involving most muscle groups in a symmetric fashion. The phenotypic appearance of a long face with hanging jaw and hollowing of the temples develops as a result of wasting and weakness of the facial and neck muscles, as well as early-onset cataracts, is very characteristic of DM1. In contrast to many disorders of muscle, having a stereotyped proximal distribution, DM1 weakness typically has a pronounced distal predominance. These patients also have an accompanying cranial musculature weakness as characterized by ptosis, dysarthria, nasal-quality voice, and dysphagia. Muscle stretch reflexes are usually reduced or absent. Myotonia is the almost universal clinical finding; it is aggravated by cold exposure. Asking the patient to grip examiner's fingers elicits a classic slow relaxation of the fingers. In addition, the examiner can also elicit myotonia by striking the thenar eminence with a reflex hammer and observing a brisk abduction contraction of the thumb abductor pollicis brevis, followed by a slow relaxation of same with return of the thumb to neutral posture.

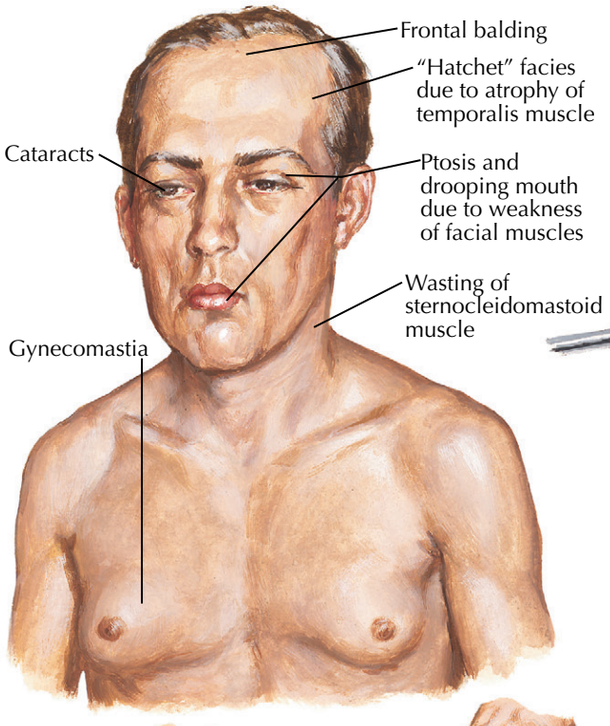
DM2, also known as *proximal myotonic myopathy* (PROMM), presents with hip-girdle weakness (difficulty arising from a squat, getting out of a chair, and climbing stairs), and in contrast to DM1, facial and distal weakness is uncommon. In DM2, pain and stiffness are major complaints, leading patients to their physician in hopes of finding a form of medical therapy. However, this form of myotonia is usually mild.

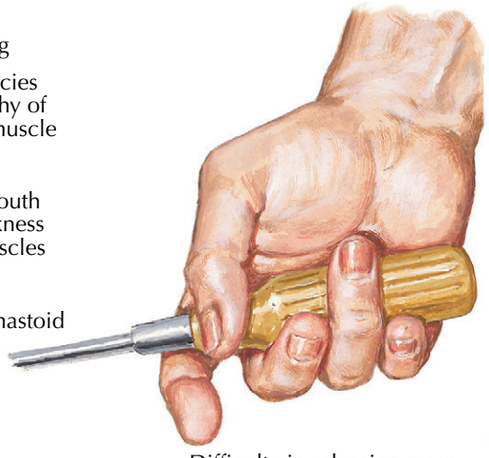
DM1 is further characterized by the concomitant presence of very significant systemic disorders; in contrast, these are typically absent or mild in DM2. *Cardiac conduction disturbances* are seen in one half to two thirds of patients with DM1 and are less common in DM2; atrial fibrillation and flutter are the most common arrhythmias. *Cataracts* occur in more than 90% of patients with DM1 and DM2; the cataracts are indistinguishable in the two disorders. *Changes in cognition and behavior* are frequently observed in patients with DM1 but not DM2. *Endocrinologic dysfunction* is also a prominent issue in DM1 men. They have decreased sperm formation and low testosterone levels; in contrast, menstrual irregularities and infertility occur in women. Early frontal and temporal balding and glucose intolerance and hyperinsulinemia are also common in DM1 and less so in DM2. *Respiratory involvement* may be seen in DM1, sometimes precipitated by general anesthesia, and excessive daytime somnolence is prevalent. There is an increased risk for *malignant hyperthermia* in DM1 so that careful planning and precautions must be taken when a general anesthetic is required.

Laboratory findings typically demonstrate no to a slight elevation in serum CK in DM1 and a mild hyperCKemia in DM2. The characteristic *electromyography (EMG)* finding in both DM1 and DM2 is electrical myotonia, typically consisting of repetitive discharges of muscle fiber action potentials at 20 to 80 Hz, which wax and wane in amplitude and frequency, producing a sound often reminiscent of a dive bomber or a motorcycle engine. Muscle biopsy in DM1 and DM2 is notable for a marked increase of internalized nuclei (arrayed in chains in longitudinal section) and severely atrophic muscle fibers with pyknotic nuclear clumps. Deoxyribonucleic acid (DNA) testing may be particularly useful in DM2, especially when EMG myotonia is not very prominent.

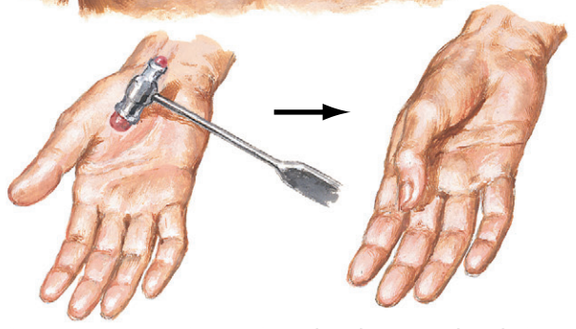
Congenital DM1 is characterized by profound hypotonia, facial diplegia, poor feeding, arthrogryposis (especially of the legs), and respiratory failure. Affected infants have a characteristic "V" shape of the upper lip that results from facial diplegia. With intensive support, most infants survive the neonatal period. In early childhood, there is often a gradual improvement of motor

Myotonic Dystrophy

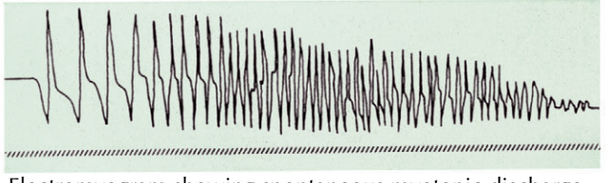




Difficulty in releasing grasp

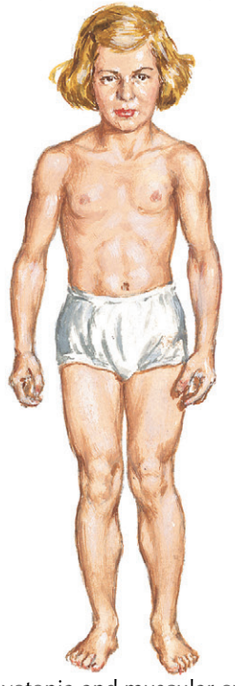


Percussion myotonic reaction: Thumb moves sharply into opposition and adduction on percussion of thenar muscles and returns to initial position slowly



Electromyogram showing spontaneous myotonic discharge evoked by needle insertion

Myotonia Congenita
(Thomsen disease)



Myotonia and muscular overdevelopment. Disease affects both males and females.

Myotonic Dystrophy and Other Myotonic Disorders
(Continued)

function, but some degree of hypotonia and facial weakness persists; at age 3 to 5 years, foot deformities, learning, and behavioral abnormalities present as the main clinical problems. Mental retardation is a predominant feature of the congenital and childhood forms of DM1. As patients with congenital DM1 age, they develop many of the symptoms and signs of classic, adult-onset DM1.

DM1 results from an expansion of a cytosine-thymine-guanine (CTG) trinucleotide repeat in the 3′-untranslated region (UTR) of the dystrophica myotonica protein kinase gene (*DMPK* gene) on chromosome 19q13.3. Wild-type individuals have 5 to 35 CTG repeats at this locus, whereas individuals with DM1 have repeats in the hundreds to thousands. Classic DM1 patients have repeats in the range of 100 to 1000. When the CTG repeats are very elevated to the range of 500 to 2700, DM1 may manifest at birth. Inheritance of congenital DM1 is overwhelmingly maternal. The length of the abnormal myotonic dystrophy repeat correlates directly with disease severity and inversely with age of onset. The phenomenon of an earlier age of onset of a more severe clinical phenotype through successive generations is the phenomenon of *anticipation*.

DM2 is caused by an expanded cytosine-cytosine-thymine-guanine (CCTG) tetranucleotide repeat expansion located in intron1 of the zinc-finger protein 9 gene (*ZNF9* gene) on chromosome 3q21.3. On normal alleles, there are 11 to 26 tetranucleotide repeats; on pathogenic alleles, the number of repeats ranges from 75 to more than 11,000, with a mean of 5000 repeats.

In contrast to DM1, there is no correlation in DM2 between CCTG repeat size and age of onset of weakness or disease severity.

In both DM1 and DM2, the respective disparate gene is transcribed into ribonucleic acid (RNA) but is not translated. The mutant RNAs accumulate in the nucleus and alter RNA binding protein activity, which, in turn, results in abnormal function of several genes, including the skeletal muscle chloride channel, the insulin receptor, and cardiac troponin T.

