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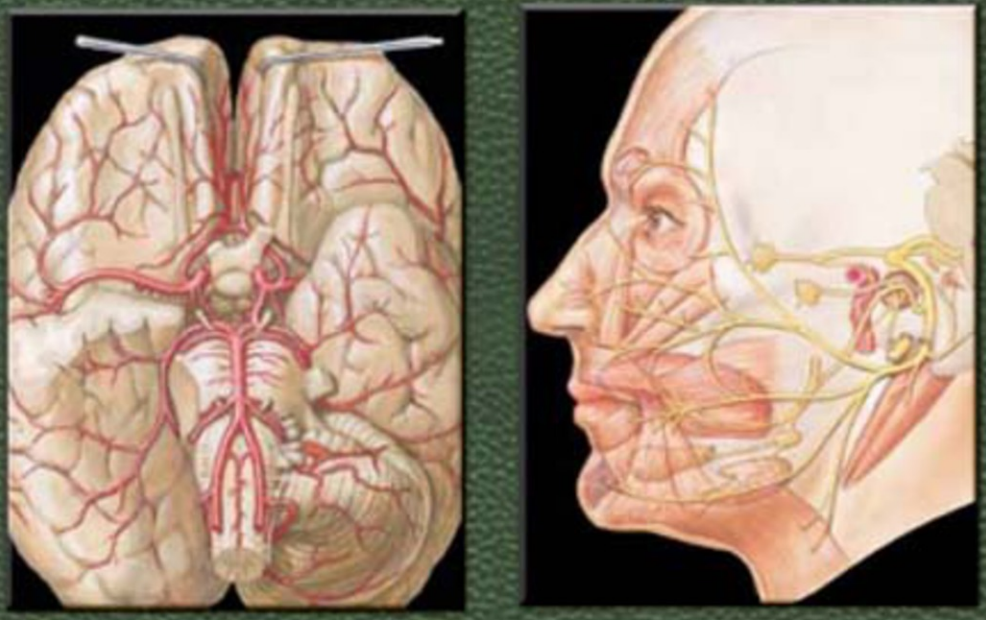
FRANK H. NETTER, MD 2nd Edition

VOLUME 7



NERVOUS SYSTEM

PART I Brain

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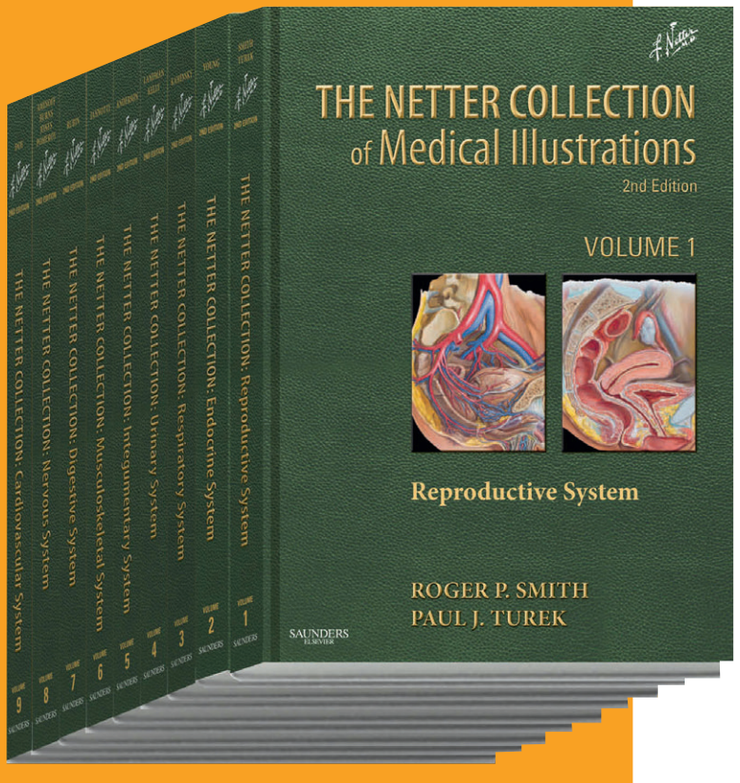

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VOLUME 7

The Netter Collection OF MEDICAL ILLUSTRATIONS

Nervous System

Part I—Brain

2nd Edition

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

Edited by

H. Royden Jones, MD
Jaime Ortiz-Patino Chair in Neurology
Lahey Clinic
Burlington, Massachusetts;
Clinical Professor of Neurology
Harvard Medical School
Boston Children's Hospital
Boston, Massachusetts

Ted M. Burns, MD
Professor and Executive Vice Chair
Department of Neurology
University of Virginia
Charlottesville, Virginia

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

Scott L. Pomeroy, MD, PhD
Bronson Crothers Professor of Neurology
Harvard Medical School
Chair, Department of Neurology
Neurologist-in-Chief
Boston Children's Hospital
Boston, Massachusetts

Additional Illustrations by Carlos A. G. Machado, MD

CONTRIBUTING ILLUSTRATORS
James A. Perkins, MS, MFA
Anita Impagliazzo, MA, CMI
Kristen Wienandt Marzejon, MS, MFA
Tiffany S. DaVanzo, MA, CMI
John A. Craig, MD

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1600 John F. Kennedy Blvd.
Ste. 1800
Philadelphia, PA 19103-2899

THE NETTER COLLECTION OF MEDICAL ILLUSTRATIONS: NERVOUS SYSTEM, PART I: BRAIN, Volume 7, Second Edition

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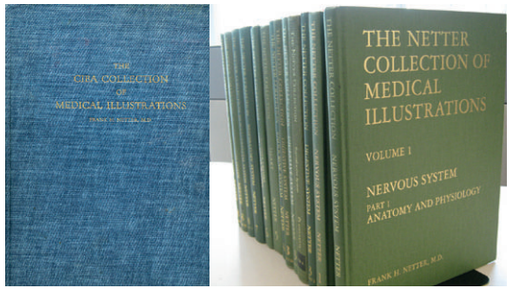
Dr. Frank Netter at work.



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."

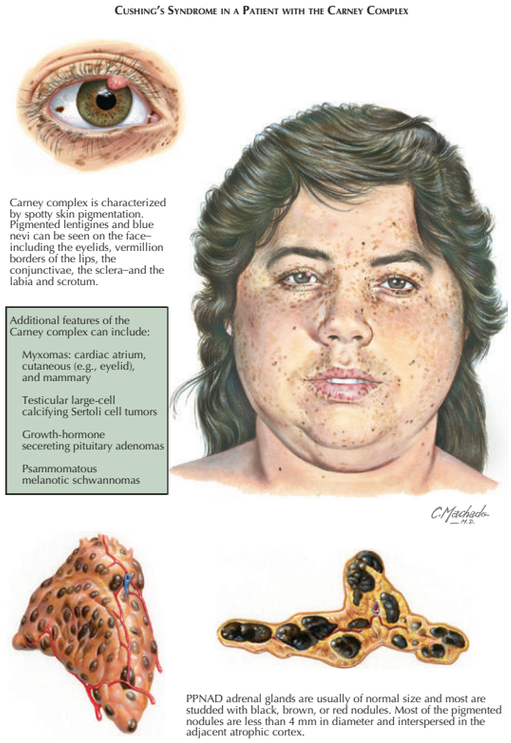
Dr. Frank H. Netter exemplified the distinct vocations of physician, artist, and teacher. Even more important—he unified them. Netter's illustrations always began with meticulous research into the detailed human clinical anatomy and pathology, a philosophy that steered his broad and deep medical understanding. 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.

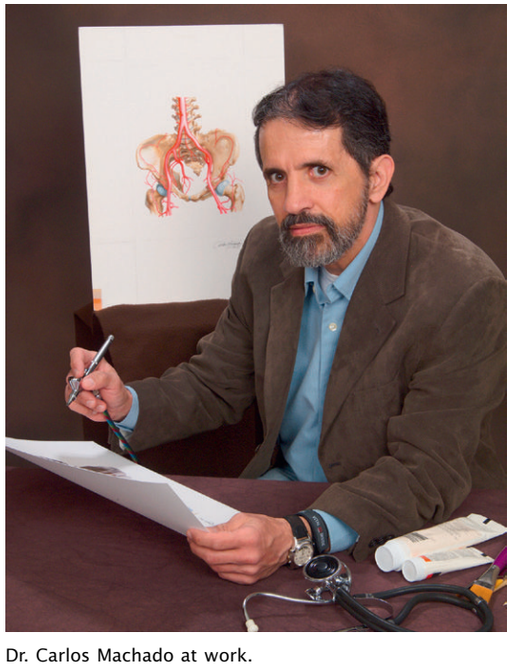
Noted artist-physician, Carlos Machado, MD, the primary successor responsible for continuing the Netter tradition, has particular appreciation for the Green Book series. "*The Reproductive System* is of special significance for those who, like me, deeply admire Dr. Netter's work. In this volume, he masters 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.

Nicholas A. Vick, MD
Clinical Professor of Neurology
Pritzker School of Medicine
University of Chicago
Chicago, Illinois;
Department of Neurology
Northshore University Healthsystem
Evanston, Illinois

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, 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 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 personal 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.

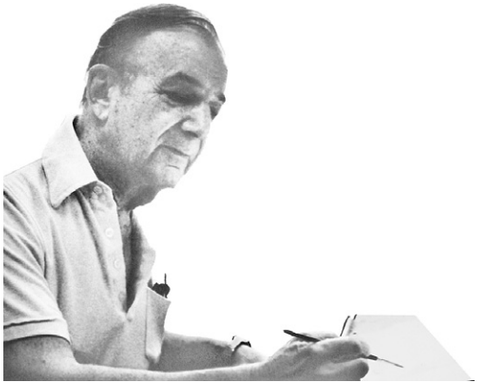
But the nervous system is not an isolated entity. It is intimately involved with the function of every other system of the body as portrayed in other volumes of the *Ciba Collection*. The association is, however, most marked with the musculoskeletal system. Indeed, there is great overlap between the 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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CONTRIBUTORS

Harold P. Adams, Jr., MD
Professor of Neurology
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Harvard Medical School
Neurodevelopmental Disabilities
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Plates 1-5–1-8, 1-10–1-12, 1-15–1-17, 1-23, 1-26–1-28

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Harvard Medical School
Massachusetts General Hospital, McLean Hospital
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Jeffrey M. Burns, MD, MS
Edward H. Hashinger Associate Professor of Neurology
University of Kansas School of Medicine
Associate Director
University of Kansas Alzheimer's Disease Center
Kansas City, Kansas
Plates 2-1–2-31

Louis R. Caplan, MD
Professor of Neurology
Harvard Medical School
Senior Neurologist
Beth Israel Deaconess Medical Center
Boston, Massachusetts
Plates 9-1–9-9, 9-18–9-27, 9-29

Claudia Chaves, MD
Assistant Clinical Professor of Neurology
Tufts University School of Medicine
Boston, Massachusetts;
Attending Neurologist
Lahey Clinic
Burlington, Massachusetts
Plates 9-10–9-17

Daniel O. Claassen, MD, MS
Assistant Professor of Neurology
Vanderbilt University
Nashville, Tennessee
Plates 2-1–2-31

Hilary Connery, MD, PhD
Assistant Professor of Psychiatry
Harvard Medical School
Boston, Massachusetts;
Clinical Director
Division of Alcohol and Drug Abuse
McLean Hospital
Belmont, Massachusetts
Plates 4-13–4-17

Cristina Cusin, MD
Harvard Medical School
Depression Clinical and Research Program
Department of Psychiatry
Massachusetts General Hospital
Boston, Massachusetts
Plates 4-2, 4-5

Fred Michael Cutrer, MD
Associate Professor of Neurology
Division Chair, Headache
College of Medicine
Mayo Clinic
Rochester, Minnesota
Plates 13-1–13-5

David R. DeMaso, MD
Professor of Psychiatry and Pediatrics
Harvard Medical School
Psychiatrist-in-Chief, Chairman of Psychiatry, and The Leon Eisenberg Chair in Psychiatry Boston Children's Hospital
Boston, Massachusetts
Plates 1-28, 4-25–4-31

Jamie M. Dupuy, MD
Behavioral Health at Harvard Vanguard
Boston, Massachusetts
Plate 4-7

Lori R. Eisner, PhD
Instructor
Harvard Medical School
Bipolar Clinic and Research Program
Massachusetts General Hospital
Boston, Massachusetts
Plates 4-18, 4-19

Oliver Freudenreich, MD, FAPM
Associate Professor of Psychiatry
Harvard Medical School
Boston, Massachusetts
Medical Director, MGH Schizophrenia Program
Department of Psychiatry
Massachusetts General Hospital
Boston, Massachusetts
Plate 4-12

Heather J. Fullerton, MD, MAS
Associate Professor of Neurology and Pediatrics
University of California San Francisco
Kenneth Rainin Chair of Pediatric Stroke Care
Director, Pediatric Stroke and Cerebrovascular Disease Center
San Francisco, California
Plate 9-44

Sandro Galea, MD, DrPH
Gelman Professor and Chair
Department of Epidemiology
Mailman School of Public Health
Columbia University
New York, New York
Plate 4-8

Néstor Gálvez-Jiménez, MD, MSc, MSHA, FACP
Pauline M. Braathen Endowed Chair in Movement Disorders
Chairman, Department of Neurology
Chief, Movement Disorders Program
Cleveland Clinic Foundation
Weston, Florida;
Clinical Professor of Neurology
Herbert Wertheim College of Medicine
Florida International University
Miami, Florida
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Georgina Garcia, MD
Instructor of Psychiatry
Harvard Medical School
Psychiatry Consultation Service
Boston Children's Hospital
Boston, Massachusetts
Plates 4-30, 4-31

Raghav Govindarajan, MD
Chief Neurology Resident
Department of Neurology
Cleveland Clinic Foundation
Weston, Florida
Plates 7-1–7-17, 7-19

Paul T. Gross, MD
Chair, Department of Neurology
Lahey Clinic Medical Center
Burlington, Massachusetts
Clinical Professor of Neurology
Tufts University School of Medicine
Boston, Massachusetts
Plates 5-23, 5-24

Gregory L. Holmes, MD
Chair, Department of Neurology
Professor of Neurology and Pediatrics
Dartmouth Medical School
Hanover, New Hampshire
Plates 3-1–3-13

Kinan Hreib MD, PhD
Assistant Clinical Professor of Neurology
Tufts University Medical School
Director Cerebrovascular Disease Center
Lahey Clinic
Burlington, Massachusetts
Plates 5-33, 5-34

Patricia Ibeziako, MD
Assistant Professor of Psychiatry
Harvard Medical School
Director, Psychiatry Consultation Service
Boston Children's Hospital
Boston, Massachusetts
Plates 1-28, 4-25–4-31

Adil Javed, MD, PhD
Assistant Professor of Neurology
The University of Chicago School of Medicine
Chicago, Illinois
Plates 10-15, 10-16

Justin Johnston, MS-3
Drexel University College of Medicine
Philadelphia, Pennsylvania
Plates 14-1–14-8, 14-10–14-17

Carlos S. Kase, MD
Professor of Neurology
Boston University School of Medicine
Chief of Neurology
Boston Medical Center
Boston, Massachusetts
Plates 9-28, 9-36–9-38

Milissa L. Kaufman, MD, PhD
Instructor in Psychiatry
Harvard Medical School
Medical Director, The Hill Center for Women Dissociative Disorders and Trauma Program at McLean Hospital
Belmont, Massachusetts
Plates 4-10, 4-11, 4-20, 4-21

Alex Sogomon Keuroghlian, MD, MSc
Clinical Fellow in Psychiatry
Harvard Medical School
Massachusetts General Hospital, McLean Hospital,
Boston, Massachusetts
Plates 4-10, 4-11, 4-20, 4-21

Karestan C. Koenen, PhD
Associate Professor
Department of Epidemiology
Mailman School of Public Health
Columbia University
New York, New York
Plate 4-8

Daniel Honore Lachance, MD
Associate Professor of Neurology
Mayo Medical School
Department of Neurology
Division of Neuro-Oncology
Mayo Clinic
Rochester, Minnesota
Plates 10-17–10-22

Anthony-Samuel LaMantia, PhD
Professor of Pharmacology and Physiology
The George Washington University School of Medicine and Health Sciences
Director, The George Washington Institute for Neuroscience
Washington, DC
Plates 1-1–1-4, 1-9, 1-13, 1-14, 1-18–1-22, 1-24, 1-25

Christine Lu-Emerson, MD
Clinical Fellow in Neuro-Oncology
Harvard Medical School
Massachusetts General Hospital
Department of Neuro-Oncology
Boston, Massachusetts
Plates 12-1–12-18

Jonathan Lipton, MD, PhD
Instructor, Department of Neurology
Harvard Medical School
Boston Children's Hospital
Division of Sleep Medicine
Boston, Massachusetts
Plates 5-1–5-22

Kenneth J. Mack, MD, PhD
Associate Professor of Neurology
College of Medicine
Mayo Clinic
Child and Adolescent Neurology
Rochester, Minnesota
Plate 13-9

Ruta Nonacs, MD, PhD
Department of Psychiatry
Harvard Medical School
Division of Psychiatry
Massachusetts General Hospital
Boston, Massachusetts
Plates 4-3

Darren P. O'Neill, MD
Assistant Professor of Clinical Radiology
Indiana University School of Medicine
Chief of Neuroradiology
Department of Radiology and Imaging Sciences
Indianapolis, Indiana
Plates 11-1–11-11, 11-15–11-17, 11-21

Joel M. Oster, MD
Assistant Clinical Professor of Neurology
Tufts University School of Medicine
Boston, Massachusetts;
Department of Neurology
Lahey Clinic
Burlington, Massachusetts
Plates 5-23, 5-24

Ayca Deniz Ozel, MD
Clinical Assistant Professor
Tufts University School of Medicine
Boston, Massachusetts;
Medical Director
New England Rehabilitation Hospital
Department of Neurology
Lahey Clinic
Burlington, Massachusetts
Plates 9-45–9-47

Alan K. Percy, MD
Professor of Pediatric Neurology and Genetics
University of Alabama
Chair Emeritus, Child Neurology
Department of Pediatrics and Neurology
Civitan International Research Center
Birmingham, Alabama
Plates 1-29, 8-19

Roy H. Perlis, MD, MSc
Associate Professor of Psychiatry
Harvard Medical School
Director, Center for Experimental Drugs and Diagnostics (CEDD)
Center for Human Genetic Research
Richard B. Simches Research Center
Massachusetts General Hospital
Boston, Massachusetts
Plates 4-6, 4-9

Dennis Roberts, MD
Department of Neurosurgery
Allegheny General Hospital
Drexel University College of Medicine
Pittsburgh, Pennsylvania
Plates 14-1–14-8, 14-10–14-17

Carrie (Beth) E. Robertson, MD
Assistant Professor of Neurology
College of Medicine
Mayo Clinic
Rochester, Minnesota
Plates 13-1–13-8, 13-10–13-19

Shenandoah Robinson, MD
Department of Neurosurgery
Harvard Medical School
Department of Neurosurgery
Boston Children's Hospital
Boston, Massachusetts
Plates 1-5–1-8, 1-10–1-12, 1-15–1-17, 1-23, 1-26–1-28

Karen L. Roos, MD
John and Nancy Nelson Professor of Neurology
Professor of Neurological Surgery
Indiana University School of Medicine
Indianapolis, Indiana
Plates 11-1–11-11, 11-15–11-17, 11-21

Clifford B. Saper, MD, PhD
James Jackson Putnam Professor of Neurology and Neuroscience
Harvard Medical School
Chairman, Department of Neurology
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, Massachusetts
Plates 5-1–5-22

Jeremy Schmahmann, MD
Professor of Neurology
Harvard Medical School
Director, Ataxia Unit; Cognitive Behavioral Neurology Unit
Laboratory for Neuroanatomy and Cerebellar Neurobiology
Department of Neurology
Massachusetts General Hospital
Boston, Massachusetts
Plates 8-1–8-18

Rod C. Scott, MD, PhD
Reader in Paediatric Neurosciences
UCL Institute of Child Health
London, England;
Dartmouth Medical School
Hanover, New Hampshire
Plates 3-1–3-13

Andrea L. Seek, MD
Assistant Clinical Professor of Psychiatry
Tufts University School of Medicine
Department of Psychiatry and Behavioral Medicine
Lahey Clinic
Burlington, Massachusetts
Plates 4-22, 4-23

Magdy Selim, MD, PhD
Associate Professor of Neurology
Harvard Medical School
Co-Director, Stroke Center
Beth Israel Deaconess Medical Center
Boston, Massachusetts
Plates 9-33–9-35

V. Michelle Silvera, MD
Instructor in Radiology
Harvard Medical School
Boston Children's Hospital
Boston, Massachusetts
Imaging for Plates 12-1–12-13, 12-15–12-18

Andrew M. Southerland, MD, MSc
Assistant Professor
Division of Vascular Neurology
Department of Neurology
University of Virginia Health System
Charlottesville, Virginia
Imaging for Plate 2-22

Jerry W. Swanson, MD
Professor of Neurology
College of Medicine
Mayo Clinic
Rochester, Minnesota
Plates 13-6–13-8

Russell H. Swerdlow, MD
Professor of Neurology
Director, University of Kansas Alzheimer's Disease Center
University of Kansas School of Medicine
Kansas City, Kansas
Plates 2-1–2-31

Robert C. Tasker, MA, AM, MBBS, FRCP, MD
Professor of Neurology and Anaesthesia (Pediatrics)
Harvard Medical School
Chair in Neurocritical Care
Department of Neurology, Department of Anesthesiology, Perioperative and Pain Medicine
Division of Critical Care Medicine
Boston Children's Hospital
Boston, Massachusetts
Plates 6-1–6-9, 14-9

Christine B. Thomas, MD
Assistant Clinical Professor of Pathology
Tufts University School of Medicine
Department of Anatomic Pathology
Lahey Clinic
Burlington, Massachusetts
Plates 5-33, 5-34

Nicholas A. Tritos, MD, DSc
Assistant Professor of Medicine
Harvard Medical School
Neuroendocrine Unit
Massachusetts General Hospital
Boston, Massachusetts
Plates 5-25–5-32

Barbara Voetsch, MD, PhD
Department of Neurology
Stroke Service
Lahey Clinic
Burlington, Massachusetts
Plates 9-30–9-32

Heather J. Walter, MD, MPH
Professor of Psychiatry and Pediatrics
Vice-Chair, Psychiatry
Boston University School of Medicine
Chief, Child and Adolescent Psychiatry
Boston Medical Center
Boston, Massachusetts
Plates 4-25–4-28

Patrick Y. Wen, MD
Professor of Neurology
Harvard Medical School
Director, Center for Neuro-Oncology
Dana-Farber Cancer Institute
Boston, Massachusetts
Plates 12-1–12-18

Jack Wilberger, MD, FACS
Professor and Chairman, Department of Neurosurgery
Allegheny General Hospital
Drexel University College of Medicine
Vice President, Graduate Medical Education
West Penn Allegheny Health System
Designated Institutional Official
Chairman, Graduate Medical Education Committee
AGH-WPH Medical Education Consortium
Pittsburg, Pennsylvania
Plates 14-1–14-8, 14-10–14-17

John W. Winkelman, MD, PhD
Associate Professor of Psychiatry
Harvard Medical School
Associate Physician
Division of Sleep Medicine, Department of Medicine
Brigham and Women's Hospital
Brighton, Massachusetts
Plate 4-24

Curtis W. Wittmann, MD
Department of Psychiatry
Harvard Medical School
Division of Psychiatry
Massachusetts General Hospital
Boston, Massachusetts
Plate 4-4

Yuval Zabar, MD
Assistant Professor of Neurology
Tufts University School of Medicine
Director, Center for Geriatric Neurology
Lahey Clinic
Burlington, Massachusetts
Plates 4-1, 4-22, 4-23

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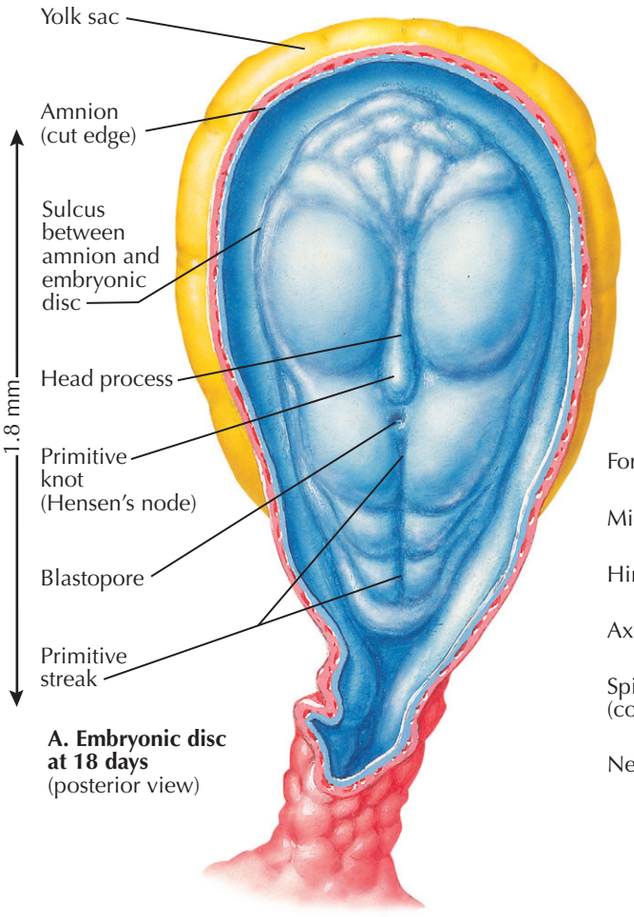
NORMAL AND ABNORMAL DEVELOPMENT

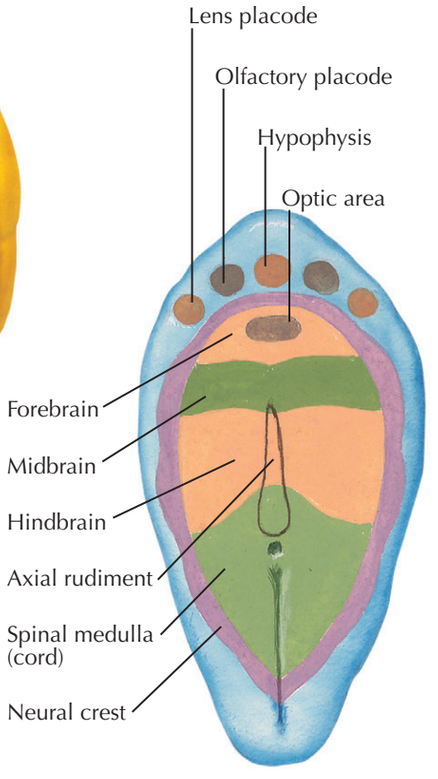
Initial Specification of the Nervous System: The Embryo at 18 Days

After fertilization and implantation, the embryo consists of a single cell layer called the inner cell mass. The inner cell mass sits at the bottom of a fluid-filled cavity defined by the key extraembryonic membrane, *the amnion*. Beneath the embryo is another cavity, the *yolk sac*, lined with a cell layer called the embryonic *hypoblast*, some of which will go on to form the *allantois*, an additional extraembryonic membrane. Cells from the inner cell mass that are immediately adjacent to the hypoblast constitute a second embryonic layer, called the *epiblast*, that will form most of the embryo. At this point in development, approximately 18 days after fertilization/implantation, epiblast cells define the *embryonic disc*. Once formed, the embryonic disc goes through a series of cell movements referred to collectively as *gastrulation*. The key movement is the local proliferation, accumulation, and ingression of cells from the epiblast that form first the *primitive knot* (or Hensen's node), then the *primitive streak*, which defines the midline axis of the embryo. The cells that have migrated "into" the embryo from the primitive knot, interposed between the epiblast and the hypoblast, coalesce to form a distinct cell layer called the *mesoderm*. Their position as the "middle" (meso) layer of the embryo defines the remaining epiblast cells on top of these mesodermal cells as *ectoderm* (ecto: outside) and the hypoblast cells that are underneath as *endoderm* (endo: inside). A subset of ectodermal cells will form the entire central and peripheral nervous system. This subset of cells is defined by their proximity to mesodermal cells that coalesce first to form the *notochordal plate*, and then further to form the *notochord* at the midline of the embryo. The notochord becomes a source of signaling molecules released by notochord cells that act on overlying ectoderm. These signals both instruct the overlying ectodermal cells to become neural stem cells capable of giving rise to neurons and glia of the mature central and peripheral nervous systems and protect these early neural stem cells (collectively, the *neuroectoderm*) from additional signals in the embryo that transform ectodermal cells into skin and other derivatives.

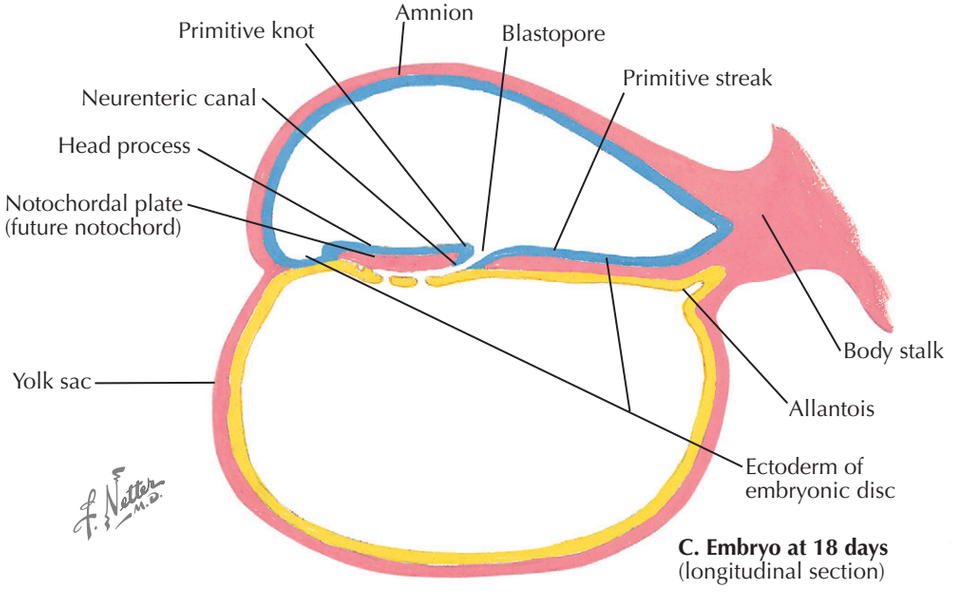
At this point, the fate of ectodermal cells, particularly that of the visibly thickened sheet of cells above the notochord called the *neural plate*, can be mapped fairly precisely. Stem cells found in local regions of the ectoderm and neuroectoderm from the front (nearer to the primitive knot/Hensen's node) to the back will go on to form sensory specializations *(lens and olfactory placode)*, endocrine tissue *(the hypophysis)*, and, most notably, distinct regions of the central nervous system (CNS), including the forebrain (cerebral cortex, hippocampus, basal ganglia, basal forebrain regions such as the amygdala, olfactory bulb, and thalamus), midbrain (superior and inferior colliculi and tegmental areas), hindbrain (cerebellum and brainstem), and spinal cord. In addition, the neuroectodermal cells at the margin of the neural plate—farthest from the notochord and its instructive as well as protective signals—become a specialized population of neural stem cells called the *neural crest*. These neural crest cells eventually delaminate from the neuroectoderm and migrate throughout the embryo, where they make sensory ganglia as well as sympathetic and parasympathetic ganglia of the peripheral nervous system. In addition, neural crest cells contribute to the adrenal glands, and make pigment cells as well as well as cranial bones, teeth, and connective tissue. This geometric division of the neuroectoderm into a *"fate map"* for early populations of neural stem cells at distinct locations reflects a more fundamental molecular process. Because of variations in local signals exchanged between the notochord, the neuroectoderm, and some other early embryonic structures that arise during gastrulation, there are local changes in patterns of gene expression that distinguish the cells that will generate the forebrain, midbrain, hindbrain, and spinal cord. For the most part, these genes are transcription factors that then influence the subsequent expression of downstream genes that confer local identity in neuronal progeny. Thus the combination of cell movements and cell-cell signaling that occur during early embryogenesis establish a spatial and molecular template for the construction of the entire central and peripheral nervous system.



A. Embryonic disc at 18 days (posterior view)



B. Developmental fates of local regions of the ectoderm of the embryonic disc at 18 days



C. Embryo at 18 days (longitudinal section)

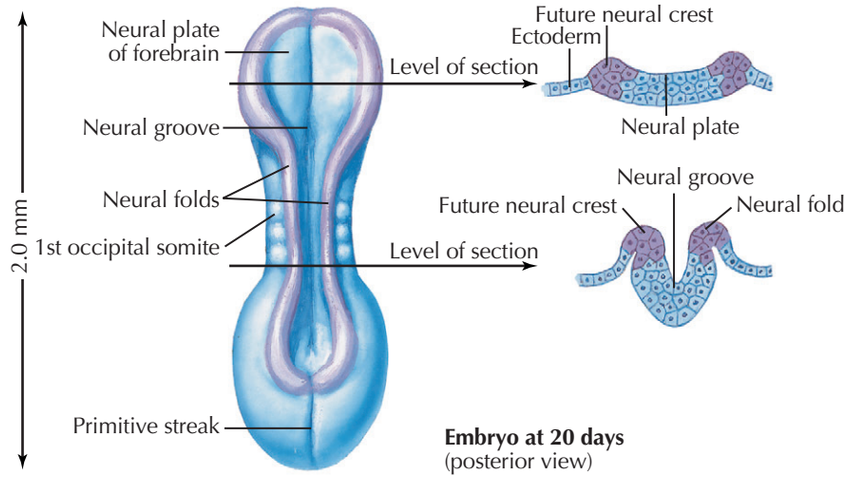
Initial Formation of the Brain and Spinal Cord: The Embryo at 20 to 24 Days

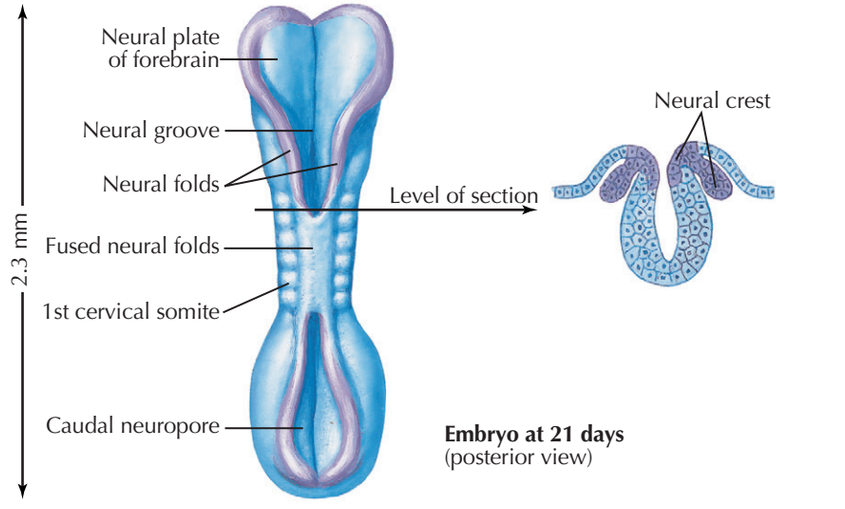
As gastrulation ends, another series of cell movements—*neurulation*—transforms the neural plate into a tube of neural stem cells: the *neural tube*. Neurulation is accompanied by elaboration of mesodermal tissues into *somites* that form the axial skeleton and musculature, and visceral differentiation by the endoderm. These events cooperate to yield an embryonic nervous system that consists of a tube surrounding a fluid-filled cavity that will eventually form *the brain ventricular system* (see below) and the *spinal cord central canal*. The geometry of the neural plate and underlying notochord remains the primary determinant of how the neural tube forms. By day 20 of development, the neural plate has thickened and flexed upward from the midline, right above the notochord. The neural crest, initially specified at the lateral (or alar) margins of the neural plate is relocated to the posterior midline as the rest of the neural plate forms a tube by joining the neural folds at each lateral margin of the neural plate at the posterior midline.

By embryonic day 21, the neural tube in the midsection of the embryo has closed; the neural folds fuse and the underlying neuroectoderm encloses a fluid-filled cavity that becomes the spinal cord central canal. The neural crest delaminates at the posterior midline. This epithelial (cell sheets) to mesenchymal (loosely arrayed, motile cells between the sheets) transition of neural crest cells is much like the epithelial to mesenchymal transition that occurs in many cancers of mature epithelial tissues. For the neural crest, however, this transition begins a highly regulated process of migration to multiple peripheral locations where neural crest precursors continue to divide and differentiate into sensory ganglia (cranial and posterior root), autonomic ganglia, enteric neurons, pigment cells, components of the posterior aorta, cranial bones, and connective tissues. The neural plate at the anterior and posterior ends of the embryo has begun to fold into a neural tube but has not yet reached the point where lateral margins meet and fuse at the posterior midline. The midline "hinge point" where neural tube formation begins is visible as the *neural groove* anteriorly and the *rhomboid sinus* posteriorly, and the forebrain neural plate as well as the posterior spinal cord remain open to the extraembryonic environment.

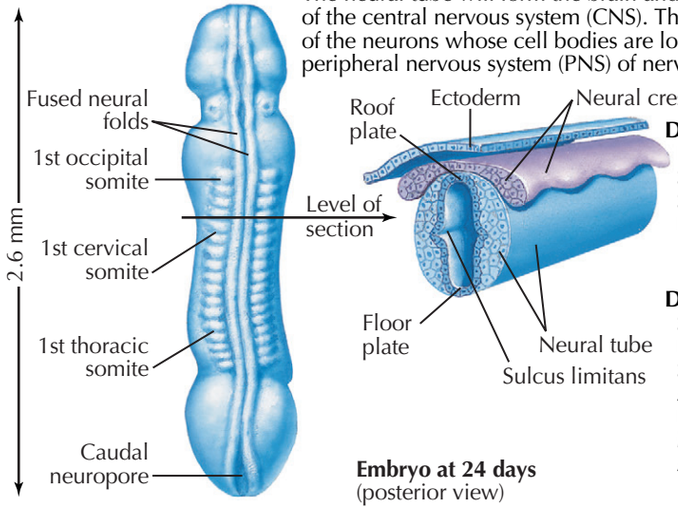
Within another 3 days, by embryonic day 24, the neural tube is closed from the anterior end (where the brain will form) throughout much of the length of the spinal cord, with the exception of an opening at the rhomboid sinus or posterior neuropore. At this stage, the neural tube has begun to acquire additional signs of differentiation that reflect the genesis of neurons with distinct functions. First, based upon the location of either the notochord, or the alar region and neural crest, two regions of the neural tube become specialized to provide signals to the rest of the neuroepithelial neural stem cells that constitute the developing nervous system. The neural tube cells above the notochord at the anterior midline constitute the *floor plate*, and those at the fusion of the neural folds at the posterior midline become the *roof plate*. Floor plate and roof plate cells secrete signals that influence neighboring cells in the neural tube, such as sonic hedgehog, a peptide hormone that regulates proliferation and differentiation. These signals further distinguish the presumptive spinal cord and hindbrain into *anterior/basal* and *posterior/alar* regions (see also Plate 1-6), separated by a midline groove referred to as the *sulcus limitans* (this structure is not always easy to see).

These geometrically defined domains of neural stem cells generate functionally distinct classes of neurons. The neural stem cells of the posterior/alar region will generate sensory projection and interneurons that relay and process incoming sensory information from peripheral sensory ganglia, and those in the anterior/basal region will give rise to motor neurons that project to peripheral muscles and autonomic ganglia, as well as interneurons that modulate the output of motor neurons. Signals from the roof plate and floor plate elicit local expression of transcription factors and other determinants in neighboring neural stem cells. These factors define the capacity of the local stem cells to generate distinct classes of sensory and motor projection or interneurons.



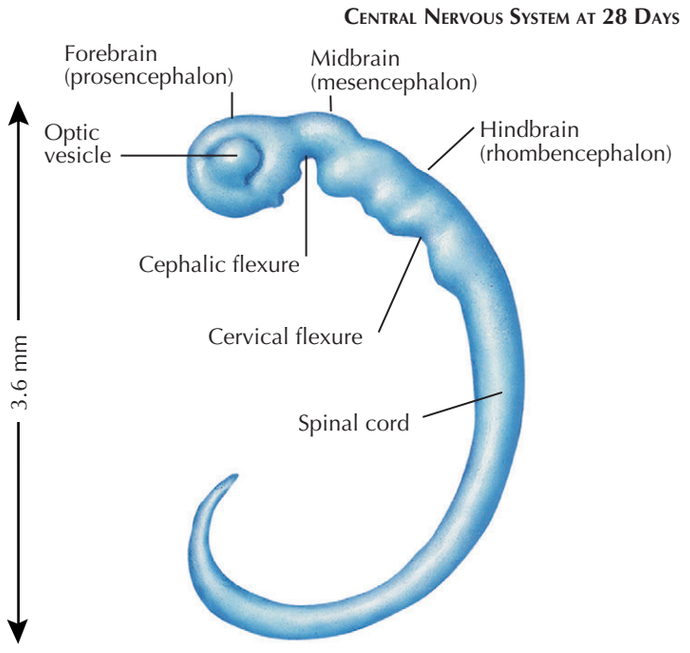


The neural tube will form the brain and spinal cord, the two components of the central nervous system (CNS). The neural crest will give rise to all of the neurons whose cell bodies are located outside the CNS in the peripheral nervous system (PNS) of nerves, ganglia, and plexuses.



Derivatives of the neural tube include
- Neurons of the CNS
- Supporting cells of the CNS
- Somatomotor neurons of the PNS
- Presynaptic autonomic neurons of the PNS

Derivatives of the neural crest include
- Sensory neurons in the PNS
- Postsynaptic autonomic neurons
- Schwann (neurolemma) cells
- Adrenal medulla cells
- Head mesenchyme
- Melanocytes in the skin
- Arachnoid and pia mater of meninges (dura mater from mesoderm)

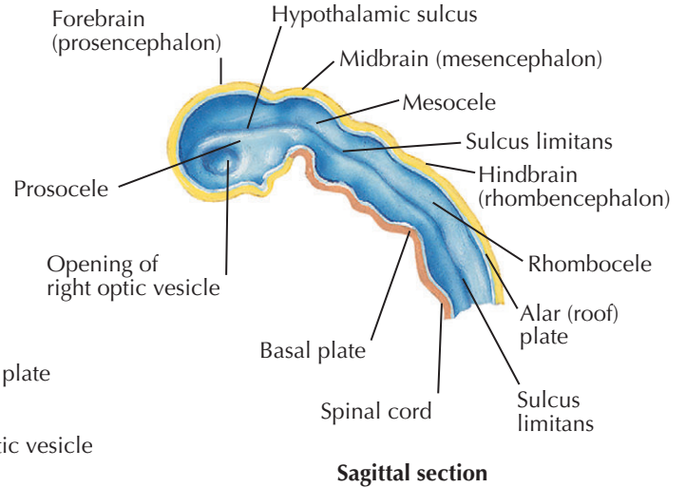


Morphogenesis of the Brain, Spinal Cord, and Peripheral Nervous System: The Embryo from 28 through 36 Days

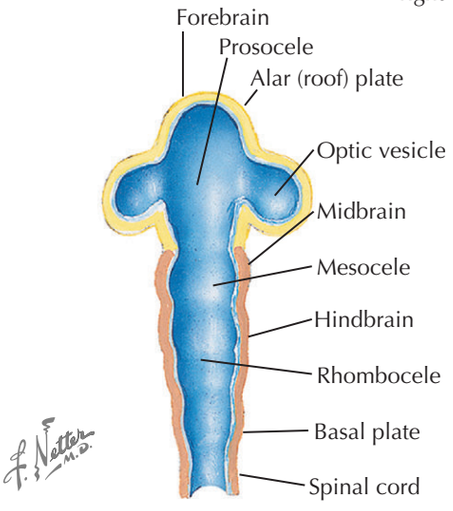
Within an additional 4 days of embryogenesis, the neural tube closes completely, and the developing nervous system undergoes additional changes that define the stem cell populations that generate all of the distinct structures of the mature brain and peripheral nervous system. These changes are seen anatomically as the emergences of a series of bulges, bends, and grooves that distinguish specific regions of the developing nervous system from the anterior to posterior end. At the anterior end of the closed neural tube, the neuroepithelium expands into a hollow globe called the *prosencephalon*. The neural stem of the prosencephalon is specified to generate all of the neurons that will comprise the major regions of the *forebrain*. Subsequently, two bilaterally symmetric structures emerge from the lateral/anterior aspect of the prosencephalon. These are the *optic vesicles* that will generate all of the neural cells of the retina. Immediately posterior to the prosencephalon, the neural tube bends at a point referred to as the *cephalic flexure*. This bending point begins the process by which the brain (and the head) will become distinct from the spinal cord and rest of the body. The stem cells in the neural tube in the region of the cephalic flexure become specified to give rise to the structures of the *midbrain* (also referred to as the mesencephalon).

The region of the neural tube posterior to the midbrain undergoes a dramatic series of morphogenetic changes that transform it into the *rhombencephalon*. The most noticeable event is the establishment of a series of repeated bulges and grooves along the anterior/posterior axis that constitute a series of transient domains referred to collectively as *rhombomeres*. The neural stem cells in each rhombomere acquire distinct patterns of gene expression based upon their location. These distinctions then facilitate local genesis of motor neurons that give rise to the cranial motor nerves, and to sensory neurons that provide the targets for peripheral cranial sensory inputs to the brainstem (including the *cerebellum/pons*, also known as the *metencephalon*, and the *medulla oblongata*, also known as the *myelencephalon*). The relationship between rhombomeres and the developing structures of the head is quite precise. Indeed, the neural crest that emerges from the neural tube in the region of each rhombomere (note that there is no neural crest associated with the prosencephalon) establishes cranial target structures that are often innervated by motor neurons generated in the same rhombomere. Similarly, cranial ganglia derived from neural crest that migrates from distinct rhombomeres have a specific relationship with target nuclei generated within the relevant rhombomere.

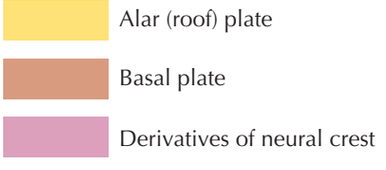
Within an additional 8 days of development (36 days), the basic topography of the entire nervous system has been established, as have most of the component

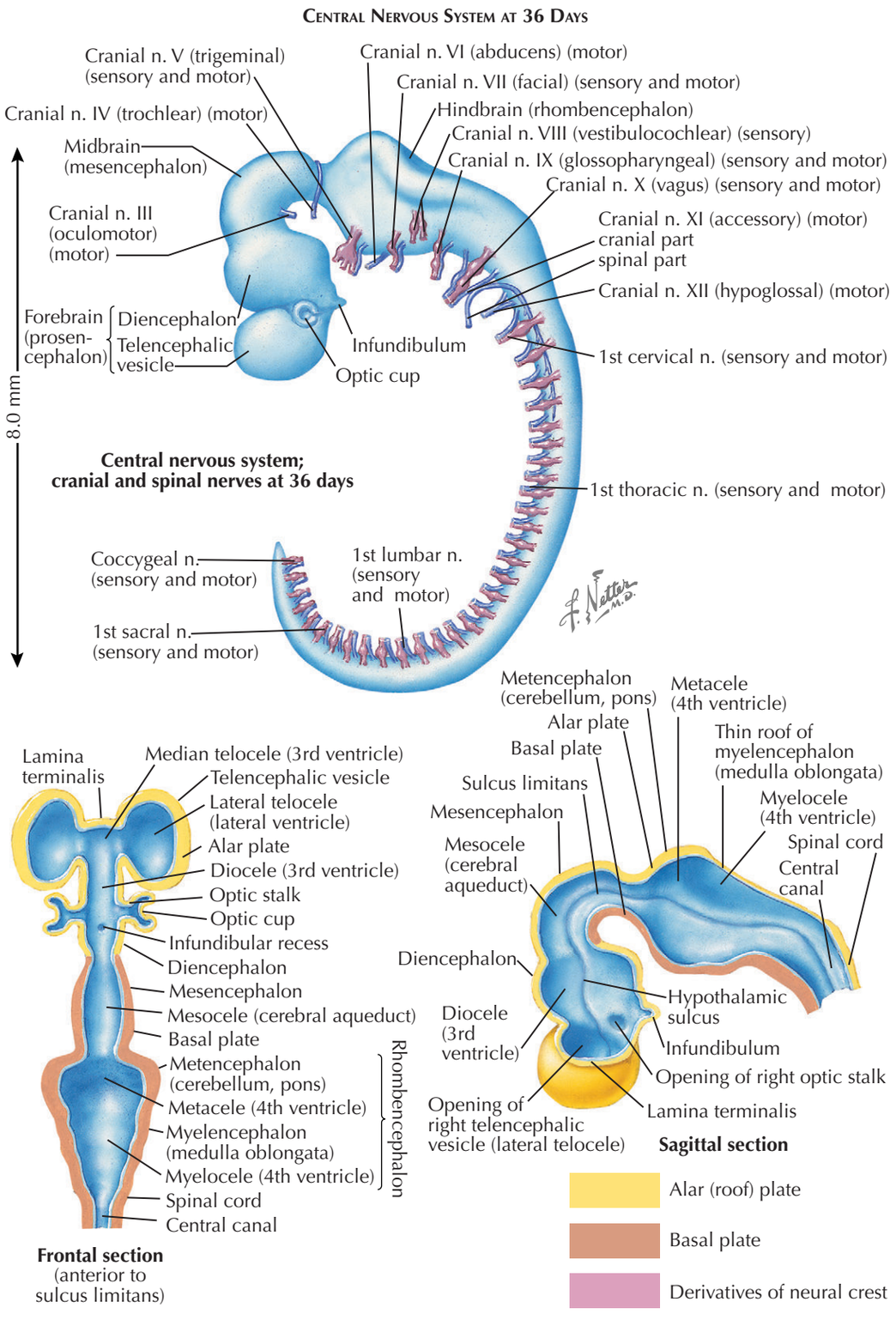


Sagittal section



Frontal section
(anterior to sulcus limitans)



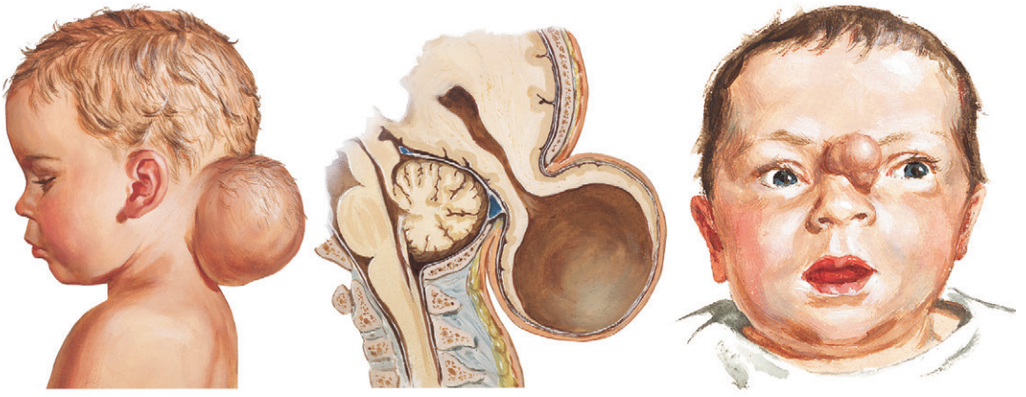


Morphogenesis of the Brain, Spinal Cord, and Peripheral Nervous System: The Embryo from 28 through 36 Days

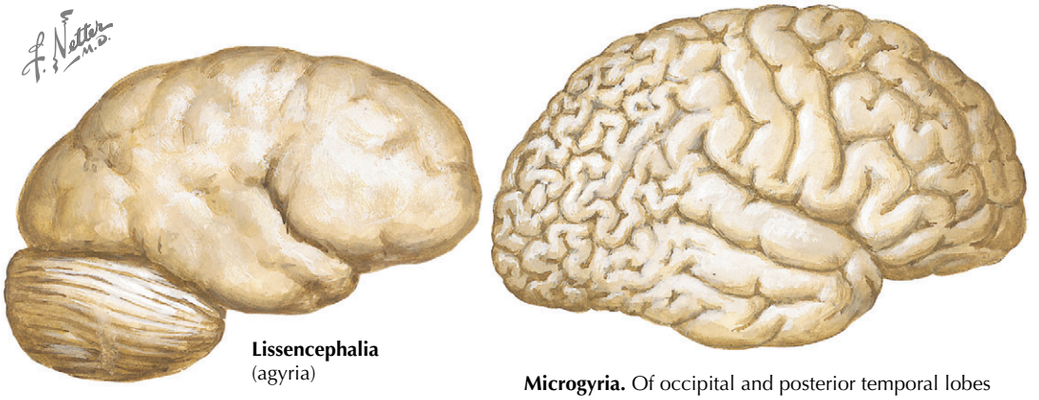
(Continued)

regions that will then grow and differentiate throughout the balance of embryogenesis. The prosencephalon becomes further subdivided into two *telencephalic vesicles* (collectively called the *telencephalon*) that will give rise to the bilaterally symmetric structures of the forebrain: the cerebral cortical hemispheres, the hippocampi, the basal ganglia, basal forebrain nuclei, and the olfactory bulbs. The remainder of the prosencephalon, posterior to the telencephalic vesicles, becomes the *diencephalon*, which will generate the epithalamus (dorsal structures known as the habenula), thalamus (the relay nuclei that project to the cerebral cortex), and hypothalamus (motor/endocrine control nuclei that regulate visceral and reproductive function and homeostasis). The mesencephalon, rhombencephalon, and myelencephalon become further differentiated, and the *cranial motor nerves* (see darker blue in the upper panel of Plate 1-4), *sensory ganglia*, and associated cranial *sensory nerves* (lighter pink, Plate 1-4) become clearly visible along the anterior to posterior extent of the midbrain and hindbrain. In parallel, the motor nerves and sensory ganglia and associated sensory nerves of the rest of the body become visible along the anterior to posterior extent of the spinal cord.

While the neural tube is acquiring additional regional identity that prefigures the final generation of the mature neurons and glia in distinct brain regions, the space enclosed by the neural tube becomes further defined as the *ventricular system*. The ventricular system will be filled with a distinctive fluid—*cerebrospinal fluid (CSF)*—that provides specific signaling molecules to neural stem cells during development and then maintains the appropriate ionic balance for electrical signaling in the more mature nervous system. Initially, at 28 days of embryonic development, the ventricular spaces are referred to as the *prosocele*, *mesocele*, and *rhombocele*, corresponding to the primitive regions of the neural tube that surround them. Within 8 days, the ventricular system has become more elaborate, in parallel with the elaboration of the forebrain, midbrain, and hindbrain. There are now two *lateral ventricles* enclosed by the telencephalic vesicles, a *diocele* that will become the *third ventricle*, a mesocele that will become the *cerebral aqueduct*, and a *metacele* and *myelocele* that will collectively grow into the *fourth ventricle*. The ventricular space enclosed by the developing spinal cord is now defined as the *central canal*. Thus by approximately 36 days—a bit more than 1 month into the 9-month period of gestation—the fetus has acquired all of the major regions of the brain and the anatomic divisions of the ventricular system.

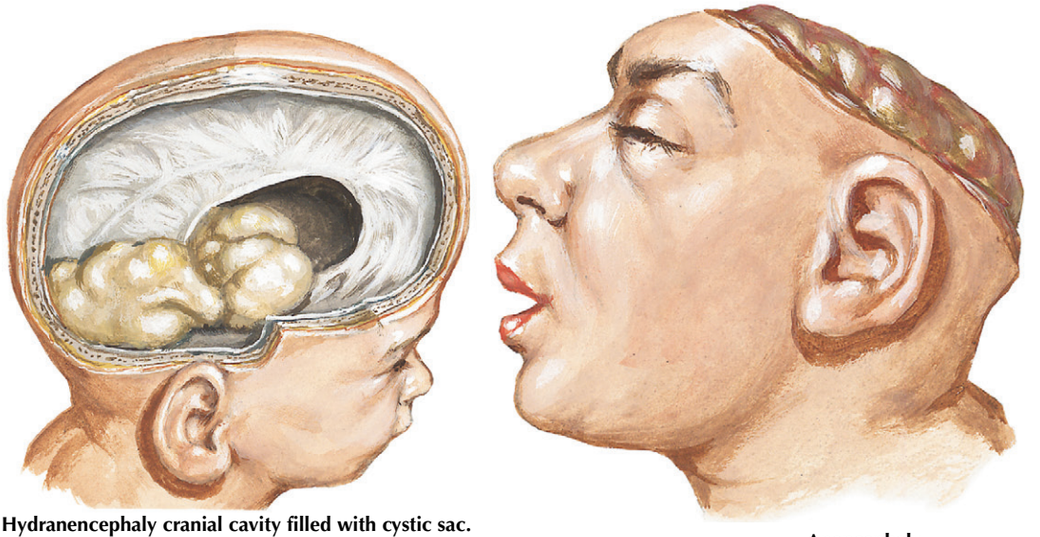


Occipital encephalocele **Frontal encephalocele**



Lissencephalia
(agyria)

Microgyria. Of occipital and posterior temporal lobes



Hydranencephaly cranial cavity filled with cystic sac.
Only remnants of basal ganglia and posterior lobe

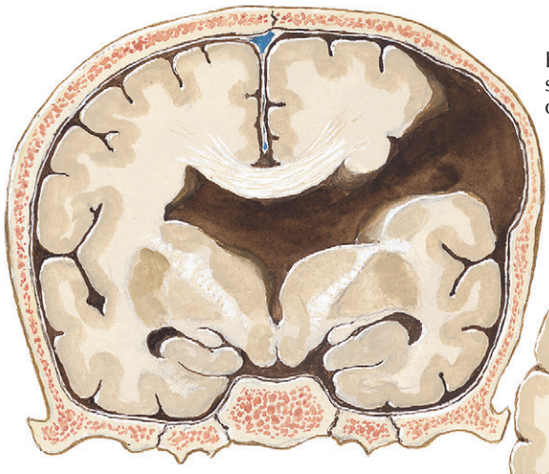
Anencephaly

Defective Neural Tube Formation

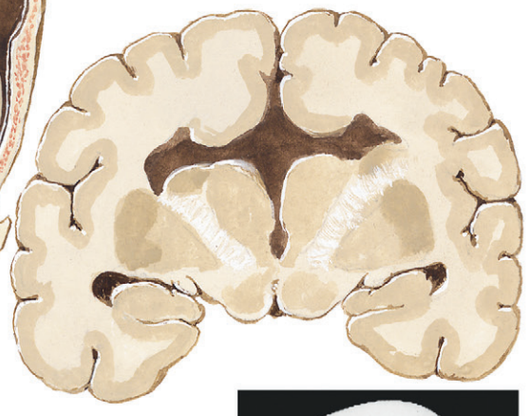
The process of neurulation, including neural tube closure, is the first target of pathogenesis that specifically compromises the developing nervous system. Neural tube defects—most frequently failure of neural tube closure—can be caused by a number of factors, including single-gene mutations, aneuploid chromosomal anomalies, toxic exposures to pharmaceuticals, chemicals and drugs of abuse, maternal diabetes, and dietary deficits—most notably low levels of *folic acid.* Failure of cranial neural tube closure results in either *anencephaly* or an *encephalocele* (see Plate 1-5), whereas a defective caudal closure results in *myelomeningocele* (see Plate 1-7). Onset of anencephaly, a fatal maldevelopment characterized by lack of a majority of the forebrain, is by the 24th day. The skull vault is absent, and the brain is a vascular mass. Ultrasound examination and an elevated alpha-fetoprotein level in maternal blood and amniotic fluid indicate the diagnosis prenatally. Risk of recurrence is 5%.

An encephalocele is a protrusion of a portion of the brain or meninges through a skull defect. Although an encephalocele usually occurs in the occipital region in patients from Europe and North America, it can develop frontally or in the nasal passages, especially in children in Southeast Asia (see Plate 1-5). The herniated brain tissue is connected through a narrow isthmus. With occipital encephaloceles, there may be associated abnormalities of the cerebellum and midbrain. The Meckel-Gruber syndrome includes a posterior encephalocele, microcephaly, microphthalmus, cleft lip and palate, polydactyly, and polycystic kidneys. This syndrome is inherited in an autosomal recessive manner, whereas for parents of a child with simple encephalocele, the risk of recurrence is 5%.

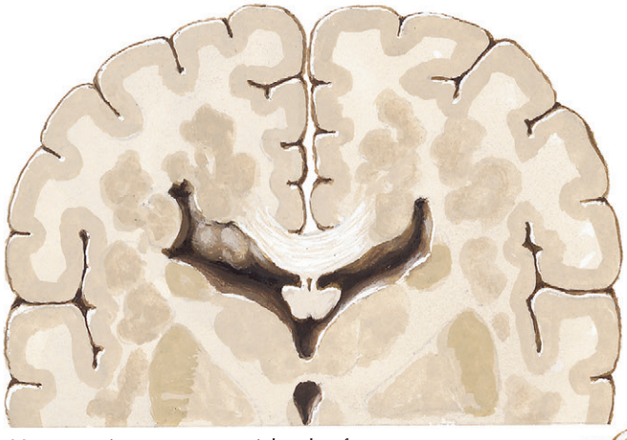
Myelomeningocele results from failure of caudal closure of the neural tube, with an 80% incidence in the lumbar region. Because closure of the central canal is essential to subsequent development of the rostral CNS, myelomeningocele also causes numerous associated brain anomalies. Prenatally, fetal ultrasonography is used to diagnose a myelomeningocele. Postnatally, magnetic resonance imaging (MRI) is particularly valuable in delineating the extent of the structural abnormalities.

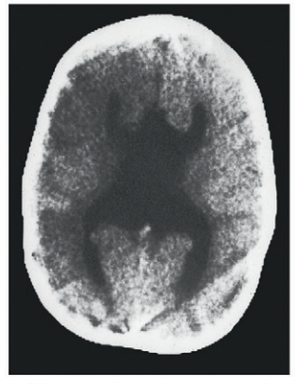


Porencephaly, with absence of septum pellucidum and thinning of overlying skull



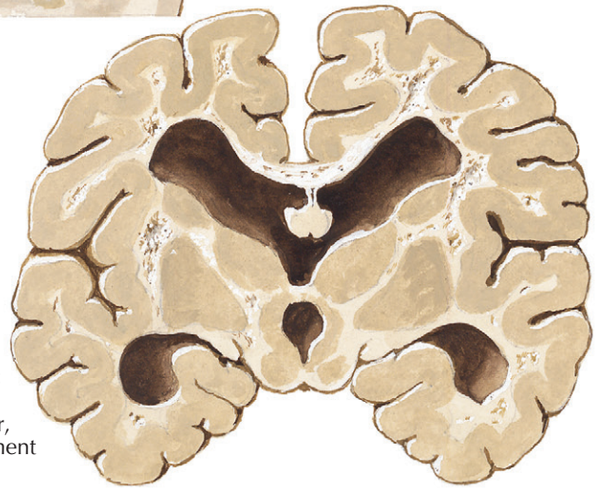
Agenesis of corpus callosum: ventricles may communicate with longitudinal fissure





CT scan showing agenesis of corpus callosum

Heterotopic gray matter: islands of gray matter within white matter in centrum ovale; in subependymal area, with projections into ventricles; and in insular regions



Perinatal telencephalic leukoencephalopathy: scarcity of white matter, with resultant enlargement of ventricles

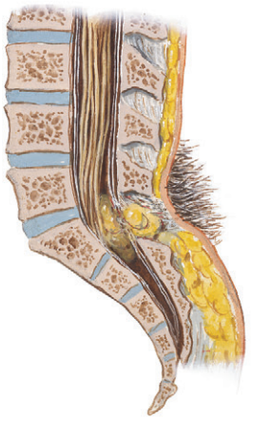
Defective Neural Tube Formation *(Continued)*

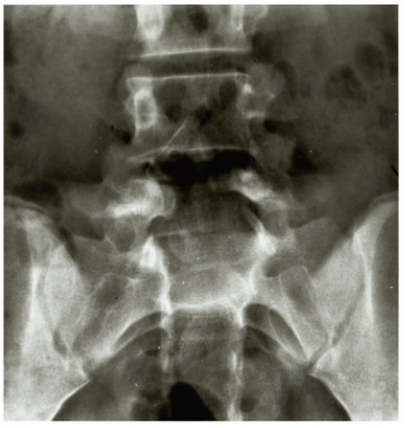
All affected infants require neurosurgical intervention. The prognosis depends on the degree of CNS involvement, which may be difficult to assess in the neonate.

The most common CNS malformation is *holoprosencephaly* (arrhinencephalia). Holoprosencephaly results from incomplete development and septation of the midline CNS structures. It may be isolated or associated with other brain defects and occurs with varying degrees of severity. The most severe form results in a single ventricle, an absent olfactory system, hypoplastic optic nerves, or even a single "cyclopean" eye. The corpus callosum is absent, and the cortex is malformed. Potential facial anomalies include a single eye (cyclops) and a single nasal protuberance (proboscis), but in less severe cases, defects include ocular hypotelorism, microphthalmus, a flat nose, and a median cleft lip and palate. Ultrasound examination indicates the prenatal diagnosis, and MRI scans can delineate the extent of the defects. Early death is predictable in severe forms. Chromosomal abnormalities (trisomy 13-15, trisomy 18) are present in 50% of cases. In a small percentage of holoprosencephalic cases (approx. 7%), genes related to sonic hedgehog signaling are mutated. Increased awareness of chromosomal anomalies and single genes associated with holoprosencephaly makes genetic counseling important for families who have a holoprosencephalic child.

Several other clinical conditions characterized by congenital failure of fusion of the midline structures of the spinal column are grouped under the general classification of *spinal dysraphism*. These various manifestations of the dysraphic state span a clinical continuum from asymptomatic and unseen bony abnormalities (spina bifida occulta), to cutaneous lesions that can suggest an associated tethered cord (dimple, subcutaneous lipoma or hemangioma), to the most severe and disabling congenital malformations of the spinal structures (myelomeningocele). Early postnatal imaging with MRI has transformed the management of infants with these lesions.

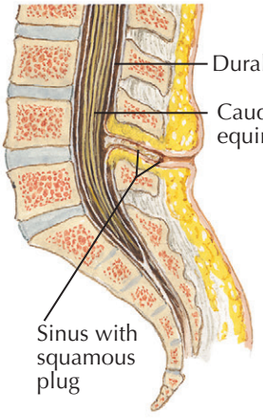
Spina bifida occulta

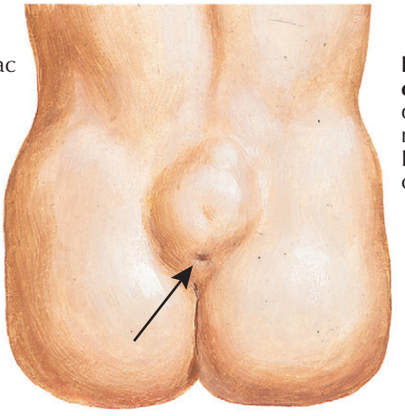




X-ray film. Showing deficit of lamina of sacrum (spina bifida occulta)

Dermal sinus





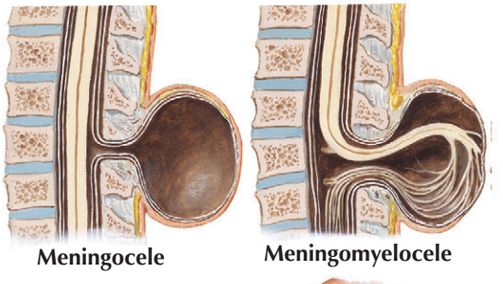
Fat pad overlying spinal bifida occulta. Tuft of hair or only skin dimple may be present, or there may be no external manifestation. Dermal sinus also present in this case (arrow).

Spinal Dysraphism

Spina bifida occulta

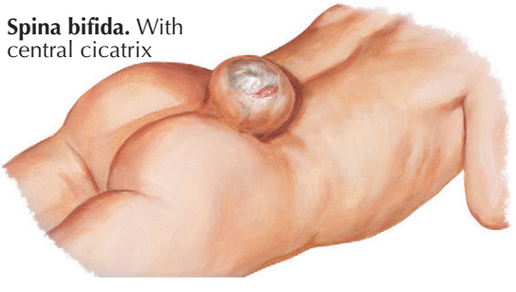
The more benign forms of spinal dysraphism include occult bony abnormalities unaccompanied by any displacement of spinal canal contents and with or without cutaneous stigmata. In these cases, there is failure of bony fusion between the two laminae of the involved vertebra (see Plate 1-7). Spina bifida occulta is of no clinical significance when it occurs alone without intraspinal involvement.

Cutaneous stigmata of spina bifida occulta include dimples, dermal sinuses, subcutaneous lipomas, tufts of hair, or hemangiomas. Cutaneous lesions may occur in isolation, or herald an underlying tethered cord due to a low-lying conus or fat-infiltrated filum. Only a small subset of cutaneous lesions is associated with an intraspinal anomaly, and MRI performed within a few months of age can often exclude the diagnosis without radiation or sedation. The *tethered spinal cord syndrome* occurs when a hypertrophied filum terminale is too inflexible and causes progressive traction and relative caudal displacement of the conus medullaris as the spine grows. This traction can produce progressive ischemia in the conus medullaris and lead to symptoms of sphincter dysfunction and gait abnormalities. One third of infants with a congenital tethered cord are likely to eventually develop neurologic dysfunction if the tethered cord is not treated. Prophylactic detethering by microsurgical sectioning of the filum terminale, ideally before 1 year of age, allows immediate ascent of the conus medullaris toward a more normal location within the spinal canal and minimizes the chance of development of neurologic deficits as the spine grows. For older children who have a late symptomatic presentation, treatment may minimize the further progression of neurologic deficits. If spina bifida occulta occurs in conjunction with a dermal sinus (an epithelium-lined tract linking the dural sac with the skin surface), there is a potential for communication between the skin and intraspinal contents and subsequent infection. Dermal sinuses located above the sacrococcygeal region should be removed surgically after MRI imaging to evaluate for other associated lesions.

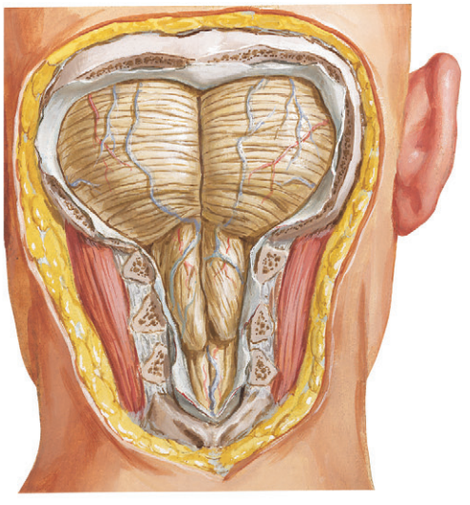


Meningocele Meningomyelocele

Spina bifida. With central cicatrix

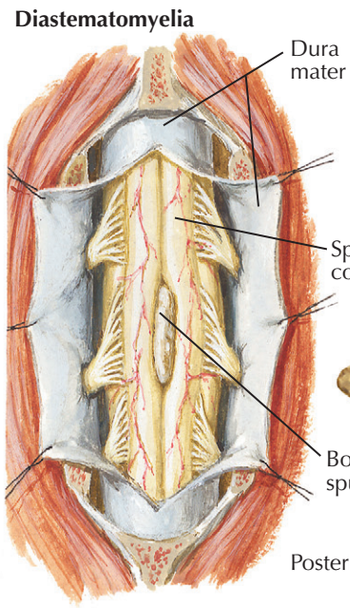


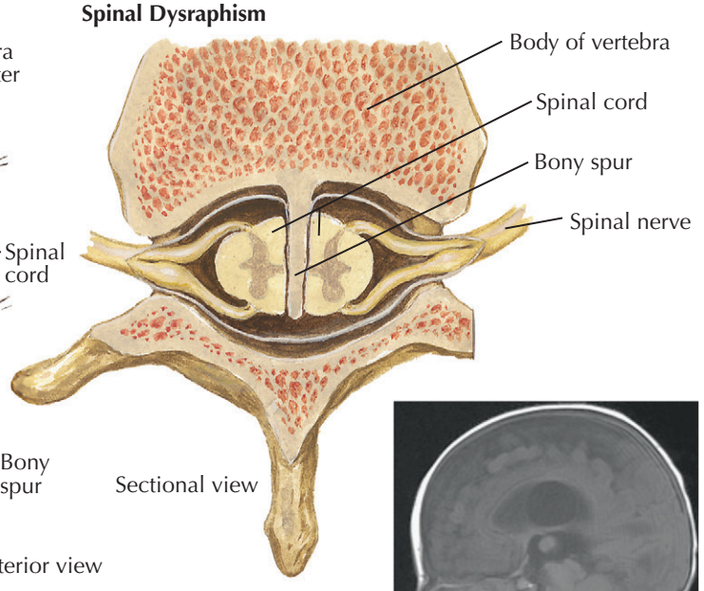
Arnold-Chiari malformation



Spina bifida aperta

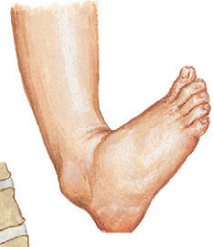
Dysraphic conditions in which there are overt manifestations of the underlying bony defect are referred to as "spina bifida aperta" (see Plate 1-8). Within this group, the progression of neurologic sequelae is defined, to a large extent, by the degree to which the contents of the spinal canal are displaced from their normal location. In the case of a *meningocele*, the most benign form of spina bifida aperta, a meningeal cyst free of neural

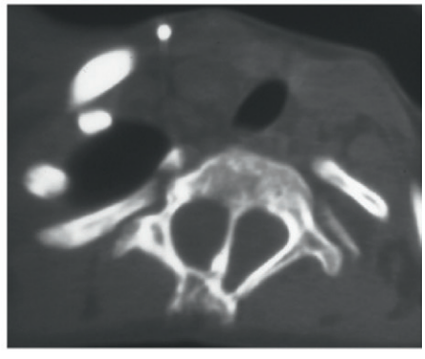




Midsagittal MRI shows Chiari II malformation with inferior displacement of the cerebellar tonsils and vermis into the cervical canal, and other typical findings of children with myelomeningocele, including partial agenesis of the corpus callosum, large massa intermedia, tectal beaking, inferiorly displaced torcular Herophili, and a small posterior fossa.

Clinical manifestations of spinal dysraphism may include foot deformity or progressive sphincter disturbances





Spinal Dysraphism *(Continued)*

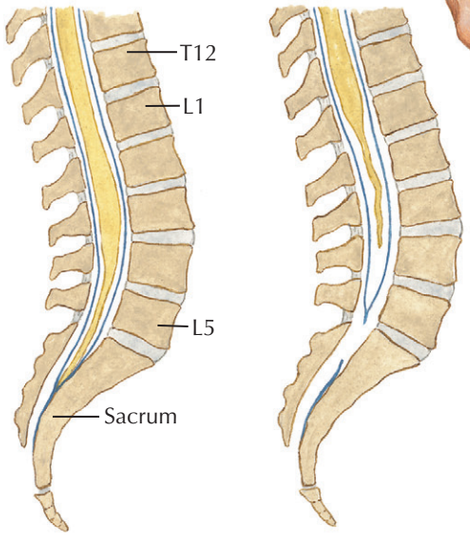
elements is extruded. Often, a meningocele can be completely removed surgically and the defect closed.

Diastematomyelia is a congenital malformation in which the spinal cord is split into two sections, or hemicords. It is frequently associated with a midline cutaneous tuft of hair, and all infants with a worrisome tuft should be screened with an MRI. Frequently, a bony or cartilaginous septum separates the divided sections. Patients with a split cord malformation are at risk of developing associated scoliosis and progressive myelopathy as the spine grows. Surgical excision of the midline septum can halt the deteriorating condition and, in some cases, lead to restored function.

A far more devastating variant of spina bifida aperta is *myelomeningocele*, in which the spinal cord or nerve roots, or both, protrude through the posterior bony and cutaneous defects due to failed closure of the posterior neuropore. The severity of deficits from a myelomeningocele correlates with its location along the spinal canal, with increasing deficits occurring with more rostral lesions. The neurologic deficits are due to abnormal *in utero* development throughout the entire CNS. Postnatal closure of the myelomeningocele in the term infant is performed within a few days of birth to minimize the risk of meningitis, and is associated with low morbidity. Prenatal fetal closure may be an option for a very select group of patients and is associated with complications, including preterm delivery.

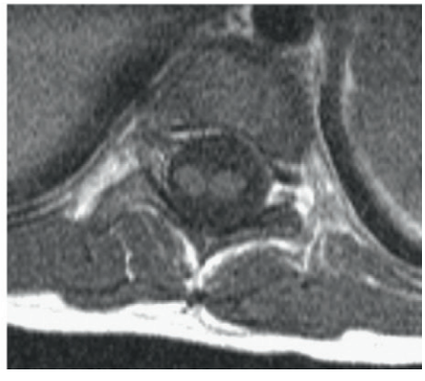
Prenatal folate supplementation has markedly decreased both the incidence of infants born with myelomeningocele and lesion severity. Infants with sacral and low lumbar lesions often achieve some degree of ambulation, and approximately 80% can achieve social bladder and bowel continence. Approximately half of infants with a lumbar or sacral myelomeningocele will develop hydrocephalus that requires surgical treatment (see Plate 1-7). Most of these infants will have an associated Chiari II malformation, with displacement of the cerebellar vermis into the cervical canal, but only a few percent will become symptomatic at any point. Children are at risk for developing the tethered cord syndrome as the myelomeningocele scar adheres to the repair site while the spine grows. All repaired myelomeningoceles will appear adherent to some degree on MRI, and the diagnosis of a tethered cord in this population is made clinically. Although multidisciplinary care is needed throughout the life span of children born with a myelomeningocele, many will become independent productive adults with a good quality of life.

Tethered spinal cord syndrome



Filum terminale of cord adherent to sacrum, with tension on spinal cord

Adhesion freed with release of cord tension



Axial CT (top) shows the bar of bone dividing the spinal canal, and MRI (bottom) shows the two hemicords of the split cord malformation.

Fetal Brain Growth in the First Trimester

After initial brain morphogenesis is complete, and neural crest migration has established the peripheral nervous system (see Plate 1-4), several bendings, invaginations, and evaginations transform the geometry of the developing brain. The addition of neurons via *neurogenesis*, which begins in the first trimester, underlies these movements. Neurogenesis reaches a maximum during midgestation to late gestation and ceases (with few exceptions) shortly after birth. Accordingly, as brain morphology emerges, neurons that will form brain circuits differentiate for a lifetime of electrical signaling.

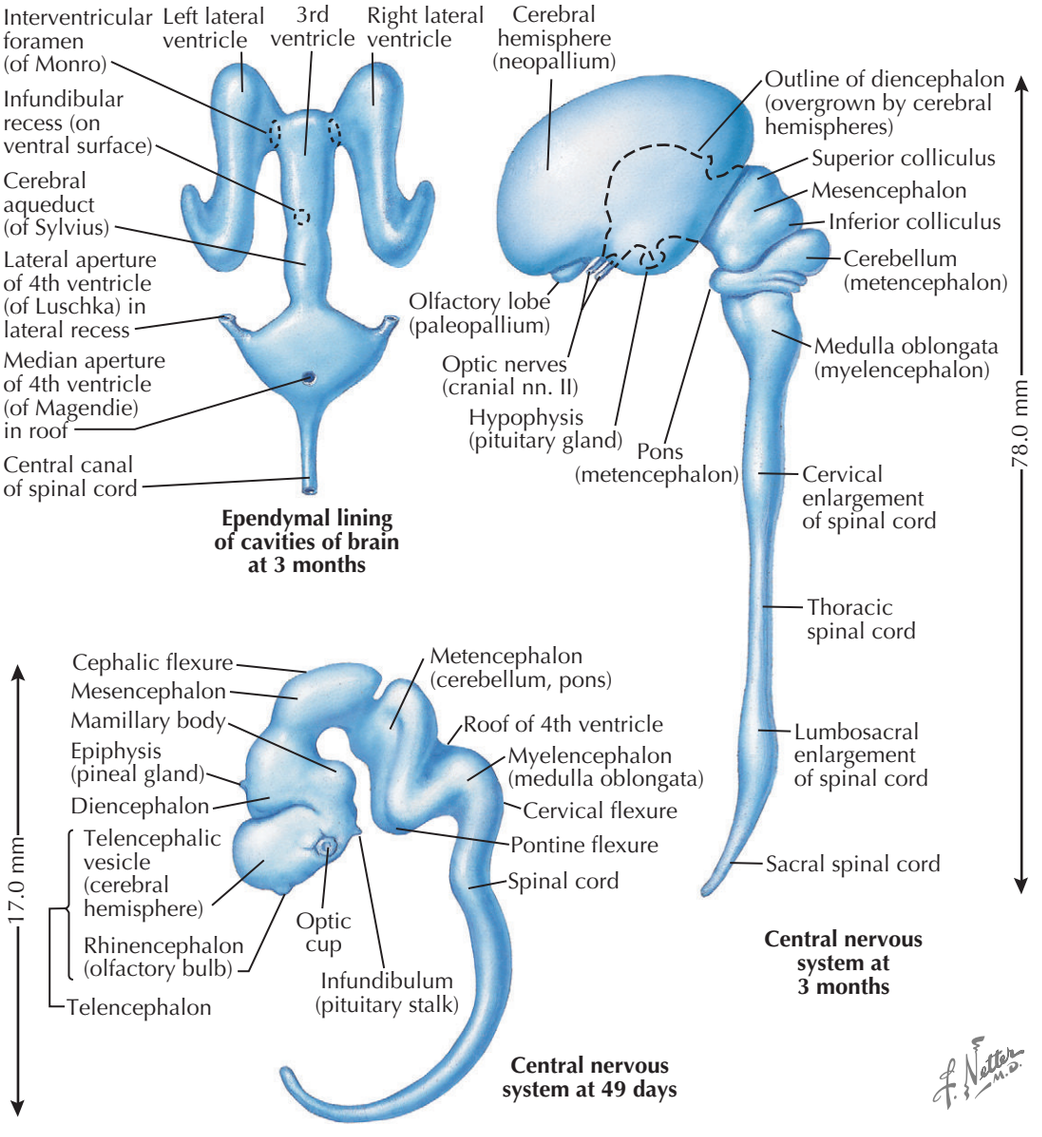
At 49 days of age (see top, Plate 1-9), the brain and spinal cord undergo further bending that situates both appropriately in the developing head and trunk. The *cephalic flexure* moves the diencephalon and telencephalon nearly parallel with the hindbrain. The *pontine flexure* anticipates the location of the cerebellum and pons, and the *cervical flexure* positions the spinal cord parallel to the body axis. At this stage, telencephalic and diencephalic landmarks are clearly visible: *olfactory bulbs* in the telencephalon; the *optic cup*, eventually located farther from the diencephalon as it generates the *neural retina;* the *infundibulum* (hypophysis), the rudimentary stalk of the *pituitary gland;* and the *epiphysis*, which forms the *pineal gland.*

Within 1.5 months, differential growth yields an even more mature embryonic brain and spinal cord. This reflects disproportionate growth of the *cerebral hemispheres* (or neopallium), from the posterior telencephalon, primarily due to addition of neural stem cells that generate neurons of the mature cerebral cortex. Dysregulation of this process has dramatic consequences. Mutations that result in *microcephaly*—dramatic reduction of cerebral hemisphere size—occur in genes that influence this expansion of cortical neural stem cells. Disproportionate cerebral hemisphere growth makes the diencephalon a "deep" structure, occluded from view. Diencephalic subdivisions, including the *thalamus*, *epithalamus* (habenular nuclei and pineal gland), *hypothalamus*, and *posterior pituitary* (neurohypophysis) are only seen by dissection, imaging, or histologic sectioning.

The hindbrain also undergoes dramatic changes. The posterior (tectum) and anterior (tegmentum) mesencephalon becomes distinct: a groove or sulcus divides two evaginating structures: the *superior* and *inferior* colliculi. The superior colliculus integrates visual information and motor commands for eye and head movements, and the inferior colliculus localizes sound in register with head movements. The posterior rhombencephalon expands dramatically as the rudimentary *cerebellum* becomes visible. The cerebellum is derived from stem cells in or near the *roof of the fourth ventricle* as well as progenitors that migrate from other rhombencephalic and mesencephalic locations. Local neurogenesis in the roof of the fourth ventricle, as well as migration of additional progenitors, results in dramatic cerebellar growth. The anterior rhombencephalon appears as the rudimentary *pons*, which expands dramatically as axons from the cerebral cortex innervate pontine relay neurons that project to the cerebellum.

The final dramatic change during this period is differentiation of spinal cord regions that innervate limbs or axial musculature. Posterior to the cervical flexure, the spinal cord appears broader, a region referred to as the *cervical enlargement* that includes larger numbers of motor and sensory relay neurons that innervate or receive inputs from muscles and sensory receptors in the shoulders, arms, and hands. The spinal cord then narrows, and this region, the *thoracic cord*, includes motor and sensory neurons that innervate or receive sensory inputs from axial musculature as well as *preganglionic neurons* that project to the *autonomic ganglia of the sympathetic chain* for central regulation of the sympathetic branch of the autonomic nervous system. The spinal cord expands again in the *lumbar enlargement*, reflecting larger numbers of motor and sensory relay neurons dedicated to the legs and feet. Finally, the narrow posterior region, *the sacral cord*, innervates and receives information from the pelvic and gluteal muscles. Thus differentiation in the spinal cord reflects distinct functional demands of arms and legs versus trunk and posterior midline structures.

As brain morphogenesis advances, the ventricles, defined initially by the space enclosed by the neural tube, become highly differentiated. The dramatic growth of the cerebral hemispheres is matched by growth of two bilaterally symmetric *lateral ventricles.* Their C shape reflects development of "deep" telencephalic structures, including the hippocampus and basal ganglia. Continuity between the lateral and *third ventricles* (surrounded by the diencephalon) occurs at the *intraventricular foramen of Monro*. Occluding this opening leads to one type of *noncommunicating hydrocephalus* (see below). Cerebrospinal fluid trapped in the lateral ventricles causes secondary expansion of the cerebral hemispheres and overlying cranium (a second form, *communicating hydrocephalus*, reflects impaired reabsorption of CSF). The third ventricle also has a modest invagination, the *infundibular recess*, that reflects the position of the pituitary gland. The *cerebral aqueduct*, surrounded by the mesencephalon, and *the fourth ventricle*, defined by the rhombencephalon, become well defined. Occlusion of the cerebral aqueduct—*aqueductal stenosis*—is the most common noncommunicating hydrocephalus. In the fourth ventricle, a series of openings, *the foramen of Luschka and Magendie* establish continuity between the ventricles and *subarachnoid space* between the *arachnoid* and the *pia*, the innermost meningeal layer. These apertures permit CSF to flow into the subarachnoid space to mechanically cushion the brain as well as distribute signaling molecules to the developing meninges and the external surface of the developing brain. Occlusion of these foramina, which is rare, also leads to noncommunicating hydrocephalus. The fourth ventricle narrows dramatically in the medulla, defining the central canal that extends most of the length of the spinal cord.



CRANIOSYNOSTOSIS

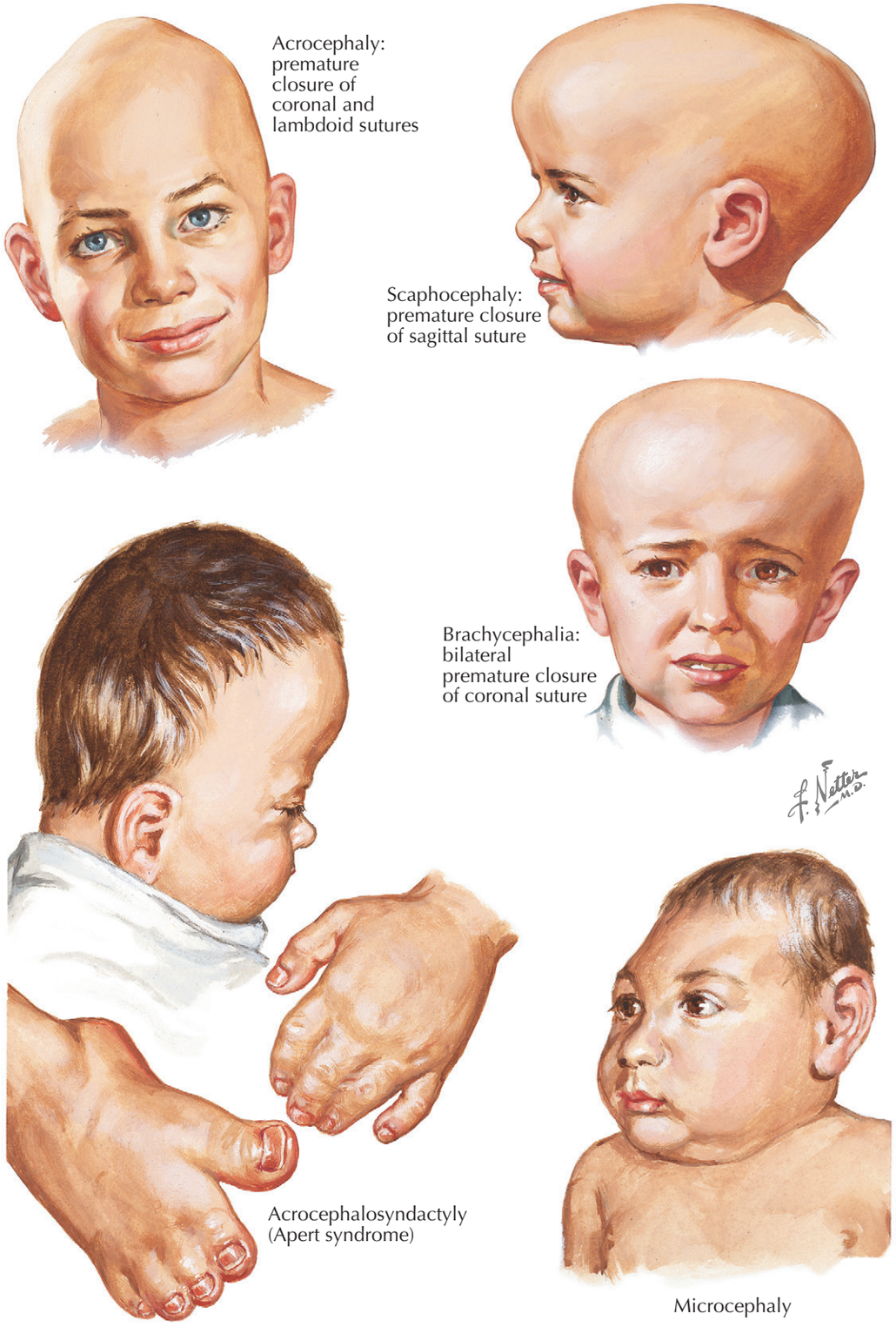
The growth of the brain is matched by the flexible growth of the cranial bones, which must establish a mechanism to expand the skull vault coincident with increased brain volume. The cranial bones, mostly generated by neural crest–derived chondrogenic and osteogenic precursors, are arranged as "plates" with elastic joints between each plate referred to as *cranial sutures*. *Craniosynostosis* implies a premature closure of one or more cranial sutures (see Plate 1-10). Early fusion of bone plates results in a progressively dysmorphic cranial shape. True craniosynostosis occurs in one of every 2,000 infants, predominates in males, and manifests in nonsyndromic and syndromic forms. Normally, the metopic, or frontal, suture closes before birth; the posterior fontanelle, at the union of the lambdoid and sagittal sutures, by 3 months; and the anterior fontanelle at the junction of the coronal, sagittal, and metopic sutures, by 18 months. After a suture is fused, growth occurs parallel to that suture; that is, growth is inhibited at 90 degrees to the suture. The fusion itself is felt as a ridge. Cranial sutures cannot be separated by increased intracranial pressure after 12 years of age.

Nonsyndromic craniosynostosis occurs much more frequently than syndromic. The most common premature closure occurs in the *sagittal suture*, which leads to *scaphocephaly*, *dolichocephaly*, or elongated head. The next most common premature closure is found in the *coronal suture*, which may be either unilateral or bilateral. If unilateral, it causes a unilateral ridge, with a pulling up of the orbit, flattening of the frontal area, and prominence near the zygoma on the affected side, which produces a quizzical expression. If premature coronal closure is bilateral, *brachycephalia*, manifested by an abnormally broad skull, is the result. Metopic craniosynostosis causes *trigonocephaly*, with a pointed frontal bone, hypotelorism, and prominent temporal hollowing. True lambdoid synostosis, which can also be unilateral or bilateral, is exceedingly rare, with an incidence less than 1:100,000. *Turricephaly*, a towering cranial vault due to multiple suture closure, is quite rare and disfiguring. Some infants will have prominent ridges along sutures without the other typical cranial findings, and these ridges will spontaneously resolve with time.

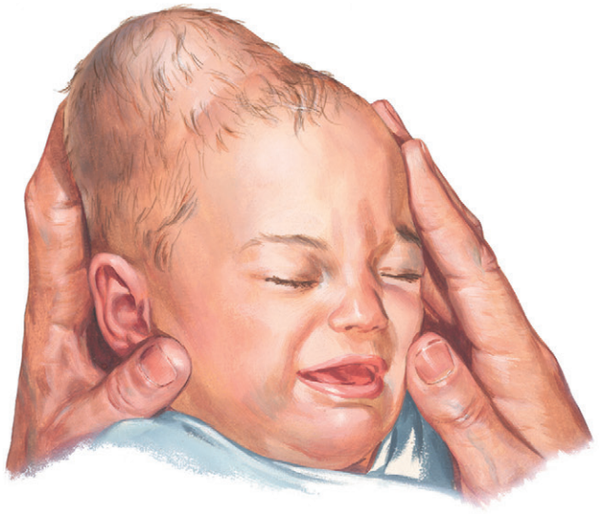
Syndromic craniosynostosis usually is autosomal dominant. Crouzon disease, with closure of *multiple sutures* and the associated facial anomalies of hypertelorism, proptosis, and choanal atresia, is known as *craniofacial dysostosis*. Intelligence is normal, but premature suture closure can cause elevated intracranial pressure. In *acrocephalosyndactyly*, or Apert syndrome, the head is elongated, the result of premature closure of all sutures; the orbits are shallow, causing exophthalmos; and either syndactyly or polydactyly is present. Saethre-Chotzen, Pfeiffer, and Carpenter have also identified syndromes of acrocephalosyndactyly that include various combinations of synostosis, syndactyly, and other anomalies. Syndromic craniosynostosis can be associated with hydrocephalus.

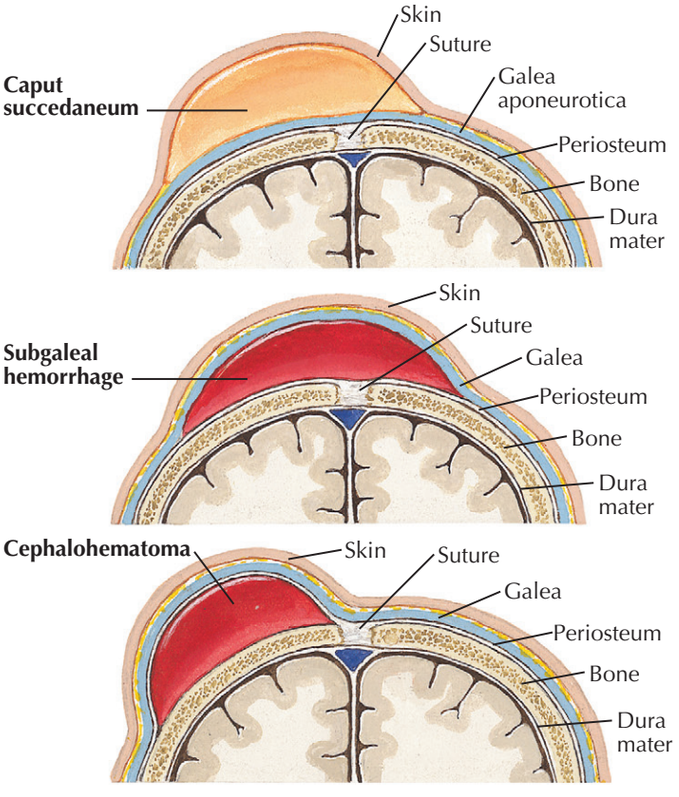
Conditions that can be confused with craniosynostosis include *microcephaly* and *deformational plagiocephaly*. *Microcephaly* from lack of brain growth is not typically accompanied by a disfigured cranial shape. *Deformational plagiocephaly* is very common and currently occurs in approximately 1 in 10 infants. The baby tends to lie on one area of the skull, which causes flattening in the affected area, anterior displacement of the unilateral ear, and ipsilateral frontal and contralateral parietal bossing, with an overall parallelogram shape. Some infants have associated torticollis. Most infants will have spontaneous improvement with exercises; very severe cases made need treatment with a cranial orthosis.

The diagnosis of craniosynostosis is made by clinical examination in most cases. Appropriate radiographic examinations are typically only needed as a roadmap for surgical repair. Treatment for true craniosynostosis is surgical, with either endoscopic or open techniques. Early referral optimizes the opportunity to use minimally invasive techniques. Treatment of syndromic and multiple suture craniosynostosis typically require multiple procedures by an experienced craniofacial team during early childhood.

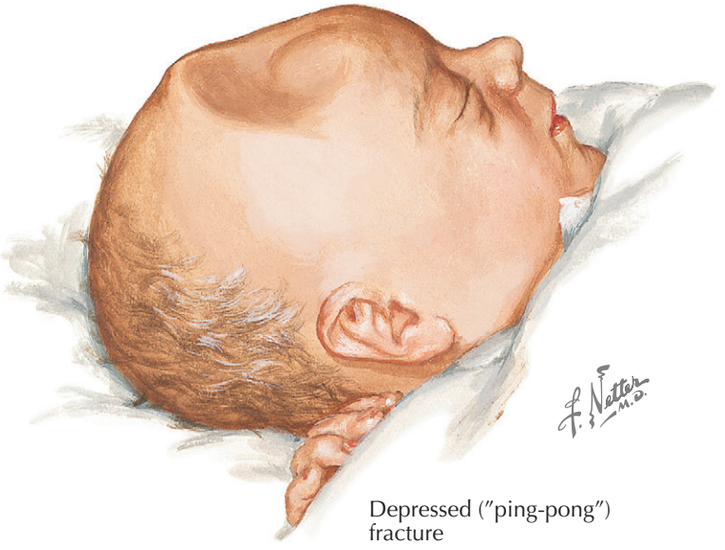


Extracranial Hemorrhage or Edema in Newborn

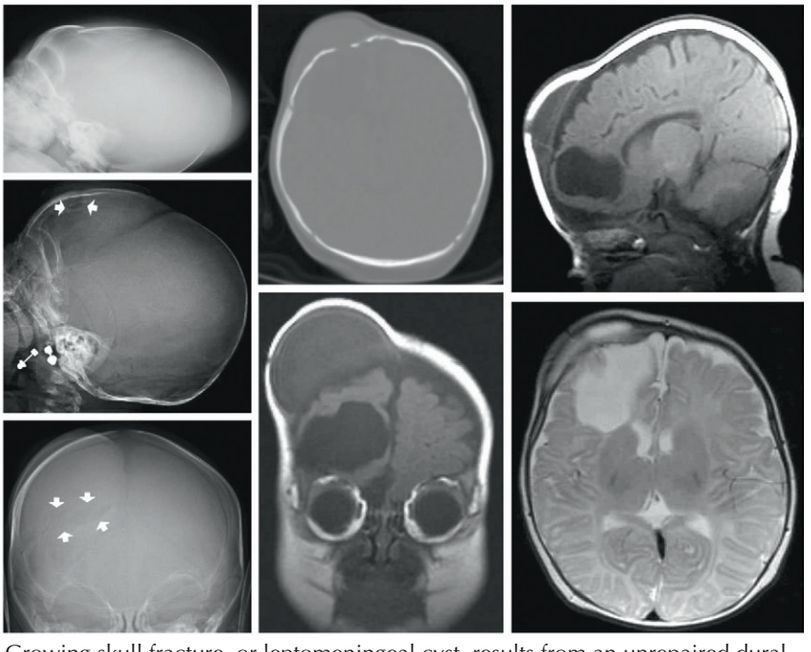




Skull Fractures in Newborn



Depressed ("ping-pong") fracture



Growing skull fracture, or leptomeningeal cyst, results from an unrepaired dural laceration in the context of a growing cranium. Plain radiographs show the initial fracture after birth, and subsequent skull defect after several months (*arrows*). CT and MRI images demonstrate the extracranial cyst, skull defect, and underlying parenchymal loss.

Extracranial Hemorrhage and Skull Fractures in the Newborn

Modern obstetric practice has decreased the incidence of trauma to the neonate that is clearly associated with primiparity, large infant size, difficult or breech delivery, and use of forceps.

Caput succedaneum, an edematous swelling that may be hemorrhagic, is seen in vaginal deliveries. It may transilluminate, is soft, pits, is usually at the vertex over suture lines, and resolves rapidly.

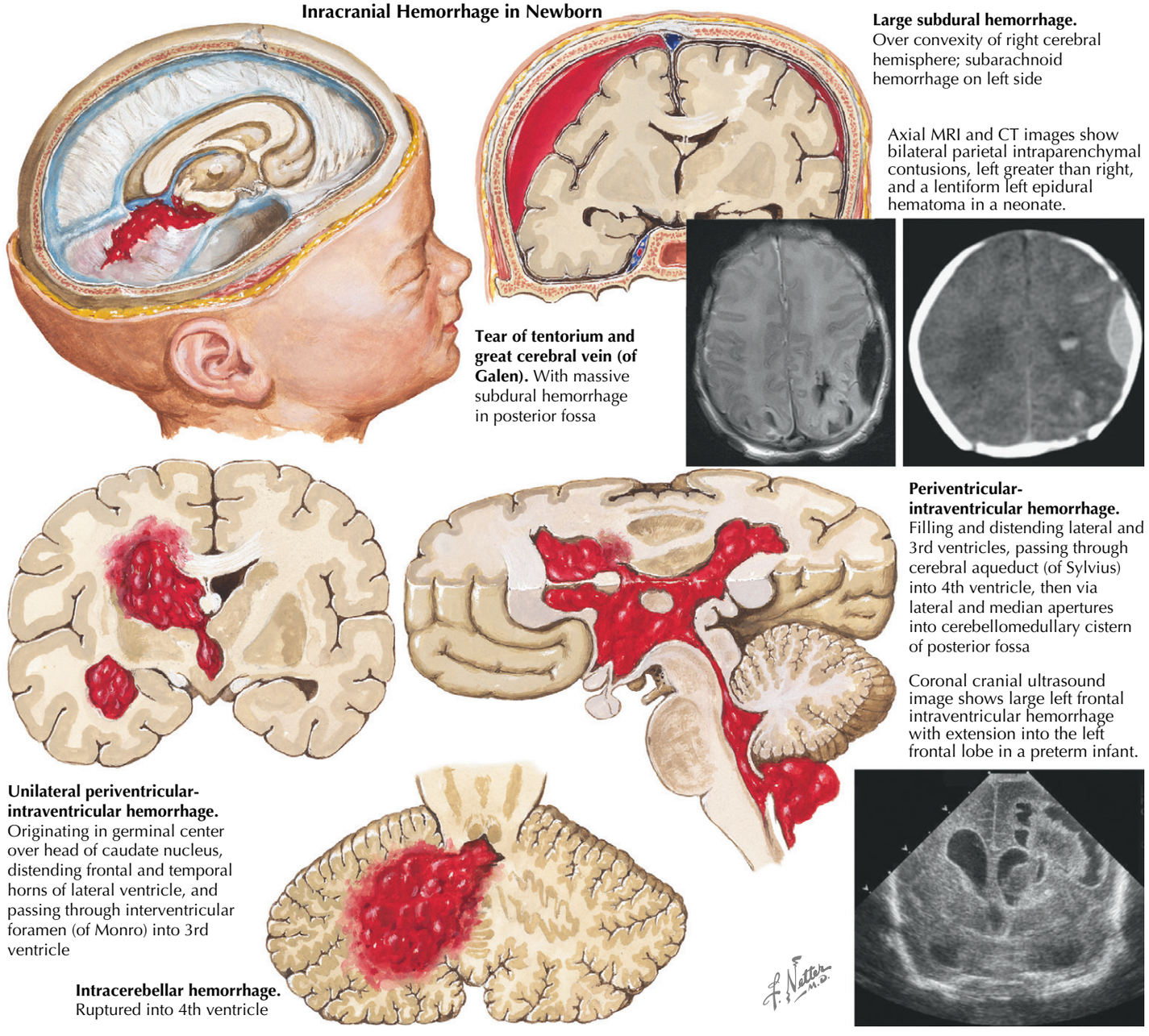
Subgaleal hemorrhage, which usually results from shearing forces tearing veins, occurs between the galea aponeurotica and the periosteum of the skull. It spreads widely, crosses suture lines, may dissect over the forehead and even into an orbit, and may take weeks to resolve. Neonates should be followed closely for symptomatic anemia.

Cephalohematoma is a subperiosteal hemorrhage associated with a linear skull fracture in about 5% of cases. It may result from the use of forceps, can also be related to mechanical factors in the pelvis and the shearing forces of active labor, and palpates like a depressed fracture. Rarely, these hematomas calcify instead of resorbing. Most calcified hematomas will spontaneously resolve as the skull grows and incorporates the area.

Skull Fractures. Neonatal skull fractures may be classified as linear, depressed, or occipital osteodiastasis. *Linear fracture* may be associated with cephalohematoma or, in traumatic deliveries, with epidural and subdural hemorrhage. Most heal without complication. Rarely, they become diastatic and are associated with a leptomeningeal cyst due to associated dural and meningeal tears that enlarge with brain growth.

Depressed ("ping-pong") fractures are of little clinical significance. Most are associated with the use of forceps, but some are related to intrauterine trauma against pelvic prominences in automobile accidents and falls, and also in active labor. Surgical elevation may be required and often can be performed with minimally invasive techniques.

Occipital osteodiastasis is seen in breech deliveries. The associated dural sinuses may be ruptured, causing a subdural hemorrhage of the posterior fossa. Surgical drainage is rarely necessary.



Intracranial Hemorrhage in the Newborn

Intracranial hemorrhage in the neonate is classified by location and in order of frequency as (1) periventricular-intraventricular, (2) subarachnoid, (3) subdural, or (4) posterior fossa hemorrhage. All neonates should be followed closely for symptomatic anemia.

Periventricular-intraventricular hemorrhage (IVH) originates in the germinal matrix near the lateral ventricles and typically is observed in infants born preterm before 34 weeks' gestation (Plate 1-12). In preterm infants, the inherent friability of the germinal matrix is often complicated by cardiopulmonary compromise during birth and physiologic stresses of adjusting to the extrauterine environment in the early neonatal period. Massive bleeding, now quite rare, precipitates a bulging fontanelle, respiratory difficulties, tonic posturing, seizures, anemia and, ultimately, multisystem failure. Minor bleeding detected with serial cranial ultrasonography is now more common. Some preterm infants will develop ventriculomegaly without cranial growth or elevated intracranial pressure, consistent with hydrocephalus ex vacuo from encephalomalacia. Approximately 15% of preterm infants with IVH will require surgical intervention for symptomatic hydrocephalus. Long-term neurologic deficits are common in preterm infants with IVH, including cerebral palsy, epilepsy, cognitive delay, and behavioral abnormalities. In full-term infants, IVH typically occurs secondary to deep central venous thrombosis, and approximately half of these infants will develop early or late hydrocephalus. Term infants with IVH are also prone to chronic neurologic deficits, including epilepsy, cognitive delay, and behavioral abnormalities.

Subarachnoid hemorrhage may be caused by asphyxia or by forces of normal delivery. In full-term infants, it may be asymptomatic or associated with focal or generalized seizures, with no focal deficits. *Subdural hemorrhage* results from tears in the falx cerebri and tentorium, rupture of bridging veins over the hemispheres, or occipital osteodiastasis in breech delivery. Causes include excessive molding forces during delivery, the infant's size, and difficult extractions. Symptoms are acute or subacute hemiparesis, focal seizures, and ipsilateral pupillary abnormalities. Surgical drainage is the appropriate treatment in select cases. Cranial ultrasonography rarely provides adequate information, and either a rapid computed tomography (CT) or MRI scan is needed for management decisions.

Posterior fossa hemorrhage can result from tentorial trauma or occipital osteodiastasis. Either a rapid CT or MRI scan is needed for management decisions; cranial ultrasonography does not provide adequate imaging to assess the mass effect of the hematoma. Surgical drainage is rarely indicated.

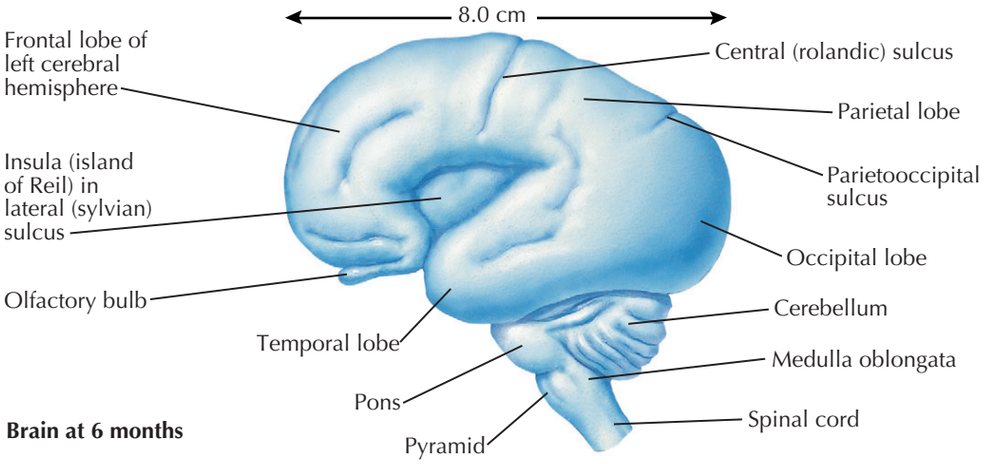
The External Development of the Brain in the Second and Third Trimesters

By sixth month of gestation, the cerebral hemispheres acquire several features that prefigure the division of the cortical surface into specific functional regions. Accordingly, one recognizes four distinct domains, or lobes, that define cortical territories. The *frontal lobe is most anterior;* it eventually includes cortical areas devoted to motor control, language production (left hemisphere only in most individuals), and *executive function*—the capacity, moment by moment, to integrate perceptions of external stimuli with internal representations of motivations, goals, and memories to plan appropriate complex behavioral responses. Midway along the anterior-posterior axis, the *central* (also known as the rolandic) *sulcus* divides the frontal and more posterior *parietal lobe*, which mediates somatosensation and attention. This anatomic landmark is one of the earliest local furrowings that defines the *sulci* (grooves) and *gyri* (bulges) that reflect the elaborate folding of the mature cerebral cortex.

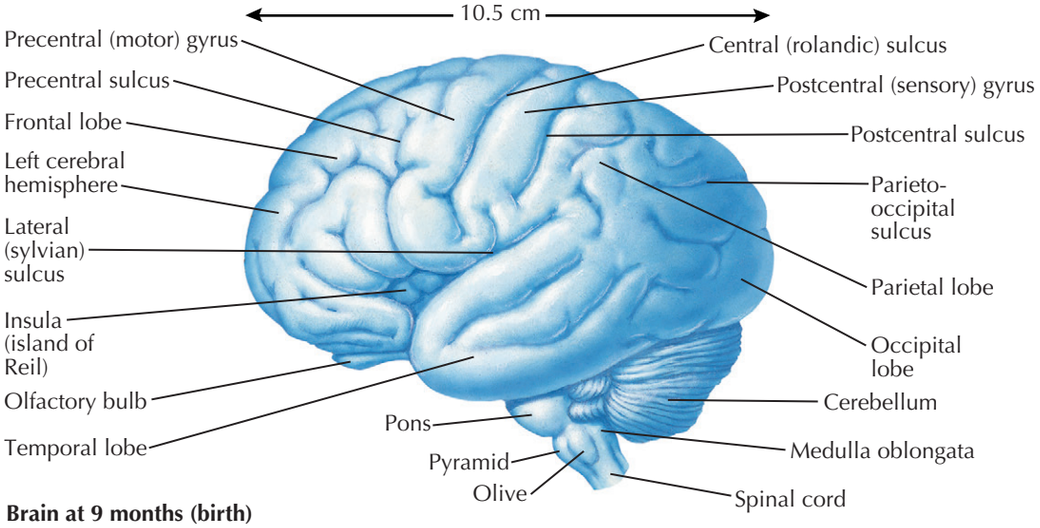
The central sulcus defines two essential functional regions. On the anterior bank is the *precentral gyrus*, the location of the *primary motor cortex*. Neurons of the primary motor cortex send axons directly to brainstem and spinal cord motor neurons that innervate muscles or to interneurons adjacent to these motor neurons. On the posterior bank is the *postcentral gyrus*, the location of the *primary somatosensory cortex*. The primary somatosensory cortex receives topographically mapped inputs from brainstem and spinal cord sensory relay nuclei that represent somatosensory information from the entire body surface. The remainder of the parietal lobe is devoted to sensory integration and attention. Posterior and ventral, marked by the *parieto-occipital sulcus*, is the *occipital lobe*, devoted exclusively to representation and processing of vision. Finally, the anterior medial extension of the hemisphere defines the *temporal lobe*, anterior to the *lateral sulcus*, including cortical regions that integrate information about the identity of visual stimuli, auditory information, and, in the left hemisphere only of most individuals, the representation of "lexical" language (the brain's "dictionary" of words). The initial growth of the frontal, parietal, occipital, and temporal lobes results in "operculation," or covering of one region of cortical tissue called the *insula*. The cortex of the insula becomes specialized for visceral and homeostatic control and the representation of taste information.

The dramatic growth of the cerebral hemispheres is accompanied by differentiation of the cerebellum and medulla. By the end of the sixth month of gestation, the cerebellum expands with furrows and ridges that eventually become the highly folded folia of the cerebellar cortex (note: a cortex is the outer sheet of cells that invests any organ). The pons is distinct, consisting of axons from the cortex that project to pontine nuclei that then send axons to the cerebellar cortex. The medulla also becomes furrowed and ridged, but for a different reason. The *pyramid*, a prominent ridge on the anterior/medial medulla is formed by growth of axons from motor cortical neurons to the brainstem and spinal cord. By the end of gestation, the pyramid is adjacent to a more lateral ridge, the *olive*. The olive reflects accumulation of neurons into the olivary nucleus; olivary neurons selectively innervate the extensive dendritic arbors of Purkinje cells.

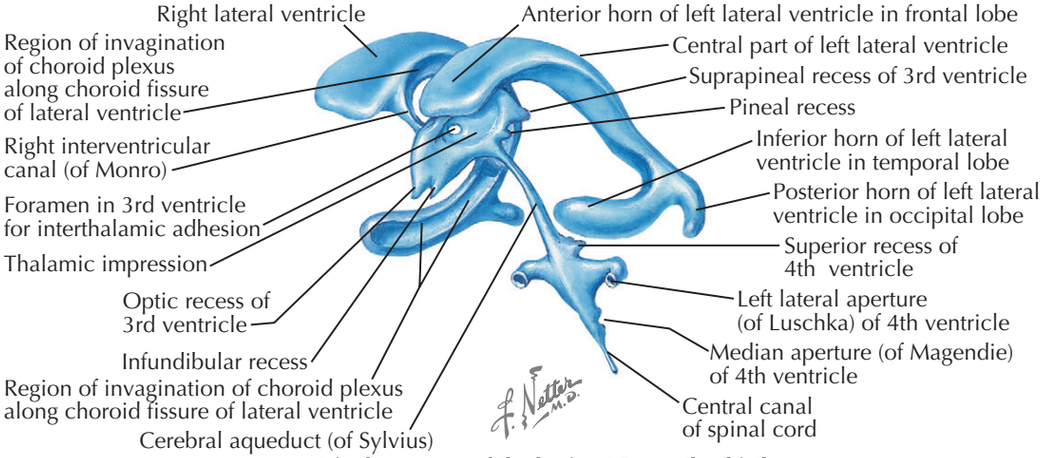
Finally, further elaboration of the ventricular system accompanies these morphogenetic transformations.



Brain at 6 months

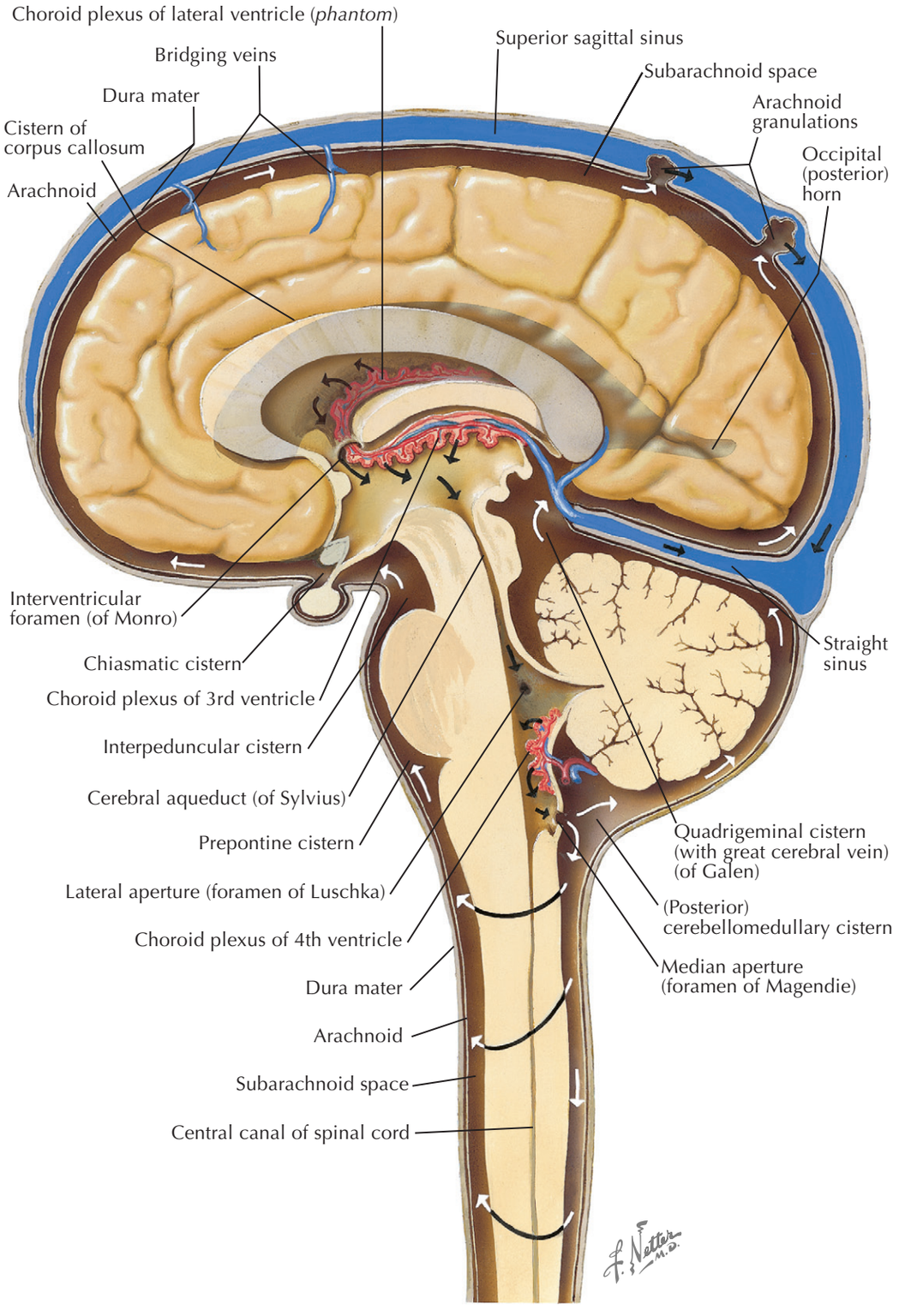


Brain at 9 months (birth)



Ventricular system of the brain at 9 months (birth)

The ventricular system is best depicted as a "cast" of space within the brain and spinal cord (neural tissue is absent). The key changes reflect differential growth of brain regions that correspond to each ventricular division. The lateral ventricles grow disproportionately and acquire further anatomic definition. The *anterior horn* extends into the frontal lobe, with the caudate nucleus of the basal ganglia as its floor. The *inferior horn* extends into the temporal lobe; on its anterior and medial surface is the hippocampus. Finally, the *posterior horn* extends into the occipital lobe. The remainder of the ventricular system is comprised of the same subdivisions that emerge in the second trimester; however, their shape and size change substantially. The third ventricle becomes a narrow midline space, further indented by the thalamus on each side *(the thalamic impression)* as well as a *foramen* surrounding the *intrathalamic adhesion.* In addition, the third ventricle is indented by the optic chiasm at the *optic recess*, the pineal gland at the *pineal* and *suprapineal recess*, and the pituitary gland at the *infundibular recess.*



Mature Brain Ventricles

Few anatomic features of the mature brain reflect brain development more directly than the brain ventricles. This continuous system of fluid-filled chambers is the very same space that was defined by the closure of the neural tube. Subsequent morphogenesis modifies this space; nevertheless, its relationship to the original lumen of the neural tube is clear. CSF, which is produced by the *choroid plexus* found in the lateral, third, and fourth ventricles, circulates throughout this space in the adult (as well as the embryonic) brain. The ventricular space also has a series of continuities with the subarachnoid space so that CSF is also bathing the external as well as deep (or ventricular) surface of the brain.

In the adult brain, the two mature cerebral hemispheres surround the *lateral ventricles*. These two ventricles, the largest of the ventricular chambers, have three extensions into distinct regions of the cerebral hemispheres. The *anterior horns* extend into the frontal lobes, the *inferior horns* into the temporal lobe (including adjacent to the hippocampus) and the *posterior horns* into the occipital lobes. The *atrium* is the junction of the anterior, posterior, and temporal horns. The relationship between the anterior horns of the lateral ventricles, the corpus callosum posteriorly, the caudate nucleus anterolaterally, and the third ventricle and thalamus anteromedially is shown in the lower panel. The lateral ventricles remain continuous with the third ventricle via the *intraventricular foramen* of Monro (the white arrow at left in the lower panel shows the continuity between lateral and third ventricles provided by the foramen of Monro: there are two). The third ventricle extends the anterior to posterior length of the diencephalon. Its proximity to the optic chiasm and pituitary gland anteriorly results in local "indentations" known as the *optic* and *infundibular* recesses. Similarly, the relationship of the third ventricle to the pineal gland defines the *pineal* and *suprapineal recesses* in the posterior aspect of the third ventricle.

The third ventricle is continuous with the *cerebral aqueduct*, which travels through the mature mesencephalon. The cerebral aqueduct connects to the *fourth ventricle*, which is adjacent to the cerebellum and pons, and extends into the upper medulla. The fourth ventricle has a significant bilateral extension, the *lateral recess* that opens into the inferior cerebellar peduncle. The fourth ventricle also has several specialized continuities with the subarachnoid space to facilitate the circulation and drainage of *cerebrospinal fluid*, which maintains the integrity of cells at the ventricular zone and also contributes to the stability of the ionic milieu in the brain tissue generally. Thus the two *lateral apertures* (also known as the foramen of Luschka) are continuous with the subarachnoid space at the lateral aspect of the pontocerebellar junction (near the inferior cerebellar peduncle) and the median aperture, located at the midline where the two lateral recesses originate, is continuous with the *cerebellomedullary cistern* (also referred to as the cisterna magna). Indeed, there is a distributed system of cisterns throughout the subarachnoid space that provide reservoirs of CSF.

Hydrocephalus

Hydrocephalus results in the enlargement of ventricles. Symptomatic hydrocephalus associated with elevated intracranial pressure results most often from decreased absorption of CSF, or blockage of outflow through the ventricular system (see Plate 1-15). Excess CSF production is quite rare and usually due only to choroid plexus papilloma, a choroid plexus tumor. Enlargement of all CSF spaces, including the ventricles, that is due to brain atrophy, or encephalomalacia, is termed *hydrocephalus ex vacuo*. The etiology of hydrocephalus can be multifactorial, and the clinical course and management can change throughout the lifetime.

Symptomatic hydrocephalus is subdivided into obstructive and nonobstructive etiologies. Obstructive hydrocephalus is due to blockage of CSF flow by a congenital malformation, such as aqueductal stenosis or suprasellar arachnoid cyst, or by an acquired condition, such as a ventricular tumor that obstructs flow (Plate 1-15). Communicating hydrocephalus was originally defined before modern imaging modalities by the ability to recover dye initially injected into the lateral ventricle from the lumbar thecal space. Communicating, or nonobstructive hydrocephalus, is due to impaired CSF absorption through the arachnoid villi and occurs most commonly secondary to intraventricular or subarachnoid hemorrhage, trauma, meningitis, or leptomeningeal tumor spread.

When symptomatic hydrocephalus occurs in infants and young children, progressive macrocephaly occurs because the cranial sutures are not yet fused. Head circumference measurement and assessment of the fontanel and cranial suture closure are routine components of the neurologic examination (see Plate 1-16). Other causes of macrocephaly in infants are *benign external hydrocephalus* and extra-axial fluid collections. Benign external hydrocephalus usually occurs in the setting of familial macrocephaly, is asymptomatic except for the excessively large head circumference, and has a characteristic imaging pattern of frontal extra-axial collections without any suggestion of mass effect. The infant has a normal neurologic examination without other symptoms or signs of elevated intracranial pressure. Extra-axial fluid collections associated with elevated intracranial pressure have other etiologies, including meningitis and subdural hematomas from abusive head trauma and rare metabolic disorders. Elevated intracranial pressure in infants, including from advanced symptomatic hydrocephalus or extra-axial fluid collections, is often characterized by lethargy, irritability, poor oral intake, engorged scalp veins, a full fontanel, and downward deviation of the eyes, referred to as "sunset eyes."

Imaging with CT or MRI can facilitate the diagnosis and management of patients with suspected hydrocephalus. Patients with suspected elevated intracranial pressure from hydrocephalus need imaging with CT or MRI before any intervention that might change the CSF dynamics, such as a lumbar puncture. Current MRI sequences can suggest points of blockage or demonstrate flow through the aqueduct of Sylvius. The coronal brain section shown in the illustration indicates that the hydrocephalus, in this instance, is caused either by obstruction of an outflow pathway distal to the third ventricle or is a form of communicating hydrocephalus, in which case the fourth ventricle would also be dilated.

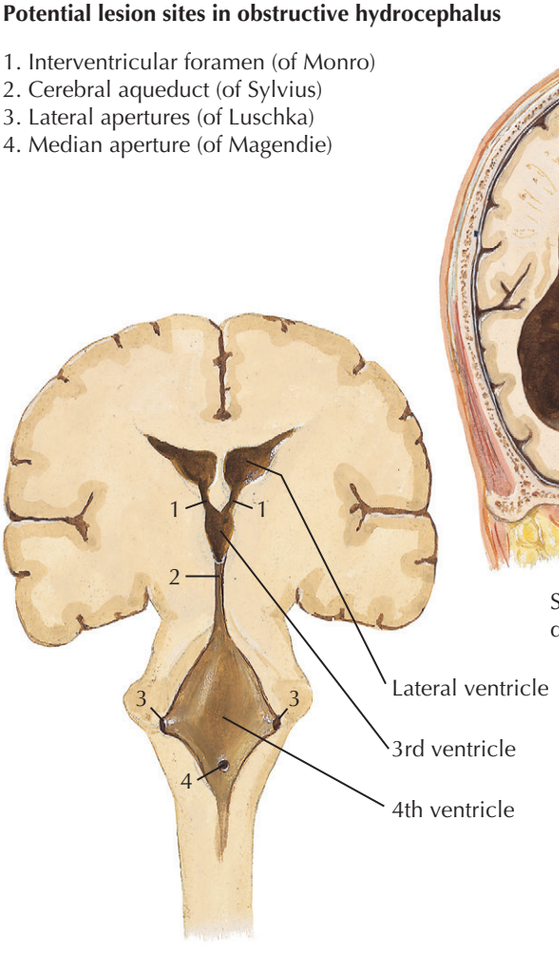
Symptomatic hydrocephalus in older children and adults is similarly divided into obstructive and nonobstructive etiologies, and this guides management decisions. Clinically, patients with symptomatic hydrocephalus are often lethargic, with headache, emesis, and other features of elevated intracranial pressure, including papilledema and cranial nerve palsies. *Idiopathic intracranial hypertension*, or pseudotumor cerebri, is characterized by elevated intracranial pressure without ventriculomegaly. Patients typically present with headache, vision loss, and diplopia and may require urgent intervention to minimize vision loss.

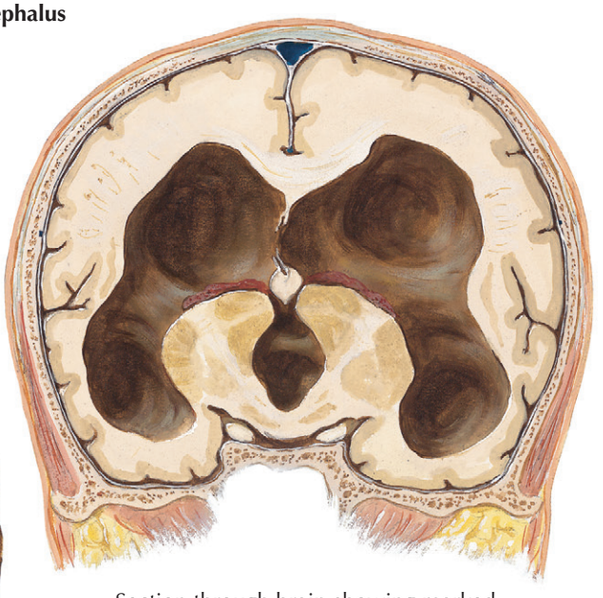
Normal-pressure hydrocephalus (NPH) is a well-described syndrome in adults that is associated with neurologic symptoms and signs without markedly elevated intracranial pressure. Initial symptoms are progressive dementia, gait disorders, and urinary incontinence. Brain imaging shows ventricular dilation, and the condition must be differentiated from ventricular dilation secondary to brain atrophy. A high-volume lumbar puncture can be diagnostic, although other clinicians prefer to use an isotope cisternogram to trace the CSF circulation (remove cisternogram images). In carefully selected patients with NPH, symptoms improve or resolve after the CSF shunt insertion (see Plate 1-16).

Clinical appearance in advanced hydrocephalus

Potential lesion sites in obstructive hydrocephalus

1. Interventricular foramen (of Monro)
2. Cerebral aqueduct (of Sylvius)
3. Lateral apertures (of Luschka)
4. Median aperture (of Magendie)





Section through brain showing marked dilation of lateral and 3rd ventricles

F. Netter M.D.

Surgical Treatment of Hydrocephalus

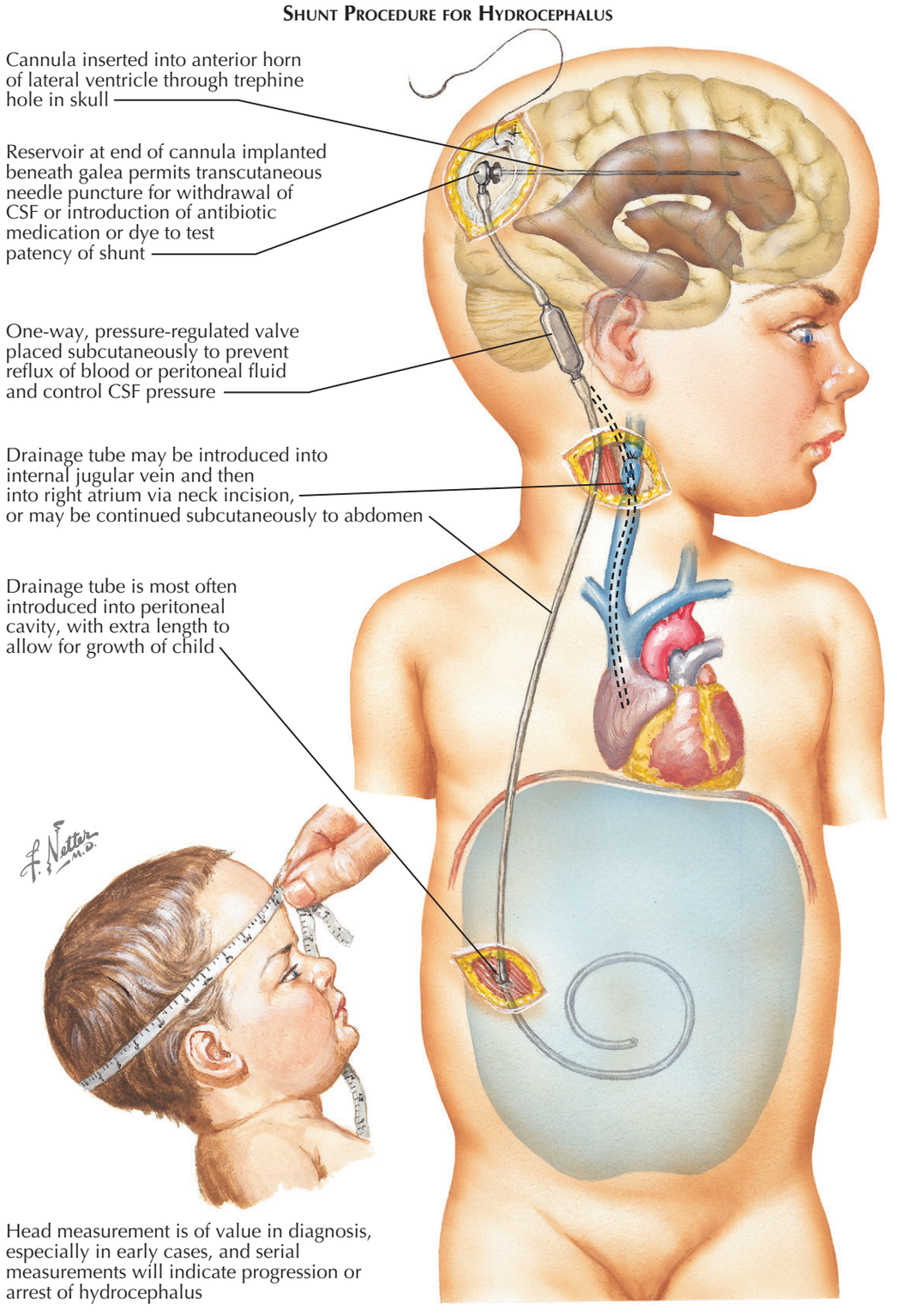
The treatment of hydrocephalus depends on the etiology and factors such as the patient's age, comorbidities, and anatomy. When hydrocephalus is secondary to a tumor or cyst blocking CSF outflow pathways, tumor removal or cyst fenestration may suffice. Most patients with communicating or obstructive hydrocephalus, however, require a CSF diversion procedure to compensate for impaired absorption or blockage. Successful CSF diversion procedures can halt progressive ventricular dilation and elevation of intracranial pressure and can frequently lead to improvement in neurologic function. CSF diversion can be accomplished by endoscopic procedures that bypass an obstruction or by insertion of a shunt to move CSF to an alternate site for absorption into the bloodstream.

Transient hydrocephalus can be temporarily treated with an external ventriculostomy or lumbar drain. These temporary drainage systems allow constant monitoring of the amount and character of CSF drainage, which can be quite helpful in patients with a limited neurologic examination. For obstructive hydrocephalus, the CSF diversion must occur above the blockage. In preterm infants, temporary treatment of symptomatic hydrocephalus is achieved with a ventriculosubgaleal shunt that drains the CSF into a subgaleal pocket or into a ventricular access device that has a reservoir to tap to remove CSF. Once the preterm infant achieves an adequate size, a more permanent CSF diversion procedure is performed, if needed.

Endoscopic procedures for CSF diversion include endoscopic third ventriculostomy (ETV), cyst fenestration, choroid plexus coagulation, and other procedures. The success of these procedures depends on multiple factors, including patient selection and specific anatomic details. The primary benefit of endoscopic procedures is the avoidance of implantation of shunt components that may later malfunction, become infected, or induce shunt dependence. Endoscopic procedures for CSF diversion can have late failure, and all patients after endoscopic procedures continue to require chronic neurosurgical supervision similar to patients with shunts.

The most common shunt system used is a ventriculoperitoneal shunt with a valve. Shunt components are made from Silastic material, and some are antibiotic-impregnated to decrease the risk of infection. The ventricular catheter tip is targeted to the frontal horn of a lateral ventricle from either a frontal or parieto-occipital trajectory. As the catheter exits the skull in the subcutaneous space, it is connected to a valve. Some surgeons use an intervening reservoir. The goal of the valve is to minimize overdrainage and subsequent collapse of the ventricular system and formation of life-threatening subdural hematomas. Various types of valves have been devised; none among them has been proved superior in a well-designed multicenter trial. Shunt tubing can also contain a valve at the distal tip. The subcutaneous distal shunt tubing is inserted into the peritoneal cavity, where the peritoneum absorbs the CSF back into systemic veins. Adequate tubing is placed in infants to decrease the chance that a lengthening procedure will be required. Alternate distal tubing sites include the right atrium or the pleural cavity. Lumboperitoneal shunts are used in select patients. Occasionally, it is necessary to obtain CSF from a patient with a shunt or to inject antibiotics or chemotherapy into the ventricular system instead of via a lumbar puncture. Rarely, contrast material may also be injected to identify loculations within the ventricular cavity. Any manipulation of a shunt by a non-neurosurgeon should be performed only in direct collaboration with a neurosurgeon.

The long-term success of the CSF diversion procedure depends upon the continued patency of the shunt or endoscopic opening. Failure of an endoscopic fenestration can lead to the same symptoms and signs of neurologic decline as a shunt failure. Once shunted, patients who may have previously absorbed a portion of their CSF may become completely dependent on the shunt for CSF diversion. The clinical presentation of a patient with failure of the CSF diversion procedure may or may not mimic the symptoms at the time of the diagnosis of hydrocephalus and initial treatment. The symptoms and signs of failure and period of illness may depend on the type of failure, the etiology of hydrocephalus and the patient's age. The most common cause of shunt malfunction is proximal catheter occlusion. Many patients with CSF diversion failure will present with recurrence of ventriculomegaly. Of importance, 10% to 20% of children presenting with a shunt malfunction will have no apparent change in the ventricular size compared with a baseline imaging study.



Cerebral Palsy

The developing brain is sensitive to essential physiologic mechanisms that maintain homeostasis. Regulation of oxygen availability is critical. Historically, *cerebral palsy* (CP) was used to describe a static, nonprogressive motor disability present at birth secondary to perinatal cerebral hypoxic and traumatic injuries. Currently, CP also encompasses other acquired nonprogressive motor disabilities and is distinct from progressive neurodegenerative processes. Although nonprogressive in the sense of deterioration, CP is not static in evolution. Individuals may display several different types of CP. Cerebral palsy is a descriptive diagnosis rather than an etiologic one. Clinically, CP manifests as motor defects that range in severity, Associated disorders include intellectual disability, epilepsy, visual and hearing difficulties, and orthopedic deformities. Other diagnoses should be excluded before CP is diagnosed.

Many children have CP related to birth trauma (see Plates 1-2 and 1-3) more attributed to hypoxic-ischemic encephalopathy (HIE). Low oxygen combined with impaired blood flow is particularly damaging. After resuscitation to overcome asphyxia, a brief (12-hour) period of stupor and hypotonia occurs before seizures and apnea.

Cerebral Lesions

Five major cerebral lesions result from HIE: (1) neuronal necrosis, (2) status marmoratus, (3) watershed infarcts, (4) periventricular telencephalic leukoencephalopathy, and (5) focal ischemic lesions. Although these lesions describe the neuropathologic findings, some may underlie damage to the CNS that is secondary to infection, trauma, vascular diseases, Dysgeneses, and migrational disorders. In neuronal necrosis, hypoxia damages neural cells throughout the CNS, resulting in spastic hemiplegia or quadriplegia.

Status marmoratus affects the basal ganglia, which become shrunken with a whitish, marble-like appearance. Affected infants are most often full term with initial hypotonia (see Plate 1-17), followed by spastic quadriparesis and choreoathetosis.

Watershed infarcts due to hypotension begin in the posterior parieto-occipital area and spread anteriorly and posteriorly. Watershed infarcts are most common in full-term infants and result in diplegia or hemiplegia.

Perinatal telencephalic leukoencephalopathy is most common in premature infants and often affects the centrum ovale, where it disturbs nerve fibers supplying the legs and acoustic and optic radiations. Minor lesions lead to white matter atrophy, whereas more severe lesions appear cystic. Minor lesions can cause learning disabilities, with severe lesions causing diplegia.

Focal ischemic lesions are large, occurring in specific blood vessel distributions, most often the middle cerebral artery. Probable causes are hypoxic-ischemic events, emboli, and thromboses. Focal ischemic lesions cause hemiplegia, with arms more affected than the leg or face. The large damaged area often becomes cavitated and develops into a porencephalic cyst. Occasionally, a cyst causes mass effect and requires surgical intervention.

Clinical Manifestations of Cerebral Palsy

The two main types of CP are spastic (pyramidal) and extrapyramidal. These classifications are based on the type and distribution of motor abnormalities, which are divided into subtypes.

Spastic (pyramidal) cerebral palsy involves damage to cortical areas responsible for voluntary movements, which contributes to spasticity. Subtypes include hemiplegia, quadriplegia, diplegia, and rarely monoplegia and tetraplegia.

Hemiplegia typically affects term infants, with most causes arising from maldevelopment and neonatal stroke. A hypotonic limb is initially noted, with subsequent spasticity. Cortical sensory loss and hemianopsia may be present.

Quadriplegia, the most severe and common form, affects all infants with a range of etiologies, from hypoxic or traumatic perinatal cerebral injuries to developmental abnormalities. Although spastic quadriplegia is usually evident early, hypotonia may manifest initially. Individuals typically have severe comorbidities including epilepsy, intellectual disability, and pseudobulbar palsy.

Diplegia primarily affects the legs, causing spasticity with scissoring. This affects both term and preterm infants, in the latter, often associated with periventricular leukomalacia (PVL). Hand function and cognition are relatively intact.

Extrapyramidal cerebral palsy: Damage is typically to the subcortical areas responsible for movement coordination and balance. Unless severe, intelligence is spared. Usually all body regions are involved; thus subtypes are named according to the type of movement.

Ataxia affects term infants and can result in incoordination, hypotonia, or spasticity.

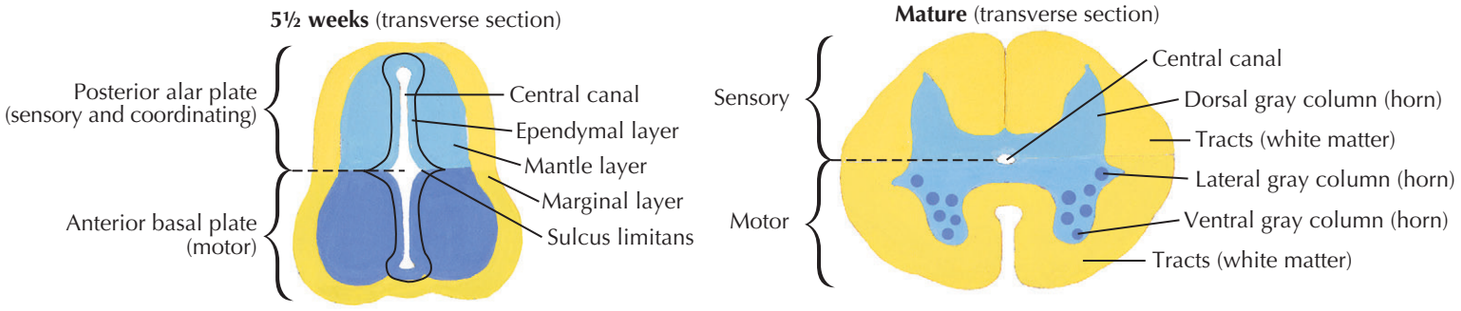
Athetosis is most often due to HIE. Infants are hypotonic, with persistence of primitive motor patterns (arching, tonic neck reflexes) that preclude orderly motor development. Involuntary movements become more consistent with choreoathetoid cerebral palsy.

Treatment

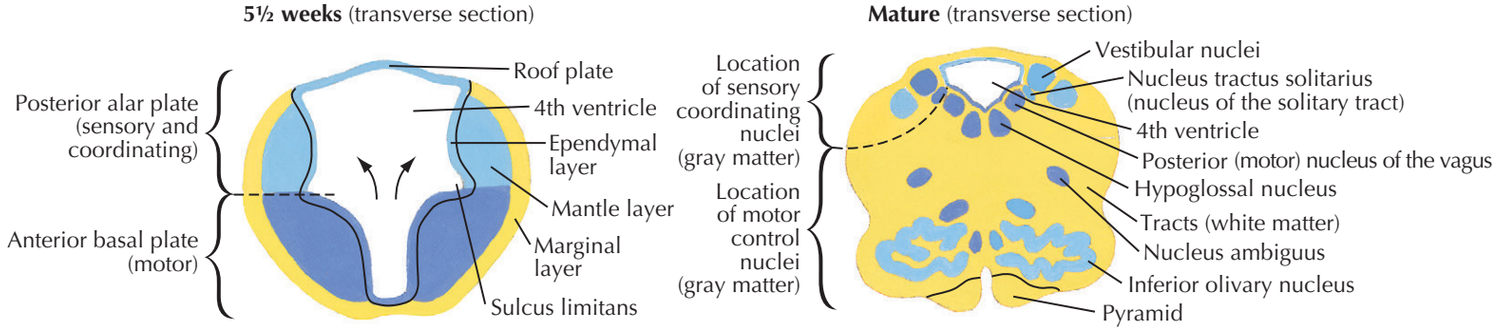
Evaluation and treatment of CP demands a multidisciplinary approach. Treatment goals focus on maximizing daily function and independence and target the child's multiple medical, social, psychologic, educational, and therapeutic needs.

Spasticity treatment includes physical therapy, oral medications, intrathecal baclofen, and orthotics. Surgical options include selective posterior rhizotomy and orthopedic procedures.

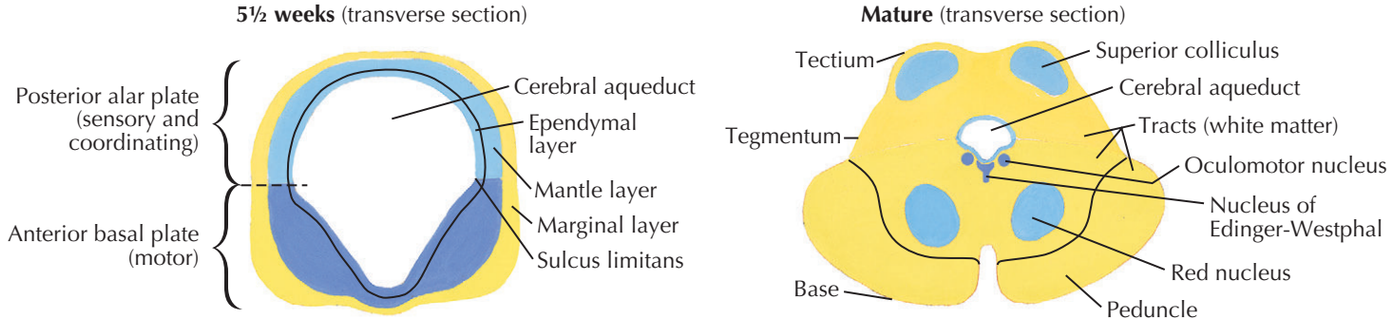
Spinal Cord



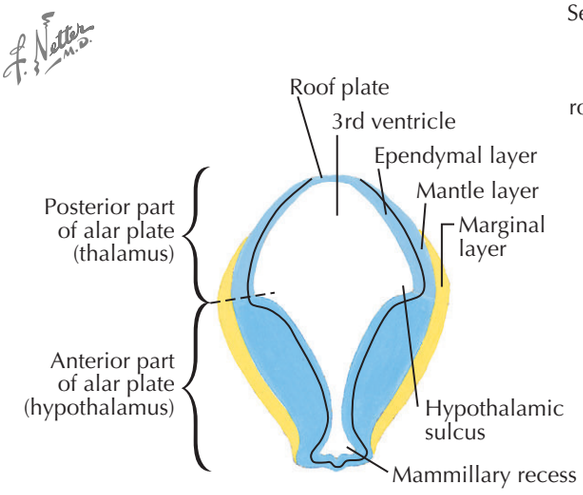
Medulla Oblongata



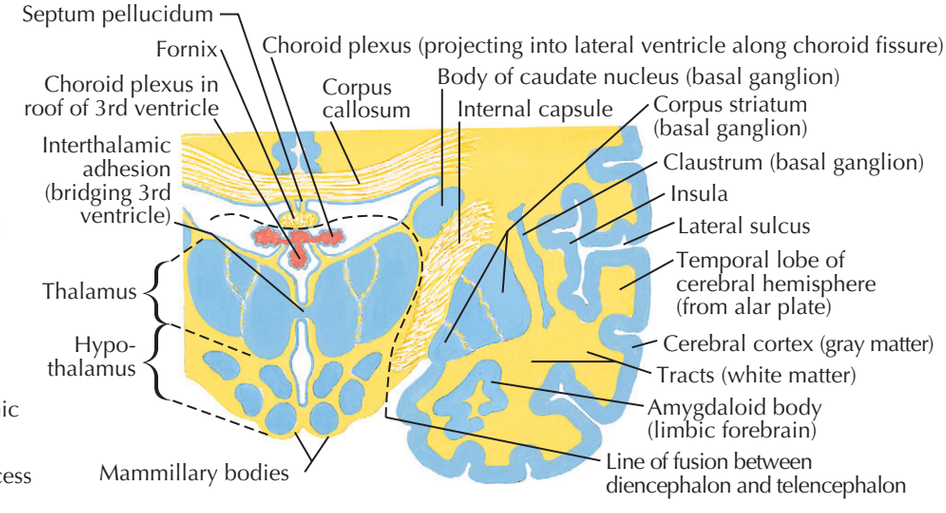
Mesencephalon



Diencephalon



Diencephalon and Telencephalon



Establishing Cellular Diversity in the Embryonic Brain and Spinal Cord

The morphogenetic transformation of the embryonic brain from a neural tube during the early first trimester to an organ that resembles the adult brain by the end of gestation is ultimately driven by ongoing stem cell proliferation, neurogenesis, and differentiation. This "histogenesis" depends on the specification and accumulation of neural stem cells with distinct capacities to generate diverse classes of neurons and glial cells. Subsequently, these stem cells, based on their position in the anterior-posterior as well as posterior-anterior axes of the neural tube and their access to both local and circulating signals, establish identity that is maintained in their postmitotic progeny. Thus the position of neural stem cells is a key determinant of the ultimate organization of each brain region. This relationship can be used to understand the basic adult organization of the entire central nervous system.

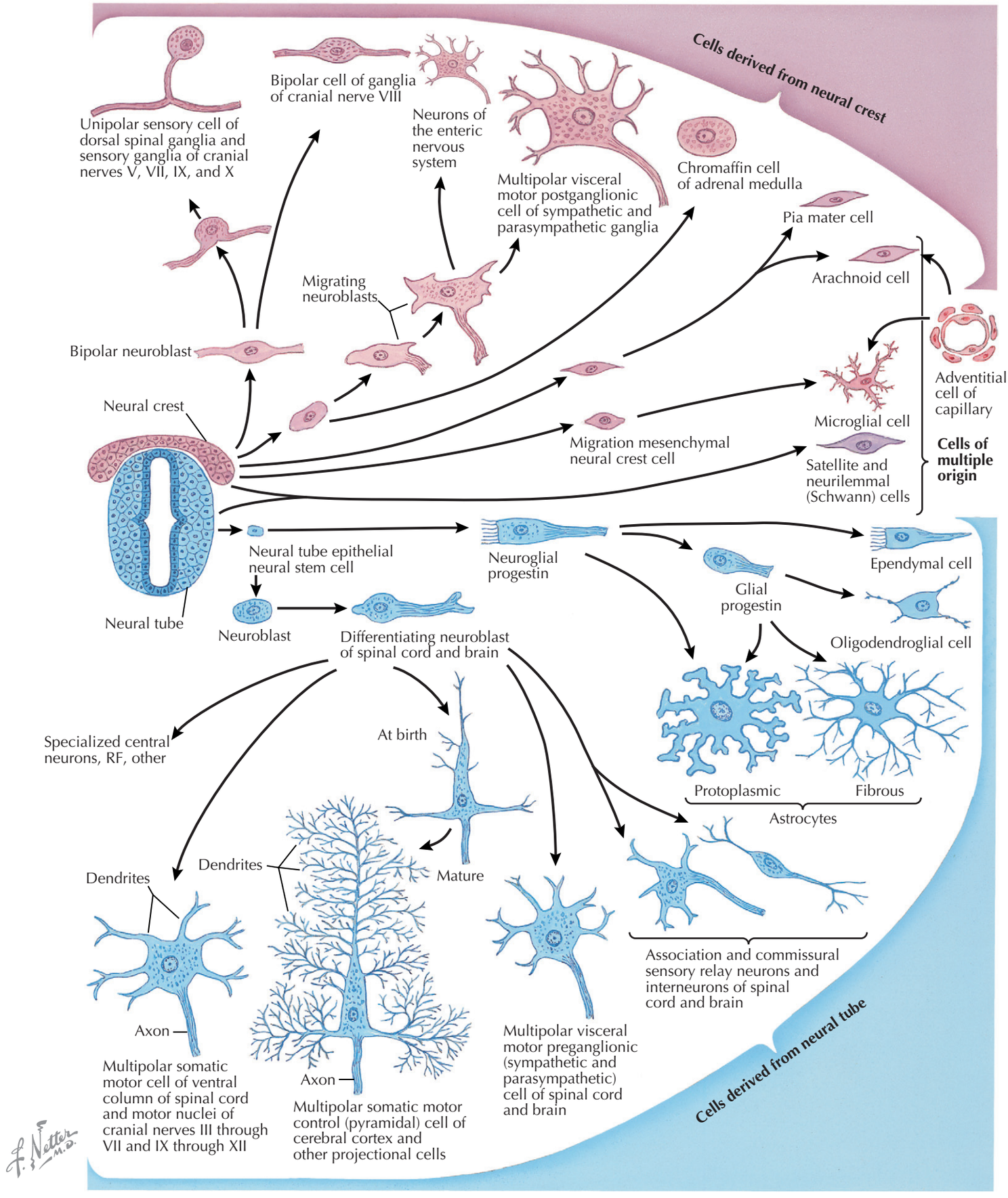
Neural stem cells that give rise to mature brain neurons and glia, with few exceptions, comprise a layer of cells that lines the ventricular space of the neural tube throughout its entire anterior-posterior extent. This layer, known either as the *ependymal layer* or *ventricular zone* of the developing neuroepithelium is usually the unique province of true *neural stem cells*: the proliferative cells in the nervous system that divide symmetrically and slowly to yield additional stem cells that have the capacity to generate all of the cell types in that region. A distinct type of proliferative cell, the *intermediate or transit amplifying progenitor*, is found in the *mantle layer* (also known as the intermediate zone). In addition, many newly postmitotic neurons are also found in the mantle layer. Finally, the outermost region of the neural tube epithelium is referred to as the *marginal layer*, or zone. The marginal zone has some postmitotic neurons and glia and some nascent axonal and dendritic processes from local differentiating neurons. In the spinal cord and hindbrain (medulla and mesencephalon), the marginal zone is also usually the site of axon pathways that grow from other regions of the brain to innervate local target neurons. Thus these three neuroepithelial layers—ependymal/ventricular, mantle/intermediate, and marginal—maintain local neural stem cells, facilitate neurogenesis, and support initial neuronal differentiation. The mantle and marginal zones are also important for support of initial neuronal differentiation and establishing initial connections between local dendrites and local or long-distance axons.

The neural tube also acquires regional distinctions in the posterior-anterior axis that reflect the ultimate division of the spinal cord, hindbrain, mesencephalon, and diencephalon into sensory and motor regions that either receive inputs from peripheral receptors (sensory) and relay this information to additional brain regions, or send axons to skeletal muscles or autonomic ganglia to regulate behavior and homeostasis. From the most posterior aspect of the spinal cord through the anterior end of the diencephalon, the neural tube becomes divided into *posterior or alar* and *anterior or basal plates*. These zones are distinguished from one another by a local groove, called the *sulcus limitans*, that indents the ependymal/ventricular zone. Throughout the entire extent of the posterior or alar plate, neurons are generated that become targets for sensory afferent axons from the periphery or that relay sensory information from other brain centers. Thus in the spinal cord, the medulla, the mesencephalon, and the diencephalon, posterior plate derivatives become sensory relay zones or distinct sensory relay nuclei. In the *spinal cord*, the sensory relay zone is referred to as the *posterior horn* and eventually becomes highly laminated in register with different classes of sensory input. In the medulla, the posterior plate gives rise to *sensory coordinating, or relay nuclei for the cranial nerves*. In the mesencephalon, the posterior plate gives rise to the superior and inferior colliculi, which receive input either directly from the eye (superior) or indirectly from the auditory nerve (inferior). These two nuclei are crucial for integrating sensory information with the initiation of motor commands. Finally, in the diencephalon, the posterior plate gives rise to all of the thalamic sensory coordinating, or relay nuclei for the senses: vision (lateral geniculate nucleus), audition (medial geniculate nucleus), somatosensation (anterobasal complex), taste (anterobasal complex), and olfaction (medioposterior nucleus). Throughout the posterior region of the spinal cord, medulla, mesencephalon, and diencephalon, the mantle zone becomes the location of *axon tracts* that carry sensory afferent axons.

In parallel with the differentiation of the posterior/alar plate, the anterior/basal plate yields groups of neurons whose axons project directly to striated muscles (skeletal motor neurons), autonomic ganglia (preganglionic motor neurons), cranial muscles largely derived from the neural crest (cranial motor neurons), or whose axons project to skeletal, preganglionic, or cranial motor neurons to provide CNS regulation of their commands to the peripheral muscles and glands. The position of various anterior plate derivatives along the anterior-posterior axis, from the spinal cord, through medulla and mesencephalon, through the diencephalon, determines the type of motor neuron that is generated. Thus throughout the entire spinal cord, most of the motor neurons in the *anterior horn* or column are skeletal motor neurons. In addition, in the thoracic spinal cord, preganglionic motor (or visceral) neurons are generated in the *lateral horn*, approximately in the region of the sulcus limitans. In the medulla, there are a variety of *cranial motor nuclei* that have cranial motor nerves that project to the muscles of the head and neck, the jaws, the tongue, and the eyes. In the mesencephalon, there are a number of tegmental nuclei that influence motor function (including the ventral tegmental area, or VTA, which has dopaminergic neurons), as well as the *red nucleus*, whose neurons project to skeletal motor neurons that regulate, among other things, gross arm movements. Finally, the basal plate of the diencephalon becomes a collection of *motor control nuclei of the hypothalamus* that project to preganglionic, visceral motor neurons that regulate a broad range of homeostatic and reproductive functions. The mantle zone of each region of the anterior plate develops into distinctive axon *tracts* that primarily carry axons of motor control neurons that project from higher centers (like the mesencephalon or hypothalamus) to motor neurons in the medulla and spinal cord.

Thus based on the position of neural stem cells in the ependymal/ventricular layer of the entire rudimentary spinal cord, medulla, mesencephalon, and diencephalon, there is an orderly specification of distinct sensory and motor neurons that serve distinct regions of the body: the trunk, limbs, and viscera for the spinal cord; the head, neck, and viscera for the medulla; mesencephalon, and diencephalon. This consistent specification relies on the establishment of centers that provide molecular signals to the posterior/alar and anterior/basal plate from the posterior spinal cord through the anterior mesencephalon. At the anterior midline is the *floor plate*, a thin region of neuroepithelial cells that secretes the key signaling molecule sonic hedgehog as well as several other signals to establish motor neuron identity. At the posterior midline is the *roof plate*, which provides signals that similarly influence the genesis and differentiation of sensory neurons. These include bone morphogenetic proteins (BMPs), wingless/integration (WNT) signals, and retinoic acid. Accordingly, the basic neuroanatomic and functional organization of the spinal cord, medulla, mesencephalon, thalamus, and hypothalamus reflects the developmental position and molecular signaling history of neural stem cells that generate the neurons of each brain region.

Somatic and Autonomic Neuron Formation



Generation of Neuronal Diversity in the Spinal Cord and Hindbrain

Morphogenesis ultimately reflects the establishment of distinct cell classes in appropriate numbers and positions throughout the neural tube. In the spinal cord and hindbrain, the basic relationships between neural stem cells and their progeny are well established. These relationships define cell lineages, broadly, for the spinal cord and hindbrain. The key distinctions that establish *lineages*—the range of cell types generated by specific classes of neural stem cells—are position in the neural tube of the stem cells and the way in which postmitotic progeny reach their final destination.

The neural stem cells in the spinal cord and hindbrain can be divided into four broad classes: *motor neurons and related interneuron progenitors*, *sensory relay neurons and related interneuron progenitors*, *glial cell progenitors*, *and neural crest progenitors.* There are key distinctions for each of these four classes. The first two stem cell classes, motor and sensory progenitors, have the capacity to give rise to both projection neurons with long axons that connect either the spinal cord with muscles and autonomic ganglia (motor) or send their axons from the spinal cord to higher brain regions to relay sensory information (sensory). These stem cells can also give rise to multiple classes of interneurons, whose axons remain in close proximity to the position of the interneuron cell body and which tend to establish inhibitory control for motor or sensory projection neurons. For these classes of stem cells (and the related intermediate progenitors), most cell division happens in the ventricular/marginal zone. The newly generated *neuroblasts* are then displaced over small distances so that they acquire an appropriate position in the dorsal or anterior horn. In the hindbrain, there is some local cell migration between distinct anterior-posterior locations (defined by the segmental organization of rhombomeres that prefigures the morphogenesis of the hindbrain) that leads to greater diversity of cells within cranial nerve motor or sensory relay nuclei. The third class of stem cells gives rise to the glia in the spinal cord and hindbrain. These stem cells are indistinguishable from the *neurepithelial progenitors* that give rise to neurons, and indeed they are mostly multipotent: they give rise to neurons as well as glial cells.

The specification and subsequent generation and differentiation of glial progeny are distinct from those of neurons. For the most part, the three primary classes of glia—*astrocytes*, *oligodendroglial cells* (see below), and *radial glia*—are generated later than the neurons of the spinal cord and hindbrain. Astrocytes are further differentiated into two classes: (1) *protoplasmic astrocytes*, which are found primarily adjacent to neuronal cell bodies and their processes, where they collectively constitute the *neuropil* (gray matter), and (2) fibrous astrocytes, which are found primarily in axon tracts (white matter) and whose processes often contact blood vessels. Radial glial resemble neuroepithelial progenitors, and indeed may be indistinguishable from these cells in many ways. A small number of radial glial cells remain in the mature ependymal zone in many regions, and these cells, when placed in appropriate cell culture conditions, can generate neurons as well as astrocytes and oligodendroglial. Thus the radial glia seem to either be neural stem cells or at least retain neural stem cell capacity that can be expressed under distinctive experimental conditions. Oligodendroglial cells interact with axons to generate the myelin sheaths that ensure efficient conduction of action potentials (see Plate 1-19). Oligodendroglial precursors initially are generated at the anterior midline and rely on some of the same secreted signaling molecules and transcription factors that also influence motor neuron determination and differentiation. Subsequently, however, oligodendroglial precursors are found throughout the developing and mature brain, and they can either retain their progenitor capacity (and in some cases, when isolated and cultured, can give rise to neurons as well as glia) or they can generate local myelinating oligodendroglia.

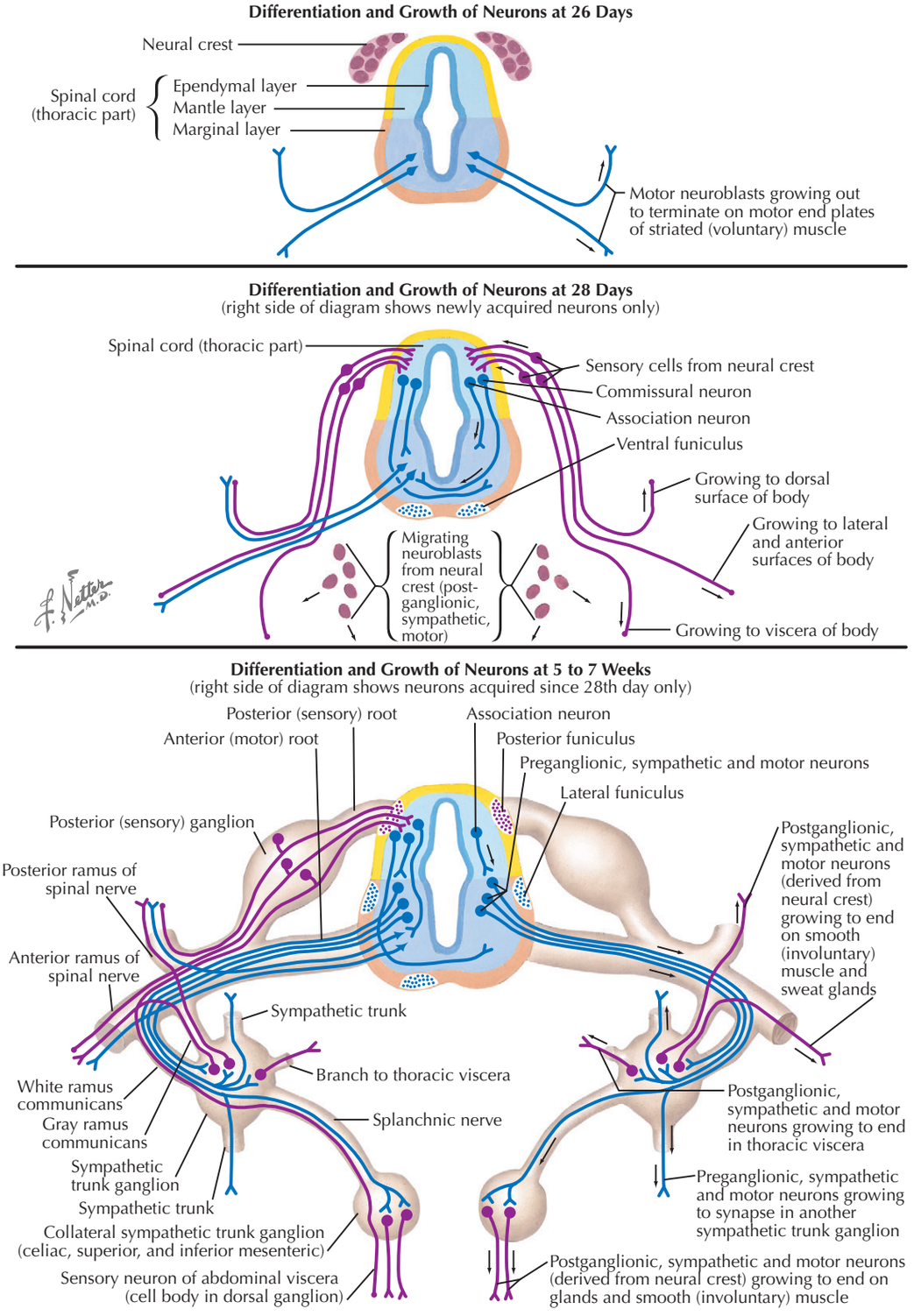
The fourth class of neural stem cell generated from the neural tube that gives rise to the spinal cord and hindbrain is the *neural crest progenitor.* As mentioned above, these stem cells either generate intermediate progenitors that then give rise to postmitotic *migrating neuroblasts* that actively move, or *migrate*, short distances from the neural tube and then reaggregate to form the sensory ganglia, including posterior root ganglia and most of the cranial nerves. Some *sensory ganglion cells* have a single cell body with a single process that bifurcates into a peripheral receptor process and central presynaptic process. This polarity facilitates generating receptor potentials in the periphery that also initiate action potentials that are conducted toward the CNS, where sensory information is then relayed via synapses made by the central process of the sensory ganglion cell. The neural crest also generates a truly bipolar sensory ganglion cell, the *bipolar sensory ganglion cells* of the spiral ganglion (auditory), or Scarpa's ganglion (vestibular). These neurons have a distinct postsynaptic process that receives synapses from auditory or vestibular hair cells and a central process that relays sensory information by making synapses made in the cochlear nucleus or vestibular nucleus in the hindbrain. The neural crest–derived neuroblasts also coalesce to form the *autonomic ganglia* of the sympathetic chain as well as the more widely distributed parasympathetic ganglia. Finally, neural crest–derived neuroblasts give rise to the *neurosecretory adrenal chromaffin cells* found in the adrenal medulla. The neural crest also gives rise to significant populations of migrating progenitor cells that divide further at their destinations. These include mesenchymal neural crest cells that populate the head and craniofacial primordia and give rise to the meninges (arachnoid, pia, and dura), some local blood vessel–associated cells, and multiple skeletal elements, including teeth and cranial bones. In addition, pigment cells in the epidermis are derived from migratory neural crest progenitors. Finally, the major class of peripheral glial cells, the Schwann cells, which have characteristics similar to oligodendroglia in the CNS, is derived from the neural crest.

Circuit Formation in the Spinal Cord

Cellular diversity provides the foundation for the next essential step of nervous system development—the construction of interconnected networks of neurons that serve specific behavioral functions. These networks are referred to as *neural circuits*, and their identity reflects the molecular distinctions between neuron classes and between the growth, adhesion, and recognition molecules that mediate elaboration of axons, dendrites, and synapses. The key constraints for circuit development reflect the genesis of the neurons that constitute each circuit: their place of final division and their final position. This process is remarkably well understood for the construction of circuits that mediate motor control, relay of sensory information in the spinal cord, and local sensory-motor integration for segmental reflex control. As described above, sensory relay neurons and related interneurons are generated from the alar plate, motor neurons and related interneurons are generated from the basal plate, and peripheral sensory ganglion cells are generated from the neural crest. Each of these cell classes will become interconnected in distinct circuits. For these circuits to form, there must be clear rules, mediated by local *chemoattractant* and *chemorepulsive* cues, for where each neuron class can extend its axons and dendrites. In addition, there are temporal gradients of neuronal differentiation so that some neuron classes grow their axons and dendrites earlier (as early as 26 days of gestation), and, within a few days, other neuron classes will begin to extend their processes. Thus the construction of circuits from the newly generated neurons in the spinal cord relies on time of origin of neurons, neuronal position, and time of axon or dendritic growth.

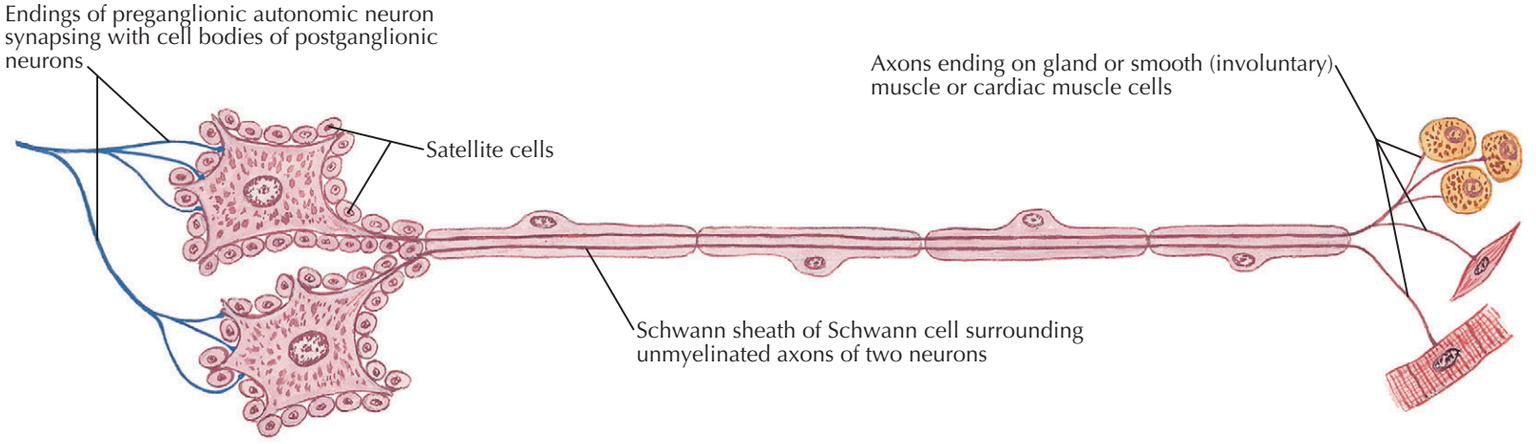
The direction of growth chosen by axons from different neuron classes must be exquisitely regulated to ensure proper connectivity within spinal cord circuits. Thus motor neurons, whose axons are the earliest to grow out of the spinal cord, are directed to an exit point lateral and anterior, based on chemoattractant signals that guide them there and cell surface adhesion molecules that facilitate their exit from the central nervous system. Additional cell adhesion molecules maintain the appropriate trajectory for these axons and facilitate the formation of a coherent nerve. Chemorepulsive signals prevent axons from growing aberrantly to inappropriate nonmuscle targets. Accordingly, motor axons grow to their skeletal muscle and autonomic ganglia targets with great fidelity.

The parallel growth of several classes of sensory neuron axons within the spinal cord illustrates the complexity—and remarkable precision—of the relationship between cell position, axon guidance, and molecular signals that attract or repel subsets of axons. Sensory relay neurons or interneurons generated from the alar plate either extend axons across the anterior midline and then into the spinothalamic tract or into the motor column on the same side to make local reflex connections (like those necessary for withdrawal in response to painful stimuli). Clearly, there need to be discriminating sets of signals: one set that attracts spinothalamic relay axons to the anterior midline and then maintains them on the contralateral side, and one set that attracts interneuron axons to the anterior horn and prevents them from extending past the midline. The signals that influence the commissural axons are now fairly well understood. These include a secreted chemoattractant molecule called *netrin*, which is similar in its molecular structure to the extracellular matrix adhesion molecule laminin, and a secreted chemorepulsive molecule called *slit*, which signals an axon that it should not cross back once it has crossed the midline. Thus the anatomic precision of pathways for relaying pain and temperature is generated by precise molecular mechanisms that attract axons to the midline, guide them across, and then maintain them on the contralateral side of the spinal cord, brainstem, thalamus, and cortex.



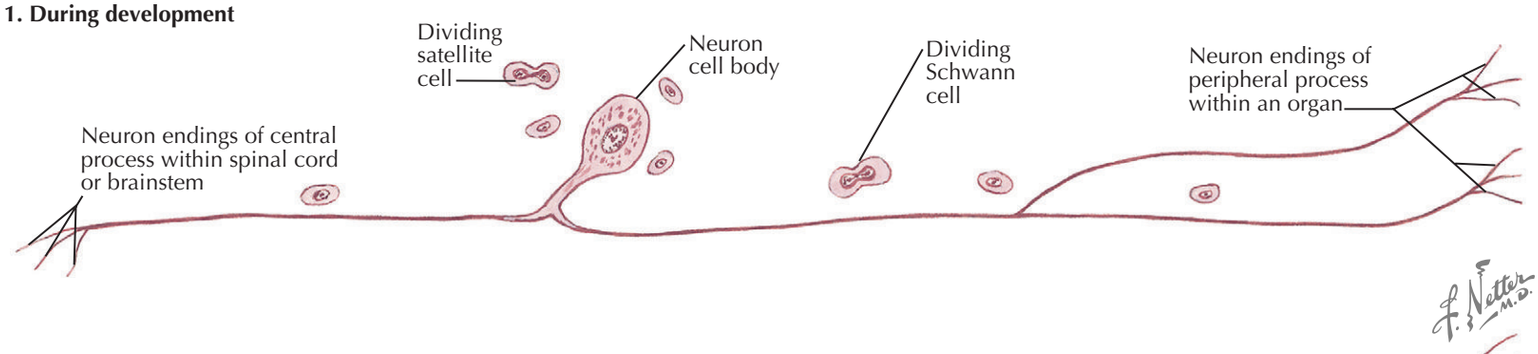
Sheath and Satellite Cell Formation

Two postganglionic autonomic neurons of a sympathetic or parasympathetic ganglion

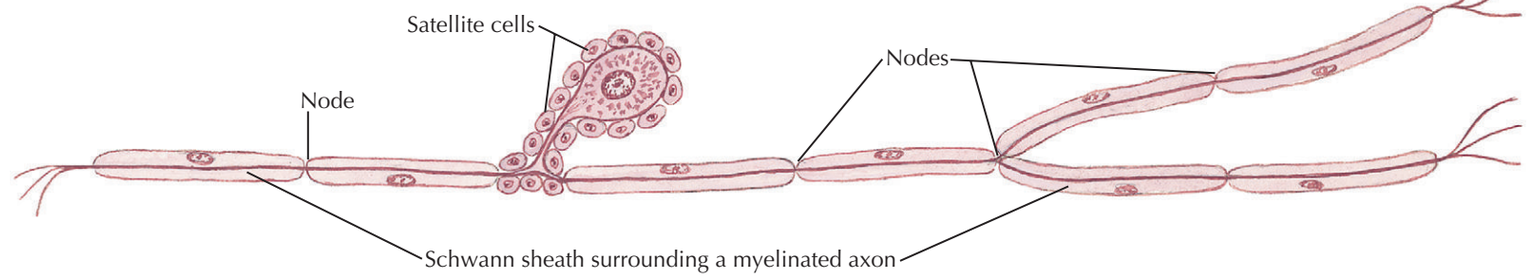


Somatic or visceral sensory neuron of a spinal ganglion or sensory ganglion of cranial nerves V, VII, IX, or X

1. During development



2. Mature

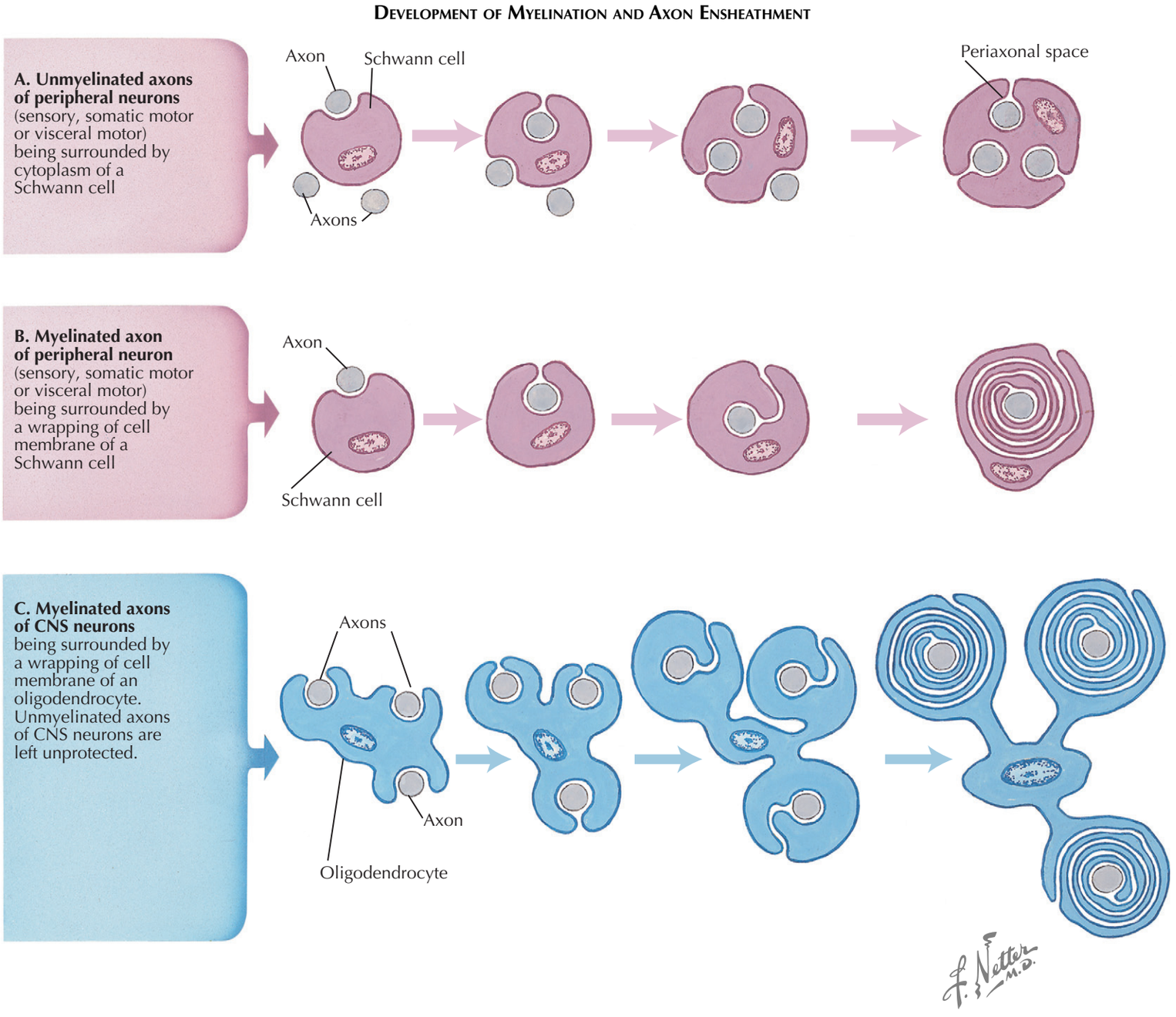


Making Peripheral Nerves and Central Tracts

Another essential aspect of establishing cellular diversity in the nervous system is the differentiation of distinct classes of glial cells that associate themselves with developing axons. These glial cells are found in both the peripheral nervous system (PNS), where they are derived from the neural crest, or in the central nervous system, where they arise from local neural stem cells (thus true multipotent neural stem cells are capable of giving rise to both neurons and glia). These glial cells then interact with peripheral axons either as they form peripheral nerves or with central axons as they form central tracts. Schwann cells establish a clear relationship with *unmyelinated axons* in the peripheral nervous system, surrounded, or ensheathed, by Schwann cell processes that constitute the neurilemma. Each Schwann cell usually ensheathes more than one axon of this type. Most axons of postganglionic autonomic (sympathetic and parasympathetic) neurons are unmyelinated. Numerous layers of the cell membrane of Schwann cells wrap *myelinated axons* of the peripheral nervous system. A single neurilemmal cell typically forms a segment of myelin sheath for only one peripheral axon.

Oligodendrocytes in the CNS and Schwann cells in the PNS form myelin sheaths by similar processes. In an action similar to the continuous wrapping of a bolt of cloth, the oligodendroglial cell membrane becomes wrapped around the axon many times. As the wrapping occurs, the oligodendroglial cytoplasm retracts or is extruded so that the two layers of the cell's plasma membrane, which originally were separated by cytoplasm, come together and fuse. Except for small islands of cytoplasm, which may be trapped between the fused membranes, the fusion is complete. The cell membrane of the myelinating oligodendrocyte, like cell membranes elsewhere, is composed of alternate layers of lipid and protein molecules. Thus myelin is made up of numerous fused layers of lipoprotein membrane.

Myelination is closely associated with the development of the functional capacity of neurons. Unmyelinated neurons have a low conduction velocity and show fatigue earlier, whereas myelinated neurons fire rapidly and have a long period of activity before fatigue occurs. Neurons that ultimately are capable of rapid



Making Peripheral Nerves and Central Tracts *(Continued)*

transmission of impulses become fully functional at about the time their axons become completely insulated with a myelin sheath. In general, the motor neurons of cranial nerves become myelinated before their sensory counterparts. The sensory neurons of the trigeminal nerve and the cochlear division of the vestibulocochlear nerve begin to acquire myelin only in the fifth and sixth months of development. The optic nerve neurons begin to be sheathed at birth, and myelination is completed by the end of the second week after birth.

As development continues, the nerve fibers (axons) of both the CNS and the PNS eventually become sheathed or encapsulated. In the PNS, neurons become completely encapsulated by parts of other cells, except at their terminal endings and at the nodes of Ranvier. The Schwann cell ensheathes both the myelinated and unmyelinated axons of somatic motor neurons and preganglionic autonomic motor neurons as they pass out of the CNS. These cells, derived from both the neural crest and the wall of the neural tube, also ensheath both the central and peripheral processes of the somatic and visceral sensory neurons, as well as the axons of postganglionic autonomic (sympathetic and parasympathetic) motor neurons.

Another type of cell, which is derived from both the neural crest and the wall of the neural tube and which participates in covering the neurons of the PNS, is the *satellite cell*. Satellite cells completely encapsulate the cell bodies of sensory neurons in the sensory ganglia of both the cranial and spinal nerves, and also the postganglionic neurons of the sympathetic and parasympathetic ganglia. Finally, there is a specialized glial cell that shares properties of Schwann and satellite cells but is only found apposed to the unmyelinated axons of the olfactory nerve; these axons originate from receptor neurons in the nose that are continually replaced throughout life and thus must regrow into the olfactory bulb in the CNS and make new synapses. These olfactory ensheathing cells are apparently specialized to support the constant regrowth of the axons and the establishment of new connections in the CNS. Accordingly, there is great interest in these cells as a substrate for improved axon growth in other regions of the CNS after injury.

Brachial Plexus and/or Cervical Nerve Root Injuries at Birth

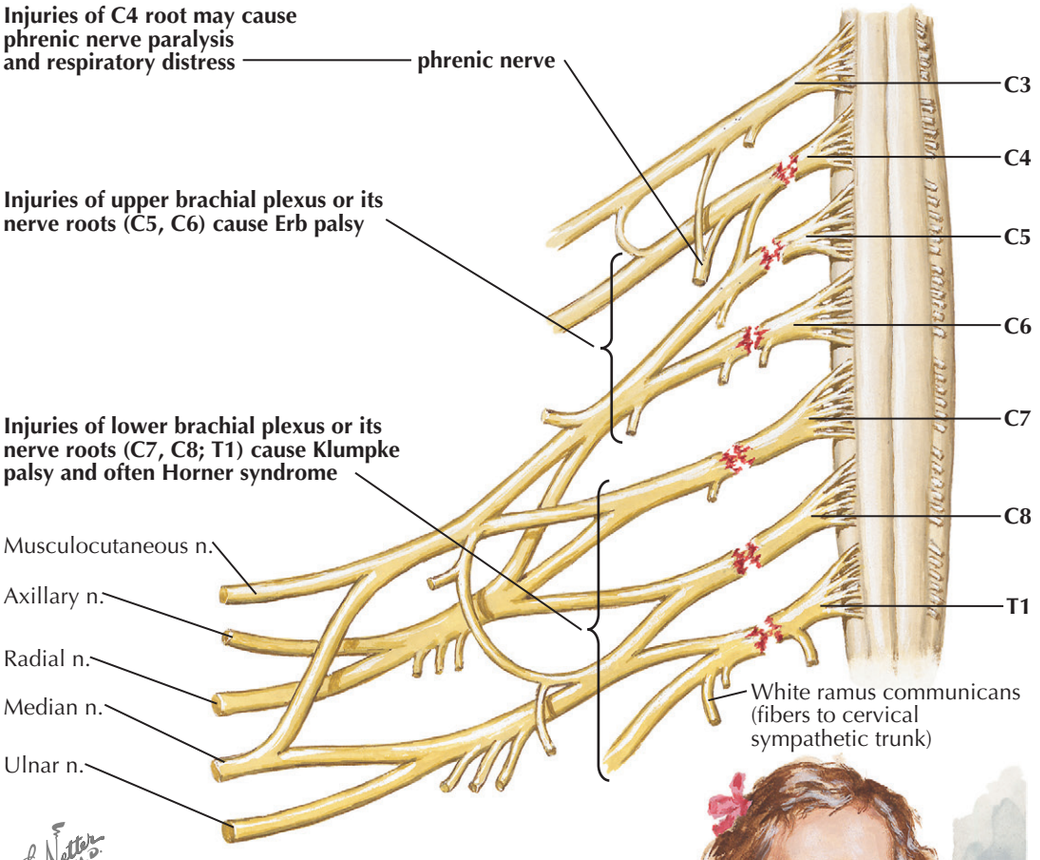
The maturation and myelination of peripheral nerves, including cranial nerves, is not complete at birth. Thus these axons, not yet fully protected by myelin, associated glial cells, and connective tissue, are susceptible to perinatal injury. Brachial plexus injuries in the newborn now occur much less commonly, although the incidence is still approximately 1 in 1,000 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 more than 3,500 g) with low Apgar scores.

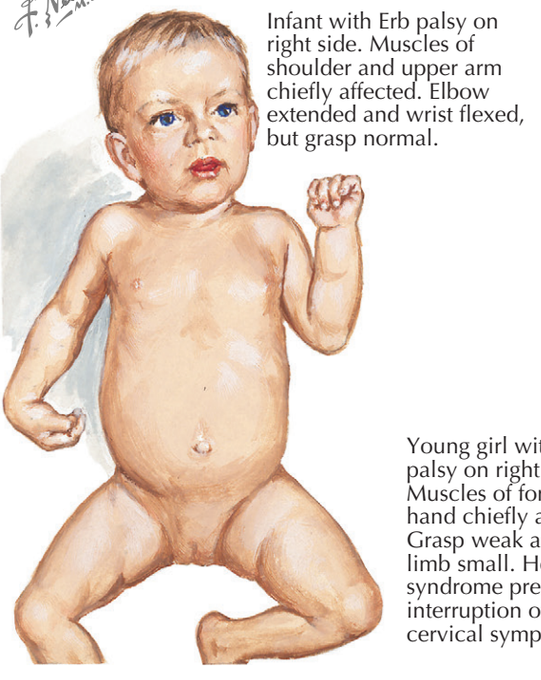
Brachial birth palsy is believed to be secondary to a stretching of the plexus by traction, with the nerve roots being anchored by the spinal column and cord. In less severe lesions, only the myelin sheath may be damaged, which is evidenced by swelling and edema that may, in turn, damage the myelin. If only a small segment of the axon is affected or if it is stretched but not ruptured, quick repair and recovery are likely. However, if the axon is interrupted, repair can take a very long time, considering that the rate of axonal growth is believed to be 1 mm/day. If the axon is completely ruptured, recovery is unlikely. Bilateral brachial injuries almost always indicate spinal involvement, and avulsion of the nerve roots may be evident on magnetic resonance imaging. Upper brachial plexus injuries involve the junction of C5 and C6 roots (Erb 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 rather difficult to distinguish. 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 quite 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. Involvement of sympathetic fibers from T1 causes Horner syndrome (ptosis, miosis, anhidrosis). A significant sensory deficit is usually present. Infants and children may sometimes traumatize their fingers unwittingly, with occasionally severe results such as loss of a fingertip. Prognosis for full recovery in these infants is poor. The upper extremity often remains small and distally foreshortened.

Treatment. In all cases of brachial plexus injury, a thorough evaluation is indicated. 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, and physical or occupational therapy should be continued throughout at least the first year of life. Hand and wrist splints can be used as necessary. Most infants will experience marked recovery of function in the first few months. If no recovery is observed, electromyography, can be useful to determine the extent of the injury. For infants with persistent severe injury and no evidence of improvement at 4 to 6 months of age, magnetic resonance imaging may be helpful in determining whether the infant will benefit from a brachial plexus repair with nerve grafts. Although brachial plexus repair does not restore normal function, it can provide carefully selected infants with functional improvement. 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.

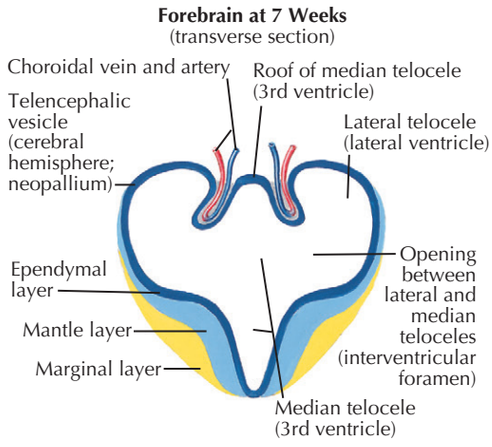
Morphogenesis and Regional Differentiation of the Forebrain

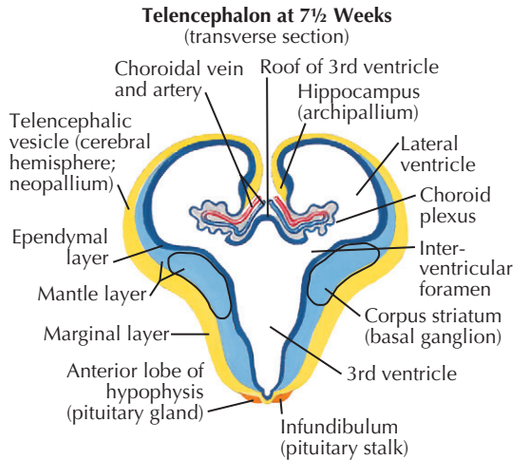
The forebrain, unlike the spinal cord, does not receive signals from the notochord and somites. Thus its regional differentiation depends upon distinct mechanisms that result in the growth and differentiation of the two telencephalic vesicles into the cerebral cortex, hippocampus, basal ganglia, basal forebrain nuclei including the amygdala, and the olfactory bulb. After the anterior neural tube has closed a population of neural crest–derived mesenchymal cells migrates into the head and surrounds the newly formed prosencephalic vesicle. These mesenchymal cells are a key source of inductive signals, playing a similar role to that of the notochord and somites in the spinal cord and hindbrain. The mesenchymal cells signal directly to the forebrain neuroepithelium to influence the establishment of signaling centers. These signaling centers resemble the floor plate and roof plate of the spinal cord and hindbrain. Thus there is an anteromedial source of sonic hedgehog and a posteromedial source of BMPs as well as WNTs that influence further regional and cellular differentiation. In addition, there is an anteromedial domain that produces fibroblast growth factor (FGF) signals that are essential for forebrain regional differentiation. Thus the interaction between mesenchyme and forebrain neuroepithelium is essential for establishing the foundations of regional differentiation in the forebrain.

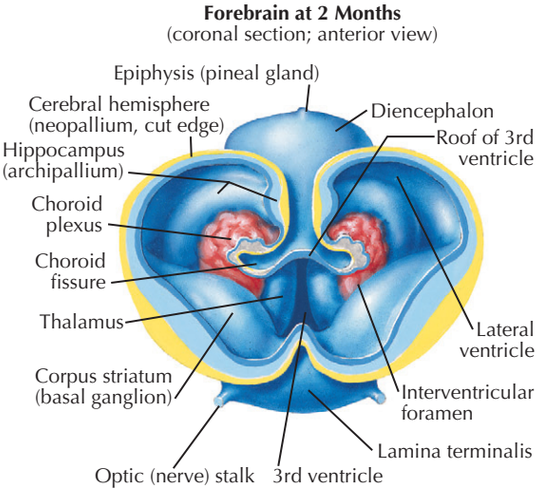
Once these interactions have progressed, the prosencephalic vesicle expands so that there are two telencephalic vesicles. Based on their proximity to anteromedial and anterior sonic hedgehog and FGF signals or posteromedial BMP and WNT signals, the telencephalic vesicles become divided into anterior and posterior territories based on differential expression of multiple transcription factors. The posterior territory is referred to as the *pallium*. It generates the *cerebral cortex (neopallium)* as well as the *hippocampus and pyriform cortex (archipallium)*. The anterior territory is referred to as the *ganglionic eminences*. These structures generate the *corpus striatum* or *basal ganglia* as well as nuclei of the basal forebrain, including the amygdala. Finally, at the ventral and anterior aspect of each telencephalic vesicle, the olfactory bulb evaginates and extends anteriorly.

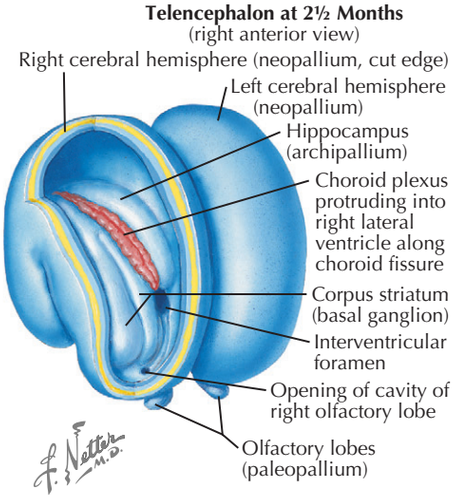
The division of the forebrain into the telencephalic vesicles is accompanied by the elaboration of the choroid plexus that emerges at the posterior midline. At this region, *choroidal veins and arteries*, generated from angiogenic mesenchymal cells outside the brain, are adjacent to the posterior neuroepithelium. Subsequently, these blood vessels continue to grow in close apposition to a very attenuated neural-derived epithelium. Together, the blood vessels and this attenuated forebrain epithelium constitute the *choroid plexus*. In the adult brain, the choroid plexus serves as an interface between systemic circulation and the cerebrospinal fluid that fills the ventricular system to maintain ionic balance and deliver molecular signals for homeostatic control. The choroid plexus actually grows into the ventricle so that the "pial" surface of the neuroepithelium is actually exposed to the cerebrospinal fluid. In the embryo, the choroid plexus is apparently part of a dynamic set of tissues (including the posterior and anterior domains that produce sonic hedgehog, BMPs and WNTs) that secrete signaling molecules into the embryonic forebrain CSF to influence forebrain stem cell proliferation and differentiation. Thus an essential source of molecular instruction for neural stem cell proliferation and specification in the forebrain is the cerebrospinal fluid, influenced by molecules secreted dynamically by the choroid plexus as it develops.

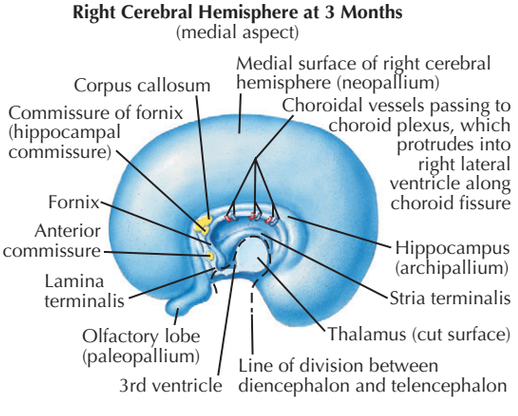
Subsequently, once neurogenesis and neuronal differentiation begin in the forebrain, a series of axon pathways, referred to collectively as the *cerebral commissures*, emerge to cross the midline, much like those that cross the midline in the spinal cord and hindbrain. These include the *corpus callosum*, *hippocampal commissure*, *and anterior commissure*. The growth of these axon pathways from one telencephalic vesicle to the other involves similar molecules and mechanisms to those that influence the midline crossing of sensory axons that constitute the spinothalamic pathway. In addition to netrin, slit and its robo receptor, members of the Ephrin/Eph receptor family of adhesion molecules, seem to be essential for the development of the cerebral commissures, as does the calcium-independent adhesion molecule L1.

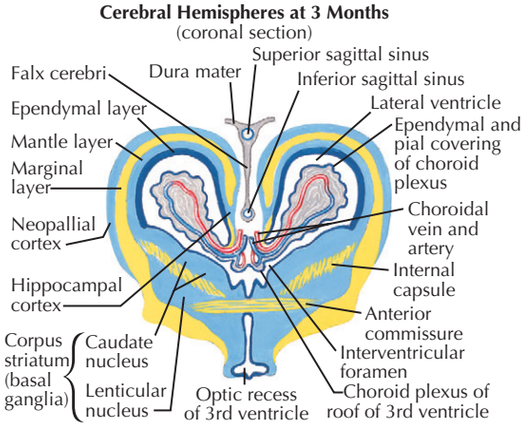


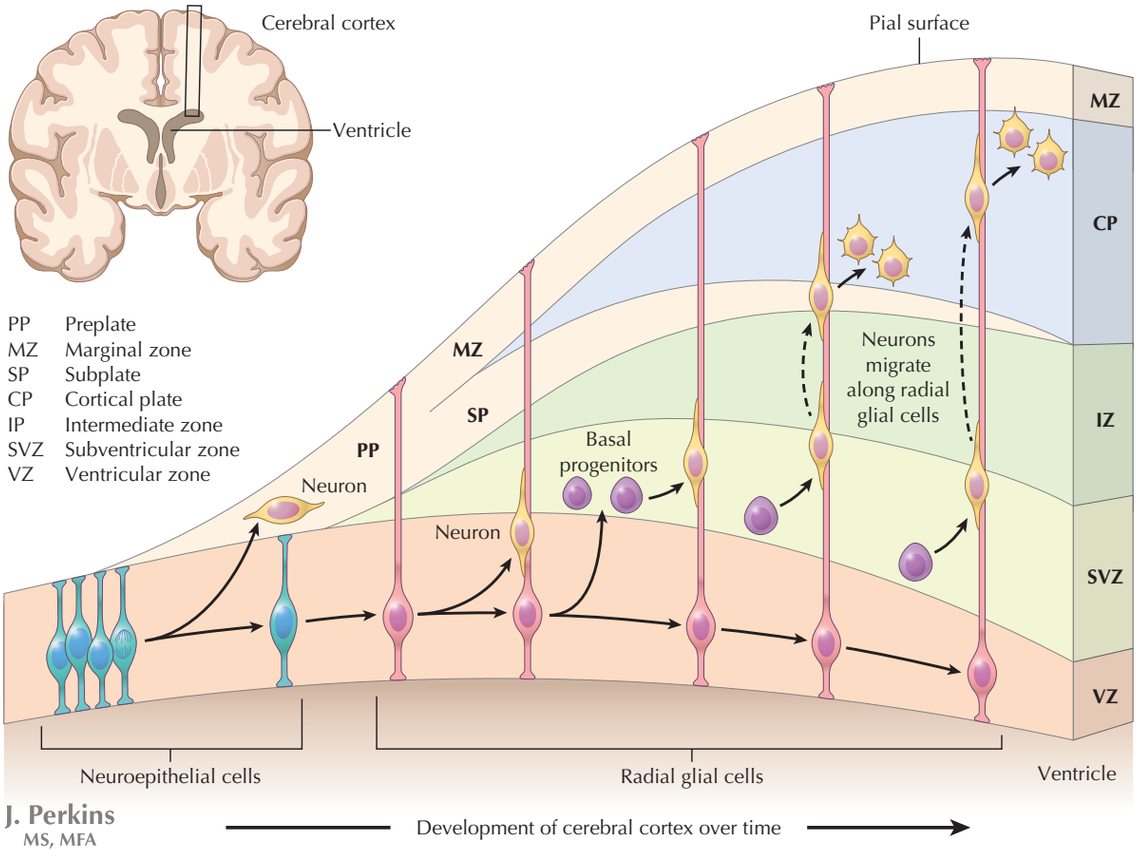












Neurogenesis and Cell Migration in the Developing Neocortex

Most, if not all, cortical neurons are generated in or near the ventricle and migrate *radially* to the cortex that forms on top of the neuroepithelial precursors. Cortical neural stem cells, *radial glia*, maintain cell bodies at the *ventricular zone*, where they divide symmetrically and slowly. Radial glia also generate rapidly, asymmetrically dividing *intermediate progenitors* slightly displaced into the *subventricular zone*, where they generate postmitotic neurons. Radial glia serve a dual function. Their long processes directed toward the pia provide a migratory guide for newly postmitotic neurons through the ventricular and subventricular zones into the cortical plate, where they disengage and differentiate. Further constraints reflect the time when cortical neurons undergo their final cell division. Cortical neurons "born" first (become pos-mitotic earliest) form the *preplate*, the earliest histologic indicator of cortical differentiation. The preplate divides into the *marginal zone*, which becomes layer 1 of the cortex, and the transient *subplate*, which guides development of the overlying cortex. Early generated marginal zone and subplate neurons provide signals that influence migration and initial axon growth. Some early generated marginal zone neurons remain in layer 1 as Cajal-Retzius cells. Subplate neurons fare less well. A few become interstitial subcortical white matter neurons; however, most die postnatally.

The earliest-born neurons of the cortex itself migrate through the preplate, splitting it into the marginal zone and subplate, thus constituting layer 6 of the cortex. Each successive cortical neuron cohort, generated during the last two thirds of gestation in humans, migrates past earlier-born neighbors to their final positions. Thus there is an "inside-out" gradient of cortical neurogenesis: early born neurons are deepest, and those born last, except for Cajal-Retzius cells, are superficial. These distinctions are accompanied by differences in which cortical neurons send their axons dendritic differentiation and connectivity.

Radial migration and the inside-out neurogenesis gradient together produce cortical *projection neurons* whose axons extend to other cortical regions or subcortical targets, such as the basal ganglia, pons, and thalamus, and use the excitatory neurotransmitter *glutamate*. Surprisingly, the other major class of cortical neurons, *interneurons* that use the inhibitory neurotransmitter gamma amino butyric acid *(GABA)*, are not generated within the cortex. Instead, interneuron progenitors are found in two anterior forebrain domains: the medial and caudal ganglion eminences. These progenitors yield postmitotic GABAergic neuroblasts within the ganglion eminences that migrate into the neocortex. Initially, this migration is tangential, that is, parallel to the plane of the cortical sheet. When these neurons reach the cortical area where they will differentiate, they migrate radially in much the same way as projection neurons, using radial glial guides.

In the *olfactory bulb*, projection neurons *(mitral cells)* are also generated locally, and GABAergic interneurons migrate from the *lateral ganglion eminence* by a distinct migratory route called the *rostral migratory stream*. In some mammals, the rostral migratory stream remains in place and guides newly generated neurons from a proliferative zone called the *anterior subventricular zone*, or *SVZ*, to the olfactory bulb, perhaps throughout life. The human brain, however, lacks a rostral migratory stream after birth, and it is unlikely that new olfactory interneurons are generated long into postnatal life. In the *cerebellum*, interneurons (glutamatergic rather than GABAergic) are generated from a proliferative layer immediately beneath the pia, called the *external granule cell layer*. The postmitotic granule cells then migrate back into the rudimentary cerebellum, past *Purkinje cells* (cerebellar projection neurons, generated locally) using a glial guide, the Bergmann glia, to facilitate migration. Thus in several brain regions projection neurons and interneurons are generated in distinct proliferative zones, followed by migration that brings these neurons together to form circuits.

The complex history makes the neocortex vulnerable to developmental changes with potential impact on disease. Behavioral disorders, from autism and attention deficit/hyperactivity disorder (ADHD) to bipolar disorder and schizophrenia, may reflect, in part, changes in neurogenesis and migration. Cortical development demands exquisite precision so that neurons are generated at the right times and get to the right places. Small, but significant disruptions could lead eventually to subtle, but significant alterations of cortical circuits and the social, communicative, and cognitive behaviors they subserve. These hypotheses, which unite a spectrum of psychiatric diseases into a continuum of disorders of development of cortical connectivity, remain to be thoroughly tested.

Neuronal Proliferation and Migration Disorders

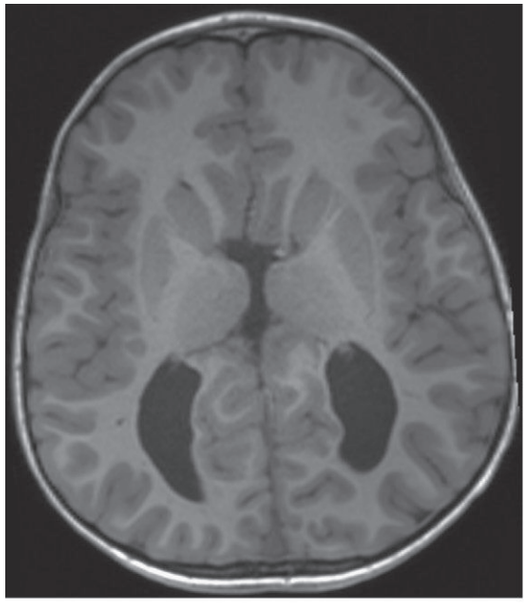
The complexity and duration of cortical neurogenesis and migration makes it a particularly vulnerable target for disruptions that result in broad range of brain disorders. These include a variety of epilepsies, intellectual disability, and potentially, disorders such as autism and attention deficit/hyperactivity disorder (ADHD). Many of these disorders, and the cell biologic and genetic analyses that better defined their pathogenesis as disruptions of cortical neuronal proliferation and migration, took advantage of structural imaging of the cortex by using magnetic resonance imaging to identify anatomic irregularities in the size, shape, and gyral and sulcal patterns of the cortical hemispheres. Nevertheless, a "normal" magnetic resonance imaging scan does not rule out microscopic localized gyral malformations or, most important, significant defects of the cortical layers and heterotopias of neurons that are initially destined for one cortical layer, but, due to altered migration, are found in an aberrant laminar location. Clearly, such disruptions of cortical neurogenesis and migration must result in altered circuits that lack the capacity to mediate maximally adaptive behaviors.

Defective Proliferation. A *decrease* in neuronal number may lead to *microcephaly* (microencephaly vera), whereas an *increase* may result in *megalencephaly*. Prenatal influences, including familial factors, are paramount in each abnormality. Microcephaly may be caused by a variety of genetic and environmental etiologies. It may be isolated or associated with other anomalies. Primary microcephaly results from a developmental insult giving rise to a reduced neuronal population. Secondary microcephaly occurs from an injury or insult to a previously normal brain.

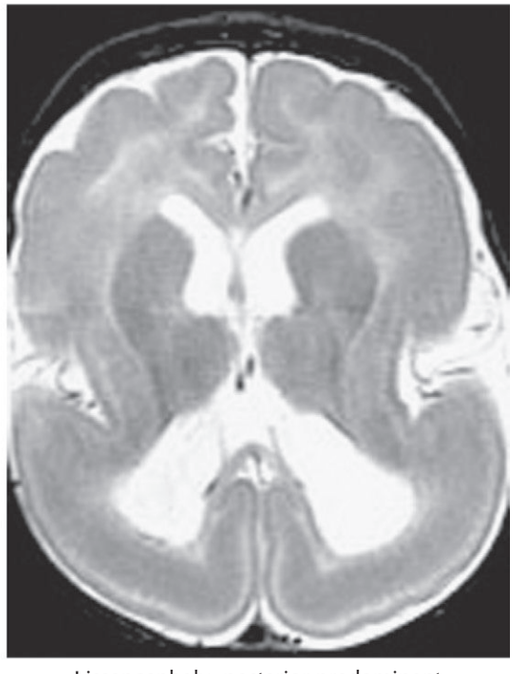
Megalencephaly is classified as either anatomic or metabolic. It may be associated with neurofibromatosis, achondroplasia, or cerebral gigantism. Familial megalencephaly, the most common and benign form, is usually inherited through the father. Excessive postnatal growth also occurs often, suggesting hydrocephalus. Measurements of the parental head circumference and MRI scans showing normal ventricles aid in diagnosis. Approximately 70% of infants with microcephaly and 30% of those with megalencephaly have developmental defects.

Defective Migration. After proliferation in the subependymal region, neurons migrate to the cortex. The neurons appear to follow radial glial cells like raindrops on telephone wires. Early migrations form the deepest cortical layers, and later migrations, the more superficial layers, ultimately forming a six-layer cortex. The cellular complement is greatest in the outer cortical layers, leading to an increased surface area, with buckling causing gyri to begin to appear between 26 and 28 weeks, and become increasingly complex in the final trimester. If the normal complement of neurons is absent, gyral formation does not take place, and *lissencephaly* (smooth brain, agyria) results (see Plate 1-5). An abnormally thick gyral formation is known as *pachygyria*. In this anomaly, the cortex lacks the six-layer configuration. Cerebral *heterotopias* appear to result from defective neuronal migration and subsequent accumulation of aberrant neurons anywhere between the ependyma and cortex (see Plate 1-5). Significant numbers of such heterotopias occurring in isolation are likely to result in some degree of intellectual disability. Most of the disorders of migration discussed previously have associated heterotopias. The presence of multiple small gyri having no resemblance to a normal gyral pattern, along with deranged lamination of the cortical mantle, is called *polymicrogyria* (see Plate 1-5). *Schizencephaly* is characterized by an abnormal cleft that joins the cortex and the ventricles. It is usually bilateral but can be unilateral. Malformed gyri (polymicrogyria) are aligned radially around the cleft.

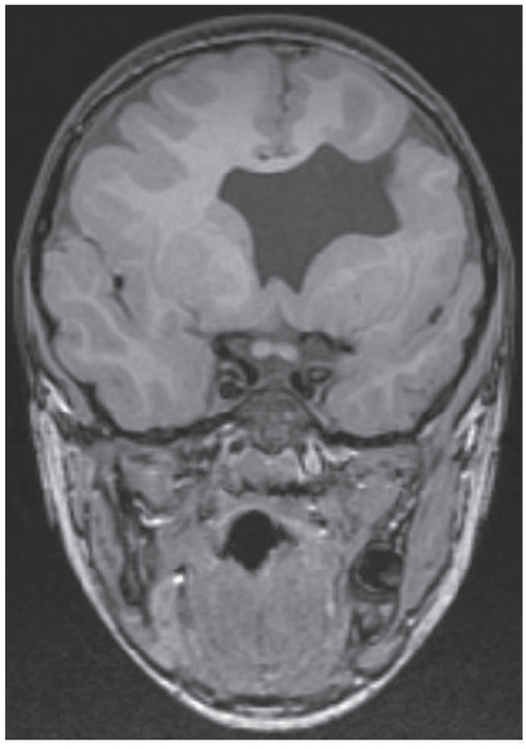
Agenesis of the corpus callosum, partial or complete, is often accompanied by disorders stemming from defective neuronal migration. This results in developmental defects, seizures, mental retardation, and occasional hydrocephalus (see Plate 1-5). The diagnosis may be suggested by ocular hypertelorism, an antimongoloid slant to the eyes, and other midline facial defects. Aicardi syndrome, a sporadically occurring abnormality seen in female infants, is associated with retinal defects that suggest chorioretinitis, infantile spasms, hypsarrhythmia, and severe psychomotor retardation. Agenesis is one of the most common anomalies diagnosed by MRI in "idiopathic" psychomotor retardation (see Plates 1-5 and 1-6).



Agenesis of the corpus callosum



Lissencephaly, posterior predominant



Left schizencephaly

Images courtesy of P. Ellen Grant, MD, Associate Professor of Radiology, Harvard Medical School.

Developmental Dyslexia

Developmental dyslexia, or developmental reading disorder, is defined as a significant impairment in the development of reading and related skills, such as spelling, writing, and reading comprehension, due to problems with phonologic processing despite adequate intelligence and conventional instruction. This disorder frequently occurs in association with other specific learning disabilities, such as disturbances in auditory comprehension, expressive language, articulation, and visual discrimination. It is the most commonly identified learning disorder, now felt to affect the sexes equally and is often present in siblings and other family members.

Because the primary deficit in developmental dyslexia is in reading and writing, the abnormality is usually not identified until the first few years of grade school, the time when children begin to read. Most parents are not aware of any disorder in their child before this stage. Because it is common and affects skills recently acquired by man, developmental dyslexia may have had certain advantages in preliterate societies, because dyslexic persons often have enhanced visual-spatial and artistic skills.

Etiologic Theories. Early investigators postulated that developmental dyslexia was caused by a lesion in the left angular gyrus, an area of the brain in which a lesion in adults produces word blindness. Later, Orton (1925) felt that the disorder was caused by equipotential visual association areas in the two cerebral hemispheres actively competing with each other, with one side seeing a mirror image of the other. Orton was particularly impressed with reversals of letters and letter sequences in words, the inconsistency of these errors, and the ability of some dyslexic students to read better with the aid of a mirror. Emotional problems and improper instruction were also thought to cause dyslexia.

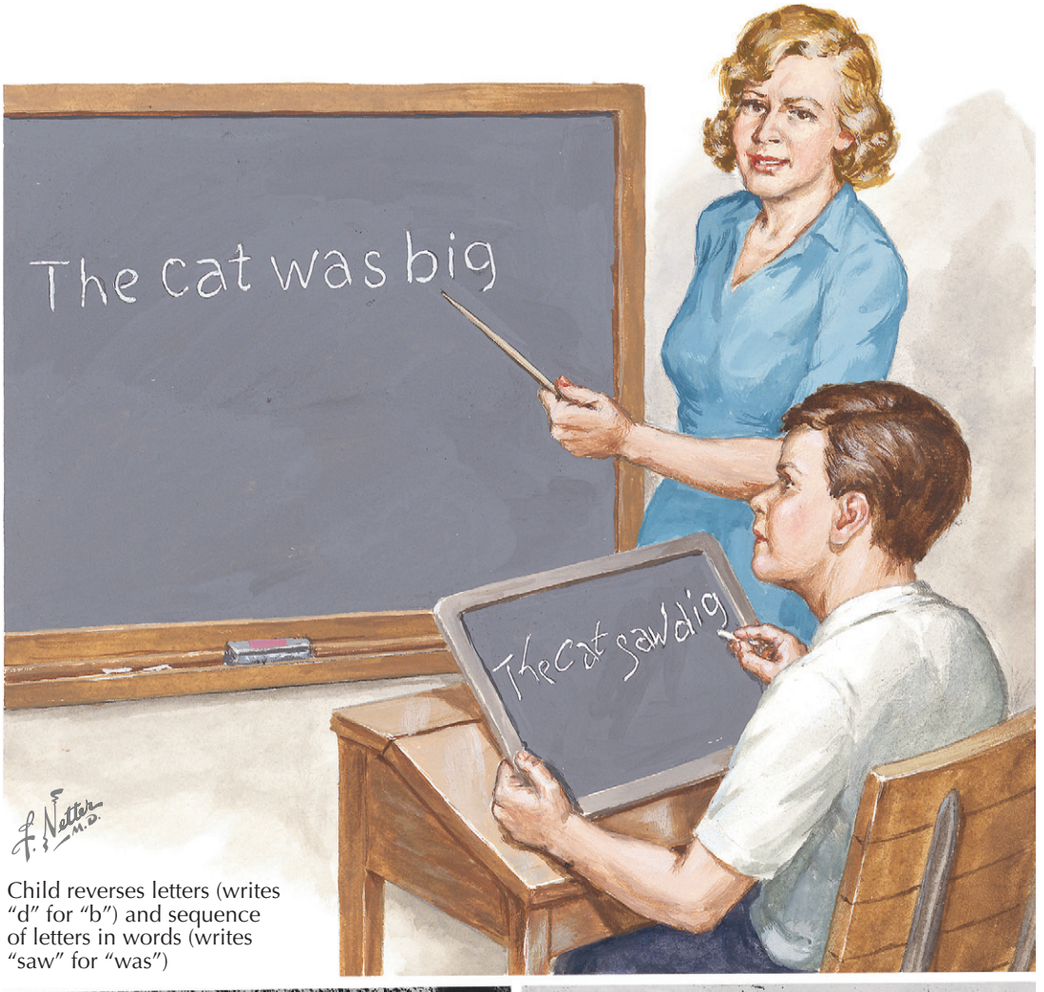
Past investigations, including computed tomography, computed evoked electroencephalographic studies, and postmortem studies of the brain have all provided evidence of a structural basis for dyslexia. More recently, MRI has demonstrated a variety of structural changes in the corpus callosum, left temporal lobes, thalamus, caudate, inferior frontal gyrus, and cerebellum (Pennington, 1999; Eliez, 2000; Brown, 2011; Leonard, 2001; Rae, 2002; Robichon, 2000; Elnakib, 2012).

Historically, Drake (1968) noted abnormally formed gyri in the parietal regions and *ectopic neurons* in the white matter, arrested during their migration to the cerebral cortex. Examination of a second brain by Galaburda and Kemper (1979) showed cerebral cortical abnormalities characterized by focal and verrucose dysplasia in the sensory speech area (Wernicke's area) and language dominant left cerebral hemisphere. The third brain examined showed only verrucose dysplasia almost exclusively confined to the left cerebral hemisphere (Kemper, 1984). Thus examination of all three brains has demonstrated minor malformations.

Analysis of human malformations and animal models indicates that the focal and verrucose dysplasia probably arise during the later stages of neuronal migration to the cerebral cortex, and appear to result from the migration of neurons into focal areas of cortical destruction. In man, neuronal migration to the cerebral cortex occurs from the 8th to approximately the 16th week of gestation. Consistent with this timing is the presence of ectopic neurons in the white matter in two of the three brains examined. The nature of this postulated destructive process is unknown. Geschwind and Behan (1982) have noted a significant clustering of dyslexia, left-handedness, autoimmune disease, and migraine in persons related to each other, indicating an association between these disorders.

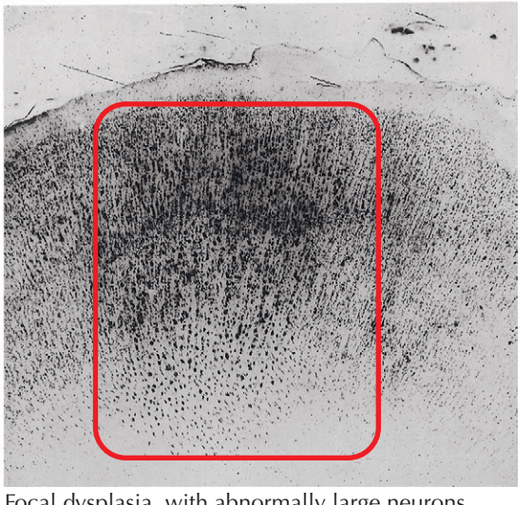
Currently, it is felt that developmental dyslexia is a disorder of network connections as demonstrated by Vandermosten (2012). By using MRI tractography, adults with dyslexia were noted to have a reduction in the left arcuate fasciculus, which connects the posterior temporal and frontal areas. This may represent an area of decreased myelination.

Treatment. Early identification and evaluation of dyslexia is essential for proper treatment. The optimal educational approach is multisensory, including phonemic awareness and enhanced phonologic processing, where virtually all respond. However, given that dyslexia is a lifelong disorder, many continue to struggle into adulthood when presented with new or less familiar words or in reading comprehension settings. Treatment should be aimed at enabling those to overcome deficits where possible and to learn strategies to circumvent and compensate for difficulties that cannot be overcome.



Child reverses letters (writes "d" for "b") and sequence of letters in words (writes "saw" for "was")

Verrucose dysplasia, with focal accumulation of neurons in layer 1 of cerebral cortex

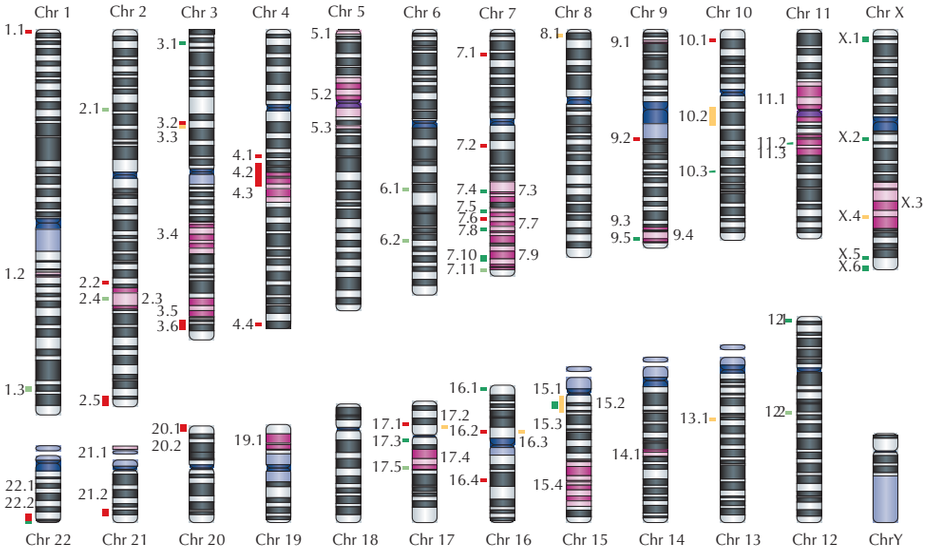


Focal dysplasia, with abnormally large neurons extending into white matter of brain

Autism Spectrum Disorders

Autism spectrum disorders (ASD), also known as pervasive developmental disorders, are a group of mental health problems in children and adolescents characterized by severe impairments in several areas of development, including communication, social interaction, and range of interests and activities. Prevalence rates for ASDs are now estimated at about 1 in 110 children in the United States. The prevalence of children with ASD has now surpassed rates of children with well-known conditions such as cancer. For educational purposes, this means that most elementary schools with a population of 500 children will have 4 or 5 children with ASD. The greatest risk factor for ASD is being male with autism, occurring approximately four times more often in boys than girls. The pathophysiology of these *pervasive developmental disorders* is not known, but it is believed to be an inherited abnormality in the structure and function of certain parts of the brain, including those that govern the development of social relatedness and language.

Boy sits apart, detached, demonstrates ritualistic behavior by spinning wheels of upside-down truck while other children play



A schematic summary of association and linkage studies of ASD, organized by chromosome. Purple bands indicate a chromosomal region that shows a linkage with ASD. Red and yellow bars (parallel to the chromosome) correspond to losses/gains in copy number, respectively, that are observed in people with ASD when compared with matched controls. Green bars correspond to genes that are observed to modulate the risk for ASD (either through a rare syndrome or genetic association): light green and dark green bars represent locations of candidate genes. Reprinted with permission from *Macmillan Publishers Ltd. Abrahams BS, Geschwind, DH:* Nat Rev Genet *2008; 9:341-355.*

Clinical Presentation

The most severe of these disorders, *autistic disorder*, is characterized by markedly abnormal development in communication and social interaction and a markedly restricted range of activity and interests. There may be a complete lack of language, or, if language is present, it does not serve to initiate or sustain conversation with others. There is severe impairment in the ability to form social relationships and to understand others' feelings. The child may not babble, point, smile, or make meaningful gestures; he or she may have poor eye contact, may appear to be hearing impaired, and may not know how to play with toys or engage in make-believe play. The child often has very restricted patterns of interest and may show little interest in the environment. There may be inflexible routines that serve no function and repetitive behaviors such as hand-flapping or body-twisting. To meet the diagnosis, the disorder must have been present before age 3 years. Autistic disorder is accompanied by intellectual disability in up to 60% of cases, and seizures are often also present in the children who have intellectual disability.

A less severe type of these disorders, *Asperger disorder*, is characterized by all of the above problems, without language impairment and intellectual disability. Children with Asperger disorder who have stronger verbal skills are sometimes referred to as sounding like little adults and struggle to pick up on the normal "give and take of a conversation." They often have very highly developed interest in and knowledge about a narrow topic. To meet the diagnosis, there must be impairment in the youth's function at home, at school, or with peers.

If some of the above behaviors are present, but not enough to meet the diagnoses, the disorder is called *pervasive developmental disorder, not otherwise specified.*

Diagnosis

Ideally, the evaluation should be conducted by a multidisciplinary team of expert clinicians, including a child psychologist, speech pathologist, and a medical professional with developmental expertise (e.g., a child psychiatrist, developmental behavioral pediatrician, neurodevelopmental pediatrician, or child neurologist), in order to address essential aspects of the child's developmental skills. The evaluation for these diagnoses is complex, and requires input from multiple people who know the child well. A diagnosis of ASD is based on descriptions of behavior from interviews, questionnaires, and a direct behavioral examination. Genetic testing is recommended because single-gene disorders or genetic variations associated with autism are seen in ≈10%.

Treatment

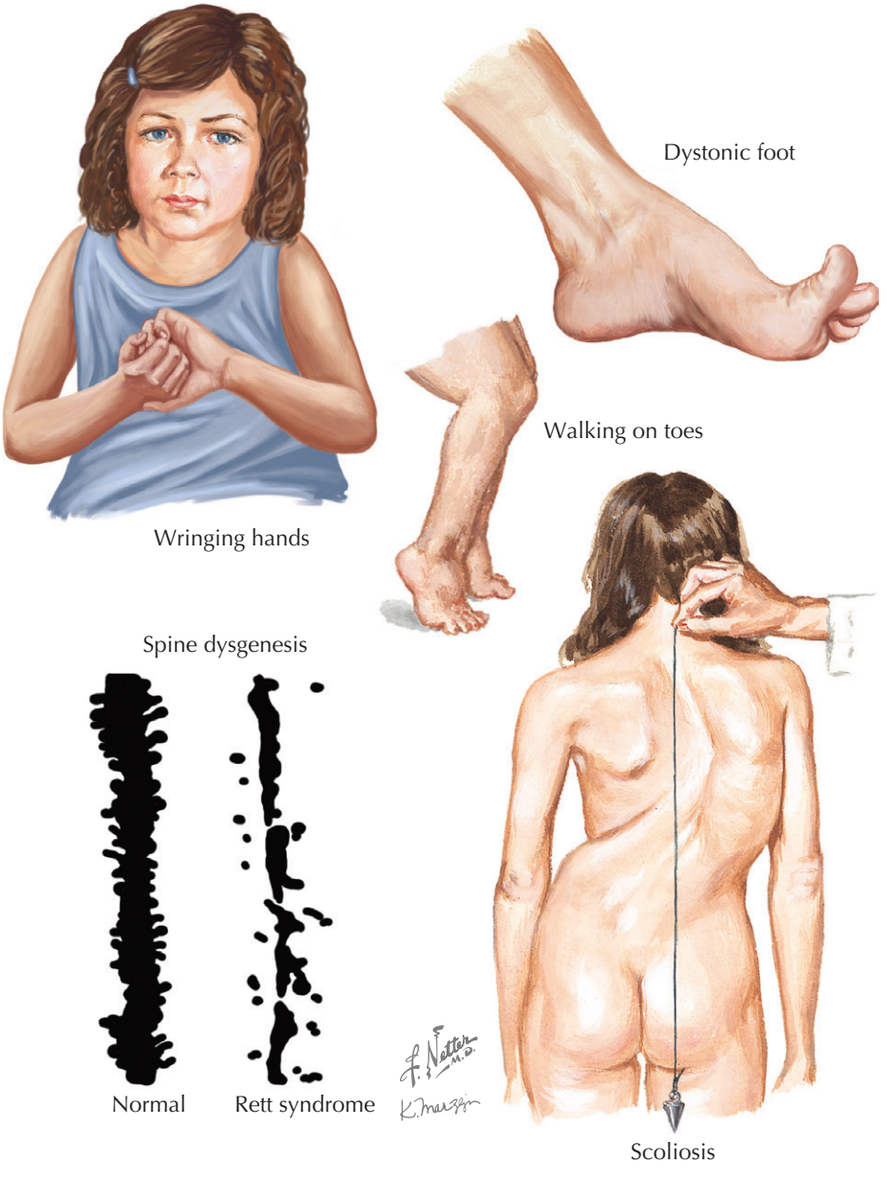
The treatment of autism spectrum disorders is aimed at enhancing the communication, social, and intellectual development of the child through language and social skills therapies and educational tutoring. The majority of these treatments are designed to take place in the home or at school. There is no single best treatment package for all children with ASD; however, early intervention has been identified as very important for these children, and most individuals with ASD respond well to highly structured, specialized programs.

If the child exhibits behaviors that are aggressive, destructive, or self-injurious, medications (such as atypical antipsychotics) may be helpful. Sometimes stimulant medication may be helpful in reducing hyperactivity and impulsivity, and antidepressants may be helpful in reducing compulsive behaviors.

Course

The autism spectrum disorders tend to be lifelong problems. Children with these disorders who are identified early, who have relatively intact language and intellectual abilities, and receive intensive treatment have the best outcomes.

Rett Syndrome



Rett syndrome (RTT; Online Mendelian Inheritance in Man [OMIM]: phenotype #312750; gene/locus #300005) is a neurodevelopmental disorder first noted about 1960 by the Austrian developmental pediatrician Andreas Rett and the Swedish child neurologist Bengt Hagberg. RTT is the leading genetic cause of severe intellectual disability in females. Its incidence is approximately 1:10,000 female births.

After a normal pregnancy and delivery, early development is apparently normal through age 6 months; however, retrospectively, subtle deviant patterns occur, including deceleration of acquired head growth. Developmental progress stalls between 6 and 18 months, followed by frank regression of fine motor skills and communication function, including loss of acquired language with poor visual and aural interactions suggesting autism.

Concomitantly, stereotyped hand movements appear during wakefulness: hand-wringing, hand-mouthing, hand-clapping or patting, or unusual finger movements. Each girl develops her own repertoire, generally evolving over time. Subtle stereotypies occur in the feet and circumorally. Although gait is acquired in about 80%, approximately 20% of Rett children require assistance. It is subsequently lost in about 25% to 35%, becoming considerably dyspraxic in the remainder, with broad-based, semipurposeful patterns, toe-walking, or retropulsion. Overall, about 70% are able to walk, 20% of whom require assistance.

After the early period of autistic-like behaviors, an increasingly interactive phase emerges, typically by age 3 to 5 years. Here the child becomes very responsive to external stimuli, with intensive eye gaze and markedly improved receptive communication skills. However, expressive language remains poor. Their inability to speak or engage in volitional fine motor functions makes intellectual assessment difficult. Improved communication is possible through picture boards and advanced computer-based technologies. Although cognitive function remains stable, gradual slowing of motor skills occurs in adulthood, with increasing rigidity and dystonic posturing of ankles and feet.

There are common associated medical problems. *Periodic breathing* consists of breath-holding, hyperventilation, or a combination. This is prominent between ages 5 and 15 years, being exacerbated by unfamiliar or stressful circumstances, including large crowds or new surroundings. Gastrointestinal dysfunction includes disordered chewing and swallowing, gastroesophageal reflux, delayed stomach emptying, constipation, gallbladder dysfunction, and impaired growth, all related to the neurologic underpinnings of Rett syndrome. Epilepsy and scoliosis are increasingly common throughout childhood and adolescence, ultimately occurring in 80%.

Seizures are infrequent before age 2 years, may be generalized or partial and usually easily managed. Many girls have unusual behaviors ("vacant spells") that are difficult to distinguish from epilepsy, thus requiring video electroencephalographic monitoring. Scoliosis becomes evident by age 4 years, with greater severity in hypotonic children lacking ability to maintain independent upright posture. Surgery is required in 12% to 14%, often improving quality of life. Bracing is employed with greater frequency; its effectiveness is inadequately evaluated. Feet and hands are generally small, unusually cold, and discolored.

Unexplained sudden death occurs, possibly related to unwitnessed seizures, respiratory failure, or prolonged QT syndrome; average survival is 50+ years. With increasing appreciation of the underlying medical issues, general well-being has improved remarkably.

PATHOPHYSIOLOGY

At present, 95% or more of those with features consistent with RTT have a mutation in the *MECP2* gene (coding for methyl-CpG-binding protein 2), located at Xq28. MECP2, a member of a family of methyl-binding proteins, is an epigenetic regulator of a large and increasing number of genes, including *BDNF* (brain-derived neurotrophic factor) and *CRH* (corticotrophin-releasing hormone). Reduced growth of dendrites and their spines are present throughout the cerebral hemispheres (an explanation for deceleration of head growth) and brainstem. All neurotransmitter function is impaired, with an imbalance between excitatory (principally glutamatergic) and inhibitory (chiefly GABAergic) expression. Conditional knockout mouse models indicate the diverse functional impact in specific neural centers. For example, knockout of GABAergic function in the forebrain, sparing the brainstem, results in an absence of periodic breathing abnormalities.

In general, RTT is a sporadic condition with recurrence in the family being $\ll 0.1\%$. In 75% or more, new mutations derive from paternal germ lines. In the small number of familial cases, the mother carries the gene but is normal or shows mild cognitive impairment or a learning disability due to favorable skewing of X-chromosome inactivation. The differential diagnosis includes autism, Angelman syndrome, and the neuronal ceroid lipofuscinoses.

Males with mutations in *MECP2* have a progressive disorder, the abnormal gene being expressed in all cells. Duplication of *MECP2* produces another distinctive disorder that is modified by the involvement of other genes. These males are quite abnormal, whereas their mothers, 70% (or more) of whom carry the same duplication, appear normal yet have significant obsessive-compulsive behaviors.

At present, substantial research is being conducted in mouse models of RTT/*MECP2* mutants, and a number of clinical trials are ongoing or in planning stages. Despite this, specific treatment designed to provide a cure remains elusive.

CEREBRAL CORTEX AND NEUROCOGNITIVE DISORDERS

Surfaces of Cerebrum

The cerebrum is divided into *right* and *left hemispheres* by a longitudinal fissure. Each hemisphere has three surfaces—superolateral, medial, and inferior—all of which have irregular fissures, or sulci, demarcating convolutions, or gyri. Although there are variations in arrangement between the two hemispheres in the same brain and in those from different persons, a basic similarity in the pattern allows the parts of the brain to be mapped and named.

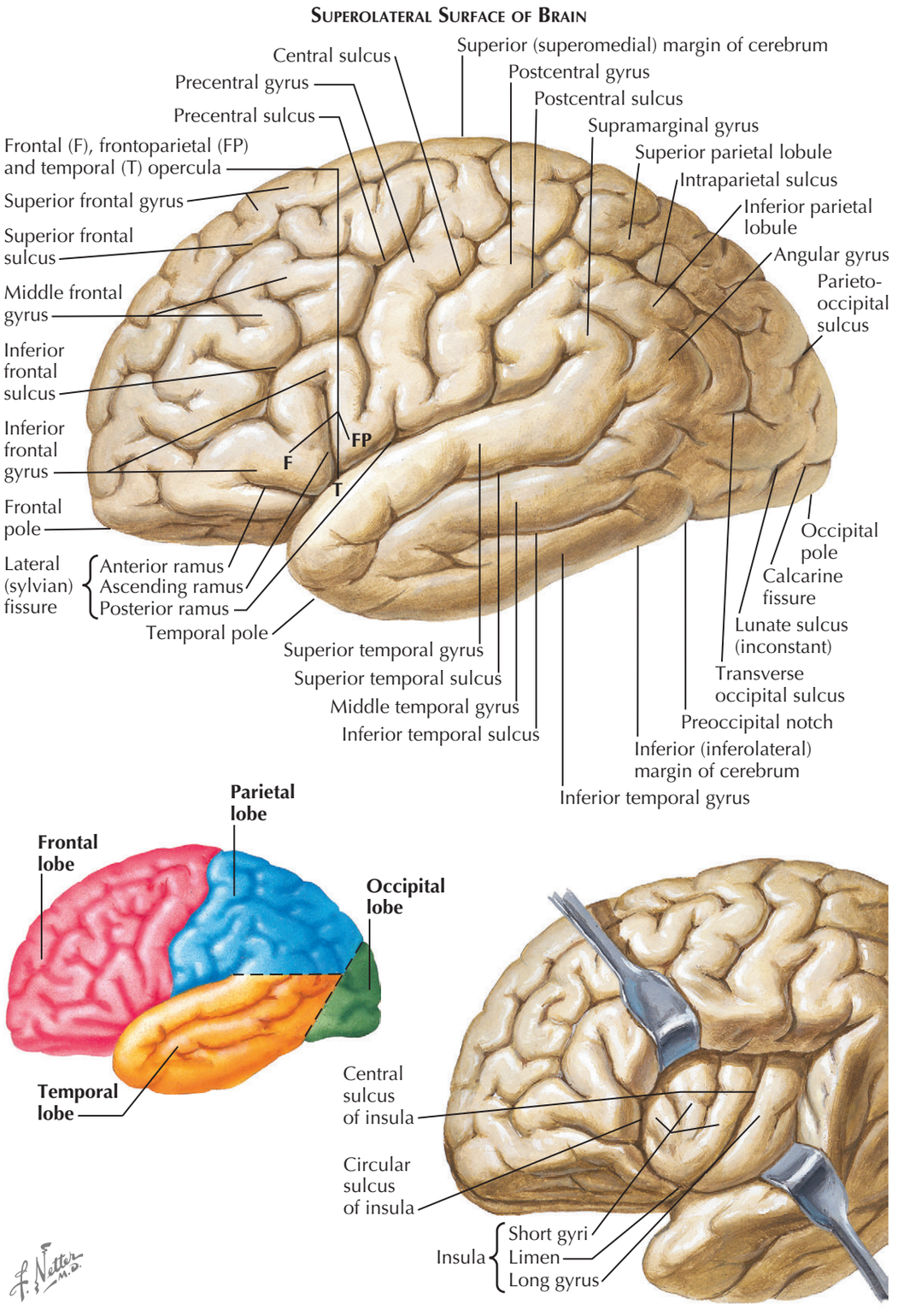
SUPEROLATERAL SURFACE

On the superolateral surface, two sulci, the lateral and the central, can be easily identified. The *lateral (sylvian) sulcus* has a short stem between the orbital surface of the frontal lobe and the temporal pole; in life, the lesser wing of the sphenoid bone projects into it. At its outer end, the stem divides into anterior, ascending, and posterior branches. The anterior and ascending rami are each about 2.5 cm long; the former runs horizontally into the inferior frontal gyrus, and the latter, vertically. The posterior ramus is about 7.5 cm long and inclines upward as it extends backward to end in the supramarginal gyrus, which is part of the inferior parietal lobule. These rami separate triangular areas of cortex called opercula, which cover a buried lobe of cortex, the insula.

The *central (rolandic) sulcus* proceeds obliquely downward and forward from a point on the superior border almost halfway between the frontal and occipital poles. It is sinuous and ends above the middle of the posterior ramus of the lateral sulcus. Its upper end usually runs onto the medial surface of the cerebrum and terminates in the paracentral lobule.

The *parietooccipital sulcus* is situated mainly on the medial surface of the cerebrum, but it cuts the superior margin and appears for a short distance on the superolateral surface about 5 cm in front of the occipital pole. At about the same distance from the occipital pole on the inferior margin, there is a shallow indentation, the *preoccipital notch*, produced by a small ridge on the upper surface of the tentorium cerebelli.

The above features divide the cerebrum into frontal, parietal, occipital, and temporal lobes. The *frontal lobe* lies in front of the central sulcus and anterosuperior to the lateral sulcus. The *parietal lobe* lies behind the central sulcus, above the posterior ramus of the lateral sulcus and in front of an imaginary line drawn between the parieto-occipital sulcus and the preoccipital notch.



The *occipital lobe* lies behind this same imaginary line. The *temporal lobe* lies below the stem and posterior ramus of the lateral sulcus, and is bounded behind by the lower part of the aforementioned imaginary line.

Frontal Lobe. The superolateral surface of the frontal lobe is traversed by three main sulci and thus divided into four gyri. The *precentral sulcus* runs parallel to the central sulcus, separated from it by the *precentral gyrus*, the great cortical somatomotor area. The *superior* and *inferior frontal sulci* curve across the remaining part of the surface, dividing it into superior, middle, and inferior frontal gyri.

Parietal Lobe. The parietal lobe has two main sulci, which divide it into three gyri. The *postcentral sulcus* lies parallel to the central sulcus, separated from it by the *postcentral gyrus*, the great somatic sensory cortical area.

Surfaces of Cerebrum
(Continued)

The remaining, larger part of the superolateral parietal surface is subdivided into superior and inferior parietal lobules (gyri) by the *intraparietal sulcus*, which runs backward from near the midpoint of the postcentral sulcus and usually extends into the occipital lobe, where it ends by joining the transverse occipital sulcus.

Occipital Lobe. The outer surface of the occipital lobe is less extensive than that of the other lobes and has a short *transverse occipital sulcus* and a *lunate sulcus*; the latter demarcates the visuosensory and visuopsychic areas of the cortex. The *calcarine sulcus* notches the occipital pole.

Temporal Lobe. The temporal lobe is divided by *superior* and *inferior temporal sulci* into superior, middle, and inferior temporal gyri. The sulci run backward and slightly upward, in the same general direction as the posterior ramus of the lateral sulcus, which lies above them. The superior sulcus ends in the lower part of the inferior parietal lobule, and the superjacent cortex is called the angular gyrus. The superior temporal gyrus contains the auditosensory and auditopsychic areas.

Insula. The insula is a sunken lobe of cortex, overlaid by opercula and buried by the exuberant growth of adjoining cortical areas. It is ovoid in shape and is surrounded by a groove, the *circular sulcus* of the insula. The apex is inferior, near the anterior (rostral) perforated substance, and is termed the *limen* of the insula. The insular surface is divided into larger and smaller posterior parts by the *central sulcus* of the insula, which is roughly parallel to the central sulcus of the cerebrum. Each part is further subdivided by minor sulci into short and long insular gyri. The claustrum and lentiform nucleus lie deep to the insula.

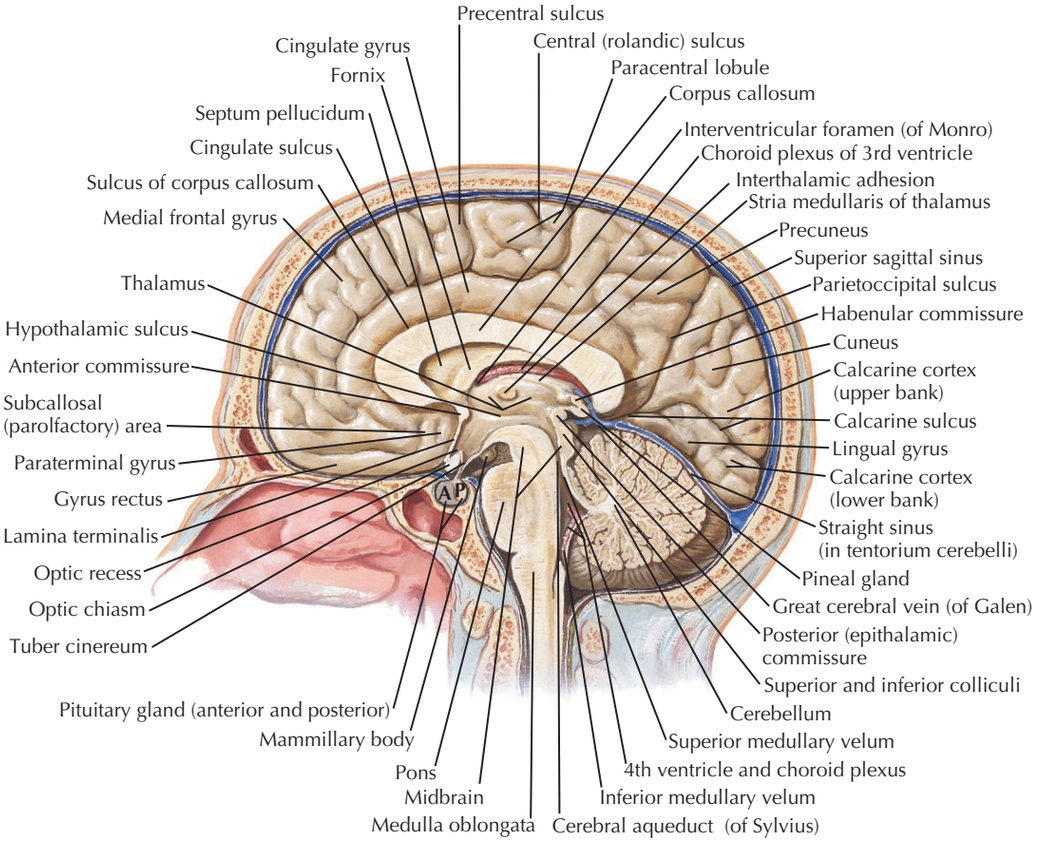
Medial Surface of Cerebral Hemispheres

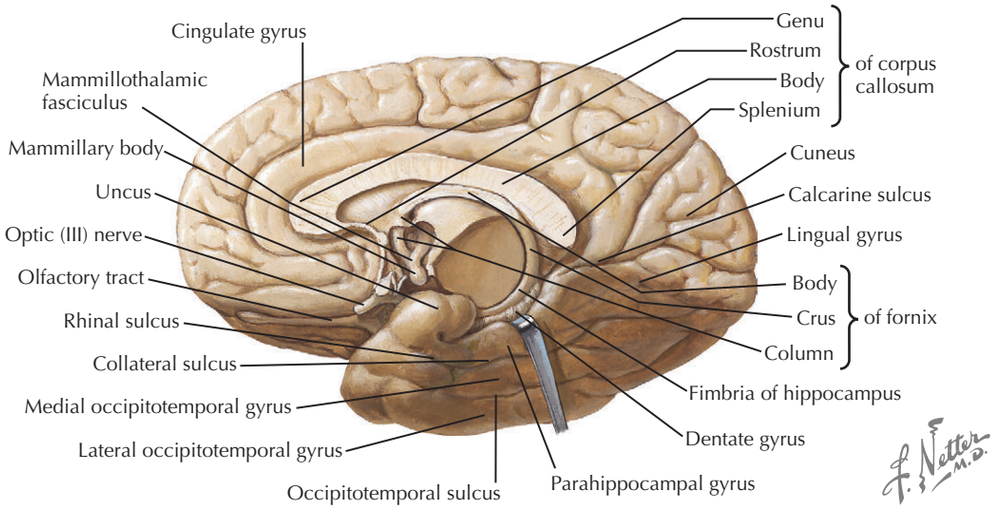
The medial surfaces of the cerebral hemispheres are flat, and, although separated for most of their extent by the longitudinal fissure and falx cerebri, they are connected in parts by the cerebral commissures and by the structures bounding the third ventricle.

Corpus Callosum. The corpus callosum is the largest of the cerebral commissures, and forms most of the roof of the lateral ventricle. In a median sagittal section, it appears as a flattened bridge of white fibers, and its central part, or *trunk*, is convex upward. The anterior end is recurved to form the *genu*, which tapers rapidly into the *rostrum*. The expanded posterior end, or *splenium*, overlies the midbrain and adjacent part of the cerebellum. The corpus callosum is about 10 cm long and 2.5 cm wide between the points where it sinks into the opposing hemispheres in the depths of the corpus callosal sulcus. Its fibers diverge to all parts of the cerebral cortex.

Fornix. Below the splenium and trunk of the corpus callosum are the symmetric arching bundles (*crura* of the fornix) that meet to form the *body* of the fornix and separate again to become the *columns* of the fornix, curving downward to the mammillary bodies. The body of the fornix lies in the roof of the third ventricle, and the tela choroidea is subjacent; the lateral fringed margins of this double fold of pia mater are the choroid plexuses of the central parts of the lateral ventricles, while an extension from the underside of the fold in

Medial Surface of Brain





Surfaces of Cerebrum
(Continued)

the midline forms the choroid plexus of the third ventricle.

Cingulate Sulcus. The cingulate sulcus is easily identified on the medial surface, lying parallel to the corpus callosum. It begins below the genu of the corpus callosum and ends above the posterior part of the trunk by turning upward to cut the superior margin of the hemisphere. Opposite the middle of the trunk is another vertical branch sulcus, and the area of cortex between these ascending sulci is the *paracentral lobule*, which contains parts of the motor and sensory cortical areas. The cingulate sulcus separates the *medial frontal* and *cingulate gyri*, and below the genu and rostrum of the corpus callosum are small *parolfactory sulci* separating the *subcallosal (parolfactory) areas* and *paraterminal gyrus*.

Posterior Medial Surface. The posterior part of the medial surface has two deep sulci. The upper *parietooccipital sulcus* inclines backward and upward to cut the superior border. The lower *calcarine sulcus* extends forward from the occipital pole to end beneath the splenium of the corpus callosum, and the isthmus of cortex between them connects the cingulate and parahippocampal gyri. The wedge-shaped region between the parietooccipital and calcarine sulci is the *cuneus*, while the area between the parietooccipital sulcus and the paracentral lobule is the *precuneus*. The main visuosensory area is located in the walls of the calcarine sulcus and in the adjacent cortex.

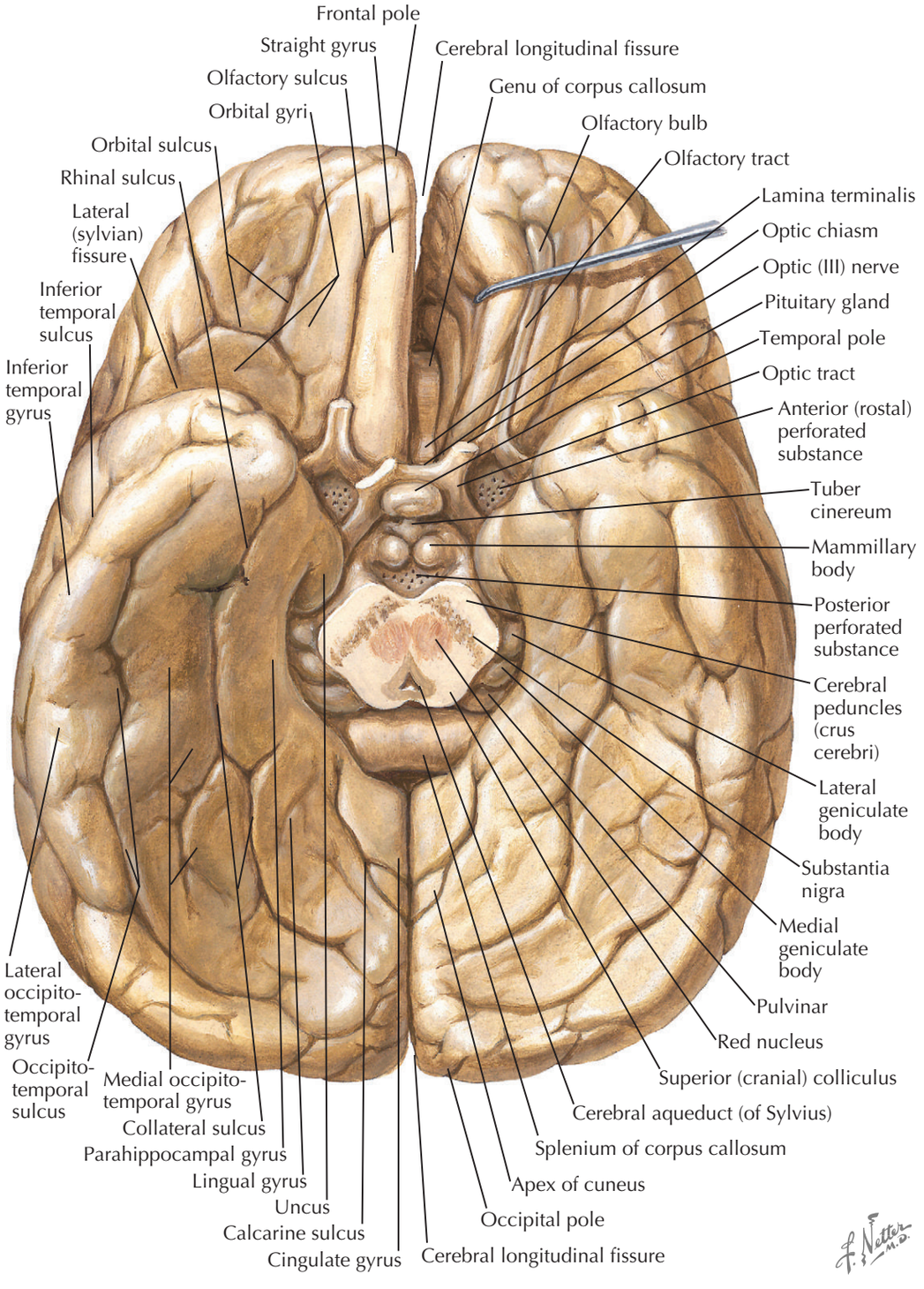
Inferior Surface of Cerebral Hemisphere

The inferior surface is divided by the stem of the lateral sulcus into smaller, orbital and larger, tentorial surfaces.

The orbital surface rests on the roofs of the orbit and nose and is marked by an H-shaped *orbital sulcus*, as well as by a straight groove on the medial side, the *olfactory sulcus*, which lodges the olfactory bulb and tract. The orbital sulcus demarcates the *orbital gyri*; the small convolution medial to the olfactory sulcus is the *straight gyrus*.