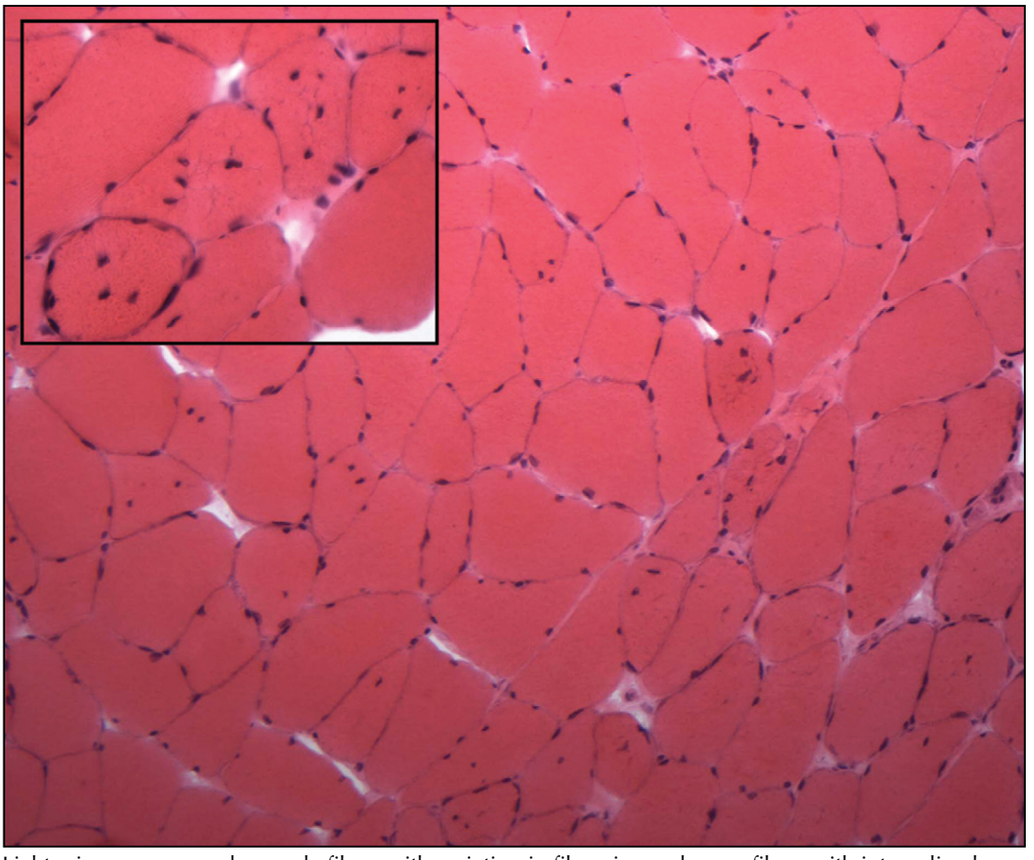
Management of DM is best carried out in a multidisciplinary neuromuscular clinic. Cardiac follow-up with yearly electrocardiograms (ECGs) is highly recommended because there is a significant risk of sudden death from cardiac dysrhythmias. A trial of medication (mexiletine) may be warranted to ease problematic clinical myotonia. Physical therapy and use of orthoses for the distal leg weakness leading to partial footdrop may be indicated and very helpful to optimize motor function.

Three other conditions are characterized by clinical myotonia; these include the *sodium channelopathies* (*hyperkalemic periodic paralysis*) causing myotonia without weakness until the fifth decade; *paramyotonia congenita*, where myotonia worsens paradoxically with activity (especially in cold environments); and the *chloride channelopathy*, *myotonia congenita*.

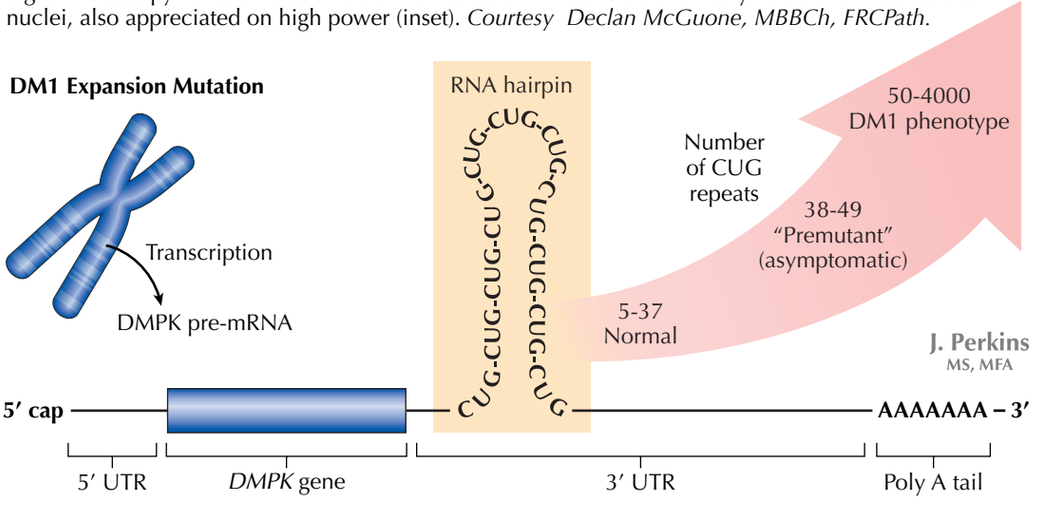
Myotonia congenita (MC) typically becomes symptomatic in infancy or early childhood. The incidence is 2 per l00, 000. The most common form is *autosomal dominant* (Thomsen disease), characterized by generalized painless myotonia and a complete absence of the extramuscular systemic features characteristic of DM1 and DM2. Affected infants may develop lid myotonia with crying and do not immediately reopen their eyes. With the exception of slowness initiating movement, that is, a tendency to fall when first standing or suddenly trying to run, these patients demonstrate relatively little functional impairment. They also complain of stiffness relieved by exercise. Their muscles need to be "warmed up": muscles stiff from myotonia are unable to exert normal power but after use are essentially normal in strength. Clinically, the muscles are enlarged to a pseudoherculean appearance, often leading athletic coaches to encourage participation in school sports, something their dysfunctional muscles cannot support.

The less common *autosomal recessive form* (Becker type) also typically has significant muscle hypertrophy. It may be associated with slowly progressive weakness and greater functional impairment than the more common Thomsen variant. Both have a similar mutation in the muscle chloride channel gene *(CLCN1)* on chromosome 7q25.

Schwartz-Jampel syndrome is not a channelopathy and, strictly speaking, is not a myotonic disorder, but it enters into the differential diagnosis of stiffness in a child. It is a rare autosomal recessive condition that consists of blepharophimosis, low-set ears, and micrognathia. Affected children are of normal intelligence, short stature with multiple joint contractures, and scoliosis. There is continuous muscle stiffness, and percussion and grip myotonia are severe. The electromyograph (EMG) reveals complex repetitive discharges and not myotonia per se.



Light microscopy reveals muscle fibers with variation in fiber size and many fibers with internalized nuclei, also appreciated on high power (inset). *Courtesy Declan McGuone, MBBCh, FRCPath.*



Other Types of Muscular Dystrophy

Classification of Muscular Dystrophies			
Disease	**Inheritance**	**Pattern of weakness**	**Affected protein**
X-linked dystrophies			
Duchenne/Becker	XR	Proximal limb girdle	Dystrophin
Emery-Dreifuss	XR	Proximal arm, distal leg	Emerin
Scapuloperoneal	XR	Proximal arm (scapular winging), distal leg	Four-and-a-half LIM domain protein (FHL1)
Limb-girdle dystrophies			
LGMD1 A-G	AD	Proximal limb girdle	Myotilin, lamin A/C, caveolin-3
LGMD2 A-N	AR	Proximal limb girdle	Calpain 3, dysferlin, sarcoglycans, Fukutin
Other dystrophies			
Facioscapulohumeral	AD	Facial weakness, scapular winging	Unknown
Oculopharyngeal	AD	Ptosis, ophthalmoplegia, pharyngeal weakness	Poly A binding protein 2 (PABP2)
Scapuloperoneal	AD	Scapular and distal leg	Desmin
Myotonic dystrophy 1	AD	Ptosis, distal limbs, myotonia	Dystrophica myotonica protein kinase (DMPK)
Myotonic dystrophy 2	AD	Proximal limbs	Zinc-finger protein 9 (ZNF9)

AD, Autosomal dominant; LGMD, limb-girdle muscular dystrophy; XR, X-linked recessive.

Facioscapulohumeral dystrophy (FSHD) is inherited as an autosomal dominant disorder with symptoms of weakness generally appearing before the age of 20 years. Weakness and atrophy affect the muscles of facial expression, the periscapular muscles (producing prominent scapular winging), the biceps, and triceps; the forearm usually remains relatively well preserved. There is early and marked bilateral footdrop. There is modest creatine kinase (CK) elevation in 50% of patients; the electromyograph (EMG) is myopathic, and the muscle biopsy may show prominent inflammatory cells.

FSHD is inherited in an autosomal dominant (AD) fashion with nearly complete penetrance and variable expressivity, with mild and severe cases seen in the same family. It is due to a deletion in the number of D4Z4 repeats in the subtelomeric region of chromosome 4q35. There is a correlation between disease severity and the size of deletion.

Treatment is aimed at encouraging activity and facilitating use of weakened limbs. Wrist splints and light foot braces are often helpful.

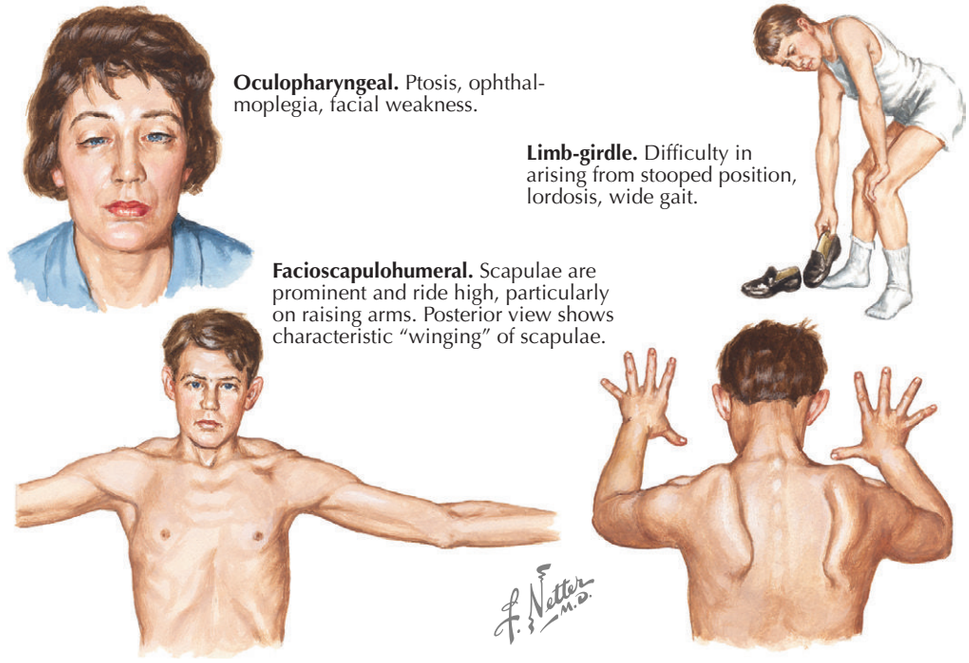
Oculopharyngeal muscular dystrophy (OPMD) is inherited as an autosomal dominant condition with onset in the fifth or sixth decades of life. OPMD is found in North American families of French-Canadian extraction but also observed in Spanish-American and in the Bukhara-Jewish population. The major clinical features are ptosis and dysphagia, which slowly progress over many years. Ptosis progresses to severe narrowing of the palpebral fissures. Over time, weakness involves the lid, extraocular, facial, neck, and proximal limb muscles in a symmetric fashion. The serum CK is normal or slightly elevated. The EMG discloses myopathic features.

OPMD is inherited in an autosomal dominant fashion, and the mutation is an 8- to 13-nucleotide expansion of a (guanine-cytosine-guanine [GCG]) 6-nucleotide repeat encoding for a polyadenylate (poly A) binding protein (PABP2), which, when expanded, is thought to cause toxicity to muscle cells by accumulating as intranuclear inclusions. Genetic testing is available to confirm the diagnosis. Dysphagia may be so severe that patients are in danger of aspiration pneumonia, dehydration, and malnutrition, and therefore a gastrostomy may be necessary.