The tentorial surface lies partly on the floor of the middle cranial fossa and partly on the tentorium cerebelli. It has two anteroposterior grooves, the *collateral* and *occipitotemporal sulci*. Both run almost directly forward from the occipital pole to the temporal pole; like other sulci, they may be subdivided, and the anterior end of the collateral sulcus is called the *rhinal sulcus*. The *parahippocampal* and *lingual gyri* lie medial to the collateral sulcus. The *dentate gyrus*, a narrow fringe of cortex with transverse markings, occupies the groove between the parahippocampal gyrus and the fimbria of the hippocampus. The anterior end of the parahippocampal gyrus becomes recurved to form the *uncus*, which is partly occupied by the cortical olfactory area. The *medial occipitotemporal gyrus* is fusiform in shape, and lies between the collateral and occipitotemporal sulci. The *lateral occipitotemporal gyrus* lies lateral to the occipitotemporal sulcus and is continuous with the *inferior temporal gyrus* around the inferior margin of the hemisphere.

Inferior Surface of Brain



Cerebral Cortex: Function and Association Pathways

In humans, the cerebral cortex is highly developed, and the complexity of the interhemispheric and intrahemispheric connections parallels this degree of development. The cerebral cortex has definite areas related to specific neurologic functions, either for primary sensory reception or for complex integrated activity.

Association Pathways. When one cortical area is activated by a stimulus, other areas also respond. This is due to the rapid activity along a large number of precisely organized, reciprocally acting association pathways. The pathways may be very short, linking neighboring areas and running only within the gray matter, or they may be longer (arcuate) bundles, passing through the white matter to connect gyrus to gyrus or lobe to lobe within a cerebral hemisphere–*intrahemispheric connection*. Other commissural bundles conduct *interhemispheric activity*: the most prominent are the *corpus callosum*, a large band of fibers, which lies immediately beneath the cingulum; the *anterior commissure*, which connects both temporal lobes; and the *hippocampal commissure (commissure of the fornix)*, which connects the right and left hippocampus.

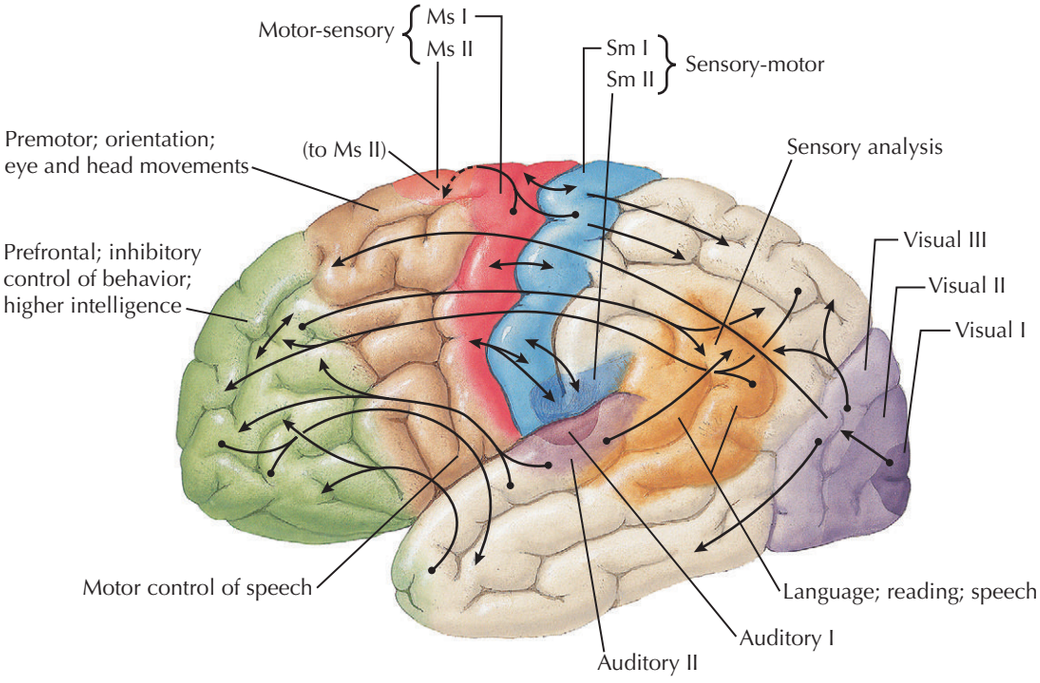
The reciprocal activity of the connections in the cerebral cortex ensures the coordination of sensory input and motor activity, as well as the regulation of higher function. For example, for the appreciation and integration of visual information, the primary visual sensory area of the occipital cortex is linked to the visual association areas. These visual centers are connected by intrahemispheric fibers to the ipsilateral parietal cortex, as well as to other areas, such as the temporal lobe, for further integrated activity. The right and left parietal and posterior temporal areas, in turn, are connected by the corpus callosum.

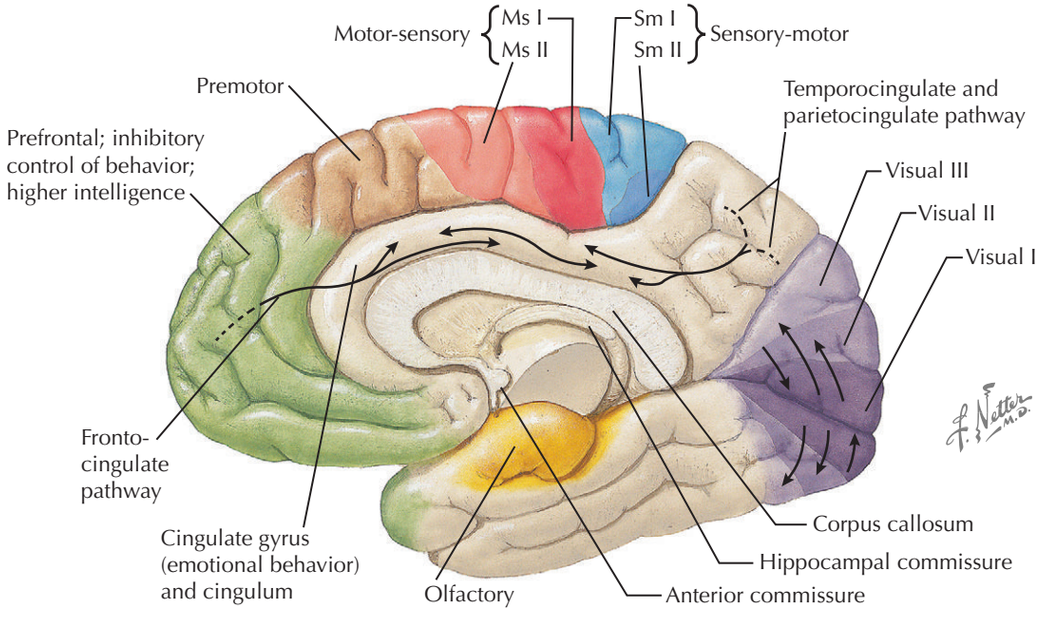
Prefrontal Cortex. The prefrontal cortex, (which includes the three frontal gyri, the orbital gyri, most of the medial frontal gyrus, and approximately half of the cingulate gyrus) is concerned with *higher mental functions*, and is involved with many behavioral aspects of man. This area receives numerous connections from the temporal and parietal lobes via pathways in the cingulum, a bundle of long association fibers lying within the cingulate gyrus. Bilateral lesions of the prefrontal area produce a loss of concentration, a decreased intellectual ability, and memory and judgment deficits.

Motor and Sensory Cortices. The *somatosensory cortex*, which occupies contiguous parts of the frontal and parietal lobes, and the *premotor cortex* of the frontal lobe are concerned with the initiation, activation and performance of *motor activity*, and the reception of *primary sensation* of the body. Lesions of the somatosensory cortex result in contralateral paralysis and loss of somatosensory reception or perception.

Parietal Lobe. The parietal lobe is primarily concerned with the *interpretation* and *integration* of information from sensory areas, that is, the visual areas and the somatosensory cortex. Lesions in the parietal lobe result in sensory ataxia, a loss of general awareness, defective recognition of sensory impulses, and a lack of interpretation of spatial relationships.

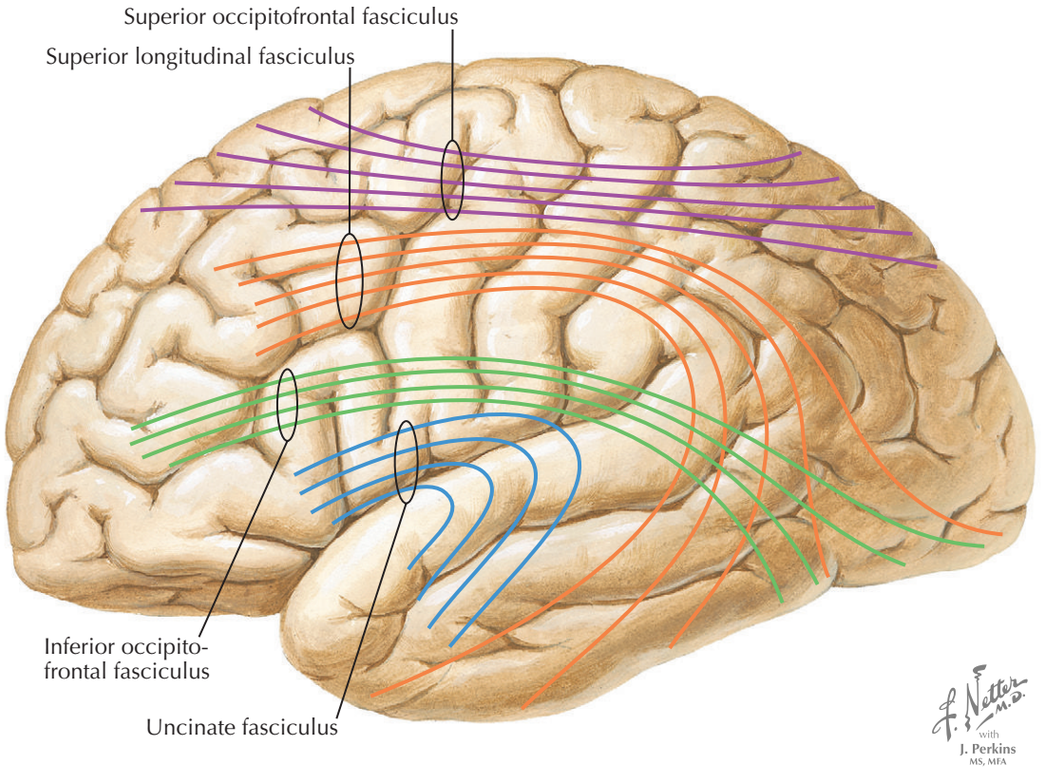
Occipital Lobe. Lesions of the striate cortex (the primary visual area) on one side result in a contralateral hemianopsia, while lesions of the secondary regions of the visual cortex cause a lack of ability to interpret visual impulses.

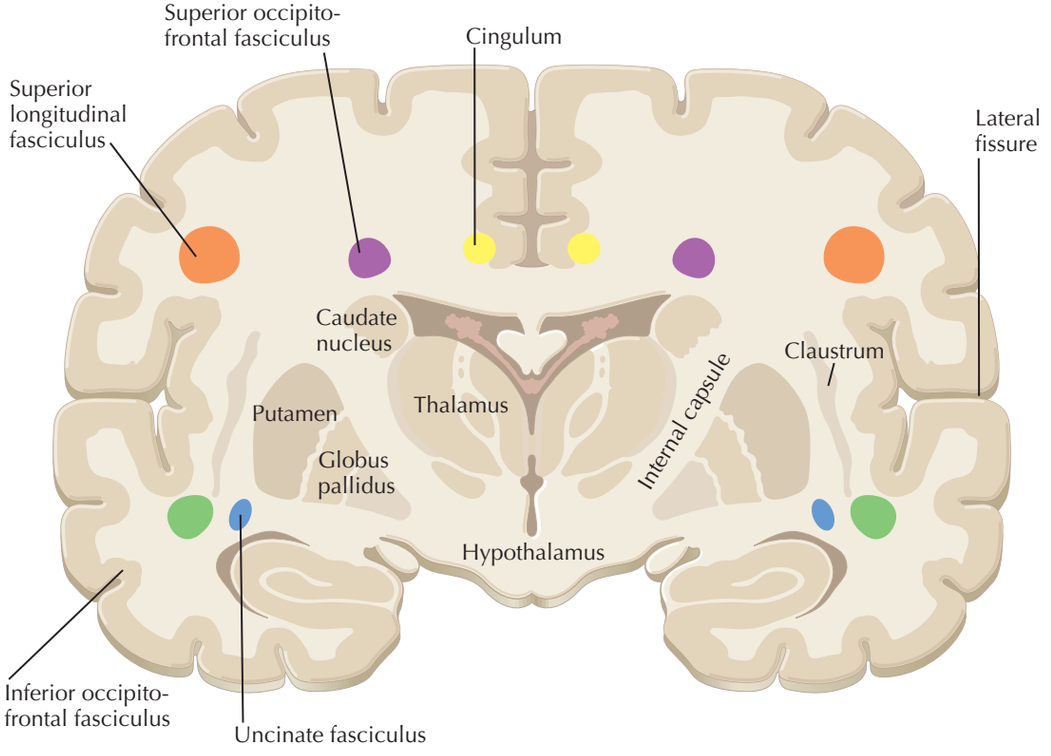




Temporal Lobe. The *posterior part of the temporal lobe* is concerned with the reception and interpretation of *auditory information*, and with some aspects of pattern recognition and higher *visual coordination*; the interconnections of the auditory and visual segments of the occipital, temporal, and parietal lobes make this a highly integrated function. The *anterior part of the temporal lobe* is concerned with *visceral motor activity* and certain aspects of *behavior*. Lesions here may be manifested by psychomotor seizures or, if they occur in the region of the uncus, by uncinate "fits" characterized by alteration of consciousness and hallucinations of taste and odor.

Lesions. In general, lesions of primary receptive areas produce identifiable deficits. A lesion in a specific area of the cerebral cortex may produce a deficit far beyond the functional identity of that particular area because the complex interconnections beneath that cortical region may be damaged.

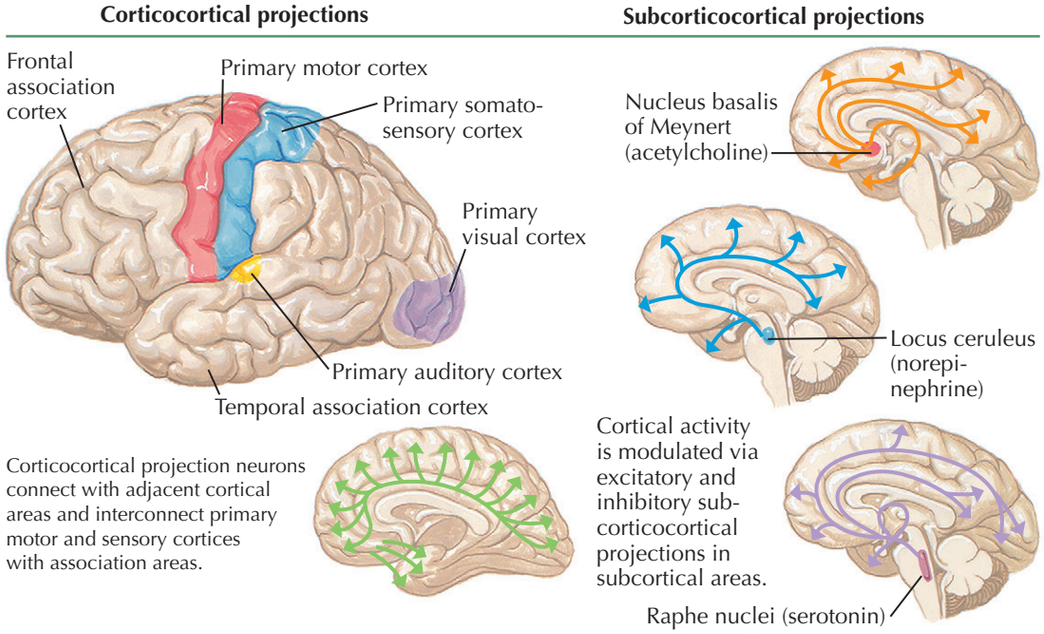


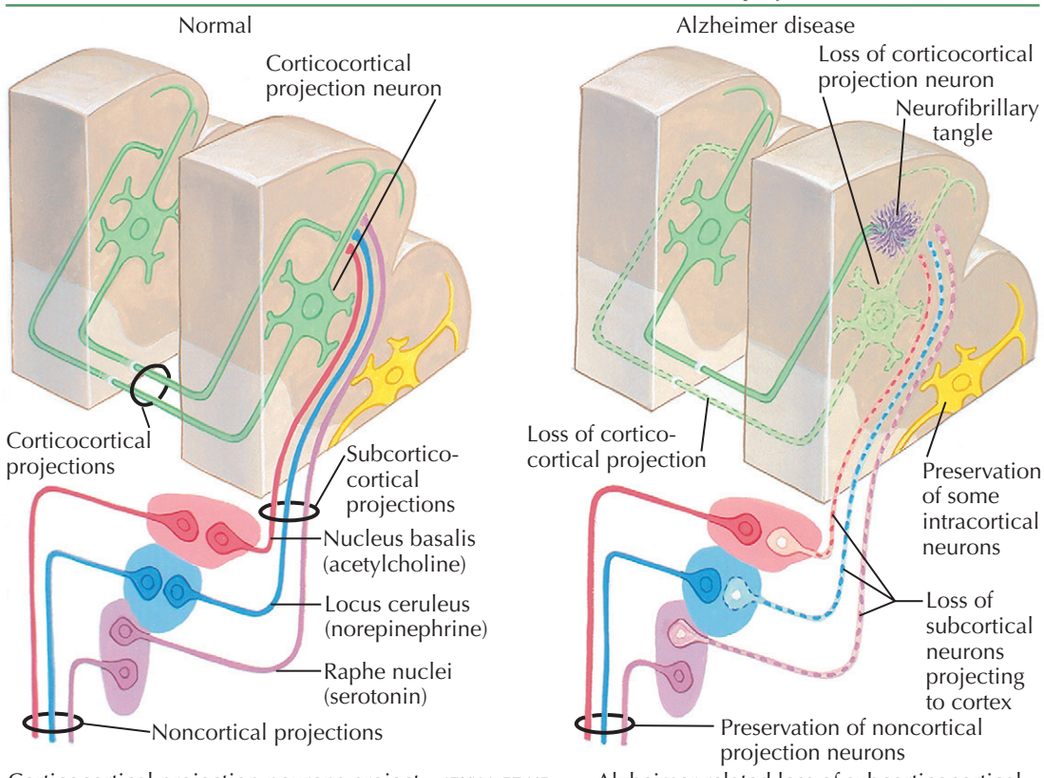


Major Cortical Association Bundles

Association fibers are predominantly located in the cerebral white matter and connect intrahemispheric cortical regions. There are two main types of association fibers, and they are differentiated by size and function. Short association fibers known as arcuate fibers or "U fibers" connect adjacent gyri, thus allowing for communication between neighboring cortical regions. Long association fibers provide the architectural basis for large-scale neurocognitive networks. These networks connect more widespread cortical regions and are visualized as "bundles of fibers" that allow communication between primary and association cortical regions. For instance, the *superior longitudinal fasciculus (SLF)* (which has three major bundles, I, II, and III) allows communication between the parietal and frontal lobes. In particular, the SLF I allows information from the superior parietal lobe, or motor cortex, to be relayed to the supplementary motor cortex. SLF II connects the caudal parietal region with the prefrontal lobes, thus allowing an individual to have a visual perception of space. SLF III connects rostral parietal areas with the frontal opercular region (the region that controls facial movements), thus enabling an individual to imitate an action. Other long association fibers include the *fronto-occipital fasciculus*, which links the posterior and medial parietal and occipital areas; *the uncinate fasciculus* (or the anterior limbic fiber bundle), which connects the temporal lobe and frontal lobes; the *inferior longitudinal fasciculus*, which connects the temporal lobe to the occipital and parietal regions, and the *cingulum bundle* (or the posterior limbic fiber bundle), which stretches from the frontal lobe to the parahippocampal gyrus. The *cingulum bundle* enables monoamines (dopamine, norepinephrine, and serotonin), along with cholinergic projections, to travel to widespread cortical targets.

Lesions to cortical association bundles can provide clinical relevance to fiber pathway tracts and cortical origins and destinations. For instance, a patient who develops acute damage to the *uncinate fasciculus* and right anterior frontal cortex (e.g., from a stroke) will have a "disconnection" between the temporal and frontal lobes. This individual may develop amnesia for experiences predating the stroke, along with impairment of self-awareness of personal experiences across time (this clinical finding is also known as a disruption of autonoetic consciousness).





Corticocortical projection neurons project to neurons in distant areas of cortex. They receive subcorticocortical projections from neurons in subcortical nuclei.

JOHN A. CRAIG—MD
C. Machado—M.D.

Alzheimer-related loss of subcorticocortical projection-neurons results in loss of those circuits and cognitive dysfunction.

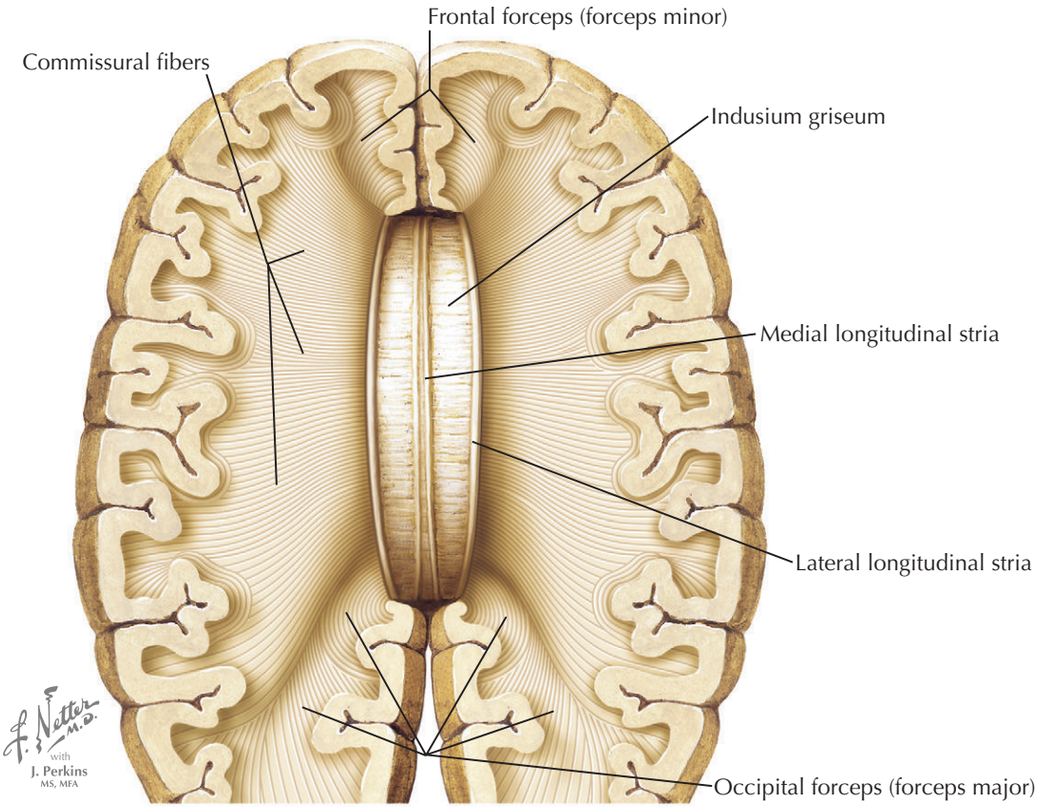
Corticocortical and Subcorticocortical Projection Circuits

The cerebral white matter consists of myelinated axons that link cortical areas with both cortical and subcortical regions. There exist three main categories of efferent fibers from a cortical area: association fibers, striatal fibers, and commissural/subcortical fibers. Corticocortical projections allow both adjacent and distant cortical regions to communicate, whereas corticosubcortical projections allow reciprocal communication between cortical regions and subcortical structures. These subcorticocortical projections connect the cortex to the thalamus, the pontocerebellar system, brainstem, and spinal cord.

Corticocortical Circuits. Local short association fibers, or U fibers, connect adjacent cortical gyri and lie beneath the sixth cortical layer. Neighborhood association fibers traverse longer distances than U fibers, but still connect nearby cortical regions. Long association fibers travel within the same hemisphere and connect more distant cortical regions. These include the superior, middle, and inferior longitudinal fasciculi, arcuate fasciculus, extreme capsule, fronto-occipital fasciculus, uncinate fasciculus, and cingulum bundle (see Plate 2-5, Major Cortical Association Bundles).

Subcorticocortical Circuits. Striatal fibers describe fiber groups that connect cortical regions to the striatum (the caudate and putamen). For instance, these fibers allow cortical motor control. The commissural bundle is a collection of fibers that travel from a cortical region to the opposite hemisphere via the corpus callosum or anterior commissure. Subcortical fibers travel via the internal capsule to diencephalic structures (e.g., thalamus) and brainstem (e.g., pons). The origins of the subcorticocortical cell bodies are laminae V and VI. Cortical activity is modulated via excitatory and inhibitory projections in subcortical areas. For instance, diffuse cortical cholinergic projections to the cortex rise from the nucleus basalis of Meynert, and norepinephrine projections from the locus ceruleus.

In the case of Alzheimer disease, a loss of corticocortical projection neurons is associated with neurofibrillary tangle formation. This indicates a "disconnection" of adjacent cortex and cortical association areas. The disconnection of subcorticocortical circuits is evident in the reduction of cholinergic projections throughout the cortex, resulting in reduced acetylcholine levels in the cortex. This observation led to the development of the first effective therapies for Alzheimer disease, acetylcholinesterase inhibitors, which boost acetylcholine levels in the brain.

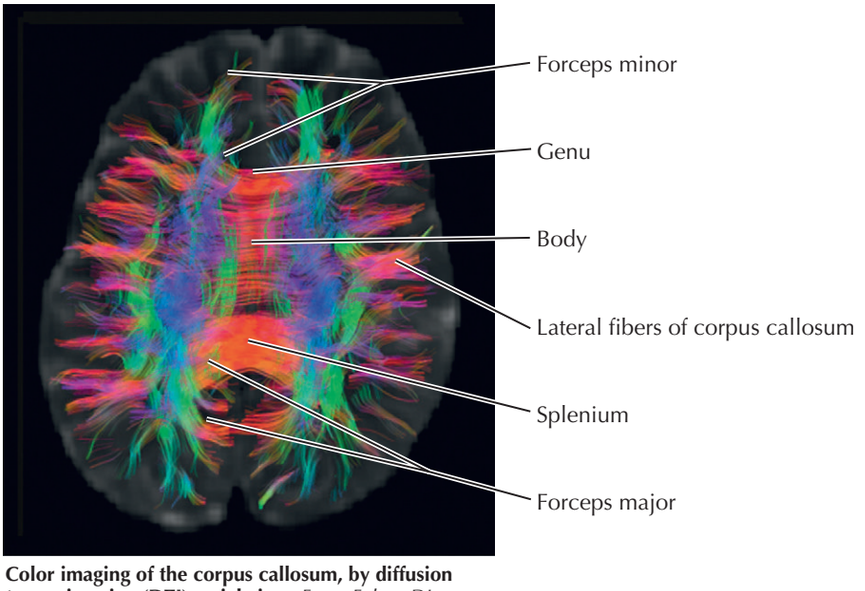


Schematic view of the lateral extent of major components

Corpus Callosum

The corpus callosum is the major commissure of the forebrain, connecting homologous cortical regions of the two cerebral hemispheres. The corpus callosum is divided into anterior and posterior parts, known as the genu and splenium, respectively. The genu includes fibers of the frontal forceps (forceps minor) interconnecting frontal areas. Posteriorly, the splenium includes the occipital forceps (forceps major), interconnecting the parietal, occipital, and temporal lobes. A corpus callosotomy, a surgical lesioning of the corpus callosum, has been performed in patients with medication-refractory epilepsy. The goal of this surgery is to prevent seizure spread from one hemisphere to another.

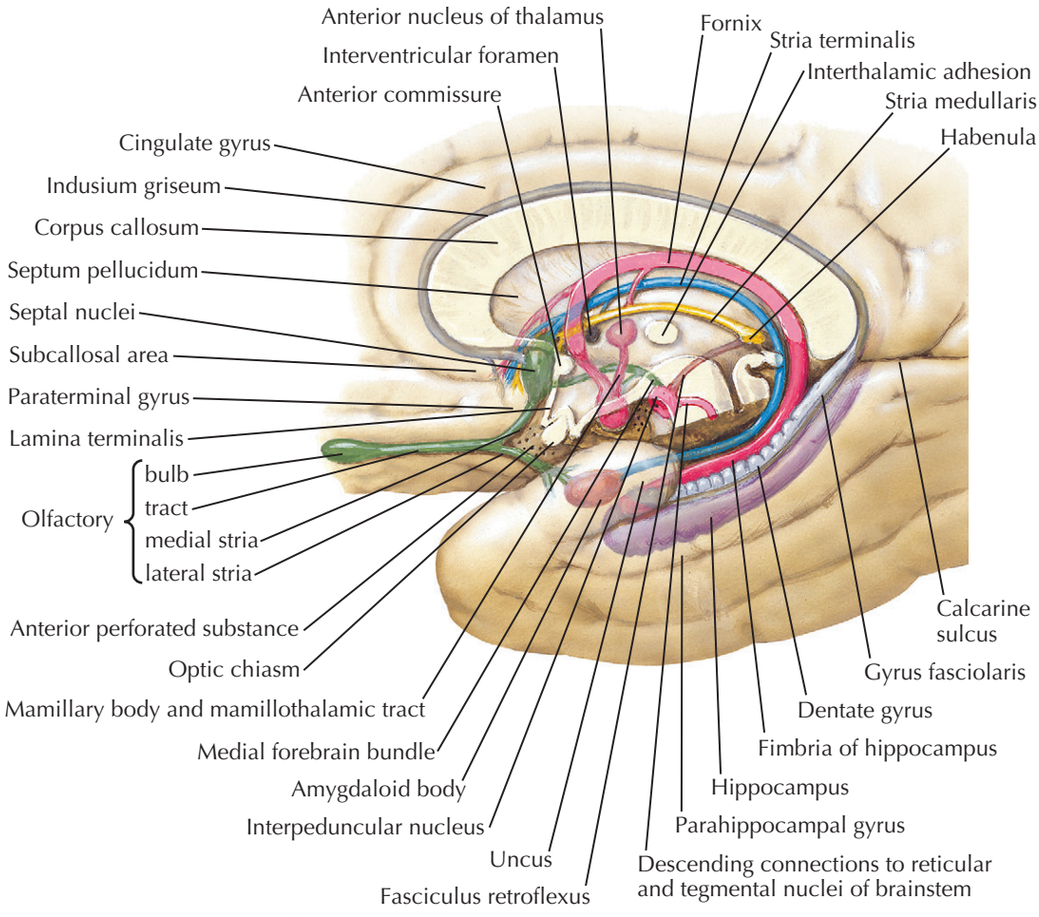
Agenesis of the corpus callosum (ACC) is a congenital birth defect characterized by an absence of a corpus callosum. This condition can occur in isolation (with little to no impact on cognitive performance) or can occur as part of abnormalities such as Dandy-Walker syndrome, Arnold-Chiari malformation, schizencephaly, holoprosencephaly, Andermann syndrome, or Aicardi syndrome (a syndrome more commonly seen in females). Midline facial defects often accompany ACC.



Color imaging of the corpus callosum, by diffusion tensor imaging (DTI), axial view. *From Felten DL, Shetty AN. Netter's Atlas of Neuroscience, 2nd ed. Philadelphia: Elsevier, 2010.*

Color Imaging of the Corpus Callosum by Diffusion Tensor Imaging

A-C diffusion weighted imaging (DWI) measures the rate of water diffusion in brain tissue, measured using an apparent diffusion constant (ADC). Diffusion tensor imaging (DTI) is used to measure the "anisotropy" or randomness of water diffusion. The degree of anisotropy is called fractional anisotropy (FA), and is measured from 0 to 1, where 0 is unrestricted and 1 is fully restricted and diffuses along only one axis. Due to the properties of white matter, parallel bundles of axons and the myelin sheaths allow for a certain orientation of water diffusion. Water diffuses more rapidly along the direction of aligned direction, and more slowly perpendicular to this direction. This enables "visualization" of white matter tracts based on the calculated FA values. To discriminate the direction of different fiber bundles, a color scheme is adopted in which green represents an anterior-posterior direction, red a left-right direction, and blue a superior-inferior direction. In these images of the corpus callosum, components of this major commissural bundle are represented in red.



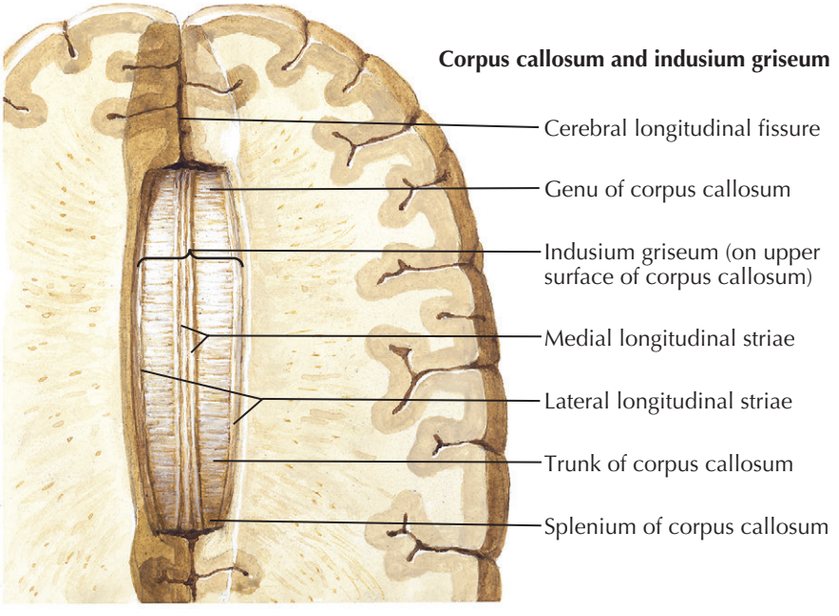
Rhinencephalon and Limbic System

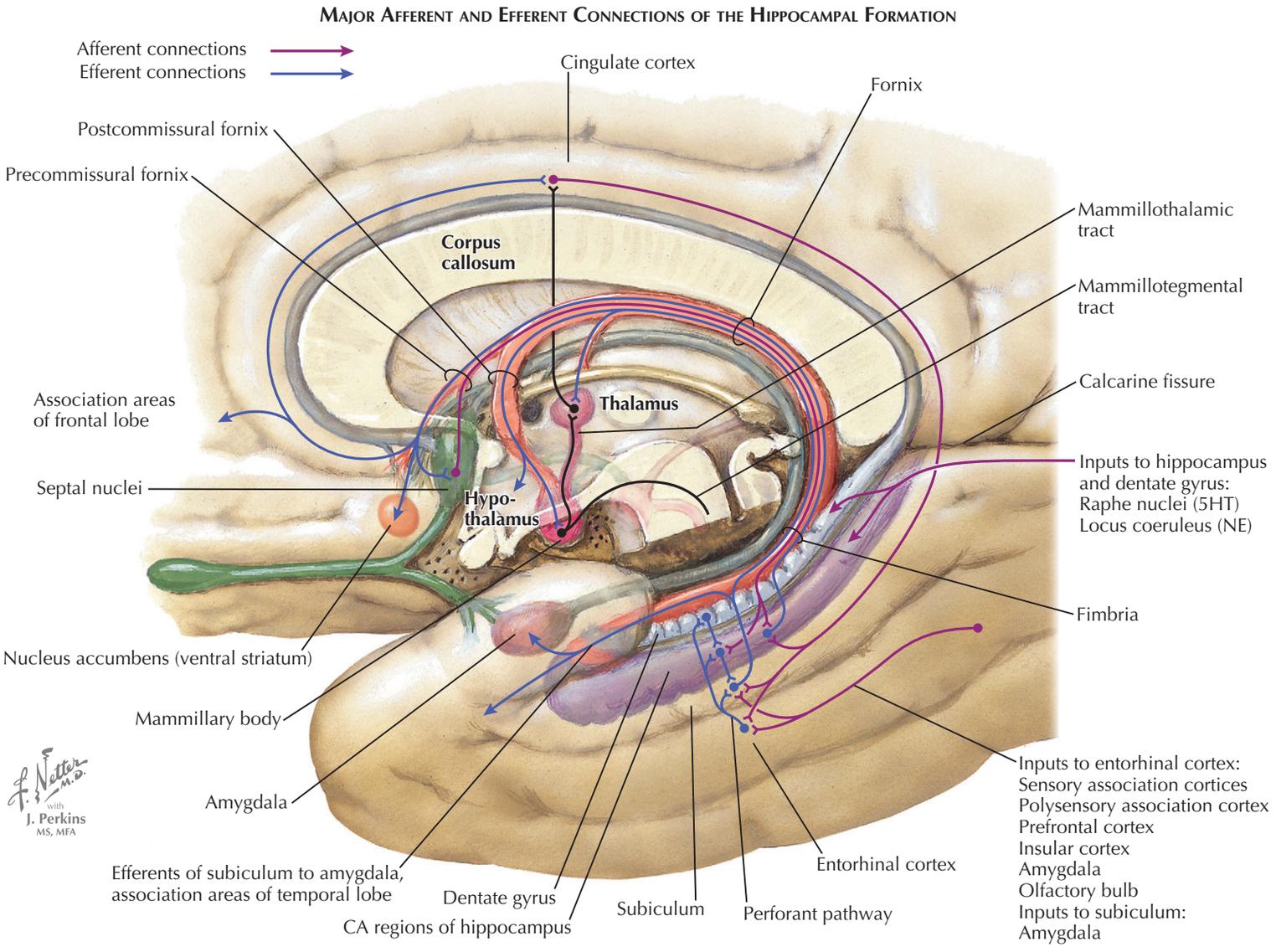
The *rhinencephalon* is a term that describes quite literally the "nose" or "smell" regions of the brain. The *limbic system* refers to the structures and tracts involved with emotion, including memory formation, as well as autonomic and endocrine response to emotional stimuli. The terms rhinencephalon and limbic system are sometimes used synonymously, but the rhinencephalon refers to olfactory structures and related pathways. Located in the medial and inferior surface of the forebrain, these parts include the olfactory bulb, tract and striae, the anterior perforated substance, the uncus, the hippocampus, the dentate gyrus, the gyrus fasciolaris, the indusium griseum, the habenular trigone, the subcallosal area, the paraterminal gyrus, the fornix, and the amygdaloid body as direct olfactory afferents project to the amygdala. The olfactory pathway is described and illustrated in Plate 5-8.

The limbic forebrain refers to the areas that are functionally and anatomically connected structures that relate to emotion, motivation, and self-preservation. The limbic system is thought to be a major substrate for regulation of emotional responsiveness and behavior, for individualized reactivity to sensory stimuli and internal stimuli, and for integrated memory tasks. The main regions of the limbic forebrain include the hypothalamus, amygdala, hippocampus, and limbic cortex (prefrontal cortex and orbital frontal cortex). The hippocampal formation and amygdala send axonal projections through the forebrain, via the fornix and stria terminalis, respectively, to the hypothalamus and septal region. The amygdala also has a more direct pathway to the hypothalamus via the anterior amygdalofugal pathway. The septal nuclei lie rostral to the hypothalamus, and send axons to the habenular nuclei via the stria medullaris thalami.

Piriform Area. The anterior (rostral) perforated substance, the uncus, the anterior end of the dentate gyrus, and the anterior part of the parahippocampal gyrus medial to the rhinal sulcus are often referred to as the piriform area. These regions function to give perception of smell. The *anterior perforated substance* is continuous with the paraterminal gyrus and separated from the anterior part of the globus pallidus of the lentiform nucleus by the anterior (rostral) commissure, ansa lenticularis, and ansa peduncularis; posteromedially, it blends into the tuber cinereum.

The *indusium griseum* is a thin layer of gray matter spread over the upper surface of the corpus callosum. Anteriorly, it curves around the genu and rostrum to merge with the paraterminal gyri; laterally, it becomes continuous with the cortex of the cingulate gyrus; and posteriorly, it passes over the splenium to blend with the dentate and parahippocampal gyri through the narrow gyrus fasciolaris. Two slender strands of white fibers, the *medial* and *lateral longitudinal striae*, are embedded in the indusium griseum.





Hippocampus

Hippocampal Formation. The hippocampus, the posterior part of the dentate gyrus and the indusium griseum are sometimes grouped together as the hippocampal formation. In humans, the attenuated gray and white structures of this formation are produced by the enormous enlargement of the corpus callosum, which encroaches upon the parahippocampal and dentate gyri and the hippocampi, thus expanding them.

The *hippocampus* is a part of the marginal cortex of the parahippocampal gyrus that has been invaginated, or rolled, into the floor of the inferior horn of the lateral ventricle by the exuberant growth of the nearby temporal cortex. The curved hippocampal eminence is composed mostly of gray matter, and its anterior end is expanded and grooved like a paw, the *pes hippocampi*. Axons conveying efferent impulses from the pyramidal cells of the hippocampus form a white layer on its surface, the *alveus*, and then converge toward its medial edge to form a white strip, the *fimbria*. The hippocampus is an important part of the olfactory apparatus in lower animals; in humans, few or no secondary olfactory fibers end in it. However, it possesses substantial connections with the hypothalamus, which regulates many visceral activities that influence emotional behavior and with temporal lobe areas reputedly associated with memory.

The *dentate gyrus* (dentate fascia) is a crenated fringe of cortex occupying the narrow furrow between the fimbria of the hippocampus and the parahippocampal gyrus. Anteriorly, this fringe fades away on the surface of the uncus, and posteriorly, it becomes continuous with the indusium griseum through the gyrus fasciolaris.

The hippocampus contains pyramidal cells in regions CA1 and CA3 that project via the efferent fornix to the septal nuclei and hypothalamus. The subiculum receives input from the hippocampal pyramidal cells and also projects via the fornix to the mammillary nuclei and anterior nucleus of the thalamus. It is connected reciprocally with the amygdala and sends axons to cortical association areas of the temporal lobe. The dentate gyrus contains granule cells that project to the pyramidal cells of the hippocampus and subiculum and receive hippocampal input. The afferent connections to the hippocampal formation include the cerebral association cortices, prefrontal cortex, cingulate cortex, the insular cortex, amygdaloid nuclei, and olfactory bulb via projections to the entorhinal cortex. Afferent cholinergic axons from septal nuclei traverse the fornix to provide the dentate gyrus and hippocampal CA regions.

There exist several clinical conditions where damage unique to the hippocampal formation occurs. CA1 neurons are particularly susceptible to ischemic conditions as seen in cardiorespiratory arrest. Also, patients with temporal lobe epilepsy can suffer CA1 neuronal loss. The most common clinical scenario affecting the hippocampal formation is Alzheimer disease (AD). AD is pathologically associated with neuronal cell loss, neurofibrillary tangles, neuritic amyloid plaques, and granule vacuolar degeneration of the hippocampal region. AD is discussed in more detail in Plates 2-24 to 2-26.

Fornix

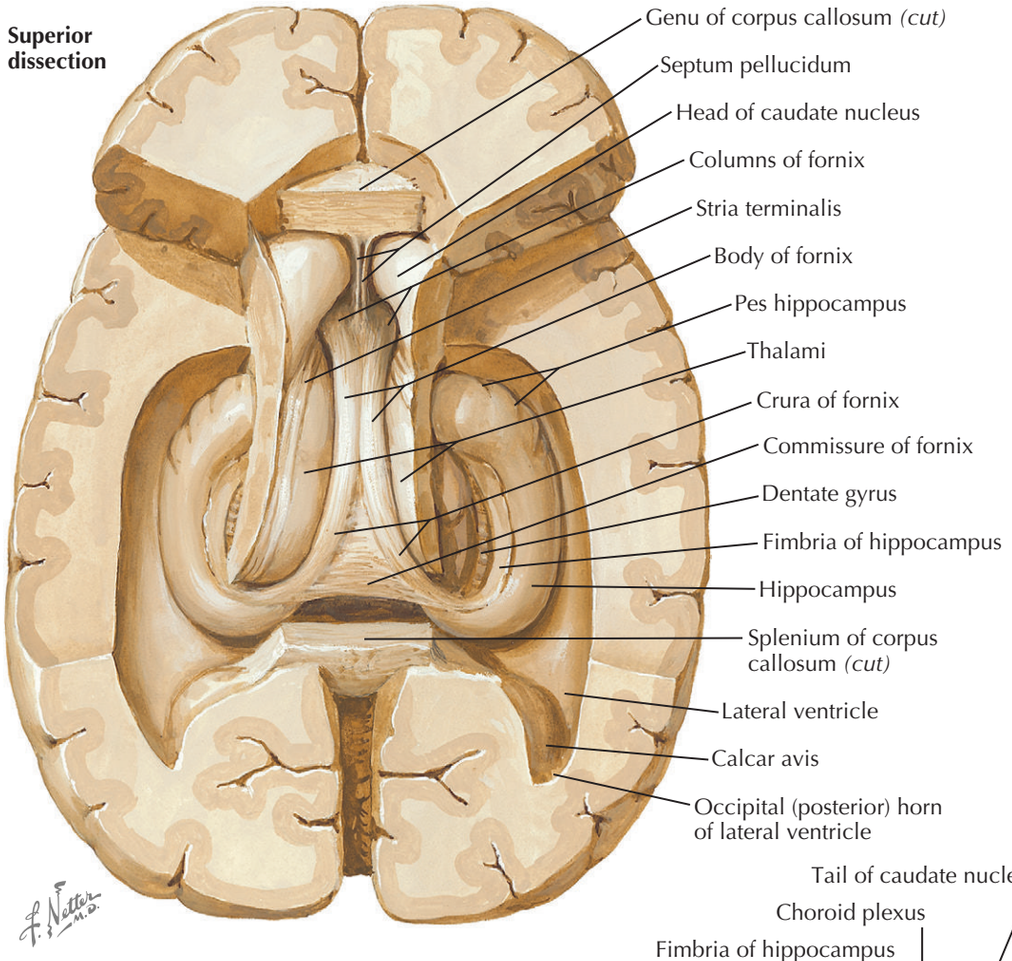
The fornix is an almost circular arrangement of white fibers conveying the great majority of the hippocampal efferents to the hypothalamus and carrying commissural fibers to the opposite hippocampus and habenular trigone. The fornix rises out of the fimbria of the hippocampus, which turns upward beneath the splenium of the corpus callosum and above the thalamus to form the *crura* (posterior columns) of the fornix. Anterior to the *commissure* of the fornix, the two crura unite for a variable distance in the midline and create the triangular *body* of the fornix. The free lateral edges of the fornix help to bind the choroid fissure, through which the pia mater of the tela choroidea becomes invaginated into the lateral ventricles.

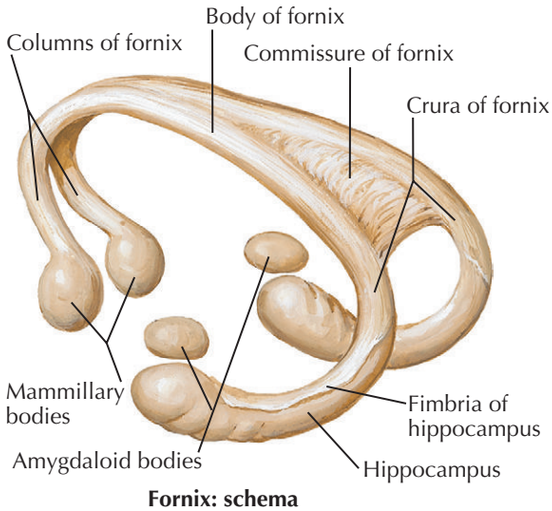
Above the interventricular foramina, the two halves of the body of the fornix separate to become the (anterior) *columns* of the fornix. As each column descends, it sinks into the corresponding lateral wall of the third ventricle; the majority of its fibers end in the *mammillary body*, although some also pass to other hypothalamic nuclei.

The fornix is the main efferent pathway from the hippocampus to the hypothalamus. Fibers ending in the mammillary body form synapses around its cells. The axons of these cells pass upward in the mammillothalamic tract to the homolateral anterior thalamic nucleus, from which they are relayed to the cingulate gyrus.

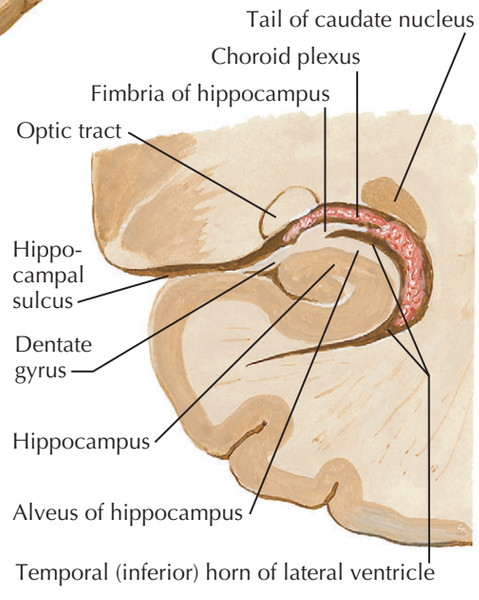
Other Structures. The *habenular trigone* is a small area found bilaterally between the posterior end of the thalamus, the superior (cranial) colliculus and the stalk of the pineal gland. Each trigone overlies a *habenular nucleus*, which receives afferent fibers via the *stria medullaris* of the thalamus (stria habenularis), a fine strand demarcating the superior and medial surfaces of the thalamus. This stria conveys fibers from the anterior perforated substance, the paraterminal gyrus and subcallosal area, and perhaps other fibers detached from the stria terminalis near the interventricular foramen. Most of these fibers end in the homolateral habenular nucleus, but some decussate in the small habenular commissure lying above the stalk of the pineal gland. The fresh relay of fibers arising in the habenular nucleus passes by way of the fasciculus retroflexus to the *interpeduncular nucleus* in the posterior (interpeduncular) perforated substance. Efferent fibers from the interpeduncular nucleus then descend in or near the medial longitudinal fasciculus to be distributed to tegmental and reticular nuclei in the brainstem. The *amygdaloid body* is described in Plate 2-11.

Hippocampus and Fornix



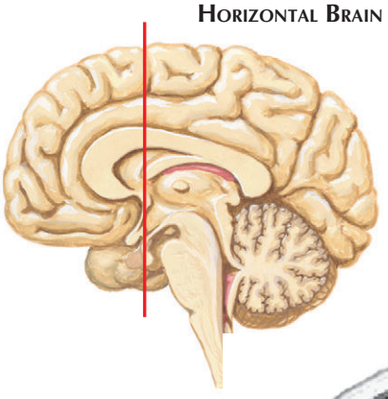


Fornix: schema

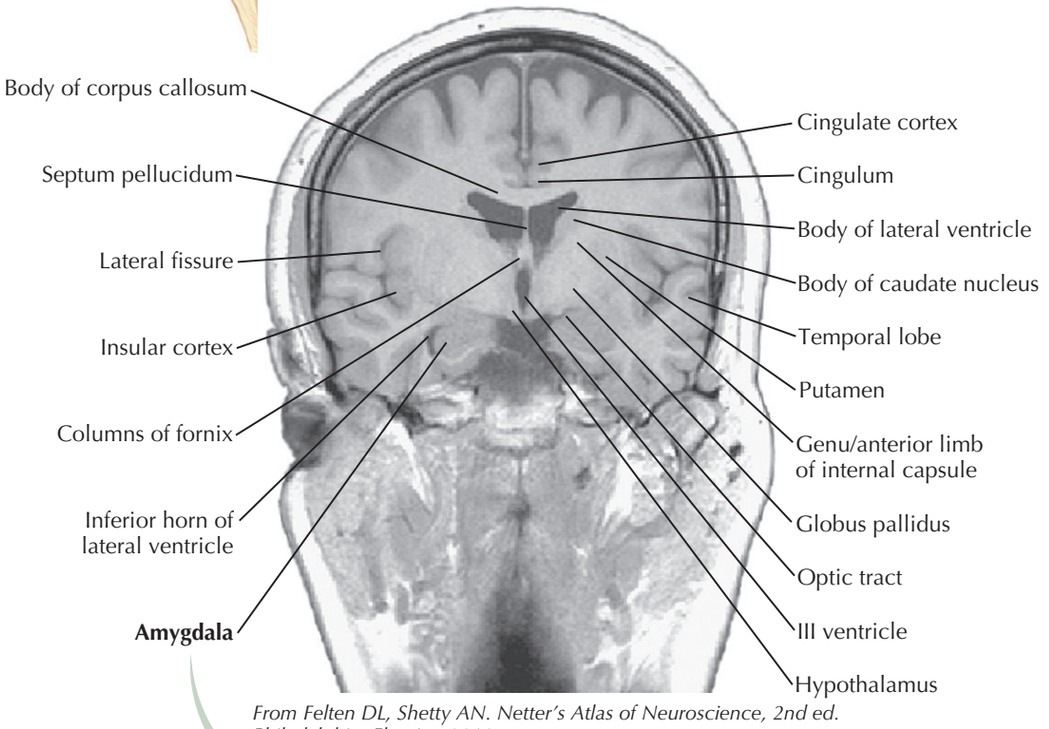


Coronal section: posterior view

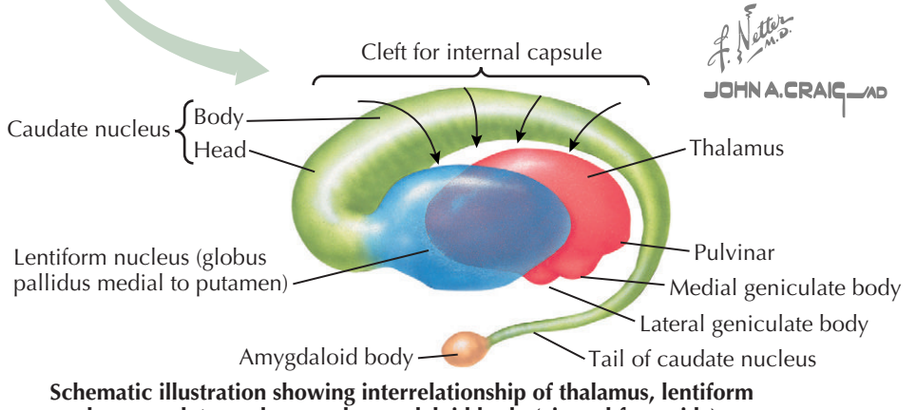
Horizontal Brain Sections Showing the Basal Ganglia



Level of section (amygdala, anterior limb of internal capsule)



From Felten DL, Shetty AN. Netter's Atlas of Neuroscience, 2nd ed. Philadelphia: Elsevier, 2010.



Schematic illustration showing interrelationship of thalamus, lentiform nucleus, caudate nucleus, and amygdaloid body (viewed from side)

Amygdala

The amygdala is an almond-shaped complex located in the medial temporal lobe, and contains approximately 13 nuclei. The three main regions are the corticomedial nuclei, basolateral nuclei (both receive afferents and project axons to target structures), and central nucleus (which provides mainly efferent projections to the brainstem). Afferent connections to the amygdala originate from cortical and thalamic areas, and hypothalamic and brainstem areas. Its function is to provide emotional relevance to external and internal sensory information and to provide a behavioral and emotional response, particularly a fearful and aversive response, to a sensory input.

The majority of afferent information arises from the glutamatergic projections arising from pyramidal neurons in layer V of the cortex. These projections largely travel ipsilaterally via the extreme capsule. Information from sensory association areas and memory-related structures, such as the hippocampus, are relayed via cortical and thalamic inputs. Autonomic and behavioral inputs arise from the hypothalamus and brainstem.

Afferents to the corticomedial nuclei arrive primarily from subcortical limbic sources, including the olfactory bulb, septal nuclei, and hypothalamic nuclei (ventromedial [VM], lateral hypothalamic area [LHA]); the thalamus (intralaminar nuclei); the stria terminalis; and excessive numbers of autonomic nuclei and monoamine nuclei of the brainstem. Afferents to the basolateral nuclei arrive mainly from the cortical areas, including extensive sensory association cortices, the prefrontal cortex, the cingulate cortex, and the subiculum.

In the late 1930s Klüver and Bucy described a behavioral syndrome characterized by hypersexuality, hyperorality, excessive exploration of visual stimuli (hypermetamorphosis), visual agnosia, apathy, and withdrawal. They linked this behavior to bilateral amygdaloid complex lesions. This syndrome has been described in patients with neurodegenerative diseases, such as Alzheimer disease and even frontotemporal dementia. Because the amygdala processes sensory information for emotional relevance, it is not surprising that atypical emotional responses, such as anger, aggressive behavior, and even apathy, can evolve in these patients. Damage to the hypothalamic connectivity of the amygdala is responsible for hyperphagia, hypersexuality, and overeating/obesity. Likewise, alterations of the visual association cortical afferent projections to the amygdala result in hypermetamorphosis and visual agnosia (patients cannot recognize facial expressions that indicate fear).

Forebrain Regions Associated with Hypothalamus

The cerebral cortex influences the "autonomic" neurovisceral outflow and the neurohumoral output of the endocrine glands, as can be demonstrated experimentally by stimulating the orbitofrontal cortex of the cingulate gyrus to produce respiratory, cardiovascular, and digestive responses, as well as certain emotional reactions. The responses are less marked than those produced by stimulating the hypothalamus but are still striking; some of them, moreover, do not depend upon the integrity of the hypothalamus, a fact that suggests mediation by corticoreticular fibers to lower "centers." In humans, subjective emotional experiences are associated with autonomic discharges (e.g., tachycardia, increased blood pressure, blushing) and changes in endocrine activity (e.g., stress-induced amenorrhea or anorexia nervosa).

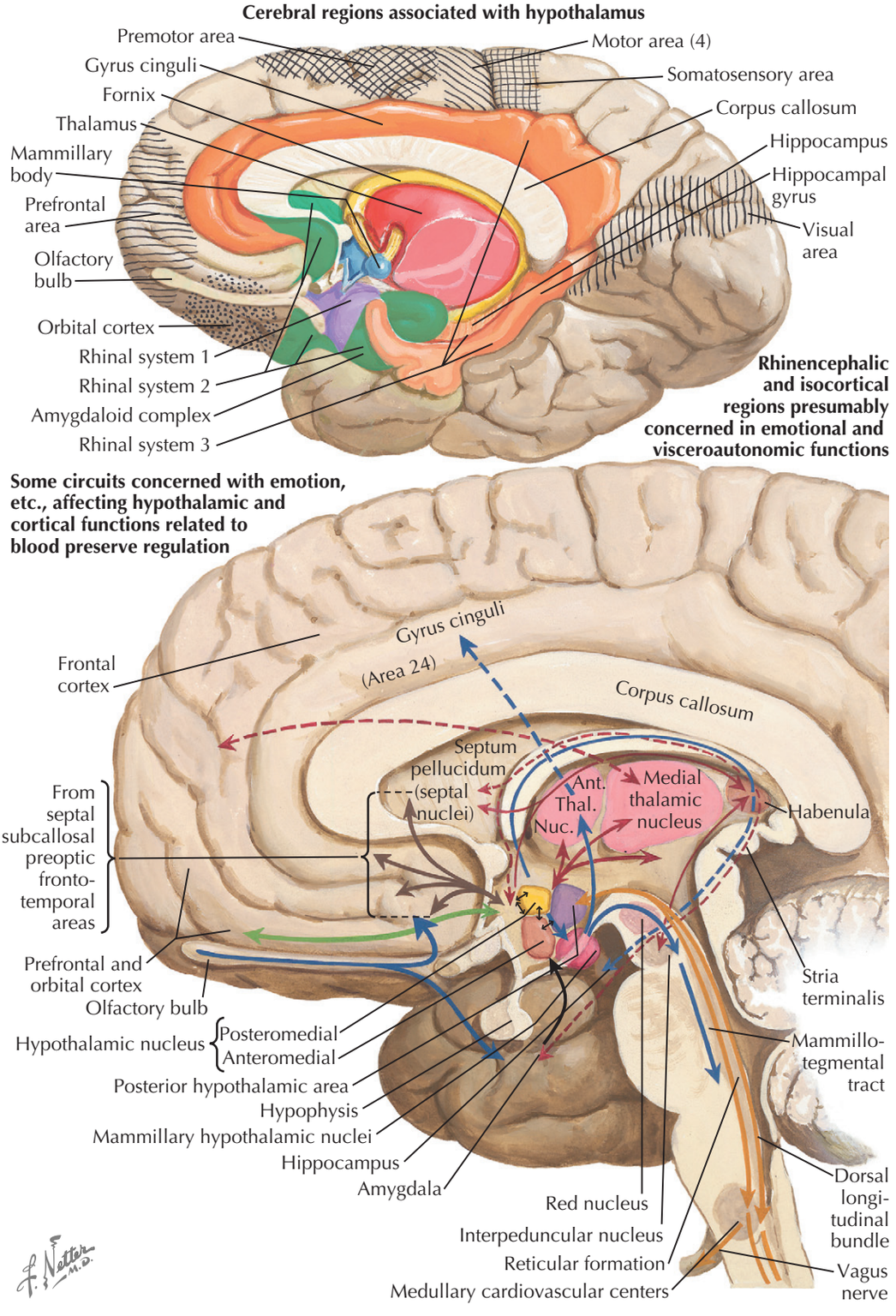
Behavioral changes produced by cortical ablations, such as prefrontal lobotomy, are well known. Other such changes, varying from mania and hyperphagia to apathy, aphagia, and somnolence, result from lesions to certain parts of the hypothalamus.

Thus hypothalamic circuitry is tied into countless other circuits—in the cerebral cortex, limbic system, brainstem reticular formation, and other parts of the diencephalon. These circuits are poorly understood, but rich connections with the frontotemporal and cingulate cortex, septal/preoptic areas, amygdala, anterior mesencephalic tegmentum, and numerous thalamic nuclei (midline, intralaminar, medial posterior, anterior, etc.) have been demonstrated.

Some of these connections are indicated schematically in the illustration. Connections between the *orbital cortex* of the frontal lobe and the hypothalamus have been demonstrated in certain mammals. Indirect connections with the *prefrontal areas* through the *medial posterior thalamic nucleus* are well established. The hypothalamus is linked with the *cingulate gyrus* by way of the *anterior thalamic nuclei* and with the *hippocampal formation* via the fornix. The *amygdala* has reciprocal connections with the hypothalamus through the *anterior amygdalofugal pathway*. Additional amygdalohypothalamic connections run through the *stria terminalis*.

The hypothalamus also receives input, through *reticulohypothalamic fiber systems* departing from the main reticulothalamic stream, from the great sensory systems. Through this offshoot, the responses evolved through thalamocortical feature analysis are paralleled by responses in the visceral realm. The limbic (border) structures of the cerebral hemisphere also participate in these responses: the olfactory bulb, amygdala, frontotemporal cortex, septal nuclei, hippocampal formation, and limbic lobe. Stimulation of limbic structures can produce respiratory and vascular changes, and psychotropic drugs, such as mescaline, apparently exert some of their effects on the limbic system.

The stria medullaris thalami and medial forebrain bundle deserve mention: the former bypasses the hypothalamus, the latter runs right through it. The *stria medullaris thalami* connects the medial olfactory area, amygdala and preoptic area with the habenular nucleus, from which fibers pass to the interpeduncular region. The *medial forebrain bundle* links the anteromedial olfactory areas with the preoptic areas, hypothalamus, and mesencephalic tegmentum. A diffuse system of fine fibers, it pervades the lateral hypothalamic area and is the key fiber tract of the hypothalamus. Lastly, fibers of the *fornix* end in both medial and lateral mammillary nuclei, as well as in the hypothalamus anterior to the mammillary region. A few fibers pass caudally into the mesencephalon.



THALAMOCORTICAL RADIATIONS

All pathways carrying information from the periphery or the brainstem to the neocortex relay in the nuclei of the *posterior thalamus*. These nuclei can be divided into two groups on the basis of their structure, connections, and function.

Nonspecific Nuclei. The first group includes the *midline (median)* and *intralaminar nuclei* and the medial portion of the *ventral anterior nucleus*. These nuclei receive ascending input from the mesencephalic reticular formation and from the spinal cord (paleospinothalamic tract), and descending input from the cerebral cortex. They project widely, both to other thalamic nuclei and to the cortex, especially to its frontal regions. These projections are thought to be essential in regulating the general excitability of neurons in the thalamus and cortex.

Another nucleus included in the first group is the *reticular nucleus*, which overlies the lateral surface of the thalamus. Neurons of this nucleus, which receive input from collaterals of thalamocortical fibers and project back to the thalamus, are thought to constitute a feedback pathway that regulates thalamic excitability.

Specific Nuclei. The second group of nuclei is termed the "specific nuclei" because they project to restricted regions of the cortex (see Plate 2-13). The major specific nuclei and the corresponding cortical regions to which they project are illustrated in matching colors. One set of specific nuclei are the sensory relay nuclei. The *ventral posterolateral (VPL)* and *ventral posteromedial (VPM) nuclei* receive their input from somatosensory relay neurons via the medial lemniscus, trigeminal lemnisci, and the neospinothalamic tract. They project to the primary (Sm I) and secondary (Sm II) somatosensory cortex. The *ventral posterointermediate (VPI) nucleus* (not shown) receives input from the vestibular system and projects to the vestibular area in the parietal lobe (see Plate 2-13). The *lateral geniculate nucleus* receives its input from the optic tract and projects to the primary visual area in the occipital lobe (see Plate 2-13). The principal part of the *medial geniculate nucleus* receives input from auditory relay nuclei and projects to the primary auditory area in the supratemporal transverse gyrus (see Plate 2-13).

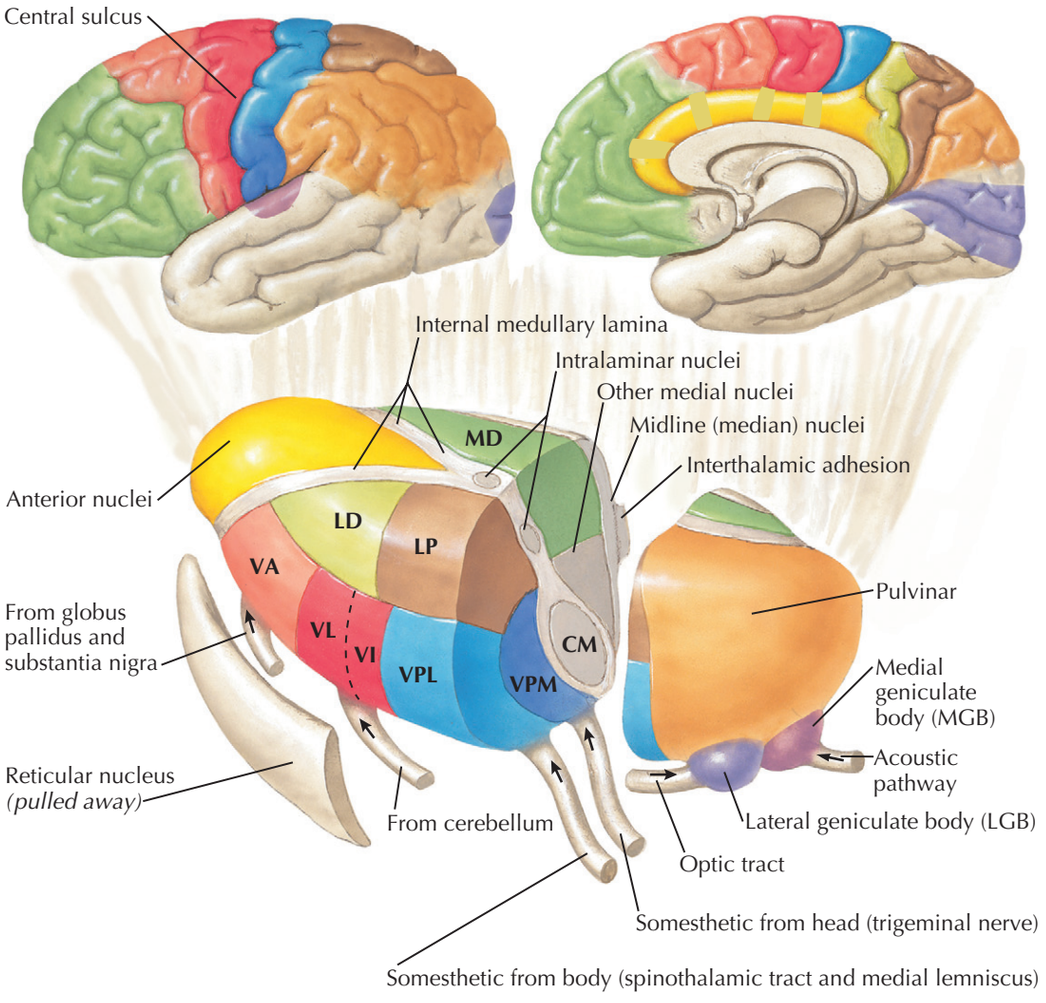
A second set of specific nuclei is involved in the control of motor activity. The *ventral lateral (VL)* and *ventral intermedial (VI) nuclei* and the lateral portion of the *ventral anterior (VA) nucleus* receive input from the cerebellum and basal ganglia, respectively, and project to the precentral motor areas (see Plate 2-13). These areas also receive input from the oral part of the ventral posterolateral nucleus.

The *anterior dorsal (AD)* (the least prominent of the anterior group of nuclei) and the *medial dorsal (MD) nuclei* are specifically related to the limbic system, which regulates emotional and autonomic activity (see Plates 2-8 and 2-13). The anterior dorsal nucleus receives input from the hippocampus relayed via the mammillothalamic tract and projects to the cingulate gyrus. The medial dorsal nucleus receives input from the hypothalamus and amygdala and projects to the frontal lobe.

The remaining specific nuclei are related to association areas of the cortex involved in higher integrative mechanisms. They include the *lateral dorsal (LD)* and *lateral posterior (LP) nuclei* and the *pulvinar complex*. The medial, magnocellular part of the *medial geniculate nucleus*, which receives widespread convergent input from many afferent systems, should probably also be included in this category.

Cortical Connections. In addition to receiving the ascending input described above, all the thalamic nuclei receive descending input from the cerebral cortex, principally from the cortical regions to which they project (see Plate 2-13). These descending projections serve as a two-way feedback system between each cortical area and its thalamic relay nucleus.

Not all the nuclei of the posterior thalamus project to the cerebral cortex. One important nucleus without a cortical projection is the *centromedian (CM) nucleus*, which communicates only with the basal ganglia.



Thalamic nuclei

CM	Centromedian
LD	Lateral dorsal
LP	Lateral posterior
MD	Medial dorsal
VA	Ventral anterior
VI	Ventral intermedial
VL	Ventral lateral
VPL	Ventral posterolateral
VPM	Ventral posteromedial

Neuronal Structure and Synapses

Neuronal Structure

A typical neuron of the central nervous system consists of three parts: dendritic tree, cell body (soma), and axon.

The highly branched *dendritic tree* has a much greater surface area than the remainder of the neuron and is the receptive part of the cell. Incoming synaptic terminals make contact directly with the dendritic surface or with the small spines (gemmules) that protrude from it. The membrane potential induced in the dendrites spreads passively onto the cell soma, which allows all inputs acting on the neuron to summate in controlling the rate of neuronal discharge through the axon.

The *soma* contains the various organelles that control and maintain neuronal structure: nucleus, Golgi apparatus, lysosomes, ribosomes, mitochondria, and smooth and rough endoplasmic reticula. The rough endoplasmic reticulum, studded with ribosomes, is called the *Nissl substance* because of its characteristic blue staining with Nissl stain. The *ribosomes* are the site of synthesis of neuronal proteins; as in other cells, the ribonucleic acid (RNA) templates that control protein structure are transcribed from patterns in the nuclear deoxyribonucleic acid (DNA). The soma membrane is also covered with synaptic endings separated by glial processes. Because of their proximity to the origin of the axon, these synaptic endings have an especially potent effect on the rate of discharge of the neuron.

In humans, the *axon* can extend for several feet. Such lengths pose supply problems because the neuron must transport proteins and other synthesized substances as far as the axon terminals. Certain key substances are transported, at a rate as high as 400 mm/day, by rapid axonal transport, a process probably associated with the microtubules that originate in the soma and run the length of the axon. Other soluble and particulate substances move by *slow axonal transport* at a rate of 1 to 4 mm/day, aided partly by the peristalsis-like motion of the axon.

The axon originates from a conical projection (axon hillock) on the soma (as shown in Plate 2-14) or on one of the proximal dendrites. The axon membrane is specialized for the transmission of action potential. Because of its shape and high excitability, the initial segment of the axon is usually the site of action potential generation. The action potential then spreads down the axon and back to the soma and proximal dendrites. Because of the low excitability of the dendrites, the impulse usually does not spread very far into the dendritic tree. At its distal end, the axon divides into numerous branches, which end in synapses.

Types of Neuronal Synapses

The most common central nervous system (CNS) synapses are those between axon terminals and dendrites (axodendritic) or between axon terminals and somata (axosomatic). *Axodendritic synapses* take several forms. Spine synapses are of particular interest, because they may be the site of morphologic changes accompanying learning. *Axosomatic synapses* are of the simple type shown in example *A*. Synaptic interconnections between a number of neurons occur within structures of a complex organization, such as the cerebellar glomerulus, although all synapses within the glomerulus are axodendritic.

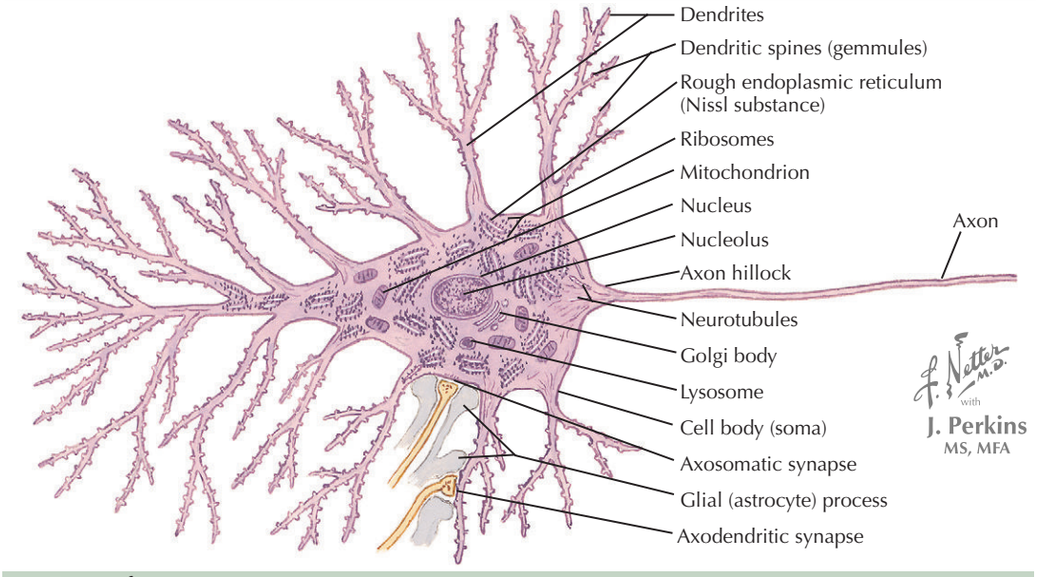
Axons also form *axoaxonic synapses* with other axon terminals, and these are responsible for the phenomenon of presynaptic inhibition. Axoaxonic synapses are also seen in the efferent vestibular system and in connection with motor neuron dendrites and other terminals ending on those dendrites.

The CNS also contains several less common types of synapses. *Dendrodendritic synapses* are found in the olfactory bulb. In the internal plexiform layer of the retina, synaptic interactions involve *synaptic triads* of bipolar, amacrine, and ganglion cell processes.

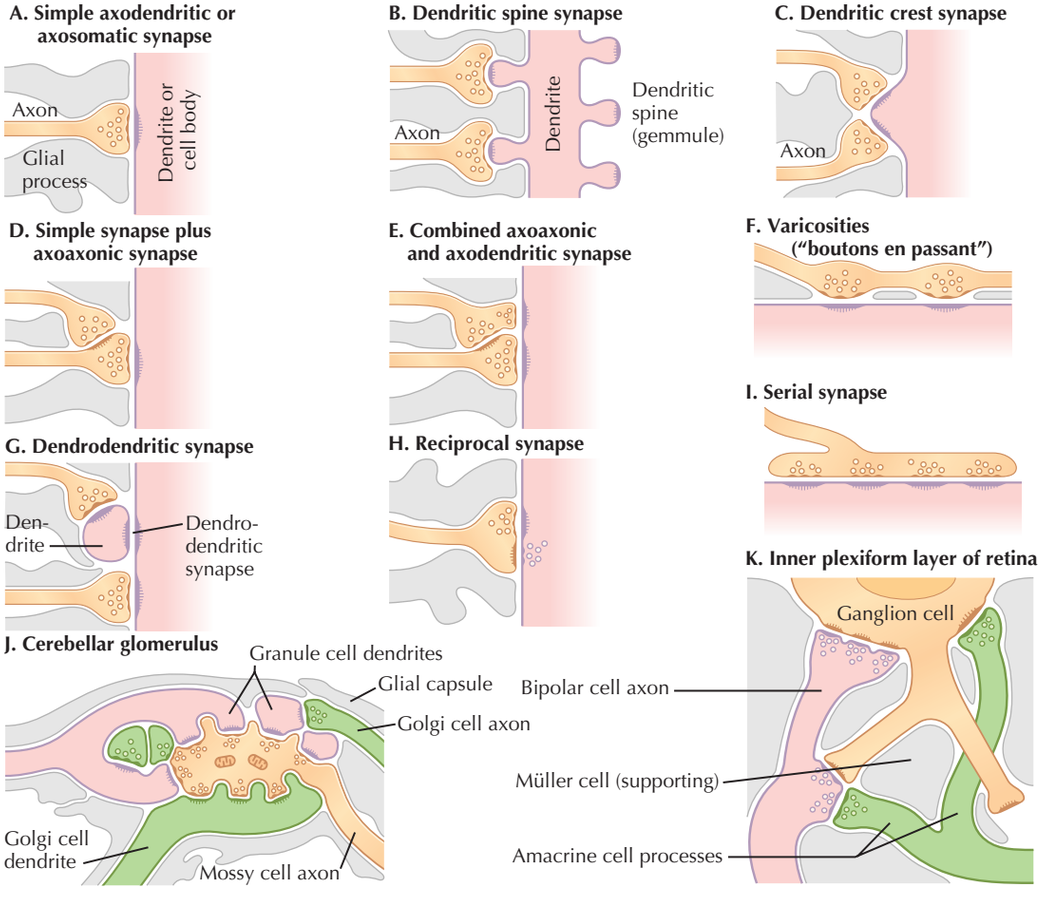
Other synapses are those formed between the peripheral axonal processes of sensory neurons and *sensory receptor cells*, as in the inner ear. Here, the axon terminal forms the postsynaptic element that is depolarized by the presynaptic sensory cell.

There are also specialized axosomatic synapses formed by efferent motor axons on muscle (motor end plates) and by autonomic axons on secretory cells.

Structure of a neuron (pyramidal cell of cerebral motor cortex)



Types of synapses



Chemical Synaptic Transmission

Chemical synaptic transmission proceeds in three steps: (1) the release of the transmitter substance from the bouton in response to the arrival of an action potential, (2) the change in the ionic permeabilities of the postsynaptic membrane caused by the transmitter, and (3) the removal of the transmitter from the synaptic cleft. Depending on the type of permeability changes produced in the second step, synaptic activation may have either an excitatory or an inhibitory effect on the postsynaptic cell.

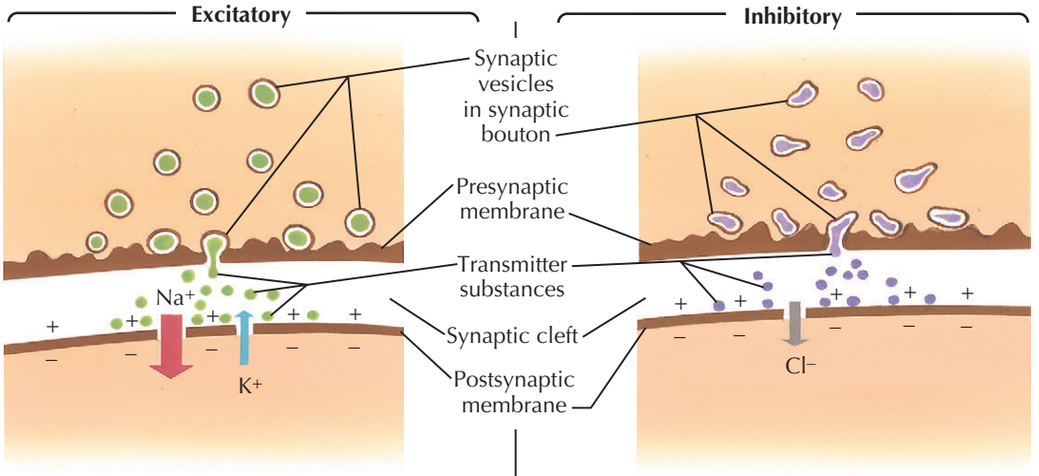
Synaptic transmitter substances are concentrated in *synaptic vesicles* within the bouton. Although the exact mechanism of its release is unknown, it appears that the transmitter substance is released in packets, or quanta, of 1,000 to 10,000 molecules at a time, and that the probability of release of these quanta increases with the degree of depolarization of the terminal membrane. Thus the intense depolarization caused by an action potential actuates the nearly simultaneous release of a large number of quanta. A reasonable hypothesis to account for the quantal nature of transmitter release is that the contents of an entire vesicle are discharged at once into the synaptic cleft, perhaps by the process of *exocytosis*.

After their release, transmitter molecules diffuse across the synaptic cleft and combine with specific receptor molecules in the postsynaptic membrane. This combination gives rise to a change in the ionic permeability of the postsynaptic membrane and results in a flow of ions down their electrochemical potential gradients. This ionic flow is not synchronous with the arrival of the action potential in the terminal but begins after a *synaptic delay* of 0.3 to 0.5 msec, which is the time required for transmitter release and diffusion and for the completion of reactions within the postsynaptic membrane, which alter membrane permeability.

The direction of current flow produced by transmitter action depends upon which ionic permeabilities are altered. In an *excitatory synapse*, the transmitter causes an increase in the permeability of the postsynaptic membrane to sodium ions (Na^+) and potassium ions (K^+). Because of their respective concentration gradients across the neuronal membrane (see Plate 2-15), Na^+ tends to move into the postsynaptic cell, and K^+, out of it. The negative potential of the neuronal cytoplasm, however, assists the inward flow of positive ions and retards their outward flow so that the combined electrochemical force for Na^+ influx greatly exceeds that for K^+ efflux. Thus the predominant ionic movement across the postsynaptic membrane is an *inward flow of Na^+*. As shown, the resulting current flow causes a shift of the postsynaptic cell membrane potential in the depolarizing direction. This depolarizing potential change, which is called an *excitatory postsynaptic potential (EPSP)*, brings the postsynaptic cell closer to its threshold for action potential initiation.

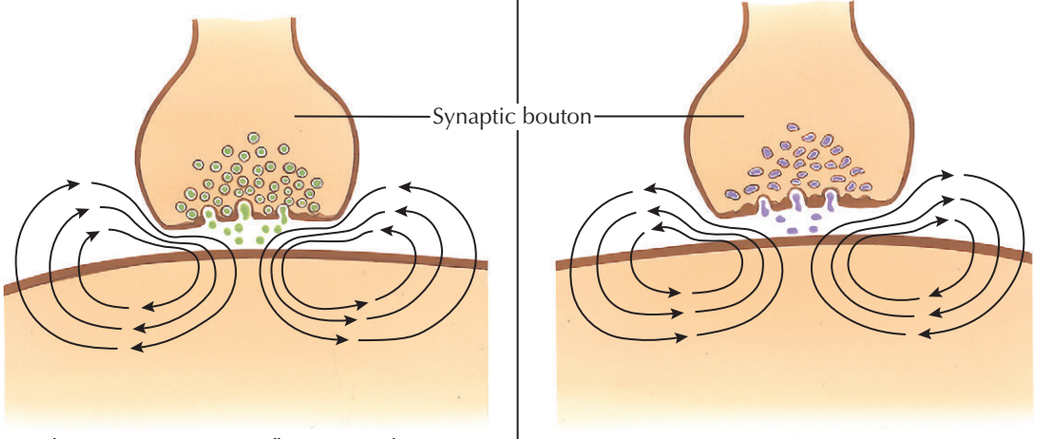
In an *inhibitory synapse*, transmitter action causes an increase of the postsynaptic membrane's permeability to K^+ and chloride ions (Cl^-) but not to Na^+. Because Cl^- is approximately at electrochemical equilibrium across the neuronal membrane, the major ionic movement is an *outward flow of K^+*. The resulting current flow is in the opposite direction to that of the current flow in an excitatory synapse, and gives rise to a shift of the postsynaptic cell membrane potential in the hyperpolarizing direction. This hyperpolarizing potential change, which is called an *inhibitory postsynaptic potential (IPSP)*, moves the membrane potential away from the threshold for action potential initiation. The increased ionic permeability of the postsynaptic membrane also contributes to the inhibitory effect by tending to "short out" any membrane depolarization occurring simultaneously.

The ionic current and the resulting membrane potential change have different time courses because the synaptic current charges the membrane capacitance, which then discharges passively over a period of 10 to 15 msec. The short duration of the synaptic current is the consequence of the removal of transmitter from the synaptic cleft. This removal is accomplished in part by passive diffusion and in part by specific mechanisms that lead to transmitter uptake by surrounding cells or transmitter breakdown by enzymatic degradation.



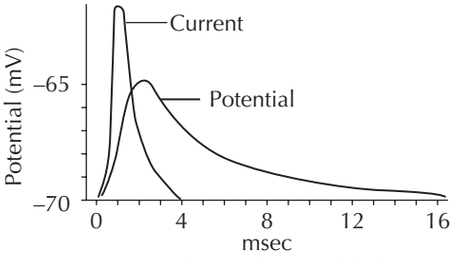
When impulse reaches excitatory synaptic bouton, it causes release of a transmitter substance into synaptic cleft. This increases permeability of postsynaptic membrane to Na^+ and K^+. More Na^+ moves into postsynaptic cell than K^+ moves out, due to greater electrochemical gradient.

At inhibitory synapse, transmitter substance released by an impulse increases permeability of the postsynaptic membrane to Cl^-. K^+ moves out of postsynaptic cell, but no net flow of Cl^- occurs at resting membrane potential.

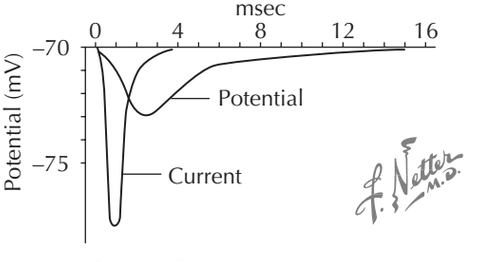


Resultant net ionic current flow is in a direction that tends to depolarize postsynaptic cell. If depolarization reaches firing threshold, an impulse is generated in postsynaptic cell.

Resultant ionic current flow is in direction that tends to hyperpolarize postsynaptic cell. This makes depolarization by excitatory synapses more difficult—more depolarization is required to reach threshold.



Current flow and potential change



Current flow and potential change

Summation of Excitation and Inhibition

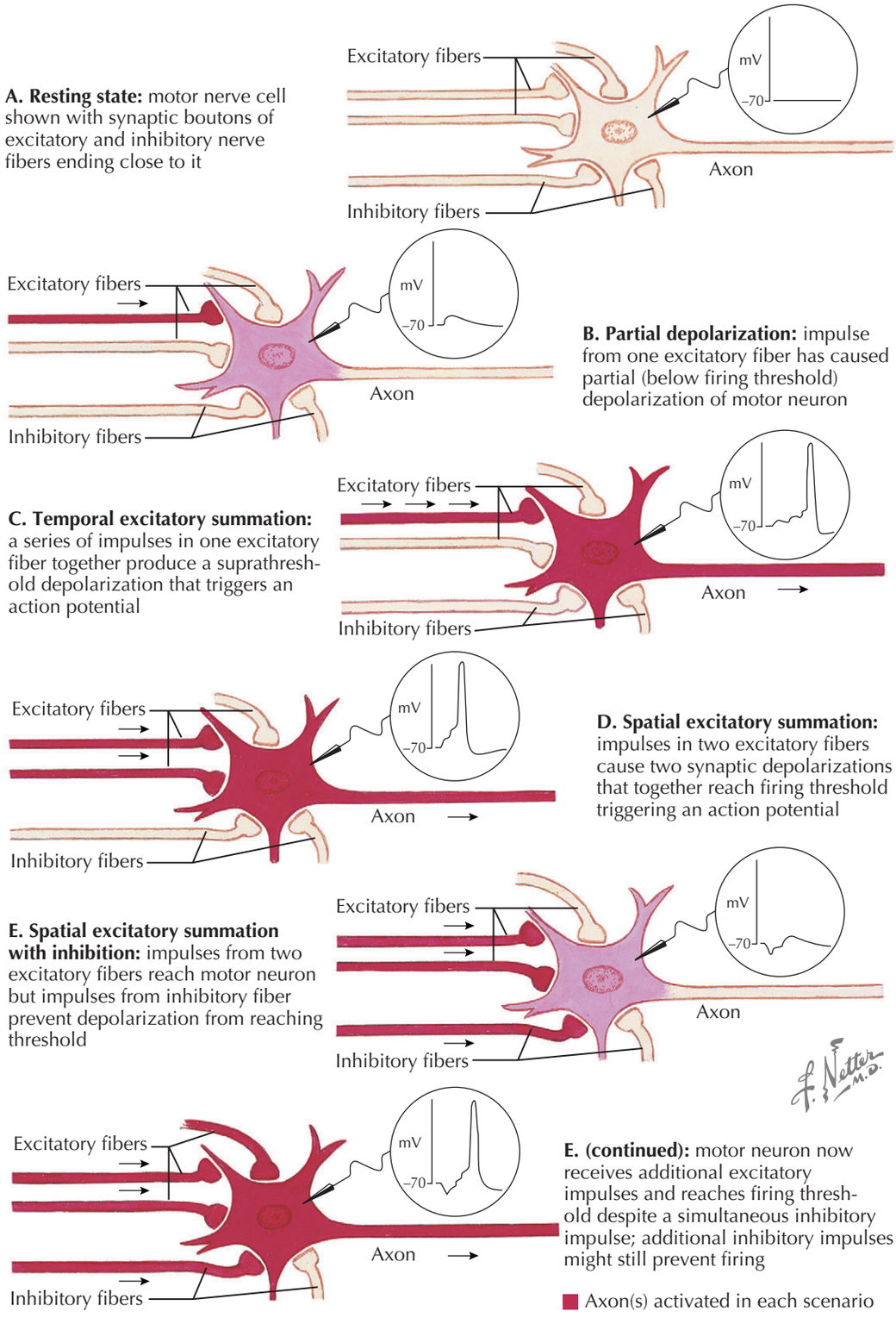
Summation of excitation and inhibition is the vital principle on which the functioning of the CNS is based. The illustration shows the various intracellular potential changes observed during temporal and spatial summation of excitation and inhibition, as voltage-versus-time tracings similar to those produced by an oscilloscope.

The principle of summation relates to the fact that a neuron typically has a large number of synaptic terminals (boutons) ending upon it; alone, each bouton is capable of producing only a small synaptic potential. The small excitatory postsynaptic potential (EPSP) produced by a single excitatory terminal is not sufficient to depolarize the motor neuron to its threshold point. For suprathreshold depolarization to be produced, either temporal or spatial summation of excitation must take place.

Temporal summation occurs when a burst of action potentials reaches a nerve fiber terminal. If the terminal is excitatory, the first action potential in the burst produces a depolarizing EPSP in the motor neuron that begins to decay toward the resting potential. Before the decay is complete, another action potential arrives in the terminal and evokes a second EPSP. The depolarization caused by this EPSP adds to the residual depolarization remaining from the first EPSP and moves the membrane potential closer to the threshold level. Finally, the EPSP evoked by a third action potential adds its depolarization to that produced by the first two to drive the membrane potential past the threshold level and to trigger an action potential in the motor neuron. Thus, because of temporal summation, a burst of action potentials in an excitatory fiber is able to evoke the firing of a target neuron, even though the individual EPSPs evoked by single action potentials are too small to produce a suprathreshold depolarization. In a similar manner, the inhibitory postsynaptic potentials (IPSPs) produced by a burst of action potentials in an inhibitory fiber can summate to produce a large hyperpolarizing potential.

Spatial summation involves the activation of two or more terminals at approximately the same time. When such synchronous activation occurs, the inward and outward currents evoked by excitatory and inhibitory terminals summate to produce a net shift in the membrane potential of the target cell. If two excitatory terminals are activated, the net membrane potential shift will be a depolarization approximately equal to the sum of the EPSPs that would be evoked by each terminal acting alone; this combined depolarization exceeds the threshold level and triggers an action potential. If, in addition to the two excitatory terminals, an inhibitory terminal is also activated, the net depolarization will be reduced by an outward flow of current at the inhibitory synapse. Under these conditions, additional excitation is required to produce a suprathreshold depolarization.

Spatial summation plays a vital role in the interaction of patterns of activity originating in various neuronal pathways. For example, in the case of the effect of central motor tone on the reflex evoked by muscle stretch, the stretch produces a volley of action potentials in the group Ia fibers from the stretched muscle. The synaptic action of the Ia fiber terminals evokes medium-to-large EPSPs in motor neurons supplying the stretched muscle and small EPSPs in motor neurons supplying synergistic muscles. If the body is in a relaxed state, only the motor neurons receiving large EPSPs will discharge action potentials, causing a small twitch of the stretched muscle; the remaining motor neurons, which receive EPSPs too small to evoke firing, constitute the *subliminal fringe* of the stretch reflex. If the body is in an active state, central nervous pathways will produce a steady excitatory input to the motor neurons involved in the stretch reflex. Thus many of the neurons in the subliminal fringe will receive sufficient additional excitation to cause them to fire, and muscle stretch may result in a vigorous contraction of that muscle and its synergists. In a similar way, motor neurons that fall within the subliminal fringe of two different reflexes may be fired when both reflexes occur together. This kind of reflex interaction by spatial summation helps to adapt reflex patterns to meet the demands of different external conditions.



A. Resting state: motor nerve cell shown with synaptic boutons of excitatory and inhibitory nerve fibers ending close to it

B. Partial depolarization: impulse from one excitatory fiber has caused partial (below firing threshold) depolarization of motor neuron

C. Temporal excitatory summation: a series of impulses in one excitatory fiber together produce a suprathreshold depolarization that triggers an action potential

D. Spatial excitatory summation: impulses in two excitatory fibers cause two synaptic depolarizations that together reach firing threshold triggering an action potential

E. Spatial excitatory summation with inhibition: impulses from two excitatory fibers reach motor neuron but impulses from inhibitory fiber prevent depolarization from reaching threshold

E. (continued): motor neuron now receives additional excitatory impulses and reaches firing threshold despite a simultaneous inhibitory impulse; additional inhibitory impulses might still prevent firing

■ Axon(s) activated in each scenario

Types of Neurons in Cerebral Cortex

The six layers of the cerebral cortex contain different types of neurons, which can be broadly classified as *interneurons*, *association neurons*, and *efferent (projection) neurons*.

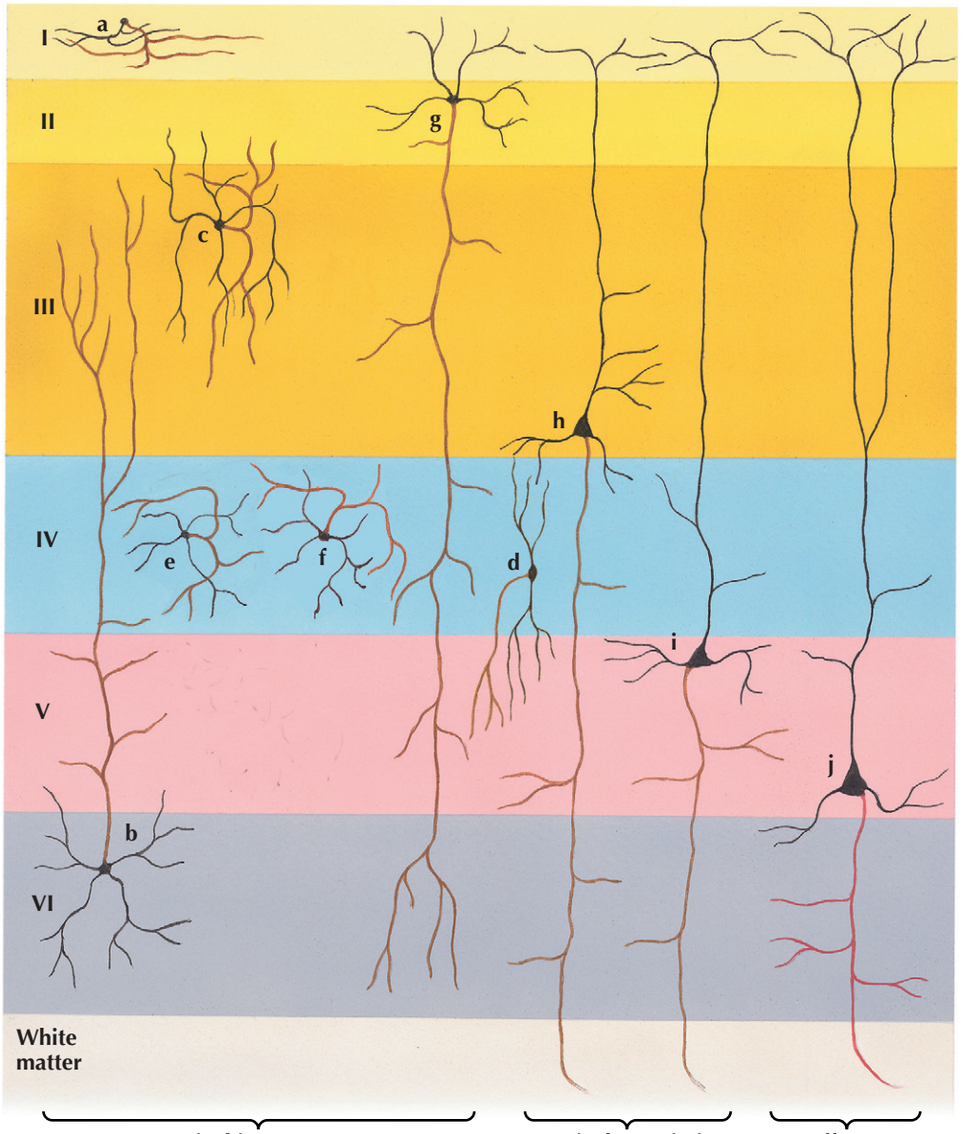
Interneurons. Interneurons have axons that do not leave the cortex and may be of several kinds. The most common are *stellate* (star-shaped), or *granule*, *cells*, which have symmetrically branching dendritic trees and short axons that end upon nearby neurons. These cells are especially prevalent in layer IV, which is accordingly named the "granule cell layer." Other interneurons are *horizontal cells*, which are found in layer I; *Martinotti's cells*, which are located in deeper layers and send axons toward the cortical surface; and the small *pyramidal cells* of layers II and III, which send axons to deeper layers.

Association Neurons. Association neurons are small pyramidal cells found in the deep parts of layer III or in the superficial parts of layer V; they send axons through the white matter to other regions of the cortex.

Efferent Neurons. Efferent neurons leave the cortex to innervate structures in the brainstem or spinal cord and originate from the *giant pyramidal (Betz) cells* in layer V or from spindle-shaped cells in layer VI. In addition to their main axons, which leave the cortex, efferent neurons may also have collateral axons, which project to nearby cortical neurons for association.

Afferent Fibers. Two major classes of nerve fibers bring information to the cortex. *Specific cortical afferent fibers*, which originate in corresponding thalamic relay nuclei, project to layer IV to end in a highly branched terminal arborization. *Nonspecific cortical afferent fibers*, which originate in the thalamus or in other areas of the cortex and ascend through the entire depth of the cortical gray matter, giving off terminal branches in all layers. Specific afferent fibers may thus activate granule cells and efferent neurons of layers III, V, and VI (via their dendrites in layer IV), whereas nonspecific afferents may influence all classes of cortical neurons. Neurons activated by incoming fibers relay information to other cortical neurons via intrinsic connections within the cortex.

Cortical Organization. An important aspect of the flow of information mediated by cortical neurons is that it occurs predominantly in a *vertical direction* across the six cortical layers. With the exception of the horizontal cells of layer I, there are very few cortical neurons that relay activity laterally over any significant distance. The vertical cell axons and dendrites are arranged within the cortex in columns of neurons that have similar properties. These columns are approximately 0.5 to 1.0 mm wide and extend across all six cortical layers. In the sensory cortex, neurons within an individual column all respond to the same stimulus; within the motor cortex, the activity of all neurons in one column is related to the activity of a single muscle or muscle group. These columns, as well as the underlying vertical neural organization, appear to represent one of the central features of information processing by the cerebral cortex.

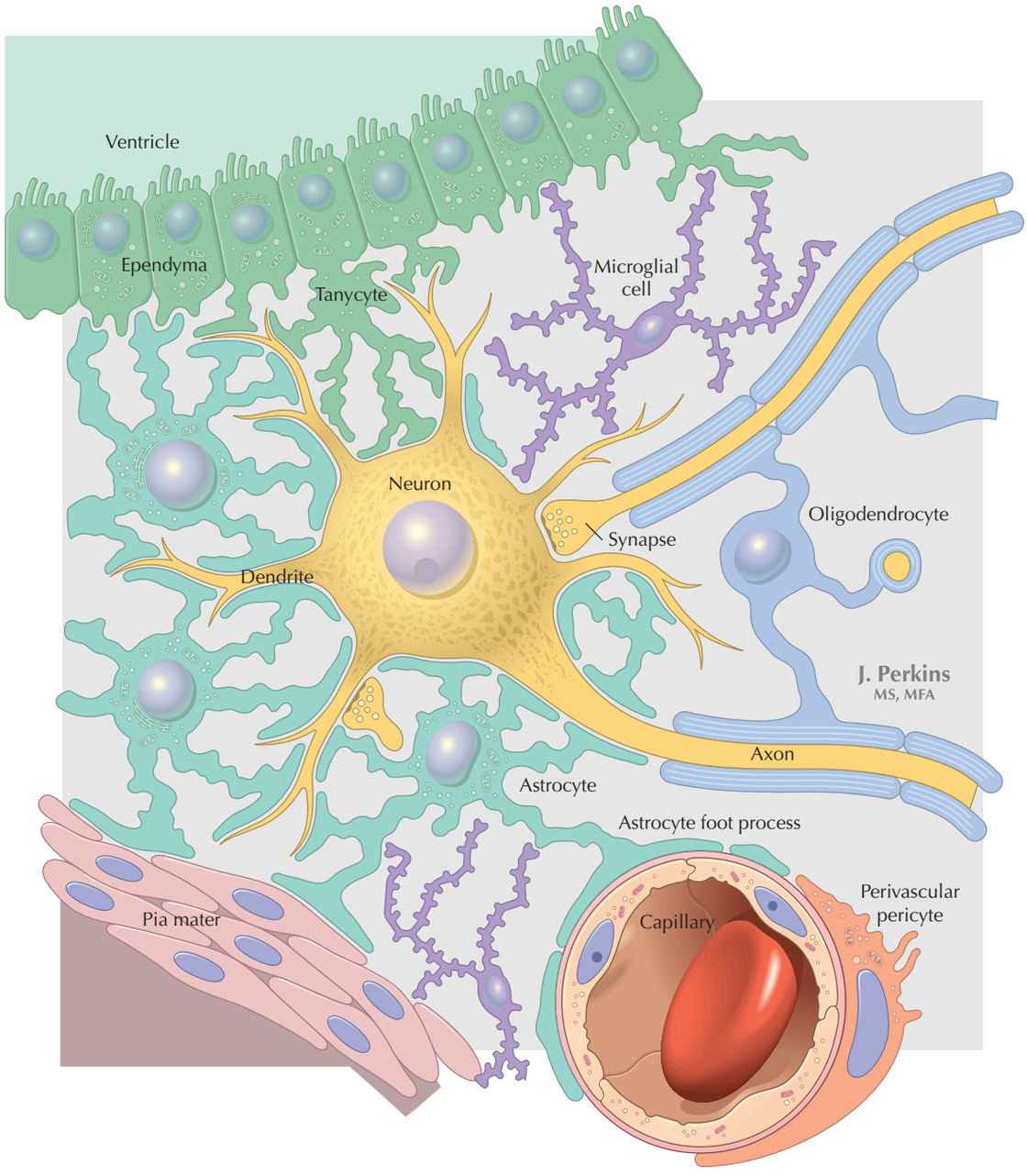


Black—cell bodies and dendrites
Brown—axons of interneurons and association neurons
Red—axon of efferent neurons

Key for Abbreviations

- **a** Horizontal cell
- **b** Cell of Martinotti
- **c** Chandelier cell
- **d** Aspiny granule cell
- **e** Spiny granule cell
- **f** Stellate (granule) cell
- **g** Small pyramidal cell of layers II, III
- **h** Small pyramidal association cell
- **i** Small pyramidal association and projection cells of layer V
- **j** Large pyramidal projection cell (Betz cell)

Neurons and Glial Cells



Astrocytes

Astrocytes provide structural isolation of neurons and their synapses and provide ionic (K^+) sequestration, trophic support, and support for growth and signaling functions to neurons. Oligodendroglia provide myelination of axons in the CNS. Microglia are scavenger cells that participate in phagocytosis, inflammatory responses, cytokine and growth factor secretion, and some immune reactivity in the CNS. Perivascular cells participate in similar activities at sites near the blood vessels. Schwann cells provide myelination, ensheathment, trophic support, and actions that contribute to the growth and repair of peripheral neurons. Activated T lymphocytes normally can enter and traverse the CNS for immune surveillance for a period of approximately 24 hours.

Recent years have witnessed a growing appreciation for functional roles astrocytes play within the CNS. It increasingly appears to be the case that astrocytes are integral to brain energy utilization. For example, at glutamate synapses astrocytes take up the glutamate that is released into the synaptic space by the presynaptic neuron. The glutamate is co-imported into the astrocyte along with a sodium cation. The sodium cation, in turn, is removed from the astrocyte by the action of the plasma membrane adenosine triphosphate (ATP)-dependent Na^+-K^+ pump. This consumes ATP, which activates astrocyte glycolysis, and, in turn, this stimulates glucose uptake from neighboring capillaries. By consuming more glucose through glycolysis, the astrocyte restores its energy supply but, in the process, also generates lactate. Astrocyte-generated lactate is then exported to the recently activated synapse neurons to help meet its increased energy needs. This relationship defines what is called the "astrocyte-neuron lactate shuttle hypothesis," and suggests the classic bipartite synapse of a presynaptic and postsynaptic neuron might more accurately be thought of as a tripartite synapse consisting of a presynaptic neuron, postsynaptic neuron, and associated astrocyte. It is also important to note that glutamate absorbed by the synaptic astrocyte is recycled back to the presynaptic neuron. This is accomplished by converting it to glutamine before releasing it into the extracellular space. The presynaptic neuron is able to take up the glutamine, and once it is back inside the neuron, the glutamine is converted back to glutamate.

TESTING FOR DEFECTS OF HIGHER CORTICAL FUNCTION

It is useful to test functions that can be localized to individual brain regions because abnormalities on these tests can help localize a neuroanatomic defect and thereby suggest a specific etiology. Screening for disorders of higher cortical function can be completed within the context of an office visit, whereas extensive examinations can take up to several hours.

Test Language Function. Judge the fluency of the patient's language. Note whether language is effortful or not, and if there are mistakenly spoken phonemes or mistakes in grammar. Evaluate comprehension by testing the patient's ability to follow simple or complex commands. Determine whether the patient can repeat, read, write, and name. Some people may express themselves well and understand what is said, yet still have a language problem. More sensitive approaches that could prove useful in this setting include counting how many animals the patient can name in 1 minute (a test of semantic fluency). In most language is a relatively left brain–mediated cognitive domain, so inability to perform any of these tasks indicates dysfunction of the perisylvian region of the dominant, usually left, cerebral hemisphere.

Test Memory. Memory is often thought of as long versus short term, but these are potentially misleading terms. What is referred to as short-term memory is really memory stored in "buffer" storage, particularly the posterolateral prefrontal cortices. Long-term memory is information stored in the brain "hard drive," which requires function of the medial temporal structures such as the hippocampus. These different problems can be distinguished by giving the patient information to encode, ensuring that information has entered the buffer memory, and then distracting the patient. Later on, determine if the information is still available to the patient. Good preservation and easy accessing of the information suggests intact memory "retention," whereas good preservation that requires cueing implies a deficit of "retrieval."

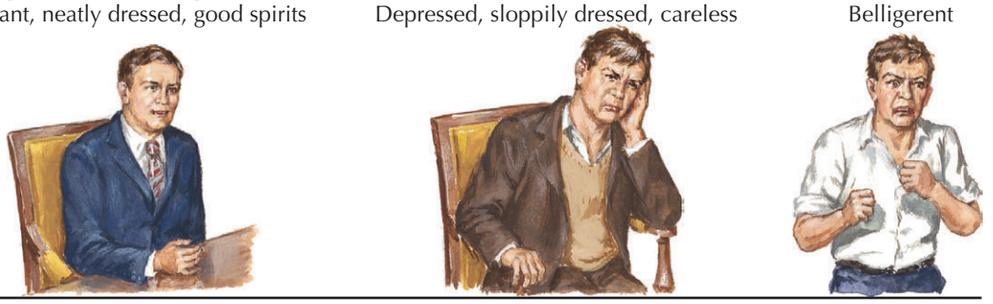
Test Visual-Spatial Functions. Have the patient draw a clock, house, daisy, or bicycle, and check for organization, angulation, and asymmetry. Also ask the patient to copy a simple design. If the drawings indicate abnormal visual-spatial orientation, the patient may have a lesion in the right cerebral hemisphere.

A. Appearance and interpersonal behavior

Pleasant, neatly dressed, good spirits

Depressed, sloppily dressed, careless

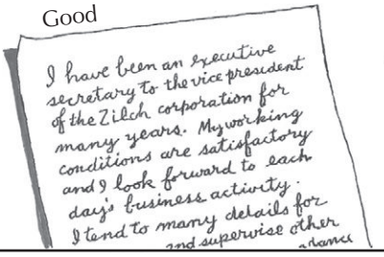
Belligerent



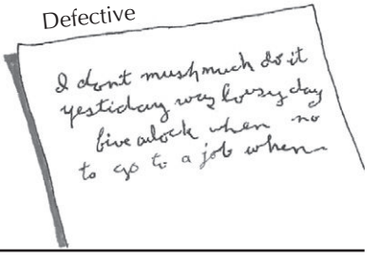
B. Language

Doctor: "Write me a brief paragraph about your work."

Good

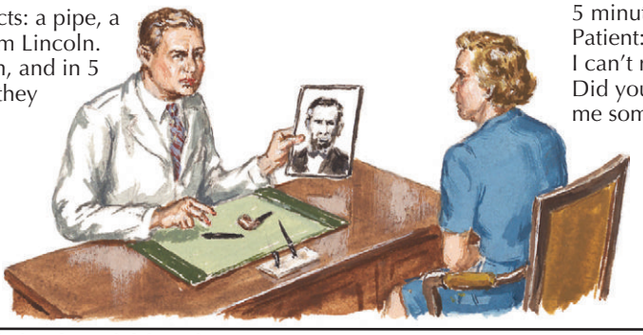


Defective



C. Memory

Doctor: "Here are three objects: a pipe, a pen, and a picture of Abraham Lincoln. I want you to remember them, and in 5 minutes, I will ask you what they were."



5 minutes later: Patient: "I'm sorry, I can't remember. Did you show me something?"

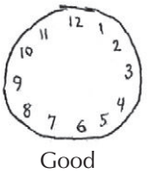
D. Constructional praxis and visual-spatial function

Doctor: "Draw me a simple picture of a house."

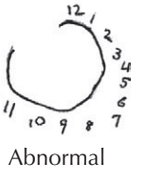
Good

Abnormal

"Draw a clock face for me."



Good



Abnormal

E. Reverse counting

Doctor: "Count backward from 20 by 3's." Patient: "17...15...16, ...17...18..."

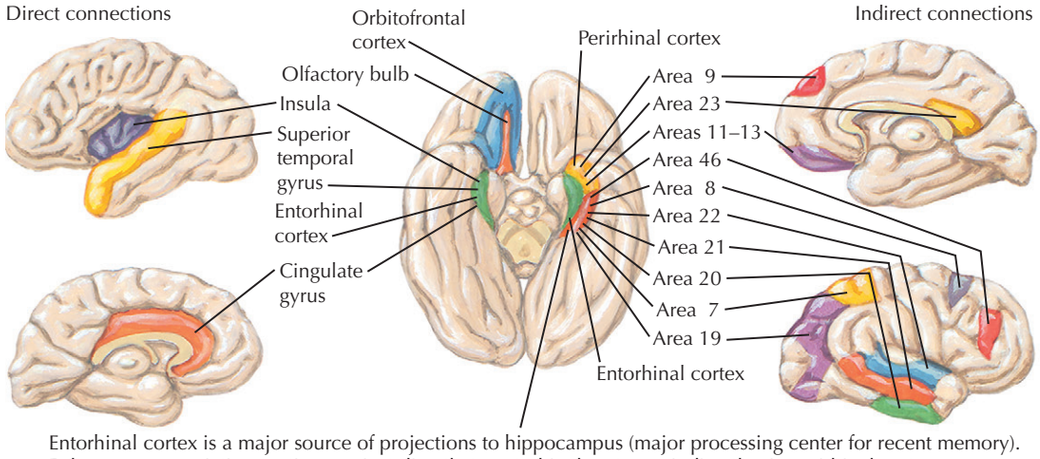
Doctor: "Spell the word *world* backward for me." Patient: "W..L..R..D."

F. Netter M.D.

Test Ability to Concentrate. Ask the patient to recite in reverse a series of numbers or to subtract 7s serially from 100. Also observe the patient's degree of alertness and orientation, manner of dress, and grooming, and note whether the patient is happy, sad, or indifferent and how he relates to others. Such objective observations are an important part of a complete neurologic examination.

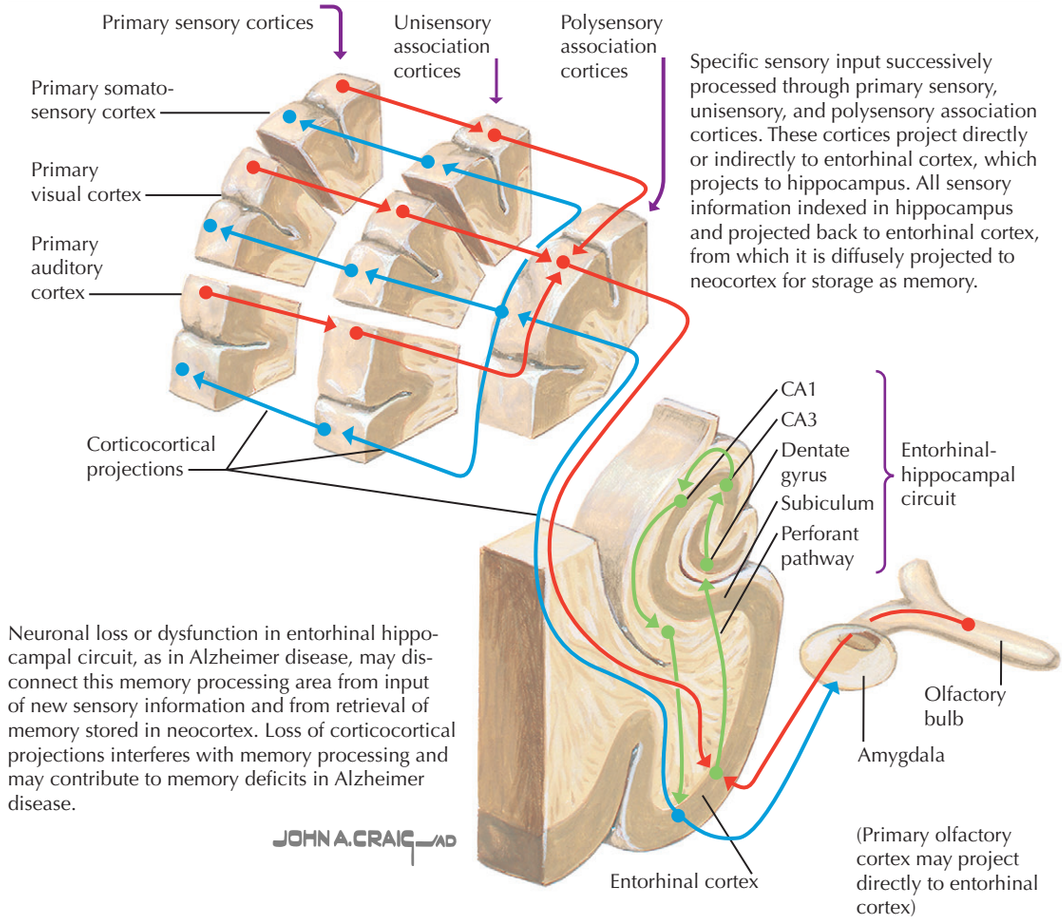
Test Executive Function. Determine whether the patient can shift from one set to another, perform actions in a sequence, think abstractly, and calculate. For example, asking the patient how much money is "two quarters, two dimes, and two nickels" screens several of these skills. Executive dysfunction suggests a lesion of the posterolateral prefrontal cortex, or a disconnection between this area and other brain regions.

Afferent and efferent cortical connections of entorhinal cortex



Entorhinal cortex is a major source of projections to hippocampus (major processing center for recent memory). Polysensory association cortices project directly to entorhinal cortex or indirectly via perirhinal cortex or parahippocampal gyrus. Association cortices receive reciprocal projections from entorhinal cortex. Area numbers refer to Brodmann classifications.

Possible processing circuit for recent memory



Neuronal loss or dysfunction in entorhinal hippocampal circuit, as in Alzheimer disease, may disconnect this memory processing area from input of new sensory information and from retrieval of memory stored in neocortex. Loss of corticocortical projections interferes with memory processing and may contribute to memory deficits in Alzheimer disease.

Memory Circuits

Long-term memory is a term that encapsulates the brain's ability to store information. It is subdivided into two main types: explicit memory (also known as declarative memory) and implicit memory (also known as nondeclarative memory). Explicit memory refers to the acquisition of information about objects, stimuli, and information that is consciously noted and recallable. The mesial temporal lobe, which includes the *hippocampal formation* (CA1, CA3, and dentate gyrus) and *entorhinal cortex*, is the region responsible for this process. While the hippocampal formation stores memories, the *entorhinal cortex* mediates learning and memory via its interaction with the hippocampus and neocortex. For instance, neocortical information from a visual stimulus is translated via the *entorhinal cortex* to higher-order complex memory representations such that an emotion can trigger a visual memory. Layer II of the *entorhinal cortex* is the first region affected in Alzheimer disease (AD). The memory circuit that integrates the mesial temporal lobe and hippocampal formation includes several pathways: the *perforant pathway* (input to the hippocampus from the entorhinal cortex), *Mossy fiber pathway* (dentate gyrus to CA3 region), *Schaffer collateral/associational commissural pathway* (from CA3 to CA1 region), and *CA1-subiculum-entorhinal cortex pathway* (the principal output of the hippocampus).

There are two main types of explicit memory: episodic and semantic memory. Episodic memory is likened to autobiographic memory, as an episode of one's life is recalled (remembering a certain vacation to the beach). Semantic memory refers to memory about facts, and general knowledge that is unrelated to a specific experience (for instance, I know that a zebra has stripes). Not surprisingly, CA1 and the subiculum undergo selective neuronal degeneration in AD. The loss of connections between the hippocampal formation and entorhinal cortical neurons, which project to the hippocampus via the perforant pathway, account for the clinical presentation of explicit memory problems in AD patients. Implicit memory, on the other hand, is "unconscious," can sometimes be linked to an emotion, and can be procedural (for instance, remembering how to drive a car).

The study of one particular patient, H.M., provided significant insights into the formation of memory and the role of the mesial temporal structures in memory. H. M. underwent a bilateral resection of the medial temporal regions as part of an experimental treatment for medically refractory seizures. Subsequently, he developed profound loss of personal memories but had preserved language, attention, procedural memory, and general intellectual ability.

Amnesia

The term "amnesia" is used generally to describe impairment or loss of memory. It is often subclassified as being either retrograde or anterograde. With retrograde amnesia, memories that had previously been stored are no longer available. With anterograde amnesia, information occurring in real time does not enter long-term storage. Memory is a complex process comprising three different functions: (1) registration of information, (2) storage by reinforcement, and (3) retrieval.

Registration of Information. If information is not registered initially, it will not be remembered later. Failure to register is the explanation for absentmindedness, probably the most common abnormality of memory.

Storage by Reinforcement. Repetition of information to be remembered or relating such information to other factors or events enhances later recall.

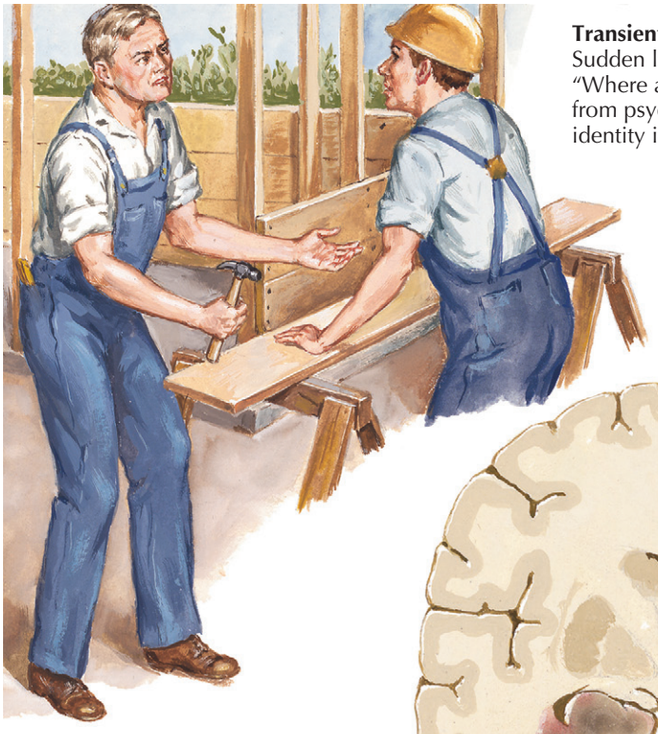
Retrieval. To recall the information, a person must search the "memory bank," where it has been stored. Inability to recall information on request could result from a defect in any of the three aspects of memory function.

The key anatomic regions for registration and storage of memory traces are in an area often referred to as the Papez circuit, in which the fornix connects the hippocampus to the mammillary bodies, which, in turn, are connected to the anterior nuclei of the thalamus by the mammillothalamic tract. The anterior thalamic nuclei project to the cingulate gyri, which then connect with the hippocampus, completing the circuit. The memory system is primarily cholinergic. The left medial temporal lobe is most concerned with verbal memory and the right temporal lobe with visual recall.

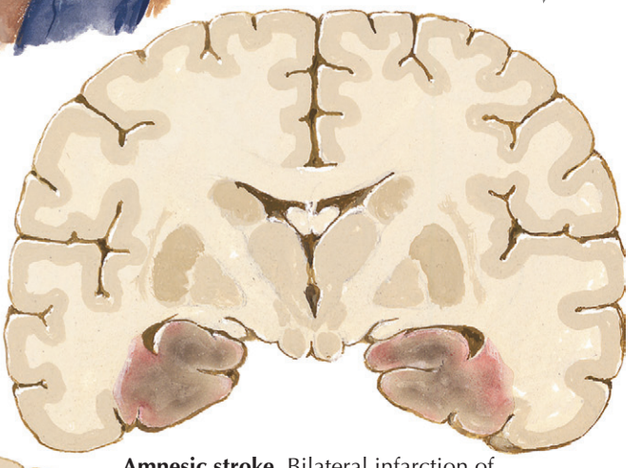
The prototype of amnestic disorders is *Korsakoff syndrome*, seen in chronic alcoholism and other states of vitamin B deficiency. This syndrome affects the medial thalamus and mammillary bodies and is characterized by an inability to record new memories and recall events of the recent past. Some patients confabulate to fill in gaps in their memory. Any bilateral destructive lesion of the thalami and medial temporal lobes can cause a similar syndrome. Such lesions include gliomas that spread bilaterally over the fornix and splenium of the corpus callosum; bilateral posterior cerebral artery infarctions, often caused by embolism of the top of the basilar artery; and herpes simplex encephalitis, a viral disease with predilection for temporal lobe damage. Lesions within the Papez circuit affect the "memory bank." The patient is unable to recall items despite being given cues or being asked to select the correct item to be recalled from a group of alternatives. Unilateral lesions of the left medial temporal lobe and thalamus can produce amnesia that may last up to 6 months.

Head trauma often disrupts functions of memory. The severity of a head injury or concussion is often classified by the degree of *retrograde amnesia* that results; the longer the period of retrograde amnesia, the worse the injury. Head injury victims may also experience a period of anterograde amnesia.

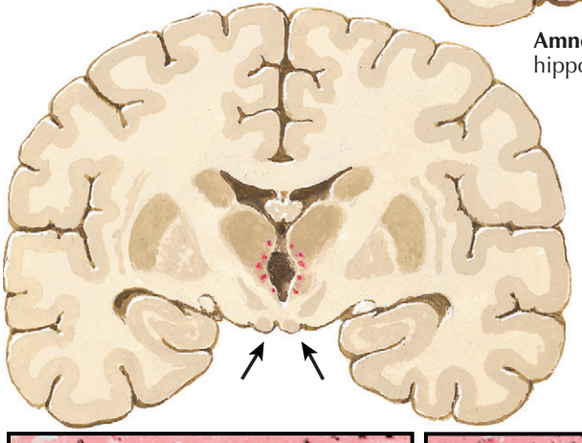
Transient Global Amnesia. Total global amnesia is a particularly common memory disorder. In this benign syndrome, the patient seems bewildered and asks repetitive questions about the environment and activities, and, despite appropriate replies, asks the same questions moments later. The patient cannot form new memories and is often unable to recall events of the past days, months, and even years. Speech, reading, writing, calculations, drawing, and copying are normal, as are the results of the rest of the neurologic examination. Behavior and memory usually return to normal within 24 hours, but the patient is never able to recall events during the period of amnesia. Such attacks may recur, but the cause of the syndrome remains obscure.



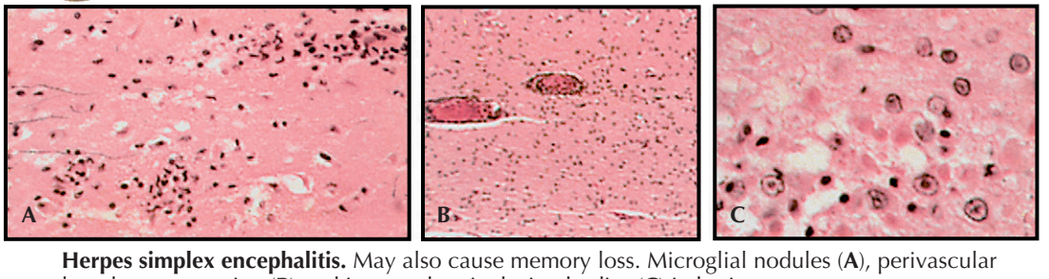
Transient global amnesia. Sudden loss of memory; e.g., workman asks "Where am I? What am I doing?" Differentiate from psychogenic amnesia, in which personal identity is often confused.



Amnesic stroke. Bilateral infarction of hippocampus and medial temporal lobes

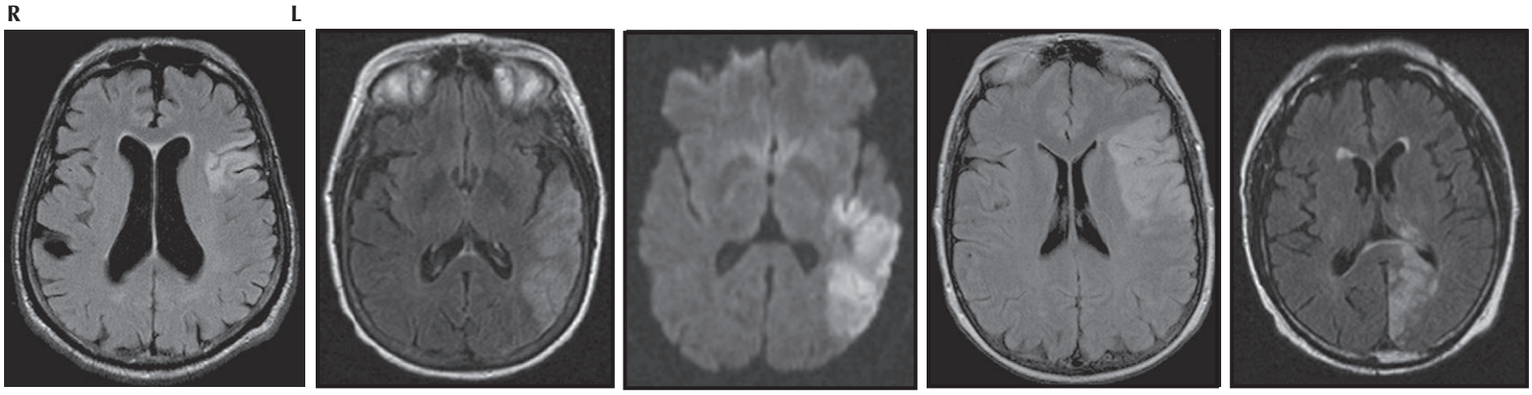


Korsakoff syndrome. Small hemorrhages around enlarged 3rd ventricle and shrunken mamillary bodies *(arrows)*. Clinical features include memory loss, confabulation, confusion, peripheral neuritis, nystagmus and opthalmoplegia.



Herpes simplex encephalitis. May also cause memory loss. Microglial nodules (**A**), perivascular lymphocyte cupping (**B**) and intranuclear inclusion bodies (**C**) in brain.

Clinical syndromes related to site of region



Broca aphasia MRI-FLAIR | **Wernicke aphasia** | **Angular gyrus-posterior temporal, inferior parietal** | **Global aphasia-T2 FLAIR** | **Alexia without agraphia**

	Broca aphasia	Wernicke aphasia	Angular gyrus	Global aphasia	Alexia without agraphia
Pronunciation, speech rhythm	Dysarthria, stuttering, effortful	Normal, fluent, loquacious	Normal	Very abnormal	Normal
Speech content	Missed syllables, agrammatical, telegraphic	Use of wrong or nonexistent words	Often normal	Very abnormal	Normal
Repetition of speech	Abnormal but better than spontaneous	Abnormal	Normal	Very abnormal	Normal
Comprehension of spoken language	Normal	Very abnormal	Normal	Very abnormal	Normal
Comprehension of written language	Not as good as for spoken language	Abnormal but better than for spoken	Very abnormal	Very abnormal	Normal
Writing	Clumsy, agrammatical, misspelling	Penmanship OK but misspelling and inaccuracies	Very abnormal, spelling errors	Very abnormal	Normal
Naming	Better than spontaneous speech	Wrong names	Often abnormal	Very abnormal	Normal
Other	Hemiplegia, apraxia	Sometimes hemianopsia and apraxia	Slight hemiparesis, trouble calculating, finger agnosia, hemianopsia	Hemiplegia	Abnormal reading

Dominant Hemisphere Language Dysfunction

Aphasia, a disorder of language usage and comprehension, should be distinguished from *dysarthria*, impaired articulation, and *mutism*, the absence of speech. Usually, the presence of aphasia accurately localizes dysfunction to the cerebral hemisphere concerned with speech.

To classify an aphasia, it is necessary to determine whether the patient can (1) speak fluently, with normal articulation and rhythm and without paraphasic, syntactic or grammatical errors or use of circumlocutory phrases; (2) accurately repeat spoken sounds, words, and phrases; (3) understand spoken language, as evidenced by accurate responses to spoken questions and ability to follow spoken commands (failure to follow a command may also be due to apraxia or paralysis and does not necessarily reflect poor comprehension); (4) consistently name common objects, presented visually, verbally, or tactilely; (5) read aloud accurately and with comprehension; (6) name words spelled aloud; and (7) write legibly and grammatically.

In *transcortical aphasia*, repetition of spoken language is preserved. *Transcortical motor aphasia* is a subtype in which there is a primary inability to produce spontaneous speech, but the ability to understand spoken language is retained. *Transcortical sensory aphasia* is a subtype that is characterized by a failure to understand spoken language; a transcortical sensory aphasia usually indicates a lesion deep in the basal ganglia or in the paramedian frontal lobe. Patients with Gerstmann syndrome have difficulty with naming of fingers, left-right orientation, calculation, constructional drawing, and writing. The lesion causing the disorder is usually located in the angular gyrus of the dominant hemisphere. The angular gyrus has been implicated in different aphasia forms. This can be due either to its actual role in language or by creating, when damaged, a disconnection syndrome. Disconnection syndromes in general can present in fascinating, well-defined ways. One of the most famous language disconnection syndrome is the alexia without agraphia syndrome, in which patients can write but not read. This is most commonly seen as a consequence of left occipital strokes that damage the visual cortex on the left and also perturb the transfer of visual information from the right occipital visual cortex to the usually language-dominant left hemisphere.

NONDOMINANT HEMISPHERE HIGHER CORTICAL DYSFUNCTION

When it comes to stroke-induced lateralized deficits, patients with left-sided hemiplegia caused by damage to the nondominant right cerebral hemisphere frequently do not recover as well as patients with similar left hemisphere lesions, despite the fact that they are not aphasic. Return to the work place and previous home and family participation occur less frequently after a stroke causing left-sided hemiplegia. Although disturbances of higher cortical function and behavior in patients with right hemisphere disease are more subtle, they are equally or more functionally disabling than the more obvious aphasia caused by left hemisphere disease. Deficits in right hemisphere disease include the following.

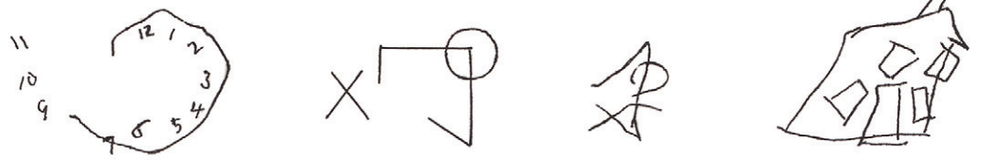
Constructional Dyspraxia. The right cerebral hemisphere, especially its inferior parietal lobe, is specialized for visual-spatial functions. Parietal lesions compromise the patient's ability to draw and copy figures and diagrams, reproduce block designs or figures made with sticks or tongue blades, read a map, and follow or give directions to a given destination. Spontaneous drawings are complex and contain all appropriate details, but proportions, angles, and picture relationships are inaccurate, and the left half of the drawing often is omitted or minimized. Copying a figure does not significantly improve the performance.

Unilateral Spatial Neglect. Patients with right hemisphere lesions, especially those involving the frontal or parietal lobe or thalamus, often neglect objects, people, or sounds on their left side. They may also fail to adequately dress the left side of their body. When asked to read a headline or paragraph or examine a picture, they do not appreciate words or objects on the left. When instructed to bisect all lines on a piece of paper, patients with right hemisphere damage often divide the right side of the line and fail to cross lines on the left side of the page. Similar spatial neglect of the right side after left hemisphere damage is unusual.

Anosognosia and Blunted Emotional Responses. Patients who have right hemisphere damage often fail to recognize or acknowledge an obvious left-sided hemiplegia. Not only do they verbally deny weakness or fail to localize it to one side, but they may fall when attempting to walk. Furthermore, even when they admit the deficit, these patients seem not to be appropriately concerned or distressed, and generally are not discouraged about their uncertain future.

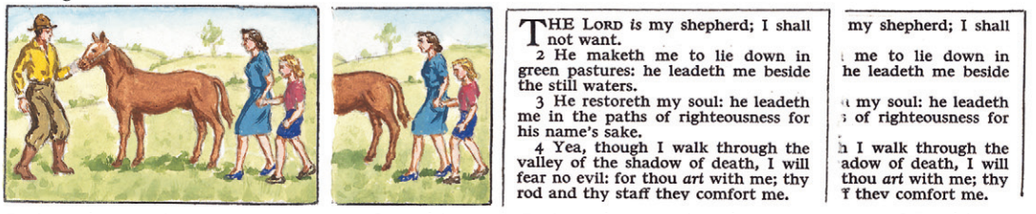
Testing of patients with right hemisphere lesions also shows that they have difficulty in appreciating the tone, mood, and emotional content of facial expressions or spoken language and miss nonlanguage cues. They also may be unable to invest their own voice or face with a given mood. Apathy and blunted recognition and transmission of emotional tone may hamper rehabilitation and resumption of an active goal-oriented life.

A. Constructional dyspraxia and spatial disorientation



Clock face drawn by patient | Patient asked to copy → Draws this | House drawn by patient

B. Neglect of left-sided stimuli



Patient shown picture → Sees this | Patient shown printed page → Sees this

C. Anosognosia (unawareness of deficit)

Patient with obvious left hemiplegia. Asked, "What is wrong with you?" Answers, "Nothing is wrong, I am perfectly all right"

Not recognizing deficit, patient insists on trying to walk and falls, but still fails to recognize deficit

D. Motor impersistence

Patient asked to raise arms over head and to keep them up

Raises arms but then drops them quickly

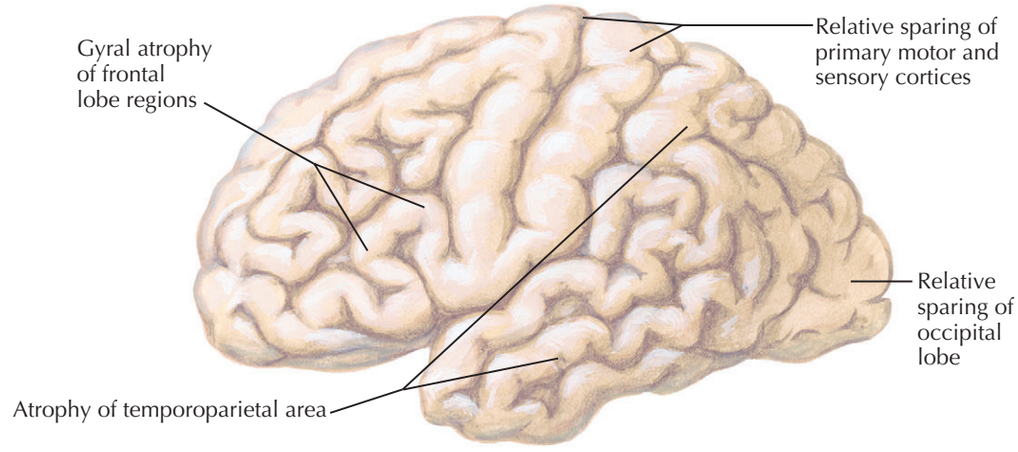
E. Abnormal recognition of nonlanguage cues (facial expression, voice tone, mood)

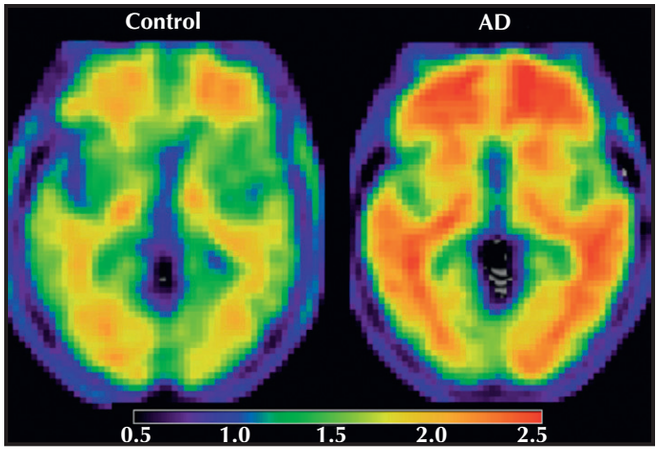
Patient shown picture. Asked, "Which is the happy face?"

Patient answers, "I don't know, they are all the same"

Impersistence. Some patients with nondominant cerebral hemisphere damage are unable to persevere with a given task. A command that is quickly followed is just as quickly forgotten. When asked to keep their eyes closed, for example, or to cross off all A's on a page, they begin the task correctly but soon abandon it. Questions are often answered before the query is complete. Impulsive behavior with little forethought and poor perseverance is also functionally disabling.

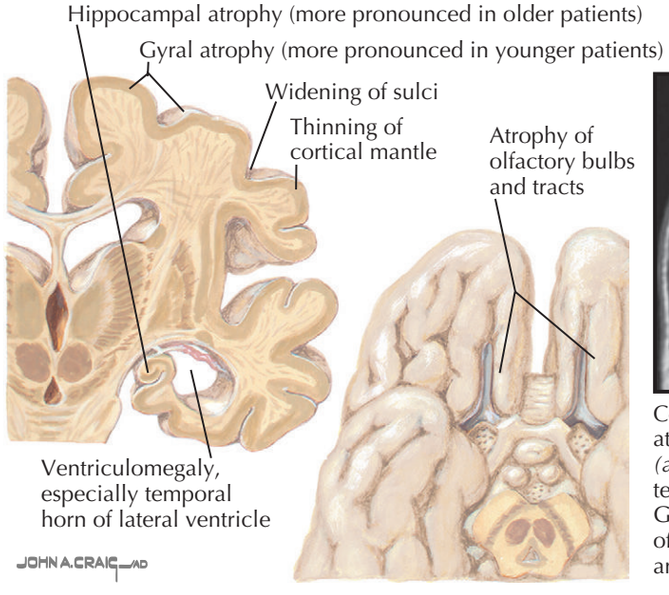
Other Dysfunctions. Damage to the right cerebral hemisphere can also affect either the ability to perceive rhythm, pitch, or tonality, or to read, write, or play music. Some patients have difficulty in recognizing familiar faces (prosopagnosia) and may be unable to visualize from memory the appearance of an object or a person. Loss of topographic recall of places and errors of localization or distance concerning buildings or geographic landmarks also occur.

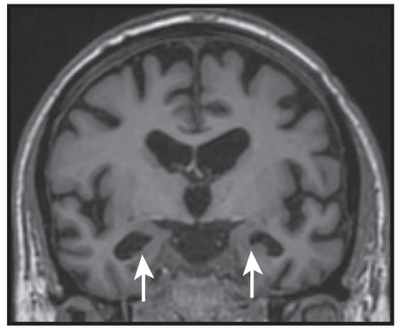




PET imaging with florbetapir reveals the presence of amyloid plaque deposits in the brain of an individual with a clinical diagnosis of Alzheimer disease (shades of red) compared to a cognitively normal older adult with little to no evidence of amyloid (lighter red and yellow).

Alzheimer Disease: Pathology





Coronal T1-weighted MRI scan showing atrophy of the hippocampus bilaterally *(arrows),* with enlagement of the temporal horns of the lateral ventricles. Global atrophy is evident with widening of the sulci and enlargement of subarachnoid spaces.

Alzheimer disease (AD) is the most common neurodegenerative disorder and affects 10% of people older than age 65 years and nearly 50% of those 85 years and older. The brain affected by AD has gross changes of brain atrophy accompanied by microscopic changes of amyloid plaques and neurofibrillary tangles.

The gross pathology of AD appears as enlargement of the ventricles and widening of the sylvian fissure secondary to cortical atrophy. Many convexal gyri are shrunken, and the sulci between these gyri are widened. The cerebral cortex may appear thin, and the basal ganglia are relatively small. The hippocampal region of the medial temporal lobe is affected early in the disease process and prominent atrophy of this region is usually observed. This region is responsible for storing new information, and its degeneration is associated with the prominent short-term memory impairment that is characteristic of AD.

Microscopic examination of the affected regions reveals plaques and neurofibrillary tangles, the pathologic hallmarks of AD. Plaques are primarily composed of extracellular accumulation of insoluble amyloid protein. The amyloid hypothesis speculates that the accumulation of amyloid is the critical trigger leading to the pathologic changes in the brain of AD patients and results in synapse loss, inflammation, neurofibrillary changes, and ultimately neuron death. Amyloid appears to accumulate years before the clinical symptoms and is associated with parallel worsening of brain atrophy. Neuroimaging techniques using positron emission tomography (PET) allow the presence and burden of amyloid deposits in the brain to be detected using radioligand labels. The molecular imaging of amyloid deposits has promise as a potential biomarker for AD and possibly may allow the identification of individuals who are still in the presymptomatic stages of the illness.

Neurofibrillary tangles are intracellular inclusions composed of aggregated tau proteins that normally function to stabilize axonal microtubules. Tau protein found in neurofibrillary tangles is in an abnormal state of hyperphosphorylation, which occurs in conjunction with its dissociation from microtubules and clumping as paired helical filaments. Neurofibrillary tangles are a ubiquitous accompaniment of aging, and accumulate with age in a predictable pattern. Individuals with AD tend to have more tangles, plaques, and neuron loss than individuals without dementia.

Alzheimer Disease: Distribution of Pathology

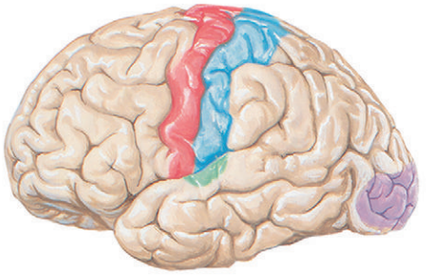
The pathologic diagnosis of Alzheimer disease is determined at autopsy based on the presence of its cardinal histopathologic features, neurofibrillary tangles, and amyloid plaques.

Amyloid plaques are abundant in the cerebral cortex of individuals with Alzheimer disease, particularly in the parietal and frontal regions. Amyloid deposition is also commonly observed in leptomeningeal arteries as amyloid angiopathy. Autopsy studies, and more recently amyloid imaging techniques, have revealed that amyloid plaques begin to accumulate in the brain years, perhaps decades, before the emergence of clinically recognizable symptoms and are found in cortical regions that are highly metabolically active, such as the default-mode network that is active when an individual is at rest and not engaged in a specific cognitive task. Regions such as the precuneus and posterior cingulate, which have strong connections with the hippocampus, are among the areas affected earliest.

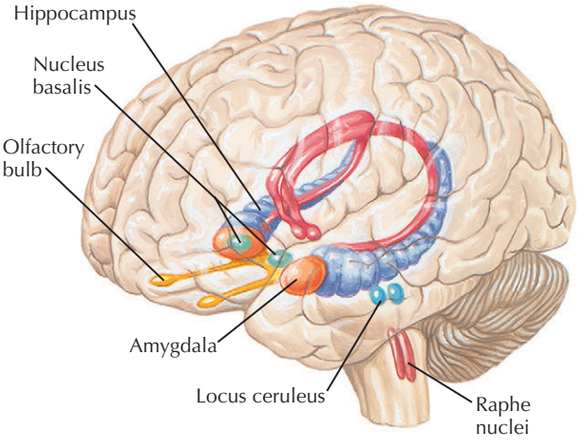
Neurofibrillary tangles (NFTs) accumulate in a predictable fashion as an individual ages and is a ubiquitous accompaniment of aging. Accumulation of neurofibrillary tangles begins in the medial temporal lobe (amygdala and entorhinal cortex) gradually extending into the limbic system (hippocampus and cingulate cortices) and later throughout the entire isocortex. This stereotypic pattern of accumulation is used in pathologic staging of the disease (Braak staging). The pathologic staging of AD is based on the hierarchic pattern of the appearance of neurofibrillary tangles in various regions. There are two "presymptomatic" transentorhinal stages, where NFTs remain in the perirhinal cortex. In stage III, the NFTs involve the limbic regions, and layer II of the entorhinal cortex. Stage IV AD is marked by more extensive NFTs in the limbic regions, entorhinal layer IV, and hippocampal CA1 region. These latter stages (III and IV) correspond clinically to mild cognitive impairment (MCI), not dementia. MCI represents an intermediate stage between normal aging and dementia. Typically, patients note subjective memory problems, the need to make lists, and short-term memory "slip ups," but these changes are not severe enough to interfere with day-to-day activities. As the pathologic stage of AD progresses, the NFTs accumulate in the inferotemporal, retrosplenial, and, eventually, association regions of the cortex, while the primary motor cortex is spared. In these stages, the clinical hallmarks of AD are present and include impairments in memory, judgment, orientation, language, and decision-making.

Of interest, some tangle pathology is present in all older adults, although individuals with AD have a greater burden of neurofibrillary tangles and a much more widespread distribution throughout the isocortex. The CA1 region of the hippocampus and the entorhinal cortex are particularly susceptible to the accumulation of both plaques and tangles in the early stages of the disease. These regions are important for mediating the formation of memories, and their degeneration accounts for the prominent impairments in short-term memory observed in AD patients.

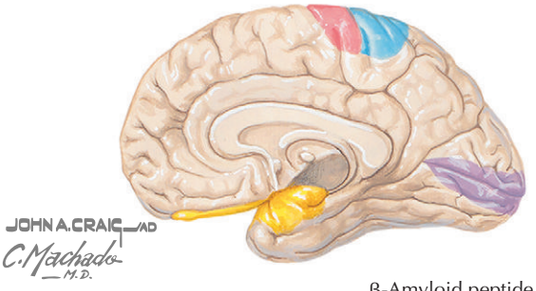
Biochemical data from patients with AD reveal an early decrease in *choline acetyltransferase* and *acetylcholinesterase*, indicating dysfunction in the neural pathways that use acetylcholine as a neurotransmitter. The number of neurons is reduced in the basal nucleus of Meynert, which has widespread cholinergic neuron innervations through most of the cerebral cortex. Selective degeneration of the basal forebrain cholinergic neurons results in a cholinergic deficit that contributes to AD symptoms. These findings led to the development of the first effective treatments in ameliorating the symptoms of AD, acetylcholinesterase inhibitors, which act by increasing acetylcholine levels in the brain.

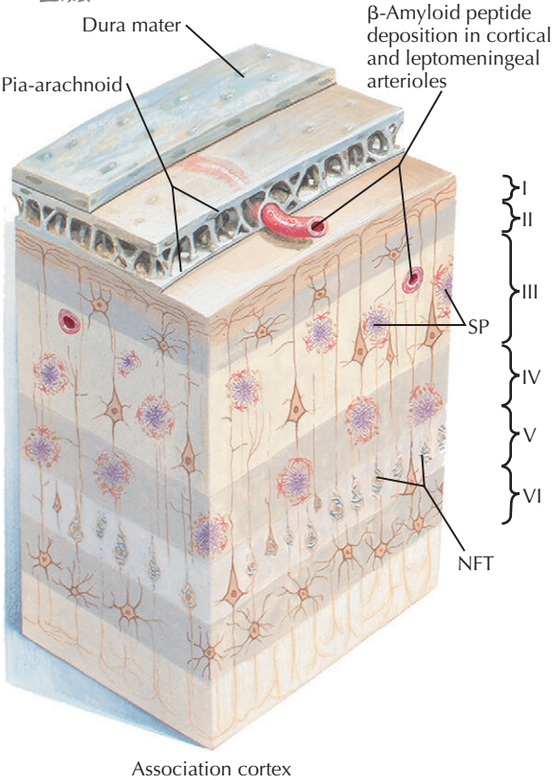


In neocortex, primary involvement of association areas (especially temporoparietal and frontal) with relative sparing of primary sensory cortices (except olfactory) and motor cortices



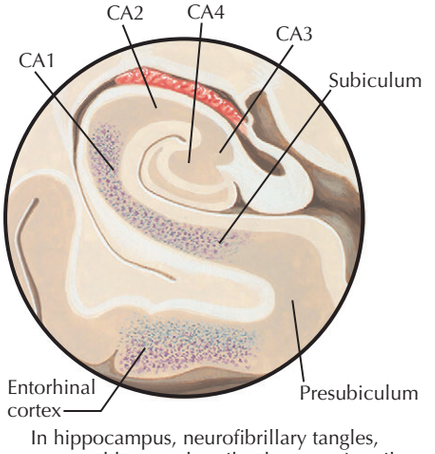
Pathologic involvement of limbic system and subcortical nuclei projecting to cortex



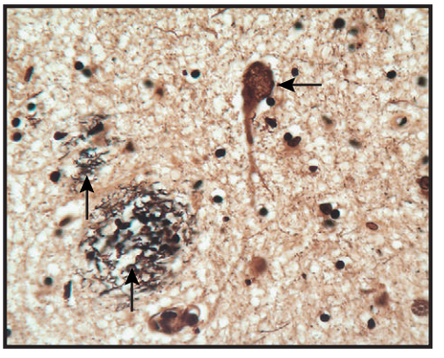


Association cortex

In association cortex, neurofibrillary tangles (NFTs) and synaptic and neuronal loss predominate in layer V. Senile plaques (SPs) occur in more superficial layers



In hippocampus, neurofibrillary tangles, neuronal loss, and senile plaques primarily located in layer CA1, subiculum, and entorhinal cortex



Characteristic pathologic findings in the brain of a patient with Alzheimer disease: Neuritic plaque and neurofibrillary tangle. Neurtitic plaques *(bottom arrows)* are extracellular deposits of amyloid in the brain. Neurofibrillary tangles *(top arrow)* are aggregates of hyperphosphorylated tau protein.

Alzheimer Disease: Clinical Manifestations, Progressive Phases

The earliest stages of Alzheimer disease are generally marked by cognitive changes in multiple domains of cognition, including memory, executive function, language, and visuospatial function. Of importance, these cognitive changes are often well-compensated, and individuals may still be independent in many activities in the community, and their symptoms may not be readily apparent in casual conversation. Observations from an attentive family member, relative, or friend describing cognitive changes interfering even mildly with the subject's usual function is a sensitive indicator of the earliest stages of AD.

1. *Memory loss:* The clinical hallmark of AD is memory loss. Patients may be forgetful of details of recent conversations and events. Family members frequently report that the patient asks repetitious questions or repeats stories, even in the same conversation. Patients have difficulty remembering appointments, taking their medications, and tend to lose things more than before.
2. *Executive dysfunction:* Executive function is loosely defined as an ability to organize information and pursue goals. Subtle problems in executive function are often observed in the early stages as problems in planning and organizing. This may manifest as difficulty in managing a checkbook and the household finances or greater difficulty in following a recipe. Patients have more difficulty making decisions and solving problems and are now more likely to enlist the help of others.
3. *Decreased language facility:* Communication may be less precise than normal and contain more "filler" words and circumlocutory elements. Patients may have difficulty recalling names of people and places although they generally retain the ability to understand and repeat spoken language and do not make paraphasic errors, in contrast to patients with aphasia due to stroke.
4. *Visuospatial dysfunction:* Patients may have navigational problems while driving and in the early stages often self-restrict their driving to the most familiar areas. Ultimately, spatial disorientation interferes with the ability to navigate even in the most familiar areas, such as the patient's neighborhood.

As the disease relentlessly progresses into the moderate stages, greater cognitive and functional decline reflects more widespread involvement of neocortical regions. Increasing difficulties with instrumental activities of daily living are prominent, such as cooking, cleaning, and dressing. Apraxia, a disorder of skilled movement despite intact strength, sensation, and coordination, develops as typical AD progresses but is not a prominent early feature. This may manifest as greater difficulty in using tools (such as silverware, unlocking a door with a key) and dressing in the proper sequence. Behavioral changes may be prominent. Patients may become increasingly apathetic and less interested in others and in their environment. They also lose interest in reading, television, and social gatherings. Less attention is paid to grooming and attire, and even formerly fastidious people allow their house, room, and belongings to become untidy and disorganized. Occasionally, agitated or belligerent behavior occurs.

In the *advanced stage* of AD, patients cannot perform the simple activities of daily living. They remain in bed unless they are helped up and require aid for dressing, eating, and toilet functions. They cannot venture out alone and become lost even in their home. They confuse night and day, and incontinence develops.

The course of the disease is usually from 7 to 12 years. In the terminal phase, patients are bedridden, mute, and stiff, and patients ultimately succumb to medical complications such as pneumonia, urosepsis or decubitus ulcers.

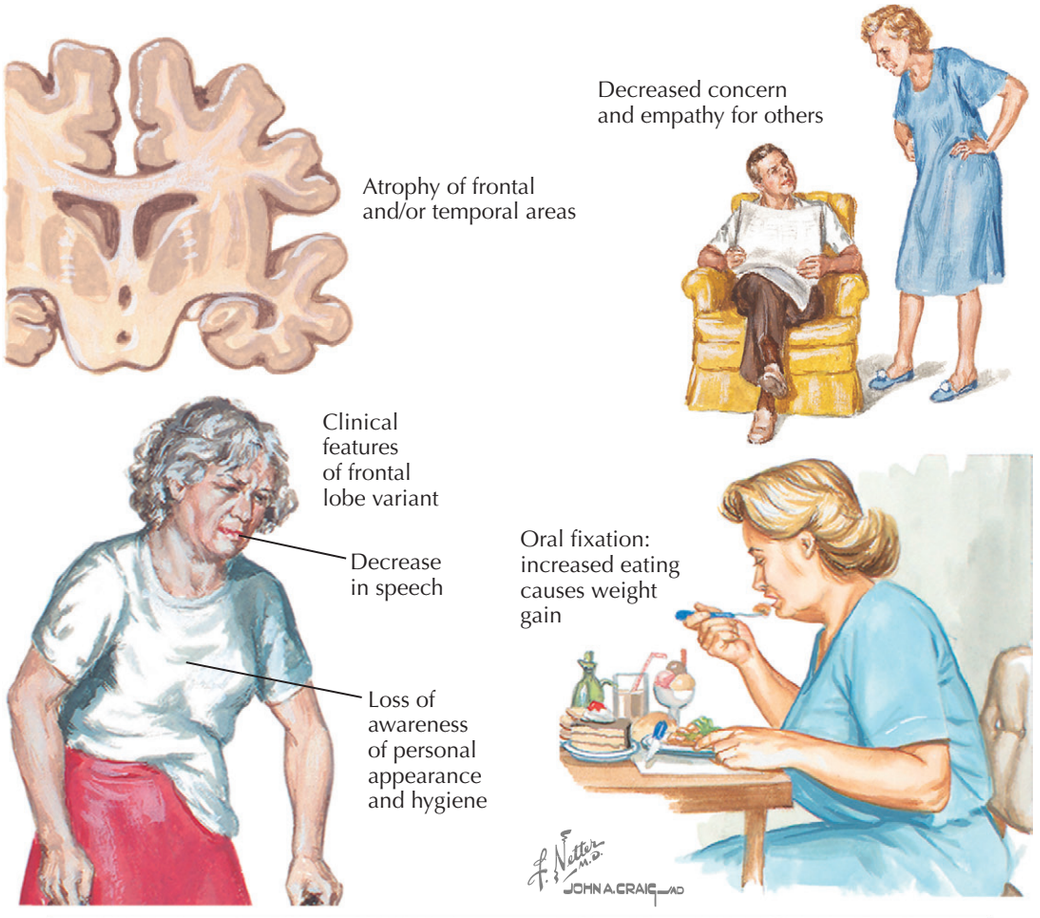
Memory loss
"Where is my checkbook?"

Spatial disorientation
"Could you direct me to my office? I have the address written down here somewhere but I can't seem to find it."

Circumlocution
Asks husband, "John dear, please call that woman who fixes my hair."

More advanced phase
Sloppily dressed, slow, apathetic, confused, disoriented, stooped posture

Terminal phase
Bedridden, stiff, unresponsive, nearly mute, incontinent



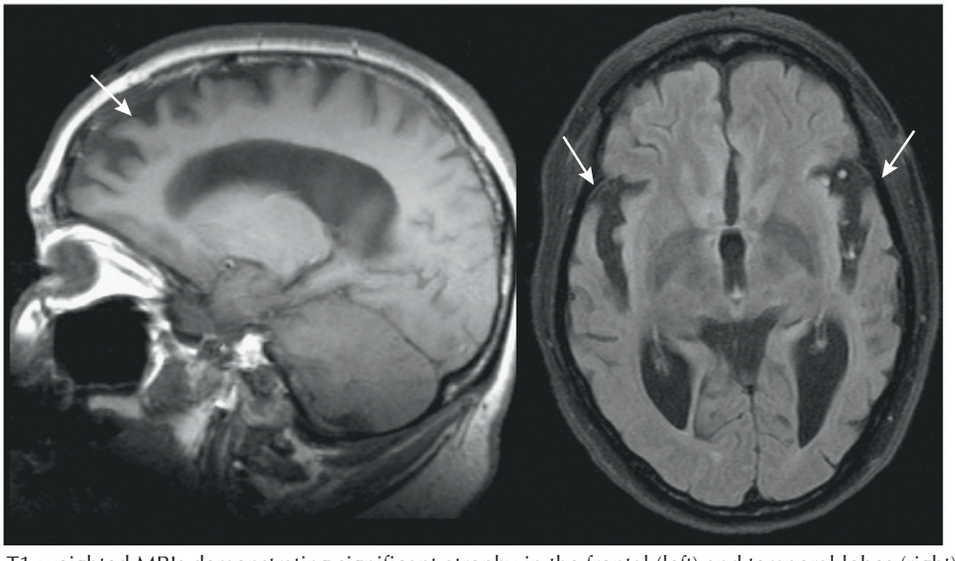
Frontotemporal Dementia

Frontotemporal dementia (FTD) is a heterogeneous spectrum of disorders marked by degeneration in the frontal and anterior temporal lobes, resulting in various symptoms of disturbed personality, behavior, and language. FTD is the third most common form of neurodegenerative dementia, ranking after Alzheimer disease and dementia with Lewy bodies, accounting for perhaps 5% of all dementia cases. FTD generally presents at a younger age than Alzheimer disease and has a mean age at onset of 58 years.

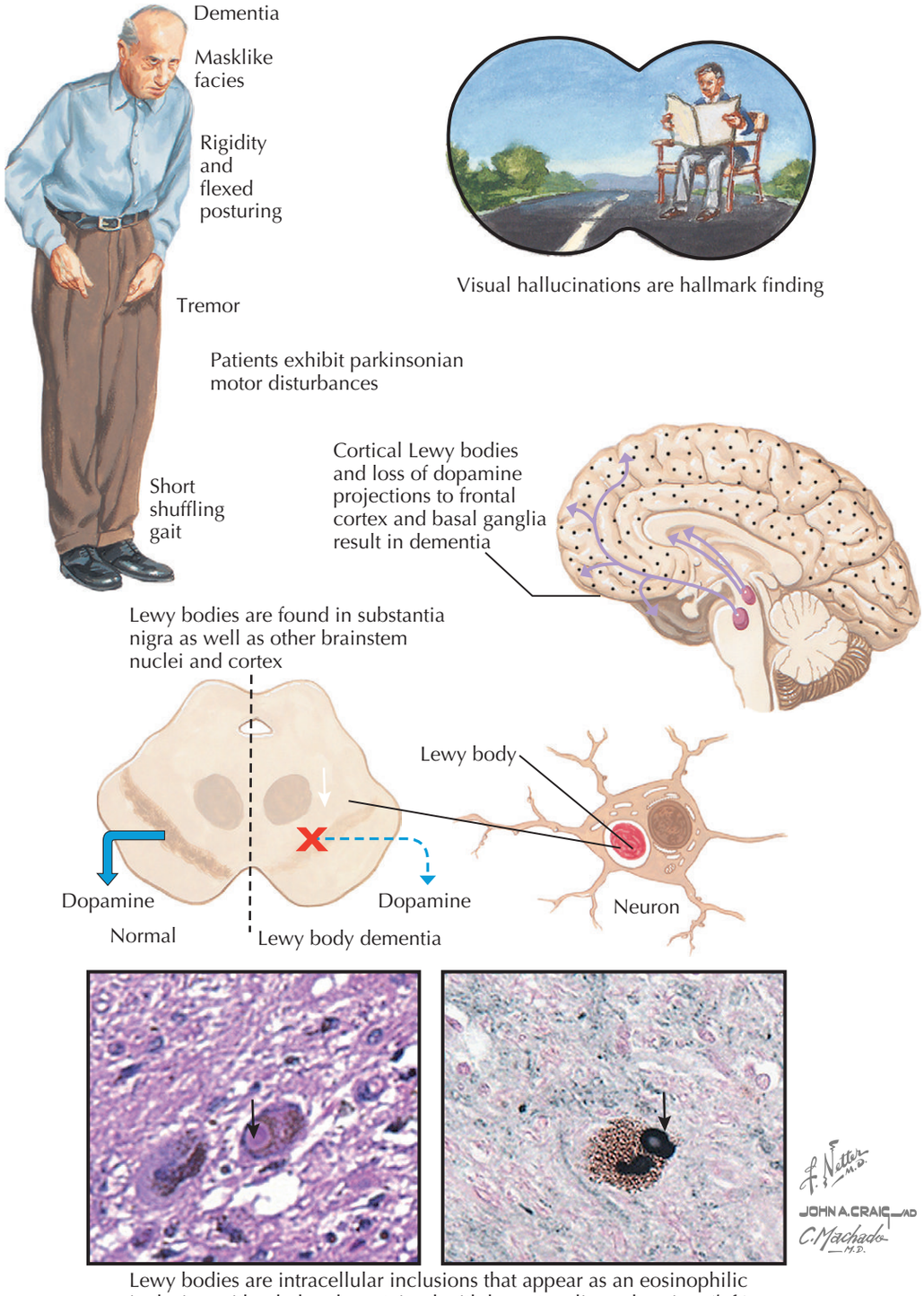
Behavioral and personality changes are prominent early features in individuals with FTD reflecting pathologic involvement of the frontal lobes, most commonly the right hemisphere. Symptoms include disinhibition, impulsivity, impaired judgment, and disturbed social skills. An individual with FTD may have inappropriate behavior, such as swearing, off-color jokes, and loss of social tact. Dietary habits may change, and an individual may only eat certain foods, such as sweets. Prominent personality changes are disturbing to the patient's family, yet the patients themselves are typically unconcerned and lack insight and empathy regarding how these changes affect their families. Some individuals develop repetitious or compulsive behavior. Severe amnesia and visuospatial impairment are typically not present. In fact, many FTD patients are oriented and able to keep track of day-to-day affairs.

The language presentation of FTD varies, depending on the distribution of the pathology and includes disturbances in speech fluency and comprehension. Broca's area is located in the inferior and middle gyri of the left frontal lobe and is involved in generating articulation sequences that transform thoughts into statements. Neurodegeneration affecting Broca's area results in progressive nonfluent aphasia that is characterized by loss of fluent speech and prominent anomia. The speech may have a halting quality due to frequent pauses for word-finding. Circumlocutions are common, because the patient has difficulty retrieving the concise words and substitutes other words or statements for the desired word. Wernicke's area in the left temporoparietal junction mediates the sensory associations encoding word meaning. Neurodegeneration affecting this region results in semantic dementia, marked by early impairment in semantics (word meaning), resulting in empty, fluent speech and a loss of speech comprehension. Speech may be effortless and without hesitancies, but little meaningful information is conveyed. These patients have prominent comprehension problems (i.e., following commands) despite their fluent and effortless speech. Because the language network prominently involved (Wernicke's area) abuts the visual association networks, semantic dementia may also be associated with complex visuoperceptual dysfunction, such as prosopagnosia and visual object recognition.

Neuroimaging should be obtained to rule out the presence of structural lesions (e.g., stroke, tumor) and may reveal the presence of disproportionate atrophy in the frontal and temporal lobes. Additionally, functional imaging in the form of positron emission tomography (PET) may reveal altered metabolic activity in the frontal and temporal lobes.



T1-weighted MRIs demonstrating significant atrophy in the frontal (left) and temporal lobes (right) in a patient with frontotemporal dementia



Lewy bodies are intracellular inclusions that appear as an eosinophilic inclusion with a halo when stained with hemotoxylin and eosion *(left)*. Newer immunostaining techniques using antibodies to alpha-synuclein densely label Lewy bodies *(right)*.

Dementia with Lewy Bodies

Dementia with Lewy bodies (DLB) is the second most common cause of dementia, accounting for 10% to 15% of dementia cases. The pathologic hallmark of DLB is the presence of Lewy bodies in neurons of the brainstem, primarily the substantia nigra, and throughout the cerebral cortex. Lewy bodies are primarily composed of abnormal aggregations of the synaptic protein alpha-synuclein. Interestingly, brain changes of Alzheimer disease (plaques and tangles) frequently co-occur with typical Lewy body pathology.

In patients with DLB, the cognitive and functional decline of dementia is accompanied by a combination of clinical features that include visual hallucinations, parkinsonism, and fluctuating cognitive impairment. Visual hallucinations may present early in the clinical course and tend to persist throughout the course. Typically, the visual hallucinations are vivid images of animate objects (e.g., children, animals) as opposed to nonspecific visual phenomena. Parkinsonism (rigidity, tremor, bradykinesia, gait abnormalities) develops in most DLB patients at some time in the course of the disease. Individuals with DLB typically present with recurrent episodes of confusion on a background of progressive deterioration. The fluctuations in cognitive function are manifest as shifting attention and levels of alertness that may vary over minutes, hours, or days.

Other features that are commonly observed in DLB patients include additional neuropsychiatric symptoms of delusions, apathy, and anxiety. Rapid eye movement (REM) sleep behavior disorders are frequently seen in DLB and other synucleinopathies such as Parkinson disease. REM sleep behavior disorders are manifested as vivid or frightening dreams associated with simple or complex motor behavior. Additionally, autonomic abnormalities are common in DLB and include orthostatic hypotension and carotid-sinus hypersensitivity. These abnormalities can result in "dizziness," presyncope, syncope, and falls as common aspects of the clinical presentation.

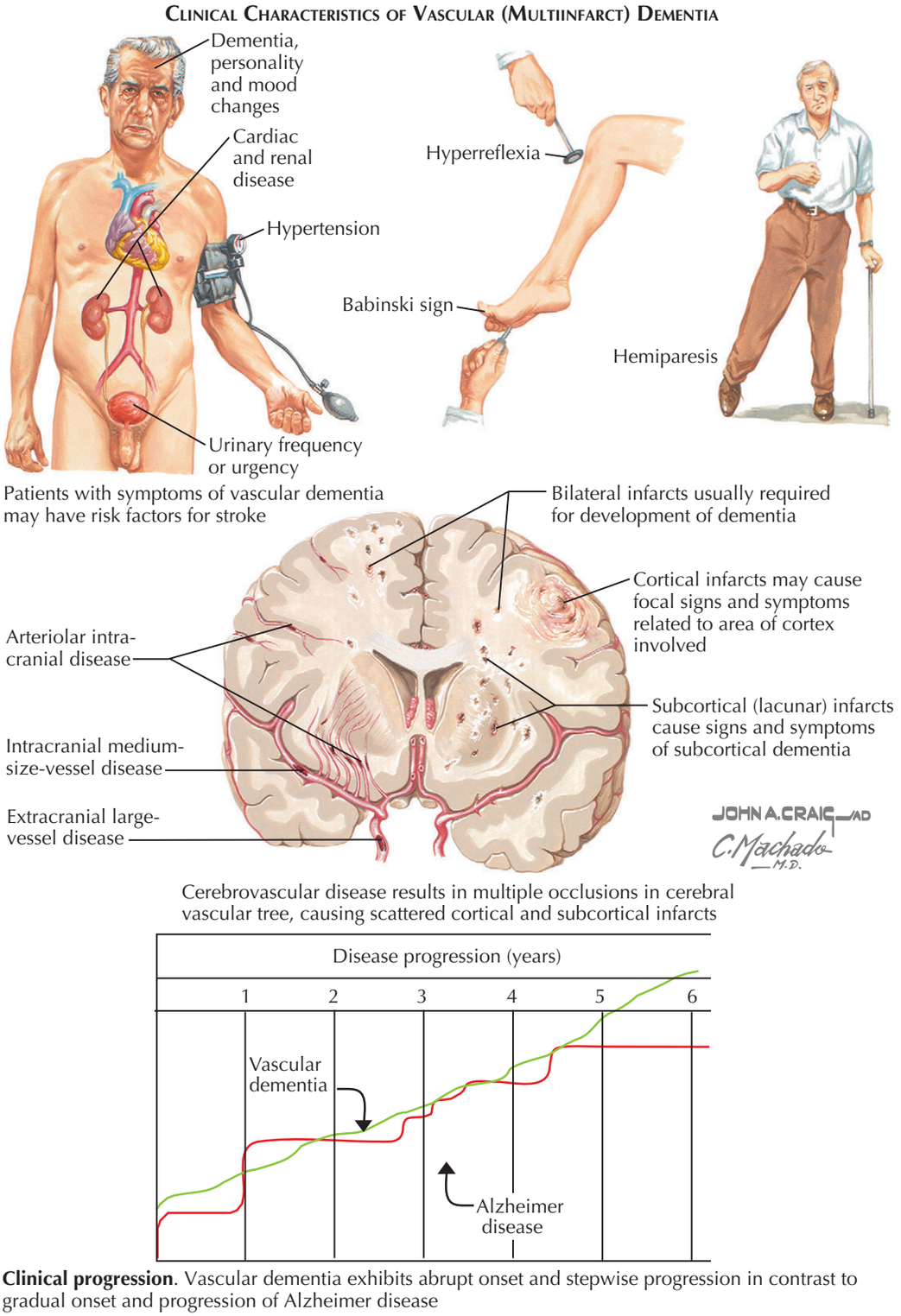
Vascular Dementia

Vascular dementia is interesting in that many of those who do have a true vascular dementia are not diagnosed with it, while many who probably do not have a vascular dementia are diagnosed with it. The most straightforward presentations are those in which an individual with normal cognition has a large stroke that causes a combination of cognitive signs, such as aphasia and a memory retrieval problem. If the patient cannot resume their prestroke day-to-day level of function because of these new cognitive deficits, the criteria for vascular dementia are met, but because the stroke so clearly caused the deficits, they are held to simply represent the consequences of a stroke (as opposed to a frank vascular dementia). On the other hand, some patients will present with a gradually progressive dementia, a retention-type memory deficit, no motor signs, no history of sensory or motor changes, and a neuroimaging study that shows subcortical changes that could be consistent with "small vessel cerebrovascular disease." In the elderly, such patients almost always have the plaques and tangles that are expected in Alzheimer disease. In such cases, despite the neuroimaging changes, it is probably more appropriate to consider Alzheimer disease as the primary etiology. Still, the frequent association between Alzheimer disease and cerebrovascular pathology suggests these conditions may be linked in some way.

Vascular dementias can be subclassified depending on whether the stroke or strokes responsible for the cognitive change are single versus multiple, and large vessel versus small vessel. As mentioned above, a single large vessel stroke can cause a dementia syndrome. Such presentations are often obvious because they typically present within the context of an acute, clearly diagnosable large vessel stroke. Some patients will have multiple large vessel strokes. Greater amounts of stroke-related brain damage commonly associate with greater degrees of cognitive dysfunction.

Single small strokes can alter cognition when they happen to fall within and damage specific areas that are critical to cognitive performance. The thalamus, caudate head, and fornix constitute some examples in which a strategically placed small stroke can impact cognition. Cognitive decline severe enough to qualify for a syndromic dementia diagnosis also results from multiple small vessel strokes that, on neuroimaging, appear as multiple lacunar strokes. As is the case with large vessel multi-infarct dementias, this type of small vessel multi-infarct vascular dementia often presents within the context of a stepwise decline in which the stepwise decline occurs in association with diagnosed acute strokes.

When it comes to diagnosing a vascular dementia, the most difficult cases are those in which the patient has developed a clinical dementia, there is no clinical history of a previously diagnosed acute stroke, but a neuroimaging study reveals extensive stroke-induced damage to the brain. In many such instances, the imaging shows extensive changes to the subcortical white matter. These changes may appear confluent or more anatomically restricted. The changes may coalesce around the lateral ventricles and may or may not also separately project into other white matter areas in a more patchy or punctuate pattern. When this white matter change is indeed driving the dementia, then a diagnosis of subcortical ischemic vascular dementia should be considered and a pathologic survey may reveal changes consistent with Binswanger disease. However, nondemented elderly individuals and patients with neurodegenerative dementias may also show similar patterns of subcortical white matter change. In the latter situation, the white matter change may represent a consequence of the true underlying disease as opposed to a cause of the dementia. When considering such cases, the overall clinical picture, including the clinical history, general neurologic exam, and cognitive neurologic exam needs to be synthesized and interpreted very cautiously. Sometimes these patients will ultimately receive a diagnosis of a mixed vascular-degenerative dementia, or "Alzheimer disease plus cerebrovascular disease."



Clinical progression. Vascular dementia exhibits abrupt onset and stepwise progression in contrast to gradual onset and progression of Alzheimer disease

Treatable Dementias

Although in some ways cognitive performance abilities evolve throughout adulthood, many elderly people remain mentally sharp into their ninth and tenth decades. The emergence of uncharacteristic changes in an individual's cognition that impacts their usual activities should, therefore, trigger an evaluation for possible etiologies.

Because Alzheimer disease is the most common cause of intellectual decline in later life, symptoms or signs that are unusual in Alzheimer disease should particularly alert the physician to a different diagnosis and the possibility of reversing the dementing process. Such features include early age at onset; prominent headache; disturbances of gait or incontinence early in the course of the illness; epileptic seizures; fever; precipitous decline over a period of weeks or months; alteration of consciousness, especially sleepiness, stupor or delirium; history of head trauma; focal neurologic signs, such as lateralized visual, motor, or sensory abnormalities; accompanying dysfunction of peripheral nerves characterized by paresthesias and absent distal reflexes; and known systemic cancer, collagen vascular disease, or endocrinopathy. The presence of any of these features should dictate further evaluation and consideration of the following treatable dementias.

Metabolic Disease with Encephalopathy. When intellectual decline is caused by systemic metabolic disease, there are usually four associated features: diminished alertness; asterixis; a global decrease in mental function, often with a flight of ideas; and variability of intellectual function during the day. The metabolic dysfunction can be either *endogenous* or *exogenous.* An endogenous abnormality indicates too much or too little of a substance or metabolite usually found in the body, such as calcium, sodium, thyroid hormone, sugar, and so forth, may be responsible.

Failure of the lungs, kidneys, or liver is also in this category. Exogenous metabolic dysfunction is caused by a deficiency of a dietary substance, such as vitamin B_{12} or nicotinic acid, or by intoxication with a growing variety of agents, such as alcohol, barbiturates, or narcotics.

Brain Tumors. Primary benign brain tumors, such as meningiomas, that affect the olfactory grooves and frontal lobes decrease mental function by pressing on brain tissue or by obstructing the ventricular system. Malignant primary metastatic tumors can also cause intellectual decline, usually with focal or multifocal signs and seizures.

Head Trauma. A history of head injury, sleepiness, and slight lateralized weakness are clues, particularly to a subdural hematoma. The physician should be aware of this possibility because many patients will have forgotten the inciting trauma by the time they seek medical attention.

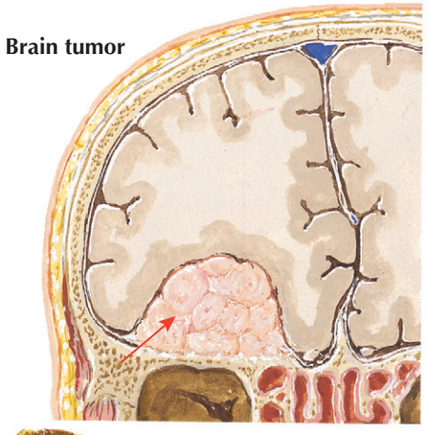
Normal-Pressure Hydrocephalus. In most patients, this occult condition is unrecognized until the pathologic state causes overt symptoms.

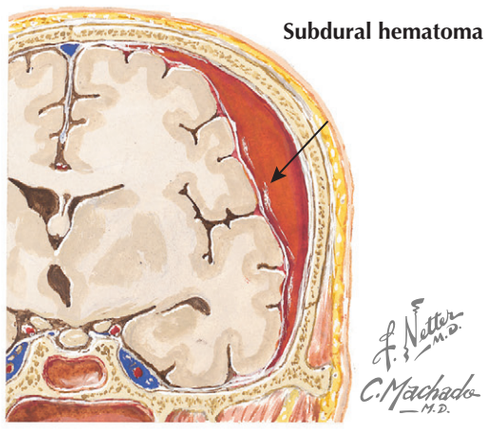
Infection. An altered mental state, usually with headache and cerebrospinal fluid (CSF) pleocytosis, may be the first indication of central nervous system (CNS) syphilis, tuberculosis, or fungal meningitis.

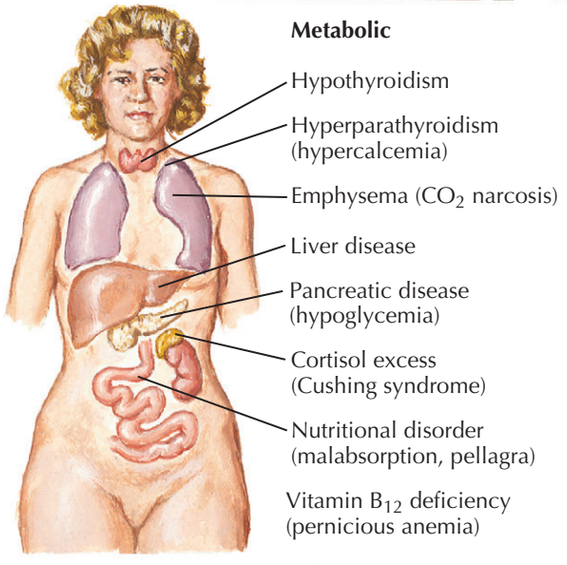
Depression. Depression is associated with measureable declines in some aspects of memory and memory complaints are a frequent symptom of depression. *Depressive pseudodementia* is a concept that arose to characterize depression as a potential mimic of dementia. Depression should be considered in patients with dementia, although depression is often an early expression of Alzheimer neuropathologic changes in the brain. Depression in Alzheimer patients contributes to greater functional decline and should be treated aggressively.

Cerebrovascular Disease. Strokes can decimate the regions of the brain that govern thought processes. When this occurs, motor and reflex abnormalities usually parallel or exceed the degree of intellectual decline. Usually, the patient also has a history of an abrupt decline, as well as hypertension and coronary or peripheral vascular disease.

Diagnostic Studies. Screening of biochemical parameters, especially the vitamin B_{12} level and thyroid, renal, liver, and lung function can be important in evaluating potential causes of dementia. Neuroimaging, electroencephalography, and CSF analysis may also detect unsuspected causes of dementia.







NORMAL-PRESSURE HYDROCEPHALUS

The "plumbing system" of the central nervous system (CNS) operates in a delicate balance. Fluid produced in the choroid plexus of the lateral ventricles circulates through the third ventricle, cerebral aqueduct (of Sylvius), and fourth ventricle. After exiting from the roof of the fourth ventricle, the cerebrospinal fluid (CSF) circulates around the brain within the subarachnoid cisterns, and is ultimately absorbed by the arachnoid granulations into the circulation. If more CSF is produced than is absorbed, the ventricles and subarachnoid space distend with fluid. In the adult, this imbalance leads to enlargement of the ventricles, which then encroach on the normal cerebral white matter, especially frontally.

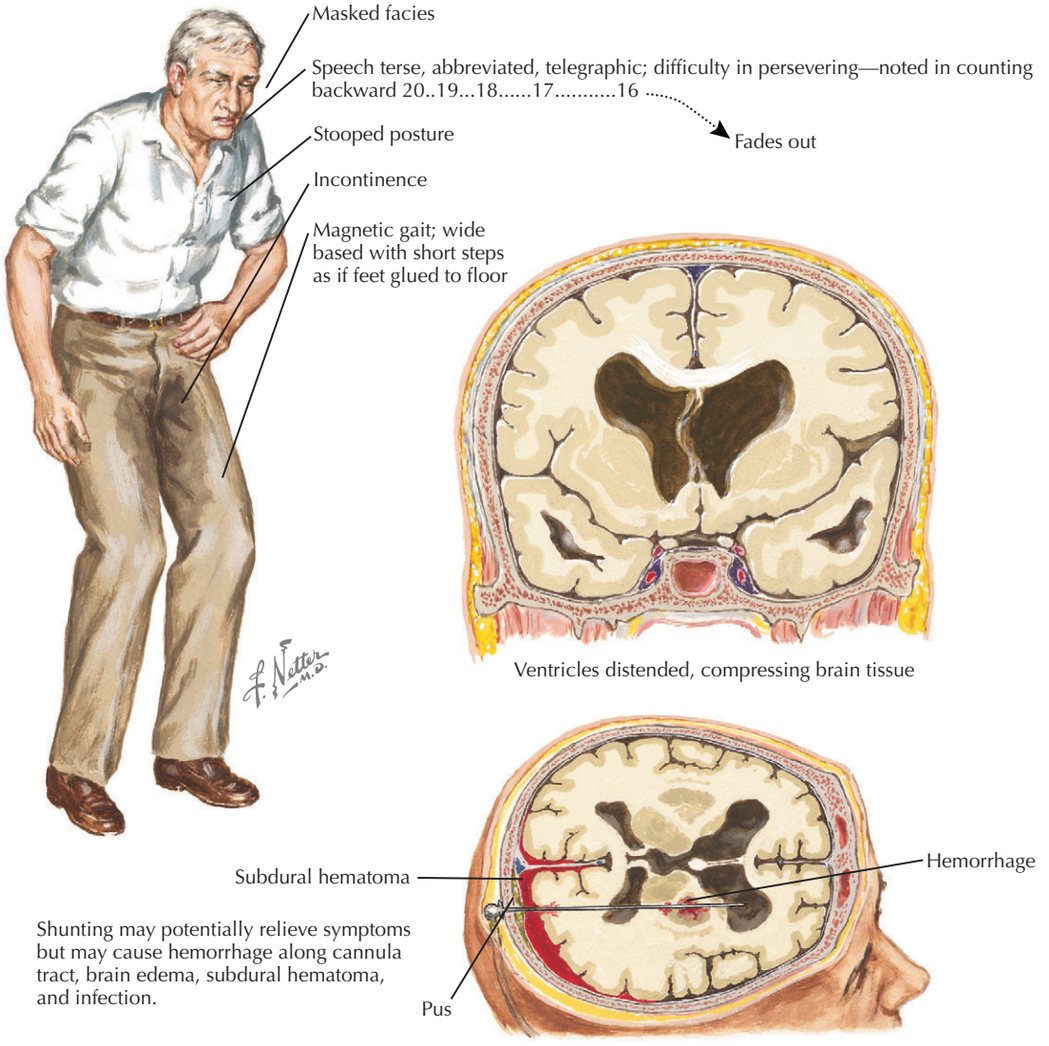
Conditions known to cause scarring of the pia-arachnoid membranes, such as meningeal infection, subarachnoid hemorrhage, or bleeding from past trauma, can cause hydrocephalus by decreasing the effectiveness of CSF absorption. In most elderly patients, communicating hydrocephalus has no easily identifiable cause. Although it could possibly result from degeneration of the arachnoid granulations and membranes, there has been little detailed study of the morphologic structure of the arachnoid in either normal persons or patients with hydrocephalus. Because the CSF pressure is usually high in obstructive hydrocephalus due to tumor and, for uncertain reasons, is within normal range in communicating hydrocephalus, the latter disorder has been called normal-pressure hydrocephalus.

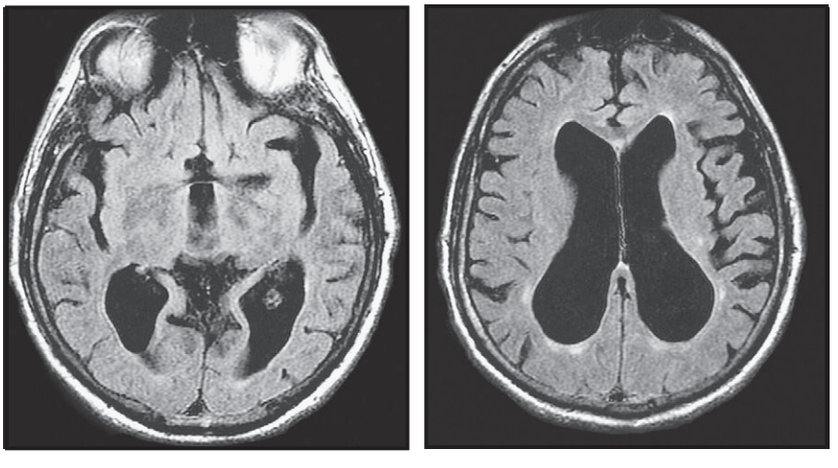
Normal-pressure hydrocephalus usually develops over a period of 6 to 12 months but at times progresses insidiously for a few years. Neuroimaging shows markedly enlarged ventricles, often with little or no cortical atrophy.

Clinical Manifestations. Most symptoms relate to enlargement of the anterior (frontal) horns and loss of frontal lobe white matter and can be described as a classic triad of dementia, gait disturbance, and urinary incontinence.

1. *Abnormality of gait:* Patients with normal pressure hydrocephalus have significant abnormalities in their gait, often described as "magnetic" because the initiation of steps is difficult and the feet appear as if they are stuck to the floor.
2. *Dementia:* The patient shows decreased interest in the environment and seems apathetic. Speech becomes less spontaneous, and words are mumbled in a voice of lower volume than normal. Later, the patient may become mute. Despite the reduced amount of conversation, vocabulary and memory are preserved, and answers to questions, although terse, are usually correct.
3. *Incontinence:* The patient loses the ability to retain urine despite normal perception of the urge and need to urinate. The rapid course; prominence of apathy and early motor, gait, and sphincter dysfunction; and slowness of preserved memory function and vocabulary contrast with the findings in Alzheimer disease.

Treatment. *Spinal puncture* with drainage of fluid can lead to temporary improvement in gait and alertness. Administration of *acetazolamide* reduces production of CSF and thus may improve the imbalance between production and absorption of CSF.





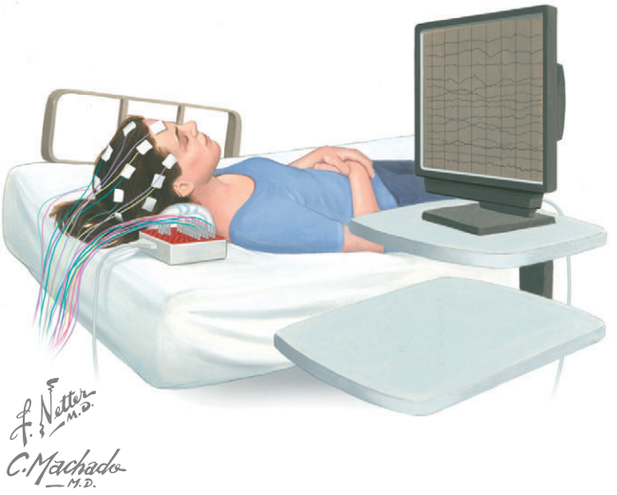
Axial FLAIR images demonstrate moderate enlargement of the third and lateral ventricles, more normal sulcal pattern, and patchy periventricular increased T2 changes.

Cisternography after introduction of a radionuclide by lumbar puncture may be of value in assessing abnormal CSF flow patterns. Unfortunately, however, there is no single definitive test that reliably predicts whether the patient will improve after surgical placement of a ventricular drain.

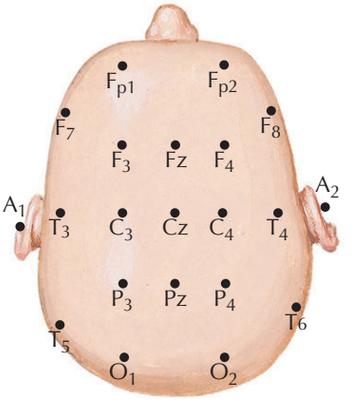
Ventricular shunts seem to be most effective in patients who have the classic triad of symptoms and in whom the course of the dementia has been short and a cause of the disorder, such as past subarachnoid hemorrhage, can be identified. Complications of ventriculoperitoneal shunts in adults include intracerebral or intraventricular hematoma during insertion of the tube; infection of the shunt and peritoneal space; oversiphoning of CSF, which causes subsequent brain swelling to take up the void; and collapse of the thin cerebral mantle, with tearing of bridging veins and formation of a subdural hematoma. The incidence of subsequent shunt infection is high.

EPILEPSY

ELECTROENCEPHALOGRAPHY



Electrode placement and lead identification



Odd numbers, left side;
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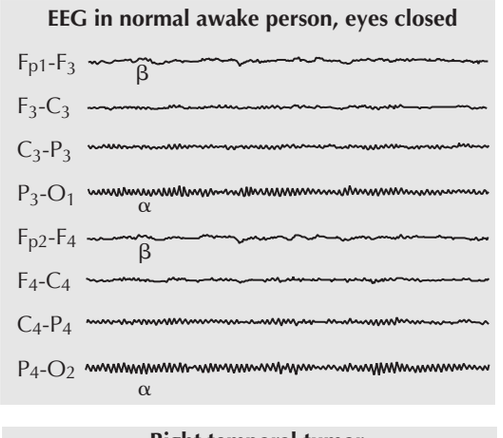
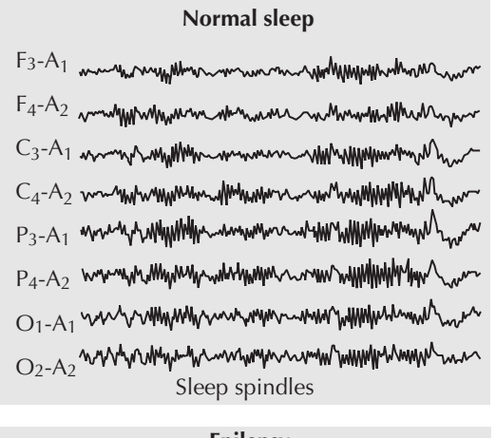
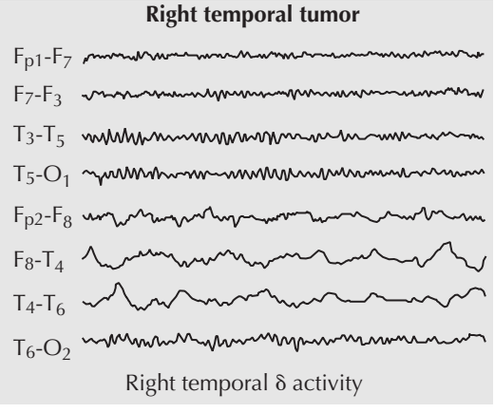
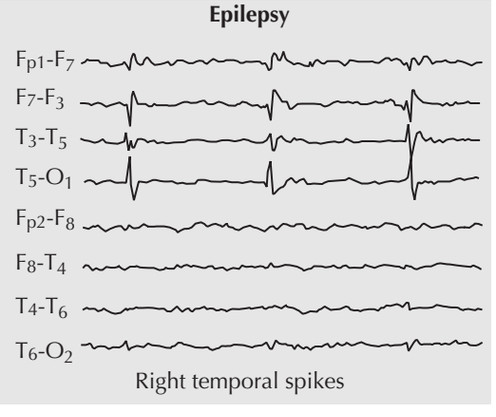








The electroencephalogram (EEG) is a record of the electrical activity of the nerve cells in the brain. The EEG is based on the measurement of electrical fields generated by volume conduction of ionic currents from nerve cells through the extracellular space. Recorded EEG potentials arise from extracellular current flow from summated excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs). The EEG does not record activity from single neurons, but is dependent on the summation of thousands to millions of postsynaptic potentials (PSPs), and therefore represents activity from a large neuronal aggregation. Although nerve action potentials have higher voltage changes than EPSPs and IPSPs, due to the lack of summation and short duration of action potentials, they usually add little to EEG activity. During seizures, there is synchronous firing of large ensembles of action potentials from neurons, which may contribute to the EEG signal. The usual way to record an EEG is to attach small metal disc electrodes to the scalp in standardized positions. The signal from these electrodes is then amplified, digitized, and electronically stored. The EEG is then read on a computer screen.

Brain Wave Activity. Brain activity consists of waveforms that vary in polarity, shape, and frequency, and usually range in voltage from 20 to 60 microvolts. Scalp EEG activity shows oscillations at a variety of frequencies, representing synchronized activity over a network of neurons. EEG waveforms are labeled according to their frequency, measured in cycles per second or Hertz (Hz). Alpha activity ranges between 8 and 13 Hz. The alpha rhythm is predominantly over the posterior head region and is the characteristic background frequency of the normal awake person. It occurs when the eyes are closed and attenuates when the eyes are open. Beta activity is low amplitude, fast activity with a frequency of 13 to 30 Hz and is usually present over the anterior head regions. Theta activity ranges from 4 to 7 Hz, and delta activity occurs at a frequency of less than 4 Hz. There is a developmental maturation of the EEG. For example, in the newborn infant, the EEG does not show continuous mixed-waveform activity, as would be expected in an adult. Instead, an infant has continuous amorphous delta activity. The other waveform frequencies progressively emerge as the infant's brain develops. EEG patterns change during different stages of sleep and contribute to the definition of sleep stages. The EEG patterns are very different for rapid eye movement (REM) stages compared with non-REM sleep. For stage II non-REM sleep, the EEG shows spindle activity (10-14 Hz sinusoidal activity) and vertex sharp waves. During stage III to IV, non-REM sleep high-voltage delta activity predominates. The EEG during REM sleep resembles the EEG during wakefulness, with a low-amplitude background consisting of a mix of frequencies.

The main types of abnormalities that may be seen in the EEG are slowing of background frequencies, epileptiform activity, and suppression of activity. Slowing of background activities can either be diffuse or focal. Diffuse slowing suggests widespread brain dysfunction, which can be caused by a variety of insults, such as global brain injury, toxins, inflammation, or degenerative processes. Focal slowing is often indicative of a structural lesion, such as a tumor or a stroke. Epileptiform activity indicates the patient is at risk for seizures. Suppression of activity can be either focal or diffuse, and it indicates a severe derangement of brain function.

Indications for EEG. The main indications for obtaining an EEG are to assess for seizure disorders, intracranial disease processes, coma, and brain death. The most common reason for an EEG is to characterize a seizure disorder. The EEG is useful in defining epilepsy syndromes and for localization of a seizure focus. Because seizures occur infrequently, EEG activity is usually measured between seizures to determine whether characteristic waveforms, such as sharp waves or spikes, are present. These waveforms signify a predisposition to epilepsy. Capturing a seizure on EEG usually requires long-term monitoring with video. For some disease processes, the EEG shows specific diagnostic patterns, such as generalized periodic sharp waves in Creutzfeldt-Jakob disease. The EEG is also very useful in the evaluation of comatose patients. There may be distinctive patterns that can confirm that diagnosis of an underlying condition, such as triphasic waves in hepatic coma, spike discharges in nonconvulsive status epilepticus, and excessive beta activity associated with a benzodiazepine or barbiturate drug overdose. Finally, the EEG can be used to confirm brain death in patients in whom the EEG activity has ceased and the clinical criteria for brain death are present.

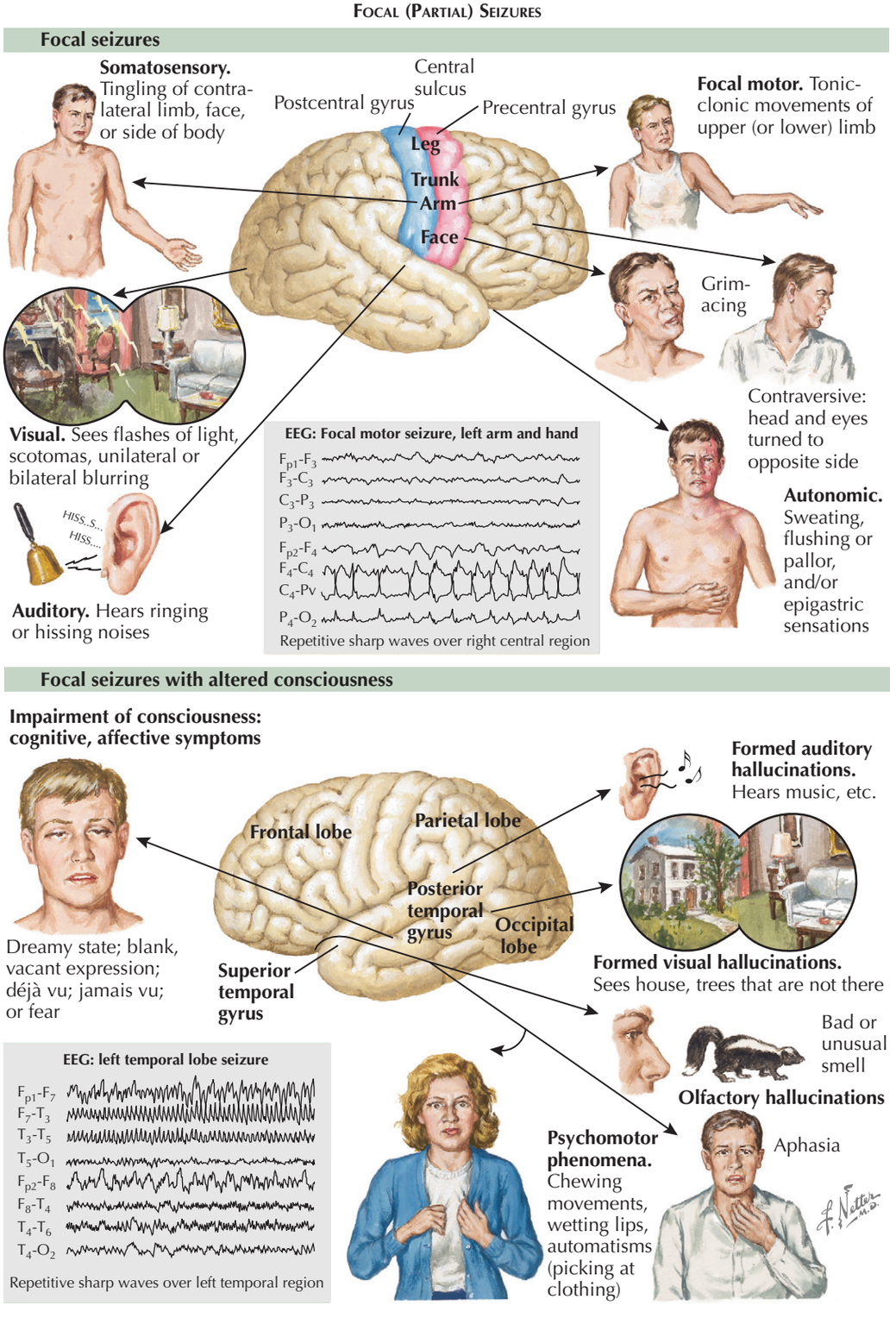
Seizures and Epilepsy

Epilepsy is medically defined as a condition characterized by an individual having two or more unprovoked seizures. A seizure is a paroxysmal disorder characterized by an abnormal excessive, hypersynchronous discharge of neurons that results in an alteration of normal brain function. This alteration of function can be quite dramatic, such as during a generalized tonic-clonic (GTC; grand mal) seizure, or much more subtle, such as during an absence (petit mal) seizure. If the seizures are consistently provoked, such as by fever or hypoglycemia, the term epilepsy should not be used. Epilepsy is not a single disorder, but rather a symptom of an underlying brain disorder. Epilepsy is a chronic disorder, although many children will go into remission. Although many people with epilepsy are normal in all other respects, approximately 50% will also have additional cognitive or behavioral impairments.

The history and neurologic examination are the cornerstones of neurologic diagnosis. When assessing when a patient may have had a seizure, it is important to obtain a description of a paroxysmal change in behavior, whether there was a loss of consciousness, the duration of the spell, and whether stimuli were encountered that might precipitate a seizure. A family history of epilepsy should always be ascertained. Of particular importance in the history is the description of the initial signs or symptoms. For example, the approach to a patient with an aura before a GTC is quite different from the patient who has a GTC without an aura. In the former case, it is likely that the patient has a focal onset to the seizure, increasing the chances that there is a structural lesion responsible for the seizure, while in the latter instance, it is likely the patient has a seizure-inducing stimulus, such as low blood sugar or perhaps an underlying genetic condition. Postictal features can also be helpful. Absence seizures of childhood are brief, typically lasting 30 seconds or less, and have a rapid offset, with the child quickly returning to normal mental status. Complex partial seizures are of longer duration, lasting 30 seconds to several minutes, and typically have some degree of confusion and tiredness after the event.

There are many episodic disorders that resemble seizures. Episodes such as night terrors, breath-holding spells, or syncope may resemble epileptic seizures. The timing of the event is important. When nocturnal, epileptic seizures typically occur in the early morning hours, while sleep disorders such as night terrors typically occur several hours after the child falls asleep. A young child for whom the event always occurs in association with provoked crying likely has breath-holding spells. Individuals who feel light-headed and clammy before losing conscious likely have syncope rather than epilepsy. If there is doubt about the diagnosis, it is usually better to wait before beginning therapy.

Seizures are classified into two major categories: focal and generalized. Focal seizures originate within a localized region of the brain, and may evolve into generalized convulsions. Generalized seizures rapidly engage both hemispheres of the brain. Generalized seizures are further classified into tonic, clonic, tonic-clonic, absence, myoclonic, and atonic.



Focal (Partial) Seizures

Focal seizures originate within networks of a limited region of the brain, often confined to one hemisphere. They can occur at any age. Focal seizures may be classified further into those without impairment of consciousness or awareness (simple partial seizures) and those with impairment of consciousness or awareness (complex partial seizures). Seizures without impairment of consciousness or awareness can be further subdivided into seizures with (1) observable motor or autonomic components or (2) subjective sensory or psychic phenomenon. The signs or symptoms of focal seizures depend on the location of the focus within the brain. Seizures involving the motor cortex most commonly consist of rhythmic or semirhythmic clonic movements of the face, arm, or leg. There is usually no difficulty in diagnosing this type of seizure. Seizures with somatosensory, autonomic, and psychic symptoms (hallucinations, illusions, déjà vu) may be more difficult to diagnose.

Most commonly, psychic symptoms occur as a component of a focal seizure with impaired consciousness or responsiveness. Focal seizures with impairment of consciousness or awareness (complex partial seizures),

Seizures and Epilepsy
(Continued)

formerly termed temporal lobe or psychomotor seizures, are one of the most common seizure types encountered in both children and adults. The beginning of the focal seizure may serve as a warning to the patient (i.e., aura) that a more severe seizure is pending. It is important to recognize that the aura may enable the clinician to determine the cortical area from which the seizure is beginning.

The impairment of consciousness or awareness may be subtle. For example, the patient may either not respond to commands or respond in an abnormally slow manner. Although focal seizures with altered consciousness or awareness may be characterized by simple staring and impaired responsiveness, behavior is usually more complex during the seizure. Automatisms, semipurposeful behaviors of which the patient is unaware and subsequently cannot recall, are common during the period of impaired consciousness. Types of automatism behaviors are quite variable and may consist of activities such as facial grimacing, gestures, chewing, lip smacking, snapping fingers and repeating phrases. The patient does not recall fully this activity after the seizure. Most patients have some degree of postictal impairment, such as tiredness or confusion after the seizure.

The EEG in focal seizures is characterized by focal spikes or sharp waves. There is often a relationship between the location of the spikes and the seizure type, that is, occipital lobe spikes are associated with occipital lobe seizures, while frontal lobe spikes are associated with frontal lobe seizures.

Different types of seizures may evolve in temporal succession in the same patient. For example, a focal seizure starting with normal consciousness and awareness may become associated with alteration in consciousness and subsequently evolve to a generalized convulsive seizure as the seizure starts within a local neural circuit and then spreads to involve an increasing proportion of the brain and ultimately both hemispheres.

GENERALIZED SEIZURES: TONIC-CLONIC SEIZURE

A generalized tonic-clonic, or grand mal seizure, is the most severe type of seizure. It starts with a sudden loss of consciousness and generalized tonic stiffening and extension of the body secondary to a widespread contraction of the muscles. The patient may utter a piercing cry resulting from forced expiration of air from the lungs through closed vocal cords. Cessation of respirations with associated cyanosis is secondary to the tonic muscle contractions that prevent normal respiratory movements. The patient often bites his tongue during this phase of the seizure. Salivation occurs because the patient cannot swallow during the seizure. In addition, urinary incontinence is often present.

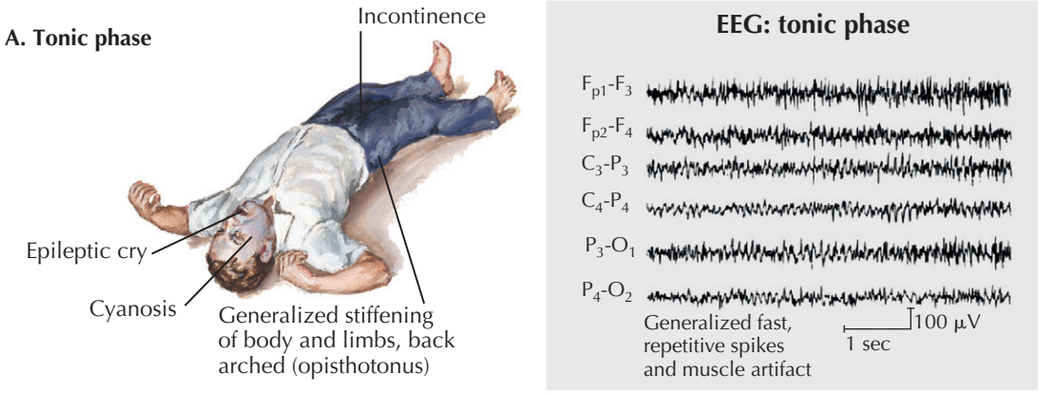
The initial *tonic phase* of the seizure is followed by the *clonic phase*, in which generalized bilaterally synchronous clonic jerks of the body alternate with brief periods of relaxation. As the periods of relaxation become more prolonged, the clonic movements gradually decrease and finally cease.

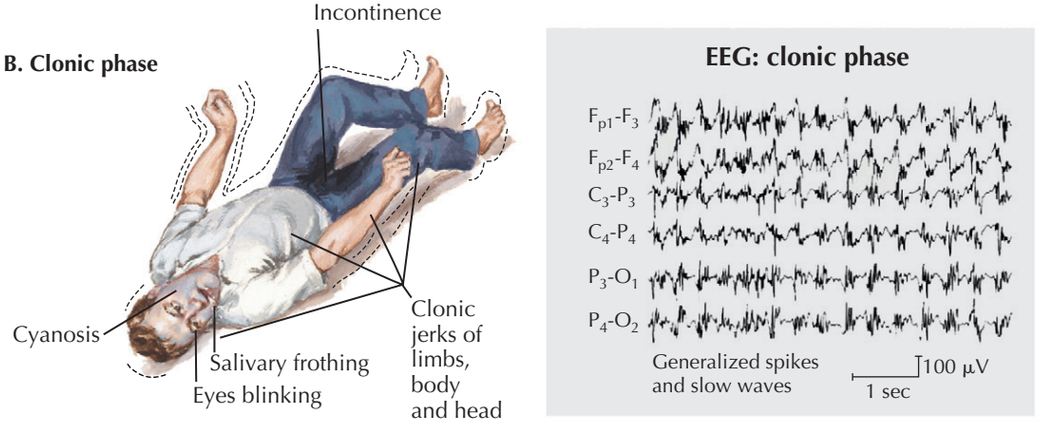
During the *postictal period* after the seizure, the patient is limp, obtunded, and unresponsive. The actual seizure may last about 1 to 2 minutes, while the postictal phase may last from 5 to 20 minutes. Afterward, the patient may arouse, but remains confused, and if left undisturbed, may sleep for an hour or so and awaken with a headache and generalized muscle soreness.

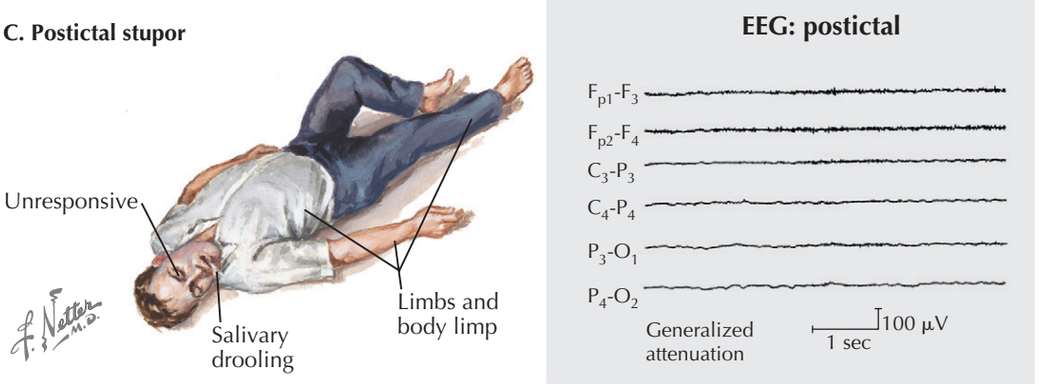
Generalized tonic-clonic seizures may occur at any age. They may be primary generalized seizures, which are generalized from onset, or secondary generalized seizures, which start as focal seizures and then become generalized as the seizure activity progresses to involve widespread areas of the brain.

The EEG of a GTC seizure shows various types of seizure activity that correspond to the different phases of the seizure. During the tonic phase, the EEG shows fast, repetitive, generalized spike discharges. During the clonic phase, the EEG shows spike-and-wave discharges, with the spike corresponding to the clonic jerks and the slow wave to the period of relaxation. Finally, during the postictal phase, the EEG shows generalized attenuation of background activity followed by

Generalized Tonic-Clonic Seizures







Seizures and Epilepsy
(Continued)

slowing, which gradually decreases as the patient recovers from the seizure.

GENERALIZED SEIZURES: ABSENCE (PETIT MAL) SEIZURES

Absence seizures typically begin and end in childhood, although they can be seen in adults. Absences start abruptly without an aura, lasting from a few seconds to half a minute and ending abruptly. Absence seizures are generalized seizures indicating bihemispheric initial involvement clinically and electroencephalographically. Absence seizures have an abrupt onset and offset. There is typically a sudden cessation of activities with a blank, distant look to the face. As the seizure continues, there are often automatisms and mild clonic motor activity, such as jerks of the arms and eye blinking. The patient is often unaware that he or she has had a seizure, but usually recognizes that he or she has had a "blank" period.

In the untreated patient, absence seizures can occur quite frequently during the day. They sometimes occur in clusters, particularly when the child is tired or drowsy. In a child not on antiepileptic drugs, typical absence seizures can almost always be precipitated by hyperventilation.

There are four major syndromes in which typical absence seizures are a major component: childhood absence epilepsy (pyknolepsy), juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with myoclonic absences. The absence epilepsies appear to have a complex genetic basis. Atypical absence seizures, a form of absence seizures, usually occur in cognitively impaired children who have other seizure types. Unlike typical absence seizures, atypical absence seizures are often longer and have a less distinct onset.

The EEG reveals a bilateral, synchronous symmetric, three-cycles-per-second, spike-and-wave discharge with normal interictal background activity. The interictal EEG in this disorder is distinctive and easily distinguished from other forms of generalized epilepsies. In atypical absence, the spike-and-wave discharges are irregular in frequency and shape and occur at a frequency that is less than three cycles per second.

OTHER GENERALIZED SEIZURES

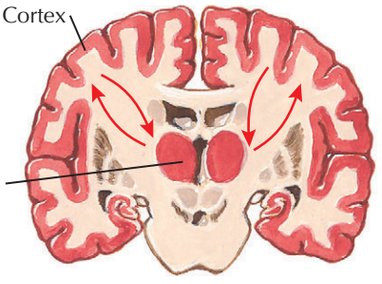
Myoclonic Seizures. Myoclonic seizures are characterized by sudden, brief (<350 msec), shocklike contractions that may be generalized or confined to the face and trunk or to one or more extremities, or even to individual muscles or groups of muscles. Myoclonic seizures result in short bursts of synchronized electromyographic activity. The contractions of muscles are quicker than the contractions with clonic seizures. Any group of muscles can be involved in the jerk. Myoclonic seizures may be dramatic, causing the patient to fall to the ground or be quite subtle, resembling tremors. Because of the brevity of the seizures, it is not possible to determine if consciousness is impaired. Myoclonus may occur as a component of an absence seizure or at the beginning of a GTC seizure. The interictal EEG pattern seen in patients with myoclonic seizures typically consists of generalized spike-wave discharges.

Tonic Seizures. Tonic seizures are brief seizures (usually less than 60 seconds) consisting of the sudden onset of increased tone in the extensor muscles. If standing, the child usually falls to the ground. The seizures are longer than myoclonic seizures. Electromyographic activity is dramatically increased in tonic seizures. There is impairment of consciousness during the seizure, although in short seizures this may be difficult to assess. The EEG ictal manifestations of tonic seizures usually consist of bilateral synchronous spikes of 10 to 25 Hz of medium to high voltage with a frontal accentuation.

Atonic Seizures. Atonic (astatic) seizures, or drop attacks, are characterized by a sudden loss of muscle tone. They begin suddenly and without warning and cause the patient, if standing, to fall quickly to the floor. Because there may be total lack of tone, the child has no means to protect himself or herself, and injuries occur. The attack may be fragmentary and lead to dropping of the head with slackening of the jaw or dropping of a limb. In atonic seizures, there should be a loss of electromyographic activity.

Absence Seizures

Absence seizures represent abnormal interactions between cortical and thalamic transmissions

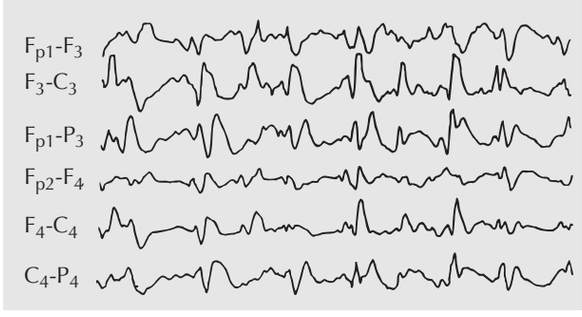


Generalized bilateral seizure activity

F. Netter M.D.
JOHN A. CRAIG, MD

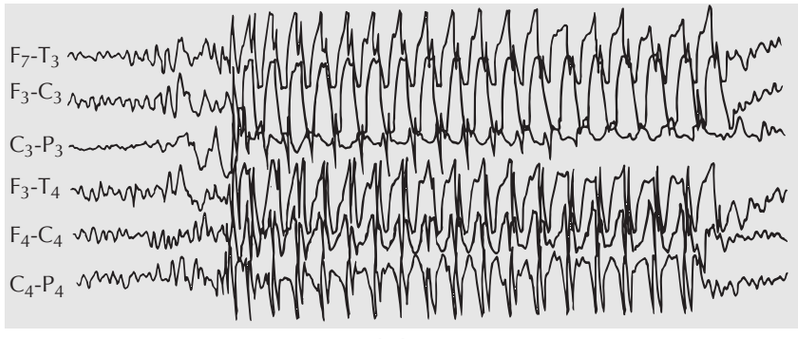
Child alert and attentive before and after seizure

Sudden onset
2-15 seconds
Sudden cessation



EEG. Atypical absence pattern. Atypical absence seizures may be associated with mental retardation and tonic or atonic seizures.

Typical absence seizure. Impaired awareness and responsiveness for 2-15 seconds.



EEG. Typical absence pattern

Epileptic Syndromes

Once the seizure type has been identified, it is very helpful for the clinician to try to determine the epileptic syndrome. An epileptic syndrome is a cluster of clinical and electroencephalographic features that occur together more commonly than by chance. Epileptic syndrome identification aides in identifying etiology and provides the clinician with guidance regarding long-term prognosis.

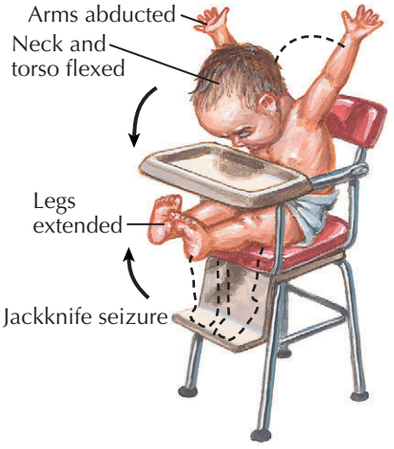
An example of an epileptic syndrome with generalized seizures is *juvenile myoclonic epilepsy* (JME). The seizure types are generalized tonic-clonic, absence, or myoclonic, which often occur upon awakening. The seizures begin in adolescence or early adulthood in an otherwise healthy individual. The interictal EEG reveals spike-and-wave activity at a frequency of 3.5 to 6.0 Hz, while neuroimaging is normal. Although the seizures are usually controlled with antiepileptic drugs, the condition is lifelong. A single-gene mutation has not been identified, and many investigators feel the condition likely involves multiple genes. Once diagnosed with JME, the patient can be provided specific information regarding prognosis and treatment.

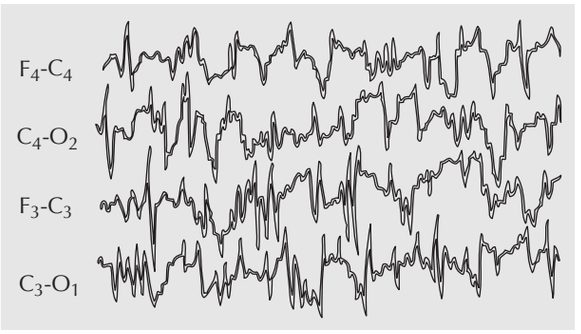
Benign rolandic epilepsy, also called benign childhood epilepsy with central-temporal spikes, is a genetic disorder confined to children, which is characterized by nocturnal generalized seizures of probable focal onset and diurnal simple partial seizures arising from the lower rolandic area and an EEG pattern consisting of midtemporal–central spike foci. The characteristic features of daytime seizures include (1) somatosensory stimulation of the oral-buccal cavity, (2) speech arrest, (3) preservation of consciousness, (4) drooling, and (5) tonic or tonic-clonic activity of the face. Less often, the somatosensory sensation spreads to the face or arm. Most attacks involve the face, and arrest of speech may initiate the attack or occur during its course. Consciousness is rarely impaired during the daytime attacks, although, because of the motor involvement, the child cannot speak. Often the child's gestures will indicate to the parents that the child is totally aware during the event. The characteristic interictal EEG abnormality is a high-amplitude, usually diphasic spike, with a prominent following slow wave. The spikes or sharp waves appear singly or in groups in the midtemporal and central (rolandic) region (C3, C4).

Infantile spasms are brief episodes of tonic flexor or extensor movements, or both, of the body and limbs. These spasms are seen in infants and young children up to 4 years of age and usually result from a severe cerebral insult before, at, or shortly after birth, or from an insult or disease process occurring within the first few months to 1 year after birth. One of the most common types of infantile spasm is characterized by forward flexion of the head and body, with the arms flung forward or outward. The EEG in infantile spasms shows a characteristic pattern called hypsarrhythmia, consisting of high-amplitude multifocal spikes and slow waves. During the spasm, the EEG shows an abrupt generalized decrement in the amplitude of the ongoing activity.

Infantile spasms are often treated with adrenocorticotropic hormone or corticosteroids. Clonazepam has been used occasionally, and in some refractory conditions, a ketogenic diet may be helpful in controlling the seizures.

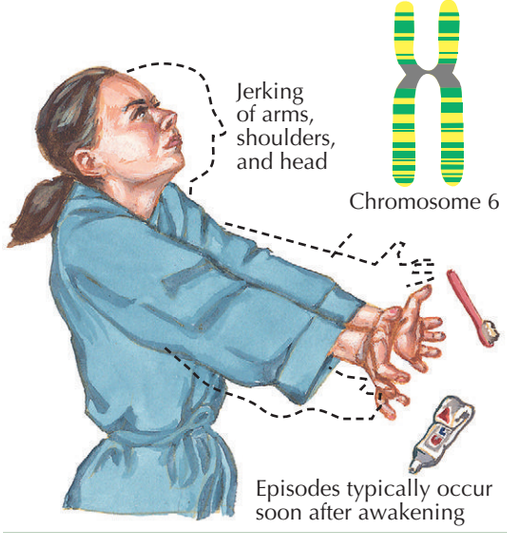
Infantile spasms (West syndrome)

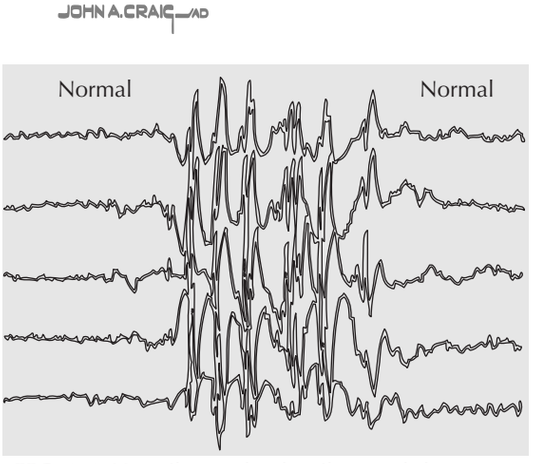




EEG. Hypsarrhythmia typical of interictal pattern in children with infantile spasms

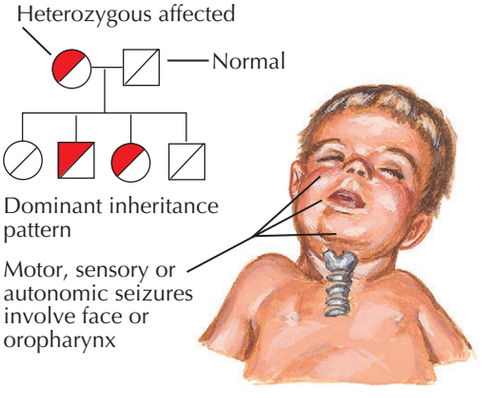
Juvenile myoclonic epilepsy



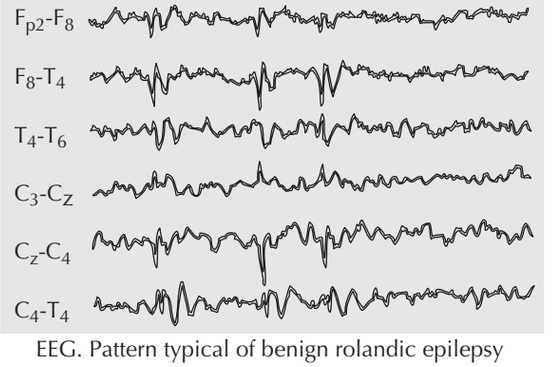


EEG. 3-6–Hz spikes and polyspikes and slow waves

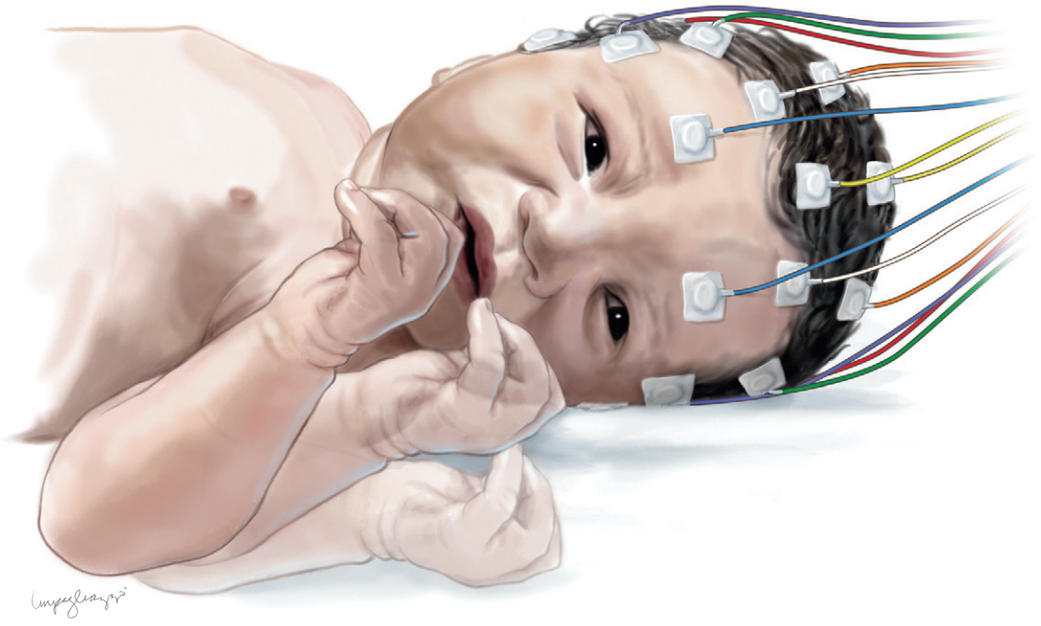
Benign rolandic epilepsy



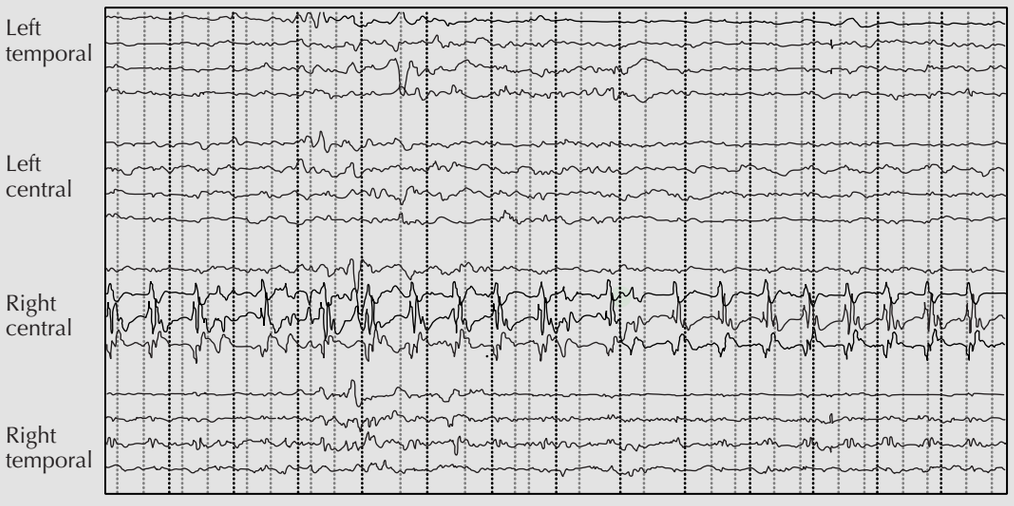
Seizures often occur during sleep



EEG. Pattern typical of benign rolandic epilepsy



The most common seizure type in neonates is focal. In this example, the newborn is having focal clonic activity of the left arm with eye deviation to the left. The EEG shows electrographic seizures with rhythmic spikes coming from the right hemisphere. The seizure in the right hemisphere is responsible for both the left arm jerking and eye deviation.



The rhythmic spike in the right central region of the EEG corresponds to the brain region in which the seizure is arising.

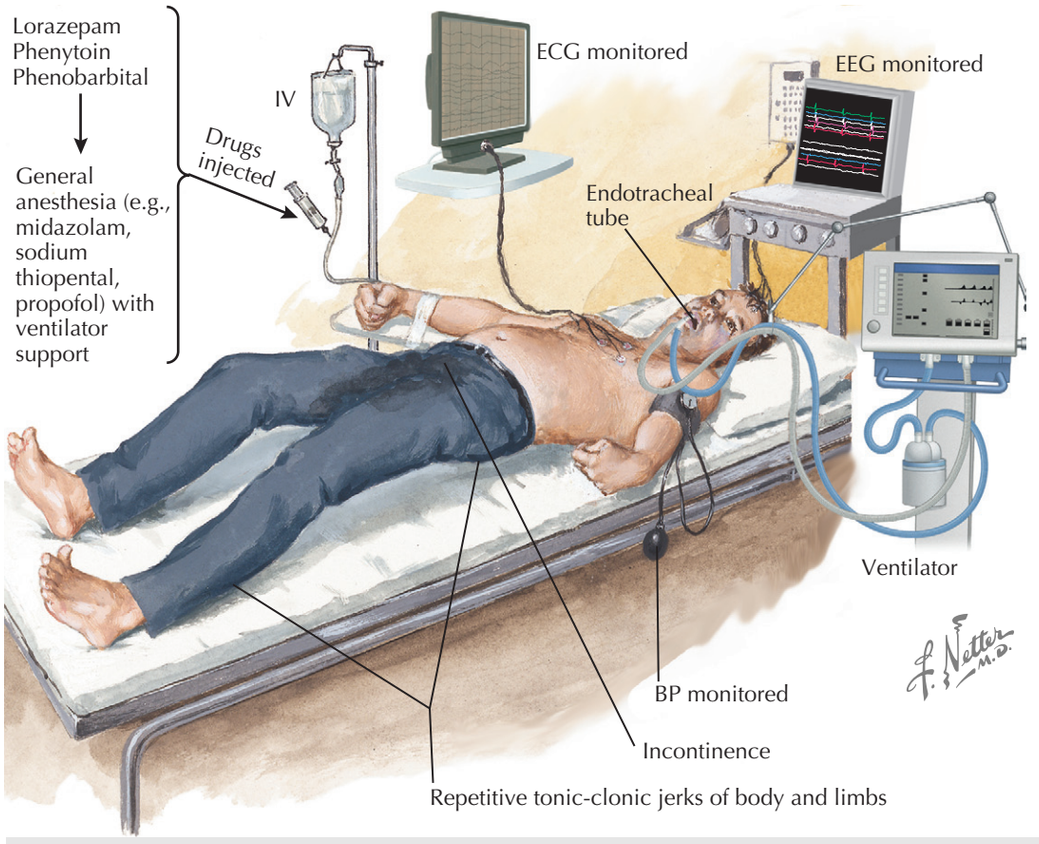
Neonatal Seizures

Neonatal seizures are one of the most common, yet most ominous, neurologic signs in newborns. Because seizures may be the first and only sign of a central nervous system disorder, their recognition is extremely important. A considerable difference is apparent in the behavior observed during seizures in neonates and the behaviors seen in older children and adults. Infants are unable to sustain organized generalized epileptiform discharges, and generalized tonic-clonic and absence seizures do not occur. The age-dependent clinical and EEG features of seizures in neonates are a result of the immaturity of cortical organization and myelination.

Neonatal seizures are classified as clonic, tonic, and myoclonic. Clonic seizures consist of rhythmic jerking of groups of muscles and occur in either a focal or multifocal pattern. In multifocal clonic seizures, movements may migrate from one part of the body to another. Although focal seizures may be seen with localized brain insults, such as neonatal strokes, they may also be seen in disorders that diffusely affect the brain, such as asphyxia, subarachnoid hemorrhage, hypoglycemia, and infection. In tonic seizures, the infant develops asymmetric posturing of the trunk or deviation of the eyes to one side. Myoclonic seizures are similar to those seen in older children, consisting of rapid jerks of muscles. The myoclonic seizures can consist of bilateral jerks, although occasionally unilateral or focal myoclonus can occur.

Sick neonates often display repetitive, stereotyped behavior that may be confused with seizures. These behaviors include repetitive sucking and other oral-buccal-lingual movements, assumption of an abnormal posture, pedaling movements of the legs or paddling movements of the arms, blinking, momentary fixation of gaze with or without eye deviation, nystagmus, and apnea. However, when these behaviors are observed during EEG recordings, epileptiform activity is usually not recorded. Likewise, when tonic posturing involves all four extremities and the trunk, an associated EEG-epileptiform discharge rarely appears. Myoclonus not associated with epileptiform discharges can also be seen in sick neonates.

Whereas the diagnosis of seizures relies primarily on clinical observation, the EEG may be extremely valuable in confirming the presence of epileptic seizures. In addition, the EEG is very useful in the detection of electrographic seizures in paralyzed infants or in assessing response to antiepileptic medications.

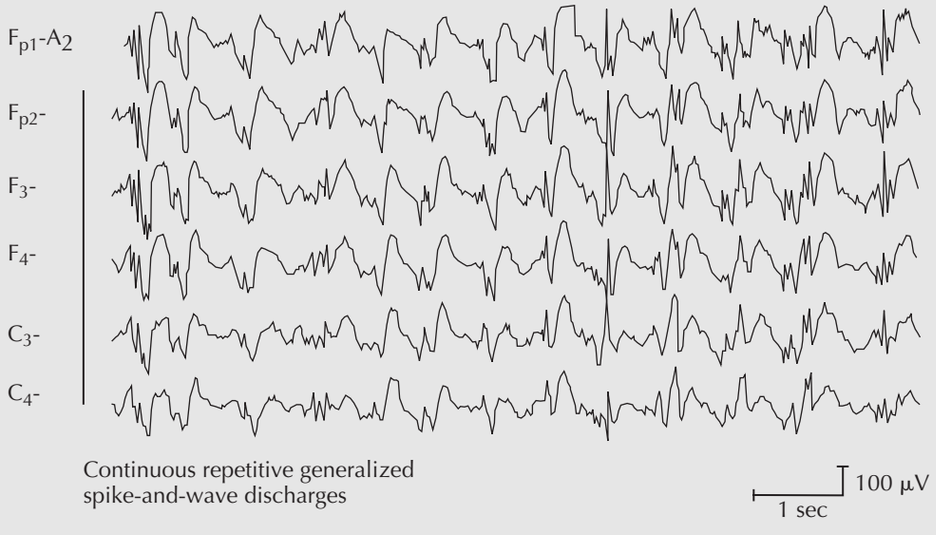


Status Epilepticus

Status epilepticus is the situation in which the mechanisms that usually terminate seizures have failed. It is usually defined as a seizure or series of seizures without full recovery of consciousness between the seizures, which last at least 30 minutes. There are two major types of status epilepticus; convulsive and nonconvulsive.

Convulsive status epilepticus (CSE) is one of the most common medical neurologic emergencies and continues to be associated with significant mortality and morbidity. In people with epilepsy, CSE is often provoked by withdrawal or reduction of antiepileptic drugs. However, more than 50% of people with CSE have never had an epileptic seizure before. The most common causes in children are febrile seizures, meningitis, and preexisting neurologic disorders such as cerebral palsy. In adults, CSE is often caused by cerebrovascular insults, cerebral anoxia, alcohol withdrawal, drug abuse, and tumors. To minimize the risk of an adverse outcome, treatment should be initiated as soon as possible. Because most seizures begin in the community, medications such as rectal diazepam should be carried by emergency medical technicians, administered in the community setting, and the patient transported urgently to the nearest emergency department. In the hospital setting, an airway should be immediately provided and maintained. Cardiorespiratory status and other vital functions should be assessed and support given if necessary. Blood samples should be drawn for analysis and an infusion of normal saline should be started. The initial in hospital, treatment is usually a benzodiazepine, such as lorazepam, administered intravenously. If benzodiazepines fail to terminate the seizure, then phenytoin or phenobarbitone may be administered. If seizures remain uncontrolled, then general anesthesia and artificial ventilation may be required.

EEG: status epilepticus



Nonconvulsive status epilepticus (NCSE) refers to the situation in which there is EEG evidence of epileptiform abnormalities that are continuous in the absence of obvious clinical motor manifestations. NCSE in patients with epilepsy often occurs in the context of absence epilepsy and focal seizures, particularly those arising in the temporal lobe. Patients with confusion may have NCSE, and patients admitted to an intensive care unit may also develop NCSE. Because NCSE may worsen the prognosis of the underlying disorder, treatment of the status is recommended. However, there is debate on whether aggressive therapy with anesthetic agents is warranted. Epilepsia partialis continua refers to the situation in which there is continuous focal motor activity that may last months to years. The most common cause is Rasmussen encephalitis.

Causes of Seizures

The etiology of epilepsy is classified into three broad categories: genetic, structural, and unknown.

Genetic and Neurometabolic Causes. There are many genetic and neurometabolic causes that lead to seizures, typically beginning in childhood. Genetic disorders include disorders such as severe myoclonic epilepsy of childhood, tuberous sclerosis, Rett syndrome, Angelman syndrome, and fragile X. Neurometabolic disorders, which may also have a genetic cause, result in disturbances of metabolism and can lead to seizures. Disorders such as urea cycle defects, pyridoxine dependency, biotinidase deficiency, and glucose transporter deficiencies can cause severe seizures.

Structural Causes. The most common types of brain lesions causing seizures are tumors, vascular lesions, head trauma, infectious diseases, congenital malformation of the brain, and biochemical or degenerative disease processes affecting the brain.

Brain tumor is an important cause of seizures, particularly in the adult patient, becoming an increasingly likely cause after the second decade of life and one of the main causes in the fourth and fifth decades. A brain tumor should be suspected in any person who has onset of seizures, especially focal seizures, after age 20 years.

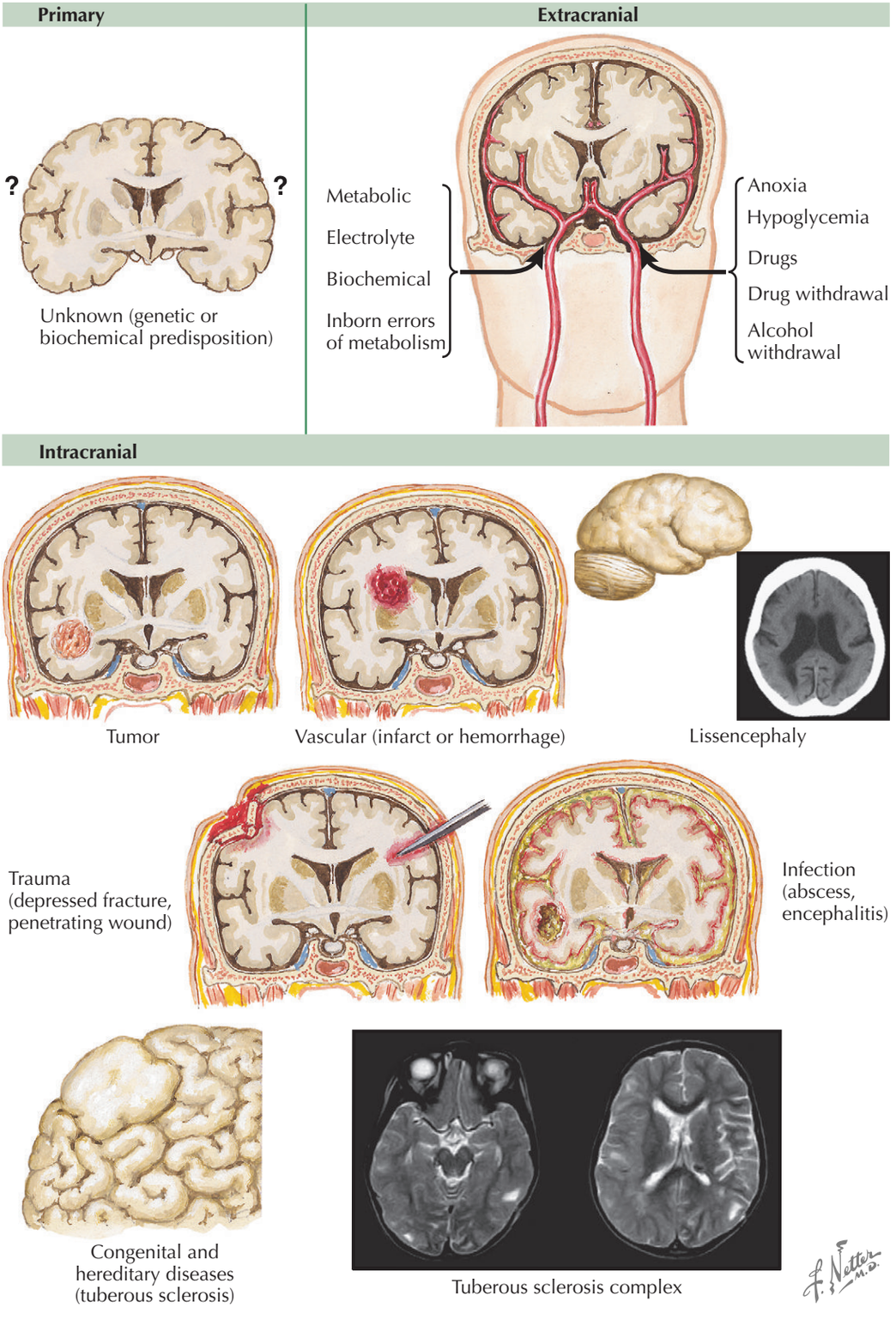
Head trauma is a major cause of seizures, which may occur shortly after the head injury or, more often, several months to several years later. Factors that increase the chance of development of post-traumatic seizures are a penetrating head injury, severe damage to the brain, prolonged periods of unconsciousness, post-traumatic amnesia, complications of wound healing, and a persistent neurologic deficit.

Vascular disease is one of the most common causes of seizures in older persons, particularly after age 50 years. Seizures can occur transiently after an acute stroke (thrombotic, embolic, or hemorrhagic) or may develop later as a sequela of cerebrovascular disease. Although uncommon, arteriovenous malformations are frequently associated with seizures. Other vascular causes include subdural hematomas, venous thrombosis, and hypertensive encephalopathy.

Seizures may occur with any *acute infection* of the nervous system or as a complication of damage to the nervous system by the inflammatory process. Patients with *cerebral abscesses* have a high incidence of seizures, and *encephalitis* and *meningoencephalitis* may be associated with either focal or generalized seizures.

Congenital brain malformations are a common cause of childhood seizures. With improved neuroimaging, many patients who were thought to have idiopathic epilepsy have now been found to have brain malformations. The severity of the seizures is related to the type and extent of the malformation.

Systemic Causes. Disease processes or disorders that can cause seizures include various types of metabolic, electrolyte, and biochemical disturbances; hypoxia; hypoglycemia; toxic processes; drugs; or abrupt withdrawal from drugs or alcohol. Various conditions, such as fever, fatigue, sleep deprivation, flashing lights, sound, or emotional factors may also precipitate seizures in susceptible individuals. In young children, fever is a common cause of seizures.



Neurobiology of Epilepsy

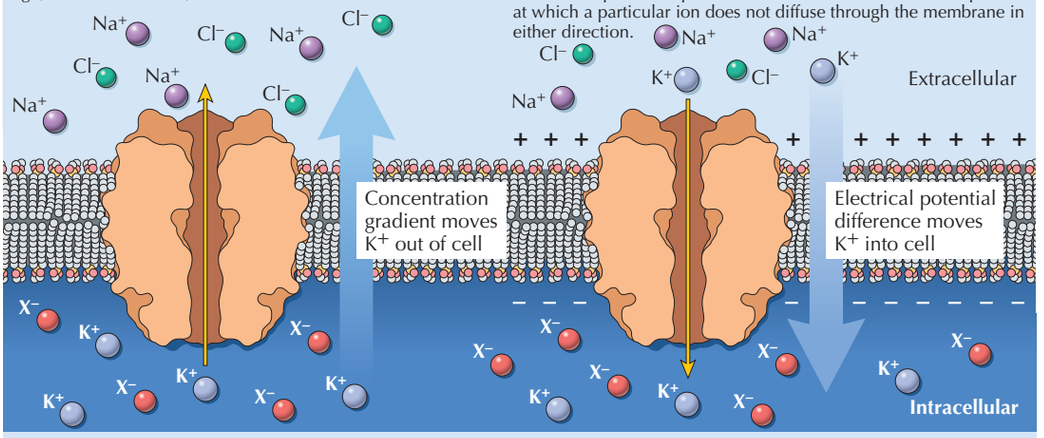
The core feature of brain electrochemical signals is the neuron membrane. Like all cell membranes, the neuron membrane is a phospholipid bilayer. This lipid bilayer prevents the exchange of ionized substrates between the cell and its environment, which is critical for electrical signaling. The inside of the cell at rest is negatively charged compared with the outside of the cell, due to concentration differences in ions. Sodium (Na^+), calcium (Ca^{2+}), and chloride (Cl^-) are predominantly found extracellularly, whereas K^+ and organic ions are concentrated intracellularly. These concentration differences are due to specific ion transporters that use the cell's energy supply to continuously move ions in and out of the cell. These pumps create concentration differences (between the inside and outside of the neuron) by transporting ions against their concentration gradients (from regions of low concentration to regions of high concentration). This concentration gradient across the membrane provides the electrochemical energy to drive signaling. These ions will flow through the membrane through protein channels. Most channels are ion-selective and will allow the passage of a specific ion. Unlike the continuous transport by the ion pumps, transport by the ion channels is noncontinuous. Ion channels open or close in response to signals from their environment. Voltage-gated channels open or close in response to changes in electrical potential across the cell membrane, whereas ligand-gated channels require a binding of a particular signaling molecule to open or close.

The two most important ions in the transmission of action potentials are Na^+ and potassium K^+. Voltage-gated Na^+ channels have three types of states: deactivated (closed), activated (open), and inactivated (closed). During excitation of the cell, Na^+ channels are activated through removal of an intracellular "activation gate," and Na^+ begins flowing into the cell. Once some Na^+ ion channels begin opening, the voltage drops further, causing more channels to open until the membrane depolarizes. Na^+ channels are more sensitive to voltage change than K^+ channels are and open more rapidly. Thus in a depolarization, the Na^+ ions will rush into the cell faster than the K^+ ions move outward. This sudden depolarization, called an action potential, will briefly result in a +30 millivolt potential difference. Once the slowly-opening voltage-gated K^+ ion channels have opened and allowed K^+ to flow out, the action potential is ended. Once Na^+ channels are activated, they quickly are inactivated due to an "inactivation gate" that blocks the inside of the channel shortly after it has been activated. During an action potential, the channel remains inactivated for a few milliseconds after depolarization. The inactivation is removed when the membrane potential of the cell repolarizes after the falling phase of the action potential. This allows the channels to be activated again during the next action potential. Thus the Na^+ ion channels initiate the action potential, and the K^+ ion channels terminate it. The channels then close, and the sodium pump can restore the resting potential of –70 millivolts.

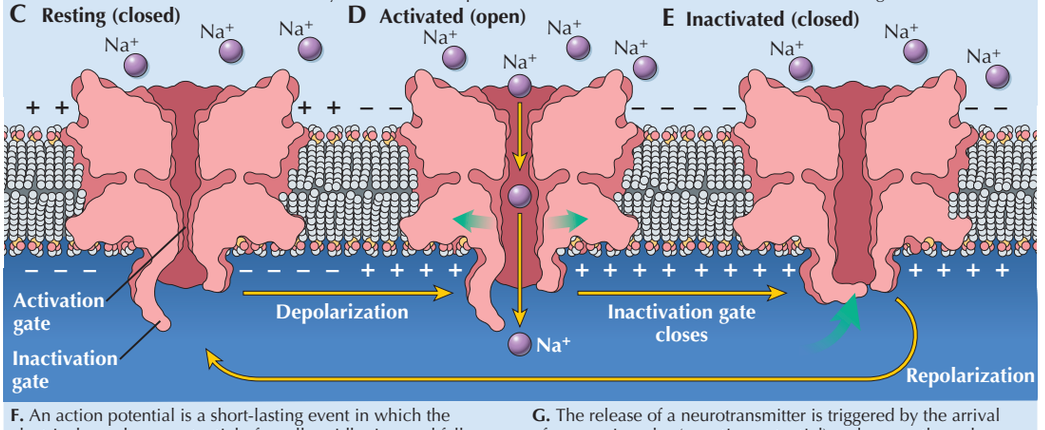
Membrane polarity is also affected by ligand-gated channels that open when neurotransmitters, the ligands of synaptic transmission, bind to specific receptors connected to the channels. Glutamate is the primary excitatory neurotransmitter and gamma-aminobutyric acid (GABA), the principal inhibitory transmitter. Synaptic transmission is mediated by glutamate that is released

A. The movement of ions across the cell membrane is dependent upon both concentration and electrostatic forces. Ions flow from high concentrations to lower concentrations as depicted by the flow of K^+ ions from inside the cell, where the concentration is high, to outside the cell, where the concentrations is lower.

B. Ions are attracted to charges of the opposite polarity. In this example, K^+ ions flow from the extracellular environment, which is positive in retationship to the intracellular space, which is negative. Both concentration and electrostatic forces determine flow of ions. The equilibrium potential for the ion is the membrane potential at which a particular ion does not diffuse through the membrane in either direction.

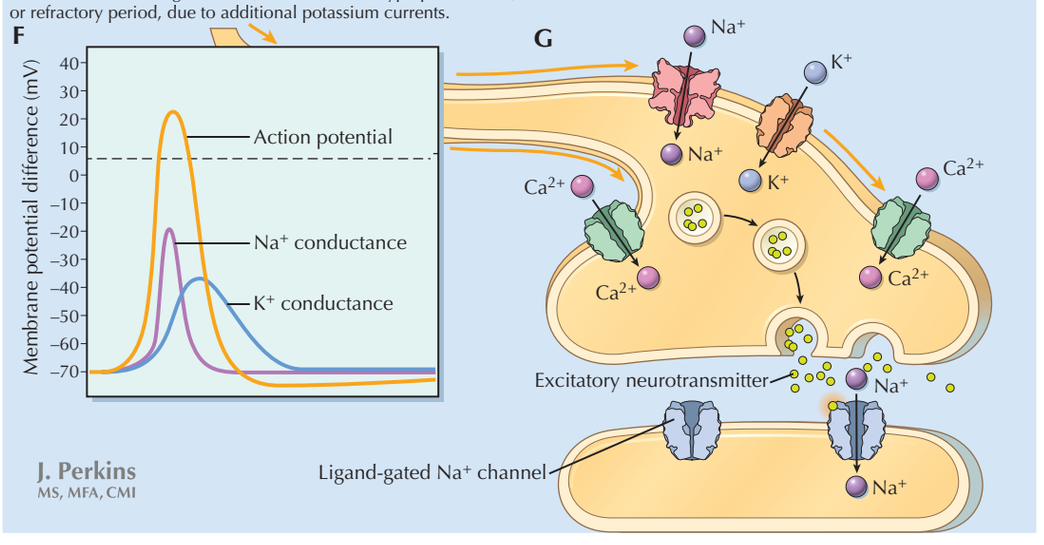


Three states of the sodium channel. C. In the resting state, no ion flow occurs due to closure of the activation gate. **D.** When the membrane begins to depolarize, the activation channel opens and ion flow occurs. **E.** As the cell becomes depolarized, the inactivation gate closes and no further ion flow occurs. Only when the cell repolarizes does the sodium channel return to the resting state.



F. An action potential is a short-lasting event in which the electrical membrane potential of a cell rapidly rises and falls. Action potentials begin with an inward flow of Na^+ ions, which changes the electrochemical gradient, which in turn produces a further change in the membrane potential. This then causes more channels to open, producing a greater electric current. The process proceeds until most of the available ion channels open, resulting in a large upswing in the membrane potential. The rapid influx of Na^+ ions causes the polarity of the plasma membrane to reverse, and the ion channels then rapidly inactivate. Potassium channels are then activated, and there is an outward current of K^+ ions, returning the electrochemical gradient to the resting state. After an action potential has occurred, there is a transient negative shift, called the afterhyperpolarization, or refractory period, due to additional potassium currents.

G. The release of a neurotransmitter is triggered by the arrival of a nerve impulse (or action potential) and occurs through a process called exocytosis. Within the presynaptic nerve terminal, vesicles containing neurotransmitter sit "docked" and ready at the synaptic membrane. The arriving action potential produces an influx of Ca^{2+} ions through voltage-dependent, Ca^{2+}-selective ion channels. Ca^{2+} ions then bind with the proteins found within the membranes of the synaptic vesicles, allowing the vesicles to "dock" with the presynaptic membrane, resulting in the creation of a fusion pore. The vesicles then release their contents to the synaptic cleft.



J. Perkins
MS, MFA, CMI

NEUROBIOLOGY OF EPILEPSY
(Continued)

from the pyramidal neurons and depolarizes and excites the target neurons via ionotropic receptors (NMDA, α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid [AMPA], and kainic acid [KA]). Glutamate channel opening allows Na^+ and Ca^{2+} to enter the cell, resulting in depolarization, whereas with GABA channel opening, Cl^- enters the cell, resulting in hyperpolarization.

Once the action potential is generated, it propagates to the synapse. Depending on the type of cell, an excitatory or inhibitory neurotransmitter is released. The effect of the neurotransmitter on the postsynaptic membrane will determine current flow into or out of the postsynaptic cell, thus determining whether the postsynaptic cell will generate action potentials.