Limb-girdle muscular dystrophy (LGMD) is inherited as either an autosomal recessive (AR) or dominant disorder and is in a category of muscular dystrophies that are distinct from the more common X-linked Duchenne and Becker dystrophies. The onset of weakness ranges from the first to the fourth decade, and the clinical course is one of slowly progressive muscle weakness and wasting with variable disability. The distribution of weakness usually spares the face and involves proximal and limb-girdle muscle groups predominantly. In most patients, the heart and respiratory muscles are spared, but exceptions occur depending upon the specific genetic subtype. The serum CK is invariably raised, the EMG reveals fibrillations and myopathic potentials, and the muscle biopsy discloses necrosis and regeneration.

Currently, 14 autosomal recessive and 7 autosomal dominant types have been identified. In most of the dominant forms, designated LGMD1, patients have been described in single, large, extended pedigrees and are considered rare. The recessive types, designated LGMD2, are more common, but prevalence is not easily ascertained. The autosomal recessive subtypes are listed alphabetically, from LGMD2A through LGMD2N. Among the 14 subtypes of LGMD2, the most common disorders are those associated with mutations in genes coding for calpain *(LGMD2A)*, dysferlin *(LGMD2B)*, alpha-sarcoglycan *(LGMD2D)*, and Fukutin-related protein *(LGMD2I)*. In addition to progressive proximal weakness, each of these disorders has distinctive features. Calpainopathy is characterized by elbow and wrist contractures and tight heel cords; dysferlinopathy, by involvement of calf muscles and muscle biopsy disclosing inflammatory infiltrates; sarcoglycanopathies, by strongly resembling dystrophinopathy (with calf hypertrophy) without cardiomyopathy; and Fukutin-related protein deficiency resembling Duchenne or Becker dystrophy, sometimes with cardiomyopathy and diaphragmatic weakness. To date, in approximately 50% of patients with LGMD2, a gene locus or defective protein product has not yet been determined.

In patients suspected of having a form of LGMD2, and after genetic testing has ruled out a dystrophinopathy, a muscle biopsy is generally obtained and evaluated with biochemical testing (immunostaining of candidate proteins). For many of the subtypes of LGMD2, genetic testing can be used to identify the specific disease-causing mutation. Patients with LGMD require a comprehensive approach to care best achieved with a multidisciplinary team. Although cardiac and respiratory complications are uncommon, heart assessment with an electrocardiogram (ECG), echocardiogram, and lung function evaluation are important to identify and treat proactively for possible underlying complications. Genetic counseling is of great importance to families, and prenatal diagnosis is available when the causative mutation has been established.



Polymyositis and Dermatomyositis

Inflammatory myopathies are acquired skeletal muscle disorders characterized by muscle weakness, elevated serum creatine kinase (CK), and muscle biopsy inflammation. The major idiopathic inflammatory myopathies are polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM). Connective tissue disorders and underlying malignancy are important associations.

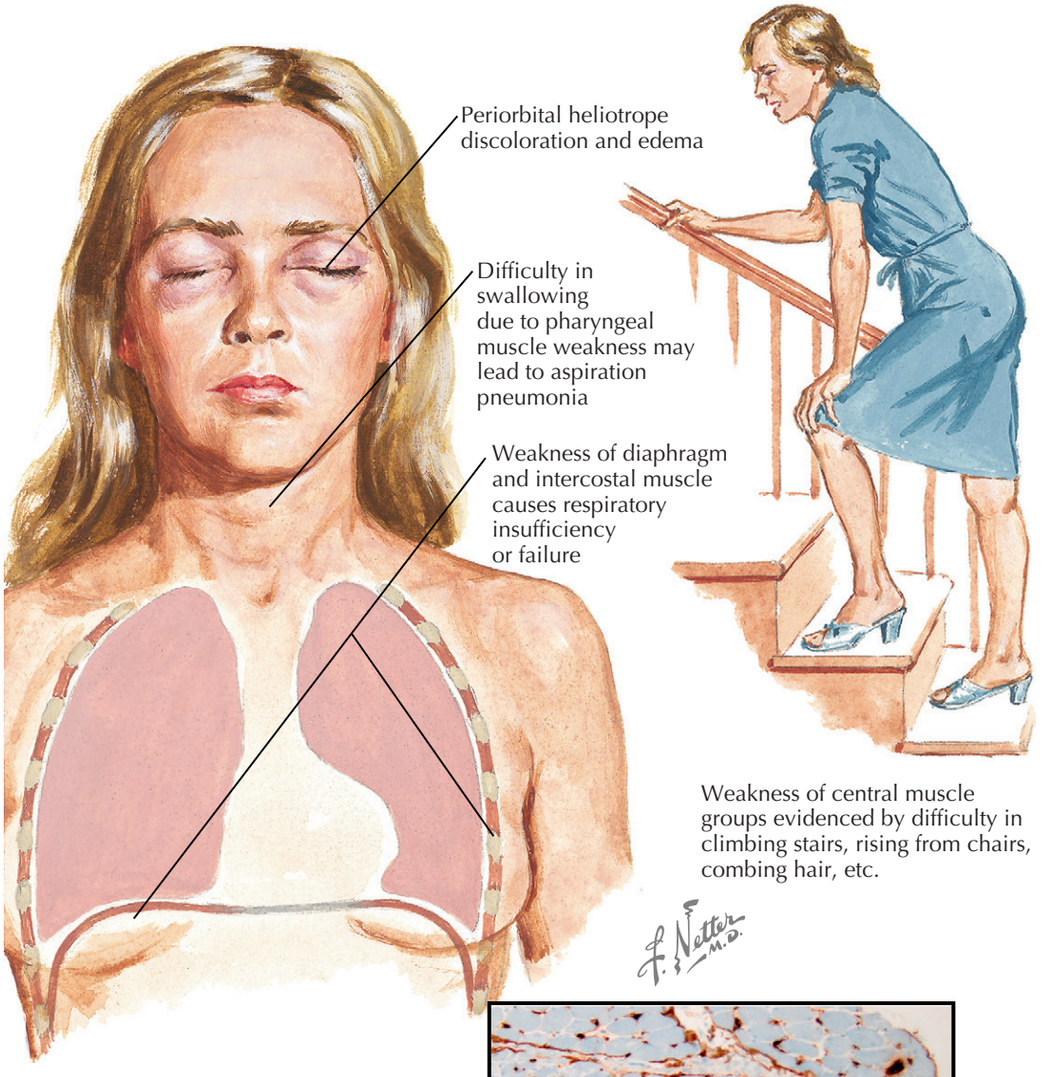
The prevalence of PM/DM is 1 per 100,000 adults, with a female to male ratio of 2 : 1; there is also a childhood form of dermatomyositis. Presenting symptoms include shoulder and pelvic-girdle muscle weakness, malaise with fatigue, and occasionally myalgia and muscle tenderness gradually worsening over weeks to months. Patients report difficulty arising from a chair, combing hair, and climbing stairs. A defining symptom of dermatomyositis is skin rash over the face, hands, neck, and extensor aspects of the extremities.

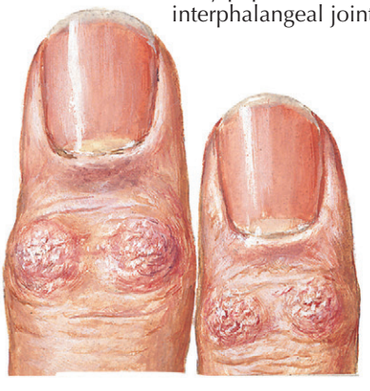
Clinical examination discloses proximal muscle weakness of the arms and legs and neck flexor muscles. Distal muscle weakness, typically, is mild. In DM, and not PM, cutaneous manifestations include Gottron's sign (scaly erythematous rash over hand and finger joints and elbow and knee extensor areas), heliotropic rash (violaceous discoloration with upper eyelid edema), shawl sign (V-shaped flat erythematous rash over the anterior neck and chest), erythematous rash over the face (malar region and forehead), periungual telangiectasia (affecting fingernail bed capillaries), mechanic's hands (cracking of skin over hands and fingers), and calcinosis cutis (subdermal calcium deposits). In both PM and DM, dysphagia (esophageal weakness), cardiac disease (heart block or congestive heart failure), and constitutional findings (fever, weight loss, arthritis) may occur.

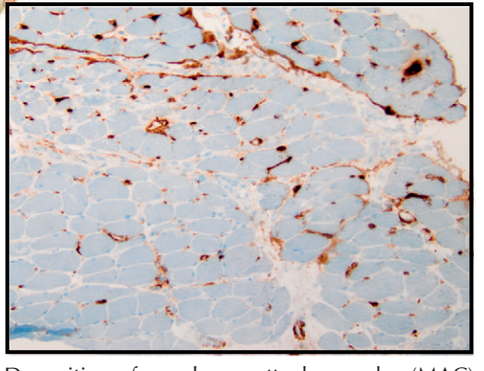
Dermatomyositis and polymyositis need to be distinguished from other conditions that may cause muscle weakness, including other muscle disorders, that is, muscular dystrophies, toxic (drug-induced), metabolic, and endocrine myopathies; chronic inflammatory demyelinating neuropathy (CIDP); myasthenia gravis; and, rarely, motor neuron disease.

Diagnosis of DM and PM is based on clinical findings supported by elevated CK and an abnormal electromyogram (EMG; at rest, fibrillation potential activity, with low levels of contraction; short-duration, low-amplitude, polyphasic motor unit potentials firing with an increased number, designated "early recruitment pattern"). Twenty percent of patients have an antibody to histidyl transfer ribonucleic acid (tRNA), called anti-Jo1, defining a patient subgroup with interstitial lung disease and mechanic's hands.

Muscle biopsy of a weak proximal muscle is the definitive study. Histopathologic features of both DM and PM include inflammatory cell infiltration and muscle fiber necrosis, with degenerating and regenerating muscle fibers scattered throughout the fascicle. In DM, the inflammatory cell infiltrate, composed mainly of B cells and $CD4^+$ cells, is predominantly perifascicular and perivascular. Muscle atrophy, occurring at the periphery of muscle fascicles, is known as perifascicular atrophy (especially prominent in childhood DM). Another characteristic finding in DM is deposition of the terminal component of the complement cascade—the membrane attack complex (MAC)—in capillary walls. In contrast, PM is characterized by inflammatory cell infiltration of T cells and macrophages occurring diffusely within the endomysium surrounding and invading non-necrotic muscle fibers within the fascicles. Cell-mediated immune mechanisms are







Deposition of membrane attack complex (MAC) around small blood vessels and capillaries demonstrated by immunoperoxidase stain. *Courtesy Mathew P. Frosch, MD, PhD, C.S. Kubik Laboratory for Neuropathology, Massachusetts General Hospital and Harvard Medical School.*

Polymyositis and Dermatomyositis *(Continued)*

important, having increased numbers of cytotoxic $CD8^+$ T cells and increased expression by muscle fibers of major histocompatibility complex (MHC) antigens.