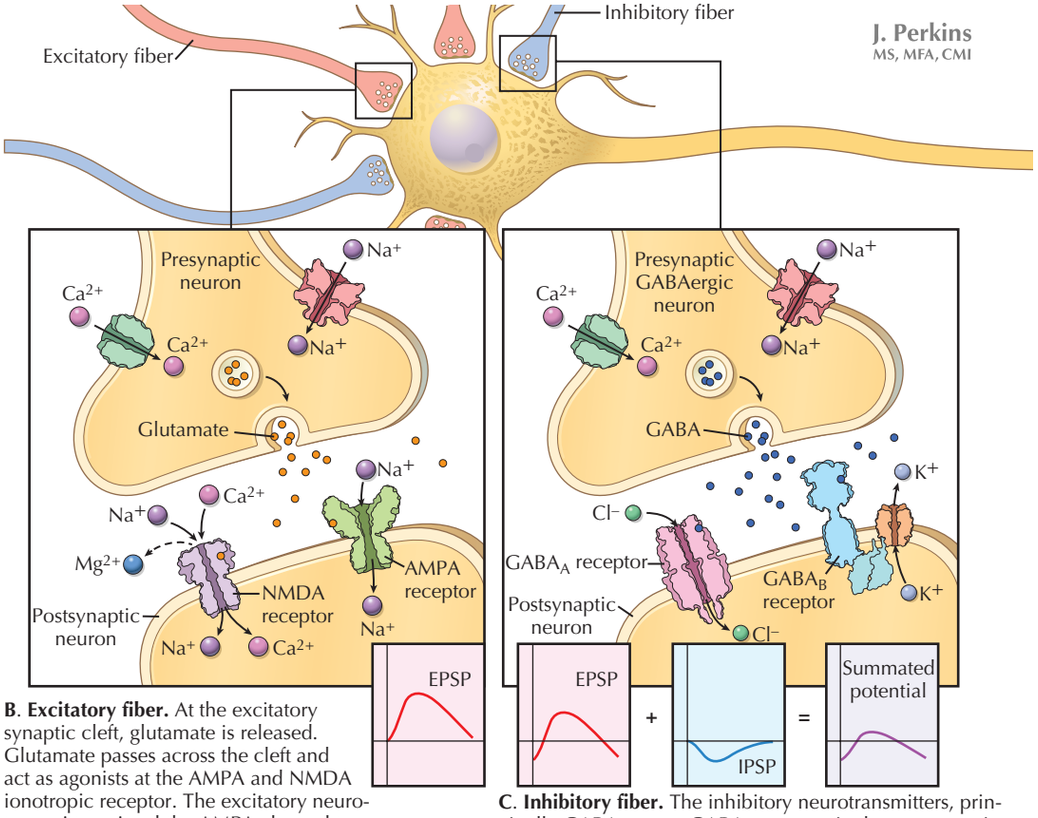
Epilepsy is a paroxysmal disorder characterized by abnormal neuronal discharges. Although epilepsy has many causes, the fundamental disorder is secondary to abnormal synchronous discharges of a network of neurons. Epilepsy is secondary to an imbalance between excitatory and inhibitory input to cells.

The hallmark of epileptic neurons in experimental models of epilepsy is membrane depolarization, which results in an interictal spike recorded by EEG. During an interictal discharge, the cell membrane near the soma undergoes a relatively high-voltage (approximately 10 to 15 mV) and relatively long (100 to 200 μsec) depolarization. The long depolarization has the effect of generating a train of action potentials that are conducted away from the soma along the axon of the neuron. This large depolarization is called the paroxysmal depolarization shift (PDS). The PDS is caused by an imbalance of excitation over inhibition. This enhanced excitation, or reduced inhibition, can be secondary to a variety of abnormalities, including disturbances in the intrinsic properties of neuronal membranes, excess excitation through NMDA and AMPA receptors, reduced inhibition through GABA channels, and abnormalities of potassium and calcium channels. The net effect is an imbalance of excitation over inhibition. The interictal PDS is followed by a large hyperpolarization, which serves to limit the duration of interictal paroxysms. It is important to remember that an epileptic area is made up of numerous abnormal neurons that discharge in an abnormal synchronous manner. The PDS may occur because of intrinsic membrane abnormalities in a group of neurons or because of excessive excitatory input (or reduced inhibitory input) to a group of neurons.

With time, a progressive loss of hyperpolarization after the PDS may occur in the epileptic focus. During seizures, the epileptic neurons undergo prolonged depolarization with waves of action potentials during the tonic phase of the seizure and oscillations of membrane potentials with bursts of action potentials, separated by quiet periods during the clonic phase. An EEG recorded at the scalp at this time shows continuous spikes, which generally coincide with the tonic stage of a generalized tonic-clonic seizure. During the next stage, large inhibitory potentials occur (with slowing or flattening on surface EEG) and alternate with recurrent, rhythmic PDSs (with spikes on surface EEG). This pattern generally coincides with the clonic stage of the seizure.

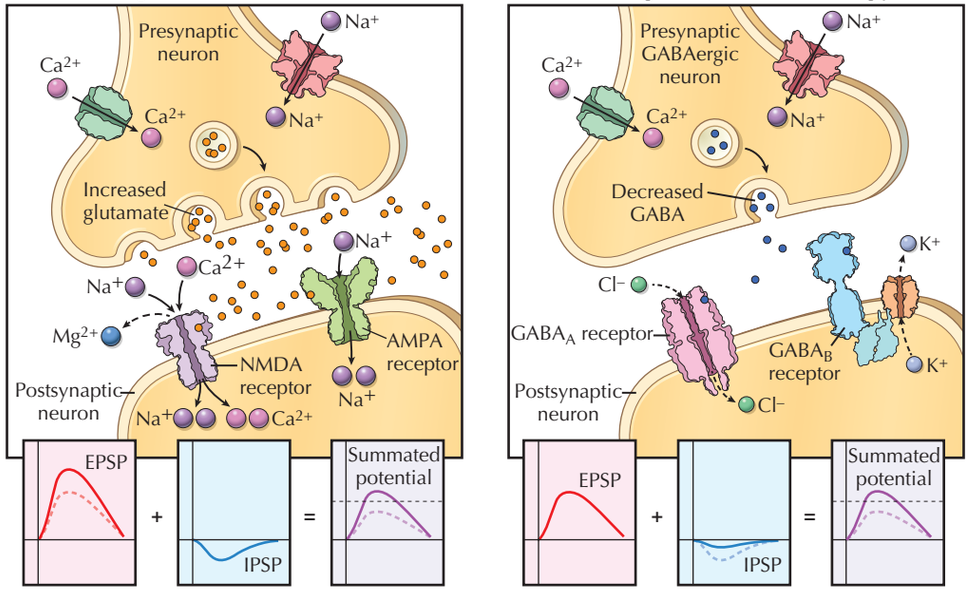
Focal seizures may spread along the cortex and propagate to distant regions via white matter tracts. Many patients with focal seizures will have an aura at the

A. Postsynaptic neuron at which several presynaptic afferent fibers terminate. Fibers colored in pink convey excitatory information across the synaptic cleft to the postsynaptic neuron, whereas the inhibitory fiber is blue and conveys inhibitory information to the postsynaptic neuron.



B. **Excitatory fiber.** At the excitatory synaptic cleft, glutamate is released. Glutamate passes across the cleft and act as agonists at the AMPA and NMDA ionotropic receptor. The excitatory neurotransmitters signal the AMPA channel to open, permitting the inflow of Na^+.This results in depolarization in the membrane potential so that the difference in potential across the membrane is shifted toward the positive, i.e., depolarization. With depolarization, there is a release of Mg^{2+} from the NMDA receptor, permitting Na^+ and Ca^{2+} ions to enter the postsynaptic neuron. An excitatory postsynaptic potential (EPSP) is generated.

C. **Inhibitory fiber.** The inhibitory neurotransmitters, principally GABA, act on GABA receptors in the postsynaptic neuron membrane, permitting the entry of Cl^- ions, shifting the membrane potential to a more negative potential, i.e., hyperpolarization. An inhibitory postsynaptic potential (IPSP) is generated. In normal synaptic transmission, there is a balance between excitatory and inhibitory neurotransmitters so that the summation of EPSP and IPSP maintains the polarization of the membrane at a level below the threshold at which bursts of firing occur, termed the resting potential.



D. **Increase in glutamate EPSP.** With an increase in excitatory neurotransmitters, the postsynaptic neuron membrane becomes more positive, producing an increase in EPSP. The summation of the excitatory and inhibitory signals moves across the threshold value, and an action potential occurs.

E. **Decrease in IPSP.** When there is a decrease in inhibitory neurotransmitters, the IPSP decrease and the postsynaptic neuron membrane becomes more positive. The summation of the excitatory and inhibitory signals moves across the threshold value and an action potential is fired.

NEUROBIOLOGY OF EPILEPSY
(Continued)

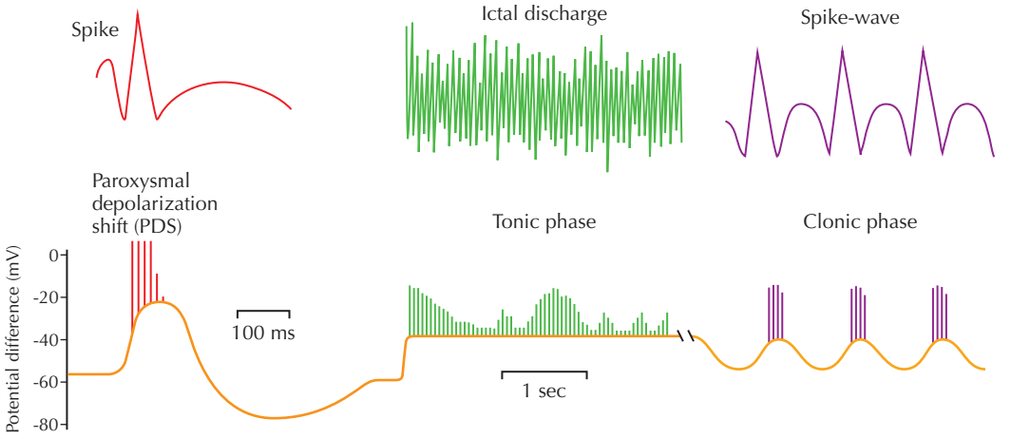
onset. The type of aura is dependent upon the region of the brain in which the seizure originated. For example, patients with temporal lobe onset may experience déjà vu (the experience of feeling sure that one has already witnessed or experienced a current situation), whereas a patient with parietal lobe onset may experience a sensation of numbness or tingling. With propagation, more and more neurons are recruited into synchronous firing, which could culminate in a generalized tonic-clonic seizure.

GENERALIZED SEIZURES

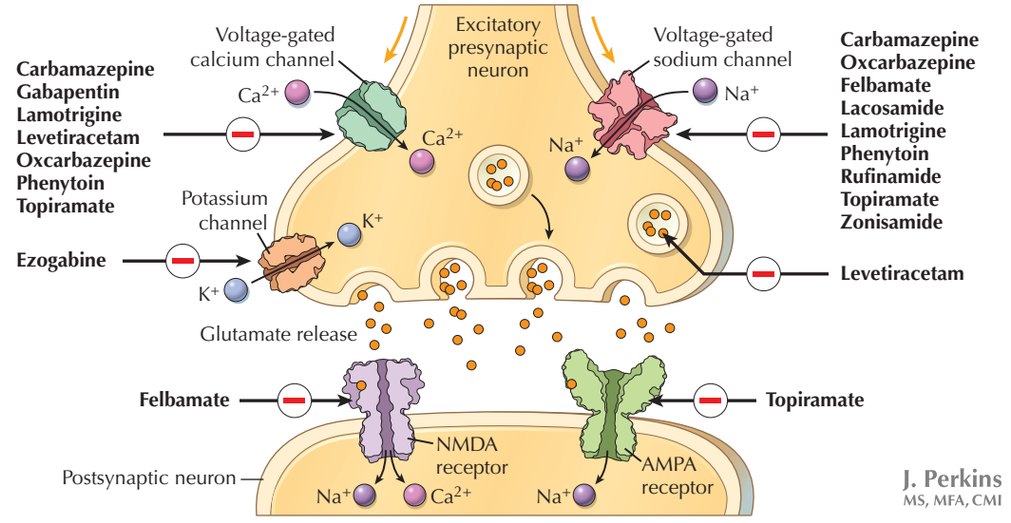
Unlike focal seizures, which involve a relatively restricted group of neurons at onset, generalized seizures result from dysfunction of networks of neurons involving multiple brain regions. The basic underlying mechanism in absence seizures, and possibly other generalized seizure types, involves thalamocortical circuitry and the generation of abnormal oscillatory rhythms in the neuronal network. The neuronal circuit responsible for the generation of the oscillatory thalamocortical burst-firing observed during absence seizures includes cortical pyramidal neurons, thalamic relay neurons, and the nucleus reticularis thalami (NRT). The principal synaptic connections of the thalamocortical circuit include glutamatergic fibers between neocortical pyramidal cells and the NRT; GABAergic connections between cells of the NRT, which activate $GABA_A$ receptors; and GABAergic fibers from NRT neurons, which activate $GABA_A$ and $GABA_B$ receptors on thalamic relay neurons.

The cellular events that underlie the ability of NRT neurons to shift between an oscillatory and tonic firing mode are the low-threshold (T) Ca^{2+} spikes that are present in thalamocortical and NRT neurons. These T-type Ca^{2+} channels are a key membrane property involved in burst-firing excitation and are associated with the change from oscillatory to burst-firing in thalamocortical cells. Mild depolarization of these neurons is sufficient to activate these channels and to allow the influx of extracellular Ca^{2+}. Further depolarization produced by Ca^{2+} inflow will exceed the threshold for firing a burst of action potentials. After T-channels are activated, they become inactivated rather quickly, hence the name transient. Deinactivation of T-channels requires a relatively lengthy hyperpolarization. $GABA_B$ receptor–mediated hyperpolarization is a primary factor in the deinactivation of T-channels.

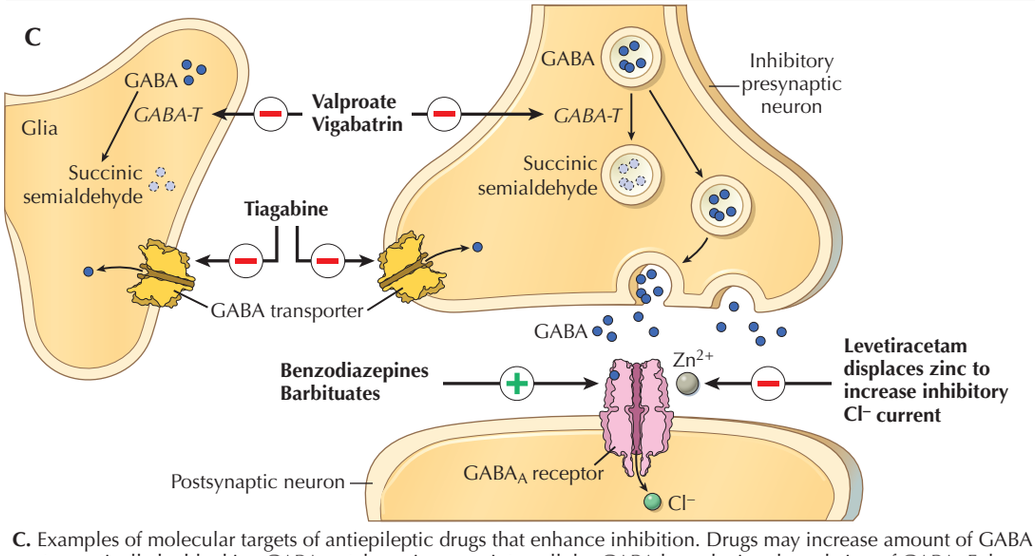
Recurrent collateral GABAergic fibers from the NRT neurons activate $GABA_A$ receptors on adjacent NRT neurons. Activating $GABA_A$ receptors in the NRT therefore results in an inhibition of inhibitory output to the thalamic relay neurons. Because of the decreased $GABA_B$ activation, there would be a reduced likelihood that Ca^{2+} deinactivation would occur. This would result in decreased oscillatory firing. However, direct $GABA_A$ and $GABA_B$ activation of thalamic relay neurons would be expected to have detrimental effects, increasing hyperpolarization and therefore increasing the likelihood of deinactivation of the T-channels. The abnormal oscillatory rhythms in absence seizures can be caused by abnormalities of the T-type Ca^{2+} channels or enhanced $GABA_B$ function.



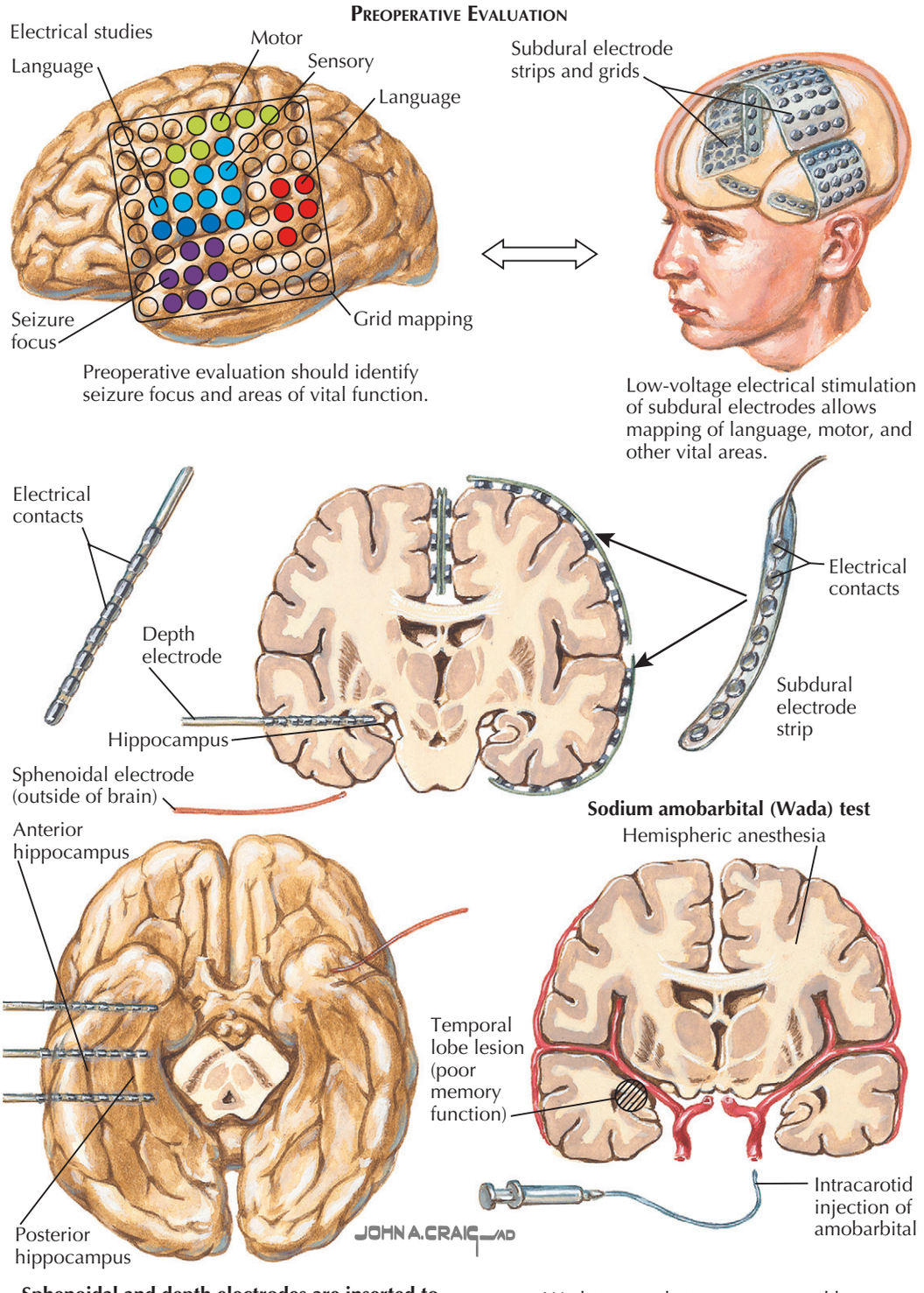
A. Paroxysmal depolarization shift (PDS) is a cellular marker of epilepsy and consists of a large depolarization of a group of neurons with action potentials, as indicated by the vertical lines on the large depolarization. The PDS is followed by repolarization. The PDS and repolarization corresponds to a spike and wave on the EEG. A seizure occurs when there is a massive depolarization of cells without intervening periods of repolarization. This would correspond to the tonic phase of the seizure. As inhibition increases during the seizure, there is a cycle of PDS followed by repolarization. This corresponds to the clonic phase of the seizure



B. Examples of molecular targets of antiepileptic drugs that reduce excitability. This may occur through blockage of calcium, sodium, and potassium channels or through reducing ion flow through NMDA and AMPA receptors. Levetiracetam binds to synaptic vesicles, which may lead to reduced neurotrasnmiter release.



C. Examples of molecular targets of antiepileptic drugs that enhance inhibition. Drugs may increase amount of GABA postsynaptically by blocking GABA uptake or increase intracellular GABA by reducing degradation of GABA. Enhancing chloride flow through the GABA receptor is a common mechanism of inhibitory drugs, such as barbiturates and benzodiazepines. Levetiracetam displaces zinc from the GABA receptor, which results in increased chloride currents.



Treatment of Epilepsy

Although there are a variety of treatment options in treating seizures, the three main approaches are antiepileptic drugs, dietary therapy, and surgery.

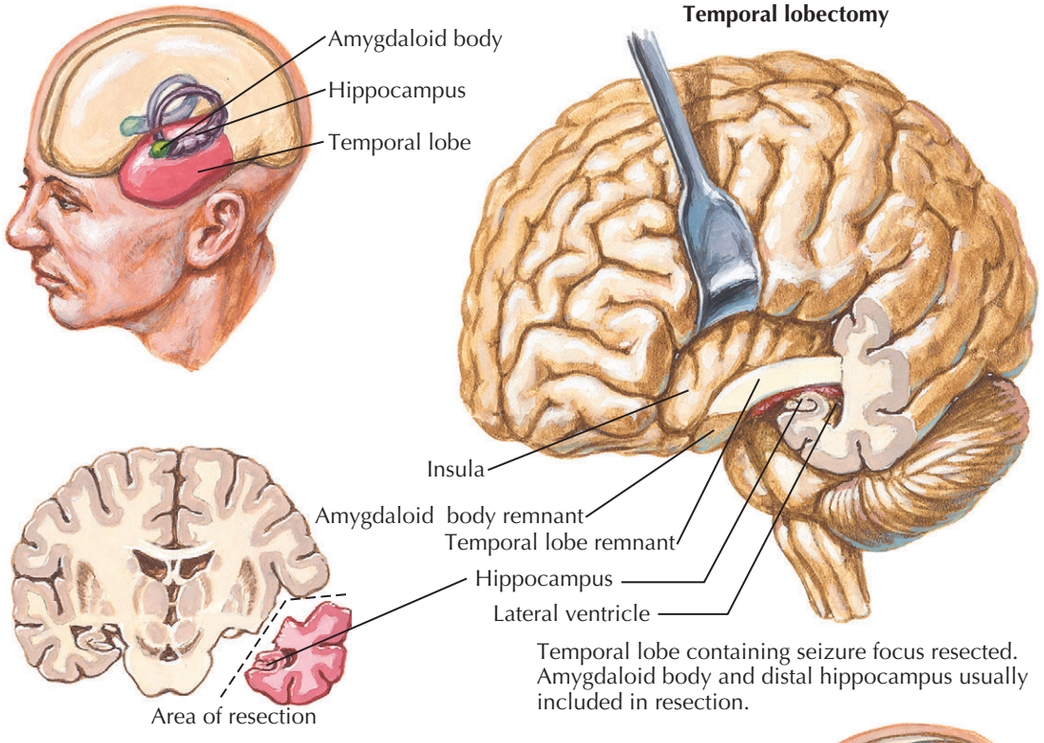
The vast majority of patients are treated with antiepileptic drugs that work on a variety of targets: (1) blocking sodium and calcium channels or opening potassium channels, (2) reducing excitation by blocking glutamate receptors, (3) increasing inhibition by enhancing GABA currents or increasing extracellular or intracellular GABA concentrations.

Drugs targeting the Na^+ channel reduce the likelihood of a seizure by either increasing the amount of time the channel stays in the inactive state or by altering the shape of the Na^+ channel. In both cases, the drugs prevent sustained repetitive firing of the cells. Likewise, Ca^{2+} channel blockers are used to block T-type Ca^{2+} channels or high-voltage activated channels, resulting in decreased excitability of the cells. Ca^{2+} is also critical in the release of a neurotransmitter from synaptic vesicles. Reducing release of glutamate would reduce the likelihood of a seizure. Levetiracetam binds to synaptic vesicles and appears to reduce seizure frequency by altering the release of neurotransmitters from synaptic vesicles.

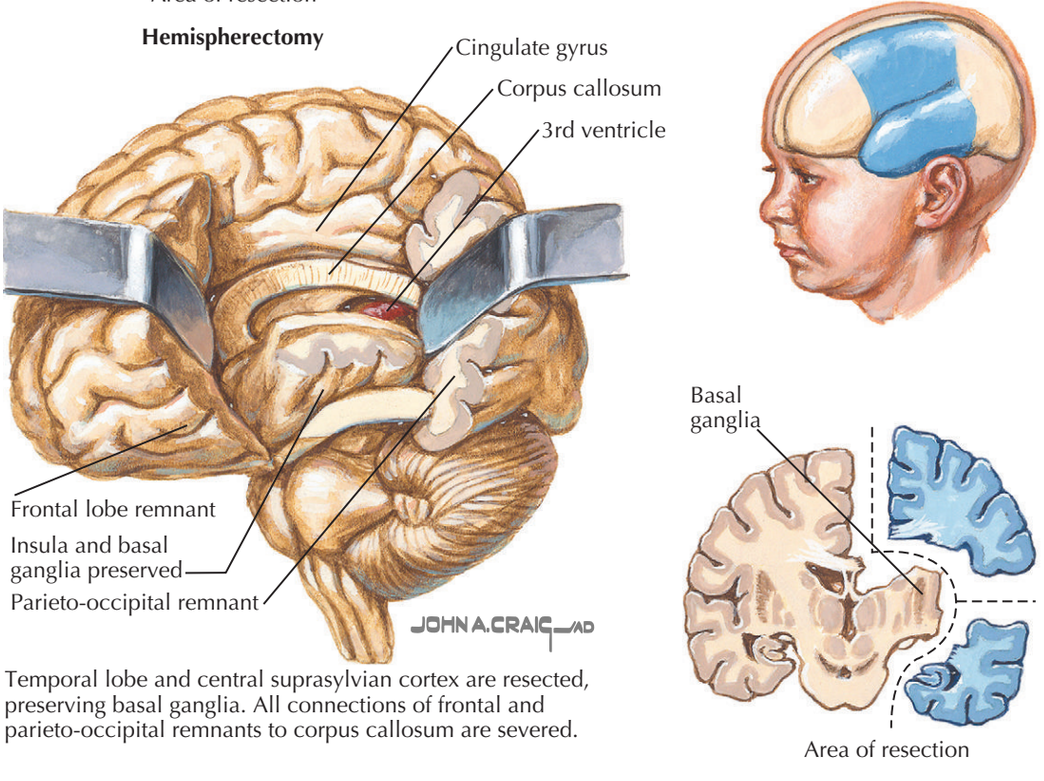
Blocking excitation through the NMDA, AMPA, and kainate receptors can reduce excitation by reducing the inward flow of Na^+ and Ca^{2+} ions. Likewise, drugs acting on $GABA_A$ receptors facilitate the passage of Cl^- into cells. Their passage into the cell makes the resting membrane potential more negative inside the cell and makes it more difficult for the cell to depolarize. The $GABA_A$ receptor has benzodiazepine and barbiturate receptor sites. Activation of the benzodiazepine receptor enhances the frequency of openings of the $GABA_A$ receptor. Activation of the barbiturate receptor increases the duration of openings of the $GABA_A$ receptor. The GABA effect can also be increased by blocking reuptake of GABA by neurons and glia, increasing the concentration of GABA at postsynaptic receptors, or reducing GABA breakdown in the neurons through inhibition of GABA transaminase.

The ketogenic diet is typically used to treat children with severe epilepsy who do not respond to antiepileptic drugs. The ketogenic diet consists of a high

Resective Surgery



Temporal lobe containing seizure focus resected. Amygdaloid body and distal hippocampus usually included in resection.



Temporal lobe and central suprasylvian cortex are resected, preserving basal ganglia. All connections of frontal and parieto-occipital remnants to corpus callosum are severed.

Treatment of Epilepsy
(Continued)

proportion of fats and small amounts of carbohydrate and protein. The basis of the therapeutic effectiveness of the ketogenic diet is thought to be the ketosis that develops when the brain is relatively deprived of glucose as an energy source and must shift to use of ketone bodies as the primary fuel.

Patients who do not respond to antiepileptic drugs or dietary therapy may benefit from surgery. In patients with well-localized seizures focus, resection of the epileptic tissue may be possible. If the epileptic focus is coming from a brain area where resection would result in a significant neurologic deficit, such as weakness, aphasia, or memory impairment, focal surgery is not recommended. The most common surgery for focal seizure is a temporal lobe resection. In rare individuals, with a severely damaged hemisphere, who have unilateral weakness and seizures arising from that hemisphere, a hemispherectomy can be curative. Patients with severe focal seizures with secondary generalization may be helped by cutting the corpus callosum (corpus callosotomy). This reduces the likelihood that a focal seizure will become generalized.

Vagus nerve stimulation (VNS) is an adjunctive treatment for certain types of intractable epilepsy and treatment-resistant depression. VNS uses an implanted stimulator that sends electric impulses to the left vagus nerve in the neck via a lead wire implanted under the skin. The tenth cranial nerve arises from the medulla and carries both afferent and efferent fibers. The afferent vagal fibers connect to the nucleus of the solitary tract, which, in turn, projects connections to other locations in the central nervous system. Little is understood about exactly how vagal nerve stimulation improves seizure control, but proposed mechanisms include alteration of norepinephrine release by projections of solitary tract to the locus coeruleus, elevated levels of inhibitory GABA related to vagal stimulation, and inhibition of aberrant cortical activity by reticular system activation.

PSYCHIATRY

Limbic System

The limbic system is the only brain area receiving major hypothalamic input and providing interconnection with widespread cortical areas. Major limbic structures include the amygdala, piriform cortex *(parahippocampal gyrus, uncus + amygdala)*, hippocampus, substantia innominata, and septal area. The limbic system's diverse roles include memory, drive, affect, autonomic tone, endocrine control, and immunoregulation.

The amygdala is connected extensively to the hypothalamus and other limbic structures. It receives input from widespread sensory cortical regions and paralimbic structures (piriform cortex, entorhinal cortex, and parahippocampal cortex on the temporal lobe medial surface and the cingulate cortex just above the corpus callosum). The amygdala is critical for channeling drive and affect. In lesion studies of monkeys, visual information from one eye was restricted to an intact amygdala, while visual information from the other eye was directed toward a lesioned amygdala. The monkey's typical aggressive behavior when visually provoked was intact only when stimulated through the intact visual pathway. When provoked via the lesioned pathway, the monkey remained passive.

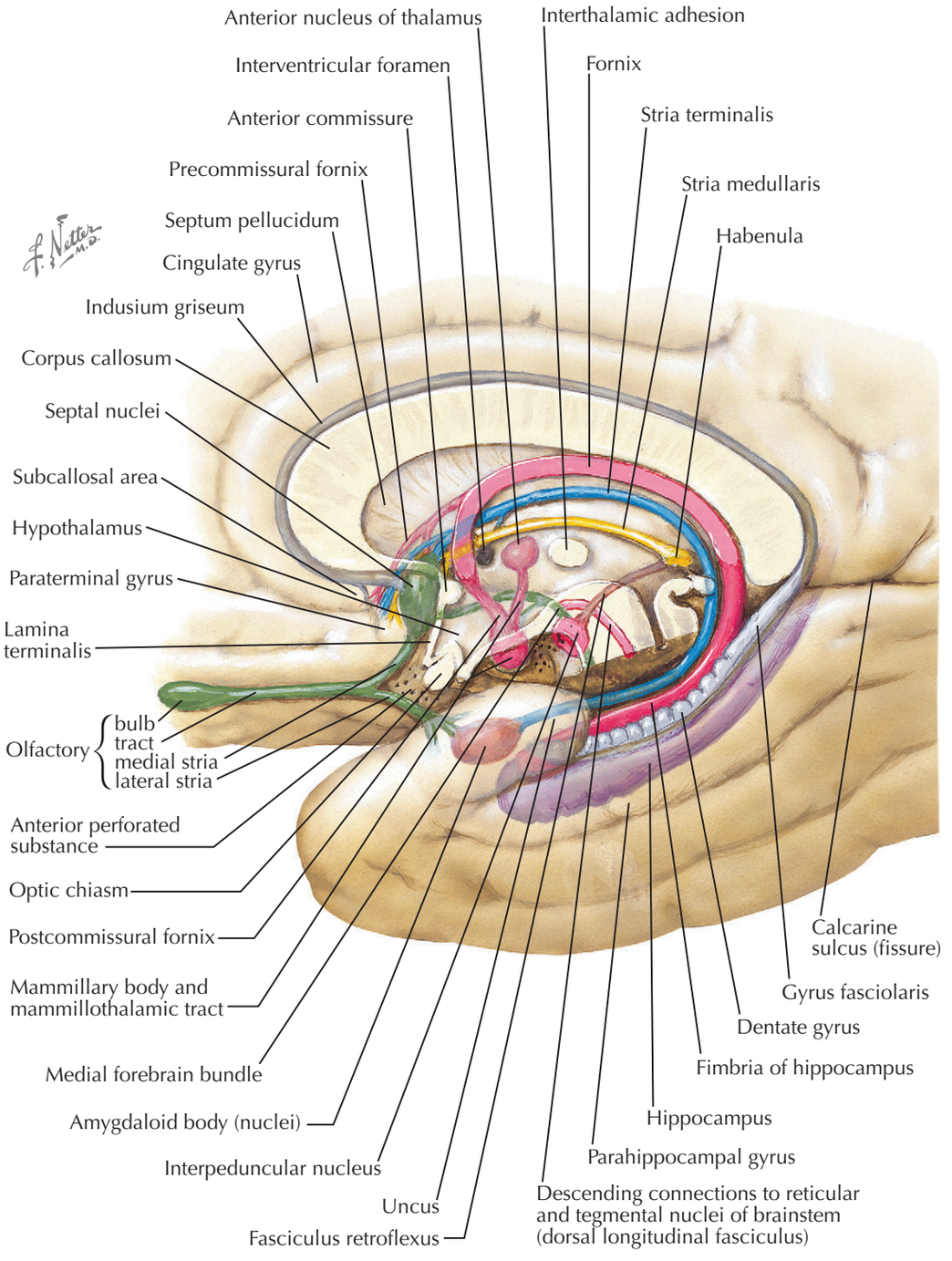
This is observed in the *Klüver-Bucy syndrome* that arises when the amygdala is disconnected from cortical sensory input. The typical features of the Klüver-Bucy syndrome include (1) indiscriminant sexual behavior toward objects in the immediate extrapersonal space, (2) absence of fight-flight reaction toward threat, and (3) inability to visually distinguish edible from inedible objects except by orally inspecting objects.

The *amygdala channels appropriate emotional response toward sensory targets while* having an *important role in the interpretation and display of affective gestures, including vocalization*. The right hemisphere is dominant here. The amygdala also plays an *integral role* in the experience of strong emotions, including *fear, rage, and experiences of familiarity*. The amygdala *imparts the affective coloring of personal experience* that reflects a person's history, present internal state, and characteristics of their present mental experience. Certain disease states engender disruptions of this balance. Thus the affective color of a *particular mental process* may be *distorted, amplified, or diminished*, thereby changing the very meaning of the entire experience. This is witnessed in *panic attacks, dissociative states, depression, and schizophreniform* conditions. In humans, the amygdala does not appear to play a direct role in memory formation, although amnesia resulting from hippocampal damage seems more severe if there is additional involvement of the amygdala. This suggests the amygdala may establish an affective link in memorization. Additional amygdala roles include regulation of autonomic, endocrine, and immunologic function.

The *piriform cortex* is a relay area for cortical and olfactory information, much the way the thalamus is the relay area for every other sensory modality. This area also has *numerous connections with hypothalamus and other limbic regions.* Animal studies suggest a role in regulation of the direction of drive within extrapersonal space, such as attack or sexual behaviors.

The *hippocampus* receives almost all of *its input from paralimbic areas*, which receive their input from cortical sensory areas. Other inputs include hypothalamus, amygdala, and septal area. Its *major role is memory and learning*. Isolated hippocampal damage is relatively rare, but combined lesions of *hippocampal and parahippocampal areas* in infarcts lead to severe amnestic states, even when the amygdala is spared. These structures are *necessary for the formation of new memories* (recording experience) rather than storage of memories. In addition, they rekindle memories during retrieval. The motivational relevance of experience makes it more likely to be memorized and recalled. This is why storage and retrieval are affected with relative preservation of memory banks (long-term memory) in diseases affecting these structures.

The *septal nuclei and substantia innominata* contain the major cholinergic cells of the brain, located in the medial septal nucleus, the vertical and horizontal *limb nuclei of Broca's diagonal band*, and the *nucleus basalis of Meynert*. These areas project to the hippocampus, olfactory region, widespread cortical regions, and the amygdala. The hypothalamus and various limbic and paralimbic structures give rise to the majority of the inputs to these structures. This cholinergic network is *essential for intact memory* function. Patients with anterior communicating artery aneurysms or with septal tumors may develop amnestic states. In *Alzheimer disease*, where memory loss is the major clinical feature, there is a profound loss of cholinergic neurons in the nucleus basalis as well as in widespread cortical regions. *Septal lesions* may also produce exaggerated emotional reactions to novel or threatening stimuli, hyperdipsia, hyperphagia, and altered taste preference. There is evidence suggesting a role in attaching motivational value to extrapersonal objects.



Major Depressive Disorder

Major depressive disorder (MDD) is a mood disorder characterized by the occurrence of one or more major depressive episodes during one's lifetime. To diagnose a major depressive episode, five (or more) of the following nine symptoms must been present every day or almost every day during the same 2-week period and represent a change from a previous level of functioning. At least one symptom must be either (1) *depressed mood* or (2) *anhedonia* (markedly diminished interest or pleasure in all, or almost all, activities. The other seven criteria are (3) a significant *decrease or increase in appetite or weight*, (4) *insomnia or hypersomnia*, (5) *psychomotor retardation or agitation*, (6) *fatigue or loss of energy*, (7) feelings of *worthlessness or excessive or inappropriate guilt*, (8) *poor concentration or difficulty making decisions*, and (9) *recurrent thoughts of death*, *suicidal ideation*, *or a suicide attempt*. These symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning and should not be due to the direct physiologic effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

Subtypes of depression may be defined by the presence of *psychotic features* (delusions, hallucinations), *catatonia* (motor disturbances, such as immobility or agitation, stereotyped movements, mutism), *melancholy* (weight loss, insomnia, morning worsening) or *atypism* (hypersomnia, hyperphagia), or *postpartum* onset of depression.

In epidemiologic studies, the 12-month and lifetime prevalence of MDD are, respectively, 5% to 7% and 13% to 18%, and the prevalence seems to be largely unrelated to ethnicity or geography (region of the country or urbanicity). In a recent U.S. epidemiologic survey, being female; Native American; widowed, separated, or divorced; being unemployed or disabled or having low income was significantly associated with higher rates of MDD. The mean age at onset for MDD is in the early 30s. The hazard for childhood onset MDD is relatively low, increases sharply between ages 12 and 16 years, and continues to increase, albeit more gradually, up to the early 40s. The diagnosis of MDD is associated with the presence of one or more psychiatric disorders during one's lifetime in nearly 75% of cases, including anxiety disorders (60%), substance use disorders (25%), and impulse control disorders (30%).

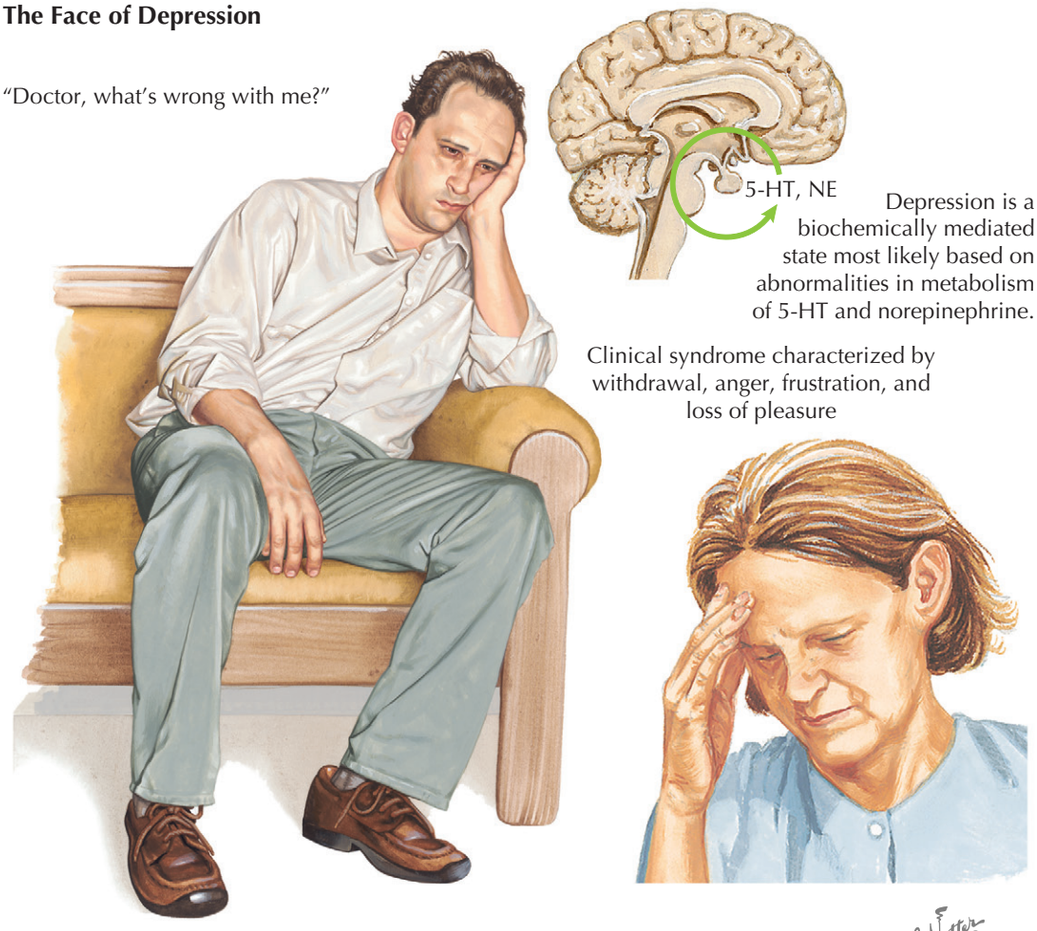
The neurobiologic basis and pathophysiology of MDD continue to be enigmatic. This is likely due in part to the heterogeneity of MDD, which may represent a group of disorders with several underlying pathologies, in which both genetic and environmental factors play a role. Studies have investigated disturbances in several neurotransmitters (serotonin [5-HT, i.e., 5-hydroxytryptamine], norepinephrine [NE], and dopamine, and more recently glutamate); in neuroendocrine and neuroimmune mechanisms, in particular, the hypothalamic-pituitary-adrenal axis involved in the response to stress; and in neurotrophic factors regulating plasticity in the brain. It is important to emphasize that neurotransmitters and hormones are integrated in anatomic and functional circuitry interacting at several levels. Imaging and postmortem studies suggest that MDD patients have structural and subtle cellular and molecular alterations within a complex neural network involving the prefrontal cortex, subgenual cingulate cortex, hippocampus, and amygdala.

MDD genetics are complex and multifactorial; this disorder frequently occurs in families, having an estimated heritability of approximately 40%. Through linkage, association, and genome-wide association studies, several candidate genes and regions of the genome are identified that may contribute to MDD; however, these findings are not consistent in variable studies. Each individual gene probably contributes only to a very small proportion of the variance, interacting with environmental factors.

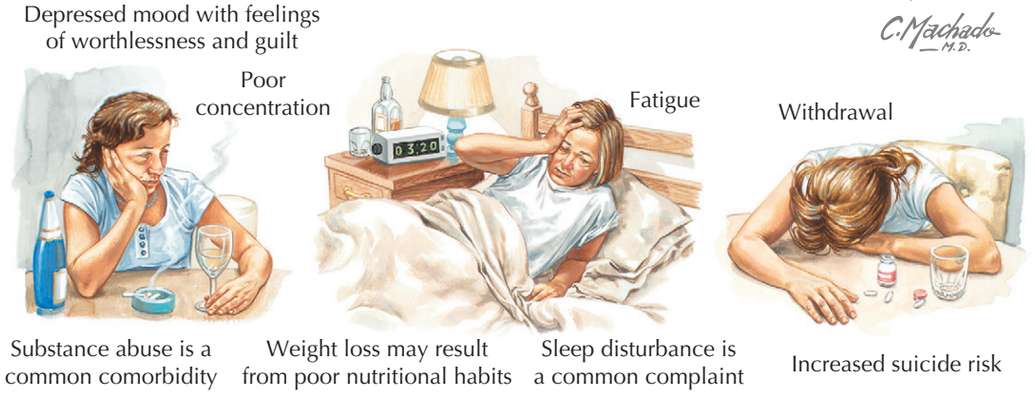
Initial treatment modality choices in MDD are influenced by a number of factors, including symptom severity, co-occurring psychiatric or medical conditions, psychosocial stressors, and the patient's preference. Antidepressant medications include selective serotonin reuptake inhibitors (SSRIs), usually used as a first choice, serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and others, including bupropion, nefazodone, trazodone, and mirtazapine. The choice of an antidepressant is based on side-effect profile, tolerability, safety, and history of prior response to treatment.

After an initial phase of pharmacologic treatment of 2 to 3 months, aimed at achieving full remission of symptoms, pharmacotherapy is typically continued for approximately 4 to 9 months to prevent early relapse. Psychotherapy, alone or combined with medications, may also be considered as initial treatment for patients with mild-to-moderate MDD. Electroconvulsive therapy (ECT) is a potentially very successful treatment option for patients who are more severely ill, present psychotic features or catatonia, and for those who are acutely suicidal.

The Face of Depression



Associated Symptoms and Comorbidities



POSTPARTUM DEPRESSION

The postpartum period has clearly been defined as a time of increased vulnerability to psychiatric illness in women; up to 85% of women experience some type of mood disturbance after childbirth. Most of these women experience transient and relatively mild mood symptoms ("the blues"); however, about 10% to 15% of women experience a more disabling and persistent form of mood disturbance, either postpartum depression (PPD) or postpartum psychosis. Although postpartum psychiatric illness was initially conceptualized as a group of disorders specifically related to childbirth, more recent evidence suggests that affective illness emerging during the postpartum period is clinically indistinguishable from affective illness occurring at other times during a woman's life. In fact, most women with postpartum illness will also go on to have mood episodes that are not related to either pregnancy or childbirth.

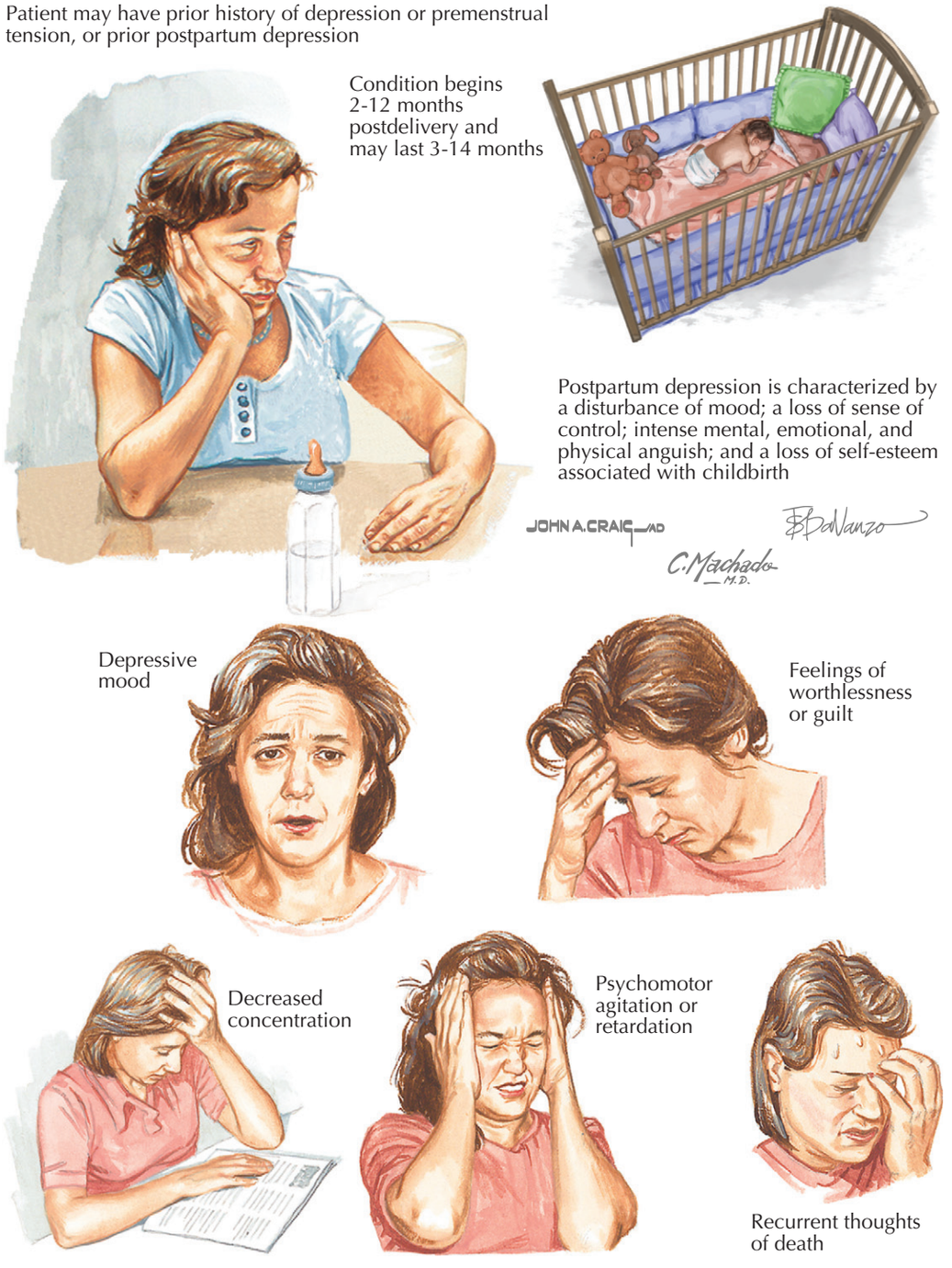
The *Diagnostic and Statistical Manual of Mental Disorders* (i.e., *DSM-IV*) does not list postpartum psychiatric disorders separately but instead uses a specifier, for example, "*with postpartum onset*" to describe *any depressive*, *manic*, *or mixed episode* (in major depressive disorder, bipolar disorder, or brief psychotic disorder) when the episode occurs *within the first 4 weeks after delivery*. Although risk of postpartum psychiatric illness is the highest in the first 4 weeks after childbirth, several different studies indicate that women remain at very high risk for affective illness during the first 3 months after delivery. In fact, women remain at heightened risk up to 1 year after childbirth. Thus many experts define *postpartum psychiatric illness* as any episode occurring *within the first year* after childbirth.

POSTPARTUM BLUES

During the first week after the birth of a child, many women experience a brief period of affective instability, commonly referred to as postpartum blues or the "baby blues." Given the high prevalence of this type of mood disturbance, it *may be more accurate* to consider the *blues* as a *normal experience* associated *with childbirth* rather than a psychiatric disorder. Women with postpartum blues report a variety of symptoms, including a rapidly fluctuating mood, tearfulness, irritability, and anxiety. These symptoms typically peak on the fourth or fifth day after delivery and may last for a few days, remitting spontaneously within 2 weeks of delivery.

POSTPARTUM DEPRESSION

Ten to 15 percent of women will present with more significant depressive symptoms or postpartum depression after childbirth. Unlike the blues, PPD is more *pervasive* and may *significantly interfere* with a mother's ability to function and to care for her child. Clinically, an episode of PPD is *indistinguishable* from *other types of major depressive episodes*, with symptoms of depressed mood, irritability, loss of interest in their usual activities, sleep disturbance, and fatigue. Women often express ambivalent or negative feelings toward their infant and may express doubts about their ability to care for their child. *Anxiety symptoms may be prominent* in this population, and women may present with *comorbid generalized anxiety*, *panic disorder*, *or obsessive-compulsive disorder (OCD)*.



POSTPARTUM PSYCHOSIS

This is the *most severe form of postpartum psychiatric illness*. It is a *rare* event that occurs in approximately *1 to 2 of 1000 women after childbirth*. Its presentation is often *dramatic*, with onset of symptoms early, typically within the *first 2 postpartum weeks*. Longitudinal studies indicate that *most* women with postpartum psychosis *suffer from bipolar disorder*, and the symptoms of postpartum psychosis most closely resemble those of a *rapidly evolving manic* or mixed episode. The earliest signs are restlessness, irritability, and insomnia, followed by a *rapidly shifting depressed or elated mood*, *disorientation or confusion*, *and disorganized behavior*. *Delusional beliefs* are common and often *center on the infant*.

TREATMENT

Because the blues are typically mild and resolve on their own, no specific treatment is required. The treatment of *postpartum depression* depends on its severity. Milder cases may respond to *psychotherapy*, whereas more severe depressive symptoms are best treated with a combination of psychotherapy and medication. In this setting, *selective serotonin reuptake inhibitor (SSRI) antidepressants* are used most commonly because they are effective for both depression and anxiety and are *compatible with breastfeeding*. Postpartum psychosis is a *psychiatric emergency* and typically *requires hospitalization*. Symptoms are treated with a *combination of antipsychotic medications*, *benzodiazepines*, *and mood stabilizers*. *Electroconvulsive therapy (ECT)* may be helpful for treating psychosis or severe postpartum depression.

Bipolar Disorder

"I bought 11 cars last week. I'll sell them all and make a fortune. I'm going to set up my own hospital and make us both famous."

Bipolar disorder is a mood disorder characterized by the occurrence of manias or hypomanias, and depressions. Manias consist of elevated, irritable, or expansive mood with at least three of the following symptoms if the mood is elevated (four if irritable): (1) decreased need for sleep, (2) flight of ideas, (3) hypertalkativeness (including pressured or excessive speech), (4) grandiosity, (5) distractibility, (6) increase in goal-directed behavior or agitation, and (7) increase in high-risk pleasurable activities, such as spending sprees, reckless driving, or sexual indiscretions. Manic episodes last at least 1 week but may be of any duration if they lead to hospitalization. Psychotic symptoms may occur in the setting of a mania and sometimes take the form of grandiose delusions, although other psychotic symptoms, including auditory hallucinations, may occur. A hypomania is less severe, does not result in hospitalization, and may last only 4 days; although otherwise, it includes similar but lesser-intensity symptoms than mania.

Depressive episodes consist of either depressed mood or anhedonia with five or more of the following concomitant symptoms: (1) significant decrease or increase in sleep, and/or (2) appetite, (3) low energy, (4) psychomotor retardation or agitation, (5) excessive guilt, (6) feelings of worthlessness, (7) poor concentration, (8) difficulty making decisions, and (9) recurrent thoughts of death, suicidal ideation, or a suicide attempt.

Bipolar disorder is divided into two primary types. *Bipolar I disorder* is diagnosed when a patient experiences a manic episode. Typically, these patients experience both manias and major depressive episodes; however, the presence of a mania alone is sufficient to make the diagnosis. *Bipolar II disorder* is diagnosed when a patient experiences at least one hypomania and at least one depressive episode. There are related illnesses that fall within the bipolar spectrum but do not meet the criteria for full bipolar disorder. These include patients who experience medication-induced mania or hypomania, as well as cyclothymia.

The epidemiology of bipolar disorder is relatively consistent throughout the world and does not appear to vary significantly between ethnic groups. Population-based studies demonstrated approximately 0.6% prevalence for bipolar disorder type I, 0.4% for bipolar disorder type II, and 1.4% for subthreshold bipolar disorder. There is not a significant gender difference in predilection for this illness. Of interest, the first episode is more likely to be a mania in men and a depressive event in women. The onset of bipolar disorder symptoms generally occurs in adolescence, particularly in the late teens. Onset of bipolar disorder is usually in the early 20s for both men and women.

Bipolar disorder genetics are complex and indicate an overlapping risk with schizophrenia. Twin studies demonstrate that bipolar disorder is strongly heritable. Estimates suggest that up to 80% of risk for bipolar disorder may be inherited. A subunit of L-type calcium channels is among the first genes consistently associated with bipolar disorder.

Functional neuroimaging studies point to significant effects on the anterior limbic network, with particular activation of the amygdala, striatum, and thalamus in bipolar disorder patients when compared with healthy control subjects. However, these studies are limited by small sample size, lack of control for medication, and a mix of mood states at the time patients were scanned. The understanding of bipolar disorder at a cellular and molecular level has advanced from a focus primarily on neurotransmitters, where there are important abnormalities, to an increased focus on signaling pathways and cellular plasticity and resilience.

Lithium preparations were the first effective therapy for bipolar disorder. Several additional classes of medications subsequently demonstrated efficacy. Current pharmacologic preferences include lithium, still considered to be one of the most effective treatments, as well as certain anticonvulsants, that is, valproic acid, lamotrigine, and carbamazepine, and second-generation antipsychotic medications. The treatment of *bipolar depression* remains a particular challenge, with relatively few medications demonstrating clear efficacy. However, there are some very valuable nonmedication treatment modalities available. Electroconvulsive therapy (ECT) is typically used during severe episodes or when other treatments are not effective. Structured psychosocial interventions, such as cognitive-behavioral therapy, are also useful in illness management.

Generalized Anxiety Disorder

Somatic symptoms, such as chest pain or difficulty breathing, are the hallmark of panic attacks. Patients often do not recognize that they are anxious and have a very real sense of impending doom. It is easy to understand why they seek emergency care.

Generalized anxiety disorder (GAD) is characterized by excessive, uncontrollable, and often irrational worry, about everyday things that is disproportionate to the actual source of worry. To diagnose GAD, excessive worry must be present for at least 6 months, the person finds it difficult to control the worry, and the anxiety and worry are associated with three (or more) out of six symptoms. These include (1) *restlessness or feeling keyed up or on edge*, (2) *being easily fatigued*, (3) *difficulty concentrating or mind going blank*, (4) *irritability*, (5) *muscle tension*, and (6) *sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)*. As with other axis I diagnoses, the symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning and are not due to the direct physiologic effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism), and do not occur exclusively during a mood disorder, psychotic disorder, or a pervasive developmental disorder.

The prevalence of GAD in the National Comorbidity Survey (NCS) was 1.6% for current GAD (defined as a 6-month period of anxiety that continued in the 30 days before the interview), 3.1% within the previous 12-month period, and 5.1% for lifetime diagnosis. In most epidemiologic studies, the lifetime prevalence of GAD is reported between 3% and 6%, with a higher prevalence in women (2:1 female/male ratio). The usual age at onset is variable—from childhood to late adulthood, with the median age at onset being approximately 31 years. There is significant comorbidity associated with other psychiatric disorders (up to 90% of patients meet criteria for another disorder), the most frequent being major depression (up to 60%), dysthymia (40%) alcohol abuse/dependence (38%), and other anxiety disorders (social phobia, agoraphobia, and panic). The presence of comorbid psychiatric disorders has significant negative effects on prognosis. Finally, GAD patients often have multiple medical comorbidities, including migraine, chronic pain, gastrointestinal problems, cardiac, and/or respiratory disorders further complicating assessment and treatment.

GAD may occur in families. Twin studies also suggest that genes are at least partly responsible for the disorder; however, the heritability is modest. The genetic correlation between major depression and GAD is very high. GAD usually begins at an earlier age, and symptoms may manifest themselves more slowly than in most other anxiety disorders. Some people with GAD report onset in early adulthood, usually in response to a life stressor. The clinical course of GAD is often chronic, with 40% of patients reporting an illness lasting more than 5 years. GAD is associated with pronounced functional impairment, resulting in decreased vocational function and reduced quality of life. Moreover, GAD patients are often high users of outpatient medical care, contributing significantly to health-care costs.

Anxiety disorders are thought to result from abnormal processing of threat-related stimuli, as well as functional deficits in brain pathways underlying fear learning and memory. Neuroimaging studies in GAD suggest increased activity in the fear circuitry involving the amygdala, anterior cingulate cortex, and insula, as well as increased activity in the prefrontal cortex, which appears to have a compensatory role in reducing GAD symptoms. Serotonergic, noradrenergic, and gamma-aminobutyric acid (GABA) inhibitory systems dysfunction may relate to expression of GAD. The adrenal system and chronic stress response is also implicated in GAD pathophysiology, with the amygdala mediating arousal and fear by activating the hypothalamic-pituitary-adrenal (HPA) axis. Other putative neuroendocrine mechanisms are currently under investigation.

Different classes of antidepressants are efficacious in GAD. Selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) are usually used as first choice, with tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and others, including buspirone and mirtazapine, as other therapeutic options. Benzodiazepines also provide effective therapies for GAD, having the advantages of a short latency of therapeutic onset and a generally favorable side-effect profile. Major drawbacks include sedation, cognitive impairment, and the possibility of long-term adverse effects (i.e., development of tolerance), physical dependence, and a withdrawal syndrome. Other drugs used in GAD management include pregabalin and sympatholytic agents (propranolol, prazosin, clonidine), and atypical antipsychotics that may have an adjunctive role to antidepressants in cases of treatment resistance. Psychotherapy, in particular cognitive-behavioral therapy, as monotherapy or combined with medications, may also be considered as initial treatment for patients with mild-to-moderate symptoms.

Social Anxiety Disorder

Introduction and Clinical Presentation. Social anxiety disorder (SAD), or social phobia, is characterized by persistent fear of social or performance situations in which an individual will face exposure to unfamiliar people or scrutiny by others. The individual typically fears behaving in an embarrassing or humiliating fashion, or revealing symptoms of anxiety. Exposure to these situations provokes anxiety or panic symptoms, leading the individual to avoid such situations whenever possible. Physical symptoms may include diaphoresis, tachycardia, trembling, nausea, flushing, and difficulty speaking, for example.

DSM-IV criteria stipulate that this condition contributes to significant functional impairment (for example, in work or relationships) or distress. Of note, the individual recognizes that the fear is excessive or unreasonable. Although the diagnosis has been criticized for ascribing a medical diagnosis to a normal population trait, shyness, the persistence and severity of these symptoms—and in particular their impact on functioning—argues otherwise.

Diagnostic criteria distinguish a generalized form, that is, occurring in most social situations, or a specific form, that is, one which occurs only in particular circumstances, such as public speaking or public performance, or writing or eating in front of others. However, these are not necessarily distinct subtypes, although the generalized form may be more disabling overall.

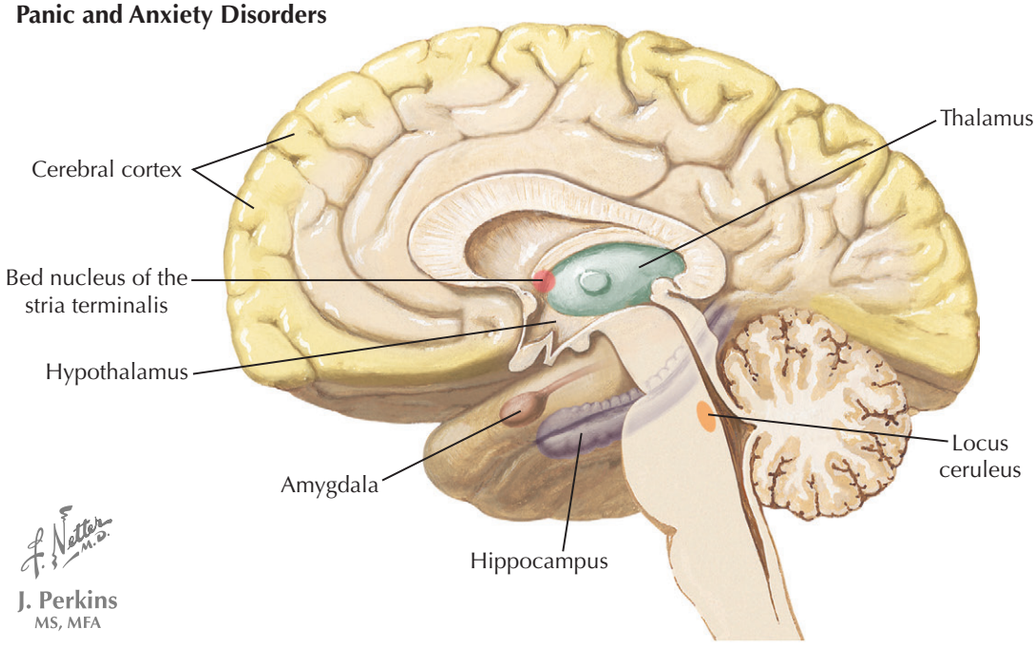
Epidemiology. The lifetime prevalence of SAD is ≈12%, with 12-month prevalence of ≈7%. SAD often has early onset, with about half of cases presenting by age 11 years; on the other hand, later onset in many patients provides further support for SAD being something other than the trait of shyness. As with major depressive disorder, SAD is seen more commonly in females. As with other psychiatric disorders, rates of comorbidity are high, having overlap with major depression and substance use disorder, for example.

Treatment of SAD relies on either cognitive-behavioral therapy, delivered individually or in a group setting, or pharmacotherapy. Standard medication treatments use selective serotonin reuptake inhibitors, although other antidepressants, including monoamine-oxidase inhibitors and serotonin-norepinephrine reuptake inhibitors have also demonstrated efficacy. Anxiolytic medications, such as benzodiazepines, are sometimes used as well. Scales such as the Liebowitz Social Anxiety Scale may be used to quantify severity over time.

Pathophysiology. SAD has been noted to be familial, and often coaggregates with major depression, panic disorder, and agoraphobia. Twin studies suggest that about 40% of liability is inherited. Although candidate gene studies have implicated multiple genes, no single association has been convincingly demonstrated, and genome-wide studies have not been reported. The potential role of neuropeptides involved in social cognition, such as oxytocin and arginine vasopressin, is also under active investigation. For example, rodent models illustrate the capacity of oxytocin to diminish social avoidance, which may inform future treatment development in SAD.

Functional magnetic resonance imaging (fMRI) implicates the amygdala and insula activation in SAD, for example, on tasks requiring processing of emotional faces. fMRI also suggests there may be abnormal connectivity evident in the resting state, involving frontal and occipital structures. Other studies also suggest basal ganglia dysfunction in SAD; of interest, SAD is seen more commonly in individuals with Parkinson disease, which may provide convergent evidence for the role of basal ganglia in these symptoms.

Brain Regions Associated With Panic and Anxiety Disorders



F. Netter M.D.

J. Perkins
MS, MFA

Panic Disorder

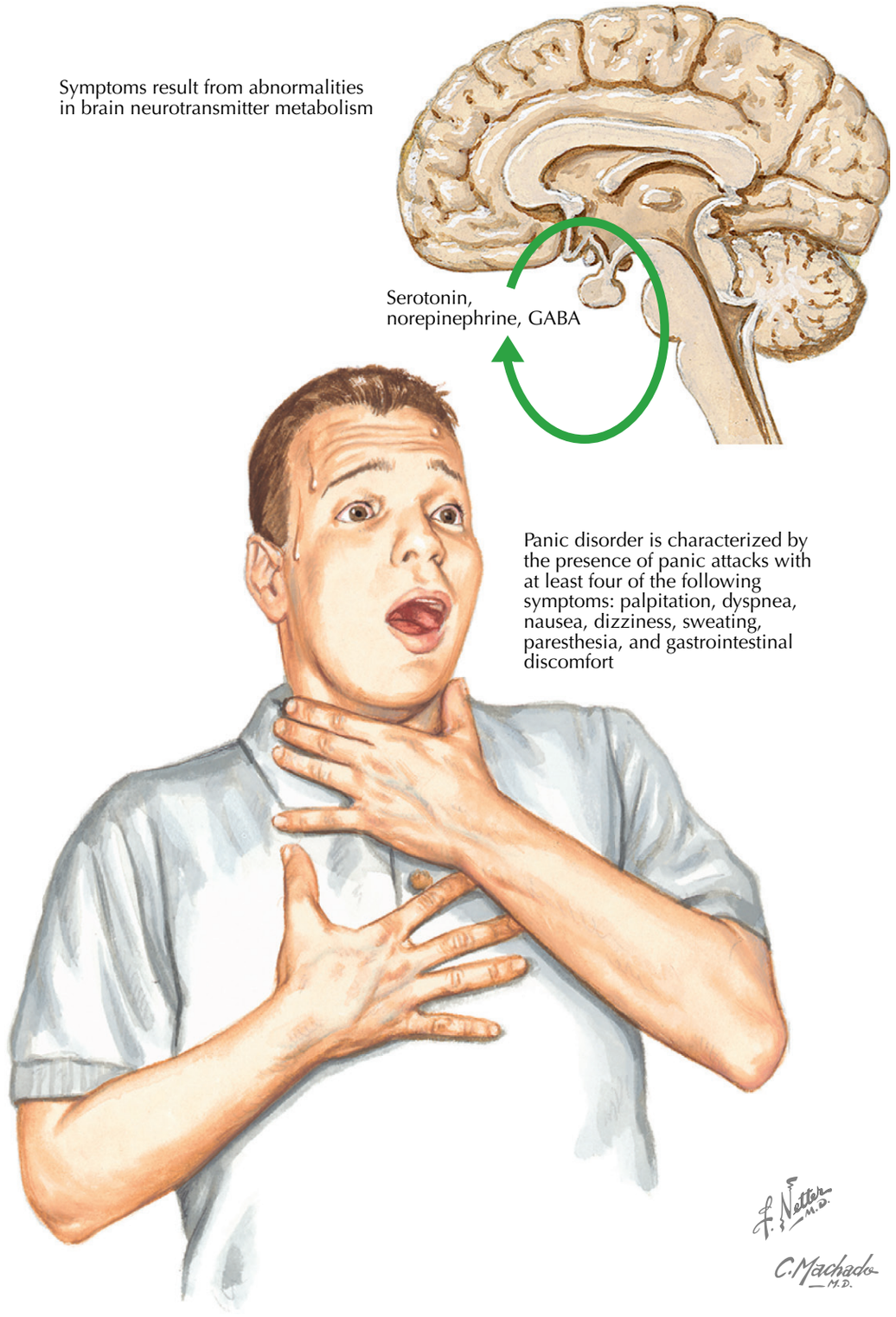
Patients complaining of panic often describe a dramatic presentation, including the sudden, unexpected onset of extreme fearfulness or alarm, quickly rising to a crescendo within minutes of commencement, and accompanied by a spectrum of physical, behavioral, and cognitive symptoms. These may include the bodily sensations of choking, chest pain, trembling, flushing, and rapid heart rate, which mimic a sympathetic, "fight or flight" response. The urge to escape, to find shelter, or to seek help can be overwhelming. Panic victims may believe they are dying, losing control, or going crazy and will often seek urgent medical care. The indelible, negative impression left by a panic attack often results in persistent fear of having another attack or in marked behavioral changes. Although isolated panic attacks are relatively common, it is these persistent sequelae that define the diagnosis of panic disorder. By *DSM-IV* criteria, this disorder may also be accompanied by agoraphobia, characterized by the phobic avoidance of situations that may be difficult or embarrassing to escape, should a panic attack recur.

Panic disorder is common, with a lifetime prevalence in the United States of up to 5%. The disorder occurs nearly twice as often in women and tends to manifest in early adulthood. Comorbid substance use disorders and psychiatric illness are very common; major depressive disorder occurs in nearly two thirds of patients with panic disorder. These comorbid conditions, if left untreated, may exacerbate the symptoms of panic or make treatment more difficult. Of particular concern, panic disorder is associated with higher risk for suicide. Of interest, the onset of panic disorder is often related to a stressful life event. Although most patients experience some remission of symptoms over time, the course of panic disorder is chronic for the majority of affected individuals. Complications can include persistent anxiety symptoms, mood disorders, phobic avoidance, drug and alcohol use disorders, and significant impairments in functioning and quality of life.

The differential diagnosis of panic disorder includes a broad list of cardiac, respiratory, endocrine, metabolic, and drug-related causes, as well as other psychiatric conditions that may include panic attacks. Individuals with panic attack often present for treatment initially at emergency departments or in primary care settings, and although the classic presentation of panic attack may be familiar to most practitioners, a careful consideration of possible organic causes must be undertaken. A personal or family history of anxiety and recent stressful life events may suggest a primary anxiety disorder.

Early family studies of panic disorder have demonstrated a higher risk in first-degree relatives of probands; twin studies estimate the heritability of anxiety disorders to be 20% to 40%. Although these studies suggest that genetic factors play a role, the investigation of particular genetic risk factors is complicated by the high level of comorbidity with other anxiety and depressive disorders. Explanatory neurobiologic models emphasize the role of neural circuits, including the amygdala, its related structures, and hypothalamus. Hypothesized abnormalities in the serotonergic, noradrenergic, and gamma-aminobutyric acid (GABAergic) neurotransmitter systems are supported by the efficacy of pharmacologic treatments aimed at these systems (e.g., SSRIs, SNRIs, and benzodiazepines).

During the early stages of presentation, before phobic avoidance or recurrent attacks begin, a patient may respond well to reassurance, education, and supportive psychotherapy. Once phobic avoidance or recurrent attacks begin, the aims of treatment are both to prevent further panic attacks, and to eliminate the associated avoidance and anticipatory anxiety. Pharmacologic treatment for panic includes antidepressants; placebo-controlled trials support the efficacy of SSRIs, the SNRI venlafaxine, and the tricyclic antidepressant imipramine. Benzodiazepines provide rapid symptomatic relief, and may be prescribed alone or together with antidepressants. Cognitive-behavioral therapy (CBT) for panic disorder is validated and studied widely, proving effective whether delivered in individual or group therapy settings. CBT conceptualizes *panic* as the acquired fear of the bodily sensations associated with autonomic arousal, and *agoraphobia* as the behavioral response to the anticipation of such sensations. Therapists teach cognitive and somatic coping skills that are then used to manage anxiety during exposure to feared situations and bodily sensations. Multiple studies and meta-analyses show that the combination of both medication and psychotherapy is more effective in treating panic than either therapy alone.



Individuals with PTSD may relive traumatic events in their thoughts during the day and in nightmares when they sleep

C. Machado, M.D.

Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is a mental disorder that develops in response to a traumatic event, such as a sexual assault, military combat, natural disaster, or a serious accident. PTSD is characterized by three clusters of symptoms: (1) *reexperiencing symptoms* wherein the patient relives the trauma in his or her thoughts and dreams and cannot get it out of his or her mind; (2) *avoidance and numbing symptoms* wherein the patient avoids people, places, and anything that reminds her or him of the trauma and shuts off his or her emotional responses; and (3) *hyperarousal symptoms* that involve difficulty concentrating, constantly feeling on-guard and in danger, difficulty sleeping, and irritability. To be diagnosed with PTSD, the patient must report that the traumatic event was accompanied by feelings of helplessness and horror, these symptoms must occur for at least a month, and they must interfere with the patient's ability to function in daily life.

PTSD is distinct from other common mental disorders in that trauma exposure is a prerequisite for diagnosis. Threatening events initiate the body's "fight-or-flight" response via the hypothalamic-pituitary-adrenal axis and the locus ceruleus and noradrenergic system. These systems have important reciprocal interconnections with the amygdala and hippocampus, limbic structures involved in fear conditioning and memory consolidation, and with prefrontal brain structures necessary for extinction of fear memories and reward motivation. Initially, this neurobiologic stress response is considered adaptive; it mobilizes energy, increases vigilance and focus, facilitates memory formation, and depresses the immune response. When the acute threat has passed, an elaborate negative feedback system will return the body to homeostasis. However, in some individuals, this acute adaptive response to threat becomes persistent and pathologic.

Although a majority of adults will experience at least one traumatic event in their lifetime, only a minority develop PTSD; the lifetime prevalence of PTSD in the United States is estimated at 6.7%. The disorder is twice as common in women as in men. Although many individuals will experience some PTSD symptoms in the immediate days and weeks following a trauma, only a minority of individuals show the persistent symptoms required for the PTSD diagnosis. Uncontrollable and threatening events, such as rape, childhood abuse, and military combat, are consistently associated with the highest risk for developing PTSD after an event. The risk of developing PTSD is less than 50% even for severe events such as a forcible rape. This contrast between trauma exposure and PTSD prevalence has driven the search for risk and protective factors for the disorder. Extant research suggests pretrauma characteristics, such as family and personal history of psychopathology, childhood adversity, and low cognitive ability; trauma-related factors, such as type of event, perceived life threat, and peritraumatic psychologic response; and posttrauma factors, such as social support, all play a role determining who develops the disorder. There are three studies that suggest that PTSD is moderately heritable and that genetic factors influence who develops the disorder.

The disorder becomes chronic (i.e., lasts for more than 3 months) for almost 50% of those who meet diagnostic criteria; these patients can benefit from treatment. The treatment of choice for PTSD is primarily trauma-focused cognitive-behavioral therapy and possibly pharmacotherapy. Two types of cognitive-behavioral therapy, prolonged exposure and cognitive processing therapy, were specifically developed for the treatment of PTSD. Both techniques are based, to some degree, on a conceptualization of PTSD as a disorder of failure to recover from the traumatic event due to avoidance of the traumatic event, per se, including thoughts, feelings, places, and people associated with the memory. Prolonged exposure therapy targets avoidance through having the patient reexperience the memory of the traumatic event and engaging with, rather than avoiding, reminders of the trauma both in and outside the therapy session. Cognitive processing therapy targets the avoidance issue by addressing erroneous beliefs about the causes and consequences of traumatic events. A primary focus of cognitive processing therapy is to use cognitive techniques to help patients gain an understanding of the event, per se, and subsequently modify the meaning attributed to their traumatic event. Prolonged exposure and cognitive processing therapy are similarly effective for treatment of PTSD. The only U.S. Food and Drug Administration (FDA)-approved pharmacologic agents for the treatment of PTSD are the SSRIs sertraline and paroxetine, and the evidence for their effectiveness in treatment PTSD is inadequate. Pharmacologic augmentation of trauma-focused cognitive-behavioral therapy is the focus of ongoing research.

Obsessive-Compulsive Disorder

Introduction. Obsessive-compulsive disorder (OCD) is diagnosed on the basis of recurrent and intrusive thoughts, referred to as obsessions, and/or compulsive behaviors or rituals. The obsessions or compulsions are recognized by the patient, at least at some point, as excessive and unreasonable, leading to marked distress or functional impairment; they may be extremely time-consuming. These symptoms are experienced as intrusive and inappropriate and are not simply excessive worries about real-world concerns.

Multiple subtypes of OCD are identified primarily based on factor analysis. Typical obsessions may include fears of contamination, sexual/religious or other moral transgression, harming others, or unrecognized illness. Compulsions may include hoarding, checking, cleaning, and ordering. Of these, the most common symptom is checking behavior, seen in nearly 80% of cases, followed by hoarding behavior. Patients may, for example, check repeatedly that the stove is turned off, re-read paragraphs for typographic errors, or contact family members to confirm that they are healthy. Of importance, such behavior does not occur once, but may persist for hours at a time. Hoarding often involves newspapers, receipts, or other documents, to the point that patients' homes may become cluttered and even unsafe. Of note, compulsions may be mental rituals as well: needing to count or recite a prayer to prevent a catastrophic event, for example. OCD is highly comorbid with other psychiatric disorders, particularly anxiety disorders, mood disorders (particularly bipolar disorder), and substance use or impulse control disorders. OCD is sometimes observed in individuals with Tourette syndrome).

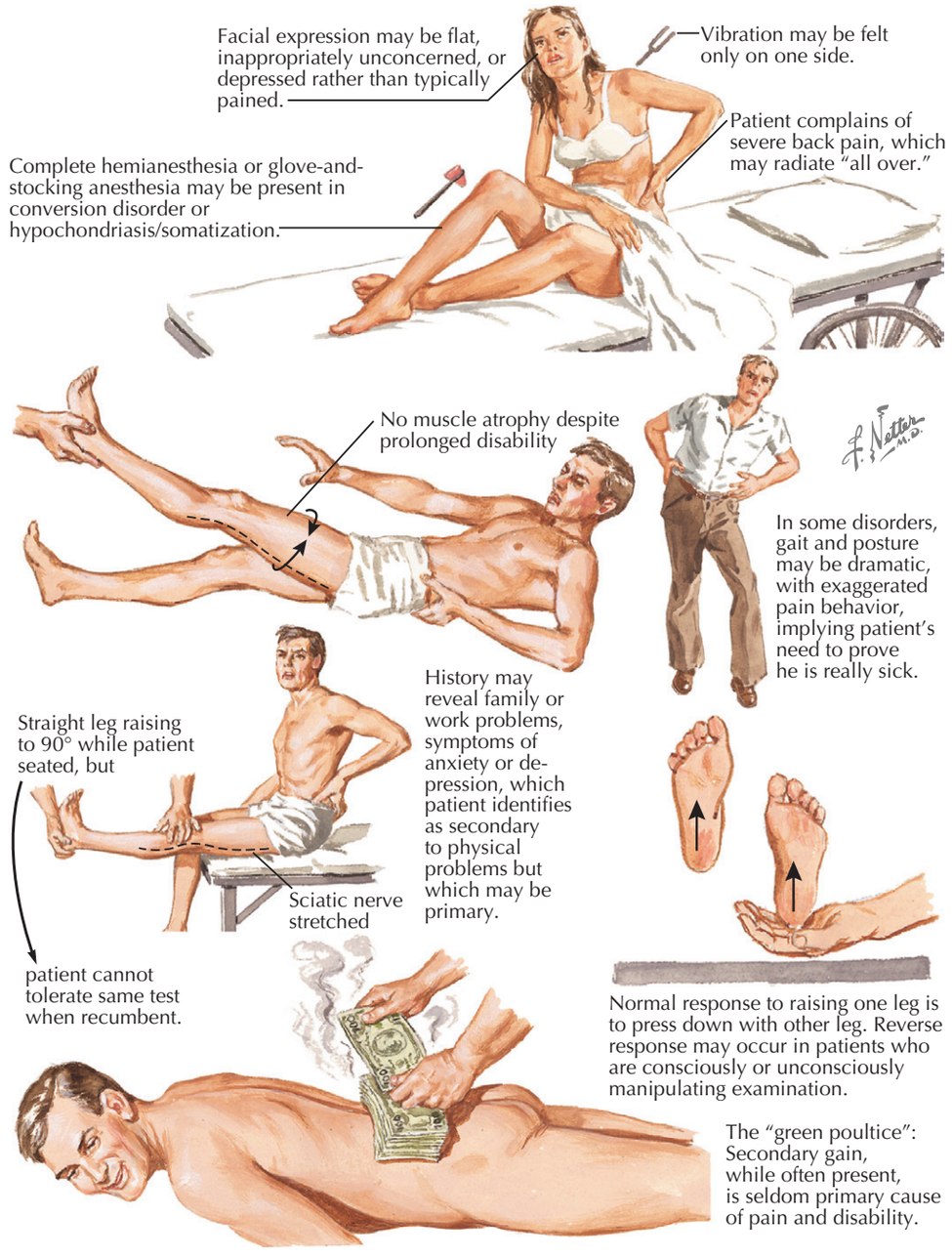
Epidemiologic studies indicate a lifetime prevalence of ≈2% among the general population, with 1% reporting symptoms in the past 12 months. Subthreshold symptoms may be far more common, with up to one quarter of respondents reporting some lifetime obsessions or compulsions. Mean onset age is between 19 and 20 years, but up to one quarter of males may have onset before age 10 years; female incidence increases in adolescence. New cases are rarely observed after age 35 years. Twin and family studies suggest that OCD is a heritable disorder, particularly childhood-onset OCD, with between 45% and 65% of liability due to inherited risk.

Clinical Presentation. OCD symptoms are generally chronic and contribute to substantial functional and social impairment, although their severity may fluctuate over time. Treatment for OCD typically relies on either cognitive-behavioral therapy, medication treatment, or both; the individual treatments have similar effect sizes. Most commonly selective serotonin reuptake inhibitors or the tricyclic antidepressant clomipramine are prescribed; these medications may require greater dosages and longer treatment durations (i.e., 12 weeks or more) to achieve response, compared with the treatment of other psychiatric disorders. A variety of next-step pharmacotherapies are under active investigation. An emerging treatment for refractory OCD is deep-brain stimulation in regions such as the subthalamic nucleus.

Pathophysiology. Imaging and other studies implicate corticostriatal-thalamic circuits in the pathophysiology of OCD symptoms, but recent investigation suggests a somewhat broader network. Functional imaging has particularly focused attention on caudate, orbitofrontal cortex, and anterior cingulate cortex. In one model, intrusive thoughts are associated with increased activity in orbitofrontal cortex, whereas the sense of anxiety is associated with activation of anterior cingulate cortex. Investigation of OCD is facilitated by the availability of mouse models with OCD-like symptoms, particularly excessive grooming behavior. Despite the efficacy of serotonergic antidepressants in this disorder, the role of glutamatergic neurotransmission is receiving increasing focus based on animal studies and genetic data.

In rare cases, OCD symptoms may emerge in children after streptococcal infection, a phenomenon referred to as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). This syndrome has focused attention on the role of basal ganglia and immune mechanisms in OCD.

SOMATIZATION



Somatization is one of six major somatoform disorders identified by the American Psychiatric Association's *Diagnostic and Statistical Manual (DSM)*. Other somatoform disorders include undifferentiated somatoform disorder, conversion disorder, hypochondriasis, pain disorder associated with psychologic factors, pain disorder associated with both psychologic factors and a general medical condition. Fundamentally, *somatization is a constellation of physical symptoms lacking medical explanation*. The *DSM-IV-TR* designates eight symptom requirements for diagnosis, including four bodily pain symptoms, two gastrointestinal (GI) symptoms, one neurologic symptom, and one sexual symptom, resulting in impairment in function. However, these symptoms appear to exist along a spectrum, and the current diagnostic categorization may not accurately reflect the clinical presentation. Therefore the status and characterization of somatoform disorders are being reexamined for the soon-to-be-published *DSM-V*, to reclassify them under the general heading of *bodily distress syndrome* to encompass *both psychiatric and nonpsychiatric functional disorders*.

Patients currently classified as having somatization disorder present with multiple physical symptoms that range from mild and self-limited to severely disabling. In addition, they express *excessive health concerns* that are demonstrated *emotionally* (depression, anxiety), *cognitively* (rumination on symptoms, poor attention), and *behaviorally* (treatment seeking, "doctor shopping"). As a result, they suffer from impairments in functioning, and their help-seeking behaviors make them large consumers of health care, most often presenting to primary care and medical specialty clinics. They often mistakenly are diagnosed with fibromyalgia, chronic fatigue syndrome, noncardiac chest pain, and irritable bowel syndrome.

Epidemiologic data suggest somatoform disorder prevalence estimates of 2% to 6% in the general population and 5% to 20% in primary care patients. Rates are greater in the primary care setting because they are actively seeking health care compared with the general population. Most patients with somatoform disorders are women. Despite these high prevalence rates, the somatoform diagnoses rarely are assigned to patients by clinicians. Studies show diagnostic rates of less than 0.01%. It is postulated that reluctance of clinicians to "label" patients, lack of generalizability of the diagnoses to the clinical presentations, and lack of physician familiarity with the complex criteria for diagnosis result in the underuse of the somatoform diagnoses. Deficiencies in treatment, poor reassurance by medical practitioners, and avoidance of the proper diagnosis leads to excessive testing, high health-care utilization, and specialty referrals, all leading to high health-care costs and poor quality of life.

The pathophysiology of somatization and somatoform disorders currently is not well understood. The observed clinical presentations may be due to aberrant functioning in neural pathways via the autonomic nervous system and hypothalamic-pituitary-adrenal axis, in addition to alterations in central processing of sensory input. Other data suggest proinflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha), can lead to a constellation of behaviors, including exaggerated pain sensitivity (hyperalgesia), sleep disturbances, and fatigue referred to as "sickness behavior." This constellation is observed in patients having either depression and/or somatoform disorders. Activation of the proinflammatory cytokines by internal and external stressors may lead to sensitization of the central nervous system (CNS) and afferent peripheral nerves and cause altered bodily perceptions.

Some back pain patients have primary or exacerbating psychologic factors requiring consideration when examination demonstrates inappropriate, nonanatomic, clinically incongruous findings. Some individuals are polysymptomatic, with multiple work-domestic issues often engraved on a complex history of other non–organic-defined disorders. Examination demonstrates over-reaction, inexplicable inconsistent straight-leg raising difficulty, nondermatomal sensory loss, poorly sustained effort on muscle testing, with inconsistencies between findings on muscle testing and "unobserved" spontaneous activity (i.e., ability to get off the examination couch despite apparently "severe extremity weakness"). The most common mistake while evaluating such patients is inadequate attention to the differential diagnosis. Outright *malingering* for material gain is usually fairly apparent and should simply be confronted.

Despite the serious magnitude of effects somatization and somatoform disorders have on patients, families, and the health-care system at large, these disorders are seriously understudied. Currently, limited evidence-based treatment and very limited specialized care exists for patients with somatization somatoform disorders. Purely medical approaches to evaluation and treatment by "ruling out" general medical disorders leads to serial negative tests, ineffective interventions, and mutual physician and patient frustration. Of interest, most treatments targeting specific symptoms appear nonessential, although probiotics in the use of irritable bowel syndrome and other GI-focused somatic complaints are sometimes beneficial. The most beneficial treatment uses a combination of pharmacology to target the central nervous system, such as antidepressants, exercise, and cognitive-behavioral therapy. In addition, physicians suspecting a somatoform disorder diagnosis should schedule frequent, time-limited visits to address patient concerns and to provide reassurance.

Conversion Disorder

Conversion disorder, previously referred to as hysteria, is defined by the *DSM-IV-TR* as a type of somatoform disorder with a loss or distortion of a neurologic function that is (1) not explained by an organic neurologic lesion or medical disease, (2) arising in relation to some psychologic stress or conflict, and (3) not consciously produced or intentionally feigned. Despite being thought of as a psychiatric disorder, neurologists predominantly manage and diagnose conversion disorder.

Diagnosis requires appropriate neurologic assessment and testing that finds the physical symptoms to be incompatible with neurologic pathophysiology and/or internally inconsistent to fulfill the first criteria. Criteria two and three are considered more difficult to demonstrate and will be de-emphasized in the diagnostic criteria for conversion disorder in the *DSM-V.*

Examples of conversion disorder include functional limb weakness and paralysis, tremors, anesthesia that does not follow nerve distributions or dermatomes, vision deficits that are incongruent with anatomically possible visual field deficits, nonepileptic seizures (pseudoseizures) having a normal electroencephalogram (EEG) during events, deafness, amnesia, and abnormal movements. Focused physical examination can elicit findings that highly suggest diagnosis of conversion disorder. Functional leg weakness is demonstrated with Hoover's sign (as in this plate), where weakness of hip extension resolves during contralateral hip flexion against resistance. Patients with astasia-abasia exhibit an unusual and dramatic gait disturbance, lurching wildly in various directions, and falling only when a nearby physician, family member, or soft object will catch them. Functional tremors may be suspected when the tremor resolves or develops the same frequency during voluntary rhythmic movement of the unaffected arm (entrainment). An overall pattern is that symptoms typically become worse with attention and can lessen or disappear with distraction.

Conversion disorders represent 1% to 4% of all diagnoses in general hospitals throughout Western countries. It is estimated that 30% to 60% of outpatients in neurologic clinics in the United Kingdom have medically unexplained symptoms. Similar to other somatoform disorders, patients with conversion disorder have symptoms that cause significant impairment and high use of health care, leading to elevated costs and poor quality of life. In addition, some treating physicians tend to have a negative bias toward these patients because of difficulty distinguishing conversion disorder from malingering and other factitious disorders. Coupled with a deficiency in medical training in how to approach and appropriately manage patients with conversion disorder because of health-care providers' discomfort, patients tend to feel dissatisfied with care and seek multiple providers without resolution, leading to inefficiency in the system.

The term "conversion" implies a mechanism whereby psychologic stress is converted into bodily symptoms unconsciously. However, the mechanism is largely unknown and poorly understood. Hypotheses historically have focused around anosognosia, the distortion between performance and awareness of performance that is believed to stem from an altered state of self-consciousness or altered awareness of a bodily state.

Imaging techniques provide a means to study potential neurologic mechanisms involved in conversion disorder. However, these studies are limited by small patient numbers and difficulty controlling for confounding variables. Functional neuroimaging has revealed decreases in activity of frontal and subcortical circuits involved in motor control in hysterical paralysis, decreases in somatosensory cortices during hysterical anesthesia, and decreases in visual cortex during hysterical blindness. In addition, activation has been shown in limbic regions such as the cingulate and orbitofrontal cortices. These findings suggest that conversion disorder may involve modulation of sensorimotor representations by primary affective or stress-related factors.

The majority (50% to 60%) of conversion symptoms spontaneously remit within 2 years of onset, and only 3% of younger patients (<27 years old) have symptoms for more than 1 month. Cognitive-behavioral therapy leads to rapid remission and is considered more effective than pharmacologic approaches, although antidepressants may have a role. Young age, sensory rather than motor symptoms, acuteness of presentation, association with a stressful event, good premorbid health, good socioeconomic status, and absence of comorbidities (psychiatric or medical) are associated with a favorable prognosis. The presence of concurrent depression and/or personality disorders is associated with more chronic handicap.

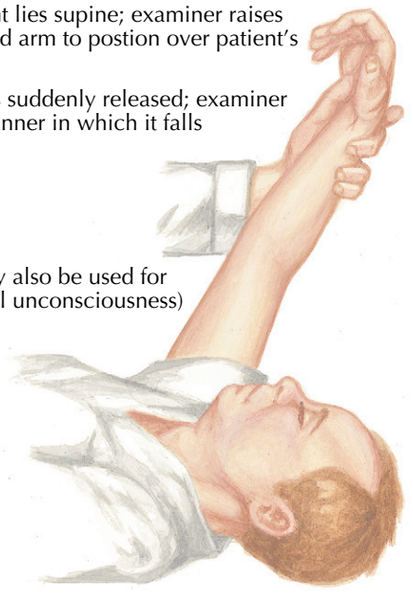
Conversion disorder raises interesting questions about the relationships between the body and the mind, but additional studies and research are needed to further understand the underlying cause and potential treatments and may improve understanding of normal attention and volition. For now, emphasis should be placed on confirming the diagnosis clinically by presence of positive symptoms, placing less emphasis on psychologic factors and whether or not the patient is feigning the illness.

Tests for Paralysis of Upper Extremity

1. Patient lies supine; examiner raises paralyzed arm to postion over patient's face

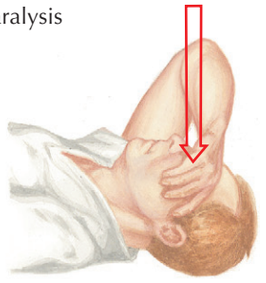
2. Arm is suddenly released; examiner notes manner in which it falls

(Test may also be used for hysterical unconsciousness)



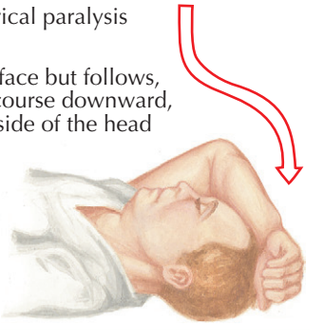
A. Response in organic paralysis

Arm falls directly downward into the face because patient is unable to support the flaccid, paralyzed extremity



B. Response in hysterical paralysis

Arm does not hit the face but follows, a slow or circuitous course downward, landing safely to the side of the head

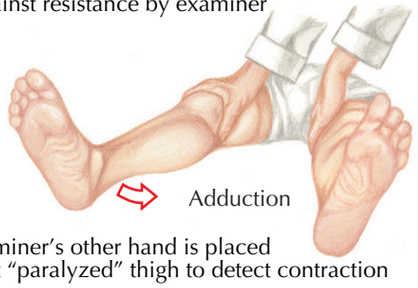


JOHN A. CRAIG, MD

Tests for Weakness in Lower Extremity

Thigh adduction test

1. Patient is instructed to adduct "good" leg against resistance by examiner



2. Examiner's other hand is placed against "paralyzed" thigh to detect contraction

A. Response in organic paralysis

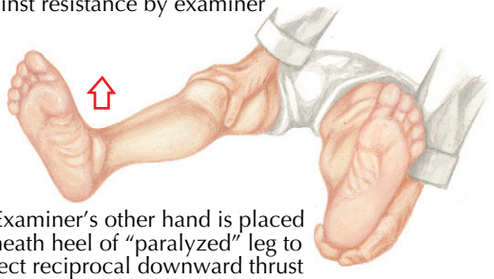
Patient can accomplish adduction with no contralateral adduction palpable in paralyzed leg

B. Response in hysterical paralysis

In adduction of "good" leg, patient involuntarily adducts "paralyzed" leg

Hoover test

1. Patient is instructed to elevate "good" leg against resistance by examiner



2. Examiner's other hand is placed beneath heel of "paralyzed" leg to detect reciprocal downward thrust used by patient for leverage

A. Response in organic paralysis

Patient is able to elevate good leg without concomitant downward thrust of paralyzed leg

B. Response in hysterical paralysis

Elevation of "good" leg is accompanied by downward thrust of "paralyzed" leg

SCHIZOPHRENIA

Schizophrenia is the prototype of a psychotic disorder, with the core symptoms of delusions and hallucinations as well as disorganized speech. Some patients also display prominent psychomotor disturbances, including catatonia. Together, these florid and often dramatic symptoms are referred to as *positive symptoms* and contrasted with negative and cognitive symptoms, the latter being responsible for much of the disability that characterizes schizophrenia. *Negative symptoms* are categorized into a reduced emotional expressivity cluster (restricted or flat affect) and an avolition/apathy/anhedonia cluster. Many schizophrenia patients struggle with cognitive impairment in the realms of working memory, attention/vigilance, verbal learning and memory, visual learning and memory, reasoning and problem solving, speed of processing, and social cognition. Schizophrenic patients can often have prominent mood symptoms; these are not inconsistent with a diagnosis of schizophrenia. However, if mood symptoms dominate the overall course of a psychotic illness, a diagnosis of *schizoaffective disorder* can be given. *Schizophrenia* is *a diagnosis of exclusion*; various street drug usage, medications, and medical causes of psychosis must initially be excluded before diagnosis because these can mimic the core symptoms of schizophrenia.

Many patients with schizophrenia experience symptoms that in hindsight are recognized as a prodrome before the onset of their florid psychosis. Unspecific prodromal symptoms (anxiety, depression, social withdrawal) eventually give rise to attenuated psychotic symptoms before schizophrenia declares itself by the onset of psychosis. Because schizophrenia is a syndrome, not all patients experience symptoms from all domains. Schizophrenia is also characterized by a fluctuating illness course, where periods of exacerbation with prominent psychosis alternate with periods of remission.

Schizophrenia has a prevalence of ≈1.5%, with large public health implications due to its onset during young adulthood and persistence throughout life. The typical age at onset is between 15 and 30 years, with onset after age 45 years being rare. Males are 40% more likely to develop schizophrenia than females (ratio of 1.4:1) and have an earlier onset. Only about 20% of patients have a good overall prognosis. Patients with schizophrenia often die decades earlier than people in the general population. Its excess medical mortality is partly preventable because modifiable risk factors (i.e., nicotine dependence and the metabolic syndrome) contribute to deaths from cardiovascular disease. Suicide is responsible for 12% of deaths.

Schizophrenia is highly heritable. Other important risk factors for schizophrenia include in utero insults during brain development, such as exposure to infections; obstetric complications; advanced paternal age; social factors, such as urbanicity or immigration status; and early heavy cannabis use.

The neuropathology and pathophysiology of the network dysfunction in schizophrenia remain to be resolved. Critical brain regions involved include frontal cortical areas, particularly dorsolateral prefrontal cortex, the thalamus, and various limbic and dopaminergic midbrain areas. Although varied developmental pathways can eventually lead to schizophrenia, psychosis emerges as the result of dopamine (DA) dysregulation as a final common pathway.

Schizophrenia can be viewed as a neurodevelopmental disorder that affects brain circuits and develops in stages. A prodromal stage is characterized by beginning, subtle symptoms and role failure; eventually, this results in an active psychosis stage and subsequently gives rise to a stage of chronic disability. According to this model, psychosis is a late symptom. Therefore prevention of this severe outcome requires treatment of target patients at earlier stages.

Antipsychotic medications are the treatment of choice for acute psychosis. After resolution of the initial psychosis, most patients require maintenance treatment with an antipsychotic medication to reduce the likelihood of a psychotic relapse. All antipsychotics are antagonists of dopamine 2 (D2) receptors, and many antipsychotics combine D2 with 5-hydroxytryptamine 2a (5-HT2a) receptor blockade as their basic receptor profile. Despite great differences in individual receptor pharmacologic sites of activity, currently available antipsychotics are equally effective and differ mostly in their propensity toward side effects. Only clozapine is shown to be more effective in treatment-refractory patients with schizophrenia. Problematic long-term side effects of all antipsychotics include tardive dyskinesia and the metabolic syndrome.

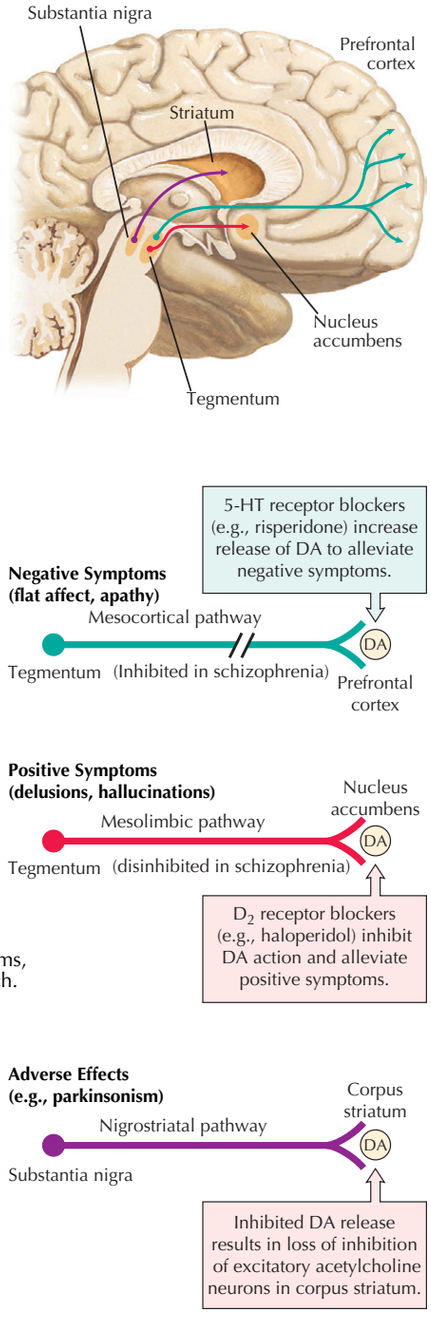
Antipsychotics are not effective against all aspects of schizophrenia. Negative and cognitive symptoms, in particular, show little improvement with antipsychotics alone. Instead, the comprehensive treatment of schizophrenia requires integration of pharmacologic treatment with psychologic therapies and concomitant psychosocial rehabilitation. The availability of cognitive-behavioral therapy and cognitive remediation with rehabilitation holds promise for treating persistent symptoms and cognitive deficits.

Schizophrenia

This patient exhibits the flat affect that is common to schizophrenia. She appears to be responding to internal stimuli—perhaps attending to auditory hallucinations. Alternatively, she may have significant negative symptoms, including anhedonia, amotivation, and poverty of speech. Finally, she may have parkinsonism secondary to antipsychotic medication.

F. Netter M.D. J. Perkins MS, MFA

Neural Pathways Involved in Schizophrenia



Alcohol Use Disorders

Alcohol use is associated with 1.8 million deaths annually; global alcohol use is increasing. Yet many who drink alcohol do not experience negative health or social consequences, and some health-care studies suggest health benefits may be associated with alcohol consumption. How can we distinguish between risky drinking and safe drinking? The National Institute on Alcohol Abuse and Alcoholism (NIAAA), dedicated to providing scientific leadership in the assessment of alcohol use and its health and social consequences, has established gender-specific guidelines based on current evidence for "low-risk" drinking. To normalize these guidelines, a "standard drink" is defined as an ethanol alcohol content of 14 grams (equivalent to 12 ounces of beer, 5 ounces of table wine, or 1.5 ounces of liquor). It is considered "low-risk" for healthy adult men under age 65 years to consume no more than 14 standard drinks per week, with up to 4 drinks per day, and for healthy adult nonpregnant women under age 65 years and healthy men and women age 65 years and older, no more than 7 standard drinks per week and up to 3 standard drinks per day.

The following risk factors may increase the potential negative health consequences of drinking even with "low-risk" patterns of consumption: (1) first-degree relative with alcohol or drug dependence (i.e., heritable risk for developing an alcohol use disorder), (2) history or family history of mental illness, (3) history or family history of cancer, and (4) any concern about how alcohol affects you personally. Conditions wherein no amount of alcohol is established as safe or any amount of alcohol is established as harmful include (1) pregnancy, (2) age younger than 21 years, (3) operating a vehicle or other machinery, (4) taking medications interacting with alcohol, and (5) having active physical or mental health symptoms.

Alcohol use disorders are defined by the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* as alcohol abuse and alcohol dependence; *DSM-V* (in preparation) will update this to one category—alcohol use disorder—defined by a spectrum of severity. The *cardinal aspect of an alcohol use disorder* is *loss of control or self-regulation* over one's alcohol intake, resulting in negative functional consequences in health, safety, occupational performance, and social/family roles. Although alcohol dependence used to be thought of as a naturally progressing disease known as "alcoholism," NIAAA research has refined this profile into five phenotypic subtypes of alcohol dependence based on data from large national community survey studies. These subtypes are briefly described below and represent typical patient presentations (excluding geriatric presentation of alcohol dependence, which typically involves a prominence of alcohol-related health consequences, cognitive deficits, and loss of independent self-care and functioning).

Young Adult (31.5%). Comprising the largest group with alcohol dependence nationally, they tend to lack common risk factors for alcohol dependence (family history of alcohol dependence, co-occurring drug use, or mental illness). This subtype is a priority for medical screening, since they rarely seek treatment.

Young Antisocial (21%). Mid-20s with high rates of co-occurring drug use (>75% smoke cigarettes and cannabis), with strong family alcohol dependence histories. Onset of drinking begins in youth, which may in part account for the severity of alcohol dependence at a young age. Co-occurring mental illnesses are common (depression, anxiety, and personality disorders). One third actively seeks treatment. This group is of particular importance for pediatrician- and school-based screenings for substance use.

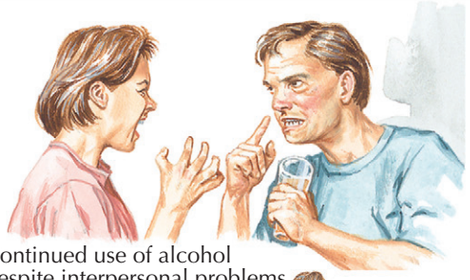
Functional (19.5%). Typically, these are well-educated, middle-aged individuals with stable jobs and relationships, colloquially referred to as "high-functioning alcoholics." A lack of prominent negative consequences to drinking creates a strong vulnerability to denial of illness and lack of incentive for seeking treatment; thus medical screening for alcohol-related problems is important to engage them in treatment. About half smoke cigarettes, one third have strong family histories of alcohol dependence, and one quarter have a lifetime history of depression.

Intermediate Family (19%). This group of middle-aged individuals, half of whom have a lifetime history of depression and strong family histories of alcohol dependence, has high rates of co-occurring mental illness and drug use, and the majority smoke cigarettes. Despite overt problems with functioning, only 25% actively seek treatment for drinking. This group frequently presents for psychiatric care where screening for substance use is critical to diagnosing alcohol dependence.

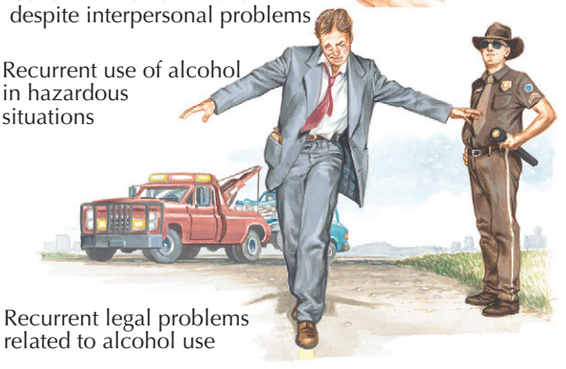
Chronic Severe (9%). This group of middle-aged individuals has early age onset of drinking, high rates of co-occurring mental illness and drug use, and high rates of antisocial personality disorder and criminal behavior with legal consequences. Two thirds will actively seek treatment due to prominent negative consequences of drinking.

Criteria: Three distinct episodes in one year are indicative of alcohol abuse

Failure to fulfill major obligations at work, school, or home



Continued use of alcohol despite interpersonal problems



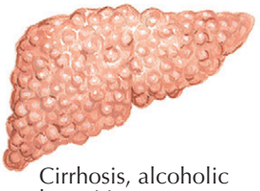
Recurrent use of alcohol in hazardous situations

Recurrent legal problems related to alcohol use

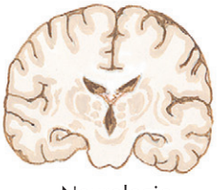
JOHN A. CRAIG, M.D. C. Machado, M.D.

Other problem patterns of drinking

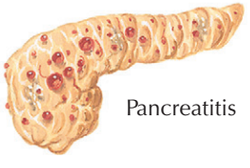
Mon	Tues	Wed	Thur	Fri	Sat	Sun	Mon	Tues	Wed	Thur	Fri	Sat	Sun



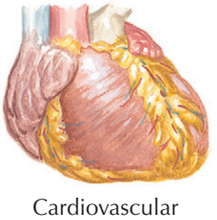
Cirrhosis, alcoholic hepatitis



Neurologic



Pancreatitis

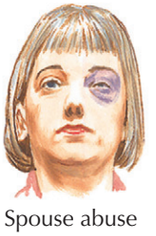


Cardiovascular

Daily alcohol use at levels likely to cause end organ damage

Hazardous behavior

Belligerence



Spouse abuse

Intermittent abuse of alcohol at levels that result in dangerous and destructive behavior

Treatment for Alcohol Use Disorders

Alcohol use disorders are common and treatable. All patients should be routinely screened with evidence-based assessments, such as the 3-item AUDIT-C and offered medical assistance for positive screening.

Brief counseling assists patients with alcohol use disorders to create and maintain effective treatment plans to reduce or quit drinking. Lifestyle changes and reducing social drinking risks are recommended to prevent relapse.

Patients with alcohol dependence are encouraged to use medication therapies to assist efforts to stop drinking; these include naltrexone, acamprosate, and disulfiram.

Patients who actively use mutual support groups (Alcoholics Anonymous or SMART Recovery) in addition to professional help improve their chances of achieving and sustaining recovery from alcohol use disorders.

In the United States, alcohol use disorders had 12-month prevalence rates of 4.65% alcohol abuse and 3.81% alcohol dependence from 2001 to 2002. Self-reported drinking (2010) among those age 12 years and older indicates that 23% binge drink (more than five drinks per drinking day), and nearly 7% are heavy drinkers (binge drink on five or more days per month); yet fewer than 2% of the population needing substance use treatment receives treatment.

Screening for alcohol use disorders identifies individuals at risk for developing alcohol-related problems and those already meeting criteria for an alcohol use disorder. Evidence-based screening, brief intervention, referral to treatment (SBIRT) is recommended for all patients and results in earlier intervention for at-risk drinkers and reduced drinking among those with an alcohol use disorder.

Treatment for at-risk drinkers generally involves education about risk factors for developing alcohol use disorders and alcohol-related problems, a review of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) guidelines to "low-risk" drinking, and a brief intervention consisting of clear advice to reduce or abstain from drinking and referral to self-help tools, such as keeping a drinking calendar, writing down reasons to reduce or stop, setting weekly reduction goals that are reviewed with a clinician or supportive peer, reducing stress, cultivating healthy leisure activities and sober social supports, and considering mutual-help groups, such as Alcoholics Anonymous (AA) or SMART Recovery.

Treatment for alcohol use disorders begins with an assessment of whether medical detoxification is required for physiologic dependence at risk for dangerous alcohol withdrawal syndromes; this is especially important for patients with co-occurring hypertension, diabetes mellitus, seizure disorder, and history of suicidality. Detoxification may be monitored on an outpatient basis, but many patients will require inpatient detoxification to prevent relapse to drinking. Medically stabilized patients with alcohol use disorders are referred to professional counseling for drinking reduction and relapse prevention and to mutual-help groups (participation in AA doubles the efficacy of professional counseling). For alcohol-dependent individuals, abstinence from alcohol is most effective at maintaining recovery gains.

Primary care physicians have a prominent role in treating alcohol dependence using medical management (MM) models of care. MM consists of (1) *frequent visits* to assess progress and health, (2) *education* about alcohol use disorders, (3) *prescribing and monitoring tolerance and adherence* to an alcohol treatment medication, (4) *facilitating weekly drinking goals* and recovery behaviors, (5) *encouraging* participation in *mutual-help* or specialty counseling if indicated, and (6) *screening and treating disorders* that commonly *co-occur with alcohol use disorders* (e.g., medical, mental illness, domestic violence). There are three FDA-approved and one non–FDA approved medications to treat alcohol dependence. Medications are reviewed briefly below.

Naltrexone. An *antagonist at central mu-opioid receptors*, naltrexone attenuates opioid-mediated reward of drinking and *clinically reduces alcohol cravings*, *relapse*, *and drinking days*, and it increases the probability of containing recurrent drinking to a brief episode rather than full relapse. Naltrexone is available in daily oral dosage and in an extended-release monthly intramuscular formulation that improves adherence. It poses *hepatotoxicity risk* and is contraindicated in those with hepatic disease and those requiring narcotic analgesia. Naltrexone is currently the *only evidence-based medication for geriatric alcohol dependence*.

Acamprosate (N-Acetylhomotaurine). A glutamate neuromodulator, acamprosate is an *abstinence-promoting medication* appropriate for patients who have achieved early abstinence. It increases time to first drinking recurrence. It is metabolized within the kidney, providing a good choice for those with hepatic disease. However, it has poor bioavailability, and the required TID dosing may pose adherence risks.

Disulfiram. This *aldehyde dehydrogenase inhibitor* prevents the final metabolic conversion of ethanol to water; usage results in accumulation of toxic acetaldehyde metabolites, leading to flushing, headache, hypertension, sweating, and nausea/vomiting. Disulfiram is most effective at *reducing anticipated rewards of alcohol* and thus reducing drinking days. Adherence is problematic, and there is a 1 in 50,000 risk of idiopathic fulminant hepatotoxicity; thus careful hepatic monitoring is required. It is *contraindicated* in those with autonomic instability (e.g., diabetes). It is a preferred treatment for impaired professionals and parents at risk of losing child custody.

Topiramate. Topiramate is a non–FDA-approved but evidence-based medication that reduces drinking in treatment-seeking alcohol-dependent patients.

This *GABAergic potentiator* can be administered to treatment-seeking patients with alcohol dependence who are actively drinking but want to reduce and are willing to commit to drinking reduction goals and medication adherence. Topiramate reduces heavy drinking days and promotes abstinence. Because of its renal metabolism, it is contraindicated with renal calculi or glaucoma.

Alcohol Withdrawal

An *alcohol withdrawal syndrome* (AWS) occurs when an individual who has alcohol dependence with physiologic dependence experiences a period of reduced dosage or abstinence from drinking. *AWS is life-threatening* as it poses a risk for seizures, hypertensive crisis, and autonomic instability (especially in patients with comorbid hypertension or diabetes) as well as delirium tremens, leading to death if not rapidly treated. AWS must be medically managed with close monitoring in either an outpatient or inpatient setting, depending on the patient risk profile.

Pathophysiology. Alcohol tolerance occurs with neuroadaptations to chronic alcohol exposure. Alcohol is a sedative; chronic exposure leads to compensatory changes with *reduced* neurotransmission at inhibitory type A gamma-aminobutyric acid *(GABA)* receptors and *enhanced* neurotransmission at excitatory *N*-methyl-D-aspartate *(NMDA)* glutamatergic receptors. During abrupt abstinence episodes, the unopposed activity of these compensatory changes results in central hyperexcitability responsible for objective and subjective AWS symptoms.

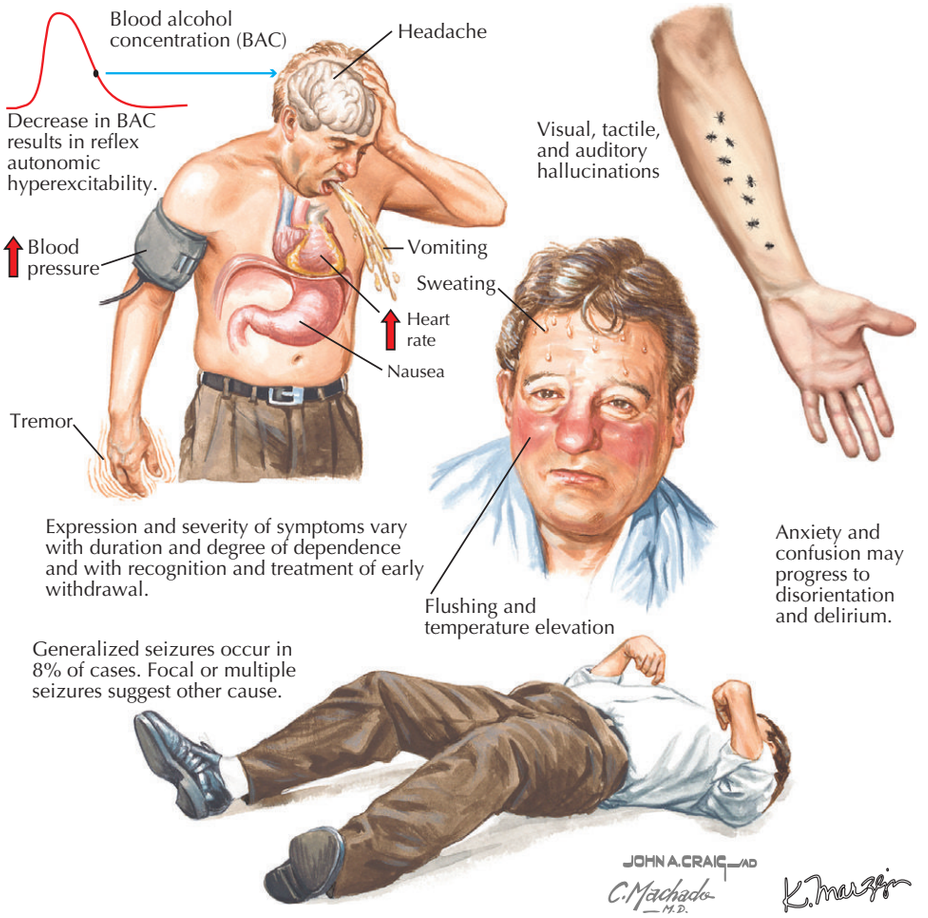
Presentation. AWS onset typically peaks within 48 to 72 hours of the last ethyl alcohol intake. Clinical signs of AWS include diaphoresis, tachycardia, hypertension, fever, vomiting, insomnia, anxiety, tremor, hyperreflexia, delirium, and grand mal seizures. Delirium tremens ("DTs") is a very severe withdrawal syndrome, with a fatal potential if not recognized or if undertreated. This involves autonomic instability, agitation, altered mental state, hallucinations, and tremor. Risk factors include advanced age, advanced alcohol dependence, prior episodes of DTs, and medical illness. Clinical symptoms of AWS include anxiety, irritability, dysphoria, nausea, anorexia, alcohol craving, headache, fatigue, and auditory, visual and/or tactile hallucinations. AWS is measured using a standardized instrument, the Clinical Institute Withdrawal Assessment for Alcohol (CIWA). This measures 10 AWS symptoms categories with a 0 to 7 scoring range for each. Moderate scores (8 to 15) reflect autonomic hyperactivity, and high scores (>15) predict seizures and delirium; these scores warrant immediate initiation of medical treatment.

Persistent AWS may endure 1 to 6 months and consists of anxiety or dysphoria, insomnia, and restlessness as well as frequent cravings for alcohol. Some medical treatments assisting recovery and promoting abstinence are hypothesized to address persistent central hyperexcitability. These include acamprosate, naltrexone, disulfiram, and topiramate (see Plate 4-14). These medications must be combined with complete alcohol abstinence and active attendance at Alcoholics Anonymous or similar support groups. This will reduce symptoms that frequently lead to alcohol relapse.

Treatment. Benzodiazepines are the gold standard AWS treatment due to their cross-reactivity with alcohol at type A GABA receptors. Symptom-triggered detoxification protocols are used because these prevent medical morbidity, and even a very occasional death, while minimizing dosing requirements for benzodiazepines and thus adverse effects. Typical protocols initiate treatment with either short-acting (lorazepam) or longer-acting (diazepam, chlordiazepoxide) benzodiazepines once autonomic arousal is recognized; this is followed by repeated dosing during the first 24 hours, based on resolution of autonomic arousal and patient comfort. Chlordiazepoxide may be administered at 25- to 50-mg doses every 2 hours PRN during the first 24 hours; subsequently, a continuing taper protocol follows, reducing the total 24-hour requirement by not more than 25% per day. These protocols are guidelines because ongoing clinical assessment is required for safety; doses should be held if increasing sedation or gait instability develops. Treatment must include nutritional repletion of thiamine, folate, and multivitamins.

Carbamazepine and valproate are anticonvulsants that may be useful AWS therapeutic adjuncts. However, the very favorable efficacy and safety of benzodiazepines does not support their use with their weaker evidence for efficacy as primary treatments.

Medical stabilization of the acute AWS must always be paired with appropriate referral to maintenance treatment to prevent alcohol use relapse. This includes medication management per Plate 4-13, treatment of co-occurring psychiatric and medical illnesses, and referral to ongoing care for substance abuse. Level of care determinations may be assisted by evidence-based Patient Placement Criteria developed by clinical researchers in the American Society of Addiction Medicine. Six domains influencing probability of good outcome are assessed to help determine the appropriate level of care; these include (1) severity of intoxication and withdrawal, (2) medical comorbidity, (3) psychiatric illness and psychosocial stability, (4) patient readiness to participate actively in treatment, (5) history of past treatment outcomes, and (6) recovery environment. Levels of care range from least restrictive outpatient to increasing medical and psychiatric outpatient supervision (intensive outpatient, partial hospital) to residential treatment. The highest level of care is inpatient hospitalization with both intensive medical and psychiatric stabilization of life-threatening symptoms.



Stages of alcohol withdrawal

	Stage 1	Stage 2	Stage 3
Hours after alcohol consumption	24 36 (peak) 48	(48-72)	(72-105)
Symptoms	Mild-to-moderate anxiety, tremor, nausea, vomiting, sweating, elevation of heart rate and blood pressure, sleep disturbance, hallucinations, illusions, seizures	Aggravated forms of stage 1 symptoms with severe tremors, agitation, and hallucinations	Acute organic psychosis (delirium), confusion, and disorientation with severe autonomic symptoms

Stage 1 withdrawal usually self-limited. Only small percentage of cases progress to stages 2 and 3. Progression prevented by prompt and adequate treatment.

Opioid Use Disorders

Opioid misuse, abuse, and dependence (opioid use disorders) refer to the *pathologic self-administration* of substances that *activate central mu-opiate receptors*, for the purpose of experiencing an altered mental state (euphoria or relaxation), or in the opioid-dependent individual for the purpose of avoiding opioid withdrawal. *Naturally-occurring opiates* (morphine, codeine) are found in *Papaver somniferum* poppy pods as a latex sap, opium; heroin is a *semisynthetic opioid* derived from opium. Prescription analgesics include *semisynthetic* (e.g., hydrocodone, oxycodone) and *synthetic* (e.g., methadone, fentanyl) opioids. Both heroin and opioid analgesics may be insufflated or injected to get "high"; other routes include smoking heroin and swallowing/chewing opioid analgesics. Routine toxicology detects only opiates (heroin metabolites), and special gas chromatograph/mass spectrometry (GC/MS) detection is required for semisynthetic and synthetic opioid analgesics.

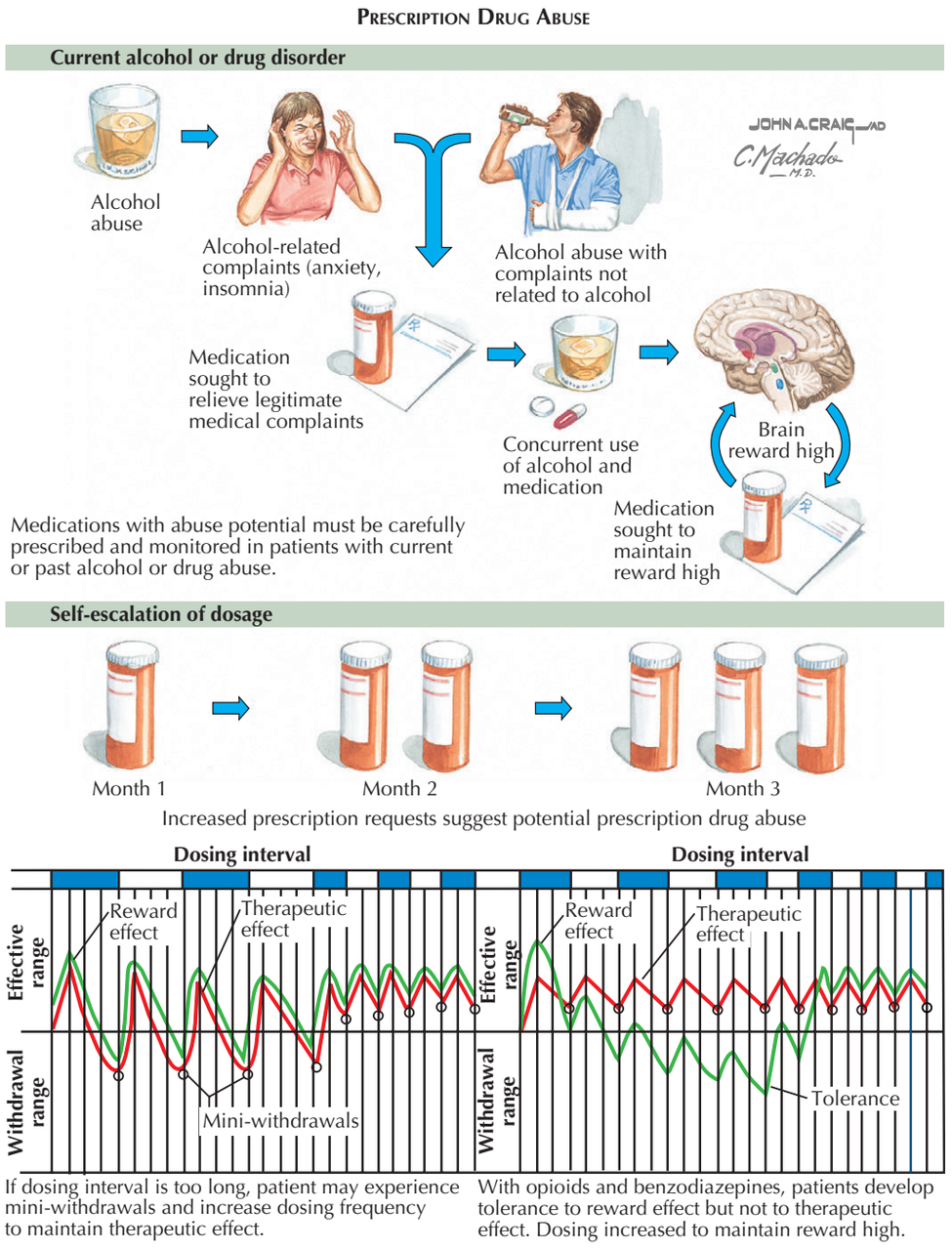
According to the 2010 National Survey on Drug Use and Health, 200,000 U.S. residents age 12 years and older endorse past-month heroin use, and 5.1 million residents endorse past-month prescription opioid misuse. Prescription opioid misuse has increased threefold in the past decade in conjunction with similar increases in opioid prescribing and unintentional opioid overdose deaths. Family and friends are the most frequently reported source of illicit opioid analgesics, contributing to increased youth exposure, high rates (6% past-month prevalence) of opioid analgesic misuse among 18- to 25-year-olds, and an alarming number of accidental pediatric ingestions and deaths.