In DM, a skin biopsy reveals perivascular lymphoid infiltrate. Immunofluorescence here demonstrates deposits of complement, membrane attack complex, and immunoglobulin at the dermal–epidermal junction. Magnetic resonance imaging (MRI) of muscle is a useful noninvasive adjunct that highlights areas of muscle inflammation, edema, fibrosis, calcification, and enhancement associated with myositis. MRI can also serve as a guide for muscle biopsy and therapeutic response.

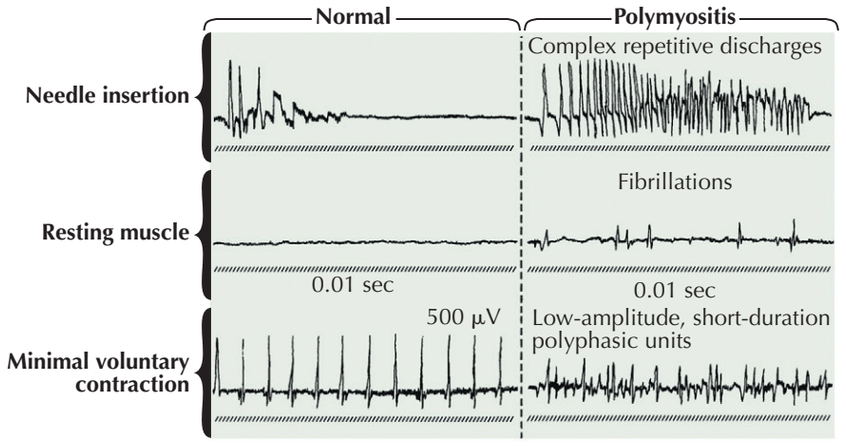
Because malignancy may be associated with PM (up to 10% of patients), and especially with DM (up to 25% of patients older than 40 years), screening for cancer (carcinomas of the breast and ovary in women and lower gastrointestinal tract in men) is important, especially in older adults; routine laboratory studies, testing stool for occult blood, and selected imaging studies, including mammography and computed tomography (CT) scanning of the chest and abdomen, are performed.

The severity of disease, as well as response to treatment and prognosis of DM and PM, are quite variable and range from those with mild weakness, who quickly respond to treatment, to progressively worsening weakness that may be resistant to a number of therapies. Poor prognostic factors are associated with a more than 6-month delay in initiation of therapy from the onset of weakness, dysphagia, interstitial lung disease (Jo-1–positive patients), underlying malignancy, presence of collagen-vascular disorders, and cardiac involvement. Other clinical features, such as advanced age, severity of weakness, peak of CK elevation, and degree of abnormality on muscle biopsy, do not reliably predict the disease course or treatment response.

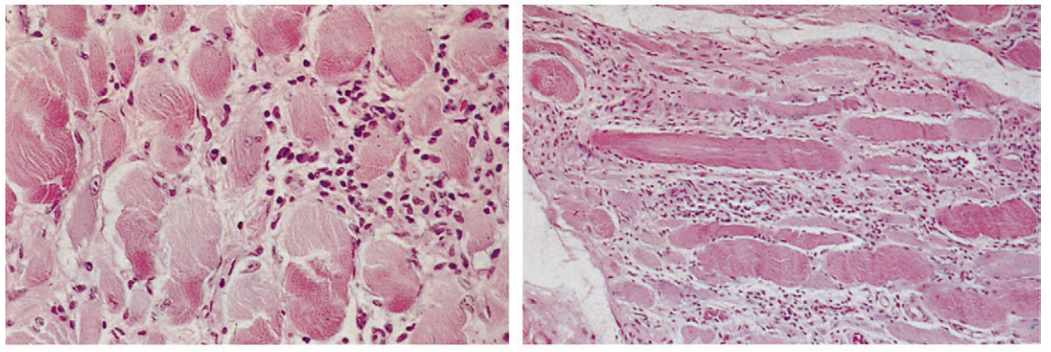
Corticosteroids treatment is the initial therapy for both DM and PM. Typically, prednisone is started at 1 mg/kg per day, with a maximum daily dose of 80 mg. For patients with severe weakness, intravenous glucocorticoid therapy is indicated (methylprednisone 1000 mg/day for 3 days), followed by high-dose oral prednisone. Weakness usually improves over days to a few weeks. Once muscle strength is significantly improved and stabilized, a slow, gradual taper of prednisone (5-10 mg every 2-3 weeks) is started, aiming for the lowest and yet still effective dose to achieve sustained improvement. This may take up to a year. Patients on long-term corticosteroid treatment are treated with calcium, vitamin D, and bisphosphonates (for osteoporosis prevention); antacid or H2 blocker (for gastric mucosa protection); and prophylaxis (usually with Bactrim) for opportunistic infections. In up to 30% of patients, weakness recurs as the dose of prednisone is tapered, and a corticosteroid-sparing immunosuppressive agent is required. Azathioprine, methotrexate, cyclosporine, and mycophenolate mofetil are useful agents in this setting.

Physical therapy and exercise are recommended early in the course of treatment and are tailored to the degree of weakness. Stretching and range of motion exercises are helpful in preventing joint contractures (especially in weak muscles). Appropriate exercise programs, from low levels of isometric and resistive exercises in those with moderate weakness to increasing levels of activity in those with mild weakness, are encouraged throughout the course of disease. Patients with DM may have increased photosensitivity and are asked to avoid prolonged exposure to ultraviolet light.

Electromyography

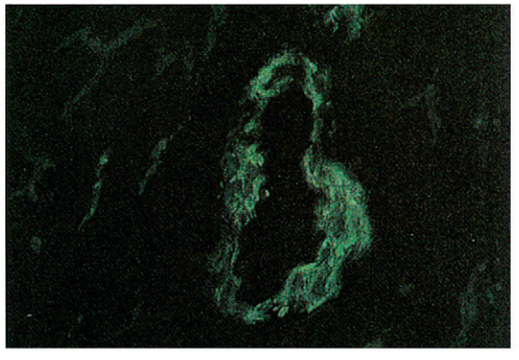


Muscle Biopsy

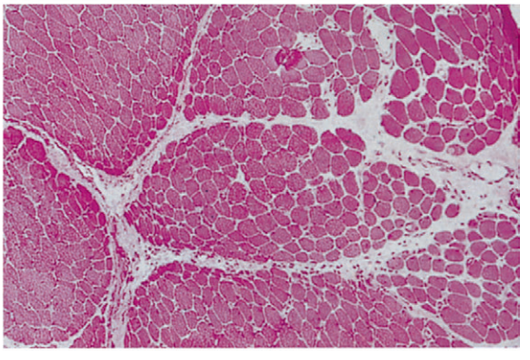


Transverse section ← **Muscle biopsy specimens** → Longitudinal section

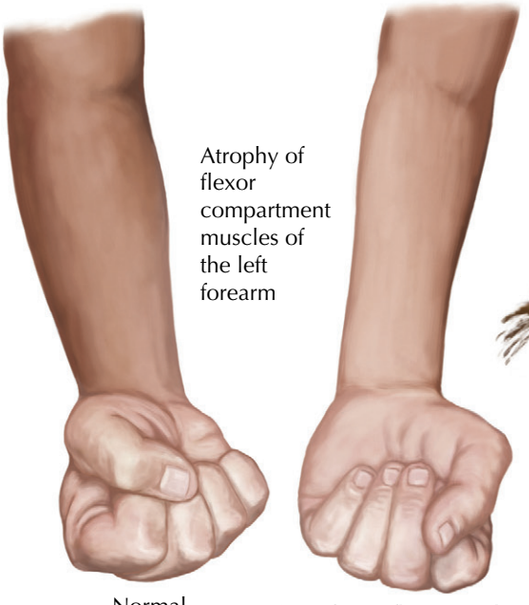
Inflammatory reaction: muscle fiber necrosis and regeneration



Anti-IgG immunofluorescence of frozen muscle section with positive staining within blood vesssel wall, indicating immunologic basis of dermatomyositis



Perifascicular muscle atrophy in child with dermatomyositis



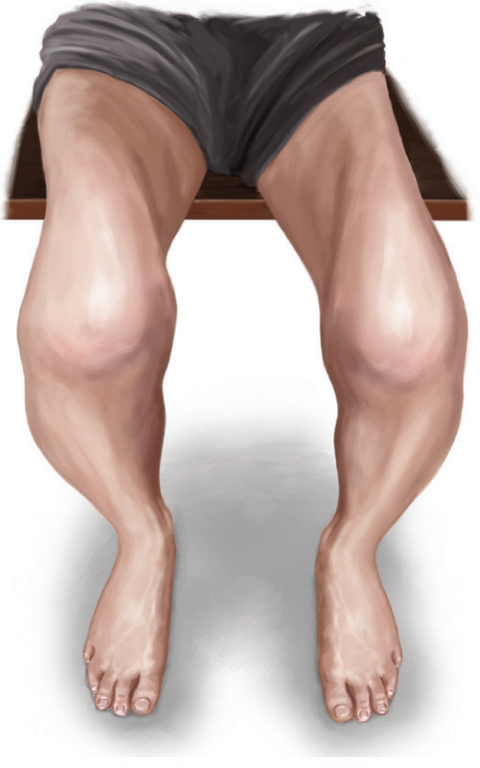
Inclusion Body Myositis

Inclusion body myositis (IBM) is another idiopathic inflammatory myopathy. Although IBM shares some clinical features and histologic findings with PM and DM, a constellation of distinctive clinical and histopathologic attributes makes IBM unique among the inflammatory myopathies. This disorder, having a predilection for men older than 60 years, typically has an insidious onset with slow progression over many years. In contrast to PM and DM with symmetric proximal weakness, IBM typically has asymmetric forearm and thigh muscle weakness and atrophy. Impressive weakness and atrophy affecting finger flexors, particularly the flexors pollicis longus and digitorum profundus, quadriceps, and tibialis anterior muscles, is characteristic. Weak pinch as well as hand grip, knee buckling, and sometimes footdrop are common. Dysphagia occurs in a third of patients.

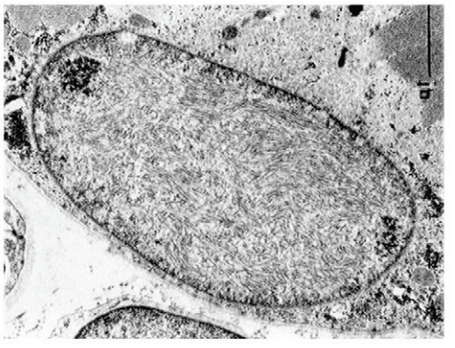
Serum creatine kinase (CK) is mildly to, at most, moderately elevated (<10 times normal). Electromyography (EMG) discloses fibrillation potentials and a mixed population of motor unit potentials (MUPs): low-amplitude myopathic potentials with reduced recruitment, as seen in DM and PM, and enlarged MUPs more typical of chronic neurogenic disorders, reflecting the very long-standing IBM course, and opportunity for muscle fibers to undergo splitting and hypertrophy. Magnetic resonance imaging (MRI) muscle signal changes occasionally aid in identifying a biopsy site.