Opioid intoxication may be recognized by miosis, dysarthria, altered mental state and sedation, constipation, impaired judgment and slowed reaction time. Recurrent opioid use results in tolerance to the central effects and progression to physiologic dependence on opioid-taking to avoid opioid withdrawal. *Physiologic dependence alone is not an opioid use disorder;* however, *it is when the individual also experiences preoccupation* with obtaining, using, and recovering from opioid use such that normal social and occupational functioning is reduced or impaired. Symptoms of opioid withdrawal include mydriasis, diaphoresis and fever, increased heart rate, abdominal cramps, nausea/vomiting and diarrhea, lacrimation, rhinorrhea, piloerection, leg cramping, yawning, insomnia, and anxiety. Although *physiologic dependence* alone is not sufficient to define an opioid use disorder, it *poses a risk for developing an opioid use disorder*, particularly in vulnerable populations, such as those with a history of substance abuse, mental illness, or genetic loading for addiction disorders.

Medical consequences of opioid misuse are many, and *risk is proportionate* to the *quantity* of opioid self-administration, the *route of administration (with injection* use carrying the highest probability of overdose death as well as high rates of blood-borne infectious disease transmission, especially hepatitis C virus [HCV] and human immunodeficiency virus [HIV]), and the *duration of use* (women being more rapidly susceptible to both medical and social consequences, often referred to as a "telescoping course"). *Overdose mortality* is associated with high-dose opioid use, co-occurring use of alcohol and other sedatives, and injection use. Injection use is commonly associated with cellulitis and staphylococcal infection, phlebitis, and endocarditis. Pain is frequently comorbid among opioid-dependent youth and adults. Social and legal consequences include loss of employment, domestic violence, and arrest for drug-related criminal behaviors.

FDA-approved medication maintenance for opioid use disorders includes the *mu-opiate receptor antagonist naltrexone*, the mu-opiate receptor *partial agonist buprenorphine*, or the mu-opiate receptor full *agonist methadone*. Behavioral therapies without medication maintenance have high failure rates (relapse to opioid use) in both youth and adults. *Optimal treatment combines medication management with behavioral therapy* and participation in self-help programs. Naltrexone therapy has been limited by poor patient adherence to oral naltrexone; the recent development of an extended-release injection formulation that endures 4 weeks may have superior outcomes. *Buprenorphine has a favorable safety and tolerability profile* compared with methadone and also offers office-based access for patients, as opposed to daily monitored dosing at methadone maintenance clinics. Patients needing close medical monitoring and more intensive social service supports may benefit more from the structure of methadone clinics.

Safe opioid prescribing will prevent diversion of opioid analgesics. Physicians must screen patients for vulnerability to opioid misuse and discuss these risks with patients. Prevention strategies include limiting quantity, using state prescription monitoring services, designated pharmacies and treatment contracts, toxicology, pill counts, and monitoring aberrant behaviors (e.g., "doctor-shopping," running out early, "lost" or stolen prescriptions). Functional improvement with opioid analgesics must be monitored closely to prevent unnecessary chronic opioid treatment. Patient education on safe storage (lockbox use), safe dosing, and safe disposal are essential and may be remembered using the mnemonic "STOP & DUMP:" *s*ecure medication, *t*ake *o*nly as *p*rescribed, & *d*iscard *u*nused *m*edications and *p*ills.



Opioid Withdrawal

An opioid withdrawal syndrome (OWS) occurs when an individual, physiologically dependent on opioids (either due to chronic opioid analgesic treatment or opioid use disorder), experiences a period of reduced dosage or abstinence from opioid-taking. OWS is both physically aversive and powerfully anxiogenic; thus individuals with moderate-to-severe OWS are highly motivated to seek opioid sources for immediate relief.

Pathophysiology. Opioid tolerance and withdrawal occur as neuroadaptations to chronic opioid exposure. This neurobiology is complex, involving adaptations at all levels of opioid-sensitive brain signaling, including (1) *mu-opiate receptor desensitization*, (2) *opioid-sensitive neuron cellular tolerance* due to up-regulation of adenylyl cyclase activity and changes to cyclic adenosine monophosphate (cAMP) response element-binding (CREB) signaling, (3) system feedback *adaptations of neuronal and glial networks* interacting with opioid-sensitive neurons, (4) *opioid-sensitive neural circuit changes* in synaptic plasticity. Clinically, *opioid signaling is inhibitory in function* (e.g., suppression of pain, respiratory drive, arousal, and anxiety); in contrast OWS symptoms are mediated by rebound hyperactivity due to reduction or removal of chronic opioid agonism.

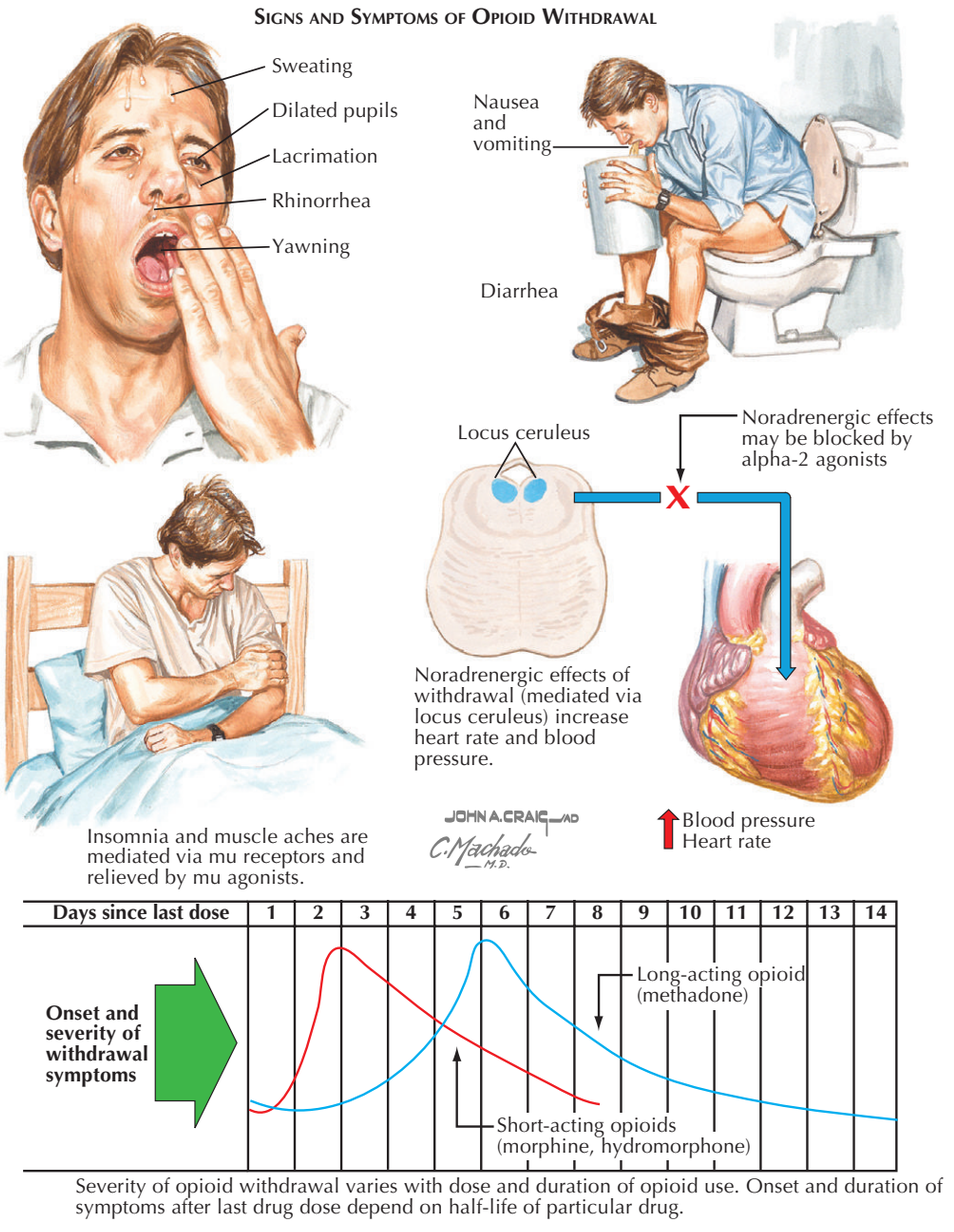
Presentation. OWS onset, duration, and severity vary according to type of opioid exposure (short-acting vs. long-acting, full agonist vs. partial agonist), exposure duration, dosing of exposure, and periodicity of withdrawal episodes. OWS is more severe with high-dose, full-agonist opioid exposure; more frequent OWS episodes worsen future withdrawal episodes. Individuals using short-acting opioids (heroin, oxycodone, or hydrocodone) experience mild-to-moderate OWS within 8 to 12 hours of last dosing, whereas persons using long-acting opioids (sustained-release oxycodone or methadone) experience mild-to-moderate OWS within 24 to 36 hours of last dosing. The duration of OWS is briefer (days) with shorter-acting opioids and may persist for weeks with longer-acting opioids. In both instances, protracted withdrawal may persist for weeks to months characterized by residual dysphoria with persistent physical discomfort often interfering with an individual's motivation and capacity for remaining abstinent from opioids. Craving and mental preoccupation associated with opioid addiction is nearly universal, persisting beyond the acute withdrawal episode, leading frequently to opioid use relapse.

Clinical symptoms of OWS include anxiety, irritability, dysphoria, nausea, anorexia, chills, muscle aches and cramps, abdominal cramping, opioid craving, headache and fatigue. OWS patients demonstrate mydriasis, lacrimation, diaphoresis, yawning, piloerection, rhinorrhea, tachycardia, hypertension, fever, diarrhea, vomiting, insomnia, and restlessness. Individuals vary in their presentation; some primarily experience gastrointestinal distress, whereas others demonstrate high anxiety with cardiovascular hyperexcitability. Of interest, each individual is consistent in his or her OWS symptom pattern episode to episode. This proves helpful for discerning OWS during follow-up.

OWS may be measured using a standardized instrument such as the Clinical Opiate Withdrawal Scale (COWS). This proves useful for medical documentation and opioid dosing needs assessment.

Treatment. Typically OWS is not considered a medical emergency; however, special circumstances may constitute medical emergencies. These include pregnancy (deleterious cardiovascular effects on the fetus and third trimester premature labor risk), cardiovascular disease, disorders involving autonomic instability, and vulnerability to dehydration. Optimal treatment includes rapid symptom stabilization to prevent opioid misuse and medical consequences of OWS.

Agonist replacement is the most rapidly effective treatment and is achieved by administering previously used opioids or an agonist substitution therapy, including the full agonist, methadone, or partial agonist, buprenorphine. Full agonists are administered to prevent OWS at any time; however, the partial agonist buprenorphine requires OWS be sufficiently moderate in severity (COWS = 9 or greater) before administration. This avoids inadvertently precipitating severe withdrawal (buprenorphine competes superiorly with full agonists at mu-opiate receptors and thereby has functional antagonist activity in this setting). Typical protocols for first-day dosing of opioid-dependent individuals are 5 to 10 mg oral methadone every 4 hours PRN, not exceeding 40 mg/24 hr, or 2 to 4 mg sublingual buprenorphine every 4 hours PRN, not exceeding 16 mg over 24 hours. Dosing in pregnancy is generally similar, although requirements may be higher during third trimester. Methadone *peak and trough monitoring* is recommended in pregnant women, concomitant with obstetric consultation. Although detoxification protocols may follow first-day dosing, opioid detoxification generally demonstrates poor outcomes in outpatient settings, with very high rates of recurrent opioid use occurring despite behavioral treatments for opioid dependence. Agonist stabilization or maintenance is frequently preferred to improve long-term stability. Although alpha-2 agonists, including clonidine are widely used to treat OWS, it only ameliorates autonomic symptoms (hypertension and tachycardia) without providing efficacy for other symptoms. Patient comfort and treatment retention with clonidine are poor compared with opioid agonist treatments. During any treatment protocol, other symptom-specific medical adjuncts may be needed, including sedatives for insomnia, antiemetics for nausea, and dicyclomine for abdominal cramping.



Severity of opioid withdrawal varies with dose and duration of opioid use. Onset and duration of symptoms after last drug dose depend on half-life of particular drug.

Borderline Personality Disorder

Psychodynamic theorists trace the origins of borderline personality disorder to disturbances in the parent-child relationship in the second and third years.

The borderline child is unable to integrate disparate experiences of parental love and hostility.

Borderline patients have unstable mood and self-image, are often inappropriately angry, and overreact to minor slights and disappointments.

The term *borderline* was initially assigned to those patients who were neither neurotic, nor psychotic, but proved to be clinically troubling cases. Today, a diagnosis of *borderline personality disorder* (BPD) refers to patients characterized by emotional turmoil and chronic suicidality. According to the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)*, BPD patients must show a "pervasive pattern of instability of interpersonal relationships, self-image, and affects, with marked impulsivity beginning by early adulthood and present in a variety of contexts." Specifically, patients must present with at least five symptoms out of a possible nine that can be organized into four categories: affective, impulsive, interpersonal, and cognitive.

Affective symptoms include extreme reactivity of mood, feelings of chronic emptiness, and inappropriate or intense anger. *Impulsive* symptoms include recurrent suicidal behavior, including ideation, threats, and suicide attempts, as well as self-destructive acts such as cutting, burning, or scratching oneself. These individuals may exhibit two or more other potentially self-damaging impulsive behaviors, including substance abuse, excessive spending, unusual sexual behavior, binge eating, or reckless driving. Sudden and dramatic shifts in their views of others frequently occur. Within the *interpersonal* domain, BPD patients may experience intense abandonment fears coupled with inappropriate anger, as well as an unstable sense of self characterized by ever-changing goals and values. *Cognitive symptoms* can occur under extreme stress and may be experienced as transient paranoid ideation or dissociative symptoms. The modern BPD individual's behavioral style is self-damaging, functioning below an actual level of intelligence or ability, varying between idealizing and devaluing within interpersonal relationships, and demonstrating an inflexible and impulsive cognitive style.

The prevalence of BPD is approximately 2% within the general population; the majority are women. BPD patients generally present clinically at age 18, tend to use more outpatient treatment services and frequent emergency rooms and psychiatric hospitals. Acts of self-injurious behavior are common, in particular during the young adult years. Completed suicide, the most devastating outcome of any psychiatric illness, occurs in 10% of BPD patients. Comorbid disorders, in particular mood and substance use disorders, complicate the picture of BPD and interfere with symptomatic recovery as well as psychosocial functioning. BPD patients are often undiagnosed because of the symptomatic overlap with other disorders. The severity and prevalence of BPD decrease with age; approximately 75% of patients regain close to normal functioning by age 40 years, and by age 50 years, almost 90% recover.

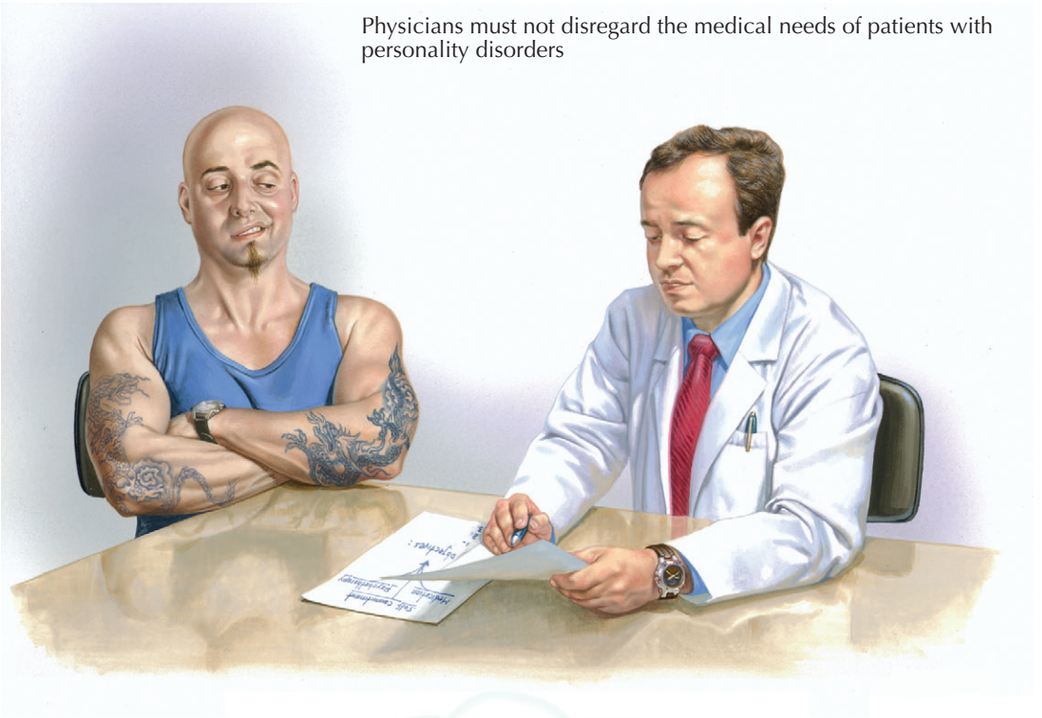
Both biologic and psychosocial factors contribute to development of BPD. Studies of twins have demonstrated a genetic influence in BPD, as well as for the core symptoms of affective instability and impulsivity. First-degree relatives of BP individuals evidence higher rates of impulsive disorders. Serotonergic deficits are linked with impulsivity, although no specific biologic markers of the overall disorder are yet identified. Psychosocial factors also contribute; these include family dysfunction, frequent traumatic childhood events, invalidating environments, and histories of sexual and physical abuse.

While pharmacotherapy plays a role in symptom management, psychosocial treatments are considered the primary method of treating BPD. Dialectical behavior therapy (DBT) is the most heavily researched psychosocial treatment. Rooted in cognitive-behavioral therapy, DBT uses individual and group therapy to address impulsivity and affective instability by teaching mindfulness, emotion regulation, and distress tolerance skills. This has reduced suicide attempts, hospitalizations and emergency room visits, and treatment dropout. Cognitive-behavioral therapy systems training for emotional predictability and problem solving, and even psychodynamic treatments (i.e., mentalization-based therapy and transference-focused therapy) demonstrate preliminary encouraging results.

There is much controversy over the use of pharmacotherapy for BPD. In the United Kingdom, pharmacotherapy is not recommended other than for the treatment of comorbid disorders. Recent meta-analysis of pharmacotherapy appears to demonstrate beneficial effects for several core symptom clusters. *Interpersonal pathology* was significantly impacted by the antipsychotic aripiprazole. Anticonvulsants, including topiramate, valproate, and lamotrigine, are preferred first-line agents for *affective dysregulation*, whereas second-generation antipsychotics (SGA) and haloperidol also showed positive results. Selective serotonin reuptake inhibitors (SSRI) treatment is only recommended for patients experiencing a comorbid axis I condition (i.e., a major depressive episode) that requires antidepressant treatment. No evidence of effectiveness emerged for other symptoms of BPD, that is, *impulsive* and *cognitive* components. When selecting a pharmacologic treatment for borderline personality disorder, it is important to consider the potential for misuse or dependence as well as potential toxic effects of overdose. Although many BPD symptoms are treatable with pharmacotherapy, treatment with medications, per se, does not lead to the remission of this disorder.

Antisocial Personality Disorder

Physicians must not disregard the medical needs of patients with personality disorders



Antisocial personality disorder (ASPD) is defined by the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)* as "a pervasive pattern of disregard for, and violation of, the rights of others" beginning in early childhood or adolescence and continuing into adulthood. To meet criteria for a diagnosis of ASPD, individuals must have a history of *conduct disorder* before the age of 15 years, characterized by aggression toward people and animals, destruction of property, deceitfulness or theft, or serious violation of rules or social norms. As adults, these persons may continue to ignore social rules, be manipulative and dishonest, be impulsive without considering the consequences, be irritable and aggressive, disregard their own or other's safety, behave irresponsibly, lack remorse for the consequences of their actions, and may be involved in criminal activity. Antisocial behavior has a negative impact on academic and professional achievement, material-life success, physical health, social relationships, psychologic well-being, and is linked to negative outcomes, such as legal problems, incarceration, and increased mortality due to reckless behavior. Although not all persons with ASPD are violent, ASPD is also more strongly associated with violence toward others compared with other psychiatric disorders.

The prevalence of ASPD is estimated to be 1% to 4% of the adult general population (3% of males and 1% of females) (APA, 2000). One potential explanation for the gender discrepancy is that women are more likely to be diagnosed with other personality disorders, such as borderline. Rates of ASPD are 10 times greater among prisoners compared with the general population. This disorder is equally represented across all races, ethnicities, and cultures. Comorbid psychiatric disorders are common among individuals with ASPD. Specifically, ASPD is highly associated with substance use disorders, other personality disorders, and anxiety disorders, in particular social phobia and PTSD. Symptoms of ASPD appear to decline with age.

The exact etiology of ASPD is unknown, although several possible biologic and psychosocial factors are identified. Adoption studies suggest a genetic link, with higher rates of ASPD present in the offspring of antisocial men. The stability of antisocial behavior also appears to be related to genetic influences, whereas nonshared environmental influences account for change in antisocial behavior over time. Biologic theories suggest that the impulsive and sometimes violent behavior seen in ASPD may be linked to low levels of serotonin, low thresholds for limbic stimulation, or brain damage secondary to injury, disease, or substances; however, causal relationships have yet to be established. ASPD is also associated with deficits in neural networks that involve the dorsolateral prefrontal cortex. Individuals with ASPD demonstrate difficulties with executive function and memory, specifically with problems requiring higher-level planning ability.

Psychosocial factors are also associated with ASPD. Adults with ASPD often have experienced insufficient emotional attachment and nurturing during childhood. Childhood behavioral disorders, which may have an onset approximately at age 7 years for boys and not usually until age 13 years for girls, also contribute to the development of ASPD in adulthood.

The general consensus regarding treatment for ASPD is that it is difficult to treat. There are little to no efficacy data on pharmacologic interventions for ASPD, and presently there are no guidelines put forth by the American Psychiatric Association for the treatment of ASPD. ASPD patients are characterized as having poor insight and minimal motivation to change behavior. When they do present for treatment, it may be due to legal mandate or because of the presence of a comorbid condition. Individual psychotherapy is not recommended for ASPD. Beyond the difficulty of establishing a therapeutic alliance with ASPD patients, therapy itself provides yet another opportunity for deception and manipulation. The most promising treatment modality for ASPD is homogeneous group-based cognitive and behavioral interventions that focus on reducing offending behavior. It is suggested that perhaps a more productive target may be early intervention and prevention programs to reduce the likelihood that conduct disorder in childhood will become ASPD in adulthood. Other studies suggest antisocial behaviors tend to decrease with age; time alone may be the best treatment for these patients.

Patients with personality disorders often provoke intense and hostile feelings in their caregivers

Intimate Partner Abuse

Intimate partner abuse refers to physical, sexual or psychologic maltreatment by a current or prior partner or spouse. It can take place in the context of heterosexual or same-sex couples and can consist of a single incident or recurrent, severe violence lasting many years.

There are four major categories of intimate partner abuse: (1) *physical abuse*, whereby physical force is used to kill, disable, injure, or otherwise hurt a partner; (2) *sexual abuse*, which involves coercing a partner to engage in a sex act without consent; 3) *threats of violence*, in which verbal statements, gestures, or weapons convey a desire to kill, disable, injure, or otherwise hurt a partner; and 4) *psychologic or emotional abuse*, including insults, controlling behavior, deliberate damage to self-esteem, stalking, and preventing a partner from accessing family, friends, information, money, or other resources.

In the United States, there are 4.8 million physical assaults and rapes of women and 2.9 million physical assaults of men annually due to intimate partner abuse. In 2007, there were 2,340 deaths in the United States due to intimate partner violence, of which 70% were women and 30% were men.

Clinical Presentation and Diagnosis. Risk factors for intimate partner abuse include poor self-esteem, poverty, substance use disorders, minimal social supports, belief in strict gender roles, social isolation, past experience of physical or psychologic abuse, borderline personality disorder (Plate 4-18), antisocial personality disorder (Plate 4-19), relationship instability, financial stressors, and community tolerance of intimate partner violence.

Victims of intimate partner abuse can present with physical injuries, such as scratches, cuts, bruises, welts, broken bones, internal bleeding, and head trauma. The psychologic trauma from intimate partner violence can manifest as depression, suicidal ideation and attempts, flashbacks, panic attacks, and difficulty sleeping.

The pneumonic *SAFE* (Sebastian, 1996) is often used to facilitate the discussion of intimate partner abuse by asking about (1) *S*tress and *S*afety in the relationship, (2) being *A*fraid of or *A*bused by one's partner, (3) having *F*riends or *F*amily who can serve as social supports, and (4) having an *E*mergency plan if in danger.

Management. Physicians must provide victims of intimate partner abuse with an environment where they feel safe. A thorough history and physical examination are required, with detailed documentation in the medical record of all findings and interventions. Intimate partner abuse must be acknowledged to the patient, who needs to be told that there is no excuse for abuse and that he or she is not at fault.

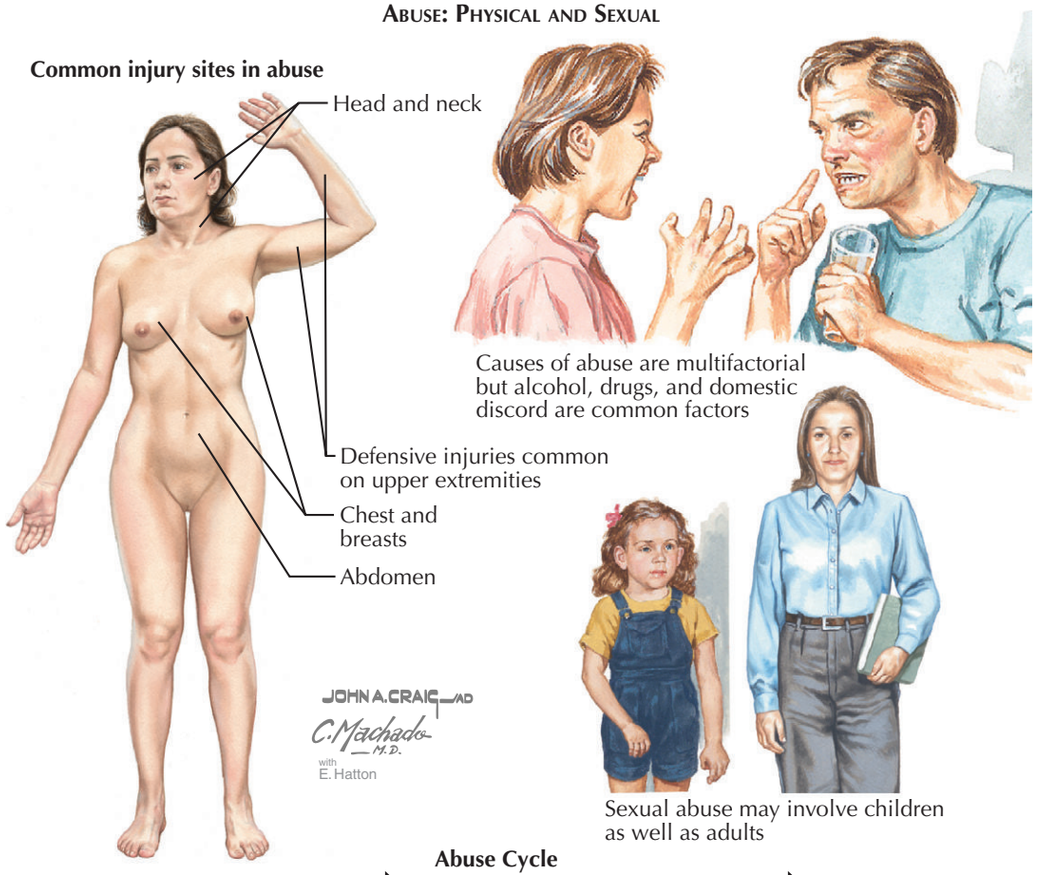
The patient must receive medical and surgical treatment as needed for sequelae of abuse, as well as evaluation for signs and symptoms of psychologic trauma. Victims need to be warned that violence often becomes more severe with time. A risk assessment should evaluate the safety of victims and their children. Intimate partner abuse must be reported to legal authorities if appropriate. Physicians need to formulate a safety plan with the patient and offer referrals for shelter, legal assistance, and mental health services.

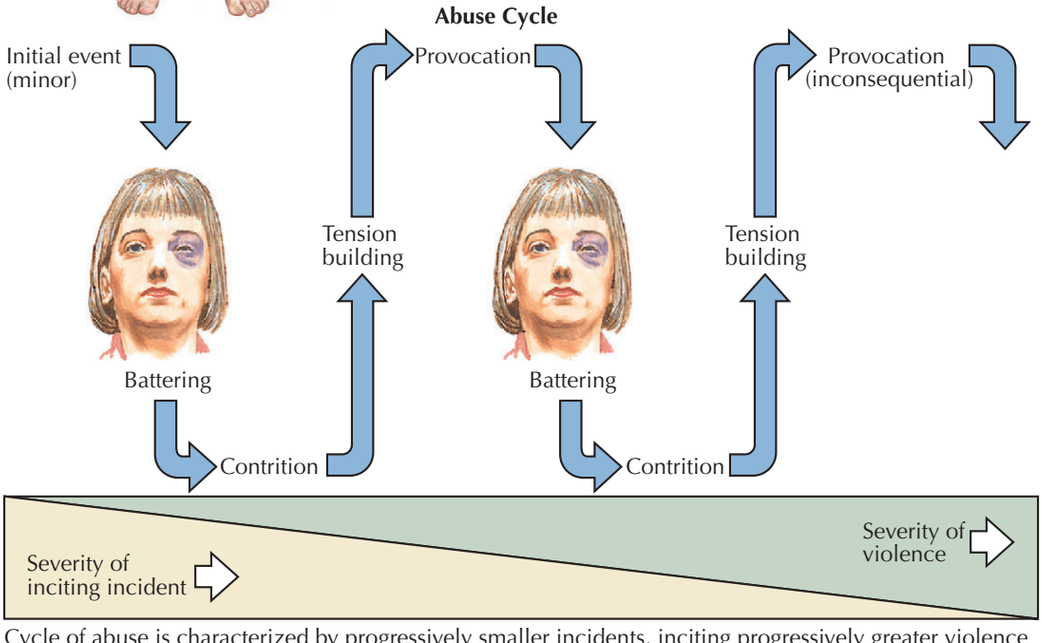
Course. Lenore Walker published a theory in 1979 that describes the cyclic pattern of abusive relationships: (1) the *tension-building phase* occurs before an abusive incident and involves mounting tension in the setting of ineffective communication and passive-aggressive behavior; (2) the *acting-out phase* involves violent or otherwise abusive acts; (3) the *reconciliation/honeymoon phase*, which consists of statements of apology, displays of affection, or attempts to overlook the preceding abuse, followed by a "calm phase."

In addition to an increased risk of bodily injury and even murder, intimate partner abuse can negatively impact a victim's physical health in the form of headaches, fibromyalgia, irritable bowel syndrome, cardiovascular disorders, gastrointestinal disorders, gynecologic disorders, neurologic disorders, sexually transmitted illnesses, and obstetric complications, such as poor neonatal health and perinatal death. Psychologic sequelae can include depression, anxiety disorders, eating disorders, substance use disorders, high-risk sexual behaviors, suicidality, low self-esteem, dissociative disorders, and posttraumatic stress disorder.

Of note, more than 3 million children in the United States witness intimate partner violence each year. Observing intimate partner abuse in the home can have an adverse effect on the emotional, social, behavioral, and cognitive development of a child, as well as increasing the likelihood that the child will engage in intimate partner abuse later in life.

Abuse: Physical and Sexual





Cycle of abuse is characterized by progressively smaller incidents, inciting progressively greater violence interspersed with periods of remorse

Elder Abuse

Elder abuse refers to the maltreatment and neglect of adults 60 years of age or older, usually by a caregiver or other person upon whom the elder is dependent. It includes *physical abuse* (injury, physical threats or inappropriate restraints), *sexual abuse* (sex acts or sexual contact without the elder's consent), *psychologic or emotional abuse*, *neglect* (failure to meet the elder's physical, emotional, and social needs or to provide protection), *abandonment*, *or financial abuse* (inappropriate use of the elder's resources for personal gain, including forgery, theft, manipulation of the elder to transfer money or belongings, and exploitation of guardianship or power of attorney).

According to the National Elder Abuse Incidence Study, in 1996 there were 551,000 documented victims of elder abuse, neglect, or self-neglect in domestic settings in the United States. Only 115,000 (21%) of those victims, however, were fully verified by adult protective services. Thus most cases of elder abuse were either never reported to adult protective services or were ultimately never confirmed by the agencies involved. Victims of elder abuse are often reluctant to report abuse due to fear of losing their caregivers or social supports.

Clinical Presentation and Diagnosis. *Risk factors for perpetrating elder abuse* include active mental illness, alcohol abuse, insufficient training for caregiving, personal history of physical or emotional abuse, significant emotional or financial dependence upon the elder, inadequate social support, lack of elder support services, negative cultural beliefs about elders and aging, and institutional settings with poor working conditions for staff and/or insufficient administrative monitoring of elder treatment.

The abused elder individual must be listened to because he or she often reports the maltreatment, per se, or there may be abrupt changes in his or her behavior; sometimes rather unusual behaviors develop. The caregiver may refuse to permit visitors from seeing the elder alone. However, when observational opportunity presents, *signs and symptoms of elder abuse* include bruises, welts, cuts, lacerations, rope marks or other signs of being restrained, broken bones, or internal bleeding. In addition, the abused elder patient may evidence injury to the breasts or genitals, unexplained sexually transmitted illnesses, dehydration, malnutrition, bed sores, poor hygiene, and unauthorized or unexplained banking transactions. Laboratory results often indicate medication overdose or inadequate dosing.

Prevention and Management. Caregivers can use a variety of strategies to reduce stress and decrease their own likelihood of perpetrating elder abuse. First, obtaining adequate training before assuming elder care responsibilities can markedly reduce feelings of inadequacy and frustration during caregiving. Caregivers should also enlist the help of other members of the community, including family, friends, and local services that have additional resources to assist in caregiving.

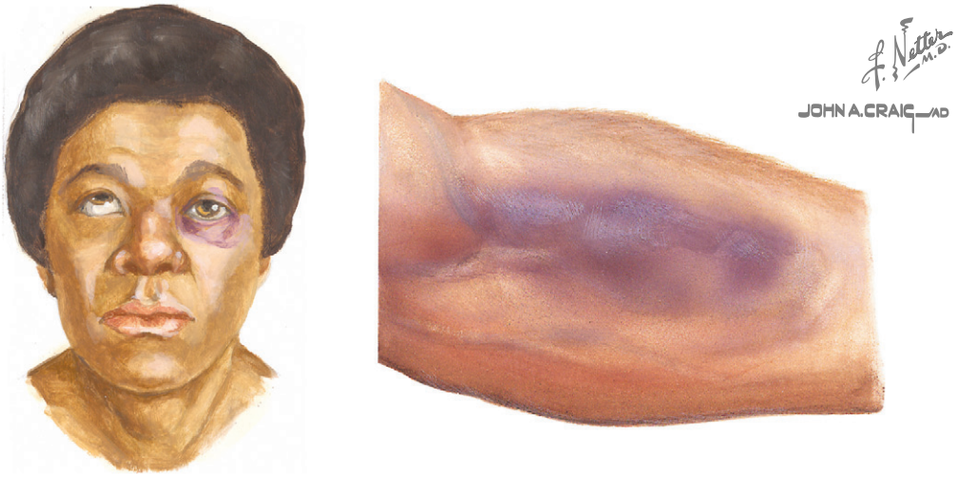
Respite for caregivers between long shifts can significantly decrease stress and is made feasible by volunteer programs that offer temporary relief from caregiving tasks and related errands. Adult daycare programs can be highly beneficial. Moreover, involving independent financial planning services in the management of an elder's assets can decrease the risk of financial abuse. Finally, caregivers should never hesitate to seek mental health counseling for themselves, should they develop feelings of depression or a substance use disorder.

At elder care facilities, regular monitoring for abuse, clear policies and protocols outlining proper elder treatment, thorough employee training, and regular visits to the facility by community members may all decrease the risk of elder abuse.

Suspected elder abuse should be reported to adult protective services. The patient may require hospital admission to ensure safety and provide medical or surgical treatment in the aftermath of abuse. Attempts should be made to help place the patient in a safe home, or alternatively, the patient should be allowed to return home if he or she has decision-making capacity and declines treatment interventions. A multidisciplinary team approach to elder abuse interventions is optimal and should include physicians, nurses, social workers, visiting nurses, and caseworkers from adult protective services.

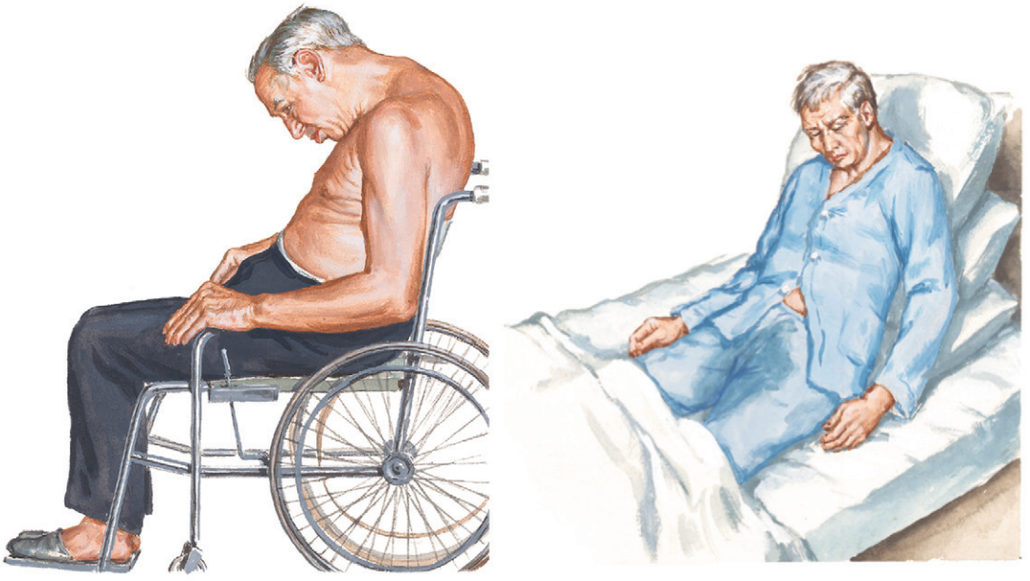
Course. Victims of elder abuse are at increased risk of adverse health consequences that can differ from the health impact of normal aging, including physical injuries, malnutrition, dehydration, poor sleep, elevated risk of sexually transmitted illnesses, exacerbation of preexisting medical conditions, and premature death. Psychologic sequelae include increased rates of depression, anxiety disorders, symptoms of posttraumatic stress disorder, and other forms of distress.

Physical Abuse



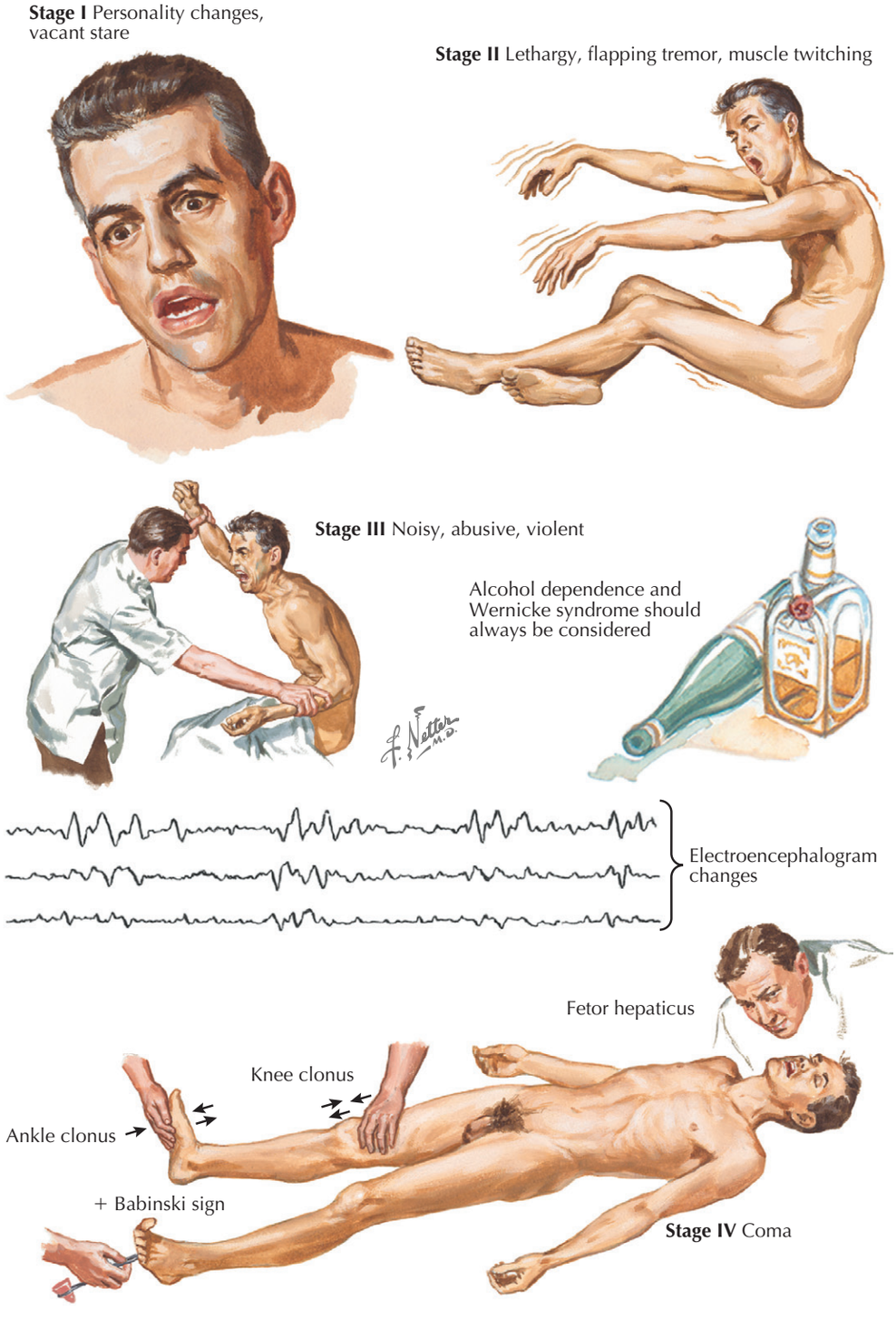
Physical abuse demonstrated through assaults, rough handling, burns, and sexual abuse

Physical Neglect



Physical neglect demonstrated through poor hygiene, malnutrition, soiled clothing, giving wrong medicines, not getting medical care when needed, or complete abandonment without supervision or care

Delirium and Acute Personality Changes



Delirium is an acute confusional state commonly seen in patients with medical illness, especially among the geriatric population. Delirium encompasses four key clinical features, including (1) a disturbance of consciousness with *impaired attention and concentration*, (2) the disturbance *develops* over a short period of time (*hours to days*) and often *fluctuates* in severity. (3) a *perceptual disturbance* that is not related to a pre-existing condition such as dementia, and (4) an *underlying medical condition*, *intoxication*, *or medication* side effect is evident. Approximately 30% of older patients experience delirium in the course of hospitalization, with higher rates among more frail patients and those undergoing complex surgery. In the intensive care unit (ICU), the prevalence of delirium is about 70% as measured by standardized screening and diagnostic tools.

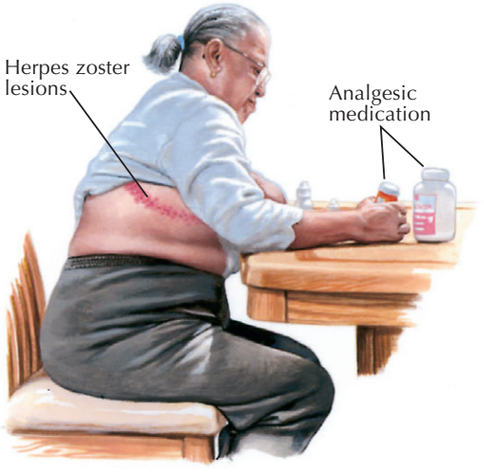
There are multiple pathophysiologic mechanisms that may cause delirium; there is no final common pathway allowing a simple approach to diagnosis or treatment. The neurobiologic basis of delirium is, therefore, poorly understood, and diagnosis relies on a comprehensive clinical assessment with judicious use of ancillary studies. In general, areas of the brain that govern arousal, attention, insight, and judgment are affected. These include the subcortical ascending reticular activating system (ARAS) and integrated cortical regions. The ARAS predominantly serves arousal mechanisms, whereas integrated cortical function is necessary for proper orientation to person, place, and time, as well as higher cognitive functions.

Of the neurochemical pathogenic mechanisms of delirium, the best understood is the cholinergic system. Anticholinergic drugs are commonly associated with delirium in healthy patients but much more so in the elderly. Conditions that may predispose to delirium secondary to acetylcholine depletion include hypoxia, hypoglycemia, thiamine deficiency, and Alzheimer disease. In addition, many commonly used drugs may precipitate delirium due to secondary anticholinergic effects. Additional neurotransmitter systems that may precipitate delirium include GABA, endorphins, neuropeptides, serotonin, and norepinephrine. Other neurochemical precipitants of delirium include endogenous chemicals, such as proinflammatory cytokines and tumor necrosis factor-alpha, which may explain delirium occurring in the context of infection/sepsis, surgery, and hip fractures. *The blood-brain barrier is weakened by sepsis, even in pediatric cases.* Other than advanced age, pre-existing CNS disease, such as Alzheimer disease, Parkinson disease, stroke, etc., accounts for a significant increase in risk for delirium. Indeed, a new delirium in an elder patient may be a heralding sign of previously unrecognized or impending dementia.

The presentation of delirium is typically acute, over hours or days, and may persist for days to months. There may be a *prodromal phase*, especially in elder patients, including fatigue and lethargy, sleep disturbance, anxiety and/or depression, or restlessness. The *acuity of onset differentiates delirium from dementia* in most cases, although delirium in a demented patient may be difficult to detect, especially early in the course. Moreover, the severity of confusion may fluctuate throughout the day, becoming particularly more prominent toward night-time. Initially, there may be a subtle change in mental clarity, inattention, and disorientation before more obvious behavior changes take place. The patient is *often very distractible*, *unable to maintain a cohesive train of thought or action*. Patients are typically *disoriented to time*. In more advanced cases, patients may become more obviously *drowsy and lethargic*, even obtunded. However, the opposite may occur in some forms of delirium, where the patient becomes *hypervigilant*, *irritable*, *and agitated*, *as seen in alcohol withdrawal*. Hallucinations may occur. *Cognitive deficits*, including amnesia, aphasia, agnosia, and apraxia may also appear. Other clinical manifestations may include *emotional lability*, *disturbance of sleep cycle*, *motor restlessness*, and sometimes motor signs, such as asterixis, myoclonus, or action tremor. In the *elder patient*, the most common presentation is of a withdrawn, quiet state that may be easily mistaken for depression.

Delirium is often misattributed to psychiatric diagnoses—usually depression and catatonic schizophrenia in hypoactive deliriums, and personality disorders and psychosis in hyperactive deliriums. A patient with a first-episode psychosis or mania should be of typical age, that is, a young adult, and should appear generally well, not diaphoretic, flushed, befuddled, jaundiced, or clumsy. Psychiatric illness usually does NOT account for disorientation, and does NOT cause motor symptoms or fevers. Fluctuations in degree of alertness, variable motor signs, and uneven cognitive performance are expected in delirium and do not signify a manipulative personality. Use of antipsychotic medication may enable care, shorten duration of delirium, and improve

Delirium and Acute Personality Changes
(Continued)



Use of analgesics and sedatives can precipitate delirium in patients with limited cognitive reserve, especially the elderly and the demented.

Delirium is a medical emergency.

The mental state of delirious patients often changes from hour to hour.

C. Machado M.D.

"Sundowning." Delirious patients are often more confused and agitated at night.

mortality, even when the underlying cause is not psychiatric.

Psychiatric illness is a diagnosis of exclusion for delirium and should be confirmed with a psychiatric consultant when suspected. Similarly, if a delirious patient is under psychiatric care, neurologic consultation should be obtained. Frontal brain tumors, multiple sclerosis, epilepsy, encephalitis, and dementia can all have delusions, hallucinations, mania, and aggression as manifesting signs. Repeating sequences of odd behavior, indifferent attitude, amnesia, atypical age, absence of prior or family history of mental illness, and presence of primitive reflexes indicate more screening for neurologic disease.

Substance abuse very frequently leads to various confusional presentations. The use of illicit substances and overuse of alcohol are usually denied in medical settings; however, ingestion of toxins and drug overdose, either recreational or suicidal, should be considered in all cases of delirium. A*lcohol, barbiturates, and benzodiazepines all have life-threatening withdrawal syndromes, as well as syndromes of intoxication*. Antipsychotics are not a treatment for withdrawal syndromes. Replacement therapy and controlled taper for alcohol, benzodiazepine, and barbiturate-dependent patients are lifesaving.

Very rarely, anti–*N*-methyl-D-aspartate receptor (NMDAR) encephalitis, a novel and significantly underdiagnosed diffuse encephalopathy, manifests primarily (80%) in women with a combination of psychosis, including catatonia, as well as dyskinesias, memory deficits, and convulsions. The abnormal movements are varied, often including oral-lingual-facial akathisia but also choreoathetosis, dystonia, oculogyric crisis, dystonia, rigidity, and opisthotonos. Often, there is a less than 2-week history of a prodromal febrile illness, including headache and respiratory or gastrointestinal symptoms. This anti-NMDAR encephalitis is either a paraneoplastic disorder, secondary to an underlying ovarian teratoma, or a primary autoimmune disorder occurring in young adults or children. This is potentially reversible if recognized early and treated with surgery and/or immunosuppression. Prognosis largely depends on adequate immunotherapy and, in paraneoplastic cases, complete tumor removal.

Regardless of the individual case, a comprehensive history, examination, and review of the medical record must be completed to determine the underlying cause(s). Seizures and focal signs on examination require brain imaging (magnetic resonance imaging [MRI]/computed tomography [CT]) and/or electroencephalography (EEG) to assess for acute structural lesions, infection, or inflammation. The nature of the patient's underlying medical condition requires standard laboratory tests, including blood cultures as well as cerebrospinal fluid examination to demonstrate evidence of possible systemic infections, electrolyte disturbance, volume depletion, liver failure, uremia, thyrotoxicosis, and other systemic disorders.

The examiner must consider potential permanently damaging conditions, such as thiamine deficiency (Wernicke encephalopathy), herpes encephalitis, or NMDAR encephalitis, all requiring emergent therapy. A careful review of medications and toxicology screens is essential. Drug toxicity accounts for 30% of delirium cases; over-the-counter drugs, such as diphenhydramine, require attention, and other specific drug syndromes exist as well. When no mechanism is identified for the acute personality change, particularly in young women, abdominal/pelvic imaging studies as well as anti-NMDAR autoantibodies must be evaluated in serum or cerebrospinal fluid to exclude anti-NMDAR encephalitis.

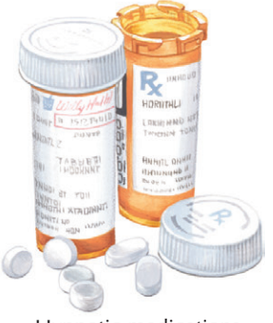
Antipsychotic medications can precipitate the *neuroleptic malignant syndrome, a triad of acute confusion, rigidity, and hyperthermia*. Antipsychotic medications, often useful for behavioral control of an agitated patient, may also cause their own *behavioral syndrome of severe motor restlessness, or akathisia*, which is usually accompanied by markedly increased muscular tone and cramping. Combinations of antidepressants, migraine medications, and some antibiotics can trigger the *serotonin syndrome, causing a triad of confusion, autonomic instability, and clonus*. Lithium, along with other narrow-window therapeutic drugs, such as digitalis, can cause delirium even with levels in the recommended therapeutic range. Lithium toxicity usually manifests with vomiting or diarrhea, severe tremors, and ataxia, whereas digitalis toxicity often causes paranoia and hallucinations. Serum *levels of any drug the patient is taking should be checked when available*, and all nonessential medications should be held.

Treatment of delirium requires identification of the underlying medical problem, judicious use of psychoactive medication to keep the patient and others safe from aberrant behavior, and maintaining a peaceful environment. The presence of delirium is a well-established source of increased morbidity and mortality—and a syndrome in urgent need of a diagnosis.

Insomnia

Reading in bed can assist those with insomnia relax, although watching the clock is not recommended.

Symptoms of insomnia include fatigue, depressed mood, poor concentration, and worry.



Hypnotic medications can be of great value for those who have failed cognitive-behavioral treatments.

Most people experience occasional insomnia sometime in their lives. However, a diagnosis of insomnia disorder, which is present in 10% to 15% of adults, requires a *symptom*, that is, difficulty with sleep onset, sleep maintenance, or nonrestorative sleep; a *frequency and duration* present on most nights over a period of at least 4 weeks; and a *consequence*, associated distress, or social occupational dysfunction. Insomnia disorder is most commonly *comorbid* (75%), in which the insomnia occurs in the context of a medical, psychiatric, or sleep disorder that initiated or maintained the sleep disturbance, or *primary insomnia*, with no comorbid disorders.

Insomnia disorder is more common with increasing age, female gender, poor physical health, and increased social and familial stress. Often, this is a chronic condition, with 50% of insomnia disorder patients continuing to meet criteria after 3 years, particularly with more severe symptoms. However, specific insomnia symptoms (initial insomnia, nocturnal awakenings) are often dynamic, shifting over the course of the disorder. In comorbid insomnia, sleep disturbance is a marker of greater medical, neurologic, and psychiatric illness severity. Insomnia disorder is an independent risk factor for incident major depressive episodes. It is not established whether comorbid insomnia treatment improves outcomes in such disorders. Insomnia sufferers have an increased risk of hypertension and diabetes.

The construct of hyperarousal helps understand much of the physiology of insomnia disorder, although it is unclear whether the hyperarousal is a cause or consequence (or both) of insomnia. Evening cortisol elevations, increased body temperature and basal metabolic rate, waking EEG patterns, elevated glucose metabolism (using positron emission tomography [PET]) during non-REM sleep, and reductions in brain GABA during wakefulness all point to nervous and autonomic system hyperarousal in insomnia disorder. Insomnia disorder may not be primarily a nocturnal disorder but rather something that actually lasts throughout the 24-hour day, with insomnia its primary expression.

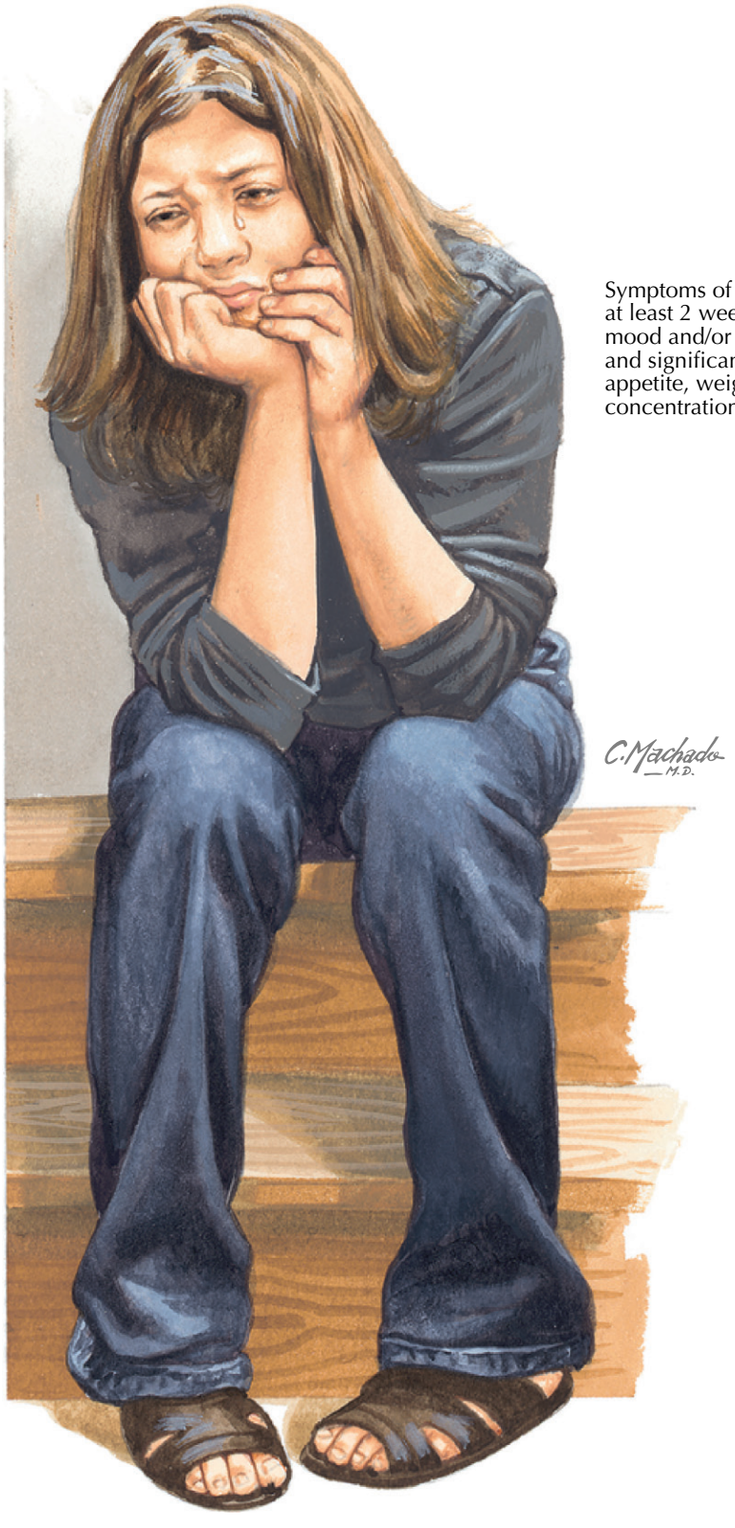
Insomnia neurobiology is not fully defined, although advances in sleep biology provide guidance to potential CNS substrates. The brain contains multiple systems promoting sleep and others enhancing wakefulness. Pedunculopontine and laterodorsal tegmental nuclei (PPT and LDT, respectively) *cholinergic neurons* innervate the thalamus and cortex firing most actively during wakefulness. Similarly, *noradrenergic*, *serotonergic*, *and histaminergic cells* in the locus coeruleus, raphe nucleus, and tuberomammilary nucleus project to the lateral hypothalamus, thalamus, and frontal cortex, respectively, and fire most actively during the waking state. *Orexin-containing cells* in the lateral hypothalamus project widely to the cerebral cortex and fire actively during waking to support arousal. The latter receive afferents from monoaminergic brainstem arousal centers, also providing extensive input to these centers. The cortex itself provides assistance to the arousal centers with reciprocal innervations.

GABAergic-containing neurons in the ventrolateral preoptic nucleus (VLPO) promote sleep by inhibiting arousal centers. Thus our current simplified understanding of sleep physiology informs us that redundant and interactive neural systems control sleep. It is not surprising that despite a powerful sleep drive, there are many neuroanatomic substrates for pathology to develop. Thus insomnia may be related to either inadequate inhibitory activity from VLPO sleep-promoting neurons or excess brainstem activation of arousal centers, or even simultaneous activation of both excitatory and inhibitory influences, leading to unstable sleep states.

The multiple neural systems controlling sleep provide diverse targets for behavioral and pharmacologic intervention for insomnia treatment. Cognitive-behavioral therapy for insomnia (CBT-I) includes education about productive sleep habits (sleep hygiene), reduction of time awake in bed (stimulus control), sleep restriction to produce sleep deprivation and increase sleep drive, instruction in relaxation techniques such as meditation and progressive muscle relaxation, and substitution of realistic attitudes about the consequences of sleeplessness for prevailing catastrophic beliefs. CBT-I is effective for improving sleep satisfaction and reducing wake time before sleep and during the night.

Marketed medications known to assist with sleep have existed for more than 100 years, although alcohol and opioids have been used for this purpose for much longer. The commonly prescribed medications bind to benzodiazepine receptors, an allosteric site on the GABA-A receptor, enhancing GABAergic (inhibitory) transmission. Many benzodiazepine receptor agonists exist, and they differ from each other predominantly only in their half-life. These medications are also anticonvulsant, anxiolytic, and myorelaxant and may produce tolerance, physical dependence, and withdrawal symptoms upon rapid discontinuation. Therefore their use is controlled. Other common medications used to promote sleep act at the monoaminergic receptors involved in CNS arousal. For instance, drugs with antihistaminergic properties are available for treatment of allergic reactions, as antidepressants and antipsychotics. Other drugs bind to the melatonin receptor in the CNS, promoting sleep by uncertain mechanisms.

PEDIATRICS: DEPRESSIVE DISORDERS



Symptoms of depressive disorder include at least 2 weeks of marked change in mood and/or loss of interest and pleasure, and significant changes in patterns of appetite, weight, sleep, activity, concentration, energy level, or motivation.

The depressive disorders are a group of mental health problems in children and adolescents characterized by a sad or irritable mood. In simple terms, these disorders are caused by a difference in the structure and function of the part of the brain that controls the intensity of sad and irritable moods. Vulnerability to the development of depressive disorders can be genetically determined. Concomitantly, there is often something in the youth's environment that triggers the sad or irritable feelings, such as poor relationship(s) with peers or with a parent or loss of loved ones. It is estimated that 4 to 5 of 100 youths have depressive disorders.

The most severe of these disorders, *major depressive disorder*, is characterized by a distinct period of at least 2 weeks during which the child/adolescent experiences a depressed or irritable mood that is present most of the day nearly every day and/or is associated with loss of interest or pleasure in nearly all activities. There are often severe problems with eating, sleeping, energy, concentration, feelings of worthlessness or extreme guilt, and loss of the desire to live. These symptoms may manifest as the youth being cranky, having loss of interest in hanging out with friends, refusal to get out of bed for school in the morning, or preoccupation with song lyrics that suggest life is meaningless. To meet the diagnosis, the problems must cause distress and/or impair the youth's function at home, at school, or with peers. After puberty, major depressive disorder is more common in girls than boys.

The less severe but longer lasting of these disorders, *dysthymic disorder*, is characterized by a depressed or irritable mood for most of the day, more days than not, for at least 1 year. There also are problems with eating, sleeping, energy, and concentration, feelings of hopelessness, and low self-esteem. To meet the diagnosis, the problems must cause distress and/or impair the youth's function at home, at school, or with peers. Dysthymic disorder occurs equally in boys and girls, and children with this disorder are more likely to develop major depressive disorder in their teenage or early adult years.

Diagnosis. Qualified health professionals experienced with children, including child and adolescent psychiatrists, pediatricians, child psychologists, child-trained social workers, counselors, and clinical nurse specialists are best trained and have the most experience to accurately diagnose these depressive disorders. The evaluation typically requires input from multiple people who know the child, and the diagnosis is based upon the findings from interviews of parents/caregivers as well as interviews with the child and a mental status examination. There are no imaging studies, blood tests, or other specific medical testing modalities to diagnose these disorders.

Treatment. Psychotherapy is an effective treatment for these disorders, especially because it particularly helps the youth understand and learn how to cope with sad feelings. These coping strategies include learning how to identify and talk about feelings, how to stop thinking automatic negative thoughts, how to find activities that are soothing and comforting, how to discover and appreciate good things about themselves, and how to build hope for the future. If environmental circumstances are triggering the sad feelings, it is important to change these circumstances, if at all possible, to increase the chance of a successful treatment.

If the depressive disorder is severe, for example, if the youth is thinking about wanting to die or has lost most ability to function, then antidepressant medication may be used as a treatment in addition to psychotherapy. Antidepressant medication may help the youth feel more motivated to work on coping skills in therapy.

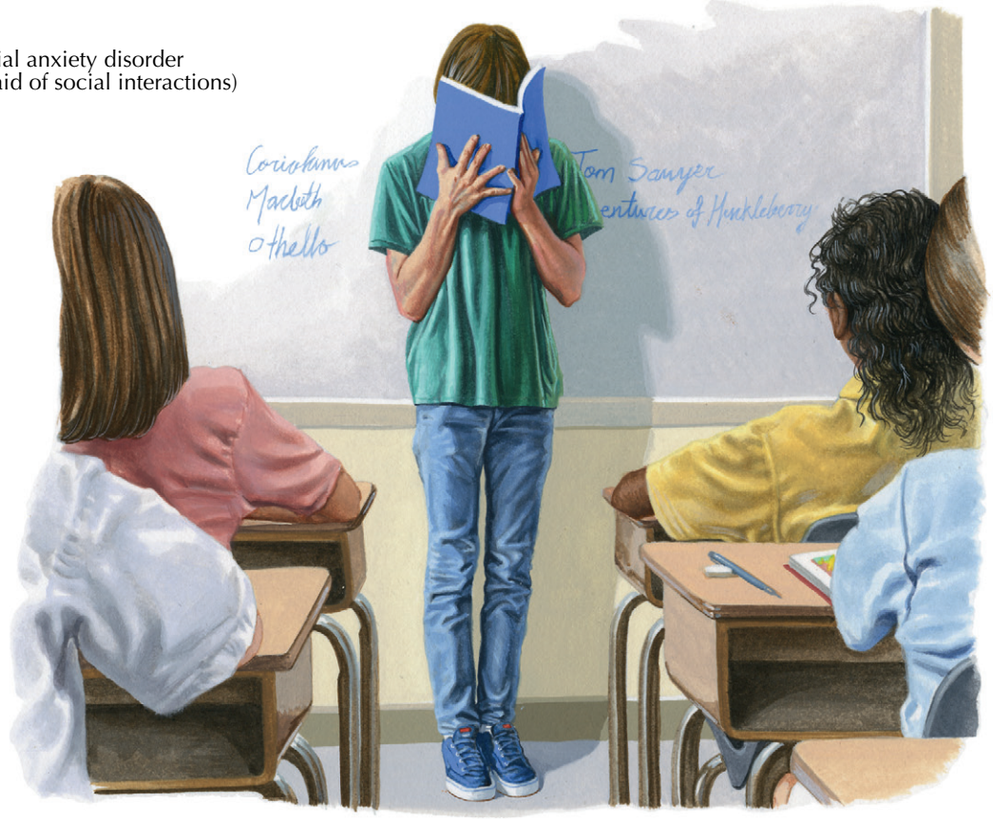
Course. The depressive disorders respond well to the above treatments when delivered by qualified mental health professionals. If left untreated, the depressive disorders can lead to death through suicide. This very serious illness also can cause failure in school and involvement in risky behaviors and subsequent difficulties with maintaining or establishing relationships and jobs in adulthood.

Pediatrics: Anxiety Disorders

Generalized anxiety disorder (many worries and fears)

C. Machado M.D.

Social anxiety disorder (afraid of social interactions)



The anxiety disorders (AD) are mental health problems found in children and adolescents, characterized by disabling scared or worried feelings. These disorders are common, with 10 to 15 of 100 youths estimated to have one of these disorders. These occur more commonly in girls. ADs are caused by a difference in the structure or function of the brain that controls worries and fears. Vulnerability to the development of anxiety disorders can be genetically transmitted. Parents who are overprotective or overcontrolling appear more likely to have anxious children, and children also can learn to be anxious from parents who are anxious. Sometimes environmental events can trigger an anxiety disorder. For example, *separation anxiety disorder* can be caused by exposure to frightening events, such as domestic violence.

Generalized Anxiety Disorder. Generalized anxiety disorder is characterized by excessive worry/angst occurring on more days than not about a variety of areas, such as schoolwork, friendships, family, health/safety, and world events. The worry is accompanied by feeling tired, tense, restless or irritable; having difficulty focusing; and having trouble falling or staying asleep. Sometimes these youngsters have associated physical symptoms, including muscle aches, stomach cramps, or nausea. The youth finds it difficult to control the worry. To meet the diagnosis, the problems must be present for at least 6 months, and must cause distress and/or impair the youth's function at home, at school, or with peers.

Separation Anxiety Disorder. Separation anxiety disorder is characterized by excessive worry about being separated from the home or from parents. The child may feel very upset about leaving home to go to school, about being separated from the parent, about sleeping alone in his or her own bedroom, about something bad happening to the parent, or something bad happening to the child that will separate him or her from the parent. These children may refuse to go to school or may develop physical problems (headaches, nausea) before going to school or when at school. Some youngsters may experience bad dreams about being separated from the parent. To meet the diagnostic criteria, these problems must be at least a 1-month duration, causing distress and/or impairing the youth's function at home, at school, or with peers.

Social Anxiety Disorder. Social anxiety disorder is characterized by excessive worry about social or performance situations where embarrassment may occur. This angst can arise when meeting new people or performing in front of others (i.e., speaking up in the classroom or performing musically or athletically). When this becomes so severe that it causes panic, a pattern develops, leading to the youth avoiding social or performance situations. To meet the diagnosis, the problems must have been present for at least 6 months, causing distress and/or impairing the youth's function at home, at school, or with peers.

Diagnosis. Qualified mental health professionals experienced with children (child and adolescent psychiatrists, child psychologists, child-trained social workers, counselors, and clinical nurse specialists) are best trained to accurately diagnose the various anxiety disorders. The evaluation for these diagnoses typically takes several hours and requires input from multiple people who know the child very well. The diagnosis is based upon the findings from parent and child interviews, questionnaires, and a mental status examination. In contrast to disruptive disorders, anxiety disorders often cause more distress in the child than the parents, and children tend to report their anxiety symptoms more accurately than their parents who may not even be aware of the child's symptoms. There are no imaging studies, blood tests, or other medical tests to diagnose these disorders.

Treatment. Psychotherapy to help the youth to learn how to cope with worry and fear is the best treatment. These coping strategies include learning how to identify and talk about feelings, how to stop thinking automatic negative thoughts, and how to relax the mind and body. When a child's anxiety disorder does not respond to traditional therapy, then antianxiety medication may be considered. Antianxiety medication may help the youth feel more relaxed when working on coping skills in therapy.

Course. The anxiety disorders respond well to the above treatments when delivered by qualified mental health professionals. If left untreated, the anxiety disorders can cause long-standing distress and problems with social relationships and school performance.

Pediatrics: Disruptive Behavior Disorders

Conduct disorder
(bullying and aggression to others)

Disruptive behavior disorder

Oppositional defiant disorder
(defiant and disobedient)

C. Machado, M.D.

The disruptive behavior disorders (DBDs) are mental health problems occurring in children and adolescents, more commonly in boys, characterized by out-of-control behavior. Prevalence rates vary from 1% to 16%. A cluster of factors, including the child's characteristics, parental interactions, and environmental factors contribute to their development.

Ineffective parenting strategies often underlie these disorders. Parents may have insufficient time and emotional energy for the child or may use inconsistent methods of disciplining and limit setting. These ineffective strategies include *authoritarian* parenting, wherein the parent demonstrates too much anger or is too harsh, and *permissive* parenting, with the parent giving in to the child's excessive demands. *Authoritative* parenting is defined as having high levels of both warmth and firmness and is the most effective parenting strategy.

The DBD child may be strong-willed because of genetically inherited personality characteristics, certain intrauterine exposures (such as cigarette smoking), lack of positive parental attachment, because of stress, or a lack of predictable structure in the home or community environment. Disruptive behavior disorders are more common in families with serious marital discord, families of low socioeconomic status and in neighborhoods characterized by high crime rates and social disorganization.

Oppositional Defiant Disorder. Oppositional defiant disorder is the less severe. It is characterized by a recurrent pattern of negativistic, defiant, disobedient, and hostile behavior, such as deliberately annoying others, frequent arguments, and angry outbursts directed toward authority figures, that is, parents and teachers. To confirm the diagnosis, these behaviors must be more frequent and more severe than normal children exhibit, present at least 6 months and impair the youth's function at home, at school, or with peers.

The more serious DBD—*conduct disorder*—is characterized by a persistent pattern of serious rule-violating behavior, including instances that harm or have the potential to harm others. Physical aggression to people and animals, destruction of property, lying or stealing, running away from home, and truancy are typical examples. Boys are more likely to have conduct disorder compared with oppositional defiant disorder. Rather than physical aggression, girls are more prone to use verbal attacks, ostracism, or character defamation. To confirm this diagnosis, DBDs must be present at least 1 year, impairing the youth's home, school, and/or peer function.

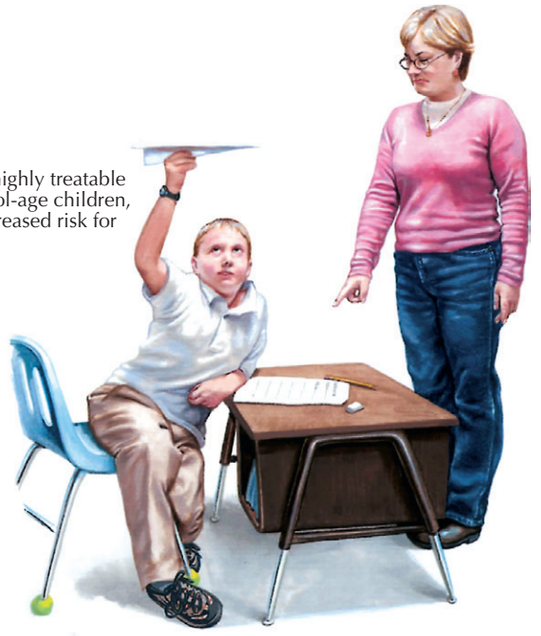
Diagnosis. DBDs are most accurately diagnosed by child and adolescent psychiatrists, child psychologists, child-trained social workers, and clinical nurse specialists. The evaluation requires input from multiple individuals who know the child. The diagnosis is based upon findings from interviews and a mental status examination. There are no specific diagnostic imaging studies, blood tests, or other medical tests that are diagnostic.

Treatment. The best therapy for oppositional defiant disorder is helping the parent learn effective parenting strategies. Treatment goals include helping the youngster become more cooperative and less argumentative or destructive. It is very useful to ascertain the child's and family's strengths and build on them in addition to focusing on their problems. Behavior modification strategies include developing a warm, loving relationship between parent and child; providing a predictable, structured environment; setting clear and simple household rules; consistently praising and rewarding positive behaviors (such as completing chores or homework); consistently ignoring annoying behaviors (such as whining or arguing), followed by praise when the annoying behavior ceases; and consistently outlining potential consequences (such as loss of privileges) for dangerous or destructive behaviors. Social-emotional skills training for the child, helps them develop skills to identify and manage feelings, get along with others, and make good decisions based on thinking rather than feeling.

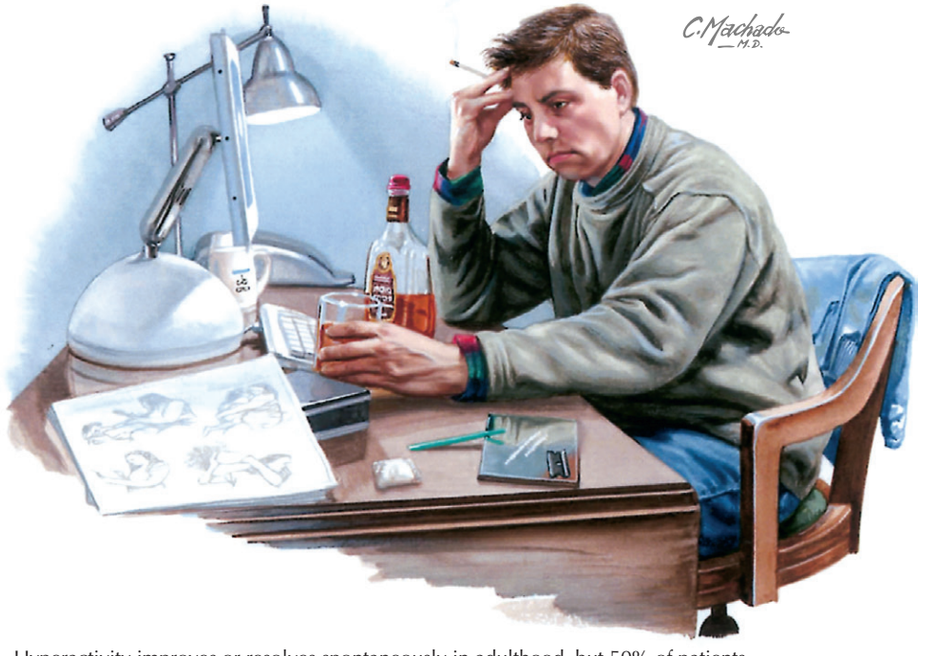
Because conduct disorder is an extremely serious condition, treatment must be more intensive and extensive, sometimes involving other child-serving agencies (i.e., juvenile justice and child welfare). Treatment is likely to be effective when administered early in the course of the disorder before maladaptive behaviors become more entrenched. If physically aggressive behavior is prominent in conduct disorder, medications (including atypical antipsychotics) can be helpful.

Course. Oppositional defiant disorder, and to a lesser extent, conduct disorder respond well to the above treatments when delivered by qualified mental health professionals. Although some children grow out of the DBDs, if untreated, these disorders can go on to cause significant problems, including difficult relationships with parents and other adults, failure at school and delinquency, and in adulthood, antisocial or criminal behavior.

Pediatrics: Attention-Deficit/Hyperactivity Disorders



Attention-deficit/hyperactivity disorder is a highly treatable neuropsychiatric disorder, common in school-age children, especially boys. Affected children are at increased risk for academic failure.



Hyperactivity improves or resolves spontaneously in adulthood, but 50% of patients maintain their cognitive disabilities. Substance abuse and antisocial personality disorder are commonly associated with ADHD.

The attention-deficit hyperactivity disorders (ADHD) are a group of childhood, adolescent mental health problems characterized by difficulty controlling attention, motivation, and behavioral impulses. These are common childhood psychiatric conditions, affecting 5% to 12% of children worldwide. More common in boys, there is increasing evidence that the principal cause of ADHD is genetically based. A greater American prevalence may result from varied diagnostic practices and cultural expectations. ADHD is related to differences in prefrontal cerebral cortex structure and function. These are important for controlling organization, planning, attention, and impulses. Maternal drinking or smoking during pregnancy, low birth weight, chemical injuries to the brain (e.g., lead poisoning), and severe child neglect are associated with ADHD.

Clinical Presentation. Four types of ADHD are recognized. ADHD, as the *predominantly* inattentive type, is characterized by a persistent pattern of poor attention and lack of motivation, particularly when sustained mental effort is required (such as for schoolwork or homework). These children are often described as "daydreamers" or "spacey." ADHD, as the *predominantly hyperactive/impulsive type*, is characterized by a persistent pattern of overactive behavior (such as being fidgety, restless, walking around without permission in class, or talking excessively when it is important to behave quietly), as well as impulsive behavior (such as difficulty waiting, not stopping to think before acting or blurting out answers). ADHD, as the *combined type* is characterized by both inattention and hyperactivity/impulsivity. To meet such diagnoses, these problems must be more frequent and severe than children normally exhibit, start before age 7 years, be present for at least 6 months, be noted in two or more settings, and impair the youth's function at home, at school, or with peers. A child with ADHD observed in a highly structured environment or engaged in a stimulating activity (i.e., playing video games), may not exhibit any symptoms. Unstructured, boring, and minimally supervised environments tend to enhance typical ADHD symptoms.

If some of the above problems are present, but not enough to meet the diagnoses, the disorder is called *attention-deficit/hyperactivity disorder, not otherwise specified.*

Diagnosis. Child and adolescent psychiatrists, pediatricians, child psychologists, child-trained social workers, counselors, and clinical nurse specialists are best trained to accurately diagnose ADHD. The evaluation typically takes several hours, requiring input in the form of interviews and/or questionnaires from parents/caregivers and teachers as well as a careful mental status examination of the child. There are no specific blood tests, imaging studies, or other medical tests to diagnose these disorders.

Treatment. The cornerstones of treatment are education about the disorder, appropriate school class placement, and medication. Medications are the most effective treatment for ADHD, with stimulant medications the first line of treatment. Stimulant medication is effective because it works by "stimulating" the brain, presumably the prefrontal cortex that controls attention, motivation, and behavioral impulses.

Tutoring the child in effective study skills (such as setting goals, planning ahead, self-rewarding) is helpful. At school, accommodations for inattention can be requested. These include frequent reminders to stay on task, reducing distractions, rewarding persistence, providing reminders to complete assignments (e.g., turning in homework), and giving extra time to complete work. Other school accommodations can be requested, such as providing opportunities for physical activity or "boredom breaks" during the day, providing a variety of interesting approaches to learning, giving rewards for control of behavioral impulses, and giving consequences for failing to control behavioral impulses.

Other useful strategies include providing a predictable, structured environment at home and a supportive environment for homework, such as a quiet place to work, breaking tasks into small portions, while offering small rewards for completing each item. About one third of ADHD youths demonstrate learning and/or language disabilities. These are identified through psycho-educational testing, and remediated with tutoring and/or speech therapy. Testing (and remediation if needed) should be requested from the school.

Course. ADHD responds well to the above treatments. About one third of children grow out of ADHD in the teen or early adult years. The remaining two thirds of children may continue to need support as they grow into adulthood, including ongoing use of medication as well as accommodations and supports at school, at work, and at home. If untreated, ADHD can go on to cause significant problems, including failure at school, injuries and accidents, substance abuse, other risky behaviors, difficult relationships with parents and peers, and poor self-esteem.

Pediatrics: Eating Disorders

Refusal to maintain weight at or above a minimally normal weight or failure to gain weight during a period of expected growth; intense fear of gaining weight; disturbance in body image; and the absence of at least 3 spontaneous menstrual cycles in postmenarcheal females are symptoms/signs of an eating disorder.

"No matter what anyone says, I am too fat!"

Eating disorders occur in adolescents who have intense preoccupation with body weight and shape and impaired eating habits. Patients have distorted thoughts and emotions concerning their appearance as well as abnormal eating behaviors; these lead to alterations in body composition and functioning occur. The etiology of eating disorders is multifactorial and includes a genetic component, sociocultural pressures to be thin, and the promotion of dieting. Performers and athletes, particularly those participating in activities that reward a lean body (e.g., gymnastics, running, wrestling, dance, or modeling) are at particular risk. Girls who feel most negatively about their bodies at puberty are at highest risk for the development of eating difficulties. The prevalence of eating disorders is variably reported, 0.8% to 14%. Their epidemiology has gradually changed concomitantly in the United States and worldwide, with an increasing prevalence in males, younger age groups, minority populations in the United States, and now countries where eating disorders uncommonly occurred. Acculturation to Western values is a risk factor for eating disorders in U.S. immigrants.

Clinical Presentation. There are two primary eating disorders: *anorexia nervosa* (AN) and *bulimia nervosa* (BN). A third category, eating disorder not otherwise specified (ED NOS), represents those disorders not meeting criteria for AN or BN. ED NOS includes more patients than the other two primary diagnoses.

Anorexia nervosa is characterized by fear of gaining weight, low body mass index, denial of current low weight and its impact on health, and amenorrhea. Prevalence is highest in teenage girls; up to 0.7% may be affected. Behaviors used to reduce weight include restricting meals and calories, hyperexercising, self-induced vomiting (purging), and use of diet pills or laxatives. Psychiatric and personality disorders, such as depression, anxiety disorders, obsessive-compulsive disorder, and perfectionism, are common.

Bulimia nervosa patients have regular episodes of uncontrolled overeating (binge eating) associated with extreme measures to counteract the feared effects of the overeating, such as occur with AN. Approximately 90% of BN patients are women who become symptomatic in late adolescence; their binge eating typically begins in the context of dieting. As BN patients may have normal weight or be overweight, this diagnosis is more difficult to entertain. Although BN patients experience weight variations, they rarely approach the low AN weights. Higher obesity rates, mood disorder, sexual and physical abuse, parental obesity, and substance misuse exist in BN patients.

Short-term medical complications include electrolyte disturbances, esophageal tears, gastric disturbances, dehydration, orthostatic blood hypotension, and cardiac dysfunction and sometimes require hospitalization. Long-term medical complications typically resulting from chronic malnutrition include growth hormone changes, hypothalamic hypogonadism, bone marrow hypoplasia, and brain structural abnormalities.

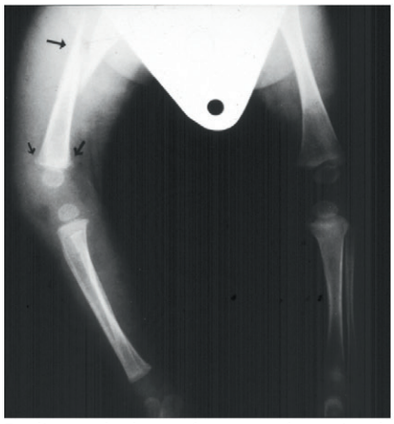
Diagnosis. Pediatricians, child and adolescent psychiatrists, child psychologists, child-trained social workers, counselors, and clinical nurse specialists are best trained to accurately diagnose eating disorders. Because these can affect every organ system, and the medical complications can be serious to life-threatening, a comprehensive history and physical examination is required.

Treatment. This requires that individual, family, medical, and nutritional aspects be addressed. The initial therapeutic goal for AN patients is the restoration of physical health. Family therapy provides the most promising results in adolescent AN and BN. Cognitive-behavioral therapeutic strategies are helpful in BN for behavioral changes, for example, for binge-purge reduction. No medications are approved by the FDA for AN treatment. Although pharmacotherapy is sometimes prescribed, it is typically targeted at comorbid depression and anxiety. Selective serotonin reuptake inhibitor antidepressants may reduce binge eating episodes and purging.

Course. Although most eating disorder individuals recover completely or partially, about 5% die and 20% develop a chronic eating disorder. Even after recovery, there are high rates of residual psychiatric illness, predominantly depression and anxiety. The potential for significant growth retardation, pubertal delay or interruption, and peak bone mass reduction are significant medical problems for adolescents in contrast to adults. Young anorectic women have an increased risk of fractures later in life. Eating disorders in adolescents are identified as the psychiatric condition with the highest mortality rate; however, these are lower than those historically reported. In a recent meta-analysis, the mortality rate among AN adolescents was 1.8% compared with 5.9% when adults and adolescents were considered together. Mortality is most often attributable to the complications of starvation or to suicide.

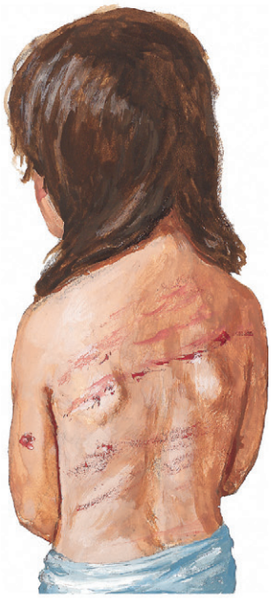
Two Forms	Restrictive anorexia nervosa Bulimia nervosa; binge eating
Common Findings	Body image distortion at ages 14-18; women > men Amenorrhea at least 3 months, and often precedes Weight loss >15% of ideal body weight Preserved secondary sex characteristics
Psychiatric Associated Disorders	Affective Anxiety Obsessive-compulsive disorder Personality Substance abuse
Differential Diagnosis	Adrenal insufficiency Inflammatory bowel and other GI disease Diabetes mellitus recent onset CNS posterior fossa lesions Primary depression
Endocrine Findings	Serum cortisol and growth hormone increased Serum LH and FSH low Insulin-like growth factor-(IGF-I) low

Fractures in Abused Children

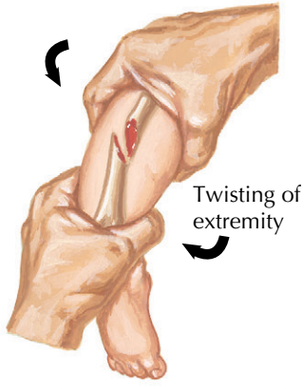


Radiograph shows fracture of proximal right femur for which patient was brought to the hospital. Healing fracture of growth plate of distal femur noted, arousing suspicion of child abuse.

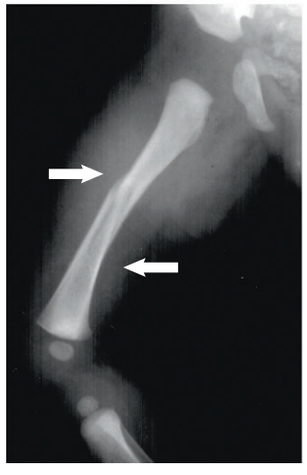
Abused child characteristically sad or withdrawn. Signs such as poor skin and hair care or malnutrition should increase suspicion.



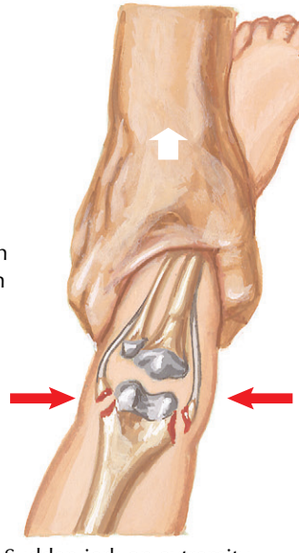
Further examination may reveal bruises, welts, or cigarette burns in various stages of healing on other parts of body.



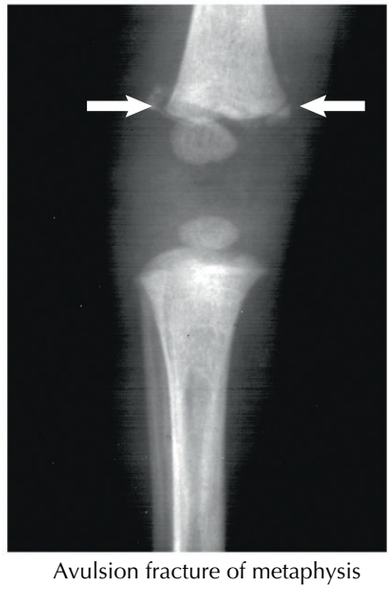
Spiral fractures in young children may occur accidentally but often due to abuse



Spiral fracture in infant



Sudden jerk on extremity avulses metaphyseal tips



Avulsion fracture of metaphysis

Child Abuse

Child abuse is defined by the *Child Abuse Prevention and Treatment Act* (CAPTA) as "Any recent act or failure to act on the part of a parent or caretaker that results in death, serious physical or emotional harm, sexual abuse or exploitation; or an act or failure to act that presents an imminent risk of harm." There are four major types of maltreatment: *neglect*, *physical abuse*, *psychologic maltreatment*, *and sexual abuse*. Most states set up their own guidelines indicating the level of evidence to make the distinguishing finding or disposition for the abuse.

The National Child Abuse and Neglect System (NCANDS) of the Administration of Children, Youth, and Families (ACYF) Annual Report 2009 indicates that there were 9.3 unique abuse victims confirmed per 1,000 children in the United States. Children 1 year and younger had the highest rate of victimization; there was an almost equal distribution of boys and girls; some children experienced multiple abuses. Neglect was most frequent (78.3%), followed by physical abuse (17.8%). Sexual and psychologic maltreatment each occurred in 10% of abused children overall. The 2009 national fatality rate was 2.34 per 100,000 and has been increasing over the past 5 years. Health and mental health-care professionals should maintain the possibility of abuse on their differential every time they see a child.

Clinical Presentation. Presentations vary greatly depending on the type(s) of abuse as well as social and emotional developmental stage. Children with developmental disabilities, that is, mental retardation, emotional disturbances, visual or hearing impairment, learning disabilities, physical disabilities, behavior problems, or other medical problems are at increased risk of being victims.

Physical abuse most often manifests with signs of abuse, including bruising and/or skeletal injury. In addition, *physical abuse is often associated with psychologic impacts*, *including increased anger*, *aggression*, *poor academic performance*, *sleep problems*, *drug abuse*, *and suicidality*. Sexually abused children often present to physicians for evaluation of genital injury. The *sequelae* includes impaired mental health with *increase in rates of depression*, *anxiety disorders*, *sleep disorders*, *suicide attempts*, *and posttraumatic disorder (PTSD)*, but not schizophrenia or somatoform disorders.

With psychologic abuse, it is more difficult to quantify and identify consistent patterns of presentation. Children of psychologic abuse present with *increased levels of depression*, *academic difficulties*, *aggression*, *and behavior problems*. Often, children are exposed to more than one type of abuse, and so the impact of abuse can be complex. In addition, physical, sexual, and psychologic

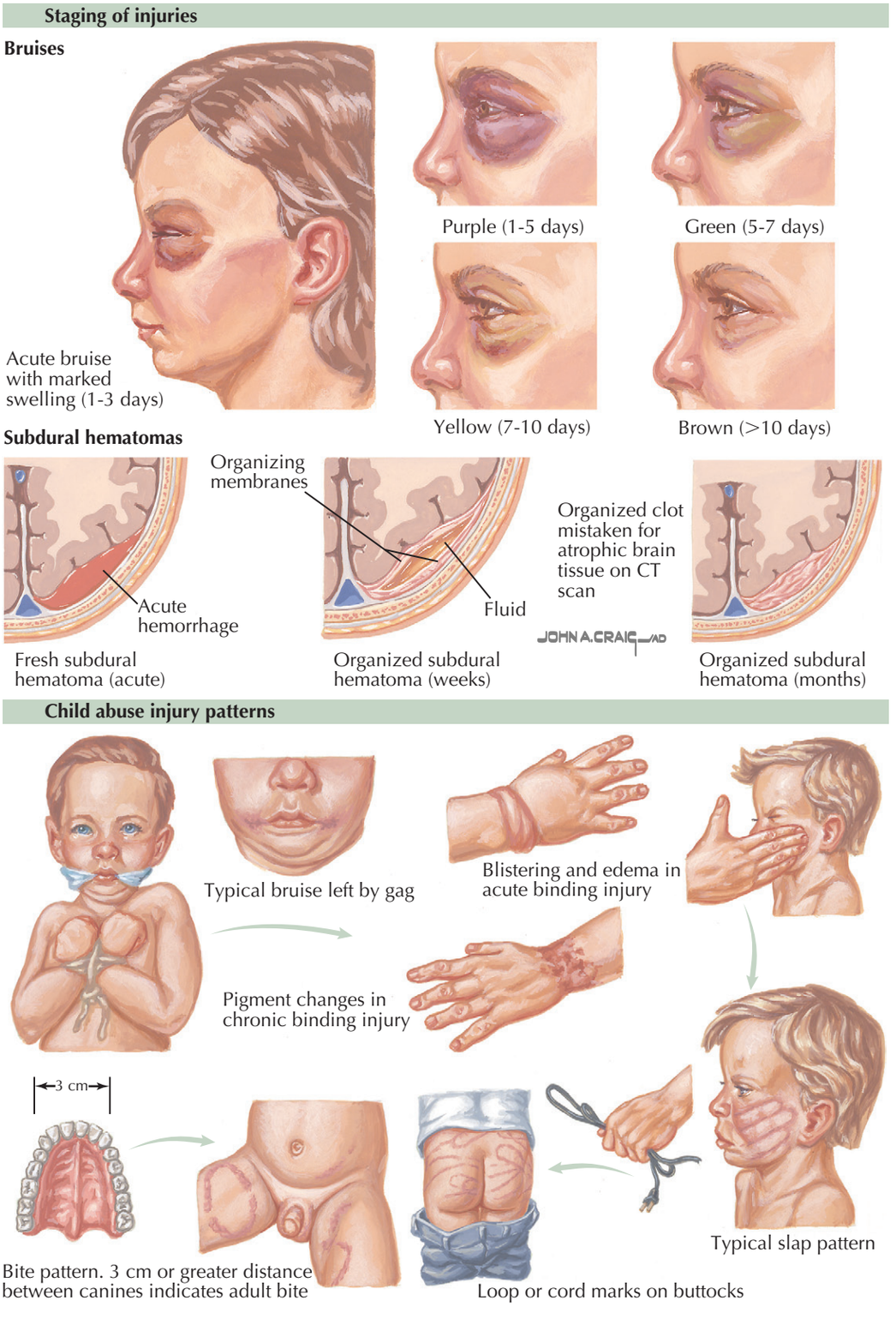
CHILD ABUSE *(Continued)*

abuse are associated with poor self-esteem, personality disorders, and impaired interpersonal relationships.

Diagnosis. Evaluations must be carried out by qualified pediatric health-care professionals, such as child and adolescent psychiatrists, pediatricians, child psychologists, child-trained social workers, pediatric counselors, and clinical nurse specialists, depending on the type of abuse—physical and/or psychologic. If there is a concern about physical abuse, physical and diagnostic examinations should be performed as soon as abuse is suspected. With concern about sexual abuse, pregnancy tests and/or sexually transmitted infections must be evaluated. In all instances, information should be gathered from multiple people within the child's psychosocial sphere (e.g., parents/caregivers, family members, teachers, counselors).

Treatment. The first step after identification of suspected abuse is reporting to a child protective service (CPS) agency. The CPS will carry out a thorough investigation of the suspected person(s) abusing the child and their living situation. The CPS will engage a treatment team to support the child and his or her family. In instances where the child's safety has been compromised and/or future abuse is suspected without intervention, then the child may be placed in a safe environment until the investigation is complete or sufficient supports are put in place for the child to return home. The primary treatment for child abuse includes psychotherapy, which can include components of cognitive-behavioral therapy (change behavior by addressing distorted cognitions), behavioral and learning therapy (modifying habitual responses to situations/stimuli), family therapy (explore patterns of family interactions), and developmental victimology (describes the processes involved in the onset and maintenance of abusive behavior).

Course. Child abuse is hypothesized to mediate response biases, resulting in impaired emotional and cognitive regulation. Adult victims of prior childhood abuse are found to have higher rates of sleep disorders, abdominal disorders, obesity, chronic pain (e.g., headache, back ache, premenstrual syndrome), fatigue, and exaggerated startle responses. Longitudinal studies indicate that adults continue to suffer from low self-esteem, maladaptive sexual behavior, and impaired interpersonal relationships (e.g., parenting, romantic/intimate). Despite these findings, not every child who experiences abuse develops these symptoms, indicating a role for protective factors, such as cognitive factors, meaningful relationships, and the impact of treatment interventions.



HYPOTHALAMUS, PITUITARY, SLEEP, AND THALAMUS

Anatomic Relationships of the Hypothalamus

The hypothalamus is a small area, weighing about 4 g of the total 1,400 g of adult brain weight, but it is the only 4 g of brain without which life itself is impossible. The hypothalamus is so critical for life because it contains the integrative circuitry that coordinates autonomic, endocrine, and behavioral responses that are necessary for basic life functions, such as thermoregulation, control of electrolyte and fluid balance, feeding and metabolism, responses to stress, and reproduction.

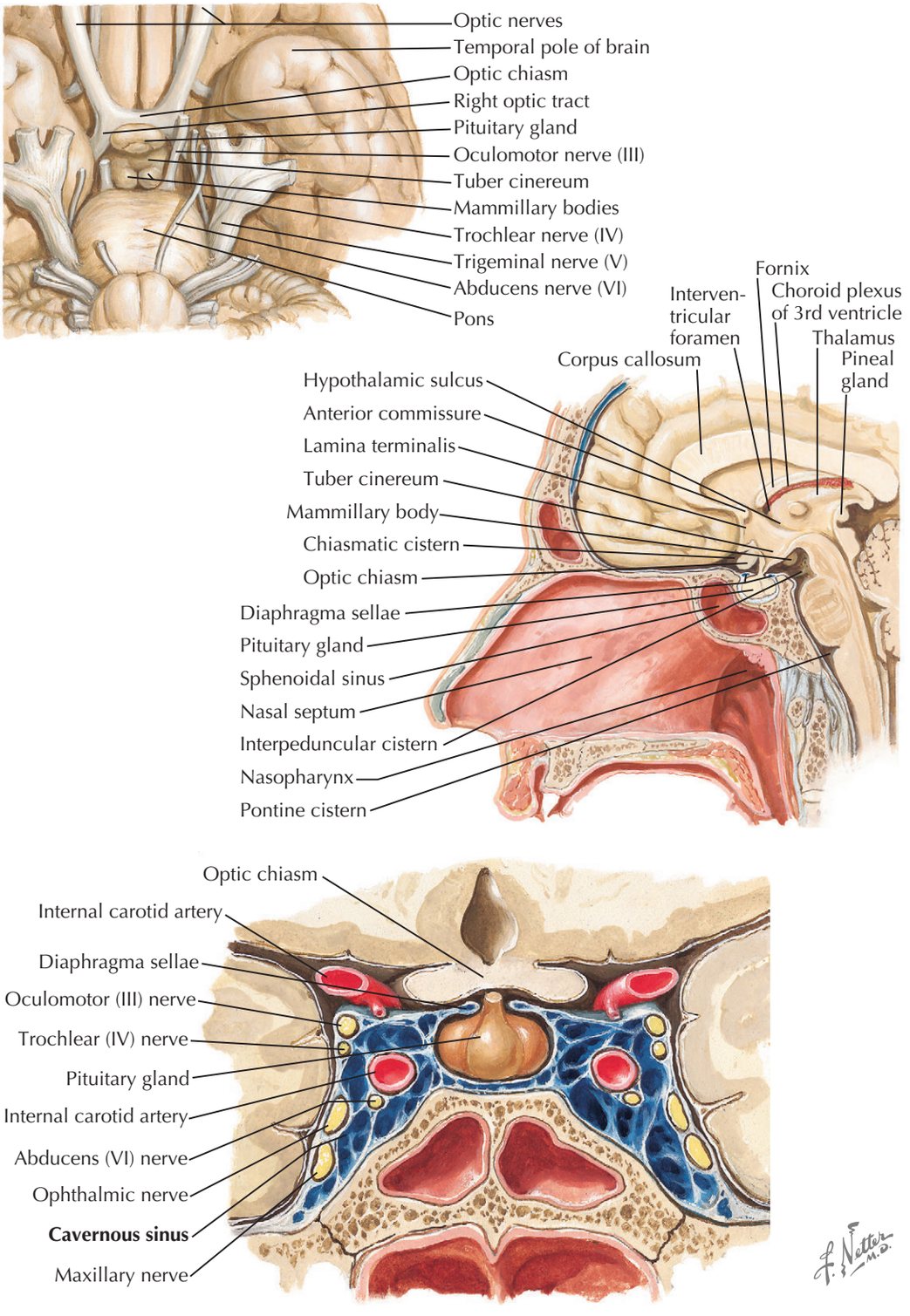
Perhaps for this reason, the hypothalamus is particularly well protected. It lies at the base of the skull, just above the pituitary gland, to which it is attached by the infundibulum, or pituitary stalk. As a result, trauma that affects the hypothalamus would almost always be lethal. It receives its blood supply directly from the circle of Willis (see Plate 5-3), so it is rarely compromised by stroke, and it is bilaterally reduplicated, with survival of either side being sufficient to sustain normal life.

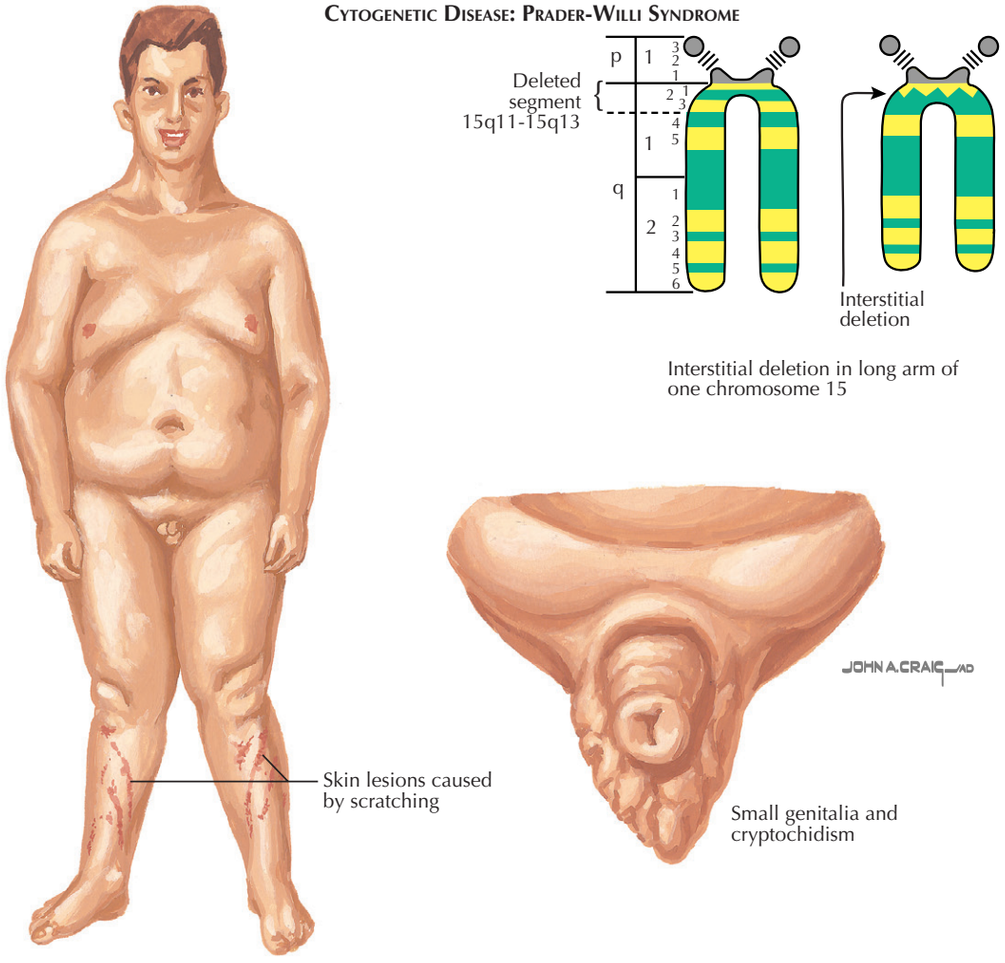
On the other hand, the hypothalamus may be involved by a number of pathologic processes that arise from structures that surround it, and the signs and symptoms that first attract attention in those disorders are often due to the involvement of those neighboring structures. Examination of the ventral surface of the brain shows that the hypothalamus is framed by fiber tracts. The optic chiasm marks the rostral extent of the hypothalamus, and the optic tracts and cerebral peduncles identify its lateral borders. The pituitary stalk emerges from the midportion of the hypothalamus, sometimes called the tuber cinereum (gray swelling), just caudal to the optic chiasm. As a result, tumors of the pituitary gland, which are among the more common causes of hypothalamic dysfunction, typically involve the optic chiasm (producing bitemporal visual field defects) or the optic tracts as an early sign.

The posterior part of the hypothalamus is defined by the mammillary bodies, which are bordered caudally by the interpeduncular cistern, from which emerge the oculomotor nerves. These are joined in the cavernous sinus, which runs just below the hypothalamus and lateral to the pituitary gland, by the trochlear and abducens nerves. Hence pathologies such as aneurysms of the internal carotid artery or infection or thrombosis of the cavernous sinus, which may impinge on the hypothalamus, typically involve the nerves controlling eye movements at an early stage. If there is a mass of sufficient size, it may also involve the trigeminal nerve. The ophthalmic division, which traverses the cavernous sinus, is most commonly involved, but if the mass is large enough and posteriorly located, it can involve the maxillary or even the mandibular division of the trigeminal nerve as well. Just lateral to the cavernous sinus sits the medial temporal lobe. As a result, pathology in this area can also cause seizures, most commonly of the complex partial type, with loss of awareness for a brief period.

In the midline, the hypothalamus borders the ventral part of the third ventricle. The supraoptic recess of the third ventricle, which surmounts the optic chiasm, ends at the lamina terminalis, the anterior wall of the ventricle. This is the most anterior part of the diencephalon in the developing brain. The infundibular recess defines the floor of the hypothalamus that overlies the pituitary stalk. This portion of the hypothalamus is called the median eminence and is the site at which hypothalamic releasing hormones are secreted into the pituitary portal circulation (see Plate 5-3).

Anatomy and Relations of the Hypothalamus and Pituitary Gland





DEVELOPMENT AND DEVELOPMENTAL DISORDERS OF THE HYPOTHALAMUS

The hypothalamus in mammals arises as a part of the ventral diencephalon and the adjacent telencephalon, and its embryologic origins are intimately related to those of the optic chiasm and tracts and to the pituitary gland. Thus disorders that affect the hypothalamus frequently manifest with signs and symptoms resulting from dysfunction of neighboring, developmentally related structures. The developing neural tube is divided into three primary regions: forebrain, midbrain, and hindbrain. The forebrain is further subdivided into the telencephalon, which gives rise to the cerebral cortex and basal ganglia, and the diencephalon, from which the thalamus and hypothalamus are derived. The hypothalamus develops from the anterior portion of the diencephalon in a series of steps that involve the activation of suites of transcription factors, which determine the fates of the developing cell populations.

First, the prechordal mesoderm that underlies the developing neural tube secretes sonic hedgehog (Shh) that induces the normal patterning of the anterior midline of the brain, including the formation of the hypothalamus and the separation of the optic system. Abnormal mesodermal induction occurs with mutations that affect Shh signaling and can result in one of the most common human brain malformations, holoprosencephaly, which manifests with a spectrum of failed division of the midline structures of the brain. In its most severe form, holoprosencephaly results in cyclopia and complete or partial loss of the hypothalamus, which is not compatible with life. In its more mild forms, holoprosencephaly can manifest with endocrine abnormalities because of defective development of the hypothalamic-pituitary system. After initial patterning by Shh-mediated induction, hypothalamic precursor cells proliferate before exiting the cell cycle and undergo terminal differentiation into the many cells types that comprise the hypothalamus' compact, yet complex structure. Finally, the developing neurons express unique combinations of transcription factors, such as Nkx and Lhx family members, and Sim1, and Six3. Deletions of individual transcription factors have profound effects upon development of specific hypothalamic nuclei.

Terminal differentiation of the hypothalamic nuclei requires the combined action of "codes" of transcription factors that, when expressed with anatomically restricted and developmentally timed precision, give rise to the regional complexity of the hypothalamus. Although still poorly understood, rare genetic mutations have been identified in humans and tested in animal models that demonstrate that dysfunction of specific genes results in loss of specific hypothalamic neurons and corresponding phenotypes. For example, the Prader-Willi syndrome, which manifests as morbid obesity, hypersomnolence, hypogonadism, and intellectual disability, is caused by a deletion of the paternally inherited chromosome 15q11. This genomic region contains several genes implicated in the normal development of the paraventricular nucleus, a cell group with critical integrative functions in feeding and responses to stress (see later).

The relationship of the hypothalamus and pituitary gland has its embryologic origins as an anatomic juxtaposition between the anterior diencephalon and the ectodermally derived Rathke's pouch, from which portions of the ventral pituitary are derived. Thus both the hypothalamus and pituitary are patterned by similar signaling pathways, and dysfunction in these systems may disrupt the development and function of both structures. Craniopharyngiomas are the most common non-neural intracranial tumors in childhood and derive from the remnants of Rathke's pouch. Clinical presentation includes optic, pituitary, and/or hypothalamic symptoms, including obesity, hypopituitarism, and sleep and circadian rhythm dysfunction.

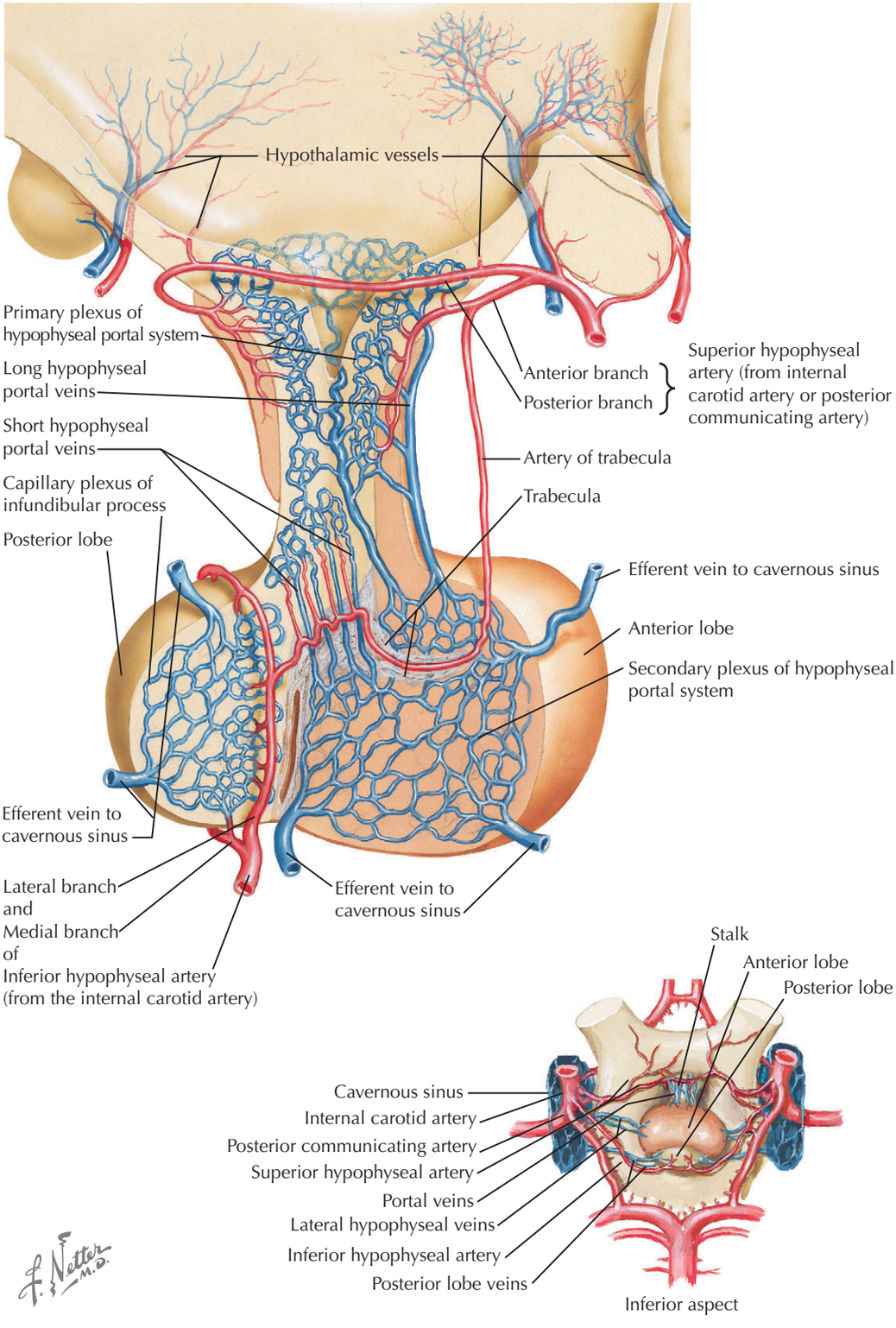
Blood Supply of the Hypothalamus and Pituitary Gland

The hypothalamus is what the circle of Willis encircles. The internal carotid artery runs through the cavernous sinus, which is just below the hypothalamus, and the site of its venous drainage. As the internal carotid artery emerges from the cavernous sinus, it ends in the middle cerebral artery laterally, the posterior communicating artery caudally, and the anterior cerebral artery rostrally. The anterior cerebral artery runs above the optic nerve, crosses the olfactory tract, and meets the anterior communicating artery in the midline before turning upward and back. The posterior communicating artery runs back to meet the posterior cerebral artery shortly after it emerges from the basilar artery. As a result, the hypothalamus is fed by small penetrating arteries that originate directly from the tributaries of the circle of Willis.

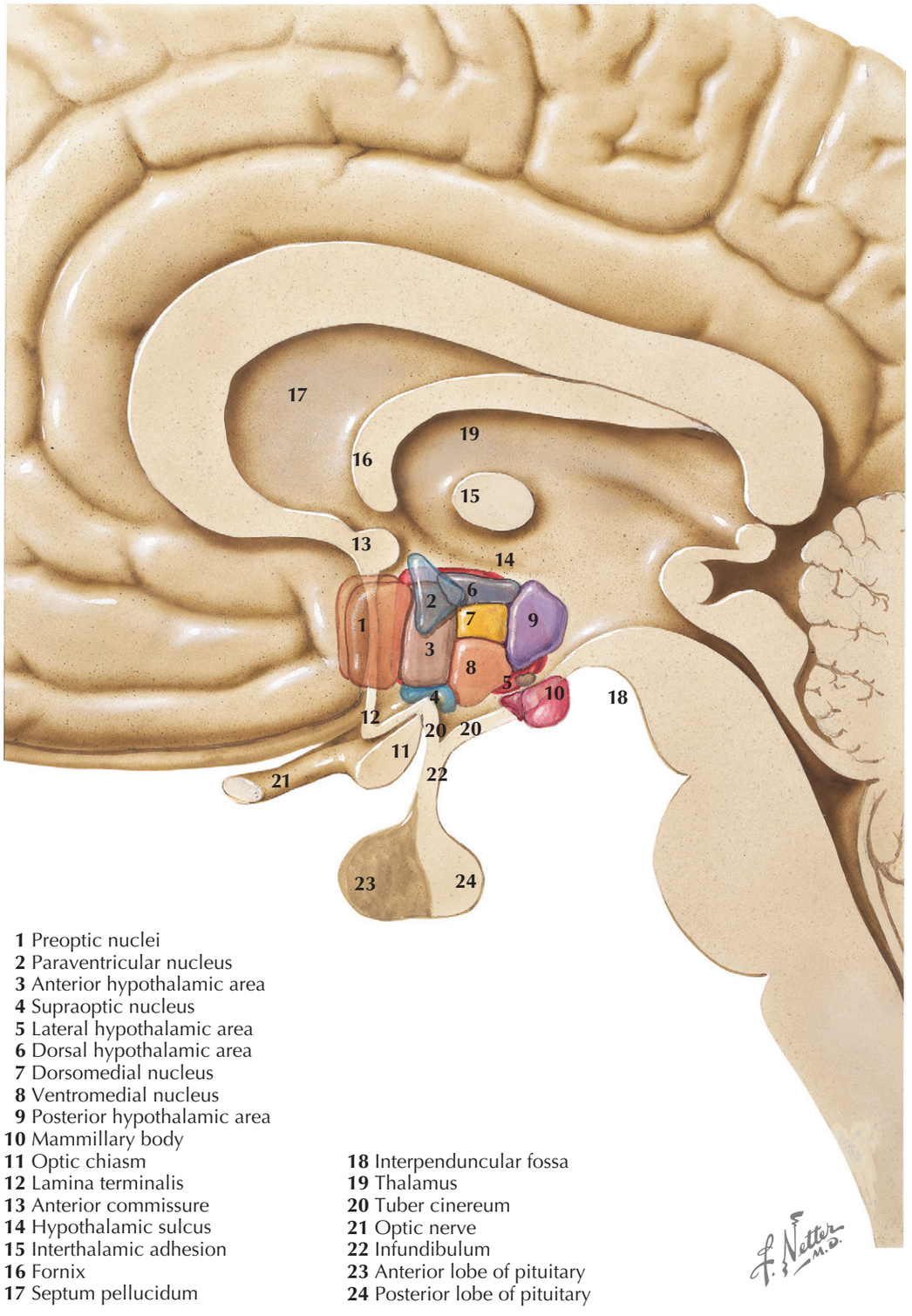
The anterior part of the hypothalamus, above the optic chiasm, is supplied by arterial feeding vessels from the anterior cerebral artery. These vessels densely penetrate the basal forebrain just in front of the optic chiasm, giving it the name the "anterior perforated substance." The tuberal, or midlevel of the hypothalamus, is fed mainly by small branches directly from the internal carotid artery and the posterior communicating artery. Posteriorly, small penetrating vessels from the posterior cerebral arteries running through the interpeduncular fossa give it the name "posterior perforated substance." Many of these small blood vessels supply the posterior part of the thalamus, but some also provide blood to the posterior hypothalamus. The cell groups within the hypothalamus are not uniformly supplied with blood vessels. The paraventricular and supraoptic nuclei, which contain neurons that make the vasoactive hormones oxytocin and vasopressin, have particularly rich capillary networks.

The superior hypophyseal artery is one of the branches derived from the internal carotid artery. It supplies the pituitary stalk, where it breaks up into a series of looplike capillaries in the median eminence and pituitary stalk. The hypothalamic neurons that make pituitary releasing (and release-inhibiting) hormones send axons that terminate on these loops, which, unlike most brain capillaries, have fenestrations to permit easy penetration by these small peptide hormones (see Plate 5-6). These capillaries drain into the hypophyseal portal veins, which along with some branches of the inferior hypophyseal artery, provide blood flow to the adenohypophysis or anterior pituitary gland. The posterior pituitary gland is supplied almost entirely by the inferior hypophyseal artery. Because most of the blood flow to the anterior pituitary gland is from the portal system, it is possible, on occasions, for the gland to outgrow its blood supply. This occurs mainly during pregnancy or can occur when a pituitary adenoma, an otherwise benign tumor, becomes larger than can be accommodated by the blood supply. At this point, there is infarction of the pituitary, often with bleeding, which may become life threatening (pituitary apoplexy). The typical presentation is sudden onset of dysfunction of cranial nerve II, III, IV, or VI, with a severe headache that is generally localized between the eyes, and often impaired consciousness.

Finally, the fenestrated capillary loops in the median eminence not only allow egress of hypothalamic-releasing hormones to the anterior pituitary gland, but also permit blood-borne substances to enter the brain. The hormone leptin, which is made by white adipose tissue during times of plenty, is believed to enter the brain via the median eminence to signal satiety to cell groups in the basal medial hypothalamus. There is another area of fenestrated capillaries along the anterior wall of the third ventricle, called the organum vasculosum of the lamina terminalis, which may allow entry of other hormones, such as angiotensin, which may be involved in thirst and water balance, and perhaps some cytokines that may play a role in the fever response. These regions are called circumventricular organs because they are around the edges of the ventricles. Another circumventricular organ, the area postrema, is found at the outflow of the fourth ventricle in the medulla and is probably involved in emetic reflexes based on blood-borne toxins or hormones, such as glucagon-like protein 1.



General Topography of the Hypothalamus



1 Preoptic nuclei
2 Paraventricular nucleus
3 Anterior hypothalamic area
4 Supraoptic nucleus
5 Lateral hypothalamic area
6 Dorsal hypothalamic area
7 Dorsomedial nucleus
8 Ventromedial nucleus
9 Posterior hypothalamic area
10 Mammillary body
11 Optic chiasm
12 Lamina terminalis
13 Anterior commissure
14 Hypothalamic sulcus
15 Interthalamic adhesion
16 Fornix
17 Septum pellucidum
18 Interpenduncular fossa
19 Thalamus
20 Tuber cinereum
21 Optic nerve
22 Infundibulum
23 Anterior lobe of pituitary
24 Posterior lobe of pituitary

Overview of Hypothalamic Cell Groups

The hypothalamus consists of a complex assemblage of cell groups. The borders of these cell groups often are not quite as distinct as those shown in the drawings, but the different cell groups are also distinguished based upon their neurotransmitters, functions, and connections.

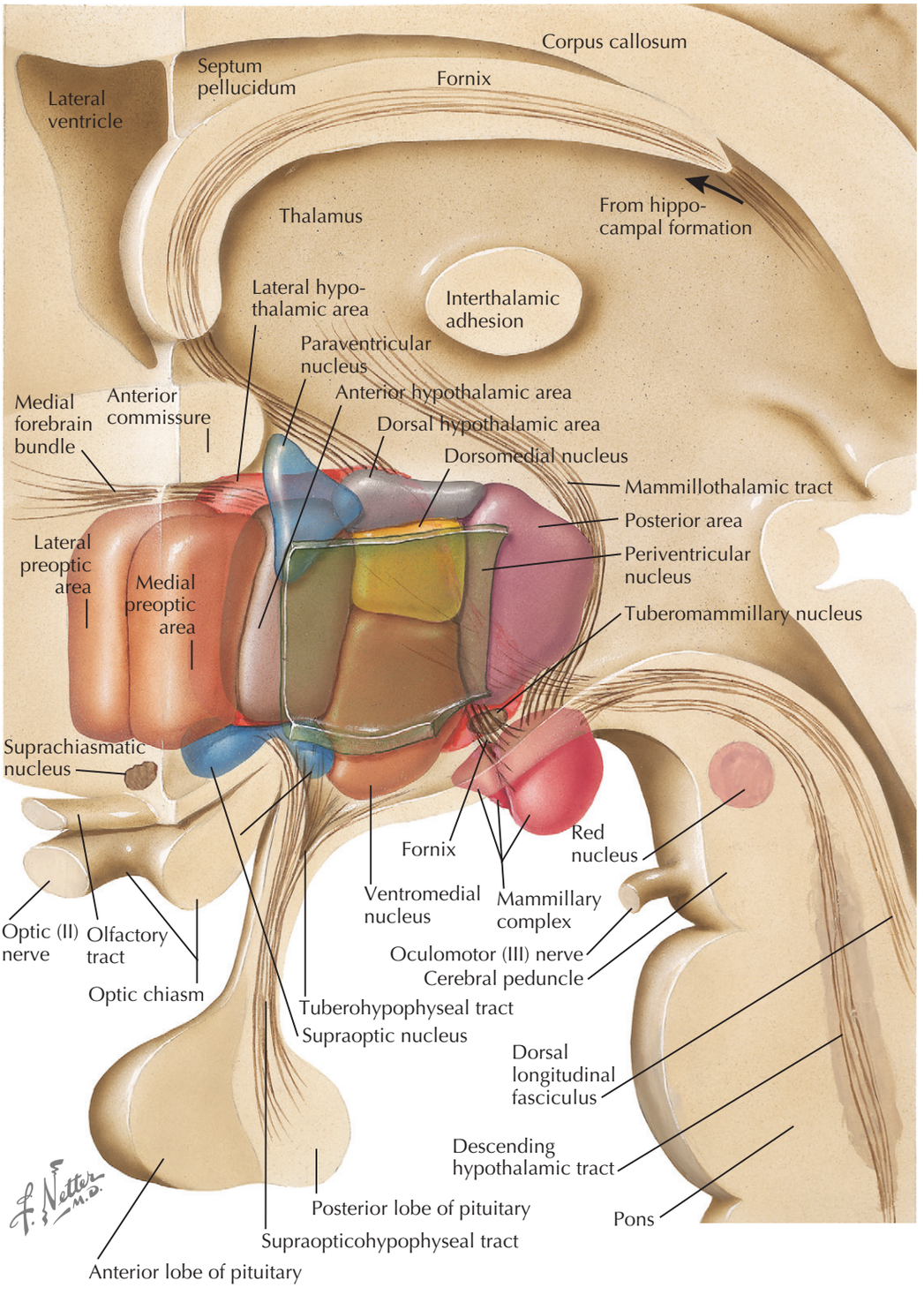
In general, the hypothalamus can be divided into three tiers of nuclei. Most medially, along the wall of the third ventricle, is the periventricular nucleus, shown here in green. Along the base of the periventricular nucleus is an expansion laterally along the edge of the median eminence, known as the arcuate or infundibular nucleus. The periventricular stratum contains many neurons that make releasing or release-inhibiting hormones (see Plate 5-6) and whose axons end on the capillary loops of the hypophysial portal vessels in the median eminence. Many axons from the brainstem run through the periventricular gray matter, in the posterior longitudinal fasciculus, and into the periventricular region of the hypothalamus.