Muscle biopsy demonstrates distinctive muscle fiber changes, including vacuoles containing basophilic granules (rimmed vacuoles), small angular atrophic fibers groups with eosinophilic inclusions, and endomysial mononuclear inflammatory infiltrate similar to PM. Electron microscopy is essential for defining morphologic findings characteristic of IBM: 18-nm filamentous inclusions within muscle nuclei and cytoplasm. Some filamentous inclusions bind to antibodies directed against beta-amyloid.

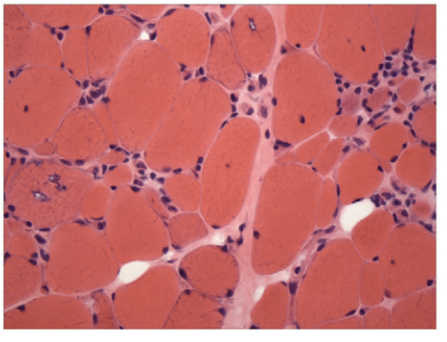
IBM can often be mistaken as polymyositis clinically, when the weakness is proximal and symmetric, accompanied by a modest CK elevation, and has similar EMG abnormalities. It is differentiated by muscle biopsy. Toxic (drug-induced) myopathies may show similar vacuoles on muscle biopsy but typically have a subacute course. Hereditary IBMs present similarly with slowly progressive weakness and muscle biopsy demonstrating a vacuolar myopathy with inclusions. However, the family history and sparse inflammation noted in hereditary IBM distinguish it from sporadic IBM. Often, IBM patients with predominant distal and/or asymmetric weakness are confused with motor neuron disorders and less commonly peripheral neuropathies.



Atrophy and weakness of both quadriceps muscles

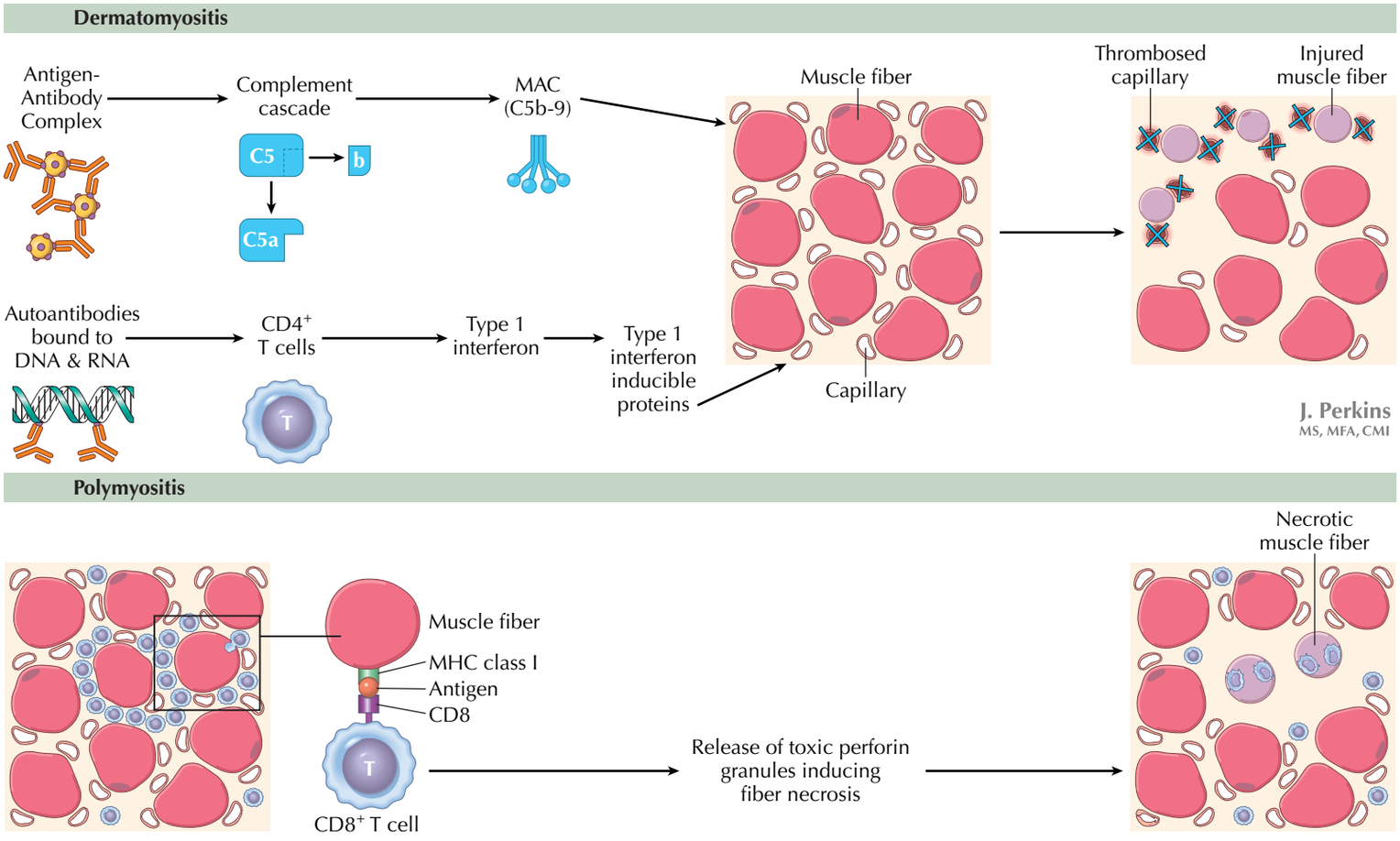


Electron microscopy. 15-21 nanometer tubulofilamentous inclusions may be seen in the cytoplasm and nucleus of vacuolated muscle fibers. *From Chad D, Good P, Adelman L, et al: Inclusion body myositis associated with Sjogren's syndrome. Arch Neurol 1982; 39:186-188.*



Light microscopy. Muscle fibers with rimmed vacuoles. Vacuoles contain blue amorphous material. Clusters of small atrophied fibers. *Courtesy Christian J. Davidson, MD.*

In contrast to other inflammatory myopathies responding robustly to corticosteroids and other immunosuppressive agents, IBM is refractory to immunotherapy. Weakness is gradually progressive; after 10 to 30 years, most patients will require assistance with activities of daily living, a walker for ambulation, and ultimately, a motorized wheelchair or scooter. Supportive measures for dysphagia and physical therapy help to improve quality of life.



Immunopathology of Inflammatory Myopathies

Dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM) share certain pathologic features, including muscle inflammation, fiber necrosis, and regeneration; individual distinctive histopathologic aspects suggest varied pathogenetic mechanisms.

Pathogenesis of Dermatomyositis. A striking feature observed in muscle biopsies taken from patients with DM is the presence of a diverse collection of cell types: *$CD4^+$ T lymphocytes*, *B lymphocytes*, *plasma cells*, *macrophages*, *and dendritic cells located predominantly in a perivascular and perimysial distribution*. The role of the macrophage and the dendritic cell is to present antigen—attached to a major histocompatibility (MHC) class II molecule—to a helper $CD4^+$ T cell that, in turn, produces cytokines (such as the interleukins whose targets are principally leukocytes, type 1 interferons, and chemokines); these molecules amplify the immune response within the muscle microenvironment and have direct deleterious effects on muscle fiber function (see later). The interleukins stimulate B cells to multiply and mature into antibody-producing plasma cells. Additional hallmarks of the DM muscle biopsy are atrophy of muscle fibers occurring rather specifically on the edges of muscle fascicles, leading to a distinctive pathologic feature known as *perifascicular atrophy*, and there is the presence of *membrane attack complex (MAC)* with *antibodies deposited in capillaries and small blood vessels* throughout the endomysium.

One hypothesis proposes that the pathophysiology central to DM is a *microangiopathy* resulting from antibody and MAC-mediated injury of capillaries (see Plate 12-17). MAC is the end product of the complement cascade—consisting of complement components C5b, C6, C7, C8, and polymeric C9—that forms damaging transmembrane channels in the cell membranes of target cells, such as endothelial cells, and causes cell lysis and, ultimately, cell death. (The specific molecular agents that might trigger the complement cascade in DM have not been identified with certainty; however, antigen-antibody complexes are possible candidates.) The resulting necrosis and thrombosis of capillaries is postulated to result in muscle ischemia subsequently contributing to myofiber damage (see Plate 12-17).

A second pathogenic mechanism underlying muscle injury in DM proposes a *central role for interferon* (see Plate 12-17). Many $CD4^+$ cells are plasmacytoid dendritic cells secreting type 1 interferon (type 1 INF), possibly in response to autoantibodies bound to deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) located in DM muscle. There is strong evidence that type 1 INF, in turn, induces gene transcription of a host of proteins, some of which have the potential to injure muscle capillaries and muscle fibers and contribute to the pathologic picture of DM, although the precise mechanism of cell injury is not known.

Pathogenesis of Polymyositis. Examination of muscles biopsies from PM patients reveals an appearance rather different from that seen in DM. The population of inflammatory cells is variegated, but there is a predominance of $CD8^+$ T cells, with a relative smaller percentage of $CD4^+$ T lymphocytes; these cells, together with macrophages and dendritic cells, are located within the endomysium. A *pathologic signature of PM* is the presence of *cytotoxic $CD8^+$ T cells surrounding and invading non-necrotic muscle fibers*. The $CD8^+$ cytotoxic T lymphocytes recognize their targets by binding to antigen associated with major histocompatibility complex (MHC) class I on muscle fibers and may mediate muscle fiber damage by releasing toxic perforin granules that induce muscle fiber necrosis (see Plate 12-17). The precise character of the antigen or antigens that triggers the immune response and is presented to the T cell by the MHC I protein molecule in PM is not known; it may be an endogenous self-antigen or perhaps an antigen induced by a viral infection. Unlike DM, perifascicular atrophy is not seen, and there is no capillary deposition of complement and immunoglobulin.

Pathogenesis of Inclusion Body Myositis. The histopathology of IBM is notable for architectural changes within many fibers: *eosinophilic inclusions in muscle fibers as well as rimmed vacuoles are seen*, Congo red stains demonstrate amyloid deposits, and electron microscopy discloses tubulofilamentous inclusions in the cytoplasm and nucleus. These findings are perhaps more reminiscent of a neurodegenerative process than one that is immune mediated, and yet, a *prominent feature* is the presence of the invasion of muscle fibers by *CD8+ cytotoxic cells with MHC class I antigen on the invaded fibers, similar to the cellular reaction in PM. Current thinking* about the mechanism of myofiber damage in IBM—influenced largely by the lack of meaningful clinical response to vigorous immunosuppression, in contrast to the robust response seen in DM and PM—is that the disorder is *more like neurodegeneration* than immune-mediated injury.