The next tier of nuclei is sometimes called the medial tier. These nuclei are generally involved in intrinsic connections within the hypothalamus that allow integration of various functions. The most rostral of the medial nuclei is the medial preoptic region (orange), which sits along the wall of the third ventricle as it opens. Along the anterior wall of the third ventricle is the median preoptic nucleus (not shown here). These two cell groups are involved in integrating control of body temperature with fluid and electrolyte balance, wake-sleep cycles, and reproductive function.

The next most caudal region is called the anterior hypothalamic area (purple). At the base of the anterior hypothalamic area, just above the optic chiasm, is the suprachiasmatic nucleus (see Plate 5-5). These structures are involved in regulating circadian rhythms. The suprachiasmatic nucleus is the body's main biologic clock, and it sets the timing of rhythms of sleep, feeding, body temperature, and reproduction. These functions are controlled by means of outputs to the portion of the anterior hypothalamic area between the suprachiasmatic nucleus and the paraventricular nucleus (blue), called the subparaventricular zone.

The supraoptic and paraventricular nuclei are also at this anterior level in the medial tier. Both nuclei contain large numbers of oxytocin and vasopressin neurons, whose axons travel through the pituitary stalk in the tuberohypophysial tract, to the posterior pituitary gland, where they release their hormones into the circulation. The paraventricular nucleus also contains neurons that make releasing hormones (especially corticotrophic-releasing hormone) and project to the median eminence. A third population of neurons in the paraventricular nucleus sends axons through the medial forebrain bundle in the lateral hypothalamus to the brainstem and spinal cord, to control both the sympathetic and parasympathetic nervous systems. Many of

Overview of Hypothalamic Nuclei



Overview of Hypothalamic Cell Groups *(Continued)*

these neurons use either oxytocin or vasopressin as a central neurotransmitter in this autonomic pathway, but they are an entirely separate set of neurons from those that send axons to the posterior pituitary gland.

Just caudal to the anterior hypothalamic area, in the tuberal level of the hypothalamus, the medial tier contains three cell groups. The ventromedial nucleus (tan) sits just above the median eminence and is mainly involved in feeding, aggression, and sexual behavior. The dorsomedial nucleus (yellow), which is just dorsal to it, has extensive outputs to much of the rest of the hypothalamus. The subparaventricular zone sends circadian outputs to both the dorsomedial and ventromedial nuclei, and the dorsomedial nucleus uses this input to organize circadian cycles of wake-sleep, corticosteroid secretion, feeding, and other behaviors. The dorsal hypothalamic area, just above the dorsomedial nucleus, contains neurons that are involved in regulating body temperature.

At the most posterior end of the hypothalamus, the mammillary bodies form a prominent pair of protuberances along the base of the brain. Despite having very clear-cut, heavily myelinated connections, the function of the mammillary nuclei remains mysterious. They receive a major brainstem input from the mammillary peduncle and a large bundle of efferents from the hippocampal formation through the fornix. The large fiber bundle that emerges from the mammillary body splits into a mammillotegmental tract to the brainstem and a mammillothalamic tract to the anterior thalamic nucleus. Neurons in the mammillary body appear to be concerned with head position in space, and may be related to hippocampal circuits that remember the positions of objects in space (so-called place cells). However, lesions of the mammillary bodies in primates have relatively subtle effects on memory.

The lateral tier of the hypothalamus includes the lateral preoptic and lateral hypothalamic areas. These regions are traversed by the medial forebrain bundle, which connects the brainstem below with the hypothalamus and the forebrain above. Many neurons in the lateral hypothalamic area project through the medial forebrain bundle, either to the basal forebrain or cerebral cortex, or to the brainstem or spinal cord. Among these are the neurons that contain the peptides orexins (also known as hypocretins) or melanin-concentrating hormone (MCH). These neurons are involved in regulating wake-sleep cycles as well as metabolism, feeding, and other types of motivated behaviors. Loss of the orexin neurons causes the disorder known as narcolepsy (see Plate 5-22).

At the posterior hypothalamic level, there is also a cluster of histaminergic neurons, called the tuberomammillary nucleus, in the lateral hypothalamus adjacent to the mammillary body. These neurons play a role in regulation of wakefulness and body temperature and have projections from the cerebral cortex to the spinal cord. The posterior hypothalamic area sits just above the mammillary body. In humans, many of the orexin, MCH, and histaminergic neurons are found in this region.

Hypothalamic Control of the Pituitary Gland

The hypothalamus contains two sets of neuroendocrine neurons, the magnocellular neurons, which send axons to the posterior pituitary gland, and the parvicellular neurons, which secrete releasing or release-inhibiting hormones into the pituitary portal circulation.

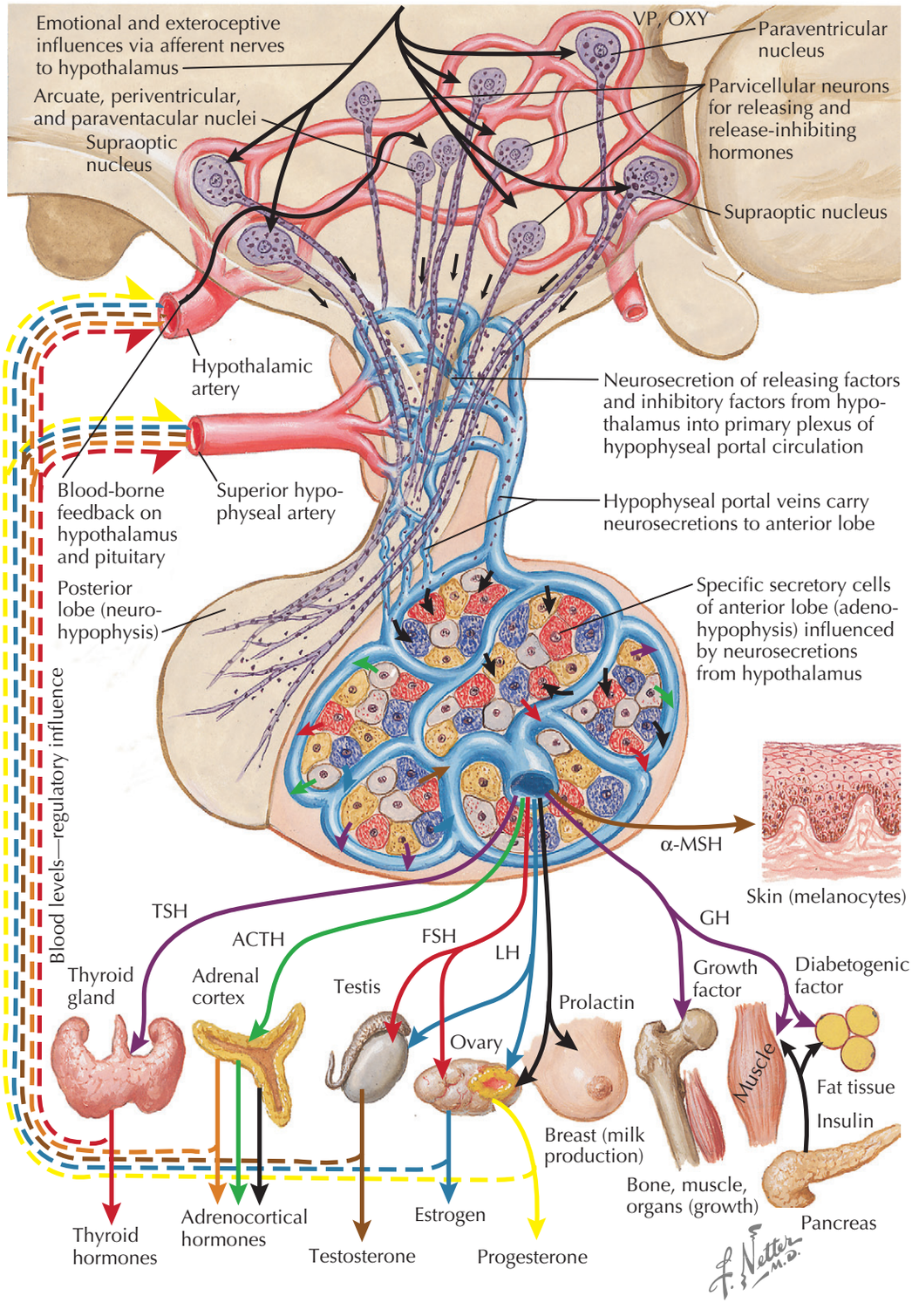
The magnocellular neurons consist of two clusters: the supraoptic and paraventricular nuclei. Each cell group contains both oxytocin (OXY) and vasopressin (VP) neurons. These cells secrete the hormones from their terminals in the posterior pituitary gland into the general circulation. Vasopressin controls urinary water and sodium excretion, as well as having direct vasoconstrictor effects on blood vessels. Oxytocin has some vasoconstrictor properties and causes uterine contractions but also is involved in the milk let-down reflex during suckling. Cutting the pituitary stalk causes loss of secretion of both hormones, but the predominant symptom is diabetes insipidus, due to lack of vasopressin. Such individuals have excess loss of water in the urine, requiring the ingestion of up to 20 liters of water per day to maintain blood osmolality in the normal range, unless the hormone is replaced.

The parvicellular neurons are located along the wall of the third ventricle in the periventricular, paraventricular, and arcuate nuclei. Different populations of parvicellular endocrine neurons, secreting specific pituitary releasing or release-inhibiting hormones, have characteristic locations within this region. The corticotropin-releasing hormone neurons, which cause secretion of adrenocorticotrophic hormone (ACTH), and ultimately adrenal corticosteroids, are mainly located in the paraventricular nucleus. Many neurons that secrete thyrotropin-releasing hormone neurons, which cause secretion of thyroid-stimulating hormone (TSH), or somatostatin, which inhibits secretion of growth hormone (GH), are also in the paraventricular nucleus, but some are found rostral to it in the periventricular nucleus. Neurons that secrete gonadotropin-releasing hormone neurons (which cause secretion of luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) are found in the most rostral part of the periventricular nucleus and dorsal arcuate nucleus. The rostral part of the arcuate nucleus also contains growth hormone–releasing hormone neurons. Neurons secreting dopamine (a prolactin release–inhibiting hormone) are found widely distributed along the wall of the third ventricle in the periventricular, paraventricular, and arcuate nuclei. The arcuate nucleus also contains neurons that express pro-opiomelanocortin (POMC), a precursor protein that can be differentially processed to produce ACTH (e.g., in the pituitary gland), but that is processed into α-melanocyte–stimulating hormone (α-MSH) and β-endorphin in the arcuate nucleus, which uses them as neurotransmitters.

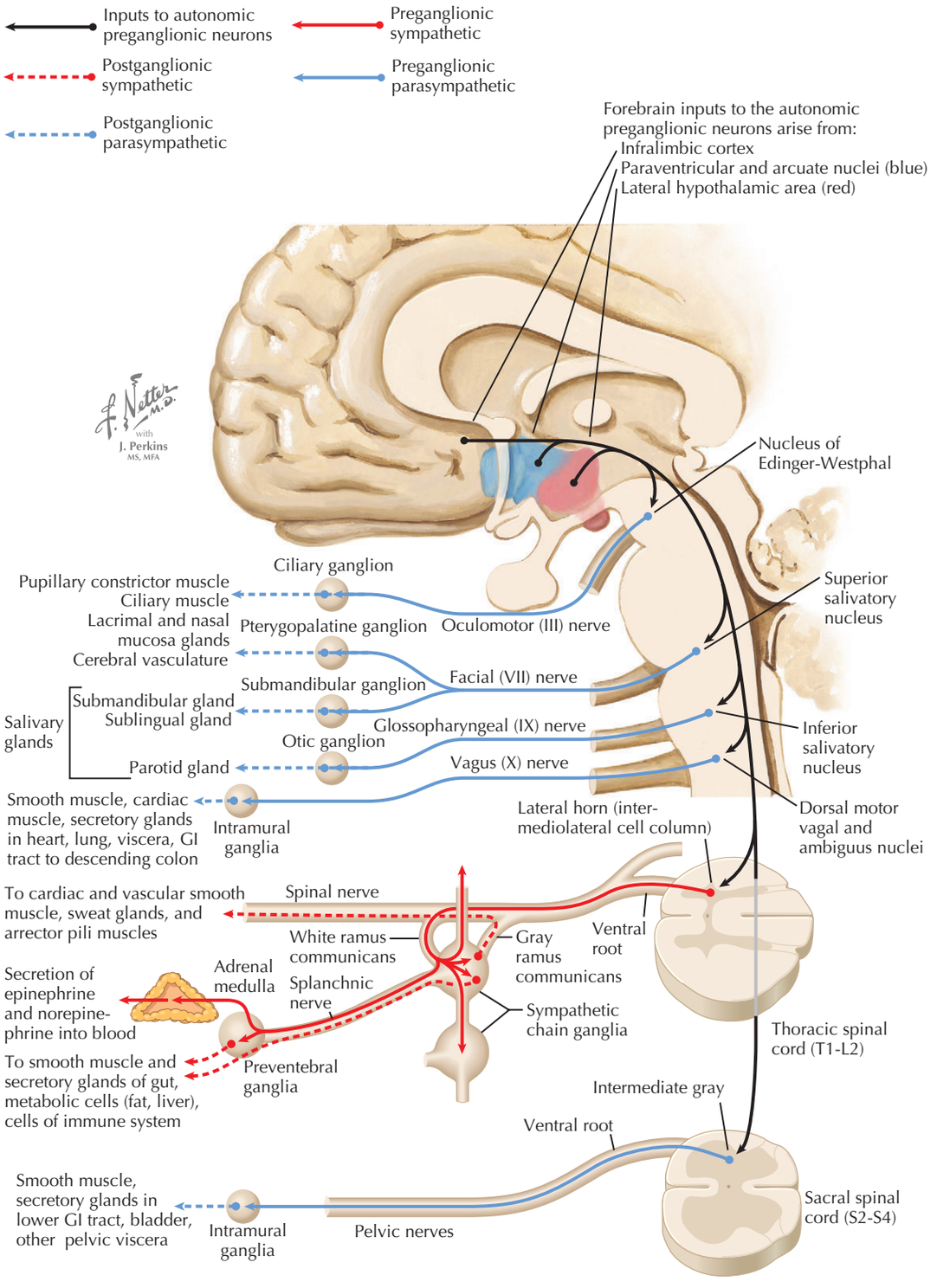
The anterior pituitary gland contains a mixed population of pituitary cells, each of which secretes a different hormone: TSH, ACTH/α-MSH, FSH/LH, prolactin, or GH. These hormones as well as their releasing and release-inhibiting factors can feed back upon the parvicellular endocrine neurons, providing short loop feedback. Prolactin is the only pituitary hormone that is primarily under inhibitory tone from the hypothalamus. Hence, when the pituitary stalk is damaged, the secretion of other anterior pituitary hormones is diminished, but prolactin increases.

Endocrine disorders may ensue from either excess secretion or lack of secretion of either an anterior pituitary hormone or its hypothalamic-releasing or release-inhibiting hormones. Thus precocious puberty is sometimes seen with hypothalamic hamartomas that secrete gonadotropin-secreting factor. On the other hand, amenorrhea may occur from increased secretion of prolactin. Cushing syndrome—the oversecretion of adrenal corticosteroids—may result from a steroid-secreting adrenal tumor, a pituitary tumor (or sometimes a lung or other tumor) that secretes ACTH, or hypersecretion of corticotropin-releasing hormone.

Hypothalamic Control of the Anterior and Posterior Pituitary Gland



Hypothalamic Control of the Autonomic Nervous System



Other than a relatively modest projection to the preganglionic neurons from the infralimbic cortex, the hypothalamus is the highest level of the neuraxis that provides substantial input to the autonomic nervous system. It regulates virtually all autonomic functions and coordinates them with each other, and with ongoing behavioral, metabolic, and emotional activity. The hypothalamus contains several sets of neurons, using different neurotransmitters, that provide innervation to the sympathetic and parasympathetic preganglionic neurons, as well as brainstem areas that regulate the autonomic nervous system. Many of these neurons are in the paraventricular nucleus of the hypothalamus. These form populations of small neurons that are typically dorsal or ventral to the main endocrine groups, and most of the paraventricular-autonomic neurons contain messenger ribonucleic acid (mRNA) for either oxytocin or vasopressin. The descending pathways also stain immunohistochemically for these peptides and are probably involved in stress responses.

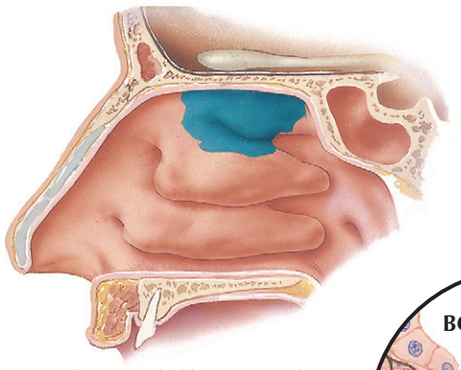
A second set of hypothalamic-autonomic neurons is found in the lateral hypothalamic area. These consist mainly of neurons containing orexin or melanin-concentrating hormone (MCH) neurons, and sometimes the peptide cocaine- and amphetamine-regulated transcript (CART), which is thought to be involved in regulation of feeding and metabolism as well as wake-sleep and locomotor activity. A third population of hypothalamic-autonomic cells is found in the arcuate nucleus and adjacent retrochiasmatic area. These neurons contain α-melanocyte–stimulating hormone and CART and may also be involved in feeding and metabolic regulation.

All three sets of neurons send axons to the brainstem, where they innervate the nucleus of the solitary tract (which receives visceral afferent input from the glossopharyngeal and vagus nerves), as well as the regions that coordinate autonomic and respiratory reflexes in the ventrolateral medulla. Other axons innervate the parasympathetic preganglionic neurons in the Edinger-Westphal nucleus (pupillary constriction), the superior salivatory nucleus (associated with the facial nerve, which supplies the submandibular and sublingual salivary glands as well as the cerebral vasculature), the inferior salivatory nucleus (associated with the rostral tip of the nucleus of the solitary tract, supplying the parotid gland), the dorsal motor vagal nucleus (which supplies the abdominal organs), and the nucleus ambiguus (which is the main source of vagal input to the thoracic organs, including the esophagus, heart, and lungs).

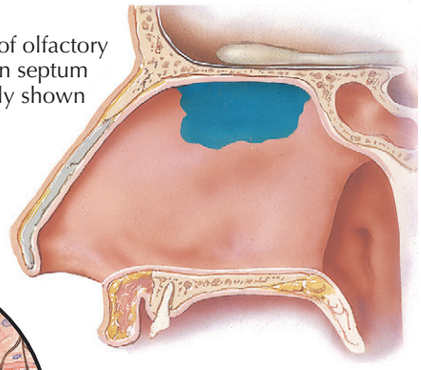
Finally, there are descending axons from the hypothalamus that innervate the sympathetic preganglionic neurons in the thoracic spinal cord. Different populations of hypothalamospinal neurons contact distinct targets. For example, the main projection from the orexin neurons is to the upper thoracic spinal cord, which may be important for autonomic functions associated with ingestion. The oxytocin neurons innervate specific clusters of sympathetic preganglionic neurons at multiple spinal cord levels.

In addition, there is a major input to the medullary raphe nuclei from the preoptic area and dorsomedial nucleus of the hypothalamus. The medullary raphe nuclei contain both serotoninergic and glutamatergic neurons that innervate the sympathetic preganglionic column at multiple levels and regulate populations of neurons involved in thermoregulation. This pathway is thought to be a major mechanism for regulating body temperature.

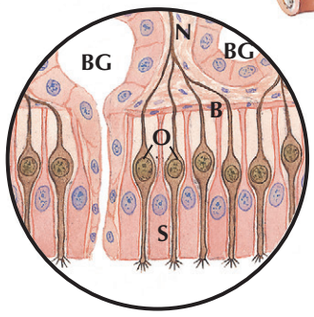
Damage to the descending hypothalamic-autonomic pathway, in the lateral medulla or spinal cord, causes an ipsilateral central Horner syndrome. Such patients not only have a small pupil and ptosis on that side but lack sweating on the affected side of the face and body.



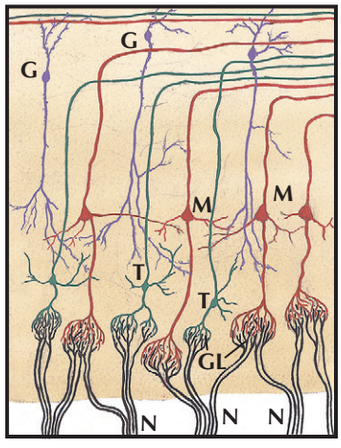
Distribution of olfactory epithelium on lateral nasal wall (schematically shown in blue).



Distribution of olfactory epithelium on septum (schematically shown in blue).



Structure of olfactory mucosa (schematic):
B: Basal cells
BG: Bowman's gland
N: Olfactory nerve filament
O: Olfactory bipolar cells
S: Supporting cells



Structure of olfactory bulb:
G: Granular cell
GI: Glomerulus
M: Mitral cell
N: Olfactory nerve filaments
T: Tufted cell

Schematic representation of the olfactory system

J. Perkins
MS, MFA, CMI

Olfactory Inputs to the Hypothalamus

There are about 1,000 olfactory receptor genes, each of which recognizes a different class of chemical olfactory stimulus. Each olfactory receptor cell expresses a single olfactory receptor type, and each gene is expressed in several hundred cells, spread across the olfactory mucosa. The axons from olfactory receptor cells then run through openings in the cribriform plate, which forms the base of the skull over the olfactory mucosa, and axons from individual cells, which express a single receptor gene, then converge in the olfactory bulb on one or a few individual olfactory glomeruli.

The glomeruli are on the surface of the olfactory bulb and are spherical areas, each about one third millimeter across. The outside of the glomerulus is lined with tiny periglomerular cells, which are interneurons. Just deep to the glomerular layer are mitral and tufted cells, which send their apical dendrites up into the glomeruli, where they receive olfactory sensory information. These excite granule cells, which, in turn, inhibit the other mitral and tufted cells, as well as receiving centrifugal axons, which allow them to modulate the perception of the sensory stimulus. Only the mitral and tufted cells send their axons into the brain via the olfactory tract. In humans, this is a long white matter bundle that runs the length of the frontal lobe and is sometimes erroneously called the "olfactory nerve."

The olfactory tract supplies information about smell to a variety of targets in the brain. It bifurcates as it approaches the temporal lobe into one branch that runs medially into the basal forebrain and another that runs laterally to supply olfactory inputs to cortical structures. The basal forebrain branch provides inputs to the anterior olfactory nucleus, which sends axons through the anterior commissure to the opposite hemisphere, and the olfactory tubercle, which is the part of the striatum that receives olfactory inputs. The lateral olfactory branch provides inputs to the primary olfactory cortex, which appears to be necessary for processing the conscious appreciation of odors, as well as the entorhinal cortex, which is a point of convergence of information from multiple sensory systems and a major relay into the hippocampal formation. There is also input to the amygdala, which may be important for relaying olfactory signals related to food acquisition and sexual behavior to the hypothalamus.

In many mammals, there is an accessory olfactory system. A small pit in the nasal mucosa, called the vomeronasal organ, contains olfactory sensory neurons that are important for sensing pheromones. These olfactory neurons synapse in a specialized region called the accessory olfactory bulb and relay information concerned with social behaviors into the amygdala and hypothalamus. Such a system has never been clearly identified in humans, and its very existence remains controversial.

Visual Inputs to the Hypothalamus

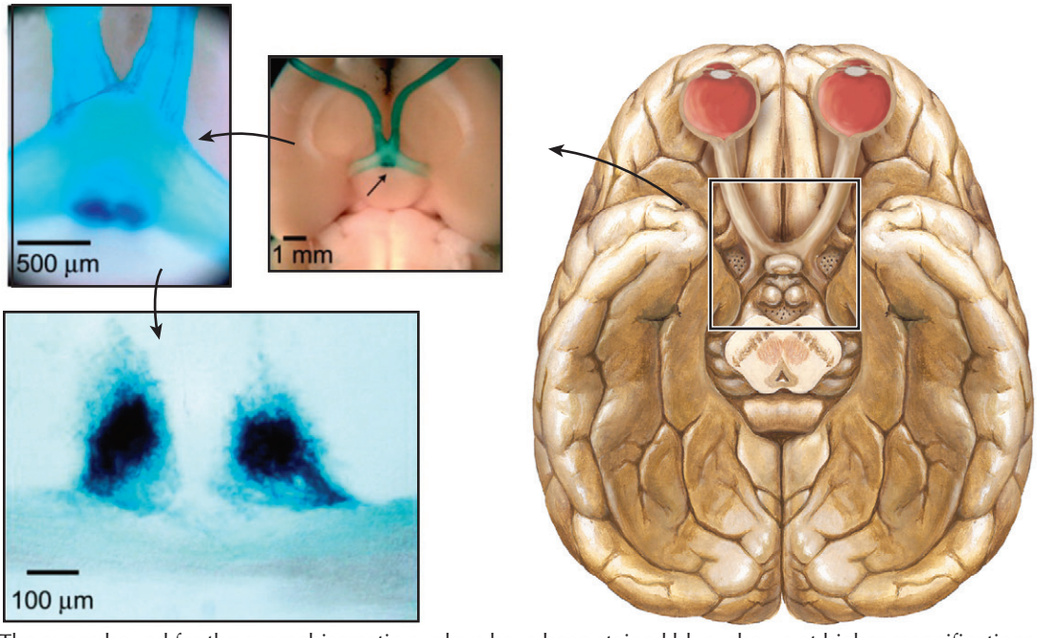
The hypothalamus is largely framed by the optic chiasm, which underlies its most rostral part (the preoptic area) and provides the lateral boundary for its middle, tuberal part. Despite this close relationship, it remained a mystery for many years how the hypothalamus used visual input to synchronize its biologic clock with the external world. In 1972, two groups of scientists demonstrated that some axons leave the optic chiasm as it passes by the hypothalamus and provide an input that is now called the retinohypothalamic tract.

The retinohypothalamic tract originates from about 1,000 scattered retinal ganglion cells in each retina. In 2001, it was discovered that these retinal ganglion cells have the peculiar property of making their own light-sensing pigment, called melanopsin. So, although other retinal ganglion cells that are concerned with patterned vision are "blind" and depend upon input from rods and cones to signal to them the presence of light in their receptive fields, the melanopsin-containing retinal ganglion cells are intrinsically photosensitive. These neurons act essentially as light level detectors and relay this information both to the hypothalamus as well as to the olivary pretectal nucleus, which is a critical relay in the pupillary light reflex pathway.

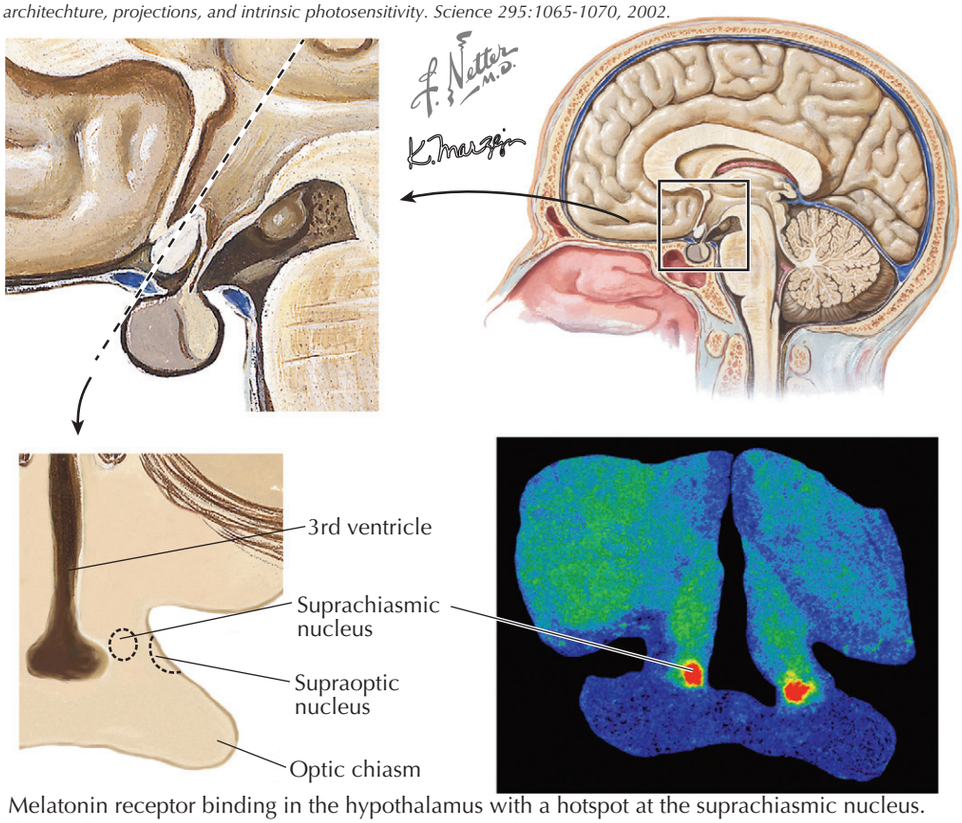
By replacing the melanopsin gene with one for β-galactosidase, one can then stain the melanopsin-containing retinal ganglion cells blue and follow their axons into the brain. The densest site of retinohypothalamic input is to the suprachiasmatic nucleus, although other axons, in smaller numbers, enter other parts of the hypothalamus. The suprachiasmatic nucleus is the brain's biologic clock; damage to this cell group causes animals and humans to lose their 24-hour patterns of activity in wake-sleep, feeding, body temperature, corticosteroid secretion, and other important physiologic and behavioral functions. Although the neurons in the suprachiasmatic nucleus maintain an approximately 24-hour rhythm of activity even when placed into tissue culture, retinal input is necessary to reset their clock rhythm to maintain synchrony with the external world. In the absence of light cues, circadian rhythms in both people and animals show a free-running cycle that is generally just a bit different from 24 hours and may vary among individual (humans average about 24.1 hours). Although this may seem like a small difference from 24 hours, without a mechanism for synchronization, someone with a 24.1-hour cycle would be 3 hours off-cycle from the rest of the world by the end of 1 month. Some blind individuals, with total loss of retinal input to the brain, show this type of shift of their circadian rhythms over time so that they go through periods every few months where their cycles go out of phase with the rest of the world. Other blind people, such as those with rod and cone degeneration, who retain intrinsically photosensitive melanopsin-containing retinal ganglion cells, remain in synchrony with the world that they cannot see.

Melatonin is one of the hormones whose 24-hour cycle of secretion is driven by the suprachiasmatic nucleus. Suprachiasmatic axons directly contact neurons in the paraventricular nucleus, which, in turn, innervates the sympathetic preganglionic neurons in the upper thoracic spinal cord. The latter project to the superior cervical ganglion, which sends axons along the internal carotid artery intracranially to innervate the pineal gland, causing secretion of melatonin. The hormone is mainly secreted at the onset of the dark period and in humans may promote sleepiness. One of the major targets in the brain for melatonin is the suprachiasmatic nucleus itself, which stands out when the brain is stained for melatonin receptors.

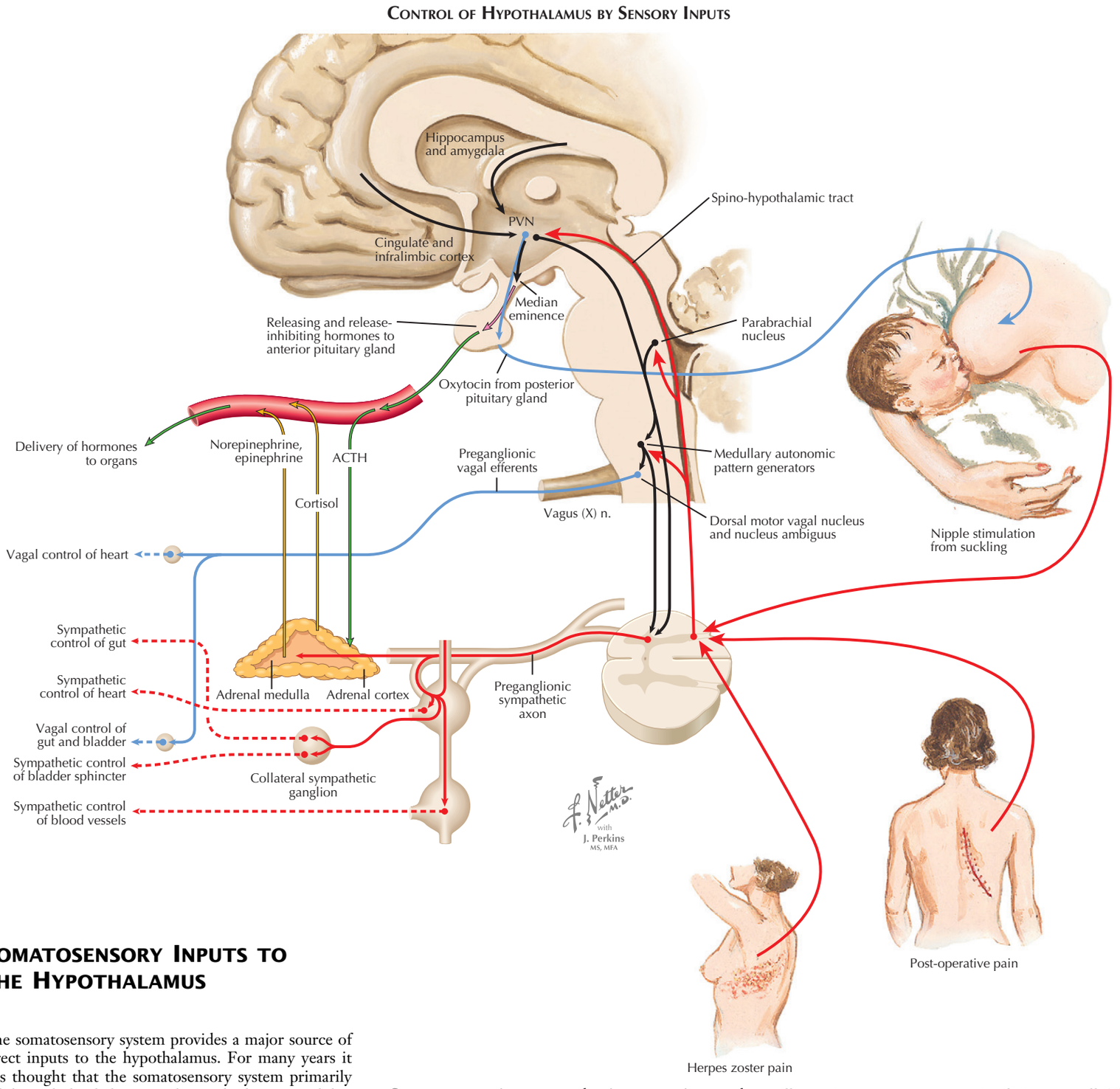
Other retinal axons to the hypothalamus may be important in providing visual inputs to neurons concerned with a variety of diverse functions. For example, retinal inputs to a sleep-promoting cell group, the ventrolateral preoptic nucleus, may explain why people turn out the lights and close their eyes when falling asleep. Other inputs to the lateral hypothalamus may contact neurons involved in regulating arousal and feeding. In rodents, who might be recognized as potential prey when they venture into a lighted area, an important response to light is immobility. This reduced locomotion in light appears to be regulated by retinal inputs to the subparaventricular zone.



The axons bound for the suprachiasmatic nucleus have been stained blue, shown at higher magnifications.
Photographs reprinted with permission from Hattar S, Liao HW, Takao M, et al. Melanopsin-containing retinal ganglion cells: architechture, projections, and intrinsic photosensitivity. Science 295:1065-1070, 2002.



Melatonin receptor binding in the hypothalamus with a hotspot at the suprachiasmic nucleus.
Courtesy Dr. David Weaver, University of Massachusetts Medical School.



Somatosensory Inputs to the Hypothalamus

The somatosensory system provides a major source of direct inputs to the hypothalamus. For many years it was thought that the somatosensory system primarily fed through the thalamus to the cerebral cortex and that sensory inputs to the hypothalamus must be relayed from the cortex. However, in 1980, it was discovered that some axons from the ascending somatosensory pathways directly reach the hypothalamus. These inputs originate from somatosensory neurons in the spinal and trigeminal dorsal horn. Many of these neurons are concerned with painful stimuli. These may be used in orchestrating emotional responses, such as anger, fight, or flight in response to a physical injury. On the other hand, they may be important stimuli for the underlying autonomic and endocrine responses associated with pain, such as elevation of blood pressure and heart rate, or secretion of cortisol.

Somatosensory inputs are also important in sexual behavior. Neurons in the preoptic area promote erection in males, and nerve cells in the ventromedial nucleus of the hypothalamus can potently drive sexual behaviors, including mounting postures in males and receptive postures in females. The neurons that produce these responses are, in turn, driven by a range of visual, olfactory, and tactile stimuli. In some species, ovulation is also triggered by sexual somatosensory stimuli (such as vaginal stimulation).

Another hypothalamically mediated response that is dependent upon somatosensory input is the milk let-down reflex during breastfeeding. Breast milk production is stimulated by prolactin, but the release of the milk requires somatosensory stimulation as well. The infant suckling at the breast causes sensory input that reaches the oxytocin neurons in the paraventricular and supraoptic nuclei in the hypothalamus. These neurons fire in bursts, which causes them to release oxytocin into the circulation from their axon terminals in the posterior pituitary gland. The oxytocin, in turn, causes milk to flow from the breast.

In each of these examples, autonomic, endocrine, and behavioral responses must be coordinated, the hallmark of a hypothalamically mediated behavior. The integration of these responses in each case depends upon somatosensory input that is delivered directly to the hypothalamus.

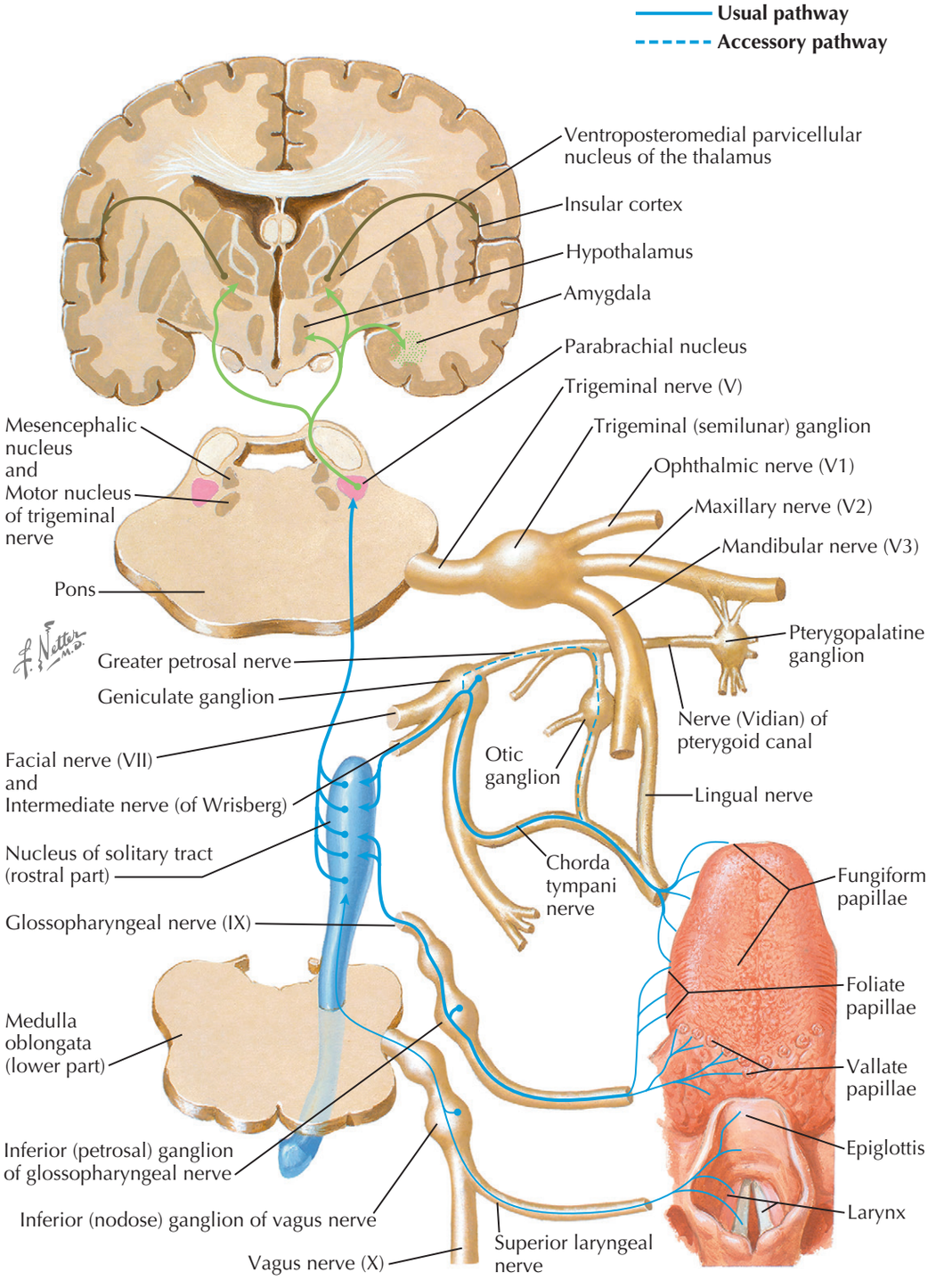
Taste and Other Visceral Sensory Inputs to the Hypothalamus

A special class of visceral sensory pathway provides taste information to the hypothalamus and other areas of the brain. Taste receptor cells are found in taste buds, located in clusters along the surface of the tongue. Different classes of taste receptors respond to different classes of chemicals in food, including acids (sour), sugars (sweet), sodium (salty), glutamate (an important amino acid component of proteins, whose taste is said to be "beefy" or "umame" in Japanese), and complex plant alkaloids that often warn of poisonous compounds (bitter). The taste receptor cells are innervated by sensory neurons from the facial (VII nerve, to the anterior two thirds of the tongue), glossopharyngeal (IX nerve, to the posterior tongue and tonsillar arches), and vagus (X nerve, to the posterior tongue and oropharynx) cranial nerves. Much like other somatosensory systems, the gustatory sensory neurons are located in ganglia (geniculate for the facial nerve, petrosal for the glossopharyngeal nerve, and nodose for the vagus nerve) and consist of pseudounipolar cells, with a single axon that bifurcates in the ganglion into a central and a peripheral branch. The central branches terminate in the rostral third of the nucleus of the solitary tract in the medulla. The axons end in a roughly topographic order with respect to the surface of the tongue (axons from the anterior two thirds of the tongue ending most rostrally). The nucleus of the solitary tract gives off local connections in the brainstem to reflex pathways for salivation and for regulation of biting, chewing, and swallowing activity.

Ascending axons from the nucleus of the solitary tract travel through the brainstem, and a large proportion of them synapse in the parabrachial nucleus. From there, axons continue on to the thalamus (for conscious appreciation of taste), amygdala (for taste associations), and hypothalamus (presumably for regulation of feeding). The inputs to the hypothalamus and amygdala are augmented by a smaller number of axons that reach these sites directly from the nucleus of the solitary tract. In primates, there is evidence that some axons from the taste portion of the nucleus of the solitary tract may reach the thalamus directly, without requiring a relay in the parabrachial nucleus. Taste neurons in the thalamus are located adjacent to the tongue somatosensory area, and they innervate the insular cortex, which is the primary taste cortex.

The posterior two thirds of the nucleus of the solitary tract receives inputs from other internal organs via the glossopharyngeal and vagus nerves. These terminate in a roughly topographic order, with gastrointestinal inputs in the middle part of the nucleus and cardiorespiratory in the caudal part. The nucleus of the solitary tract provides local inputs to cell groups in the medulla that control gastrointestinal functions, including gastric acid secretion and gut motility as well as cardiovascular and respiratory reflexes (e.g., the baroreceptor reflex that stabilizes blood pressure when moving from a lying to a standing position, and the increase in both respiratory rate and blood pressure when there is a high level of carbon dioxide in the blood).

Other axons from the posterior two thirds of the nucleus of the solitary tract terminate in the parabrachial nucleus. Parabrachial neurons then contact the visceral sensory thalamus, which, in turn, projects to the insular cortex, where sensations such as gastric fullness or air hunger reach conscious appreciation. Other parabrachial outputs are joined by smaller numbers of axons from the nucleus of the solitary tract itself in projecting to the amygdala, where they may be involved in visceral conditioned reflexes. Parabrachial inputs to the hypothalamus may play a role in a wide range of functions, from regulation of behaviors such as feeding and drinking to control of secretion of hormones such as vasopressin (during hypovolemia) and oxytocin (during emesis).



Limbic and Cortical Inputs to the Hypothalamus

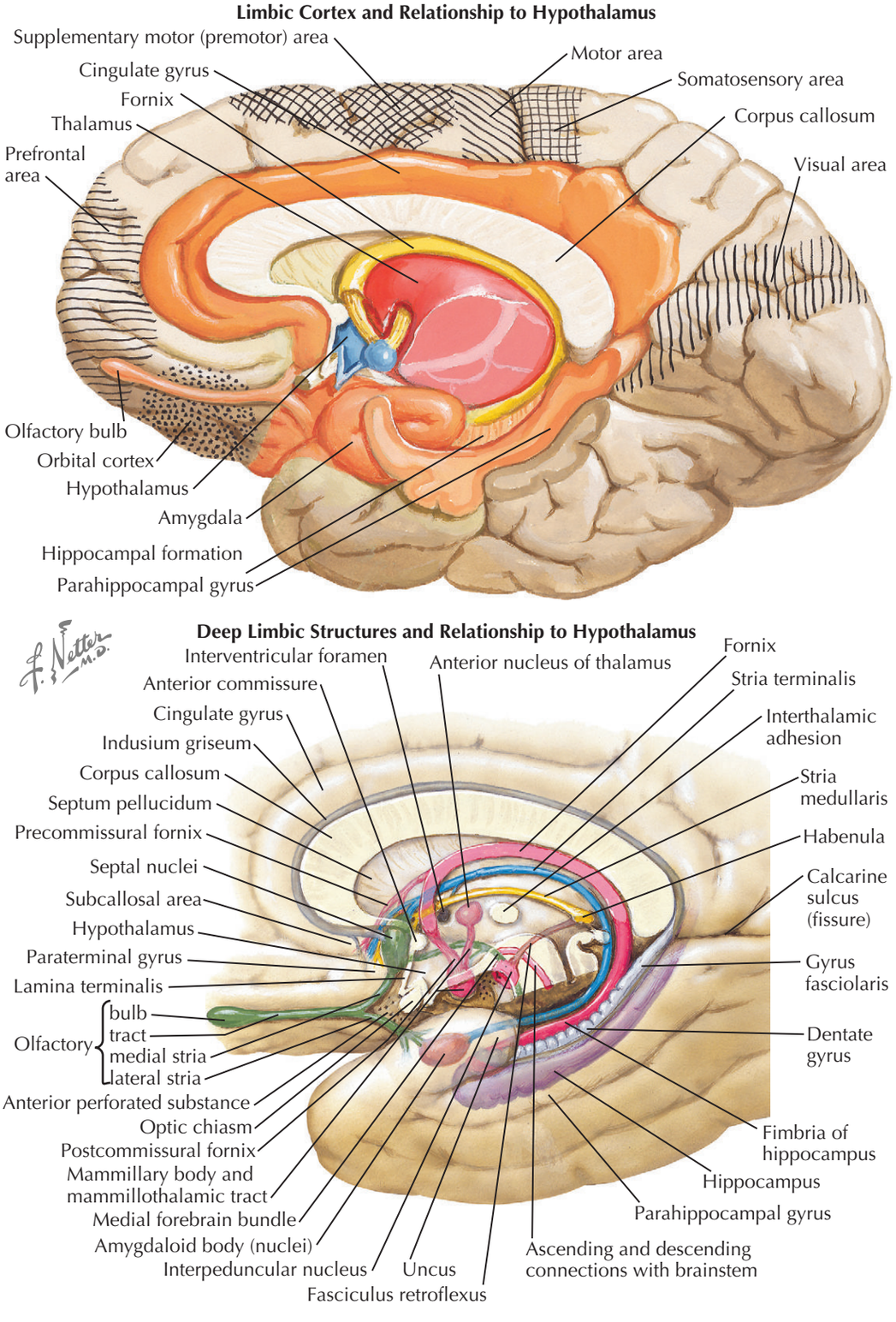
In addition to having direct sensory inputs, the hypothalamus receives highly processed information from the cerebral cortex, which is relayed via the limbic system. The limbic lobe of the brain was first defined by Paul Broca, in 1878, as the cortex surrounding the medial edge of the cerebral hemisphere, as shown in orange in the upper figure. Broca's limbic lobe includes the cingulate gyrus (the infralimbic, prelimbic, anterior cingulate, and retrosplenial areas), the hippocampal formation (including the entorhinal area, subiculum, hippocampal CA fields, and dentate gyrus), and the amygdala. These limbic regions all receive highly processed sensory information from the association regions of the cerebral cortex, process that information for its emotional content, and then project back to the association cortical areas to provide emotional coloring to cognition.

Each of the limbic areas also sends descending inputs to the hypothalamus. The inputs from the cingulate gyrus mainly originate in the infralimbic and prelimbic regions (around and just beneath the splenium of the corpus callosum). These areas mainly send axons to the lateral hypothalamus, as well as to components of the autonomic system in the brainstem and the spinal cord, and are believed to provide much of the autonomic component of emotional response.

Neurons in the hippocampal formation, particularly the CA1 field and the subiculum, send axons to the hypothalamus through the fornix. This long looping pathway, shown in yellow in the figure, curves just under the corpus callosum, and then dives into the diencephalon at the foramen of Monro. Many axons leave the fornix in the hypothalamus and provide inputs to the ventromedial nucleus. However, a dense column of fornix axons reach the mammillary body, where they terminate. These structures are shown in blue in the upper figure and red in the lower one. Although the hippocampus appears to be very important in memory consolidation, isolated damage to the fornix or mammillary bodies has more limited and inconsistent effects on memory, so the function of this pathway remains enigmatic.

The mammillary nuclei provide another salient bundle of axons to the anterior nucleus of the thalamus. This mammillothalamic tract is heavily myelinated and easily seen, but its contribution to memory formation is more subtle, like that of the mammillary body itself. Lesions of the mammillothalamic tract have been reported to prevent the generalization of limbic seizures, however, and this pathway has been suggested as a target for deep brain stimulation to prevent generalization of seizures. The anterior thalamic nucleus projects to the cingulate gyrus, and, in 1937, James Papez hypothesized that perhaps the momentum of emotions could be explained by a "reverberating circuit," completed by a projection from the cingulate cortex back to the hippocampus, to neurons that contribute to the fornix. Although there is no credible evidence for this last link in the "circuit" actually existing or for the proposed circuit actually playing a role in emotion, the theory has achieved great attention.

The amygdala provides the hypothalamus with inputs via two pathways. Some axons leave the amygdala in parallel to the fornix, running along the lateral edge of the lateral ventricle just below the tail and body of the caudate nucleus in the stria terminalis, shown in blue in the lower figure. Other amygdaloid inputs to the hypothalamus take a much more direct anterior route, running over the optic tract into the lateral hypothalamus. Many hypothalamic cell groups receive inputs from the amygdala, which are thought to be important for the visceral components of conditioned emotional responses.



Overview of Hypothalamic Function and Dysfunction

The hypothalamus works to integrate autonomic, endocrine, and behavioral functions of the brain that subserve basic life functions, such as maintaining fluid and electrolyte balance, feeding and metabolism, body temperature and energy expenditure, cycles of sleep and wakefulness, and a wide range of emergency responses. As a result, the range of disorders that occur when the hypothalamus malfunctions is also very great.

Because the hypothalamus is very small, injuries often involve multiple systems. Hence, a patient with a pituitary tumor or craniopharyngioma impinging on the hypothalamus may have disorders extending into many functions. Such patients are often quite somnolent because an important branch of the ascending arousal system runs through the lateral hypothalamic area. There may also be loss of circadian (24-hour) rhythms of behavior so that the relatively limited waking time may occur during the night rather than in the day.

Alfred Froehlich in 1901 described the patients with such lesions as having an "adiposogenital syndrome" because they became obese and had failure of sexual maturation. Research in the last decade has identified the reason for this association. Feeding in humans (and other animals) is controlled in part by the hormone leptin, which is made by white adipose tissue during times of plenty. In the absence of leptin or its receptors, both humans and animals are ravenous and become quite obese. Leptin is now known to act on the hypothalamus in the region just above the pituitary stalk, to decrease activity in circuits that promote eating. When tumors in the region of the pituitary gland damage this part of the hypothalamus, feeding circuits become disinhibited and the patient becomes obese. An adequate nutritional state is also required for the brain to trigger the hormonal changes that accompany puberty. These circuits are also dependent upon leptin to provide a signal that there are sufficient energy stores to make reproduction possible. Patients whose pituitary tumors develop before puberty may fail to go through the transition. Adults who are severely underweight may have regression of sexual organs, accompanied by amenorrhea in women.

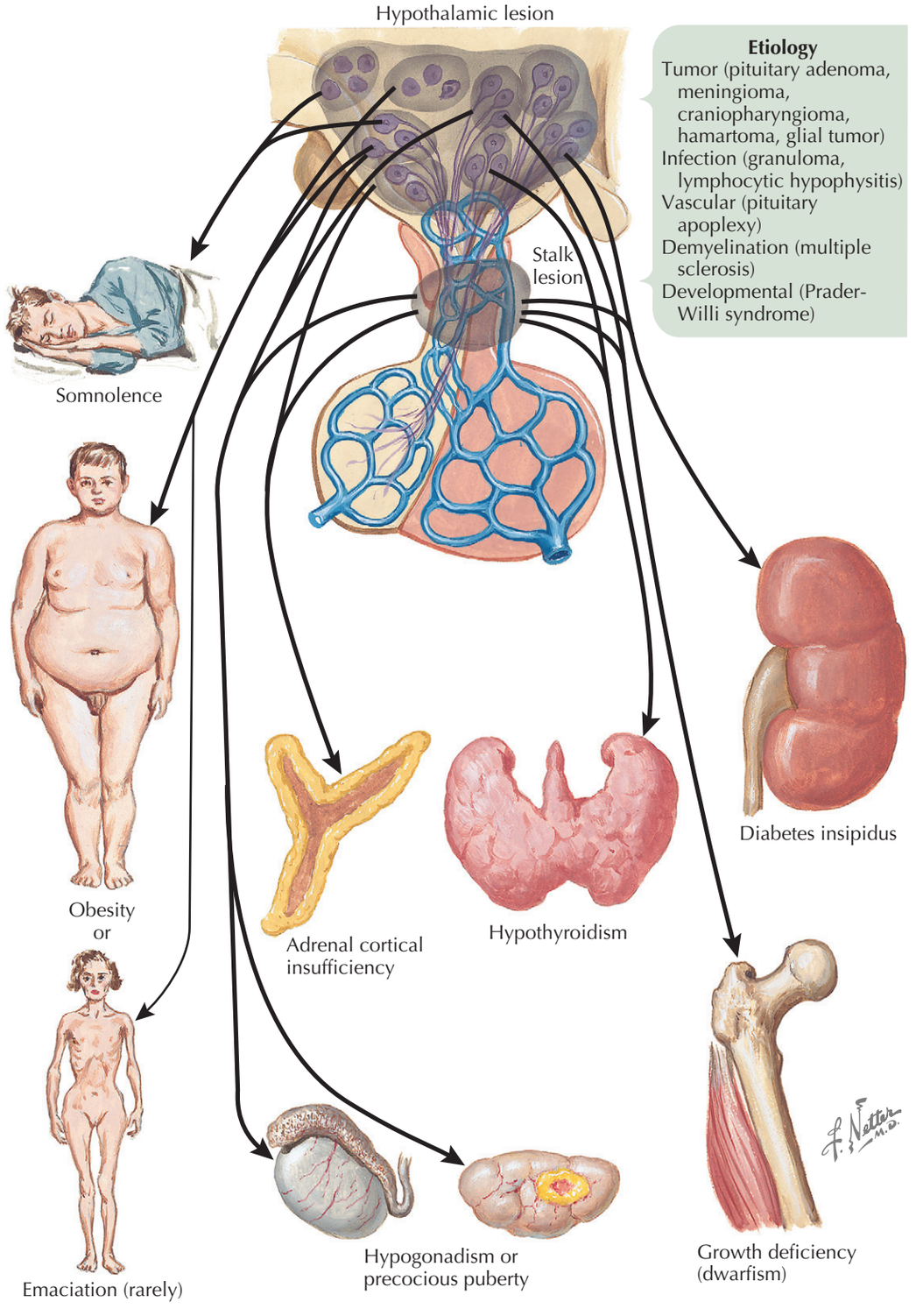
The hypothalamic-releasing hormones, in general, are required by the anterior pituitary gland to secrete adequate amounts of growth, thyroid, corticotrophic, and gonadal hormones. In the presence of a pituitary tumor that damages the hypophysial portal bed in the pituitary stalk, secretion of all of these hormones is diminished. On the other hand, prolactin is mainly under inhibitory control by the hypothalamus, primarily through release of dopamine into the portal circulation. Damage to the pituitary stalk thus causes hyperprolactinemia, with galactorrhea (breast milk production) and amenorrhea in women.

Pituitary stalk lesions also sever the axons from the paraventricular and supraoptic nuclei, which release the hormones oxytocin and vasopressin from the posterior pituitary gland. Such patients have diabetes insipidus, with excessive urination, requiring compensatory drinking to avoid volume depletion.

Smaller, focal hypothalamic lesions can sometimes have different results. For example, bilateral lateral hypothalamic lesions, such as multiple sclerosis plaques, have been reported to cause emaciation. Lesions of the preoptic area can cause loss of thirst and loss of ability to increase vasopressin secretion during dehydration. On hot days, such patients may have substantial volume depletion without becoming thirsty.

Hypothalamic lesions in children may also have somewhat different clinical presentations than in adults. Hypothalamic hamartomas can cause gelastic epilepsy, in which the child laughs uncontrollably but mirthlessly, and sometimes precocious puberty (if the hamartoma includes gonadotropic-releasing hormone neurons). On the other hand, a large hypothalamic lesion in an infant is more likely to present with wasting and emaciation than with obesity, but such children may be quite happy and playful, rather than somnolent.

Overview of Hypothalamic and Pituitary Disease



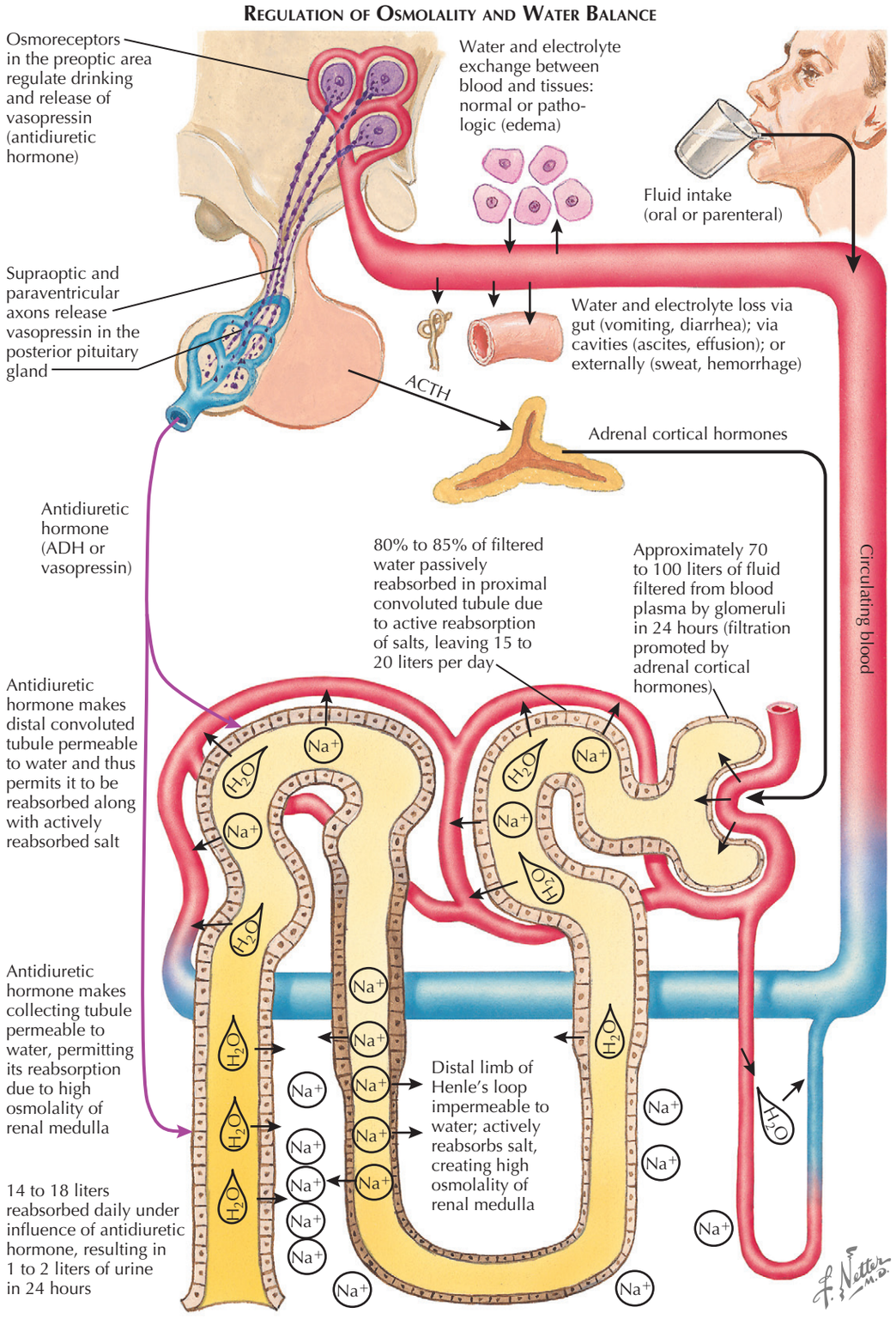
Regulation of Water Balance

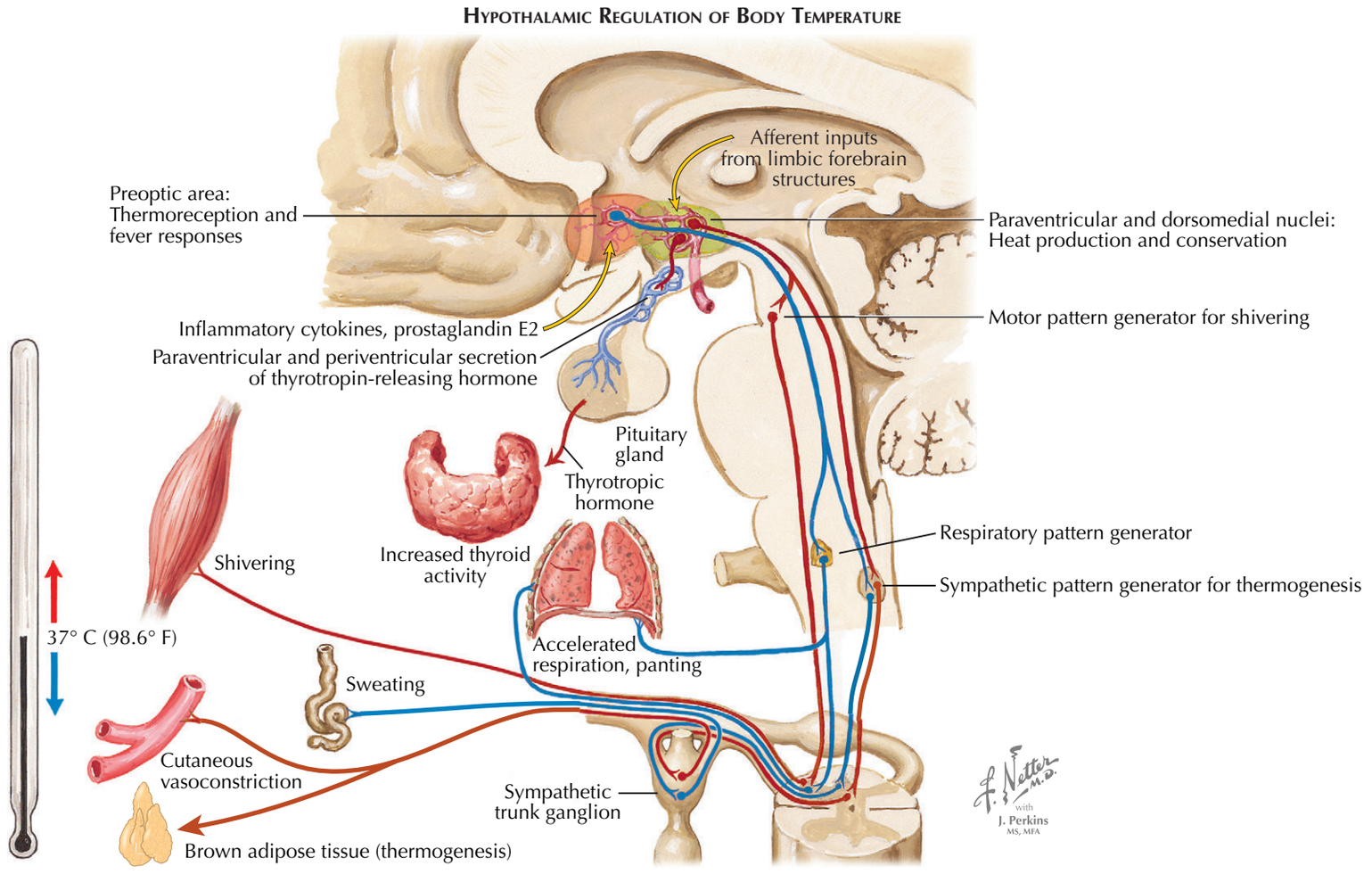
The anterior part of the preoptic area, just above the optic chiasm, contains the neurons of the median preoptic nucleus, which play an important role in sensing blood osmolality, sodium levels, and fluid volume. The individual neurons in this region appear to be sodium and osmolality sensors, and they also receive sensory inputs concerning fluid volume from atrial stretch receptors (through the vagus nerve and nucleus of the solitary tract). There are also mineralocorticoid sensor neurons in the nucleus of the solitary tract, which provide input to the hypothalamus that regulates salt appetite.

Fluid and electrolyte balance is maintained by autonomic, endocrine, and behavioral means. The renal blood flow is under autonomic control, as is the juxtaglomerular apparatus, which releases renin, an enzyme that acts on angiotensinogen to produce a range of angiotensin hormones. After conversion to angiotensin, this hormone both increases vasoconstriction (thus supporting blood pressure) and aldosterone secretion, as well as causing drinking by direct action on the brain. The drinking behavior appears to be mediated by angiotensin II leaking across the blood-brain barrier in the organum vasculosum at the anterior end of the third ventricle, near preoptic neurons expressing angiotensin II receptors. These neurons then project into the hypothalamus to affect salivary secretion (dry mouth, a signal to drink) and activate general arousal (foraging for water) and specific motor systems (that increase licking and swallowing responses) associated with drinking.

The endocrine response to dehydration has both anterior and posterior pituitary limbs. The release of vasopressin by the posterior pituitary causes active resorption of salt and water in the distal limb of the renal tubules and in the collecting ducts. At the same time, vasopressin has a direct vasoconstrictor effect that supports blood pressure. The anterior pituitary gland releases more ACTH, under control of both corticotropin-releasing hormone and vasopressin secreted into the pituitary portal circulation from the hypothalamus. Cortisol itself has some mineralocorticoid effects, but ACTH also primes the adrenal cortex to make aldosterone, the major mineralocorticoid. Aldosterone secretion is also stimulated by the presence of angiotensin III.

Individuals with lesions in the preoptic area sometimes have inability to appreciate thirst. Some of these individuals also have deficits in vasopressin secretion in response to dehydration. Such patients must be reminded to drink, especially on hot days, to avoid dehydration.





Temperature Regulation

One of the key roles of the hypothalamus is in maintaining an even body temperature. This is necessary for optimal function of neurons, metabolic enzymes, and actions of the immune system. The preoptic area contains neurons that are specialized for thermoreception. These are located in close proximity to the neurons that detect osmolality and control fluid and electrolyte balance, and some neurons may have dual roles in both systems. (For example, on a hot day it is necessary to conserve fluid for use by sweat glands to maintain cooling.) Some preoptic neurons themselves are thermoreceptors, but many also receive inputs from the skin, which informs them about the external temperature. Warm-responsive neurons inhibit a series of cell groups that increase body temperature, including the paraventricular and dorsomedial hypothalamic nuclei and the raphe nuclei in the medulla. These latter cell groups activate the sympathetic nervous system to increase body temperature by two major pathways. The first of these is heat generation, due to activation of brown adipose tissue. Once thought to be present only in small mammals, including newborn humans, recent studies have shown that even adult humans have residual brown adipose tissue. Brown adipose is found in small patches along the back and consists of adipose cells that contain large numbers of mitochondria and express uncoupling protein I. This protein permits mitochondria to burn fat to produce heat.

The other major way to increase body temperature is by heat conservation. Particularly in larger mammals, such as adult humans, the body makes sufficient heat from its internal metabolism so that body temperature can be increased merely by shunting blood flow away from the skin to deep vascular beds. In animals with fur, piloerection, another sympathetic response, increases the thickness of the fur coat and thus conserves heat. Humans also have piloerection called gooseflesh, but this is not nearly as effective in heat conservation. The thermogenic (brown adipose) and heat-conserving mechanisms are coordinated by medullary raphe neurons that activate both pathways.

A third mechanism for generating heat is by increased muscle activity or shivering. Less is known about this pathway, but it is presumed that hypothalamic neurons activate motor pattern generators that cause increased muscle activity, which is thermogenic. All three mechanisms require energy, and so the heat production system also activates the cardiovascular system to increase cardiac output and the respiratory system to maintain blood oxygenation.

Anterior pituitary hormones do not seem to play much of a role in the regulation of body temperature over a period of minutes or even hours, although in the absence of thyroid hormone, body temperature falls. Body temperature also rises (during the active cycle) and falls (during the sleep cycle) daily, and this typically occurs before the onset of motor activity or rest, and so is not due to a simple change in muscle activity. There are also changes in body temperature during the menstrual cycle, which may reflect the fact that the preoptic area is also involved in reproductive function.

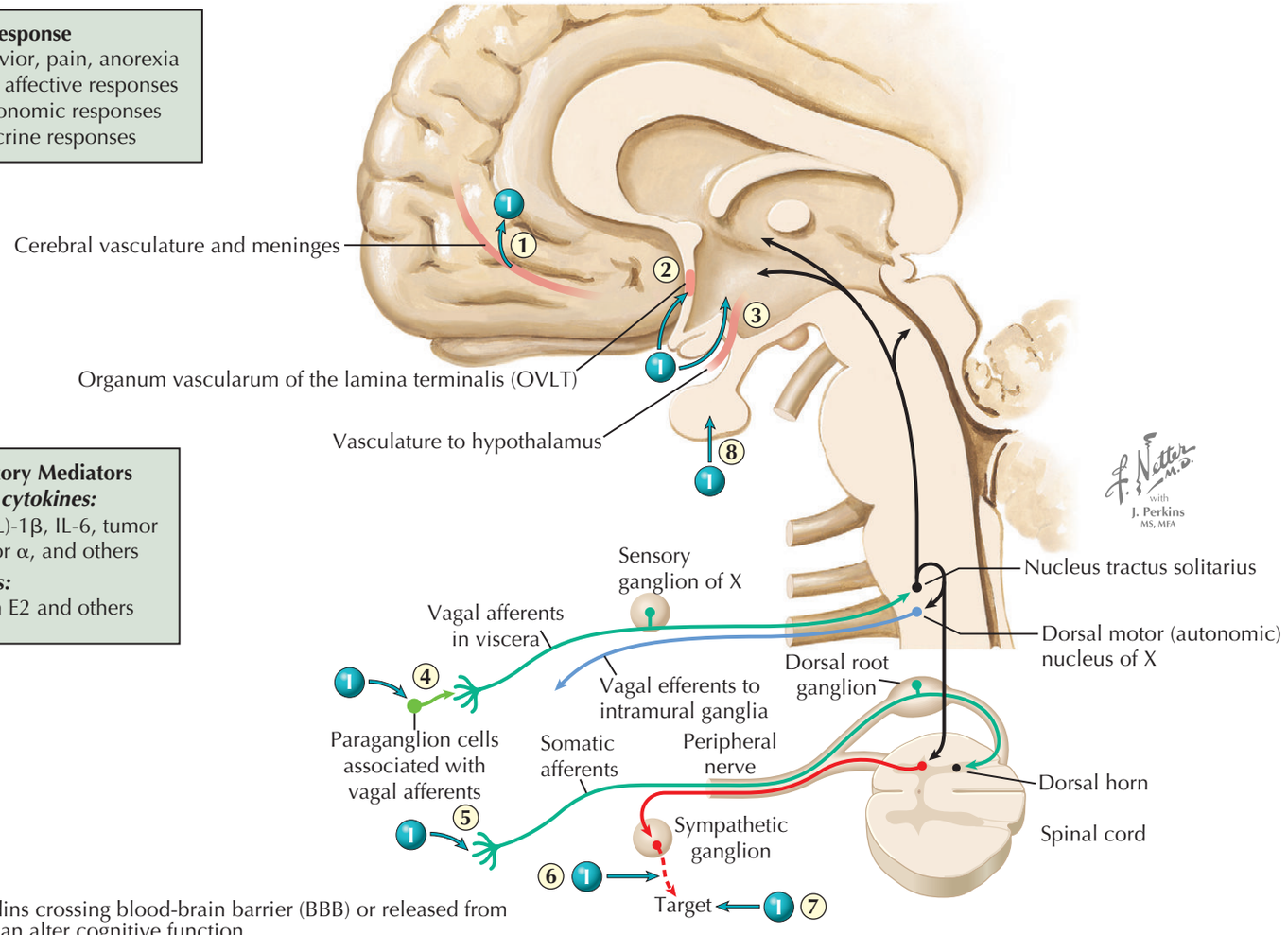
In addition to inhibiting the heat production and conservation systems, warm-sensitive neurons in the preoptic area also increase blood flow to the skin as well as sweating, to permit heat loss, and increase vasopressin secretion, which permits conservation of fluids that are necessary to support increased sweating. Sweating is mediated by two sets of sympathetic nerves, one of which is noradrenergic and the other cholinergic. The cholinergic sympathetic input appears to be of primary importance for thermoregulatory sweating, whereas the noradrenergic axons may be more important for emotional sweating.

Paroxysmal hypothermia is a rare neurologic disorder, most often seen in individuals who have agenesis of the corpus callosum (due to a failure of the anterior wall of the third ventricle to develop properly) or a congenital tumor or other lesion affecting the preoptic area. Such individuals have periods of several days at a time during which their body temperature drops to about 30° C, and they lapse into a stuporous state. Presumably this represents an unusual hypothalamic response, similar to that seen in hibernation states, but there have been too few patients with this syndrome to study it closely.

Cytokines and Prostaglandins Cause the Sickness Response

The Sickness Response
Sickness behavior, pain, anorexia
Cognitive and affective responses
Fever and autonomic responses
Cortisol/endocrine responses

I = Inflammatory Mediators
Inflammatory cytokines:
Interleukin (IL)-1β, IL-6, tumor necrosis factor α, and others
Prostaglandins:
Prostaglandin E2 and others



1. Prostaglandins crossing blood-brain barrier (BBB) or released from meninges can alter cognitive function.
2. Cytokines and prostaglandins can enter brain at circumventricular organs, such as OVLT, that lack BBB.
3. Cytokines act on cerebral blood vessels to release prostaglandin E2, which directly crosses BBB into brain.
4. Cytokines and prostaglandins act on vagal afferents and associated paraganglion cells, activating visceral sensory pathways from the nucleus of the solitary tract that influence autonomic, endocrine, and behavioral responses.
5. Cytokine and prostaglandins act on sensory neurons, modulating pain.
6. Cytokine modulation of norepinephrine release from sympathetic nerve terminals.
7. Cytokine modulation of neurotransmitter intracellular signaling in target cells.
8. Cytokine modulation of pituitary hormone release.

Fever: Hypothalamic Response to Systemic Inflammation

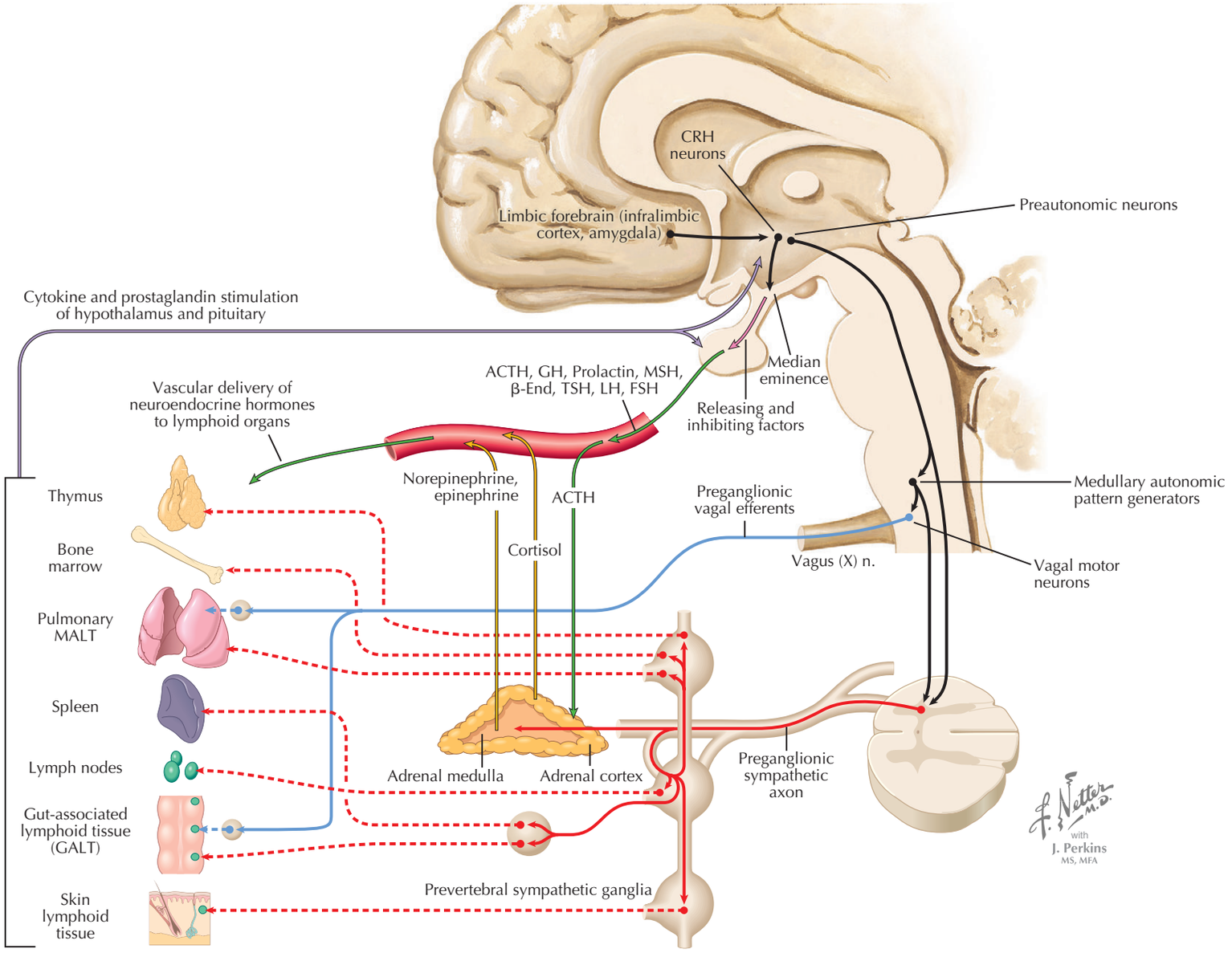
During systemic infections, there is a characteristic, hypothalamically mediated "sickness response" that includes an array of adaptive adjustments. Among these are a feeling of malaise, achiness, and sleepiness (which reinforces rest); increased secretion of adrenocorticosteroids (to mobilize adipose energy stores); and anorexia (to keep blood sugar low because many microorganisms prefer sugars as fuel, while the human body can adapt to using fat stores such as ketone bodies). However, the most prominent symptom of the "sickness response" is an elevation of body temperature called a fever. Experimental studies show that white blood cells are more active at 39° C than 37° C, while many microorganisms are less able to defend themselves at this temperature.

There are several processes by which invading infectious organisms can set off the sickness response. One is that they can act locally on white blood cells that then produce circulating hormones called cytokines. The cytokines can have direct actions on certain types of neurons, but most of the "sickness response" is due to the cytokines (or certain components of invading bacteria themselves) inducing white blood cells and vascular endothelial cells to make prostaglandins. The primary role of prostaglandins in the sickness responses is demonstrated by the fact that inhibitors of cyclooxygenase, the enzyme that produces prostaglandins, is sufficient to prevent most of these responses.

Prostaglandins can act on receptors on peripheral nerves, but they also can cross the blood-brain barrier and act directly on brain neurons that express prostaglandin receptors. The prostaglandin that is probably most important for causing sickness responses is prostaglandin E2 (PGE2), and it has a series of four different E-type prostaglandin receptors (EP receptors) that are found on different classes of cells in the central nervous system (CNS). For example, EP3 receptors in the median preoptic nucleus recognize PGE2 during an inflammatory response and are critical for causing a fever response. Activation of corticosteroid secretion during a sickness response requires EP3 receptors in the preoptic area and the ventrolateral medulla, as well as EP1 receptors, which may be in the paraventricular hypothalamic nucleus or the central nucleus of the amygdala. Increased sensitivity to pain during fever is likely to be due to EP3 receptors, but the exact locus of those receptors is not yet known.

The fever response during sickness appears to be due to neurons in the median preoptic nucleus withdrawing γ-aminobutyric acid (GABA)ergic inhibition of the neurons in the paraventricular and dorsomedial

HYPOTHALAMIC RESPONSES DURING INFLAMMATION MODULATE IMMUNE RESPONSE



FEVER: HYPOTHALAMIC RESPONSE TO SYSTEMIC INFLAMMATION *(Continued)*

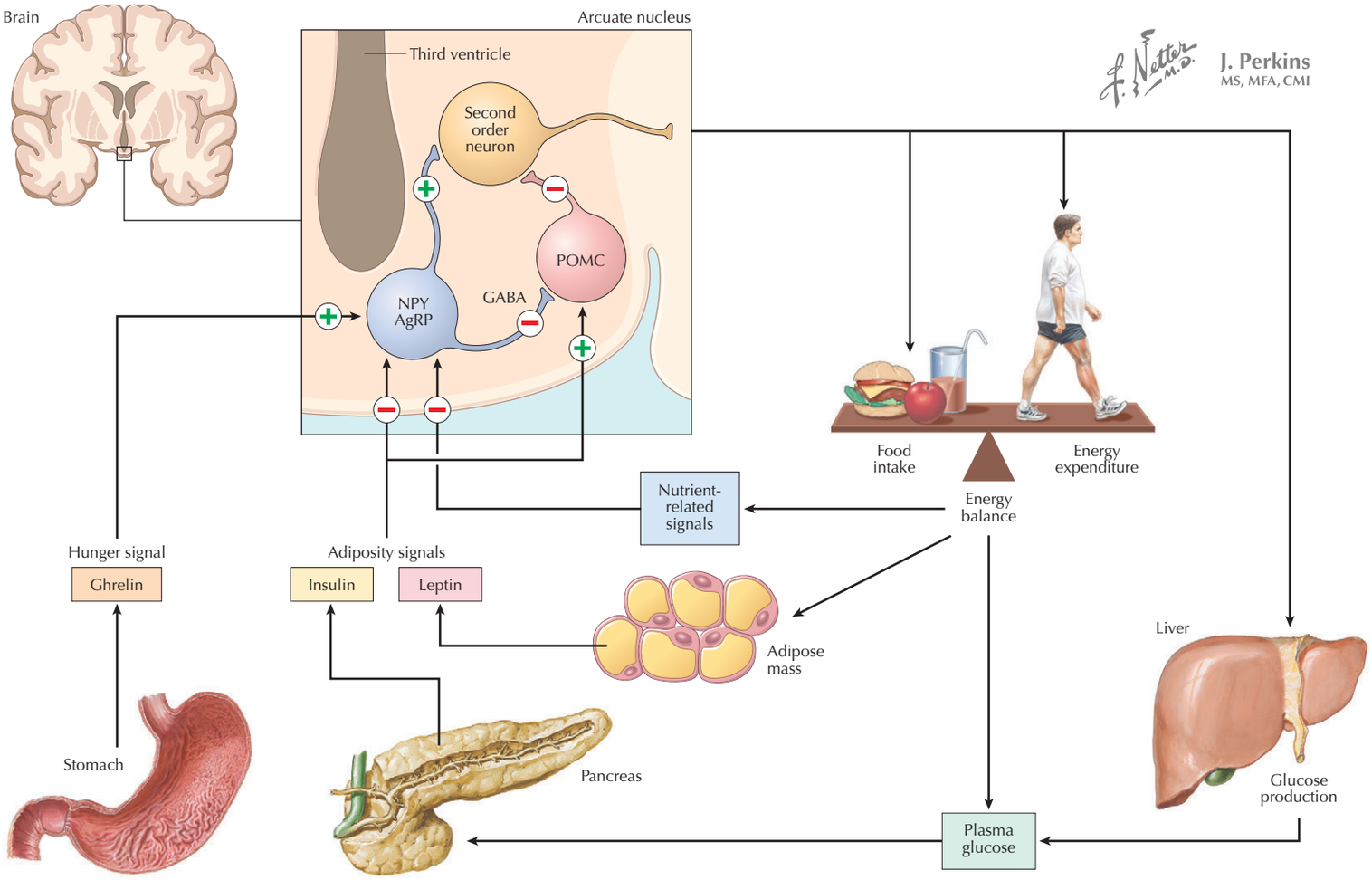
hypothalamic nuclei and the medullary raphe that produce elevated body temperature. This allows body temperature to rise by about two to three degrees centigrade. Fever in the range of 39° C to 40° C is uncomfortable but may be an adaptive response to help fight off invading organisms.

Changes in cognitive capacity and sleepiness during a sickness response are less well understood. EP1 and EP3 receptors are found on hypothalamic preoptic neurons that cause sleepiness, and EP4 receptors are found on histaminergic neurons in the posterior hypothalamus, which may cause arousal. However, prostaglandins are also made by the leptomeninges, and may have direct effects on cortical neurons. PGE2 may also exacerbate meningeal and vascular pain perception (causing headache, particularly during coughing or straining, which increase intracranial pressure).

HYPOTHALAMIC CONTROL OF LYMPHOID TISSUE IN IMMUNE RESPONSE

A critical part of fighting off any infection is the activation of an appropriate immune response. During a sickness response, prostaglandin E2 acts on neurons in the medulla, amygdala, and hypothalamus, which results in an increase in the secretion of corticotropin-releasing hormone (CRH) into the pituitary portal circulation, elevated adrenocorticotropic hormone (ACTH) secretion by the pituitary gland, and increased levels of circulating adrenal corticosteroids. Cortisol then causes demargination of white blood cells that are adherent to the endothelium of blood vessels, elevating the circulating white blood cell count. Lymphocytes in a variety of tissues also respond directly to ACTH, and to a number of other circulating hormones.

There is also direct sympathetic innervation of the lymphoid tissues. This input, which is also under hypothalamic control, may control the production and trafficking of specific lymphocyte subsets.



Regulation of Food Intake, Body Weight, and Metabolism

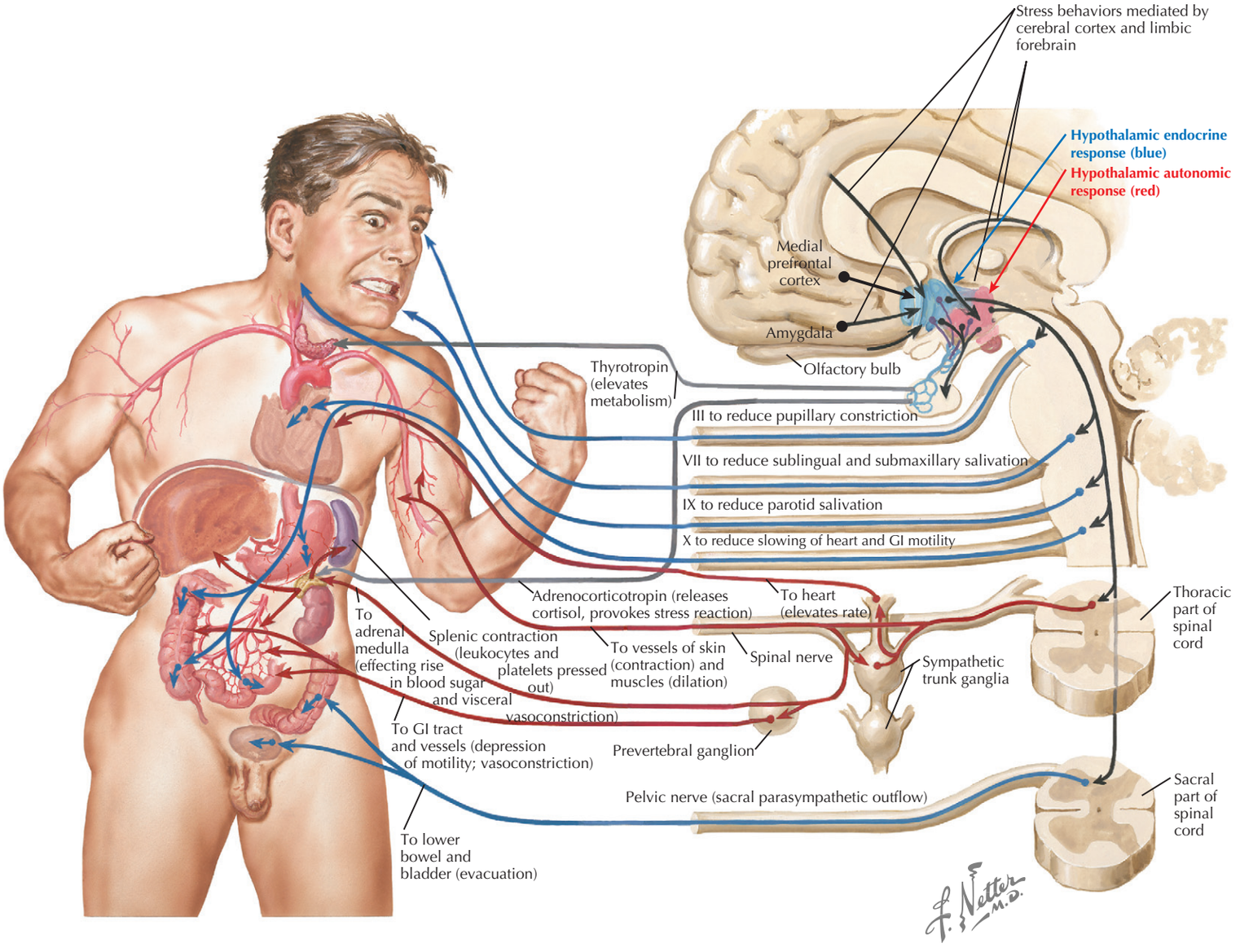
A key function of the hypothalamus is the control of feeding, body weight, and metabolism. Two systemic hormones are known to act on the hypothalamus to ensure that animals ingest sufficient food for their metabolic needs. Ghrelin, a hormone made by the gastric mucosa when the stomach is empty, causes increased eating. Similarly, low levels of leptin, a hormone made by white adipose tissue during times of metabolic plenty, also drive feeding. Hence a starving animal that has low leptin and high ghrelin levels will eat voraciously. Of interest, the opposite does not occur: in the presence of high leptin levels, animals are not inhibited from eating. Throughout evolution, starvation has been a constant problem for animals, but the prospect of obesity due to having too much available food was never a problem until humans recently learned to produce such an overabundance. Hence, humans never evolved ways to deal with this modern situation, and obesity has become rampant in modern human societies.

The actions of leptin and ghrelin appear to involve neurons in the arcuate nucleus, a part of the hypothalamus that is just above the pituitary stalk. These hormones can enter the brain through the hypophysial portal vessels, which lack a blood-brain barrier. Here they encounter neurons that have receptors for the hormones and form a key circuit in controlling eating. Neurons in the arcuate nucleus that contain the peptide neurotransmitters neuropeptide Y (NPY) and agouti-related protein (AgRP) form a positive part of the circuit. They contact cells in the paraventricular, ventromedial, and dorsomedial nuclei of the hypothalamus, as well as the lateral hypothalamic area and parabrachial nucleus, and drive feeding responses. By contrast, a different set of arcuate neurons contains the peptides derived from the pro-opiomelanocortin (POMC) precursor, including melanocyte–stimulating hormone (α-MSH), β-endorphin, and others. These POMC neurons contact many of the same targets as the NPY/AgRP neurons but use α-MSH and the melanocortin 3 and 4 receptors to inhibit the pathways that promote feeding. NPY neurons also contain γ-aminobutyric acid (GABA), and appear to inhibit the POMC neurons directly as well, while AgRP blocks melanocortin 3 and 4 receptors.

The feeding system also receives other central nervous system (CNS) inputs. For example, there is a strong circadian input to feeding, which is mediated by the pathway from the suprachiasmatic nucleus to the subparaventricular zone and then the dorsomedial nucleus. Dorsomedial hypothalamic neurons, in turn, send outputs to the lateral hypothalamic area and the paraventricular, ventromedial, and arcuate nuclei, which may drive circadian cycles of feeding.

The mechanisms by which hypothalamic neurons promote feeding are not well understood. There do not appear to be any "master neurons" that form a feeding center. Rather, different populations of neurons activate autonomic and behavioral responses that promote feeding. Some of the lateral hypothalamic neurons that are activated during starvation contain the peptide neurotransmitter orexin, and these neurons appear to cause arousal and to drive active exploration of the environment, which is necessary for most animals to acquire food. Other descending pathways may potentiate motor responses, such as sniffing, licking, chewing, and swallowing, which are a part of the ingestive behavior. Other descending pathways that control the autonomic nervous system may increase gastric motility and acid production, which may be perceived by the individual as "hunger pangs."

Autonomic, Endocrine, and Behavioral Components of Stress Responses

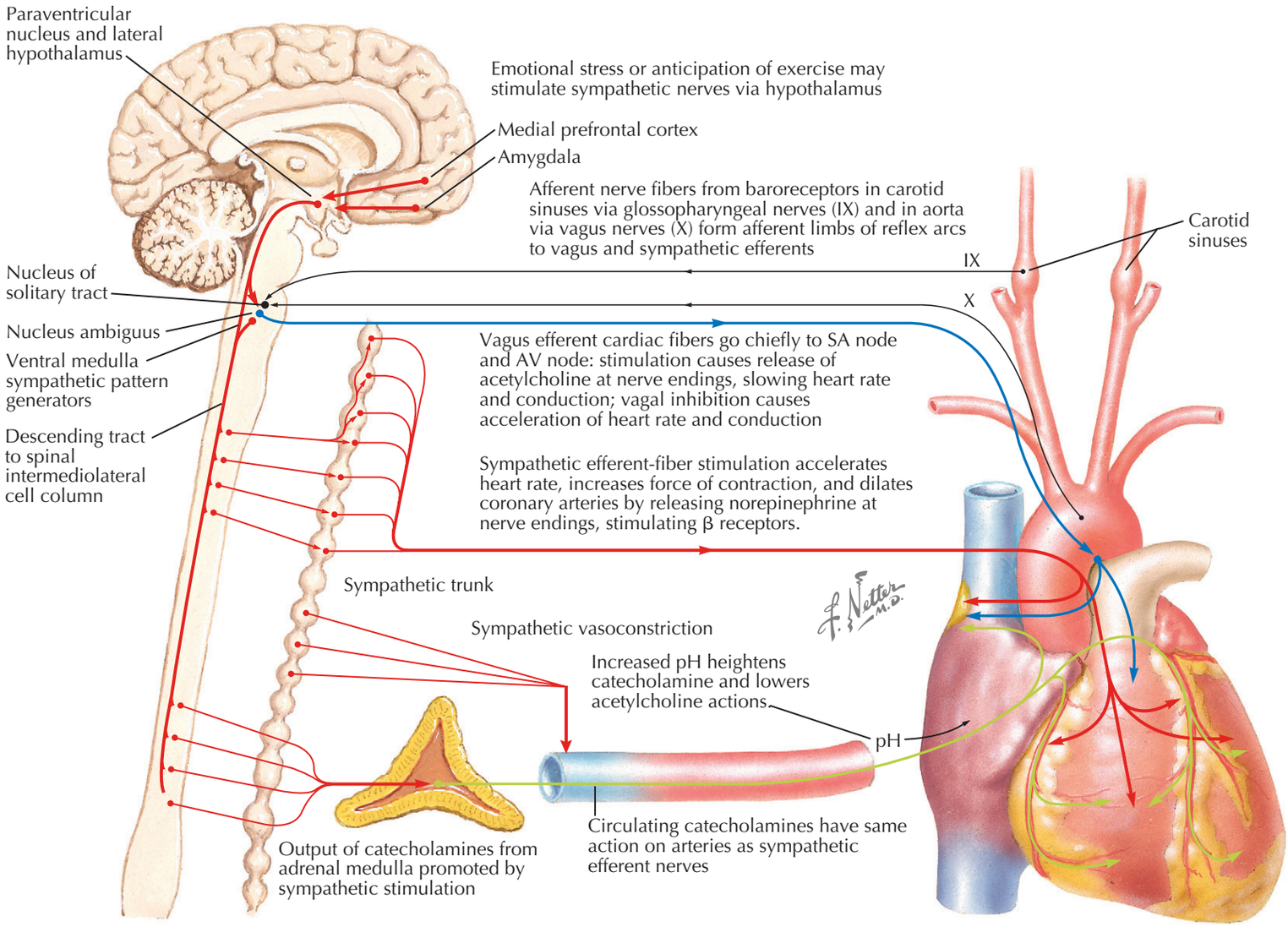


Stress Response

Stress was defined by the Nobel laureate Hans Selye as whatever increased the blood levels of corticosteroids. He was aware that the stimuli for elevated cortisol could include a very wide range of behavioral and physiologic stressors. However, as shown in Plate 5-19, stress involves much more than just corticosteroid secretion, including other endocrine as well as autonomic and behavioral components.

Behavioral stress may come from many different sources, but the areas that most frequently show increased activity under stressful conditions include the medial prefrontal cortex (particularly the cingulate gyrus) and parts of the amygdala (particularly the central nucleus). These regions also have direct inputs to the hypothalamus. The paraventricular nucleus of the hypothalamus is particularly important in producing stress responses. It contains separate populations of neurons that regulate anterior and posterior pituitary responses, as well as autonomic outputs. Most of the corticotropin-releasing hormone (CRH) neurons that regulate secretion of adrenocorticotropic hormone (ACTH) are found in the medial part of the paraventricular nucleus. These neurons are activated by virtually all stressful stimuli, and they secrete CRH and thus drive the systemic secretion of cortisol. The lateral part of the paraventricular nucleus contains neurons that release vasopressin through the posterior pituitary gland. This response permits fluid conservation in case there is hemorrhage (e.g., associated with fighting). The dorsal and anterior parts of the paraventricular nucleus contain nerve cells that innervate the sympathetic and parasympathetic preganglionic neurons in the medulla and the spinal cord. These inputs reduce fluid loss through salivation (dry mouth), ready the cardiovascular system for fight or flight (elevated heart rate and blood pressure), and direct blood flow to muscular vascular beds to prepare for action.

However, it is probably the behavioral responses to stress that are most familiar and distressing to most individuals. The most prominent symptom of stress is hyperarousal, in which the individual reacts excessively to daily stimuli. This can include a tendency to become angry or aggressive more easily. At night, individuals who are under stress often have difficulty sleeping. Positron emission tomography (PET) studies on patients with insomnia show activation of the same brain regions (medial prefrontal cortex, amygdala, hypothalamus) that are activated in animals under experimental stress.



Hypothalamic Regulation of Cardiovascular Function

The hypothalamus is a key component of a central nervous system (CNS) network that governs the heart and circulation. Different behaviors, ranging from emotional responses to motor activities, require activation of different components of the cardiovascular control network. Neurons in the cerebral cortex send inputs to the medial prefrontal cortex, particularly the infralimbic cortex, and the amygdala. These send axons to the hypothalamic neurons that govern cardiovascular response, including the paraventricular nucleus and lateral hypothalamic area. The descending hypothalamic axons innervate brainstem sites involved in producing patterns of cardiovascular response, such as the parabrachial nucleus and both ventromedial and ventrolateral medullary reticular formation.

The parabrachial nucleus receives visceral sensory and pain inputs, and organizes patterns of cardiovascular response seen during arousal due to pain, respiratory distress, or gastrointestinal discomfort (increased blood pressure and heart rate). It does this by direct projections to sympathetic and parasympathetic cell bodies, as well as to medullary pattern generators.

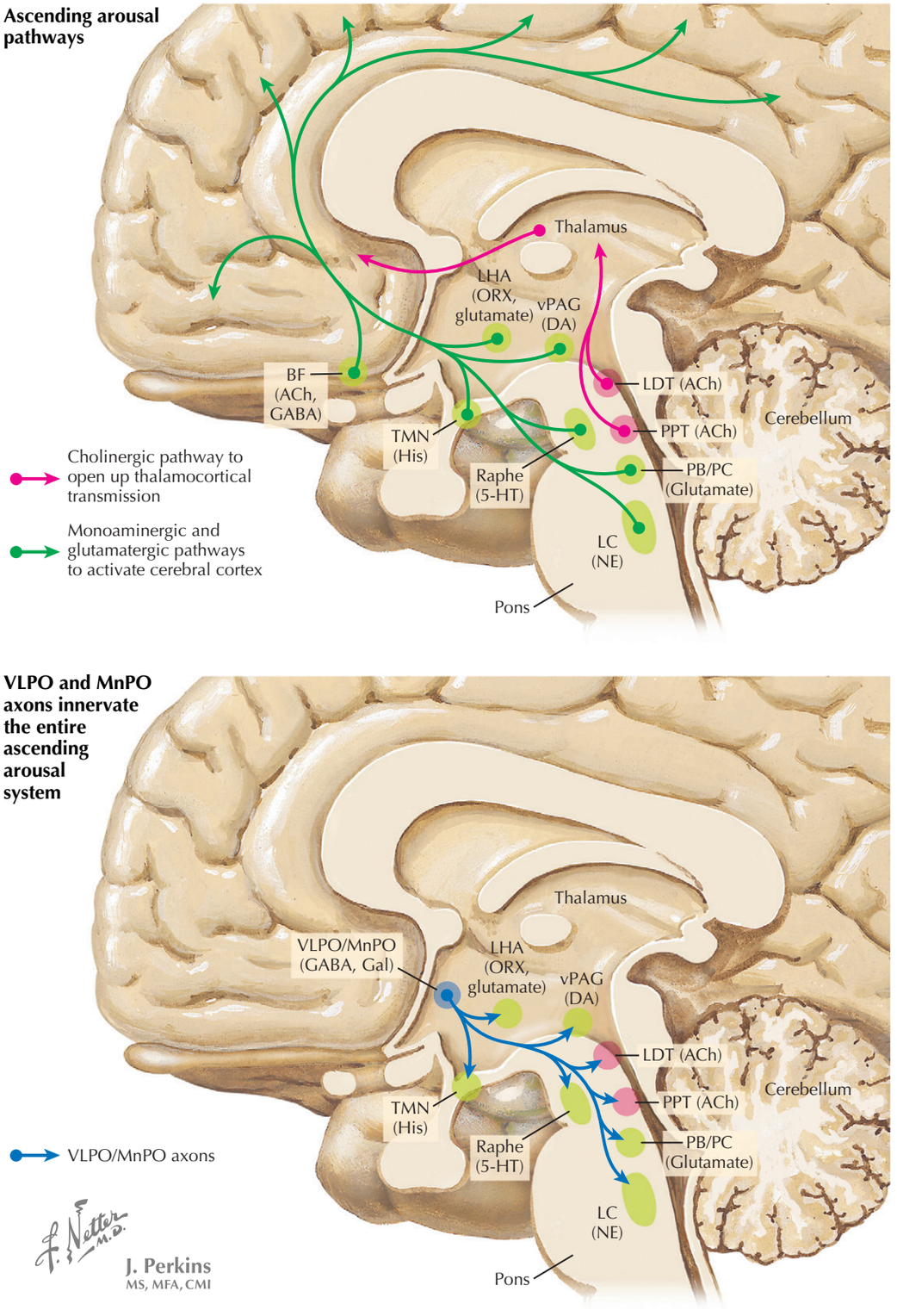
In the medulla, there are distinct pattern generators in the ventromedial and ventrolateral areas. The ventromedial medulla receives inputs from hypothalamic cell groups involved in thermoregulation, and it organizes patterns of sympathetic response necessary for thermogenesis (increased heart rate and activation of brown adipose tissue, with shifting of blood flow from cutaneous to deep vascular bed). This also requires elevation of heart rate to deal with the increased cardiac demand of hyperthermia. The ventrolateral medulla, by contrast produces patterns of cardiovascular response necessary for maintaining blood pressure during erect posture, called baroreceptor reflexes.

Other descending hypothalamic axons go directly to the nucleus of the solitary tract, as well as the preganglionic neurons in the nucleus ambiguus in the medulla, which control heart rate through the vagus nerve and the intermediolateral column of the spinal cord, which controls vasoconstriction. These may produce patterns of autonomic activation that are organized at a hypothalamic level, such as stress or starvation responses.

The brainstem targets of this descending system coordinate cardiovascular reflexes. For example, the carotid sinus nerve (a branch of the glossopharyngeal nerve) and the aortic depressor nerve (a branch of the vagus nerve) bring information to the nucleus of the solitary tract about aortic and carotid stretch. When blood pressure is high, neurons in the nucleus of the solitary tract activate cardiovagal neurons in the nucleus ambiguus to slow the heart and inhibit neurons in the ventrolateral medulla that maintain tonic blood pressure by means of activating sympathetic preganglionic vasoconstrictor neurons. This baroreceptor reflex can be modified by descending hypothalamic input so that during times of stress, for example, there can be a simultaneous increase in blood pressure and heart rate without activating the baroreceptor reflex.

Projections from the hypothalamus to the intermediolateral column can directly activate sympathetic ganglion cells concerned with cardioacceleration and the strength of contraction, to increase cardiac output. Other descending hypothalamic axons can contact adrenal preganglionic neurons, resulting in increased circulating adrenalin, which also increases vasoconstriction and cardiac output.

Hypothalamic Regulation of Sleep

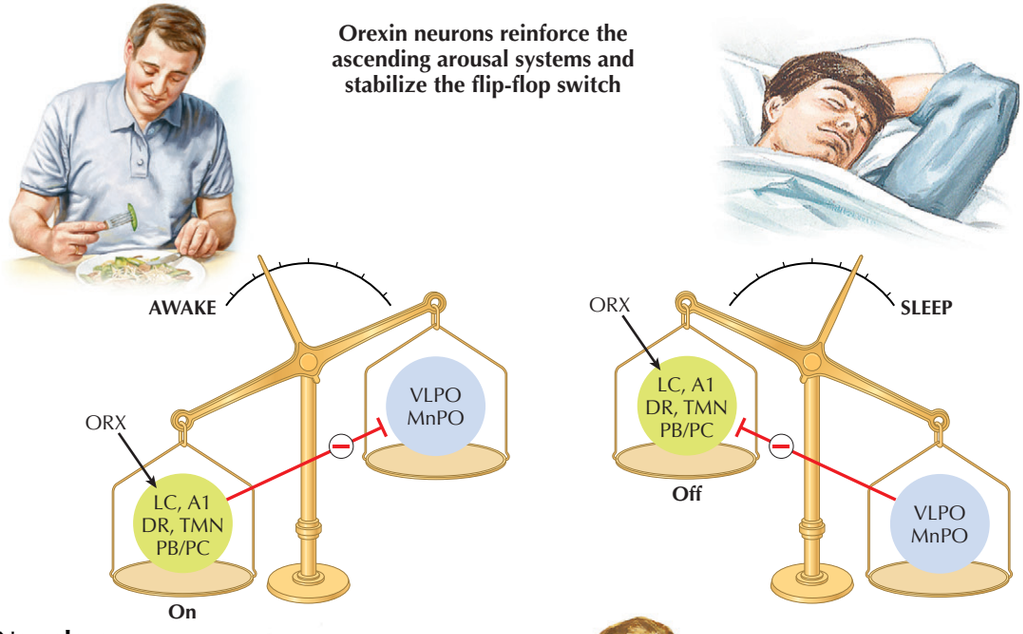


The brain is kept awake by an ascending arousal system that takes origin in the rostral pons and caudal midbrain. The neurons that activate forebrain arousal mainly consist of specific populations of cells that contain monoamine neurotransmitters, acetylcholine (ACh), and the excitatory transmitter glutamate. The cholinergic neurons in the pedunculopontine tegmental (PPT) and laterodorsal tegmental (LDT) nuclei provide the major input to the thalamic relay nuclei and the thalamic reticular nucleus. The latter is a sheet of inhibitory γ-aminobutyric acid (GABA)ergic interneurons that sit on the surface of the thalamus. The cholinergic input inhibits the reticular nucleus and activates the relay nuclei, this enhancing thalamocortical transmission of sensory information.

At the same time, a series of monoaminergic cell groups in the upper brainstem provides an ascending pathway that largely bypasses the thalamus and goes directly to the cerebral cortex. These include noradrenergic (NE) neurons in the locus coeruleus (LC), serotoninergic (5-HT) neurons in the dorsal raphe and median raphe nuclei, dopaminergic (DA) neurons in the ventral periaqueductal gray matter (vPAG) and histaminergic (His) neurons in the tuberomammillary nucleus (TMN) in the hypothalamus. These are joined by glutamatergic neurons in the parabrachial and precoeruleus (PB/PC) nuclei. All of these cell groups send axons through the lateral hypothalamic area (LHA), where they are joined by ascending axons from the orexin (ORX) neurons and from glutamatergic neurons in the lateral hypothalamic area. The pathway then passes through the basal forebrain (BF), where additional cholinergic neurons (which innervate cortical pyramidal neurons) and GABAergic neurons (which innervate cortical inhibitory interneurons) join in. These inputs are thought to excite cerebral cortical neurons and to enhance their capacity for information processing.

During wakefulness, both of these pathways are active at a maximal rate. As the brain falls asleep, the electroencephalogram slows, the individual enters slow-wave (non–rapid eye movement [NREM] sleep), and the firing of all of these cell groups is diminished. However, intermittently during the sleep cycle, when the individual enters REM, or active dreaming sleep, the cholinergic neurons and some of the glutamatergic neurons in the parabrachial nucleus begin firing again at a high rate, while the monoamine systems stop firing altogether. This disparity in activity is thought to cause the dreaming state.

Sleep is regulated at least in part by two populations of neurons in the preoptic area. Median preoptic (MnPO) neurons appear to fire in response to prolonged wakefulness but do not by themselves produce sleep. However, neurons in the ventrolateral preoptic (VLPO) nucleus begin firing at the onset of sleep, and the two both continue to fire during sleep states. The ventrolateral preoptic nucleus projects to the components of the ascending arousal system, and its neurons contain both the inhibitory neurotransmitter GABA and the inhibitory neuropeptide galanin (Gal), which appear to be important in turning off arousal and permitting sleep to occur. GABAergic neurons in the median preoptic neurons also contact some of these same targets. Animals with ventrolateral preoptic lesions may lose a third or more of their total sleep.



Narcolepsy

Excessive daytime sleepiness in narcolepsy or sleep apnea

J. Perkins
MS, MFA, CMI

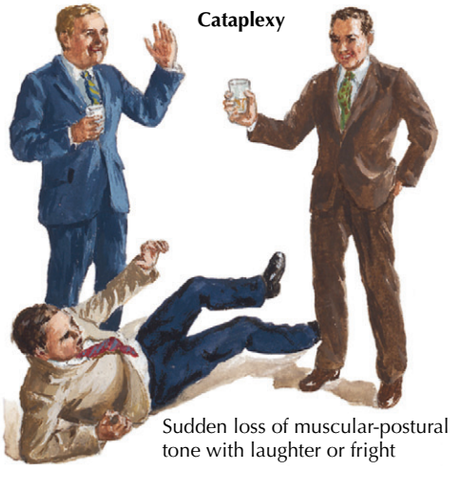
Narcolepsy: A Hypothalamic Sleep Disorder

Narcolepsy is a puzzling disorder that was first described in the late 1800s. Patients usually have onset of their symptoms in their teens or twenties, when they become unusually sleepy during the day and may fall asleep if unstimulated even for a brief time. When a friend tells a joke, they may suddenly lose their muscle strength and gradually slide to the floor, unable to stand or even sit, a condition called cataplexy. Narcoleptic patients also may have sleep paralysis when they are just falling asleep or just waking up and be conscious but unable to move, or may have dreams intrude into their waking state as they fall asleep (hypnagogic hallucinations) or wake up (hypnopompic hallucinations). All of these phenomena represent a weakening of the boundaries between different wake-sleep states, particularly with components of REM sleep (muscle atonia, dreaming) intruding on wakefulness.

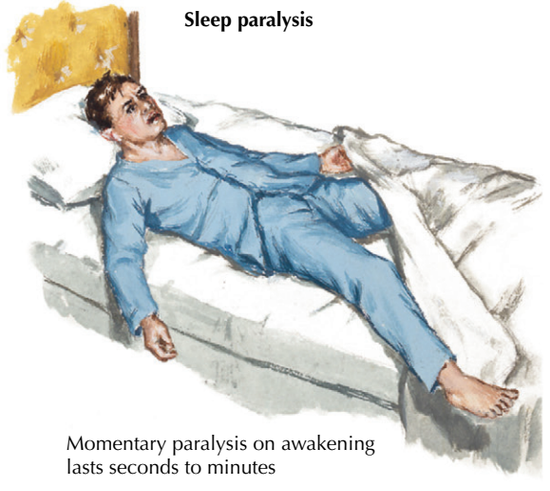
The cause of narcolepsy was quite mysterious until a new neurotransmitter, orexin (also called hypocretin) was discovered in 1998. The orexin neurons are found in the lateral hypothalamic area. They target the main components of the ascending arousal system, and both of the orexin receptors are excitatory. Orexin neurons fire most rapidly during wakefulness, particularly during wakeful exploration of the environment. Thus the orexin neurons appear to play a key role in maintaining and stabilizing a wakeful state.

Soon after their discovery, it became apparent that gene defects that cause loss of signaling by the orexin neurons could cause narcolepsy in experimental animals. In humans, however, genetic mutations are a rare cause of narcolepsy; most individuals with narcolepsy appear to have loss of their orexin neurons, perhaps due to autoimmune attack.

The orexin neurons stabilize the behavioral state by reinforcing wakefulness and blocking individuals from falling directly from wakefulness into REM sleep. In the absence of the orexin neurons, the waking state is less stable, and individuals fall asleep too easily. They also enter REM sleep very quickly after sleep onset and can have fragments of REM sleep (dreaming, muscle atonia) occurring at the wrong times, accounting for the episodes of hypnagogic hallucinations, sleep paralysis, and cataplexy.

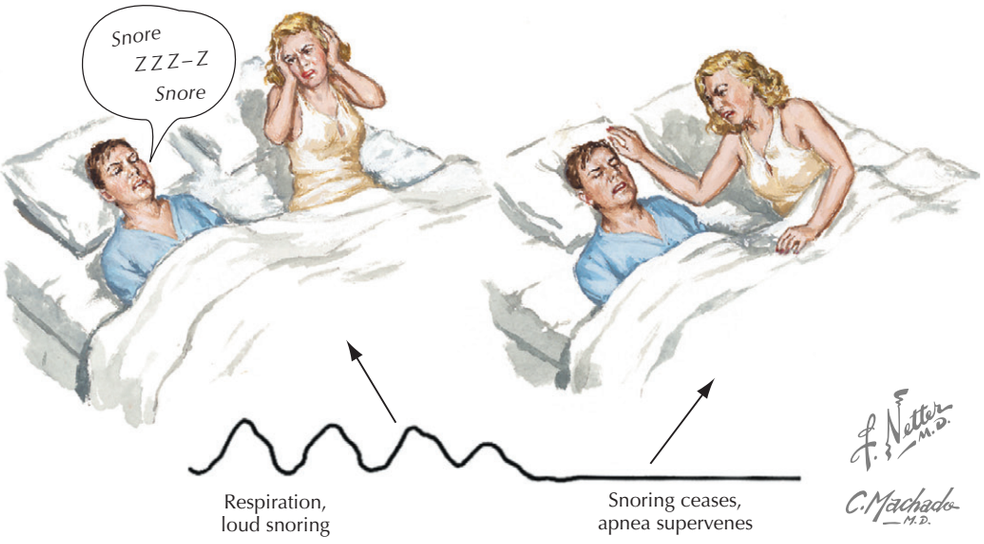


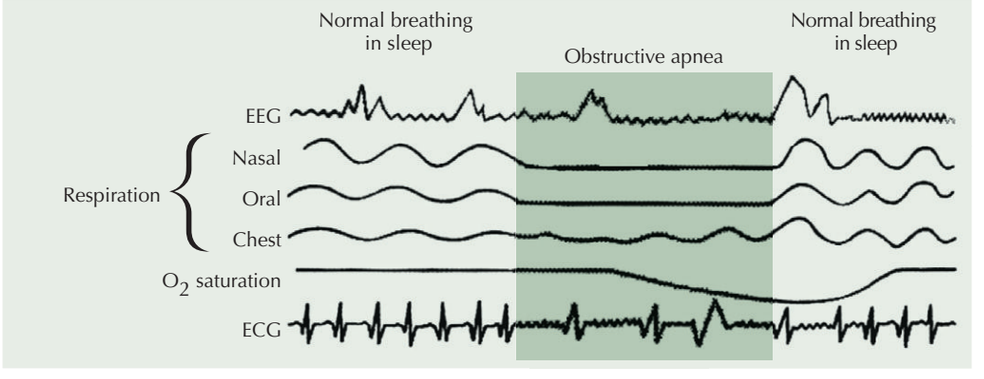
Sudden loss of muscular-postural tone with laughter or fright



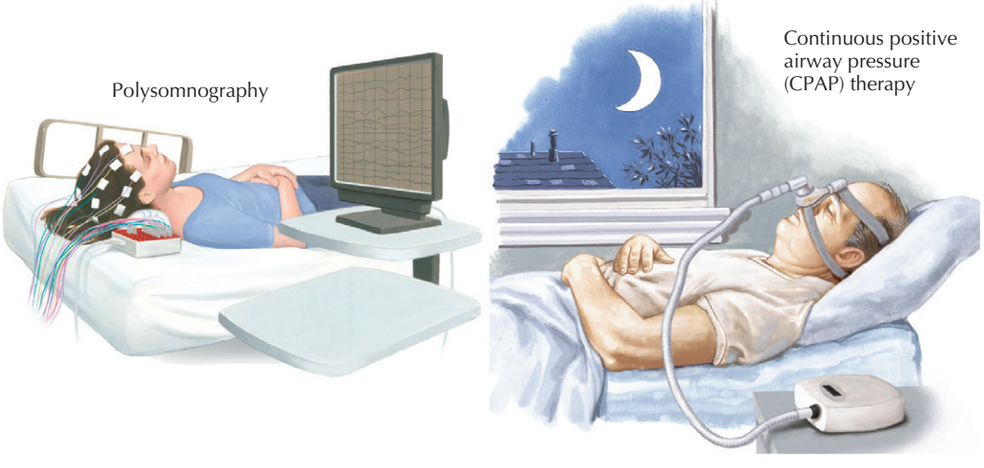
Momentary paralysis on awakening lasts seconds to minutes

Sleep-Disordered Breathing





Recordings from patient with obstructive sleep apnea



Sleep-disordered breathing includes a spectrum of disorders, ranging from snoring to frank cessation of air flow, or apnea, during sleep. *Obstructive sleep apnea* occurs when relaxation of the tongue and airway muscles during sleep causes collapse of the airway, resulting in snoring, reduction in air flow (hypopnea), or even total blockage of air flow (apnea). Patients with *central sleep apnea* have reduced drive to breathe during sleep (*central sleep apnea*). Central sleep apnea may occur as a congenital problem in children, where it may be caused by a mutation in the *Phox2b* gene, which is necessary for development of CO2 chemosensory neurons in the medulla. However, it can also be caused by damage to the medulla or spinal cord causing failure of automatic breathing during sleep ("Ondine's curse"). Central sleep apnea also is often seen in older adults who have developed congestive heart failure or respiratory disease (causing waxing and waning Cheyne-Stokes respiration during sleep). In many older adult patients, a combination of central and obstructive sleep apnea may be seen, sometimes called complex sleep-disordered breathing. The typical patient with obstructive sleep apnea arouses after a brief interval of struggling to breathe, the airway opens, and breathing resumes. This cycle may repeat every few minutes all night. The patient often is unaware that the arousals are occurring but typically feels sleepy during the day. Sometimes the patient complains of aches and pains or impaired memory or cognitive function, which can be increased by sleep loss. Often the bed partner will first realize that something is wrong when snoring sounds become intolerable or notices the periodic loss of breathing. The episodes of apnea are often increased in frequency when the patient drinks alcoholic beverages or sleeps on his back. Obstructive sleep apnea is most common among older individuals, men, and those with obesity and large shirt collar sizes, but it is also seen in older women and in children and young adults who have enlarged tonsils or adenoids, anomalies of craniofacial structure that compromise airway diameter, or neuromuscular disorders that cause laxity of the airway muscles.

Clinical Presentation. Pronounced snoring, a classic indicator for possible sleep apnea is related to vibration of upper airway tissue. Apnea occurs when the upper airway obstruction becomes complete. There is decreased blood oxygen saturation with corresponding increased blood carbon dioxide levels leading to arousal from sleep. The patient is usually unaware of these events; however, the bed partner is aroused and understandably frightened by the patient's respiratory pause. Paradoxically, the majority of patients with obstructive sleep apnea do not report choking or gasping for breath and are unaware of their apneas. Although they may feel that the have slept well, they exhibit excessive daytime sleepiness, which results in lapses in attention and inappropriately falling asleep. Impairment of cognitive function may mimic depression or dementia, and children with sleep-disordered breathing show problems with attention and behavioral dyscontrol that may disrupt their schoolwork. Severe cases (≥30 episodes per hour) and possibly those with moderate degrees of apnea (15 to 29 episodes per hour) are at significantly increased risk for cardiovascular disorders, including hypertension, myocardial infarction, cardiac arrhythmias, and stroke. Hypertension may develop from elevated catecholamine levels caused by the apneas. In addition, the negative intrathoracic pressure caused by struggling to breathe may lead to increased secretion of aldosterone, promoting increased intravascular fluid volume. The elevated central venous pressure paired with increased intrathoracic negative pressure increases transmural forces affecting the heart, which may cause cardiovascular remodeling and alteration of cardiopulmonary physiology. Sleep loss also causes insulin resistance, which can predispose to diabetes and increased body mass, which further worsens the sleep apnea and hypertension.

Diagnosis and Treatment. An all-night sleep study is the best means to detect and quantify apneic events. Healthy adults may experience up to four apneas per hour of sleep at night; in children more than 1.5 events/hour is considered abnormal. Treatment of obstructive sleep apnea begins with correction of anatomical abnormalities of the airway, including removal of enlarged adenoids and tonsils in children. Reduction of risk factors, such as obesity and drinking alcohol in the evening, may help. If this is not curative, continuous positive airway pressure (CPAP), which uses air pressure to splint open the airway during sleep, prevents apneas and reduces daytime sleepiness and cardiovascular risk. Patients with severe and moderate sleep apnea significantly benefit from CPAP use by improving daytime alertness and reducing cardiovascular risk. Often, the treated patient may comment that he had not realized how sleepy he was until he had experienced the results of treatment.

Parasomnias

Parasomnias are characterized by certain unusual or unwanted movements or behaviors that occur during nighttime sleep.

PERIODIC LIMB MOVEMENTS OF SLEEP (PLMS)

Typically, the patient experiences repeated very brief episodic leg movements ranging from simple great toe dorsiflexion to violent flexion of the entire lower extremity. This may recur at regular intervals, up to several times per minute, all night long. If the movements are mild, neither the individual patient nor the bed partner may recognize the PLMs. On the other hand, if more violent, the movements may awaken the patient, bed partner, or both. Although mild PLMS may not be associated with arousals and are of no clinical significance, in some patients the more pronounced PLMS may cause repeated arousals. As a result, the patient may develop, daytime sleepiness. PLMs can often be treated successfully with dopamine agonists, such as ropinirole or pramipexole, or with benzodiazepines, such as clonazepam.

RESTLESS LEG SYNDROME (RLS)

RLS often occurs in the same patients as those who have PLMs, although there is another group of RLS patients who do not get PLMs. The patient with RLS perceives an irresistible urge to move the legs, especially while sitting or lying down; these feelings are relieved when the patient stands or walks. The patient often describes the feeling as an uncomfortable sensation in the legs that is only relieved by leg movement. Many RLS patients demonstrate iron deficiency or low ferritin levels, and in those patients treatment with iron may help. In addition, the symptoms of RLS may be successfully treated with dopamine agonists, benzodiazepines, or opioid drugs. Antidepressants and stimulants may exacerbate RLS and PLMS. Two genome-wide screening studies have identified a genetic polymorphism that correlates with RLS with PLMs, suggesting that many cases may have a heritable cause.

REM SLEEP BEHAVIOR DISORDER

Patients with REM sleep behavior disorder (RBD) exhibit complex motor activity during REM sleep. During REM sleep, when active dreaming occurs, there is activation of reticulospinal pathways that result in profound inhibition of motor neurons, resulting in deep paralysis of voluntary muscles in intact individuals. In patients with RBD, this paralysis breaks down and there are intermittent jerky movements and sometimes complex behaviors during REM sleep. In many respects, RBD is the opposite of the cataplexy attacks seen in patients with narcolepsy, who have activation of the REM sleep paralysis system while awake. RBD patients typically appear to be fighting off attackers and report dreams that match their actions. However, as with PLMS, patients with RBD are often unaware of these occurrences, unless they are reported by a bed partner, or the patient falls out of bed and is injured during a foray. RBD is usually treatable with either clonazepam or melatonin. However, in severe cases, the bed partner may have to sleep in a different room and the mattress must be placed on the floor, the furniture removed, and windows boarded over to prevent the patient from injuring himself or his bed partner during an attack. Some patients use large straps across the bed to avoid such excursions. Most patients with idiopathic RBD (no other predisposing cause) are men, and the peak onset is in the fifties or sixties. Recent studies show that most patients with idiopathic RBD subsequently develop a synucleinopathy, usually Parkinson disease or diffuse Lewy body dementia, but occasionally multiple systems atrophy. However, the time to diagnosis of these neurodegenerative disorders may be quite prolonged, with about half the patients with RBD developing a synucleinopathy within 12 years, and almost 80% by 20 years. In one case report the patient was found by his new bride to have RBD on his wedding night at age 21 and did not develop Parkinson disease until age 71. Other risk factors include the use of antidepressants that prevent reuptake of serotonin or norepinephrine. Again, this situation represents the opposite of cataplexy, the development of REM atonia during waking in narcoleptic patients, where these antidepressants suppress the attacks.

NIGHT TERRORS, SLEEP WALKING, AND BED WETTING

These disorders commonly occur in children and rarely persist into adult life. As a group, these childhood parasomnias tend to occur during the deepest stage of slow-wave sleep and tend to become more brief and less profound during adulthood. Typically, the patient with night terrors suddenly sits up in bed, has dilated pupils, a frightened expression, and a rapid pulse. Occasionally, the affected individual may suddenly dash from the bed with such vigor that he or she may sustain an injury. Often, the child returns to sleep without any memory of the event. If awakened during the night terror, the child describes a frightened feeling or image but not a complex dream. Although there are no known adverse outcomes to night terrors, they can be quite frightening to parents, and it is important to distinguish them from other, more rare nocturnal events, such as seizures.