Endocrine, Toxic, and Critical Illness Myopathies

Corticosteroid Myopathies. Weakness is a common manifestation of both Cushing syndrome and corticosteroid therapy. Muscle weakness begins in the pelvic girdle and proximal legs and, subsequently, shoulder girdle and proximal arms. Predisposing factors include reduced muscular activity, protein malnutrition, and gender (woman are more susceptible). Creatine kinase (CK) is typically normal. Electromyography (EMG) is often normal but may demonstrate myopathic motor unit potentials (MUPs) with abnormal insertional activity. Muscle biopsy primarily demonstrates fiber diameter diminution, especially histochemical type IIb. Cushing syndrome therapy focuses on identifying and removing the corticosteroid source (i.e., adrenal or pituitary) and dose reduction in patients receiving corticosteroids. Disuse accelerates corticosteroid myopathy; this may be partially prevented by exercise or passive range of motion.

Hypothyroid Myopathy. Most patients with myxedema (chronic hypothyroidism) complain of weakness; 25% have objective proximal muscle weakness. Myoedema, an electrically silent mounding of percussed muscle, occurs in one third of patients. The relaxation phase of muscle stretch reflexes is delayed. In childhood, hypothyroid myopathy presents with hypertrophic muscles that slowly contract and relax. In adults, fatigue is associated with muscular spasms and cramps. Serum CK is mildly elevated. EMG may be normal, but in long-standing hypothyroidism, increased insertional activity, complex repetitive discharges, and myopathic motor unit potentials are seen. Judicious thyroid replacement restores function.

Hyperthyroid Myopathy. Muscle weakness is common in hyperthyroidism, often affecting the shoulder and pelvic-girdle muscles. Rarely, hyperthyroid patients have very brisk muscle stretch reflexes, muscle wasting, and fasciculations mimicking motor neuron disease. CK is normal. Muscle strength and bulk improves as the euthyroid state is restored.

Hyperparathyroid Myopathy. Weakness and fatigability frequently occur as presenting symptoms of primary hyperparathyroidism. Pelvic-girdle and leg muscles are involved before upper extremities. Some patients have unexplained osteomalacia associated with myopathy. Serum parathormone levels are elevated. CK is normal. Patients improve after parathyroidectomy.

Hypoparathyroid Myopathy. Muscle aching, spasm, twitching, and tremor may occur, but true myopathy in hypoparathyroidism is extremely rare. CK elevations result from muscle damage sustained during prolonged hypocalcemia-induced cramping.

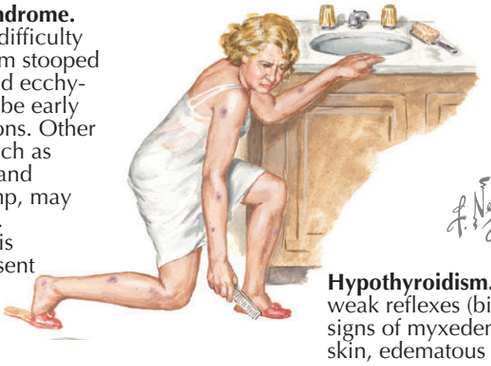
Acromegalic Myopathy. Proximal muscle weakness, developing many years after the onset of acromegaly, occurs about 50% of the time. CK and muscle biopsy are normal. The pathogenesis may relate to sustained high levels of growth hormone effects on muscle metabolism. After hypophysectomy, slow improvement occurs unrelated to postoperative growth hormone level decline.

Toxic Myopathy. Numerous drugs lead to potentially reversible myopathies. Renal insufficiency predisposes because of reduced drug clearance. *Cholesterol-lowering agents* (e.g., hydroxymethylglutaryl-coenzyme A [HMG-CoA] reductase inhibitors) cause myopathies characterized by muscle cramping, sometimes proximal muscle weakness; and often increased serum CK. Myopathic potentials with myotonia are seen on EMG and muscle fiber necrosis with biopsy. This myopathic syndrome usually resolves with drug discontinuation. Occasionally, these drugs trigger an immune-mediated myopathy with necrosis and without inflammation that responds to corticosteroids

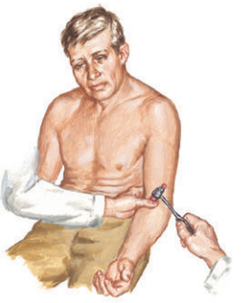
Chloroquine causes a vacuolar myopathy with insidious onset of slowly progressive proximal weakness. Electron microscopy discloses autophagic vacuoles containing lamellar or myeloid lipid-containing inclusions and curvilinear bodies. *Colchicine* induces both an axonal neuropathy and myopathy with vacuolar degeneration, almost always with associated renal insufficiency. *Azidothymidine (AZT)* is associated with a myopathy and abnormal mitochondria on muscle biopsy. On rare occasions, *penicillamine*, *cimetidine*, and *procainamide* produce an inflammatory myopathy. *Alcohol* occasionally leads to chronic myopathies difficult to identify in patients with concomitant neuropathy and malnutrition complications. Acute alcoholic myopathies occur with episodic rhabdomyolysis, acute myalgia, muscle swelling, and weakness.

Critical Illness Myopathy (CIM). Exposure to intravenous corticosteroids and neuromuscular blocking agents are major CIM risks; this also develops with severe systemic illness, multiorgan failure, and sepsis in an intensive care unit (ICU) setting. Weakness is typically diffuse—a flaccid quadriparesis with proximal greater than distal distribution—and sometimes affects the diaphragm, causing failure to wean. Muscle stretch reflexes are depressed or absent. Early in the disease course, serum CK is elevated in 50% of patients. Nerve conduction studies demonstrate low-amplitude motor responses but preserved sensory responses. EMG reveals fibrillation potentials with myopathic MUPs. Muscle biopsy typically demonstrates selective myosin loss, type II fiber muscle fiber atrophy, and occasional mild fiber necrosis. The pathogenesis is myosin thick filament loss secondary to muscle apoptosis, calpain upregulation, and a transforming growth factor beta/mitogen-activated protein kinase pathway. Inexcitable muscle results from inactivation of sodium channels at the resting membrane potential. Treatment is symptomatic. Intensive insulin therapy (targeting blood glucose concentrations of 80 to 110 mg/dL) may lower the incidence of critical illness myopathy. Most patients recover over weeks to months; residual paresis may occur, depending upon severity and duration of weakness.

Myopathies Secondary to Endocrine Disorders

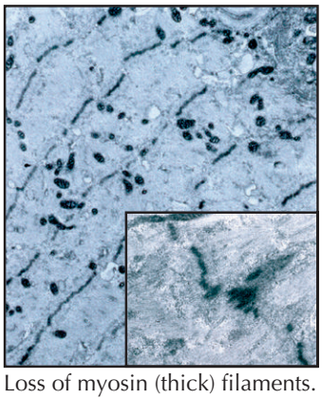


Cushing syndrome. Weakness (difficulty in rising from stooped position) and ecchymoses may be early manifestations. Other stigmata, such as moon face and buffalo hump, may be minimal. Osteoporosis may be present

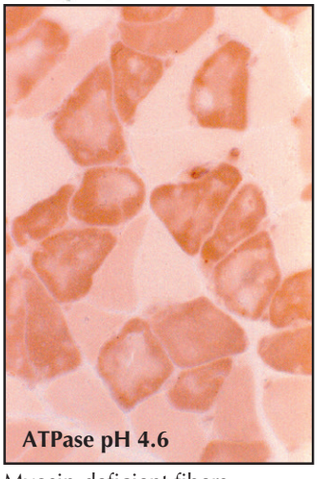


Hypothyroidism. Delayed or weak reflexes (biceps brachii) are characteristic. Other signs of myxedema, such as coarse features, dry scaling skin, edematous facies, thick lips, etc., may be striking.

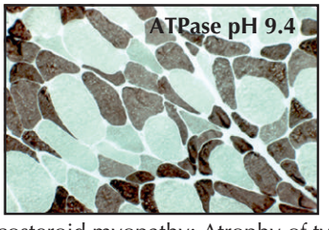
Acromegaly. Weakness in climbing ladder or stairs and enlargement of jaw and hands may be first signs.



Loss of myosin (thick) filaments.



Myosin-deficient fibers.



Corticosteroid myopathy: Atrophy of type 2 muscle fibers (dark stained), especially the fast-twitch glycolytic type 2B fibers.

Images courtesy TW Smith, MD, Pathology Department, University of Massachusetts Medical School.

Myopathies: Hypokalemia/ Hyperkalemia and Periodic Paralyses Channelopathies

Secondary Hypokalemic and Hyperkalemic Syndromes

Hypokalemia and hyperkalemia are common electrolyte disturbances associated with muscle weakness. The fall or rise in potassium concentration is often triggered by a medical disorder; the subsequent weakness is considered a secondary effect. Normal range of serum potassium is 3.5 to 5.5 mEq/L, and therefore levels less than 3.5 mEq/L and greater than 5.5 mEq/L define hypokalemia and hyperkalemia, respectively.

Hypokalemia-associated weakness does not usually become problematic until potassium levels fall toward and then below 1.5 mEq/L, with mild weakness, fatigue, and muscle cramping giving way to severe and generalized weakness, myoglobinuria, and cardiac arrhythmias. Common hypokalemia etiologies include excessive renal loss (e.g., diuretic use, primary aldosteronism) and gastrointestinal sources (e.g., vomiting and diarrhea). Mild-to-moderate hypokalemia is treated safely with oral potassium supplementation, while more severe hypokalemia requires intravenous potassium replacement.

Hyperkalemia of moderate-to-severe degree (>6.5 mEq/L) may be associated with muscle pain and paresthesias and, rarely, muscle weakness per se. However, cardiac rhythm disturbances with an abnormal electrocardiogram (ECG) (peaked T waves and QRS complex widening) are common, requiring immediate treatment. Common causes include reduced renal excretion secondary to renal failure, drugs inhibiting potassium excretion, metabolic acidosis, and primary adrenocortical insufficiency (Addison disease). Cardiac arrhythmias require treatment with insulin, bicarbonate, and beta-agonists to lower serum potassium rapidly by shifting potassium intracellularly.

Periodic Paralysis

Hypokalemia and hyperkalemia-associated weakness may be caused by membrane excitability disorders, particularly autosomal dominant (AD) channelopathies. *Hypokalemic periodic paralysis (HYPOKPP)* is caused by a skeletal muscle voltage-sensitive calcium channel gene mutation. *Hyperkalemic periodic paralysis (HYPERKPP)* is secondary to voltage-gated sodium channel *SCN4A* gene mutations. *Andersen-Tawil syndrome* is secondary to potassium channel gene mutations.

HYPOKPP is an autosomal dominant disorder more frequent and severe in men than women. Episodes of paralysis begin in the second or third decade, often preceded by sensations of muscle tightness and soreness. These vary from quadriplegia to mild weakness in a single limb; muscle stretch reflexes are almost always diminished or absent. Respiratory and cranial nerve–supplied muscles are spared. Attacks average 12 to 24 hours in duration, resolving over 3 to 6 hours, with recovery noted initially in muscles initially paralyzed. Provoking factors include rest after exertion, large carbohydrate-rich meals, cold exposure, stress, and alcohol. Attacks often begin during sleep. Between attacks, the examination is usually normal, but in some patients with multiple attacks, prominent limb-girdle weakness develops.

During an attack of total paralysis, serum potassium is usually depressed to 2 to 3 mEq/L, but it may be normal. The paralyzed muscles are electrically inexcitable. Hypokalemia induces cardiographic changes, including bradycardia, U waves, flattened T waves, and lengthened P-R and Q-T intervals. CK is elevated during and, less commonly, between attacks.

The acute attack is treated with oral potassium. As prophylaxis, the patient is instructed to avoid high-carbohydrate meals, reduce salt intake, and avoid unaccustomed physical activity. Acetazolamide (125-150 mg/day) prevents most attacks by producing a metabolic acidosis impeding potassium movement into cells.

Thyrotoxic periodic paralysis (THYPP) is a sporadic disorder typically occurring in 2% to 8% of hyperthyroid Asian populations, particularly men (80%). Clinical and biochemical features are identical to familial HYPOKPP. Patients with the familial disorder have normal thyroid function, with attacks only when a hyperthyroid state exists. Correction of the hyperthyroid state is the definitive treatment. Once the patient becomes euthyroidic, spontaneous episodes of periodic paralysis cease.

HYPERKPP is autosomal dominant, occurring equally in men and women. Attacks begin earlier than with HYPOKPP, generally before age 10 years. Attacks are usually brief and mild, lasting 0.5 to 4 hours; serum potassium may be slightly elevated but may be normal. Myotonia is prominent on both clinical and, particularly, electromyographic (EMG) evaluation. Attacks occur during the day or early in the night. Exercise at the first hint of weakness may delay an attack. Rest after exercise, stress, cold, administration of potassium, and fasting provokes attacks. As in HYPOKPP, permanent proximal limb-girdle muscle weakness may develop with age.

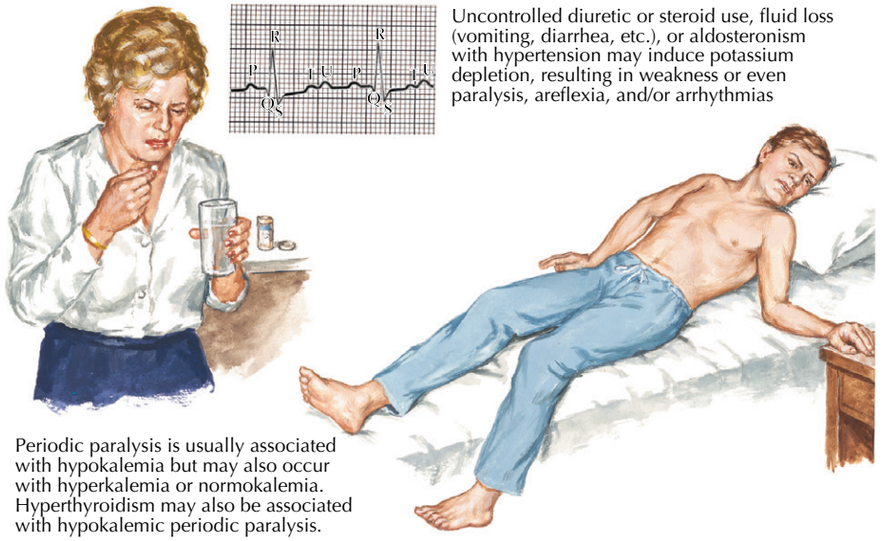
During attacks with elevated serum potassium, there may be electrocardiographic changes, including tall, slender T waves and tachyarrhythmias. CK may be elevated during and between attacks. Between attacks, EMG of weak muscles discloses myotonic discharges. In fully paralyzed muscles, the EMG is silent. Acetazolamide is effective in reducing attack frequency. Mexiletine is the treatment for clinical myotonia.

Andersen-Tawil is a rare syndrome characterized by episodic weakness, dysmorphic features (short stature, hypertelorism, low-set ears, mandibular hypoplasia, clinodactyly), and life-threatening arrhythmias, frequently bigeminy or bidirectional ventricular tachyarrhythmia. Episodic weakness may be associated with hypokalemia, hyperkalemia, or normokalemia. Acetazolamide may reduce attack frequency.

Myopathies Associated with Disorders of Potassium Metabolism

Characteristics of Familial Periodic Paralysis					
Disorder	**Inheritance**	**Chromosome**	**Gene**	**Clinical myotonia**	**Major triggers**
Hypokalemic periodic paralysis	AD	1q31-32 (type1) 17q13.1-13.3 (type 2)	*CACNA1S* (type 1) *SCN4A* (type 2)	No	Low K^+, rest after exercise, carbohydrate rich foods
Hyperkalemic periodic paralysis	AD	17q13.1-13.3	*SCN4A*	Yes	High K^+, prolonged rest, fasting
Anderson-Tawil syndrome	AD	17q23.1-24.2	*KCNJ2*	No	Prolonged rest

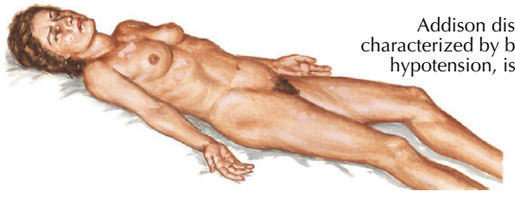
Hypokalemia



Uncontrolled diuretic or steroid use, fluid loss (vomiting, diarrhea, etc.), or aldosteronism with hypertension may induce potassium depletion, resulting in weakness or even paralysis, areflexia, and/or arrhythmias

Periodic paralysis is usually associated with hypokalemia but may also occur with hyperkalemia or normokalemia. Hyperthyroidism may also be associated with hypokalemic periodic paralysis.

Hyperkalemia



Addison disease (primary adrenocortical insufficiency), characterized by bronzing of skin, weakness, weight loss, and hypotension, is associated with elevated serum potassium. Manifestations may be mild in early stages, with weakness predominating.

F. Netter M.D.

Metabolic and Mitochondrial Myopathies

These disorders are characterized by muscle weakness stemming from three realms of muscle metabolism dysfunction: (1) glycogen breakdown to lactic acid, (2) fatty acids oxidation, and (3) mitochondria adenosine triphosphate (ATP) production.

McArdle disease, an autosomal recessive *myophosphorylase deficiency* leading to *glycolytic defects*, is the common glycogen storage disease (GSD). Other glycolytic defects—phosphofructokinase, phosphoglycerate mutase, and lactic dehydrogenase deficiencies—produce similar clinical pictures. Children experience easy fatigability and mild weakness. In adolescence, with more vigorous activity, painful muscle cramps develop. Muscle necrosis and myoglobinuria occur frequently. Individuals avoid intense activity, preferring less demanding sustained exercise, such as walking. A prominent second-wind phenomenon with renewed strength, attributed to fatty acid mobilization and increased muscle blood flow, occurs after 8 to 10 minutes exercise when the patient is no longer glycogen dependent. Between attacks, patients are well, leading reasonably normal lives. Mild, permanent weakness occurs in 25%.

Diagnostically, creatine kinase (CK) is elevated in 90% of resting patients. Venous lactate fails to rise during forearm ischemic exercise tests (FIET) because McArdle patients do not metabolize glycogen. In contrast, peak venous lactate levels normally occur within 3 to 5 minutes after exercise, reaching three to five times preexercise levels. Electromyography (EMG) is usually normal between attacks but may show mild myopathic potentials in chronic patients having permanent weakness. Muscle biopsy demonstrates subsarcolemmal glycogen accumulations and completely absent phosphorylase activity. Patients are encouraged to prevent attacks and muscle injury by avoiding high-intensity activity and ingesting glucose before activities.

Pompe disease (PD), acid maltase (α-1,4-glucosidase) deficiency, is a rapidly fatal infantile autosomal recessive GSD disorder secondary to an alpha-glucosidase gene mutation. Skeletal muscle glycogen accumulation occurs in heart and nervous system, leading to severe hypotonia, weakness, and respiratory and heart failure. Milder, later-onset (childhood and adult) forms occur. Usually symptoms begin in the third to fourth decades, with slowly progressive proximal limb, trunk, and respiratory muscle weakness leading to respiratory failure.

Serum CK is elevated. Infantile electrocardiograms are abnormal. EMG discloses myopathic motor unit potentials, fibrillations, complex repetitive potentials, and myotonia. Muscle biopsy reveals a vacuolar myopathy. Electron microscopy demonstrates glycogen granule clusters within cytoplasm and vacuoles. Dried blood spot enzyme analysis provides screening; diagnosis is confirmed by enzyme assay. PD is now treatable with intravenous recombinant human alpha-glucosidase.

Carnitine palmitoyl transferase deficiency (CPTd) is an autosomal recessive, male-predominant, lipid metabolism disorder wherein muscle cells suffer energy deficits. *CPT*, an enzyme permitting fatty acid transport into mitochondria, provides muscle cell energy via beta oxidation. Its primary hallmark is recurrent myoglobinuria provoked by prolonged exercise or fasting. Unlike glycolytic disorders, painful cramps do not occur during exercise; thus patients lack warning signals of impending muscle injury. Severe muscle pain, swelling, and tenderness occur during episodes of acute muscle weakness.

CK, normal at rest, rises sharply during attacks. In contrast to McArdle GSD, CPTd venous lactate rises normally during FIET forearm exercise testing. Muscle biopsy is normal except with previous myoglobinuric episodes, wherein scattered necrotic and regenerating fibers appear. Prolonged fasting (30-72 hours) leads to significant serum CK increase and delayed or decreased ketone body production. Muscle CPT biochemical assay or genetic testing provides definitive diagnosis.

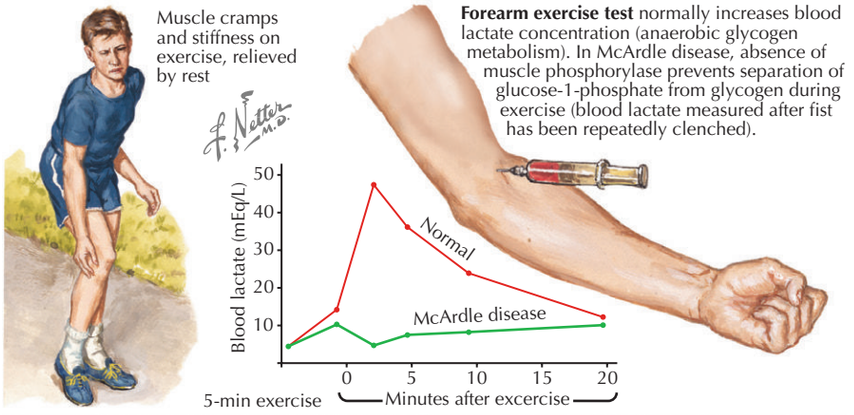
Frequent meals with a low-fat, carbohydrate-rich diet may improve exercise tolerance. These patients should receive intravenous glucose before and during general anesthesia because prolonged fasting may provoke an attack.

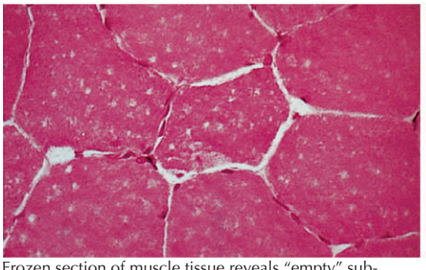
Mitochondrial myopathies are genetically determined metabolic muscle dysfunction disorders caused by mitochondrial genome mutations. This circular, double-stranded molecule, consisting of 16,569 base pairs and coding for 22 transfer ribonucleic acids (RNAs), 2 ribosomal RNAs, and 13 polypeptides contributing to various respiratory chain complexes, is the site of oxidation-reduction reactions generating adenosine triphosphate (ATP), the energy currency of the cell. These patients' mitochondria fail to produce sufficient energy for harmonious muscle metabolism function, leading to muscle weakness.

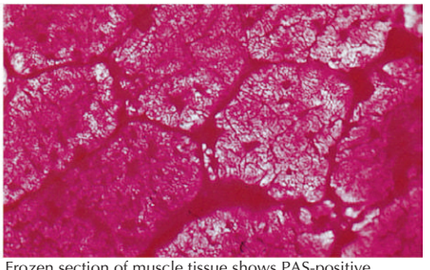
Ocular muscle weakness, notably ptosis and ophthalmoparesis, are characteristic clinical features that advance slowly, referred to as *chronic progressive ophthalmoplegia (CPEO)*. Cardinal morphologic features include muscle fibers having prominent subsarcolemmal mitochondria accumulations appearing red on modified trichrome stain, designated "*ragged red*" *fibers*. *Kearns-Sayre syndrome* is a severe mitochondrial myopathy related to mitochondrial deoxyribonucleic acid (DNA) deletion manifesting as a multisystem disorder having retinitis pigmentosa, heart block, elevated cerebrospinal fluid protein (sometimes including ataxia), short stature, endocrinopathy, and cognitive impairment.

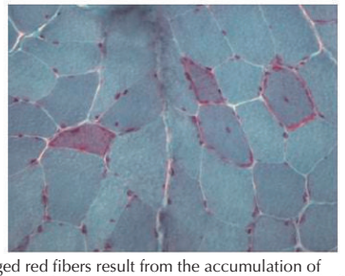
Two mitochondrial disorders, designated mitochondrial encephalomyopathies involving muscle and central nervous syndrome, are caused by transfer ribonucleic acid (tRNA) mitochondrial mutations. *Myoclonus epilepsy with ragged-red fibers (MERRF)* is characterized by mitochondrial myopathy, myoclonus, ataxia, weakness, and seizures. *Mitochondrial encephalomyopathy* with lactic acidosis and strokelike episodes *(MELAS)* has childhood onset, intermittent vomiting, proximal weakness, and recurrent strokelike episodes.

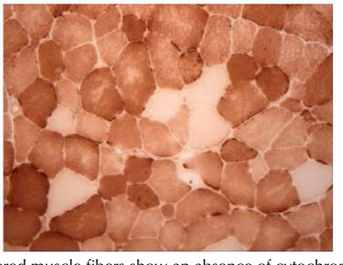
McArdle Disease




Frozen section of muscle tissue reveals "empty" subsarcolemmal vacuoles (H and E stain)


Frozen section of muscle tissue shows PAS-positive deposits of glycogen (PAS stain)


Ragged red fibers result from the accumulation of mitochondria below the sarcolemma of the muscle fibers; best appreciated on modified-Gomori trichrome stain. *Courtesy Sandra Camelo-Piragua, MD, C.S. Kubik Laboratory for Neuropathology, Massachusetts General Hospital and Harvard Medical School.*


Scattered muscle fibers show an absence of cytochrome *c* oxidase (COX) stain. COX stain is directed against one of the subunits encoded by mtDNA. COX negativity in an SDH-positive fiber is suggestive of a mtDNA mutation. *Courtesy Sandra Camelo-Piragua, MD, C.S. Kubik Laboratory for Neuropathology, Massachusetts General Hospital and Harvard Medical School.*

Myoglobinuric Syndromes Including Malignant Hyperthermia

Although virtually all disorders of muscle will eventually require the attention and expertise of the medical community for diagnosis and management, myoglobinuria is distinctive because it is a medical emergency that demands immediate attention. This disorder often signifies a life-threatening and usually reversible systemic medical illness that must be rapidly treated; left untreated it may result in irreversible kidney damage.

Myoglobinuria—the presence in urine of a 17.8-kDa, red pigment, iron-protein compound called myoglobin—results from rhabdomyolysis, which is the acute breakdown or necrosis of skeletal muscle fibers whose contents (among them myoglobin) subsequently leak into the circulation. Rhabdomyolysis reflects a fundamental problem involving disturbed muscle metabolism. The disorder is not uncommon; a recent study reported 26,000 cases per year annually from patient discharge databases. There tends to be a male predominance with a male to female ratio of 2:1.

The most common cause of rhabdomyolysis, amounting to 46% of cases, is exposure to exogenous myotoxic agents, such as illicit drugs, alcohol, and prescribed medications, including antipsychotics (the most common), statins, colchicines (in the setting of renal insufficiency), selective serotonin reuptake inhibitors (SSRIs), and lithium. Statins are commonly associated with myalgia and sometimes modest increases in creatine kinase (CK) but uncommonly with frank rhabdomyolysis; yet they are still the second largest group of drugs associated with rhabdomyolysis. When myoglobinuria does occur with a statin, the subject is more likely to have received a synthetic statin, such as atorvastatin, than a first-generation agent, such as pravastatin, and to be using other medications, such as gemfibrozil, that interfere with the statin's metabolic (CYP3A4) pathway.

Underlying muscle disease, including metabolic myopathies and inflammatory myopathy, are other rhabdomyolysis etiologies. Recurrent rhabdomyolysis occurs in 10% of patients with metabolic myopathies due to impaired glycogen metabolism or fatty acid oxidation, usually triggered by prolonged fasting or strenuous exertion. Defects in the mitochondrial respiratory chain, where adenosine triphosphate (ATP) is produced, also need consideration. These are ultimately caused by mutations or microdeletions in the cytochrome b oxidase gene or in genes encoding cytochrome oxidase (COX) subunits. Rarely, recurrent myoglobinuria may be caused by mitochondrial transfer ribonucleic acid (tRNA) mutations.

The clinical manifestations of rhabdomyolysis are muscle weakness, pain, tenderness and swelling, severely elevated serum levels of creatine kinase (CK), and tea- or cola-colored urine caused by the presence of myoglobin. This pigment is grossly visible as tea-colored when serum concentration surpasses 100 mg/dL. Weakness may be profound and generalized, but respiratory and bulbar muscles are not affected. Between attacks, strength is typically normal, but in the case of alcohol-induced rhabdomyolysis, a chronic myopathy may emerge after repeated attacks. Patients often have a low-grade fever and leukocytosis. Myoglobin is detected in the urine by dipstick and ultrafiltration and is probably found in only 20% of cases.

Acute renal failure complicates almost 15% to 30% of cases of rhabdomyolysis, and among patients with rhabdomyolysis, there is a fatality rate of 3%. However, most patients respond to hydration, sodium bicarbonate and mannitol, or furosemide diuresis.

Malignant hyperthermia (MH) is an autosomal dominant disorder caused by a ryanodine receptor gene defect on the long arm of chromosome 19. Occasionally, patients with MH have mild subclinical weakness, CK elevation, and nonspecific muscle biopsy changes. MH is associated with several well-characterized myopathies, including Duchenne muscular dystrophy, central core disease, myotonic dystrophy, and idiopathic hyperCKemia. The pathophysiology involves an abnormality in the sarcoplasmic reticulum's ability to regulate intracellular calcium.

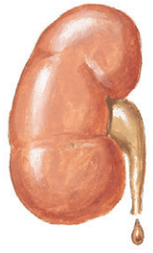
Succinylcholine or inhalational anesthetics lead to a rapid rise in intracellular calcium. Within minutes, an alarming clinical syndrome of increased muscle metabolism unfolds, characterized by rigidity secondary to muscle contracture, hyperthermia (temperature may soar, rising at a rate of 1 degree every 5 minutes, to as high as 43° C), metabolic acidosis, cardiovascular instability, and myoglobinuria. Urgent treatment consists of immediately stopping anesthesia, uncoupling excitation and contraction with dantrolene, reducing body temperature, intravenous fluids and diuresis, and correcting metabolic acidosis with bicarbonate. Certain anesthetics, including nitrous oxide, opiates, barbiturates, droperidol are considered safe to use in patients at risk of malignant hyperthermia.

Malignant hyperthermia bears some resemblance to neuroleptic malignant syndrome (NMS) because both share features of hyperthermia, rigidity, and myoglobinuria. NMS is triggered by a variety of neuroleptic agents, including phenothiazines and haloperidol, or by the withdrawal of dopaminergic drugs. It has additional clinical characteristics, including extrapyramidal and autonomic dysregulation. The primary pathophysiology is inhibition of central dopaminergic receptors so that heat generation is increased and heat dissipation is attenuated. Treatment requires dantrolene and dopamine agonists.

Paroxysmal rhabdomyolysis

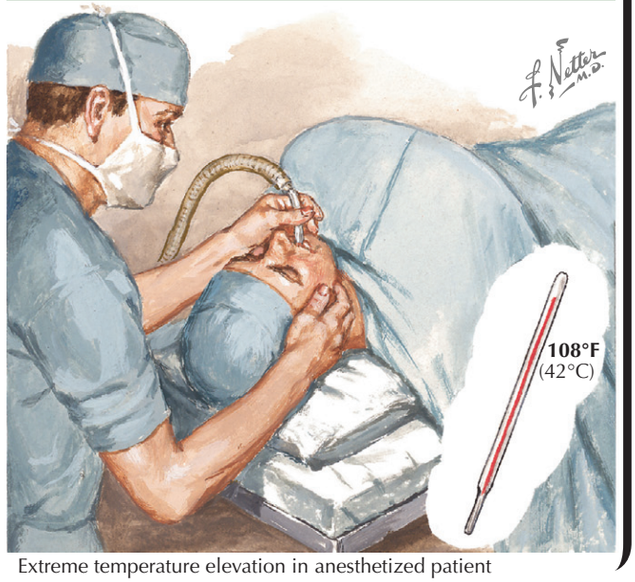
Severe muscle cramps and collapse on exertion (as in soldier on long march)

Urine brown, scanty (myoglobinuria)

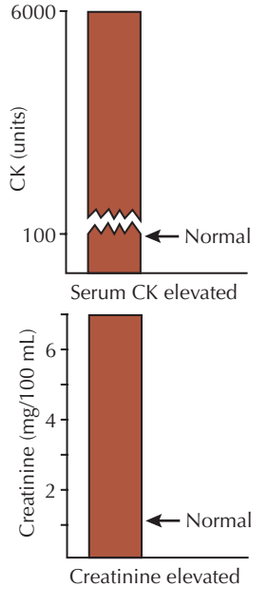


Renal shutdown

Malignant hyperthermia



Extreme temperature elevation in anesthetized patient



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Section 12—*Muscle and Its Disorders*

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