Sleep walking, or *somnambulism*, also tends to occur in children during deep slow-wave sleep. The child may walk and talk, but the speech is typically mumbled and incoherent. The patient can generally be led back to bed and will not remember the incident the following day. Often, an explanation of the problem to the family is sufficient.

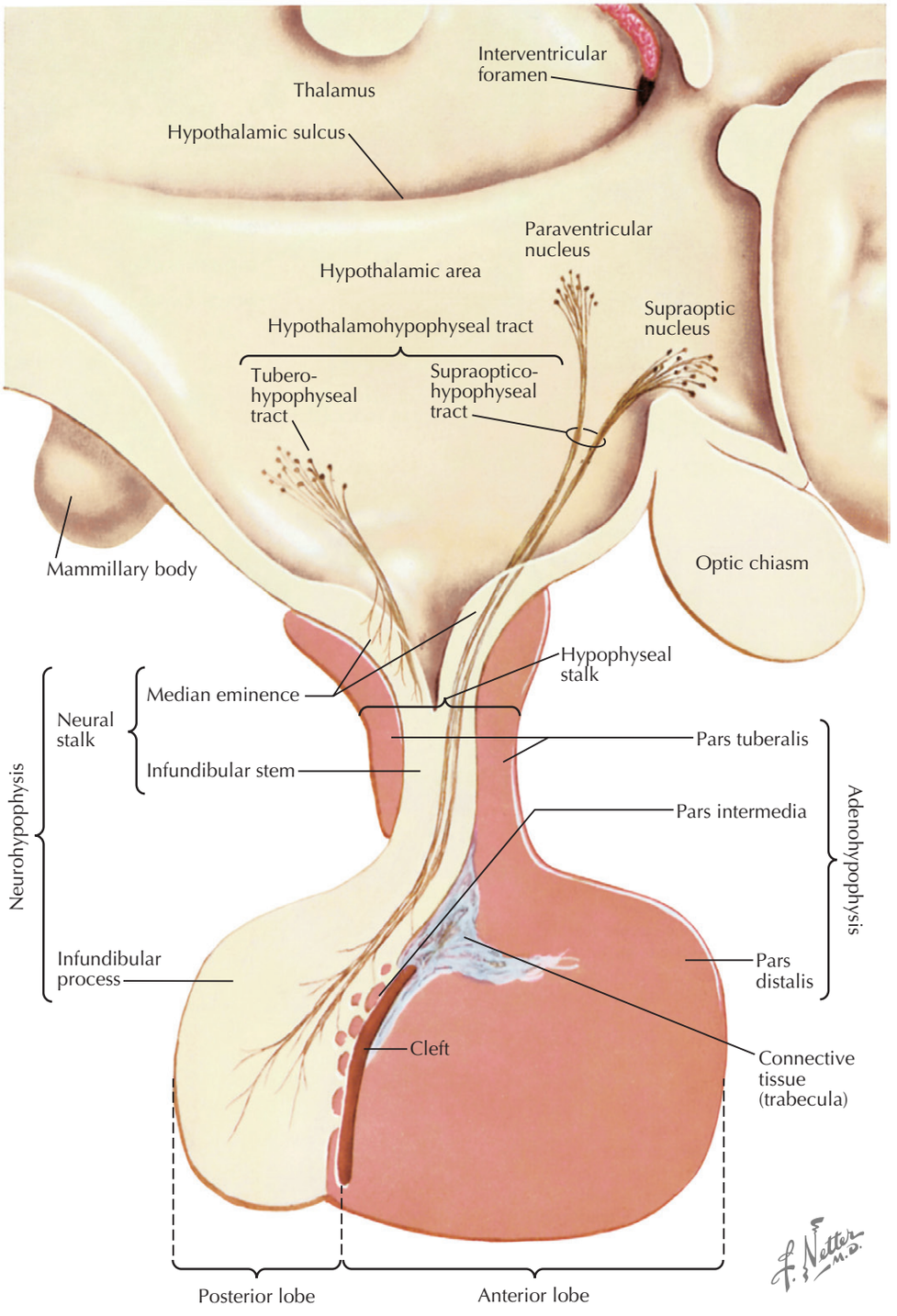
Enuresis, or *bed wetting*, typically occurs in this same age range and also during the deepest part of slow-wave sleep. In general the patient is not aware of the event, awakening in damp bed clothing.

All of these childhood parasomnias frequently respond to drugs that reduce the tendency to fall into deep slow-wave sleep, such as tricyclic antidepressants or benzodiazepines.

REM Sleep Behavior Disorder

Patients who lose their ability to be paralyzed during REM sleep begin to act out their dreams and are usually unaware of these occurrences because the episodes occur during sleep. Often the first episodes are observed by the spouses of the patients.

Divisions of the Pituitary Gland and Its Relationships to the Hypothalamus



The *pituitary gland* (*hypophysis*) is a midline structure at the base of the hypothalamus, to which it is connected through the pituitary stalk. The gland is approximately bean shaped, measures 6 mm (superior-inferior dimension) by 9 mm (anterior-posterior dimension) by 13 mm (transverse dimension), and weighs 500 to 600 mg.

The gland is composed of the adenohypophysis and the neurohypophysis, which are embryologically, anatomically, and functionally distinct. The former derives from the *Rathke's pouch*, an ectodermal outgrowth of the primordial stomodeum, whereas the latter derives from the neural ectoderm and can be considered an extension of the hypothalamus.

The adenohypophysis comprises the *pars distalis*, the *pars intermedia*, and the *pars tuberalis* (a small portion of the adenohypophysis wrapped around the neurohypophysis in the stalk). The *pars distalis* is also known as the *anterior lobe* (or pars glandularis), whereas the pars intermedia is poorly developed in humans. The pars intermedia contains a connective tissue trabecula separating the anterior and posterior lobe as well as a narrow cleft or several small cysts at the site of the embryonic Rathke's pouch. During development, populations of stem cells differentiate into distinct groups of adenohypophyseal secretory cells under the influence of specific transcription factors.

Several differentiated cell types arise from a common stem cell precursor, including somatotrophs, lactotrophs, mammosomatotrophs, and thyrotrophs. *Somatotrophs* secrete *growth hormone*, constitute about 50% of the cell population in the adenohypophysis, and are mainly present in the lateral wings of the anterior lobe.

Lactotrophs secrete *prolactin*, account for approximately 9% of adenohypophyseal cells, and are concentrated in the posterolateral areas of the anterior lobe. Mammosomatotrophs secrete both growth hormone and prolactin.

Thyrotrophs secrete thyrotropin, constitute about 5% of adenohypophyseal cells and are concentrated in the anteromedial areas of the pars distalis.

Corticotrophs synthesize pro-opiomelanocortin, which is cleaved into several proteolytic fragments, including corticotropin. Corticotrophs account for approximately 20% of cells in the adenohypophysis and are chiefly present in the midportion of the anterior lobe as well as the pars intermedia. In older individuals, some corticotrophs are also present in the adjacent neurohypophysis.

Gonadotrophs constitute approximately 10% of cells in the adenohypophysis, are distributed throughout the anterior lobe and pars tuberalis, and secrete both follicle-stimulating hormone and luteinizing hormone. Other, nonsecretory cell populations in the adenohypophysis include follicular and folliculostellate cells.

The *neurohypophysis* comprises the neural stalk, itself subdivided into the median eminence and the infundibular stem (also known as infundibulum), and the infundibular process (posterior lobe, pars nervosa or neural lobe). The neurohypophysis contains neuronal axons whose cell bodies are present in the supraoptic and paraventricular hypothalamic nuclei. Most of these axons terminate in the posterior lobe, with a minority of the axon terminals being located in the median eminence and the infundibulum. Antidiuretic hormone and oxytocin are synthesized in cell bodies of neurons in the supraoptic and paraventricular nuclei, are transported down the axons and secreted by exocytosis from axon terminals in response to nerve impulses. Pituicytes are glial cells supporting the axon terminals in the neurohypophysis.

The pituitary gland receives a rich blood supply, commensurate with its role as an endocrine organ. Its blood supply derives from paired branches of the superior and inferior hypophyseal arteries, which are branches of the internal carotid arteries. Branches of the superior hypophyseal arteries form the primary plexus of the *hypophyseal portal capillary system* in the median eminence and infundibulum, where they are apposed to numerous nerve terminals of nerve axons originating in the hypothalamus. Upon excitation, these neurons secrete several distinct releasing and inhibitory hormones into the portal system, which travel down the pituitary stalk in portal veins to reach the secondary plexus of the hypophyseal portal capillary system present in the adenohypophysis, and either stimulate or inhibit hormone secretion in a cell-specific manner. Branches of the inferior hypophyseal arteries directly supply the posterior lobe and anastomose with branches of the superior hypophyseal vessels. Blood from the adenohypophysis and neurohypophysis leaves the pituitary through several hypophyseal veins that drain into the cavernous sinuses.

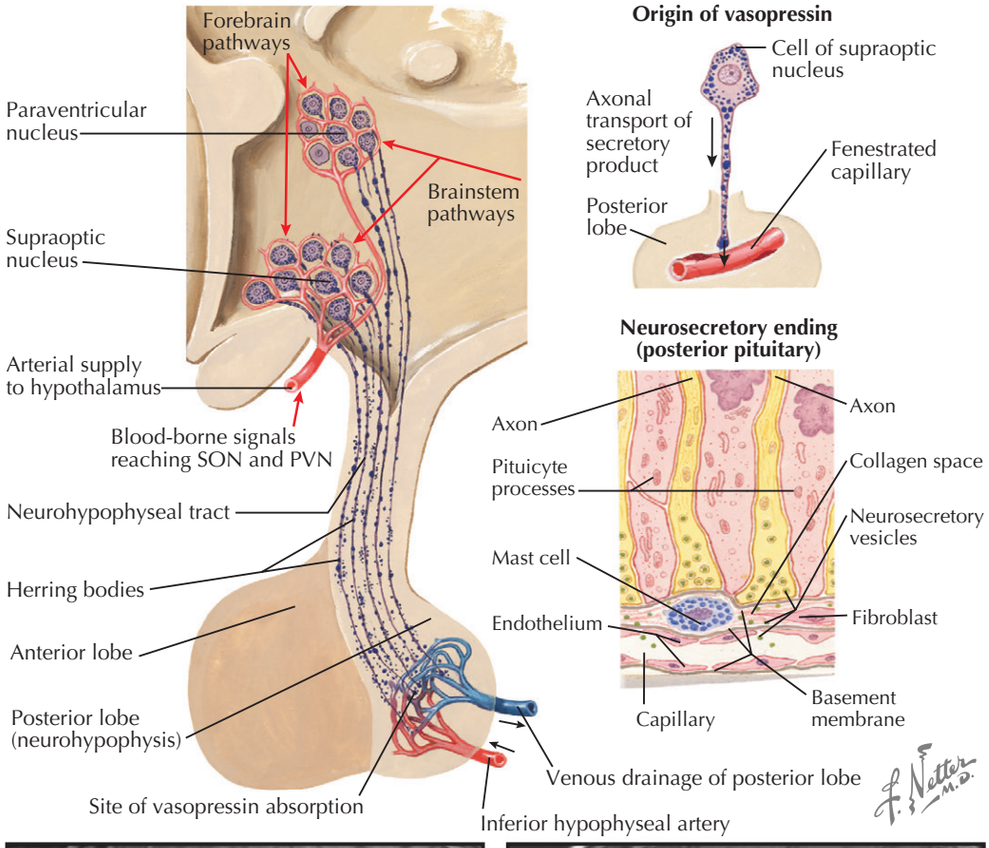
Posterior Pituitary Gland

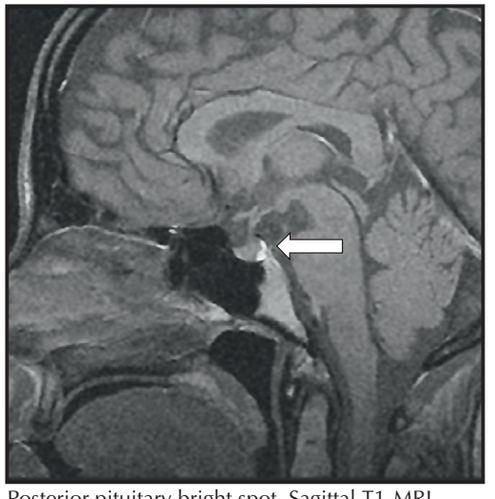
The *neurohypophysis*, including the neural stalk and the posterior pituitary lobe, is an extension of the hypothalamus. It is embryologically derived from neural ectoderm. During development, magnocellular neurons of the *supraoptic and paraventricular hypothalamic nuclei* send their axons inferiorly to form the neurohypophysis. These axons terminate in the posterior lobe of the pituitary. In addition, a smaller number of parvocellular neurons from the same nuclei send off shorter axons, which end in the median eminence or infundibular stem. *Pituicyte*s, which are glial cells, support these axon terminals. Two *nonapeptide hormones* are secreted from distinct axon terminals in the neurohypophysis, including *antidiuretic hormone (vasopressin) and oxytocin*. After secretion, these hormones enter neurohypophyseal capillaries and are carried via the inferior hypophyseal veins into the systemic circulation.

Oxytocin and antidiuretic hormone (vasopressin) are made by distinct populations of large (magnocellular) neurons in both the paraventricular (PVN) and supraoptic (SON) nuclei, which release the hormones from their axons in the neurohypophysis. The PVN also contains populations of smaller (parvicellular) neuroendocrine neurons that produce corticotropin-releasing hormone, thyrotropin-releasing hormone, or somatostatin, which are released into the hypothalamohypophyseal portal circulation. Some parvicellular neurons in the PVN also make either oxytocin or antidiuretic hormone, which are used as central neurotransmitters to control the autonomic nervous system. Oxytocin and antidiuretic hormone are coded by distinct genes, which code for precursor proteins that undergo posttranslational cleavage into the hormone, a neurophysin protein, and a carboxyterminal peptide called a copeptin. These are transported within secretory granules (vesicles), traveling along neuronal axons until they reach their respective axon terminals, where they are stored until secreted.

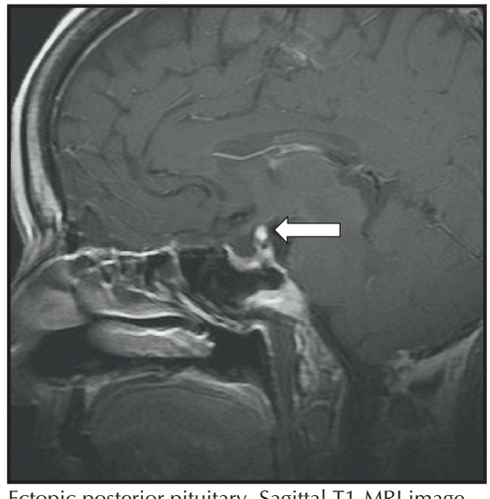
The presence of secretory granules within the posterior pituitary lobe gives rise to a bright signal on sagittal views of the pituitary on unenhanced, T1-weighted magnetic resonance images, termed the "posterior bright spot." This is present in 80% to 90% of healthy individuals. An ectopic posterior pituitary may be present at the base of the hypothalamus or the pituitary stalk in some individuals, who usually have intact posterior pituitary function. However, anterior pituitary hypoplasia and variable anterior pituitary hormone deficiencies are often present in these patients.

Release of antidiuretic hormone or oxytocin occurs via exocytosis in response to action potentials propagating along the respective axons. The release of antidiuretic hormone and oxytocin is regulated by specific neural inputs to the hypothalamic nuclei synthesizing these hormones, with glutamate representing a major stimulatory neurotransmitter and γ-aminobutyric acid being inhibitory. Both osmotic (increase in plasma osmolality, sensed by hypothalamic osmoreceptors) and nonosmotic (significant decrease in effective arterial blood volume, pain, nausea, certain medications) stimuli mediate antidiuretic hormone release. Once secreted, antidiuretic hormone leads to increased water permeability in the collecting ducts of the kidneys, resulting in water reabsorption and urine concentration. Other antidiuretic hormone effects include vasoconstriction, stimulation of glycogenolysis, and augmentation of corticotropin release from the anterior pituitary.





Posterior pituitary bright spot. Sagittal T1-MRI image showing hyperintensity (*arrow*) in the posterior aspect of the sella turcica.



Ectopic posterior pituitary. Sagittal T1-MRI image showing hyperintensity (*arrow*) along the posterior aspect of the pituitary infundibulum.

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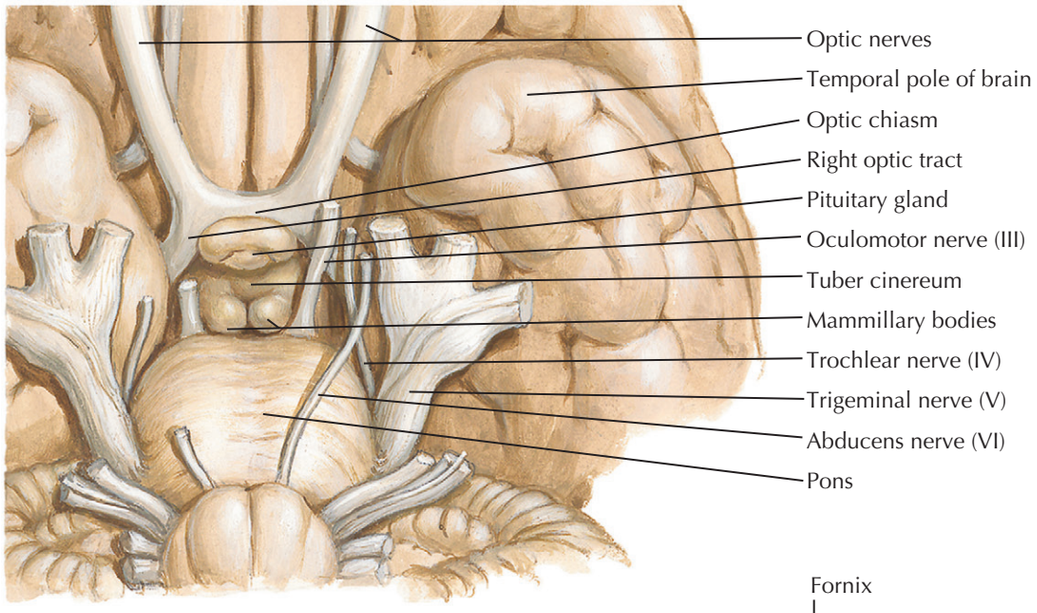
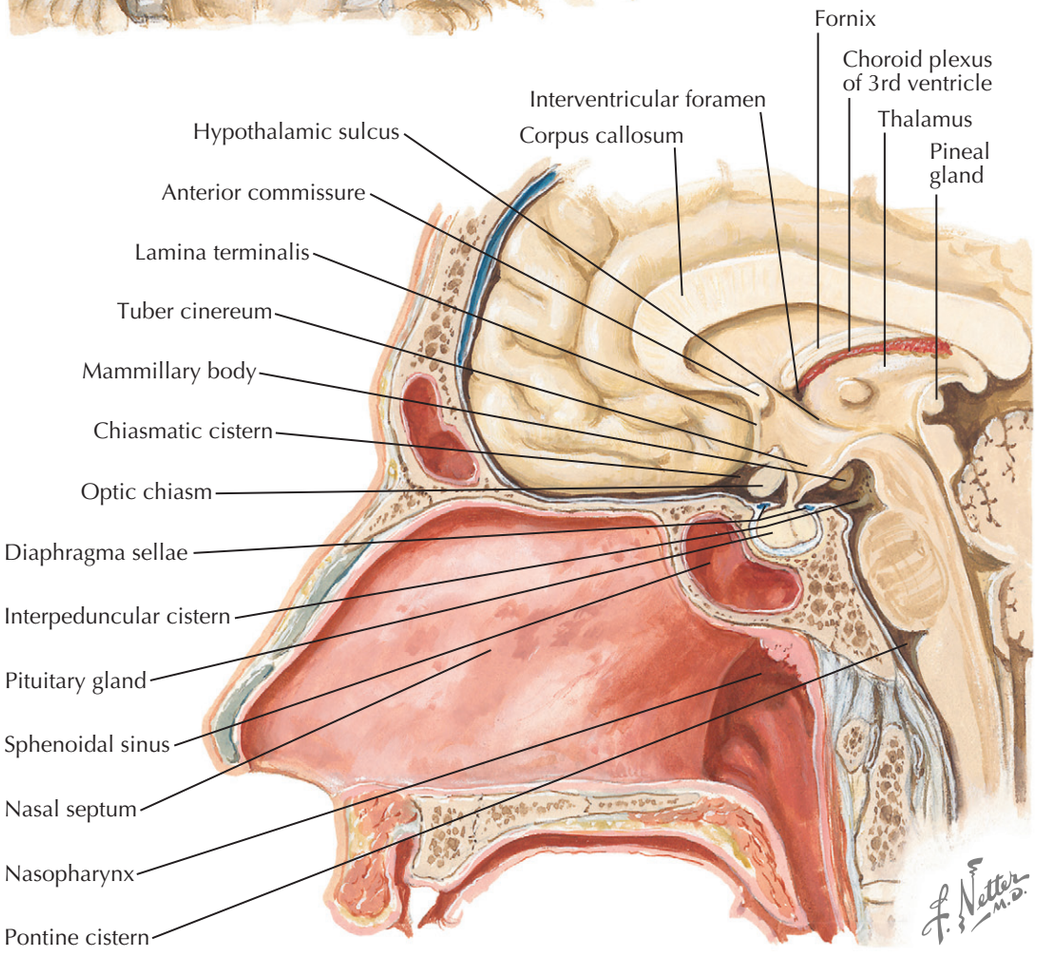
Failure of antidiuretic hormone synthesis and secretion is the cause of *central diabetes insipidus*, which is characterized by passage of large volumes of dilute urine, driving increased thirst. Dehydration and hypernatremia may generally occur if access to water is limited in untreated patients. Although diverse space-occupying lesions in the hypothalamus or within the sella may lead to central diabetes insipidus, it may also be noted that pituitary adenomas only rarely cause this condition preoperatively. The "posterior bright spot" is generally absent on magnetic resonance imaging in patients with central diabetes insipidus.

The *release of oxytocin* occurs in response to neural inputs during parturition, suckling, and intercourse. Animal data have suggested a role for oxytocin in propagation of labor and milk let-down during suckling. However, women who are deficient in oxytocin may experience normal labor and successful lactation, suggesting that the physiologic role of oxytocin in humans remains incompletely understood. A possible role of oxytocin in behavior is under study. There is also evidence in animals that oxytocin as a central neurotransmitter may promote maternal behavior and social interaction.

Anatomic Relationships of the Pituitary Gland





The pituitary gland resides in a depression (fossa) in the body of the sphenoid bone, termed the sella turcica. The tuberculum sellae forms the anterior wall of the sella, and the dorsum sellae forms its posterior wall. The pituitary is covered superiorly by a circular fold of dura mater, the diaphragma sellae. This sellar diaphragm is pierced by the pituitary stalk and the hypophyseal vessels. A fold of the arachnoid may herniate through the sellar diaphragm in some patients, thus extending the subarachnoid space within the sella (see MRI scan on the right in Plate 5-26 for an example). Chronic pulsatile pressure exerted by the cerebrospinal fluid may expand the sella, leading to the appearance of an enlarged, "*empty sella*," which may be associated with hypopituitarism in some patients.

The *optic chiasm* rests superiorly to the diaphragma sellae. Nerve fibers originating in the nasal portion of each retina cross at the chiasm to the contralateral side and join ipsilateral nerve fibers originating in the temporal portion of each retina, which do not cross at the chiasm, to form each optic tract. The anatomic relationship between the pituitary gland and the optic chiasm is clinically important, because mass lesions within the pituitary may compress either the chiasm or other portions of the optic apparatus, giving rise to a variety of visual field defects. Specific places where the arachnoid separates from the pia mater form cisterns filled with cerebrospinal fluid, including the *chiasmatic cistern* and the *interpeduncular cistern*. These spaces can be distorted by space-occupying sellar lesions growing superiorly from the pituitary.

The *hypothalamus* is located superiorly to the pituitary gland and is bounded between the *optic chiasm* anteriorly, the caudal border of the *mammillary bodies* posteriorly, and the hypothalamic sulcus superiorly. Distinct *hypothalamic nuclei* regulate anterior pituitary function through the synthesis of several stimulating hormones (growth hormone–releasing hormone, corticotropin-releasing hormone, thyrotropin-releasing hormone, and gonadotropin-releasing hormone) and inhibiting hormones (somatostatin and dopamine), released at neuronal axon terminals present in the *median eminence* and the *infundibulum*. These hormones are carried via the hypophyseal portal system to the adenohypophysis, where they regulate hormone secretion in a specific manner. The inter-relationships between the hypothalamus and the posterior pituitary are detailed in Plate 5-26. Large lesions arising above the sella may impinge on the hypothalamus, interfering with its functions.

The *cavernous sinuses* are located laterally to the pituitary gland, and receive blood from the pituitary via the hypophyseal veins. Each cavernous sinus contains several important structures, including the cavernous portion of the ipsilateral *internal carotid artery*, the *oculomotor, trochlear, and abducens nerves*, as well as the *first two divisions (ophthalmic and maxillary) of the trigeminal nerve*. Each of these nerves may be impinged upon by space-occupying lesions arising in the sella that extend into the cavernous sinus. Examples of such lesions include *meningiomas*, *chondrosarcomas* and *sellar metastases*. Characteristically, *pituitary adenomas* only rarely cause dysfunction of cranial nerves within the cavernous sinuses, with the notable exception of adenomas undergoing hemorrhagic necrosis (pituitary apoplexy).

The *circular sinus* lies between the pituitary gland and the underlying sphenoid bone in the sella, forming interconnections between the two cavernous sinuses. The thin *sellar floor* separates the pituitary gland from the underlying *sphenoid sinus*. The sellar floor can be expanded by slowly growing sellar masses, leading to remodeling of the sella, or eroded by sellar masses growing inferiorly. The close relationship between the sella, the sphenoid sinus, and the nasopharynx provides an important access route to pituitary surgeons. Using a *trans-sphenoidal* approach, many sellar masses can be resected with low morbidity.

Effects of Pituitary Mass Lesions on the Visual Apparatus

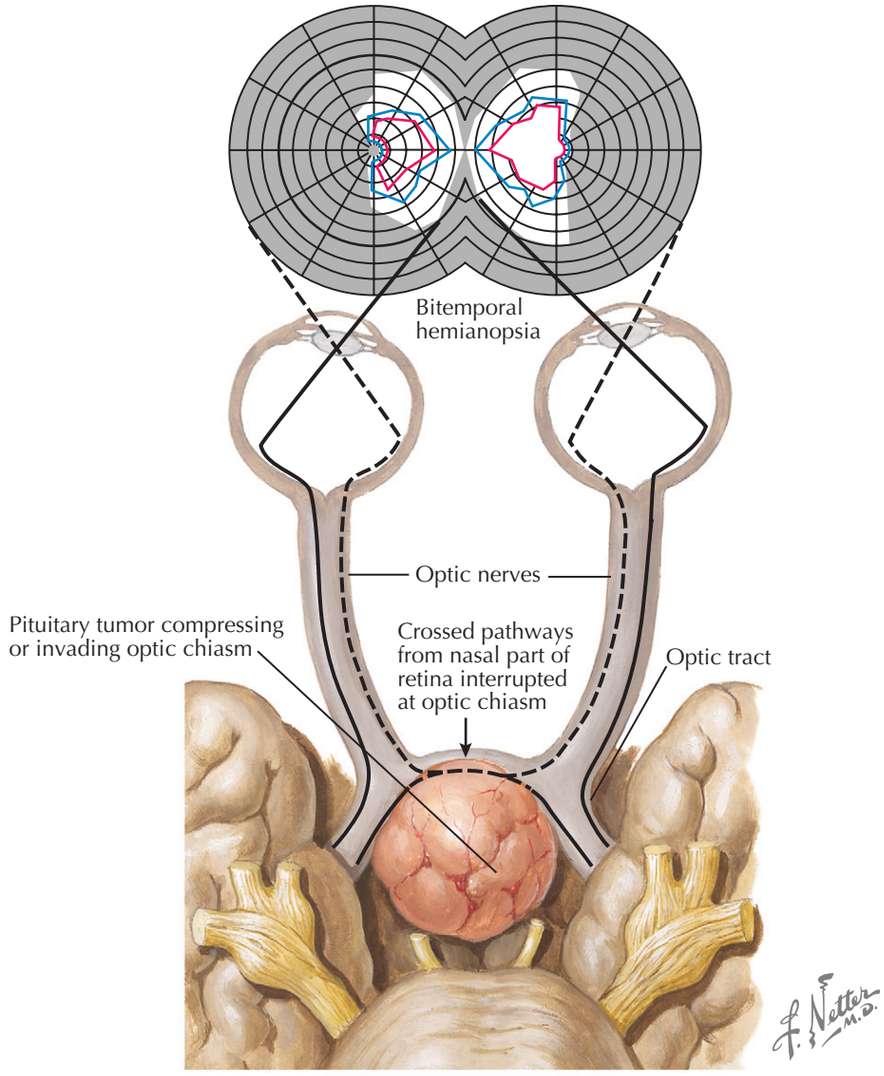
The close anatomic relationship between the pituitary and the optic apparatus, notably the optic chiasm, but also the *prechiasmatic optic nerves* and the *postchiasmatic optic tracts*, accounts for the frequent occurrence of visual deficits in patients with large pituitary mass lesions extending superiorly. At the optic chiasm, axons of the retinal ganglion cells that originate in the nasal portion of each retina cross to the contralateral side. In contrast, nerve fibers from the temporal portion of each retina remain on the ipsilateral side past the chiasm to form each optic tract, accompanied by nerve fibers crossing from the nasal portion of the contralateral retina.

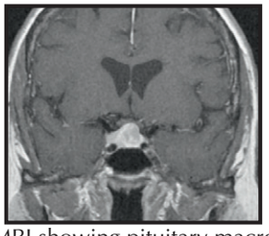
A variety of mass lesions may arise within the sella. In addition to *benign pituitary adenomas*, which account for approximately 90% of mass lesions in surgical series, there are a large number of pathologic sellar mass lesions. These include benign (*craniopharyngioma*, *meningioma*) and malignant (*chondrosarcoma*, *lymphoma*, *metastases*, or the exceedingly rare *primary pituitary carcinoma*) *neoplasms*, *cystic lesions* (Rathke's cleft cyst; arachnoid, dermoid, and epidermoid cyst), *vascular* pathologies (aneurysms, arteriovenous malformations), *inflammatory lesions* (primary or secondary hypophysitis), *infection*, *or pituitary hyperplasia*.

Mass lesions extending superiorly from the sella often impinge on the optic chiasm, which is generally located directly above the diaphragma sellae (in approximately 90% of individuals). *Early abnormalities* that occur as a result of chiasmatic compression include loss of color perception as a result of optic neuropathy, which can be documented using standard Ishihara chart testing, as well as variable loss of peripheral (temporal) field vision. Among patients with mass *lesions growing from the sella*, vision is generally lost first in either or both *superior temporal quadrants*. In contrast, mass lesions arising at the *base of the hypothalamus*, which compress the *optic chiasm from above*, may lead to early loss of vision in the *inferior temporal quadrants*.

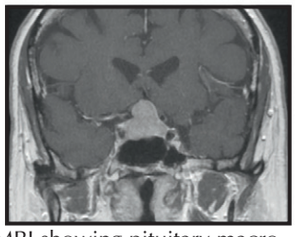
Compression of the *prechiasmatic optic nerves* may lead to *ipsilateral optic neuropathy*, giving rise to a central scotoma. Lesions that compress the *anterior portion of the chiasm* on one side may give rise to *ipsilateral optic neuropathy* (central scotoma) and *loss* of *peripheral vision in the contralateral superior temporal quadrant*, *a constellation termed "junctional scotoma."* More *posteriorly located lesions* may impinge upon one of the *optic tracts*, leading to *contralateral homonymous hemianopsia*.

Preliminary visual field testing may be conducted using bedside confrontation testing, but definitive evaluation of peripheral vision requires formal perimetry, using either an automated (Humphrey) or manual (Goldmann) method. *Primary optic atrophy* is present in cases of long-standing nerve fiber compression. *Papilledema* may rarely occur in patients with very large tumors extending toward the third ventricle, causing *obstructive hydrocephalus*. Consultation with an experienced neuro-ophthalmologist is advised for patients with mass lesions abutting or compressing the optic apparatus. Recovery of visual function occurs with relief of compression of the optic apparatus in most patients (approximately 70% to 75% of cases). However, the likelihood and extent of visual recovery are generally higher with shorter duration of nerve fiber compression. Thus early diagnosis and prompt decompression (generally via surgery, but also medical therapy in patients with prolactin-secreting adenomas) are very important to optimize visual outcomes in these patients.

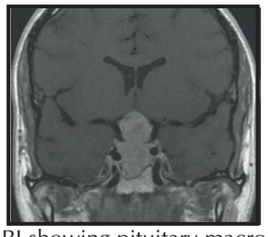




MRI showing pituitary macroadenoma with suprasellar and right cavernous sinus extension. Optic chiasm is raised slightly, but visual fields are normal.



MRI showing pituitary macroadenoma with suprasellar and bilateral cavernous sinus extension. The optic chiasm is compressed, causing bitemporal superior quadrant vision loss.



MRI showing pituitary macroadenoma with suprasellar, bilateral cavernous, and sphenoid extensions. The optic chiasm is markedly compressed, causing complete bitemporal hemianopsia.

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Anterior Pituitary Hormone Deficiencies

There are six types of secretory cells present in the adenohypophysis, including somatotrophs (synthesizing growth hormone), lactotrophs (producing prolactin), mammosomatotrophs (synthesizing both growth hormone and prolactin), thyrotrophs (producing thyrotropin), corticotrophs (synthesizing corticotropin), and gonadotrophs (synthesizing both follicle-stimulating hormone and luteinizing hormone). The synthesis and release of these hormones is well orchestrated under the influence of hypothalamic hormones (most of which are stimulatory and some of which are inhibitory) as well as systemic (endocrine) negative feedback mechanisms, aimed at maintaining homeostatic control.

A wide variety of conditions may cause dysfunction of the hypothalamus or pituitary, leading to selective or universal, partial or complete, acute or chronic loss of adenohypophyseal hormone secretion (anterior hypopituitarism). Any space-occupying lesion impinging on the anterior pituitary, stalk, or hypothalamus may lead to hypopituitarism. In adults, the most common mass lesion in the area of the sella is a benign pituitary adenoma. However, many other neoplasms (including craniopharyngioma, meningioma, chordoma, metastases, or lymphoma), cystic lesions (including Rathke's cleft cyst or arachnoid cyst), infiltrative (hemochromatosis), inflammatory (hypophysitis, sarcoidosis) or infectious disorders, aneurysm, infarction, primary empty sella, radiation therapy, trauma, surgery, or genetic conditions may all cause hypopituitarism. *The underlying cause of hypopituitarism may influence the pattern of hormone loss.* Gonadotropin deficiency and growth hormone deficiency tend to occur first in patients with pituitary adenomas or those who have received radiation therapy to the hypothalamus and sella, while thyrotropin and corticotropin function tend to be spared until later in the course of these conditions. In contrast, corticotropin and thyrotropin deficiency frequently occur first in patients with lymphocytic hypophysitis.

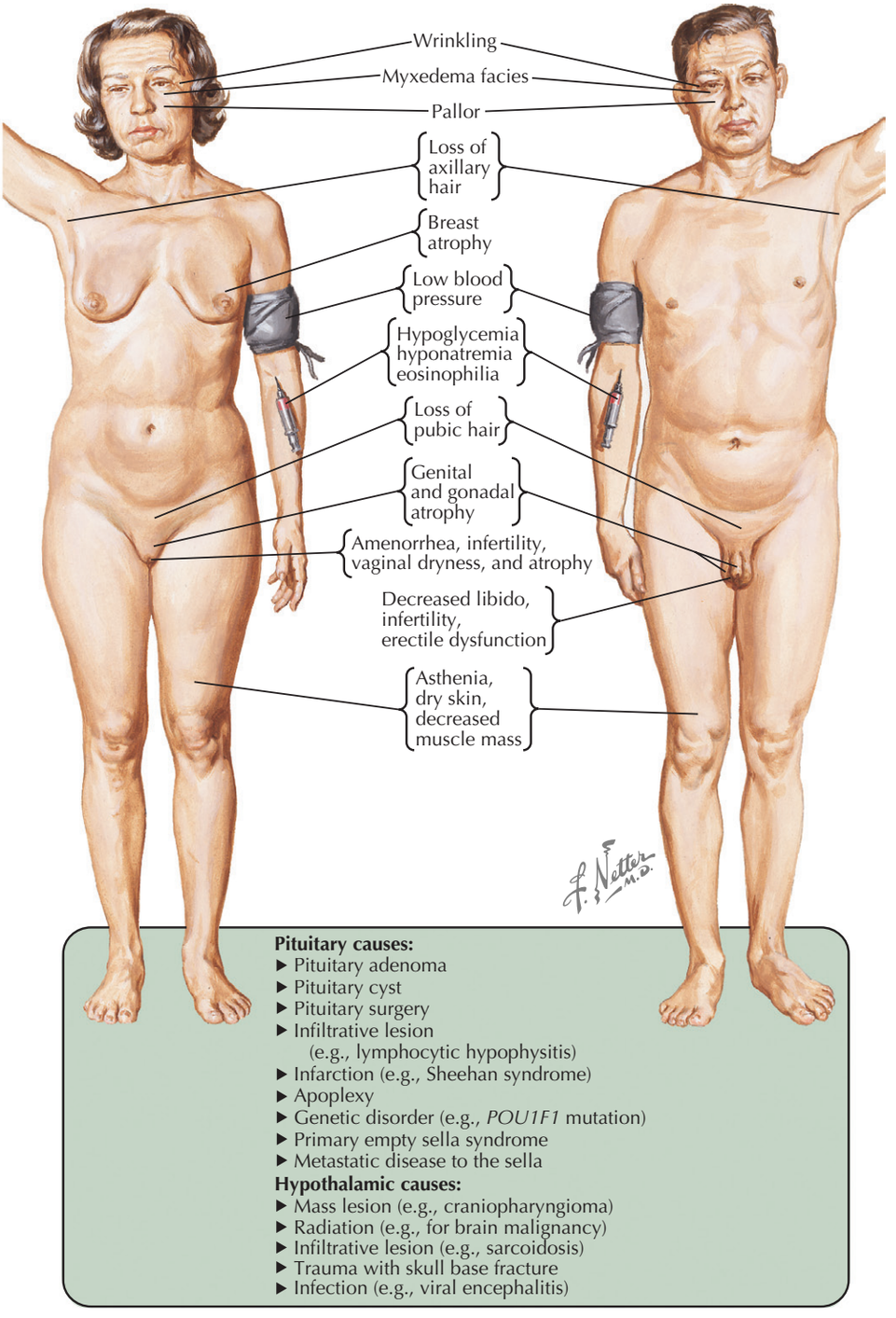
Gonadotropin deficiency presents as lack of pubertal development in adolescents, who generally develop a eunuchoid habitus. If the onset of gonadotropin deficiency occurs in adulthood, patients present with loss of gonadal function, including oligomenorrhea or amenorrhea in women, and erectile dysfunction in men. In addition, low libido and infertility may occur in patients of both genders. Patients may also experience loss of body hair (particularly in the presence of concurrent corticotropin deficiency), fine facial wrinkling, loss of bone calcium leading to increased fracture risk, and hot flashes. Women may also experience breast atrophy, vaginal dryness, and dyspareunia. Men may note loss of stamina, increased body fat, decreased lean body mass, and decreased testicular size. *Prolactin deficiency* may result in failure of lactation postpartum.

Growth hormone deficiency leads to decreased linear growth if it occurs in childhood or adolescence. In adulthood, loss of growth hormone secretion is more subtle, but may be associated with fatigue, decreased exercise capacity and muscle strength, abnormal body composition (decreased lean body mass, loss of bone calcium, and gain in body fat), dyslipidemia, insulin resistance, increased cardiovascular risk, and poor quality of life.

Thyrotropin deficiency leads to central hypothyroidism, including fatigue, lethargy, weight gain, bradycardia, dry skin, myxedema, anemia, constipation, muscle aches, decreased relaxation phase of Achilles reflexes, and cold intolerance.

Corticotropin deficiency leads to central hypoadrenalism, which is *potentially the most life threatening of all pituitary hormone deficiencies*. These patients often exhibit fatigue, weight loss, nausea and vomiting, orthostatic hypotension and dizziness, and diffuse arthralgias. Notable is the lack of cutaneous and mucosal hyperpigmentation, in contrast to patients with primary adrenal insufficiency (Addison disease). These patients may also present acutely with shock unresponsive to volume expansion and pressors. Eosinophilia and hyponatremia may be present. However, hyperkalemia is absent, because aldosterone deficiency does not occur.

Once diagnosed, target organ hormone replacement therapies are instituted. In particular, glucocorticoid replacement may prove lifesaving in patients presenting in adrenal crisis. Levothyroxine is used to replace central hypothyroidism, and sex steroid replacement is used to replace patients with central hypogonadism. However, if fertility is of interest, gonadotropin therapy is used, including human chorionic gonadotropin and follicle-stimulating hormone. Growth hormone replacement may also be considered. Despite seemingly adequate replacement therapies, patients *with hypopituitarism* are at increased risk of cardiovascular mortality, the underlying reasons still being a matter of considerable debate.



Severe Anterior Pituitary Hormone Deficiencies (Panhypopituitarism)

Extensive space-occupying lesions within the sella or hypothalamus may lead to complete loss of anterior pituitary function. Of note, the term *panhypopituitarism* is indicative of complete loss of both anterior and posterior lobe function.

Pituitary macroadenomas, which, by definition, exceed 10 mm in greatest diameter, may cause multiple anterior pituitary hormone deficiencies but only rarely cause diabetes insipidus preoperatively. In contrast, large suprasellar tumors that impinge on the hypothalamus, stalk, and pituitary, including craniopharyngiomas, may disrupt both anterior and posterior lobe function. Similarly, pituitary surgery or trauma may lead to panhypopituitarism.

Gonadotropin deficiency leads to lack of pubertal development, if it occurs before adolescence. Of note, a eunuchoid habitus is unlikely to develop in young patients with concurrent growth hormone deficiency. In adults of both genders, severe gonadotropin deficiency leads to central hypogonadism. Severe gonadotropin deficiency of long standing leads to gonadal atrophy, including decreased size of the ovaries in women and testes in men. In addition, there is a decrease in size of the uterus, vagina, and breasts in women, including thinning of the endometrium and vaginal epithelial atrophy. In men, there is a decrease in size of the penis and prostate.

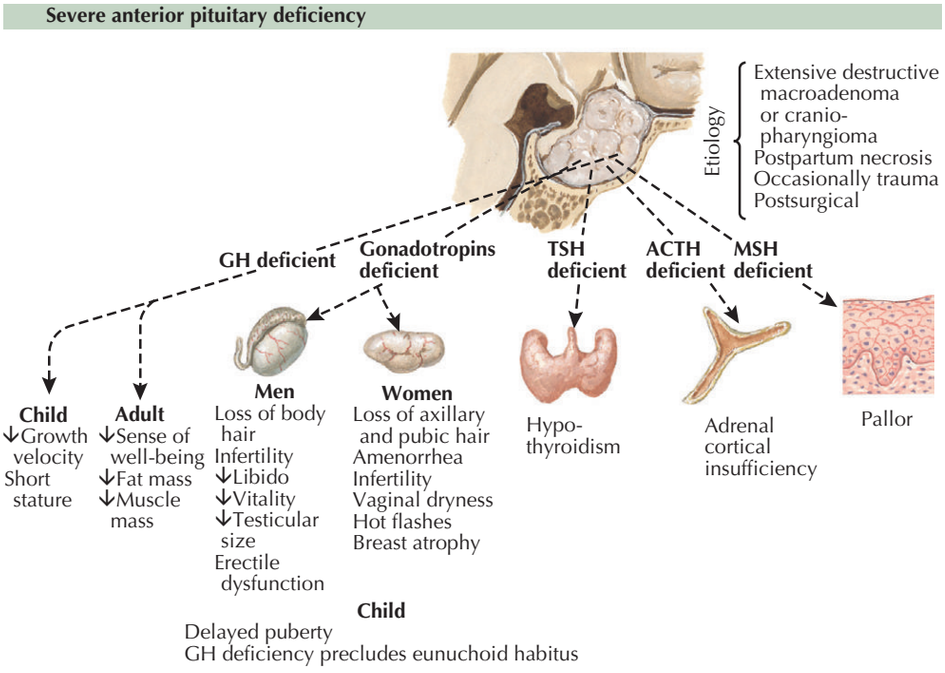
Thyrotropin deficiency leads to central hypothyroidism. The thyroid gland becomes atrophic, including thinning of the follicular epithelium. Corticotropin deficiency leads to *central hypoadrenalism*, involving loss of cortisol and adrenal androgen secretion. Portions of the adrenal cortex, including the zona fasciculata and the zona reticularis, become atrophic in these patients. In contrast, the zona glomerulosa remains structurally intact, and aldosterone secretion is unaffected. These patients may often exhibit pallor, occurring as a result of anemia and decreased skin pigmentation resulting from lack of corticotropin action on skin melanocytes.

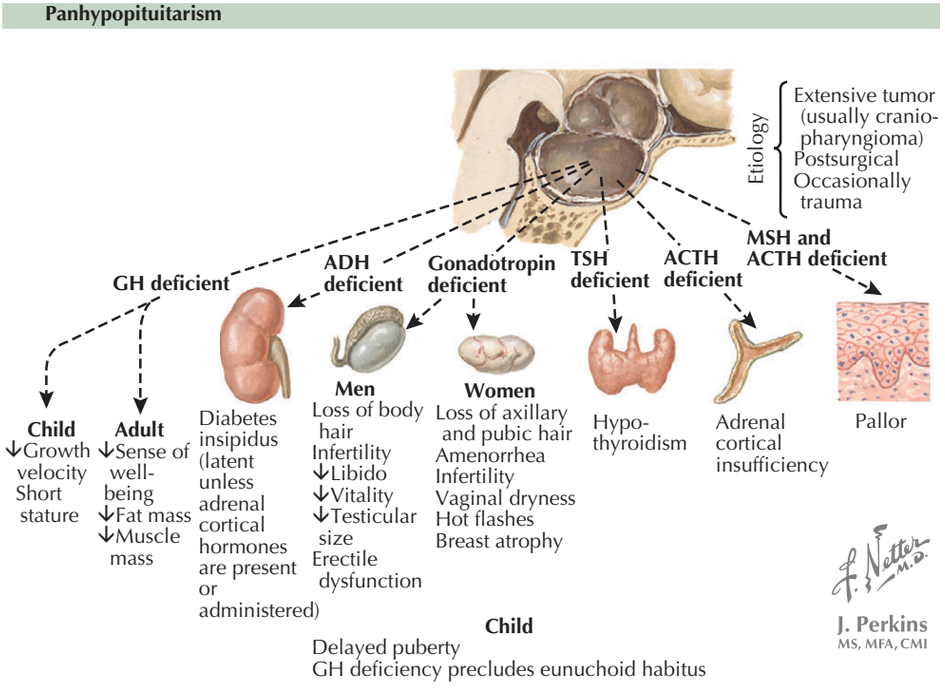
Growth hormone deficiency leads to a decrease in growth velocity in children or adolescents, resulting in short stature if untreated. Hypoglycemia may occur in childhood and appears to be a consequence of growth hormone and glucocorticoid deficiency. Growth hormone–deficient adults may exhibit low exercise capacity, abnormal body composition (decrease in lean body mass and bone mass and increase in fat mass), dyslipidemia, insulin resistance, increased cardiovascular risk, and impaired quality of life. Prolactin deficiency leads to failure of lactation in women and has no discernible effects in men.

Lack of antidiuretic hormone secretion leads to central diabetes insipidus. The presence of diabetes insipidus signifies extensive damage to the hypothalamus or stalk. Of note, disruption of the pituitary stalk below the diaphragma sellae is less likely to cause diabetes insipidus than injury to the stalk at the level of the median eminence. In cases where the stalk is damaged distally, some antidiuretic hormone–secreting axon terminals are spared and may secrete sufficient antidiuretic hormone to prevent the development of central diabetes insipidus. It may also be noted that central diabetes insipidus may be clinically latent in patients with corticotropin deficiency because glucocorticoids have an important role in increasing free water clearance in the kidneys. In these patients, glucocorticoid replacement may precipitate the clinical onset of central diabetes insipidus. Lack of oxytocin secretion leads to no discernible symptoms or deficits in humans.

Once clinically suspected, the presence of pituitary hormone deficiencies can be established through hormone testing. Assays for systemic levels of target gland hormones (morning cortisol, free thyroxine, and testosterone) are most helpful in the diagnosis of hypopituitarism. In the case of some hormones, including growth hormone and cortisol, stimulation testing is used to evaluate secretory reserve. Water deprivation testing is used to diagnose central diabetes insipidus.

Replacement therapies are available for all pituitary hormone deficiencies except prolactin and oxytocin. The respective target gland hormone is administered in patients with central hypoadrenalism (hydrocortisone or prednisone) and central hypothyroidism (levothyroxine). Sex steroid replacement (testosterone in men and estrogen-progestin in women) is generally advised, if not contraindicated. If fertility is of immediate interest, gonadotropin therapy is recommended in patients of both genders. Growth hormone replacement is advised in children, if not contraindicated. Although not essential for life, growth hormone replacement in adults is available in the United States and several other countries and may improve exercise capacity, body composition, several cardiovascular risk factors, and overall quality of life. Desmopressin, an analog of antidiuretic hormone that is devoid of vasopressor activity, is recommended in patients with central diabetes insipidus.





Postpartum Pituitary Infarction (Sheehan Syndrome)

In 1937, Sheehan first described the development of pituitary infarction in the setting of hemorrhagic shock occurring after delivery. This entity is much less commonly seen in developed countries today, likely as a result of modern advances in obstetric care.

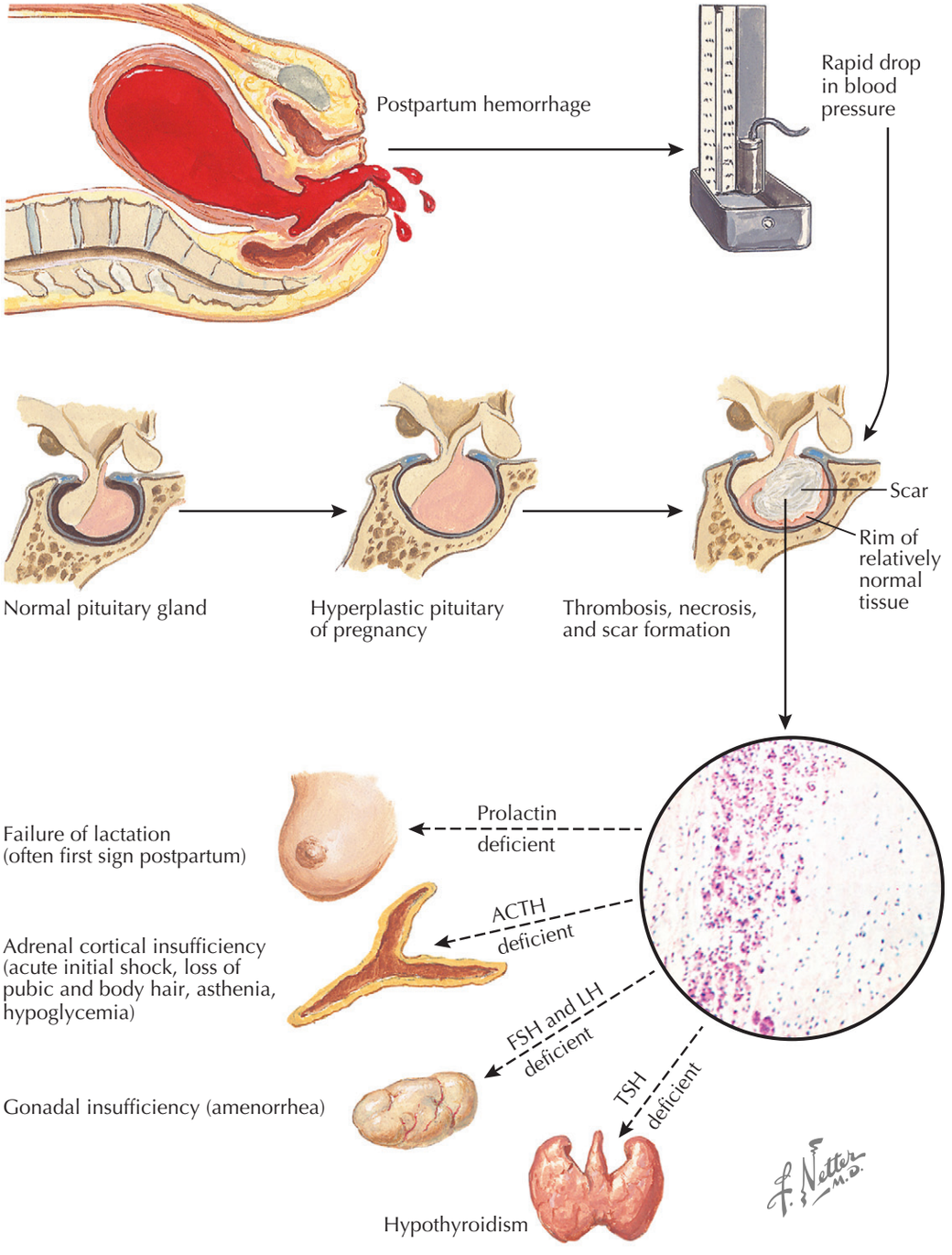
To understand the development of postpartum pituitary infarction, one has to consider that the pituitary gland becomes *hyperplastic* (approximately doubling in mass) *during pregnancy* as a result of *progressive lactotroph hyperplasia* occurring until term. Because there is no concurrent increase in blood supply to the pituitary, lactotroph hyperplasia makes the *gland more vulnerable to vascular insults* during pregnancy and *the peripartum* period. To highlight the important role of pituitary hyperplasia in the pathogenesis of infarction, it may be noted that pituitary infarction is very rare in nongravid patients in shock. The precise role of vascular spasm, thrombosis, and vascular compression as causative factors in the pathogenesis of Sheehan syndrome is still debated, but the condition ultimately involves infarction of the anterior pituitary lobe as a result of severe decrease in blood flow through the gland.

It may also be noted that the *anterior lobe* of the pituitary is *more vulnerable* to ischemia than the posterior lobe because the former receives blood supply through a low-pressure portal system. In contrast, the posterior pituitary receives direct arterial blood supply through the inferior hypophyseal arteries. As a consequence, the pars tuberalis and the posterior pituitary lobe are usually spared in these patients, who generally do not develop central diabetes insipidus.

Infarction of the anterior pituitary lobe leads to a gradual decrease in the size of the pituitary gland, which is partly replaced by fibrous scar tissue. On magnetic resonance imaging, there is a gradual decrease in the size of the pituitary gland, often culminating in the development of an "empty sella."

Anterior hypopituitarism of varying severity occurs in patients with Sheehan syndrome, depending on the extent of anterior lobe infarction. Loss of 90% of adenohypophyseal cells frequently leads to life-threatening pituitary failure, whereas loss of 50% to 70 % of anterior pituitary cells generally leads to partial hypopituitarism. Central hypoadrenalism may result in shock that is refractory to volume expansion and vasopressor administration. If loss of pituitary function is partial and/or less severe, initial symptoms may be more subtle, including failure to lactate and involution of breasts, followed by postpartum amenorrhea. Other symptoms may include fatigue, weight loss, lack of appetite, nausea, dizziness, and loss of axillary and pubic hair.

Sheehan syndrome should be *considered in women with severe postpartum blood loss requiring blood transfusion*.

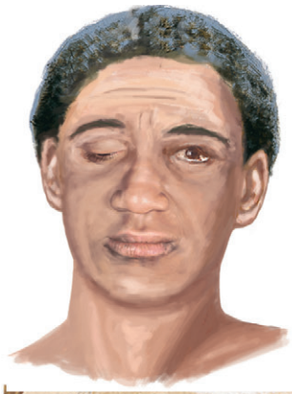


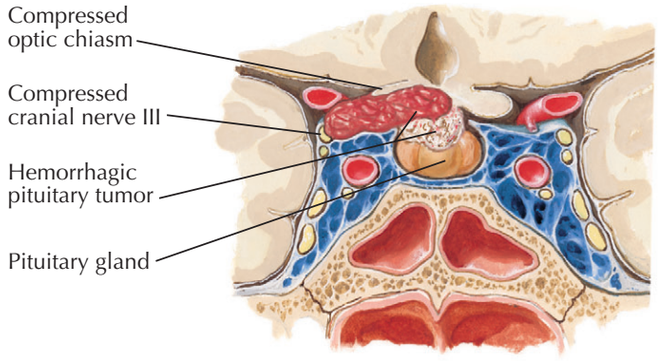
Pituitary insufficiency of variable degree usually *without* diabetes insipidus

ACTH, corticotropin; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyrotropin.

Additional risk factors include type 1 diabetes mellitus and sickle cell disease. In developed countries, *lymphocytic hypophysitis*, occurring in the third trimester of pregnancy or the postpartum period, has become more common than Sheehan syndrome as a cause of new onset hypopituitarism in pregnancy and the puerperium.

Once suspected, the diagnosis involves assays of systemic levels of target gland hormones, including morning serum cortisol, free thyroxine, estradiol, and gonadotropins. Serum prolactin levels may be very low in these patients. Stimulation testing may be needed to examine adrenocortical reserve and is essential in order to evaluate growth hormone secretion. Standard replacement therapies for pituitary hormone deficiencies are advised. In particular, prompt glucocorticoid replacement can be lifesaving. However, recovery of pituitary function is very uncommon.





Pituitary Apoplexy

Pituitary apoplexy denotes the presence of hemorrhagic necrosis of the pituitary, which generally occurs within a pituitary macroadenoma. In some cases, hemorrhage may occur within a cystic lesion (including Rathke's cleft cyst). Rarely, pituitary apoplexy may occur as a result of hemorrhage within the pituitary gland in the absence of an adenoma or cyst. Pituitary apoplexy is a *rare* condition. In contrast, asymptomatic hemorrhage within a pituitary adenoma is not uncommon (occurring in approximately 15% of patients with pituitary adenomas).

Patients with pituitary apoplexy present with severe headache of acute onset, which is typically considered as the *worst headache ever* experienced. Nausea and vomiting are very common. The rapid expansion of intrasellar contents frequently leads to compression of the optic chiasm, causing *visual field defects*. Lateral expansion resulting in compression of the nerves coursing through the cavernous sinuses (including the third, fourth, fifth, and sixth cranial nerves), frequently leads to *diplopia*, *ptosis*, *facial pain*, *or numbness*. Increased intracranial pressure may occur, leading to impairment in the level of consciousness. Interference with hypothalamic function may lead to manifestations of sympathetic nervous system dysfunction, including arrhythmias or disordered breathing.

In addition, some of the blood may enter the subarachnoid space, leading to meningeal irritation. Fever and neck stiffness may thus occur. Analysis of the cerebrospinal fluid may reveal the presence of red cells and increased protein content. It is therefore apparent that pituitary apoplexy should be *considered in the differential diagnosis of patients with suspected subarachnoid hemorrhage* or meningitis.

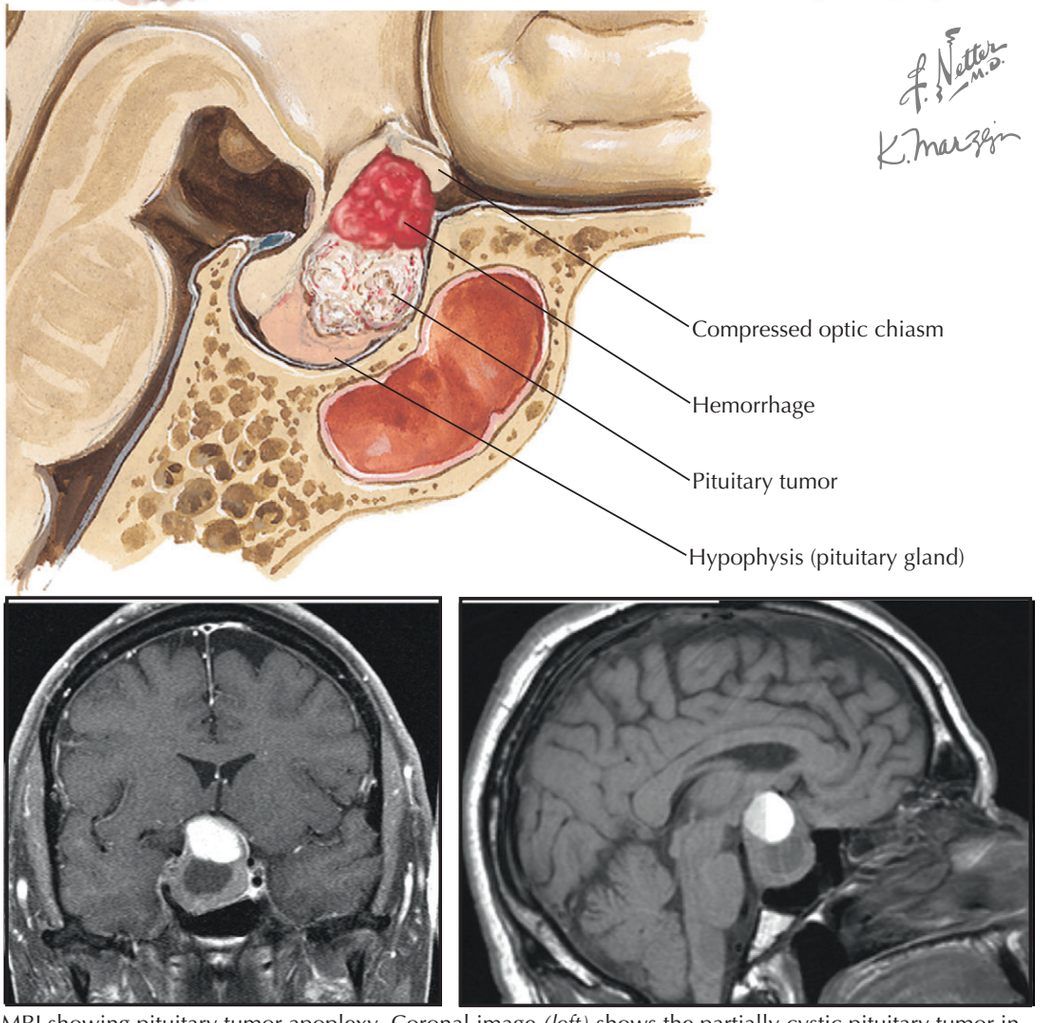
Life-threatening pituitary failure may occur as a result of central hypoadrenalism (adrenal crisis). Anterior hypopituitarism has been reported in up to 90% of patients with pituitary apoplexy. In contrast, central diabetes insipidus is uncommon.

Pituitary apoplexy is often spontaneous and often occurs at presentation of a pituitary adenoma. Identified risk factors for the development of pituitary apoplexy include trauma, anticoagulant use (including heparin or warfarin), coagulation disorders, and administration of dopamine agonists (including bromocriptine or cabergoline) or hypothalamic-releasing hormones.

Magnetic resonance imaging typically reveals a focus of hyperintensity (on noncontrast T1-weighted images) within a sellar mass. A fluid-fluid level may also be evident. Impingement on the optic chiasm or the cavernous sinuses is frequently present. Laboratory testing usually reveals evidence of hypopituitarism.

Pituitary apoplexy is a medical and neurosurgical emergency. These patients should be hospitalized and receive at minimum a stress dose glucocorticoid coverage to prevent the development of adrenal crisis. Of note, pharmacologic doses of glucocorticoids are often administered to minimize acute pressure effects from the hemorrhagic sellar mass on neighboring structures.

Patients with impaired level of consciousness or other evidence of increased intracranial pressure, visual field defects, diplopia, or ptosis should be considered for early (within 1 week) neurosurgical decompression, generally performed via the trans-sphenoidal route. Early pituitary surgery is associated with more complete recovery of visual field deficits than observation. In contrast, patients who maintain a normal level of consciousness and show no evidence of increased intracranial pressure, visual field defects, or ophthalmoplegia may be observed. These patients may be considered for pituitary surgery if the sellar mass fails to regress considerably after the hemorrhage is reabsorbed. Pituitary function needs to be monitored and hormone replacement therapies advised as required. Hypopituitarism is often permanent, regardless of whether surgery is performed.



MRI showing pituitary tumor apoplexy. Coronal image *(left)* shows the partially cystic pituitary tumor in the sella with the hemorrhagic component extending above the sella. Sagittal image *(right)* shows fluid-fluid level within the area of recent hemorrhage.

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Thalamic Anatomy and Pathology

Thalamic Anatomy

Thalamic Anatomy

The thalamus, along with the hypothalamus and subthalamus, form the diencephalon. Anatomically, the thalamus sits above the hypothalamic sulcus in the third ventricle and consists of an egg-shaped structure, one on each side of the brain, connected by a bridge in the middle, the massa intermedia. The thalamus is divided by a white matter sheet known as the internal medullary lamina, into the anterior, medial, and lateral groups of relay nuclei. The lateral group in turn is divided into a ventral tier of nuclei and the lateral nuclei proper. The relay nuclei each projects to a specific territory in the cerebral cortex, and in turn neurons in layer VI of each neocortical area project back to the same specific thalamic relay nucleus. The relay nuclei typically innervate layer IV of the cerebral cortex and provide most of the sensory information to the cerebral cortex.

In addition, there are several cell groups along the midline and embedded in the internal medullary lamina (the intralaminar nuclei). These nuclei send projections more diffusely in the cerebral cortex, with projections favoring layer V, and some project to the striatum as well. They are sometimes viewed as having a more generalized arousal function.

By contrast, the reticular nucleus sits like a thin sheet along the surface of the thalamus. While nearly all of the other thalamic neurons use the excitatory neurotransmitter glutamate, reticular neurons all use GABA and are inhibitory. They sample input both from the cerebral cortex and from the relay nuclei and send inhibitory axons to the relay nuclei, which put the relay neurons into a state where they burst rhythmically but do not transmit sensory information. This bursting behavior underlies the appearance of waxing and waning runs of rhythmic waves in the 12-14 Hz range in the EEG, called "sleep spindles," as an individual enters slow-wave sleep. It is also thought to be involved in causing the characteristic 3-Hz "spike-and-wave" pattern of EEG seen during "absence" seizures, in which subjects, usually children, lose contact with the external world for brief intervals, during which they may stare and smack their lips. The reticular nucleus is thought to be important in directing attention to discrete sensory stimuli and inhibiting competing stimuli.

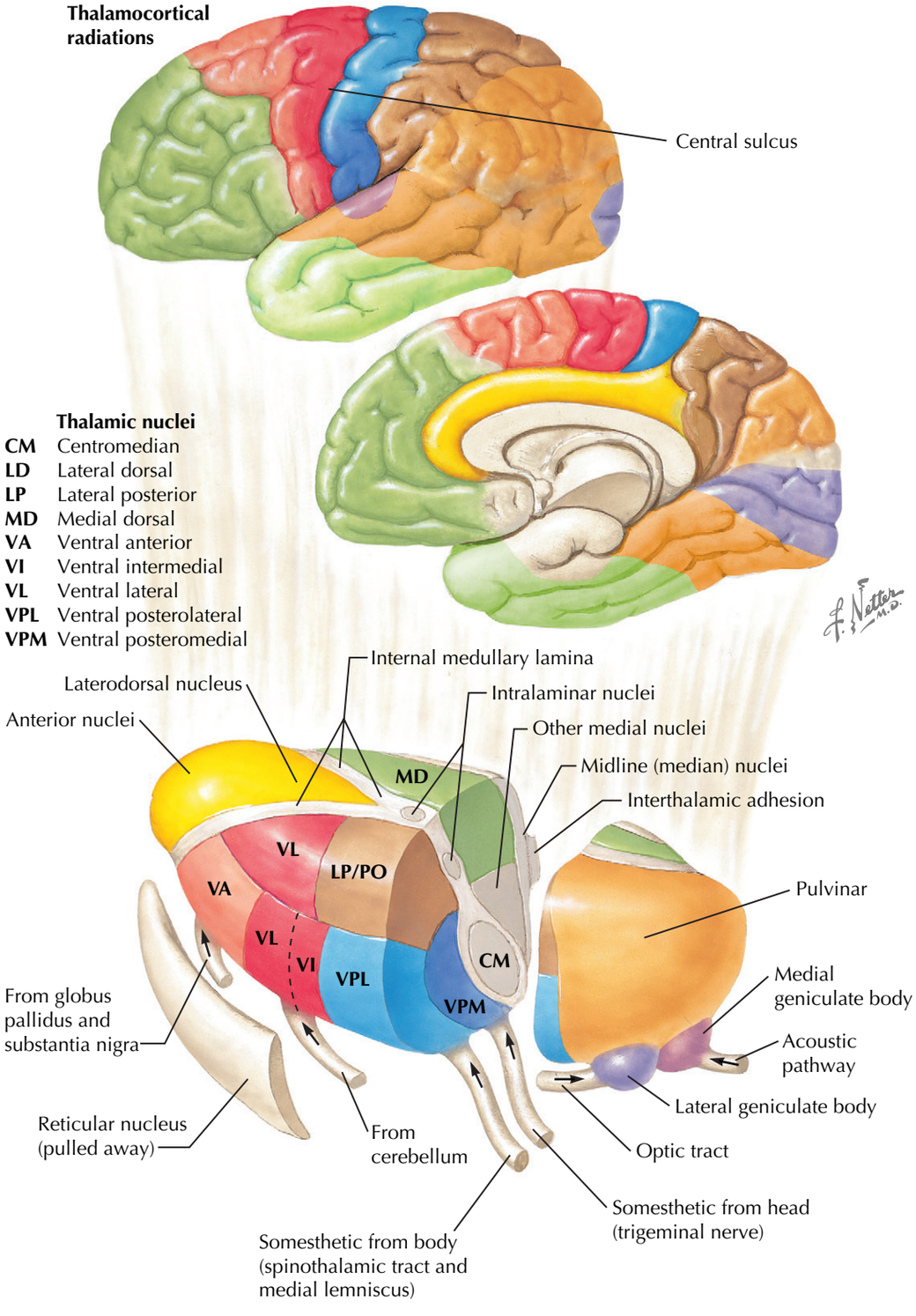
Among the relay nuclei, the largest component of the anterior group is the *anterior nucleus*. The most caudal part of the anterior group is called the *laterodorsal nucleus*. These nuclei send axons mainly to the cingulate gyrus.

The medial group is represented by a single nucleus, the *mediodorsal nucleus* (MD). MD provides input to the medial and lateral surfaces of the frontal lobe, as well as to much of the temporal lobe.

The lateral group is much more complicated. The ventral tier consists of a series of nuclei related to regions of the motor and sensory cortices. The *ventral anterior nucleus* (VA) receives input from the globus pallidus internal segment and the substantia nigra pars reticulata, concerned with initiation of movement, and projects to the premotor cortex. The *ventrolateral nucleus* (VL) is the terminus of the cerebellar output (the dentatorubrothalamic tract), which carries information about body movement and innervates the primary motor cortex. The *ventroposterior lateral nucleus* (VPL) receives sensory input from the spinal cord for the arms, legs, and trunk, and the *ventroposterior medial nucleus* (VPM) serves the same function for the face. They project topographically to the primary somatosensory cortex. Just medial to VPM is the *ventroposteromedial parvicellular nucl*eus, a small area (not pictured here) that receives taste information from the tongue and projects to a gustatory region in the anterior insular cortex. Most caudally in the ventral tier are the *medial geniculate nucleus*, which conveys auditory information from the inferior colliculus to the primary auditory cortex, and the *lateral geniculate nucleus*, which relays visual information from the optic tract to the primary visual cortex.

The dorsal tier of the lateral group includes a series of nuclei that project to progressively more posterior

Thalamic Nuclei and Thalamocortical Radiations



Thalamic Anatomy and Pathology *(Continued)*

parts of the parietal lobe temporal lobe. The *lateroposterior nucleus* (LP) and *posterior nucleus* (PO) send axons to the region just caudal to the primary somatosensory cortex. The *pulvinar nucleus* sends axons to the posterior parietal lobe and the lateral surface of the temporal lobe. The neurons in these cell groups relay integrative information that relates the visual and auditory map of the world to the personal space of the individual.

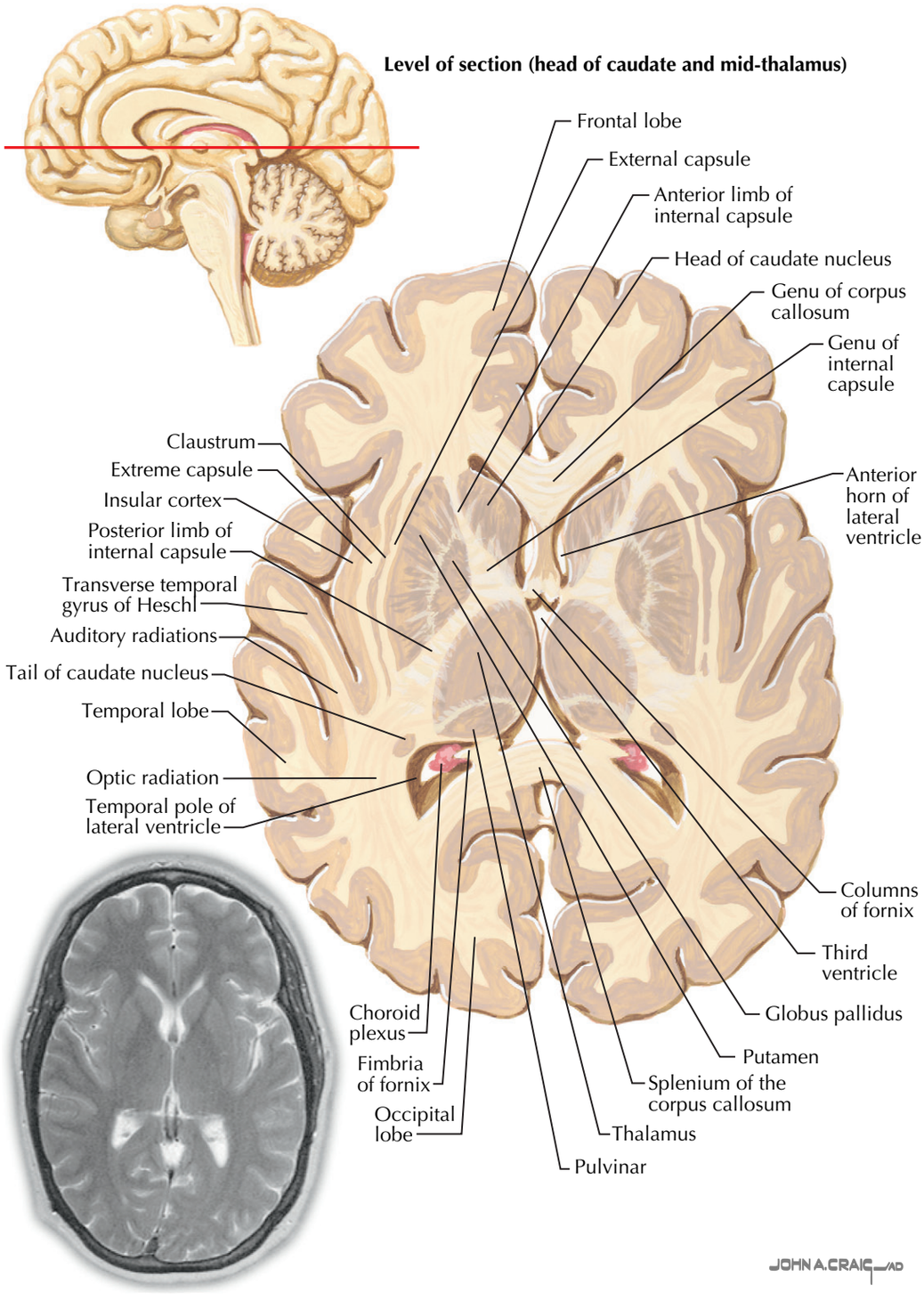
THALAMIC PATHOLOGY

The most common neurologic disorders involving the thalamus are small infarcts, sometimes called "lacunar infarcts." These are believed to be due to the occlusion of small thalamic perforating arteries that arise from the posterior cerebral and posterior communicating arteries. The infarctions are often as small as a single nucleus, causing sensory loss on the contralateral body or face if the VPL or VPM nuclei are damaged; memory impairment if the MD and anterior nuclei are involved; or motor weakness if the VL or VA nuclei are injured. The lateral geniculate nucleus may be involved by an occlusion of the anterior choroidal artery, resulting in homonymous hemianopsia. After a pure sensory thalamic infarct involving VPL or VPM, some patients go on to develop pain in the deprived region, known as the Dejerine-Roussy syndrome.

The thalamic perforating arteries may also hemorrhage. This often produces a thalamic syndrome similar to ischemic infarction. However, as the hemorrhage grows it may press downward on the midbrain, causing impairment of consciousness or a cluster of eye movement problems known as Parinaud syndrome. In Parinaud syndrome there is loss of pupillary light reflexes, upgaze, and vergence eye movements due to pressure on the pretectal area and dorsal midbrain.

The thalamus is also characteristically involved in fatal familial insomnia, a prion disorder that causes rapid onset of dementia, ataxia, and brainstem dysfunction, including almost complete inability to sleep in some cases. However, the pathology involves the cerebral cortex and brainstem as well, and it is difficult to determine how much of the symptomatology is due to the thalamic degeneration. Eastern equine encephalitis also preferentially involves the thalamus and basal ganglia.

Axial (Horizontal) Sections Through the Forebrain: Level 6 — Caudate and Mid-Thalamus



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DISORDERS OF CONSCIOUSNESS (COMA)

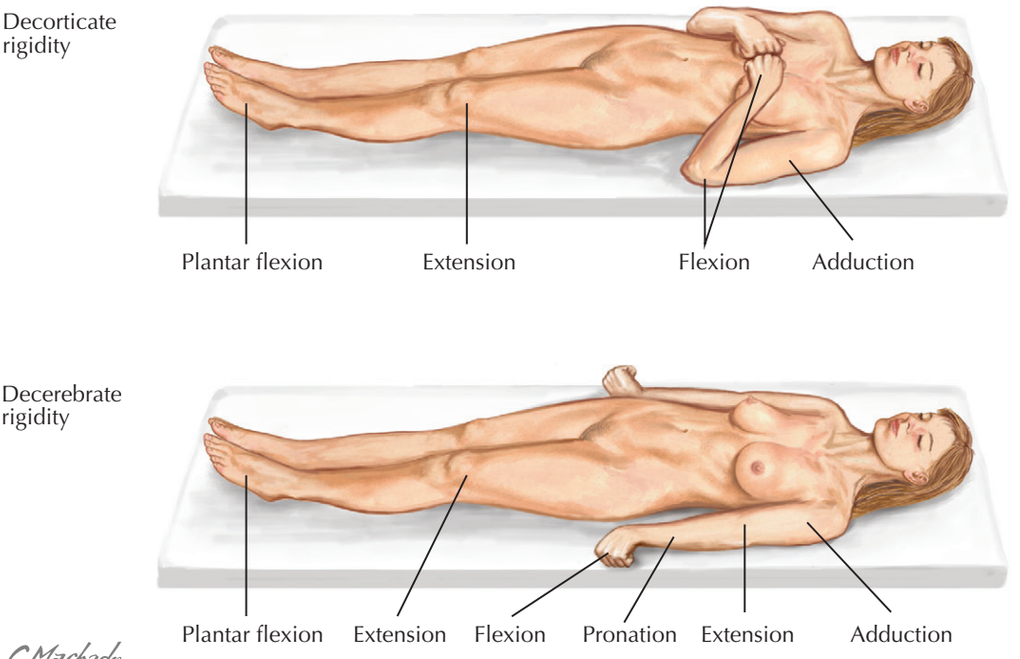
COMA

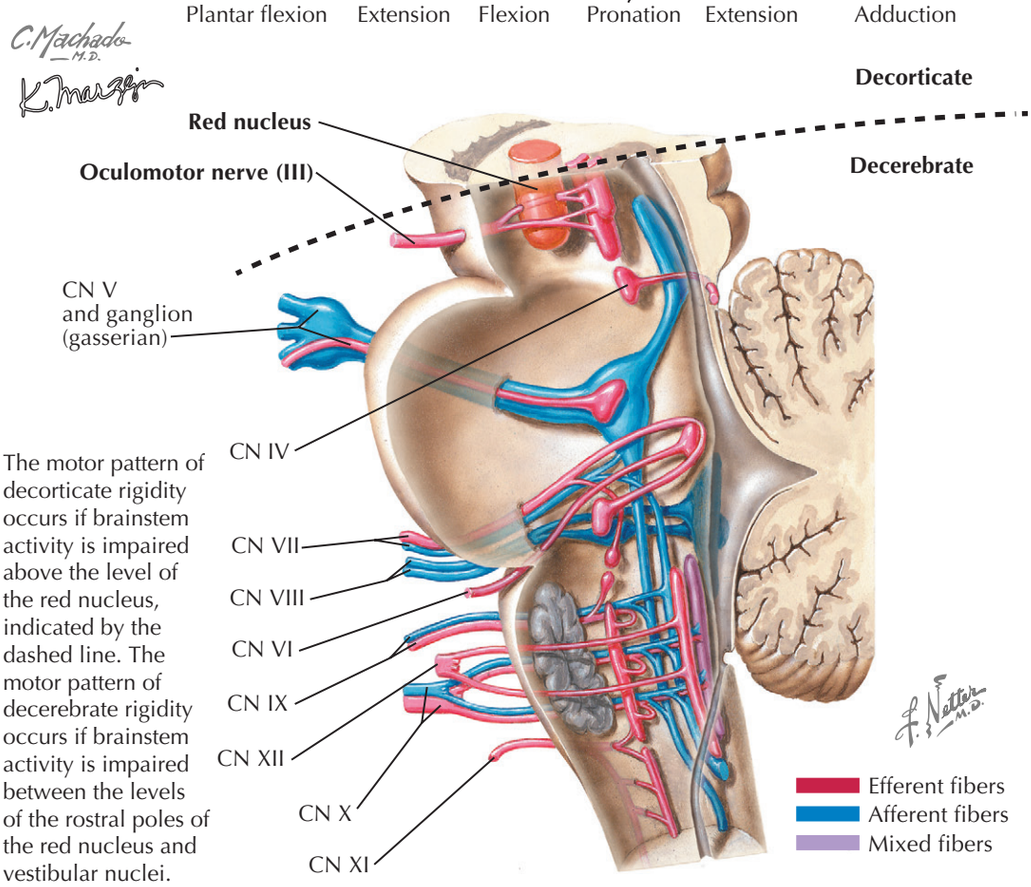
The term *consciousness* refers to a state of awareness of self and one's environment. Assessing consciousness in another person relies on judging that individual's performance or behavior in some mental function and arousal or response of awakening to a stimulus. The word *coma* originates from the Greek koma (κωμα) and komatos meaning sleep, and deep sleep, respectively. In this section, the use of the word is as a term to describe a potentially reversible state of unarousable unresponsiveness, which is not sleep at all. By this strict definition, there should not be grades of coma, but many physicians recognize the usefulness of describing and summating a patient's behavioral response in three domains of function: motor and verbal response and eye opening (see Plate 14-15 on the Glasgow Coma Scale score). However, equating the degree of abnormal motor response with a depth of coma is confusing because neural structures regulating motor function and consciousness are independent. That said, it is common practice to use the clinical integrity of the motor cortex and brainstem nuclei, and their respective projections, as an indication of the level of impairment.

Appropriate localizing and flexor responses in a comatose patient imply that sensory pathways are functioning and that the pyramidal tract from the cerebral cortex to effector is functioning at least partially (see Plate 6-5). When both sides are tested, unilateral absence of responses is consistent with interruption of the corticospinal tract somewhere along its length. Loss of response on both sides may reflect a lesion in the brainstem that interrupts the corticospinal tracts bilaterally or indicates injury to the pontomedullary reticular formation and associated extrapyramidal pathways. *Inappropriate motor responses* depend on the level of brainstem injury, as demonstrated by three main responses to a painful stimulus: *decorticate rigidity*, *decerebrate rigidity*, and *decerebrate changes in the arms combined with flexor responses in the legs*.

Decorticate rigidity consists of flexion of the arms, wrist, and fingers, with adduction in the upper extremity and extension, internal rotation, and plantar flexion in the lower extremity. This motor pattern occurs if brainstem activity is impaired *above the level of the red nucleus* because the red nucleus has a strong influence on upper limb flexion. It occurs with lesions involving the corticospinal pathways at the internal capsule, cerebral hemisphere, or rostral cerebral peduncle.

Decerebrate rigidity consists of opisthotonus with the teeth clenched, the arms extended, adducted and hyperpronated, and the legs extended with the feet plantar flexed. This motor pattern occurs if brainstem activity is impaired *between the levels of the rostral poles of the red nucleus and vestibular nuclei* (rostral midbrain to midpons), as seen during rostral-caudal deterioration with transtentorial herniation, expanding posterior fossa lesions, or neurotoxicity of the upper brainstem. It occurs because of the reduction in extensor inhibition normally exerted on the reticular formation by the cerebral cortex. As a result, the spinal extensor motor neurons are driven by extensor-facilitating parts of the reticular formation that are activated by a painful stimulus. The lateral vestibular nuclei are also intimately involved because, experimentally, extensor posturing is greatly reduced when the lateral vestibular nuclei are ablated. *Decerebrate rigidity or posturing in the arms combined with either flaccidity or weak flexor responses in the legs* is a motor pattern that is found in patients with extensive brainstem damage extending down to or across the pons at the trigeminal level.





The motor pattern of decorticate rigidity occurs if brainstem activity is impaired above the level of the red nucleus, indicated by the dashed line. The motor pattern of decerebrate rigidity occurs if brainstem activity is impaired between the levels of the rostral poles of the red nucleus and vestibular nuclei.

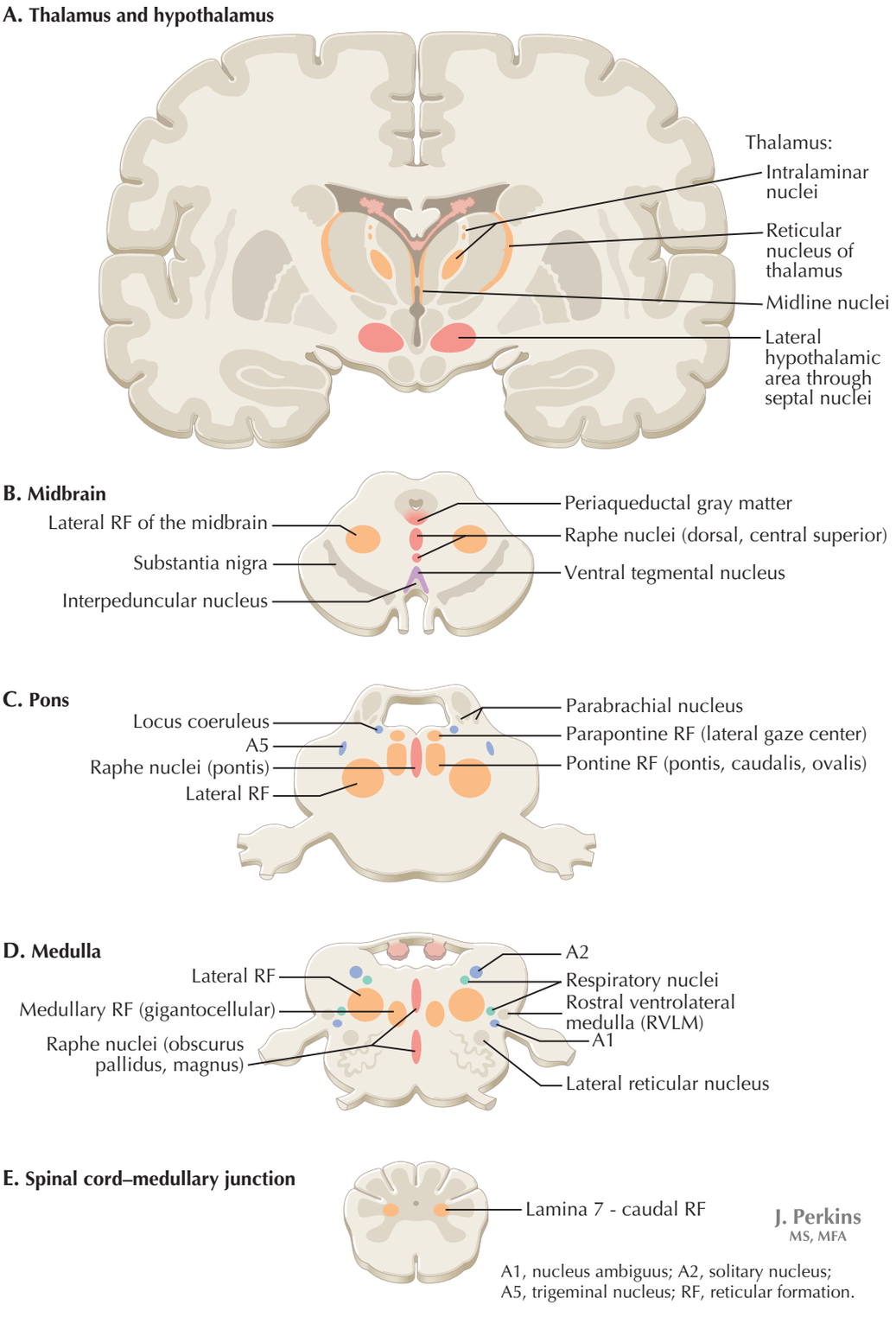
Disorders of Consciousness

Consciousness is a state of wakefulness and awareness of self and surroundings. In describing the state between normal consciousness and coma (unarousable unresponsiveness), many clinicians refer to a spectrum or gradation of states of diminished consciousness leading to coma. *Lethargy* has been used to describe a state of reduced wakefulness with deficits in attention; *obtundation*, a reduction in alertness and interaction with the environment; and *stupor*, state of unresponsiveness with little or no spontaneous movement, from which the patient can be aroused temporarily with vigorous stimulation. These descriptions are imprecise and have, in general, been applied to diffuse metabolic pathologies causing brain dysfunction. Other terminology may be more specific. For example, the *vegetative state*, which may follow coma, describes a state in which the individual is unaware but has sleep-wake cycles without detectable cerebral cortical dysfunction. The *minimally conscious state* describes severely altered consciousness in association with minimal awareness of self or environment. *Akinetic mutism* is a condition of extreme slowing or absence of bodily movement, with loss of speech. Wakefulness and awareness are preserved, but cognition is slowed because of bilateral lesions to the inferior frontal lobes, cerebral hemispheres, paramedian mesencephalic reticular formation (RF), or posterior diencephalon. The *locked-in syndrome* is a state of preserved consciousness and cognition with complete paralysis of the voluntary motor system because of complete destruction of corticospinal and corticobulbar pathways at or below the pons, or severe peripheral nervous system disease. Eye movements may be preserved, allowing for some communication, and cortical function is intact.

The anatomic substrate for a disorder in consciousness is dysfunction in the *reticular formation* and the *ascending reticular activating system* (ARAS) because activation of the cerebral cortex during arousal and wakefulness depends on the influence of these structures. In the absence of the ARAS, stimulation of any of the sensory pathways (e.g., somatosensory, auditory, and visual) cannot arouse the cerebral cortex. Three groups of nuclei in the brainstem (locus ceruleus, raphe, and ventral tegmental) contribute to the modulating effect of the ARAS. An additional group of nuclei in the basal forebrain (basal nucleus of Meynert) also contributes to the diffuse modulating system.

The main nuclei of the reticular formation are present in the medulla, pons, and midbrain. The *locus ceruleus* is located beneath the lateral part of the floor of the rostral pontine fourth ventricle. Its axons are distributed to the cerebral cortex, thalamus, hypothalamus, cerebellar cortex, brainstem, and spinal cord. These norepinephrine-containing neurons are involved in the regulation of attention, cortical arousal, and the sleep-wake cycle. The *raphe nuclei* are clustered in the midline of the medulla, pons, and midbrain and constitute the serotonergic projections involved in the sleep-wake cycle. The nuclei near the pontomedullary junction constitute the *nucleus raphe magnus*, which projects to the spinal cord for the modulation of slow pain. The nuclei in the rostral pons and midbrain project to the thalamus, the limbic system, and cerebral cortex. The *ventral tegmental area* is located posteromedial to the compact nigra, and its dopaminergic neurons project chiefly to the accumbens, amygdala, and prefrontal cortex. Last, cholinergic neurons in the pons and midbrain project to the thalamus and regulate the excitability of the thalamic nuclei. Taken together, the outputs from all of these nuclei funnel through the paramedian midbrain reticular formation and divide into posterior and lateral anterior roots in the diencephalon. The posterior root projects to relay nuclei and to intralaminar and other nuclei that have widespread cortical connections. The anterior root enters the lateral hypothalamic zone and is joined by projections from other neurons in the hypothalamus and basal forebrain. Lesions in the medulla or pons do not affect arousal and wakefulness. However, paramedian tegmental lesions in the rostral midbrain interrupt the ARAS and result in coma.

Reticular Formation: Nuclei and Areas in the Brainstem and Diencephalon



A1, nucleus ambiguus; A2, solitary nucleus; A5, trigeminal nucleus; RF, reticular formation.

Full Outline of UnResponsiveness Score (FOUR)

Eye response

4 = eyelids open or opened, tracking, or blinking to command
3 = eyelids open but not tracking
2 = eyelids closed but open to loud voice
1 = eyelids closed but open to pain
0 = eyelids remain closed with pain

Motor response

4 = thumbs-up, fist, or peace sign
3 = localizing to pain
2 = flexion response to pain
1 = extension response to pain
0 = no response to pain or generalized myoclonus status

Brainstem reflexes

4 = pupil and corneal reflexes present
3 = one pupil wide and fixed
2 = pupil or corneal reflexes absent
1 = pupil and corneal reflexes absent
0 = absent pupil, corneal, and cough reflex

Respiration

4 = not intubated, regular breathing pattern
3 = not intubated, Cheyne-Stokes breathing pattern
2 = not intubated, irregular breathing
1 = breathes above ventilator rate
0 = breathes at ventilator rate or apnea

Interpretation: Minimum score = 0, Maximum score = 16. The lower the score the greater the coma.

Reprinted with permission from Wijdicks EFM, Bamlet WR, Maramattom BV. Validation of a new coma scale: the FOUR score. Ann Neurol 58:585-593, 2005.

Emergency Management and Assessment and Neurology Examination

EMERGENCY MANAGEMENT AND ASSESSMENT

The many causes of coma are described elsewhere in this atlas (see Sections 9—Cerebrovascular Circulation and Stroke; 11—Infection of the Nervous System; 12—Neuro-Oncology; and 14—Head Trauma). Immediate care, regardless of the cause of diminished consciousness, must include attention to adequacy of spontaneous ventilation and blood pressure to maintain homeostasis. Thereafter, the *emergency treatment* of comatose patients follows accurate diagnosis that depends on history-taking, examination findings (including the evolution of neurologic symptoms and signs), and accompanying non-neurologic problems.

Coma Scales. *The Glasgow Coma Scale score* (see Section 14, Plate 14-15) for *best motor response* in either the upper or lower limbs is rated on a scale of 1 (no response) to 6 (patient-obeys commands). If there is no response or an incomplete reaction to verbal stimuli, a noxious stimulus is applied, preferably to the medial side of the arms or legs, to differentiate a localizing response from abnormal flexor or extensor posturing. If the patient moves the limb toward (rather than away from) the noxious stimulus, the response is not consistent with localization. The patient's reaction is classified as fending-off movements with localization of pain (score 5), fending-off movements without localization of pain (4), abnormal flexion (3), abnormal extension (2), and no response (1). A *localizing response* indicates that the stimulus at more than one site causes a limb to move so as to attempt to remove it. A *flexor response* in the upper limb may vary from rapid withdrawal, associated with abduction of the shoulder, to a slower decorticate posture, with adduction of the shoulder. An *extensor response* is abnormal and usually associated with adduction, internal rotation of the shoulder, and pronation of the forearm. *No response* is usually associated with hypotonia. The Glasgow Coma Scale score alone is not an adequate assessment of brainstem function. Further, it does not assess vital signs (blood pressure, heart rate, body temperature, blood sugar), ability to protect the airway and clear any airway obstruction (cough and gag), and suggests what support or intervention is required to restore homeostasis. A newer *Full Outline of UnResponsiveness (FOUR) scoring* system measures impaired consciousness and specific brainstem responses (see Plate 6-4). The four variables assessed are motor response, brainstem reflexes, eye response, and respiratory pattern. The acronym additionally reflects the number of categories and the maximum number of potential points in each category.

After immediate assessment, the next step is to initiate necessary emergency interventions for life support. For example, an adequate airway must be assured, and an intravenous line should be placed. If the patient is hypoventilating, endotracheal intubation with assisted mechanical respiration should be considered. Intravenous fluid bolus and vasopressors may be needed to treat hypotension. Blood samples should be drawn for measurement of electrolytes, glucose, toxicology, and arterial acid-base and blood gases. Serum is saved for further study if necessary. When bedside testing shows the patient to be hypoglycemic, an intravenous bolus of dextrose should be administered. If narcotic abuse is suspected or if the patient does not respond to

Emergency Management and Assessment and Neurology Examination *(Continued)*

supportive measures, an opiate-receptor antagonist, such as naloxone, can be given intravenously.

Next, after any necessary immediate treatment is instituted, steps are taken to determine the cause of coma with a robust and thorough *history* and appropriate investigation. The patient's family, friends, or physician can often supply useful diagnostic information. Inquiries may elicit a history of diabetes; previous renal, hepatic, or cardiac disease; severe depression; or drug use or abuse. It is important to know what prescription medications have been used and whether the patient had experienced any prodromal symptoms, such as headache, unilateral weakness, and ataxia, or previous episodes of stupor.

NEUROLOGIC EXAMINATION

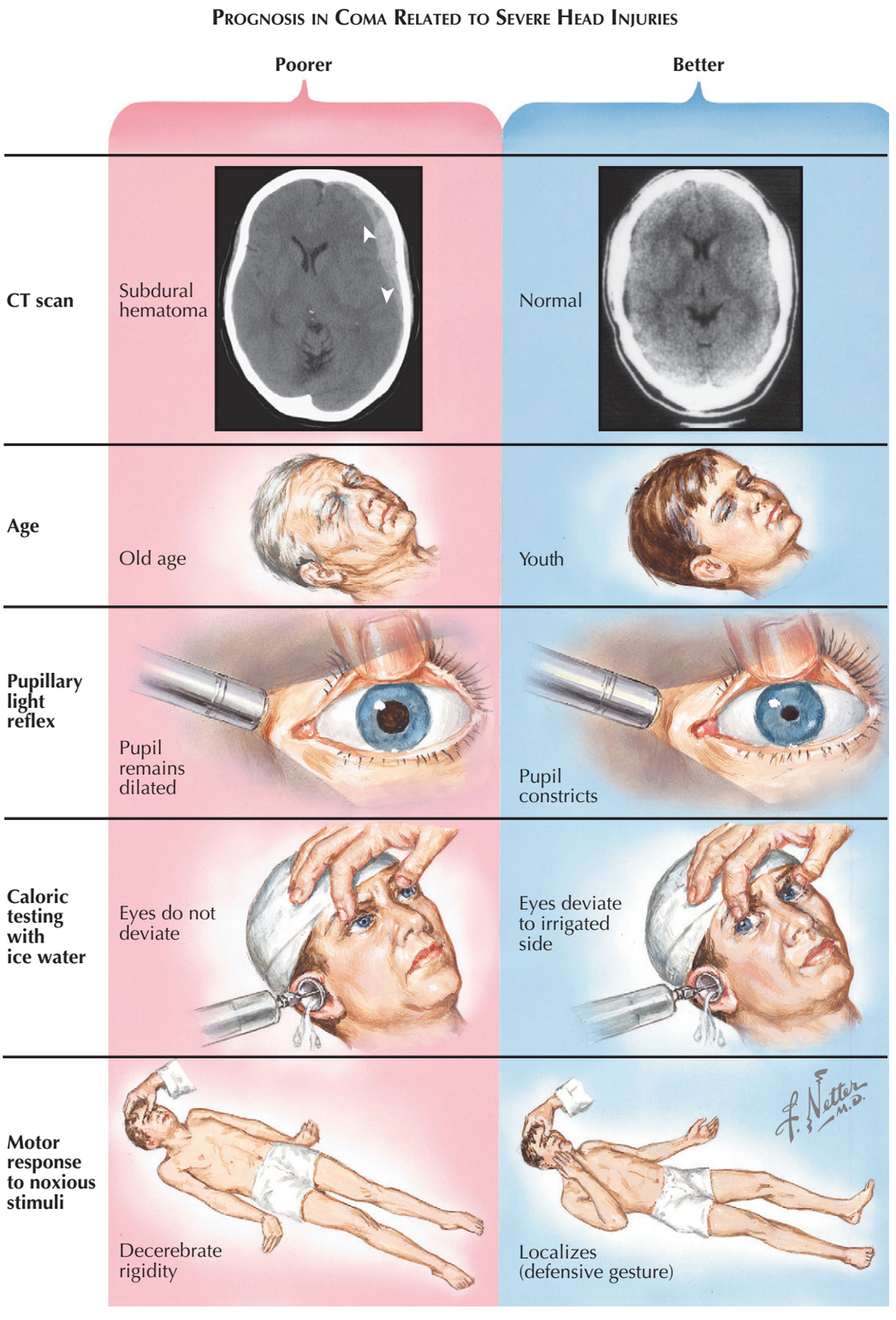
It is important to carry out careful physical and neurologic examinations. Evaluation of the patient's spontaneous limb and bulbar movements, pupillary reactions, eye movements, and response to painful stimuli usually indicates the level of brain lesion causing coma. If the patient is able to blink, yawn, lick, and swallow, which are complex brainstem reflexes, lower brainstem function is preserved.

Pupillary size depends on the balance between sympathetic function (descending sympathetic fibers course in the lateral brainstem tegmentum) and parasympathetic function (parasympathetic fibers exit with the oculomotor [cranial nerve III] in the midbrain).

Pupillary reaction depends on the afferent light stimulus reaching the superior colliculus, as well as efferent transmission through the oculomotor nerve. The light reflex arc is located in the diencephalon and midbrain.

Eye movements are observed by retracting the upper eyelids and watching spontaneous activity. When the head is rotated to one side—a maneuver to be performed only when it is clear that the cervical spine is not injured—the eyes should move fully and conjugately in the opposite direction if the appropriate brainstem oculomotor and vestibular centers are preserved (doll's eye phenomenon, or oculocephalogyric reflex). When the head is moved to the right, the eyes move conjugately to the left; when the head is moved downward, the eyes should roll upward. Ice water introduced into one ear canal with the patient's head-of-bed elevated to 30 degrees should evoke conjugate eye movements toward the side of the stimulation (vestibulo-ocular reflex). In this position, the horizontal semicircular canal is in a vertical position, and the endolymph falls within the canal, thereby decreasing the rate of vestibular afferent firing. The eyes turn toward the ipsilateral ear, with horizontal nystagmus to the contralateral ear. Horizontal reflex eye movements are controlled by the oculomotor, trochlear (cranial nerve IV), and abducens (cranial nerve VI) nerves and their nuclei; the medial longitudinal fasciculus and parapontine reticular formation (pontine lateral gaze center); and the vestibular nuclei and nerves (cranial nerve VIII). All these structures are located within the pontine tegmentum. Vertical movements are controlled by centers in the rostral midbrain and caudal diencephalon.

Last, spontaneous limb movements should be observed. If absent, then testing for a response to a noxious stimulus is appropriate.



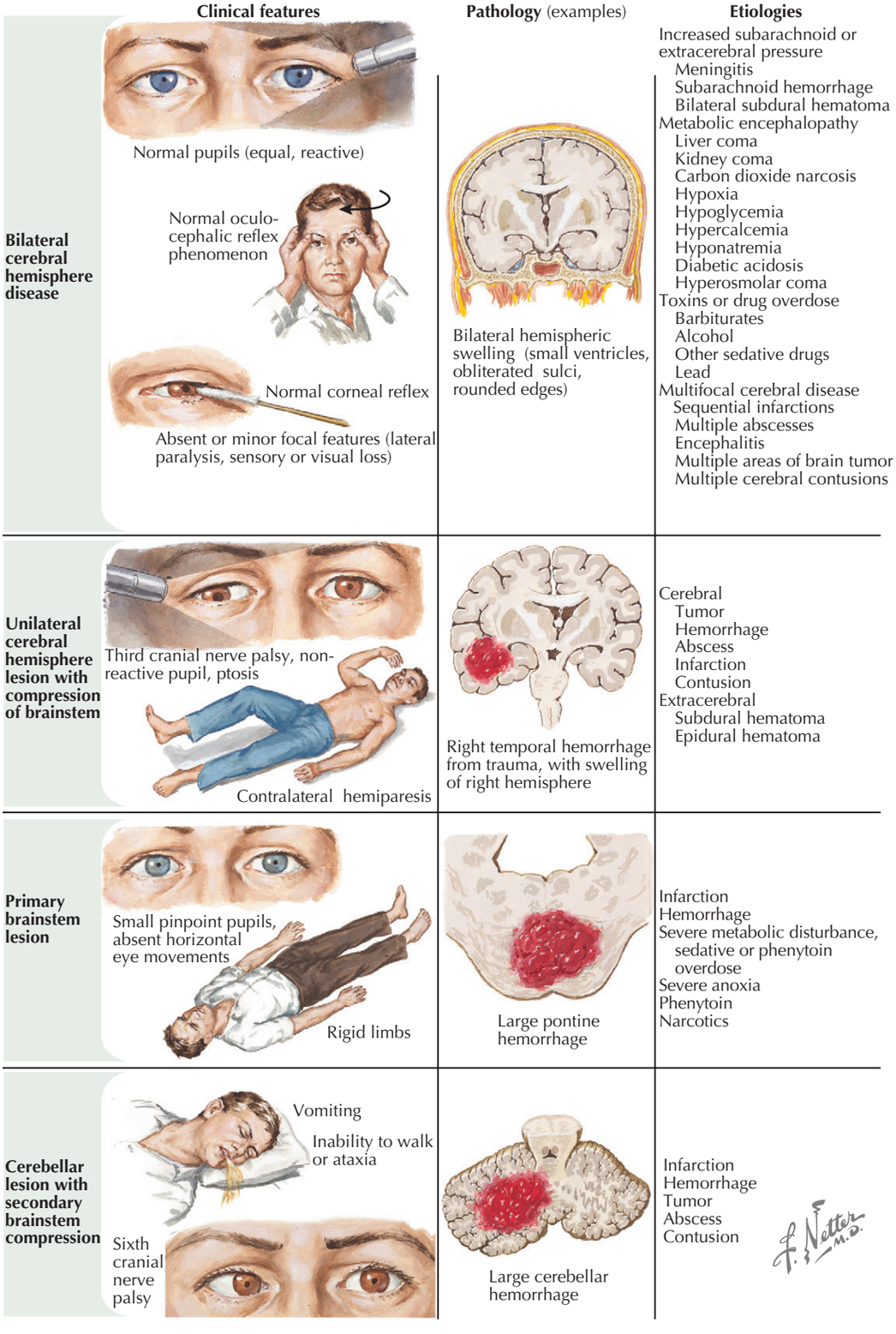
DIFFERENTIAL DIAGNOSIS OF COMA

When coma is caused by *bilateral cerebral hemisphere disease*, swallowing, yawning, and spontaneous breathing are normal. The eyes rove spontaneously from side to side, and the limbs move symmetrically to stimulus. Pupillary and oculomotor reflexes are preserved. Toxic and metabolic disorders are the most common cause of coma resulting from bilateral hemisphere dysfunction. Encephalitis, hemorrhage, or infection in the meninges and subarachnoid space can also adversely affect bilateral hemisphere function. Although infarcts, hemorrhages, tumors, or abscesses can involve both hemispheres, the neurologic deficit becomes bilateral only sequentially.

When a *hemispheric lesion* compresses the brainstem, the patient usually has signs or symptoms of hemisphere dysfunction, such as hemiparesis. Any space-occupying lesion, such as subdural hematoma, infarction, hemorrhage, or tumor, may compress the rostral brainstem and cause coma. As the lesion enlarges, intracranial pressure rises, and headache, vomiting, decreased alertness and papilledema develop. Signs of rostral brainstem diencephalic dysfunction follow. The midbrain and pons are disrupted sequentially, and signs of lower brainstem failure are added to dysfunction of rostral structures.

An intrinsic brainstem lesion can cause coma by compromising the function of the medial tegmental structures bilaterally. Primary dience*phalic brainstem lesions* are usually due to stroke, either hemorrhagic or infarction. Head trauma may also directly injure the brainstem. In *midbrain lesions*, the pupils are dilated or in midposition, and bilateral oculomotor nerve palsy occurs. The eyes rest downward and outward and do not adduct or move vertically. Decerebrate posturing of the limbs is present. Pontine infarct or hematoma cause small, poorly reactive pupils and impaired vertical gaze. The eyes may rest downward and inward, and one eye may be lower than the other. Brainstem function rostral to the lesion is preserved. *Pontine lesions* cause small, reactive pupils, failure of horizontal eye movements, preservation of vertical eye movements (sometimes with spontaneous bobbing), and decerebrate posturing. *Medullary lesions* may compromise vasomotor control and breathing. Toxic disorders affecting the brainstem and cerebral hemispheres at multiple levels cause signs inconsistent with any single anatomic locus.

Cerebellar space-occupying lesions cause ataxia and vomiting, often followed by abducens (cranial nerve VI) nerve or lateral gaze palsy to the side of the lesion. Signs of lower brainstem dysfunction in the pons and medulla then develop.



TREATMENT

If a cerebral or cerebellar lesion compresses the brainstem, immediate treatment is required to avoid irreversible injury. With a primary brainstem lesion, the situation is equally urgent. Neuroradiologic investigations are critical in determining the nature and extent of pathology. Endotracheal intubation, controlled mechanical ventilation, and osmotic diuresis are undertaken while cranial computed tomography (CT) is performed to determine whether the patient requires immediate surgical decompression, cerebrospinal ventricular drainage, or hematoma evacuation as lifesaving measures.

Bilateral cerebral hemisphere disease is usually treated medically rather than surgically. It is often the result of metabolic encephalopathy from *exogenous intoxication*, for instance, drug overdose, alcohol intoxication, or overmedication. *Endogenous intoxication* is caused by organ failure (the lungs and carbon dioxide narcosis; the liver and hyperammonemia; the kidney and uremia), hyperglycemia, hypercalcemia, or hypernatremia, or by *insufficiency of endogenous or exogenous substances*, for instance, hypoglycemia, hypothyroidism, hypocalcemia, or hyponatremia.

Hypoxic-Ischemic Brain Damage

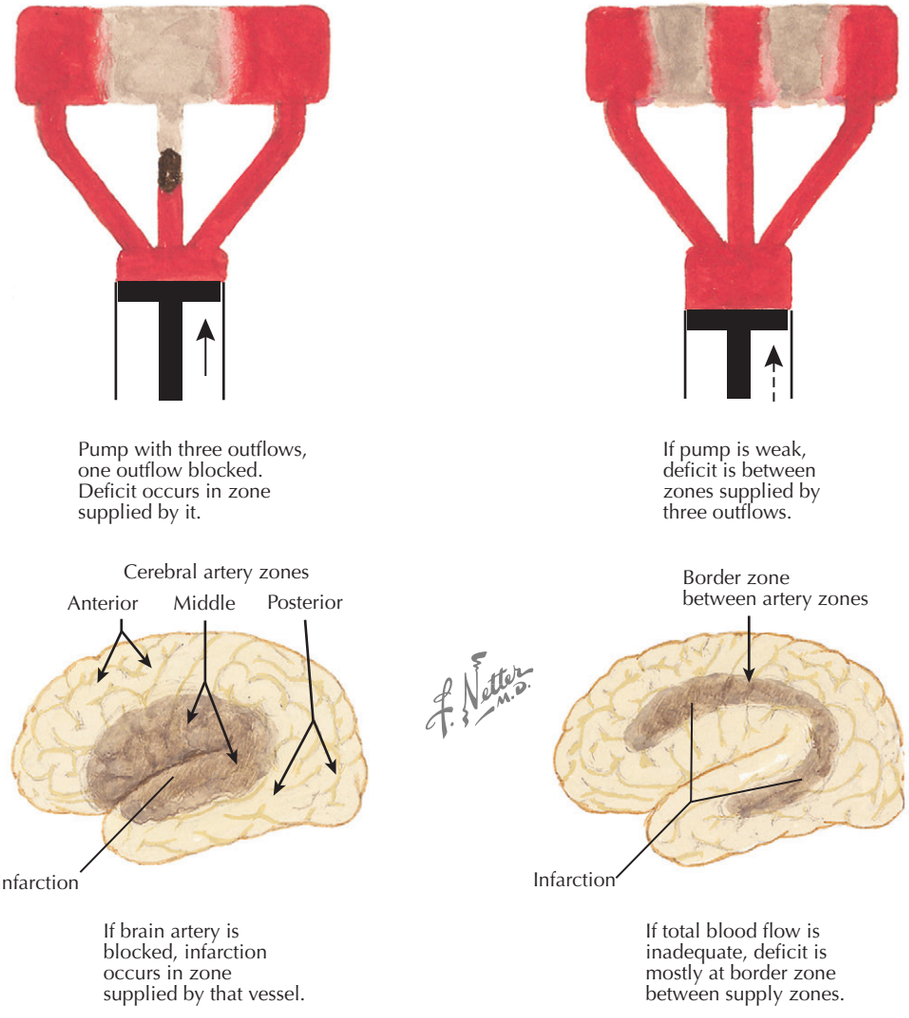
At a national level, out-of-hospital cardiac arrests are an all-too-frequent occurrence. One quarter of individuals experiencing such an arrest will receive emergency cardiopulmonary resuscitation. However, fewer than 20% of these events will lead to survival at hospital discharge even with the combined efforts of emergency and hospital critical care services. Of those who do survive, many will have profound neurologic injury and disability.

Hypoxic-Ischemic Encephalopathy. Hypoxic-ischemic encephalopathy is the term used to describe such injury after cardiac arrest or severe hypoxia causing global injury, or prolonged hypotension causing arterial border zone injury. Many variables determine the extent and location of injury: the completeness of circulatory collapse (full cardiac arrest or hypotension, with some preserved cardiac output), the duration of circulatory compromise accompanying circulatory failure, and the blood glucose level at the time of the event. *Apnea* or *hypoxia* (as in carbon monoxide poisoning or strangulation) with preserved circulatory function often results in pallidal and thalamic necrosis with preservation of cerebral cortex. *Persistent hypotension* leads to arterial border zone ischemic lesions at the limits of the anterior and middle cerebral artery territories and the middle and posterior cerebral artery territories.

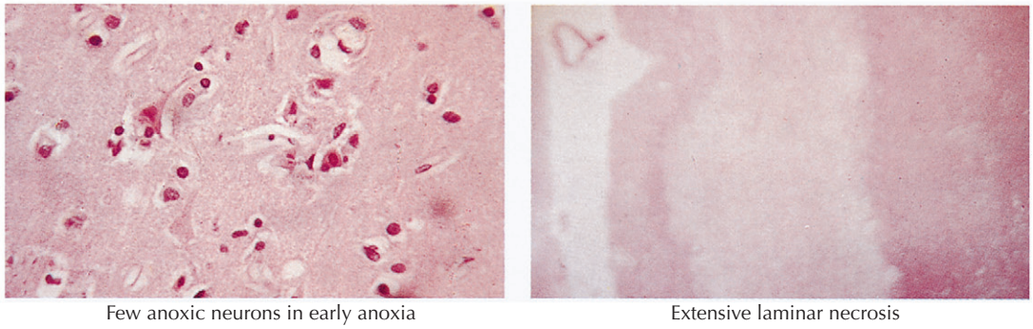
Cardiac arrest can cause hippocampal damage, basal ganglia injury, middle laminar necrosis of the cerebral cortex, and lesions of the cerebellum and brainstem nuclei. The order in these regions of the brain also represents the hierarchy of injury. The most vulnerable region to brief cerebral ischemia is the hippocampus, and the phrase often used to describe this phenomenon is *hippocampal regional vulnerability*. Arterial border zone ischemia results in arm weakness, incoordination during visually directed behavior, and defective visual and spatial perception. In children, severe hypotension can lead to more extensive injury, with severe impairment of motor development and function. *Loss of Purkinje cells* in the cerebellum leads to ataxia and action myoclonus.

Hypothermia Treatment. Many drug and anesthetic treatments have been tested in the setting of cardiac arrest. The idea has been to use agents that reduce brain metabolism or limit the cascade of cellular events that lead to neuronal death. Currently, no single drug therapy has been found to provide significant clinical benefit. The only treatment that has been shown to improve the probability of a good outcome in adults after ventricular fibrillation or pulseless ventricular tachycardia cardiac arrest, or in babies with birth asphyxia, is physical treatment with the induction of moderate hypothermia to achieve a core body temperature of 32° C to 34° C. In infants, isolated cooling of the head after birth asphyxia also achieves a desired therapeutic effect.

Border zone ischemia (shock, circulatory insufficiency)



Diffuse cortical necrosis; persistent vegetative state

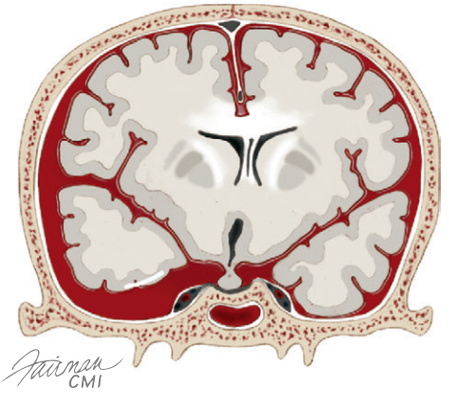


Few anoxic neurons in early anoxia

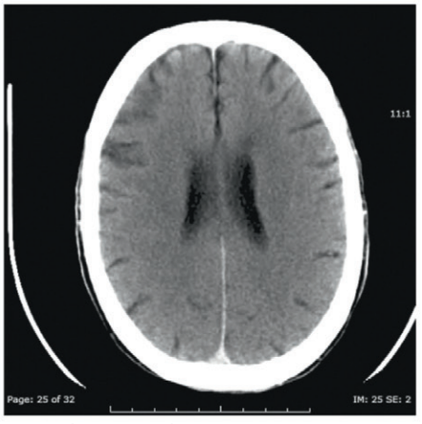
Extensive laminar necrosis

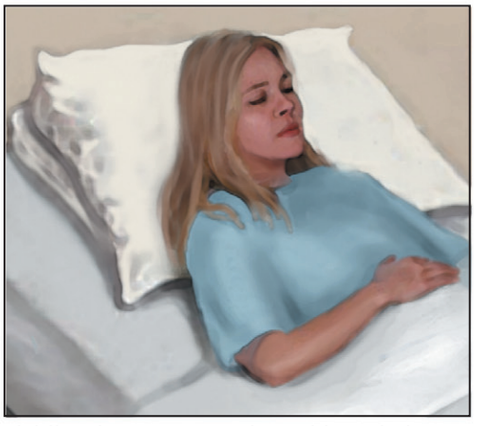
The vegetative state. The condition is called *persistent* when it lasts without change for more than 1 month.

This patient is yawning but not in conscious response. Such patients may startle, look about, or yawn, but none of these actions is in conscious response to a specific stimulus.

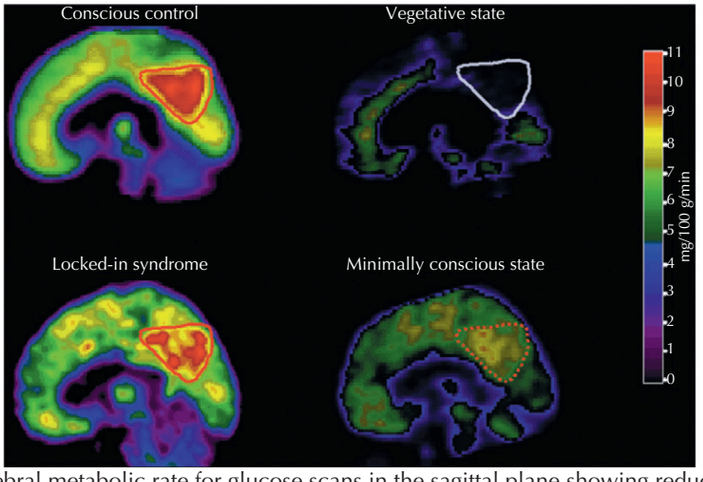


Subarachnoid hemorrhage was the cause of the patient's state.





Noncontrast brain CT demonstrating ominous sign of diffuse brain injury and possible prelude to a persistent vegetative state: subtle disappearance of normal differentiation between gray and white matter



Color-coded cerebral metabolic rate for glucose scans in the sagittal plane showing reduced metabolism in the precuneus in a patient in a vegetative state (VS, *top right*) and in a patient in a minimally conscious state (MCS, *bottom right*). The red area in the Conscious control (*top left*) and Locked-in syndrome (*bottom left*) scans indicate normal metabolism. Reprinted with permission from Laureys S, Owen AM, Schiff ND. *Brain function in coma, vegetative state, and related disorders*. Lancet Neurol 3:537-546, 2004.

Vegetative State and Minimally Conscious State

Survivors of some severe circulatory event, who are initially comatose, may pass through a spectrum of clinical conditions before partially or fully recovering consciousness. If, after having been in a coma, the patient opens the eyes but remains unable to initiate voluntary motor activity, this behavior marks the transition to what is called the *vegetative state* (VS). The further transition to *minimally conscious state* (MCS) is characterized by reproducible evidence of simple voluntary behavior. Emergence from MCS is signaled by the return of functional communication or object use. Further developments lead to outcomes ranging from severe disability to a good recovery. If, however, the patient remains in the VS for more than 1 month after the occurrence of brain damage, this condition is called the *persistent vegetative state* (PVS). This state is not necessarily irreversible. Reversibility is much less likely in patients in the *permanent vegetative state*, that is, in VS lasting more than 3 months after hypoxic-ischemic damage or 1 year after traumatic brain injury.

To date, VS and the MCS have both been defined by clinically observed behavioral responses. For example, VS is characterized by wakefulness in the absence of any awareness of self or environment. Typically, such a person retains autonomic functions with variable preservation of cranial and spinal reflexes but exhibits no clinical evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to multisensory stimulation, nor evidence of language comprehension or response to command. MCS describes a spectrum of behavior that, at its most basic description, requires evidence of visual pursuit and, at best, involves intermittent responses to command. However, it has now become apparent using newer technologies, such as functional magnetic resonance imaging, that the distinction between VS and MCS cannot be based purely on observation. A notable proportion of patients considered to be in VS retain some awareness that is not consistent with their externally observable behavior.

The neuropathology of postanoxic VS and MCS is indistinguishable. There is characteristically little or no damage in the brainstem, but such patients commonly have evidence of diffuse necrosis in the cerebral cortex, variable abnormalities in the basal ganglia, and cerebellum, and severe thalamic damage. At a functional level, cerebral metabolic studies and magnetic resonance imaging have identified that the behavior during VS and MCS represents a functional disconnection syndrome in a large-scale frontoparietal network as a result of damage to long-range connectivity. The structures involved include the lateral and medial frontal regions, parietotemporal and posterior parietal areas, and posterior cingulate and precuneal cortex.

Brain Death

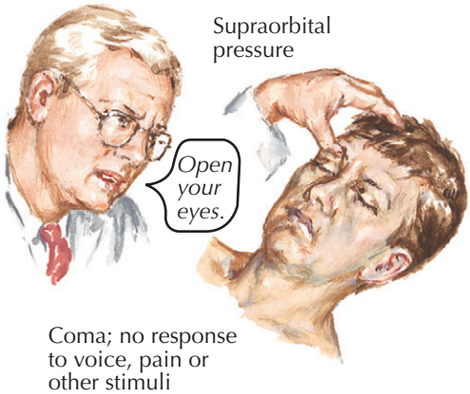
Severe hypoxic-ischemic encephalopathy may result in brain swelling of such severity that all blood flow into the cranium is blocked, thereby worsening the ischemia to a terminal stage. *Brain death* is a clinical diagnosis based on the absence of neurologic function in the context of a diagnosis that has resulted in irreversible coma. In the United States, it indicates death of the entire brain; in the United Kingdom, it refers to death of the brainstem. Coma and apnea must coexist. A complete neurologic examination that includes the elements outlined in Plates 6-4 and 6-9 is mandatory to determine brain death, with all components appropriately documented. The current recommendation in adults is that a single evaluation suffices for the diagnosis of brain death. In children, two assessments should be performed, with the duration of interval between tests varying with age.

Before starting the assessment for brain death, reversible conditions or conditions that can interfere with the neurologic examination must be excluded. For example, hypothermia, hypotension, and metabolic disturbance that could affect the neurologic examination must be corrected. After cardiopulmonary resuscitation or use of therapeutic hypothermia, evaluation for brain death should be deferred for 24 to 48 hours, or longer if there are concerns or inconsistencies in the examination. Sedatives, analgesics, neuromuscular blockers, and anticonvulsant agents should be discontinued for a reasonable period, based on the elimination half-life of the pharmacologic agent, to ensure that they do not affect the examination; blood or plasma levels can be used to confirm that the drug is in the low to midtherapeutic range.

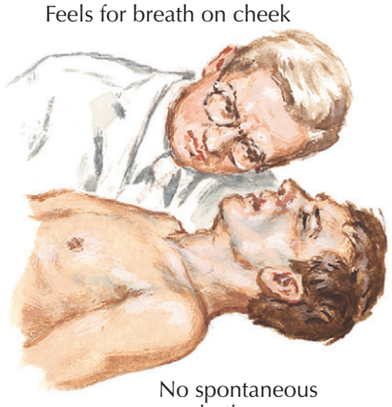
The *components of the clinical neurologic examination* consistent with brain death include presence of coma, loss of all brainstem reflexes, apnea (see Plate 6-9), and absence of spontaneous or induced movements, but excluding spinal cord events such as reflex withdrawal or spinal myoclonus.

Irreversible Coma. The patient must exhibit complete loss of consciousness, vocalization, and volitional activity. Noxious stimuli should produce no eye opening or eye movement, and no motor response other than spinal-mediated reflexes.

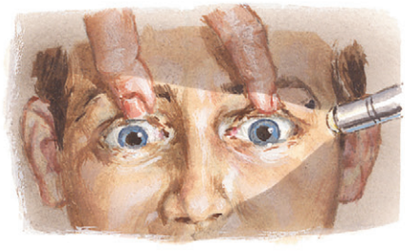
Loss of All Brainstem Reflexes. The patient exhibits the following: midposition or fully dilated pupils that do not respond to light, either directly or consensually (assessment 1); absence of movement of bulbar musculature, including facial and oropharyngeal muscles, such as in response to deep pressure on the condyles at the level of the temporomandibular joints and over the supraorbital ridge (assessment 2); absent corneal reflexes so that touching the cornea with a sterile cotton swab does not elicit any eyelid movement (assessment 3); absent oculovestibular reflexes (assessment 4); and absence of gag and cough on stimulation of the posterior pharynx with a tongue blade or suction catheter (assessment 5). Assessment of these brainstem functions should be carried out sequentially and systematically because they relate to different levels of brainstem functioning (see Plate 6-9). The oculovestibular reflex is tested by irrigating each ear with ice water (caloric testing) after first checking that the external auditory canal is not occluded by wax and that the eardrum is intact. The head of the bed is elevated to 30 degrees, and the patient's head is kept in the midline. Each ear is irrigated with 50 to 60 mL of ice water, and this should elicit no movement of the eyes during one minute of observation. The aim is to reduce local temperature at the tympanic membrane so that there is a gradient with core body temperature. Both sides are tested with an interval of several minutes. In normal individuals, nystagmus is induced in both eyes. The fast phase is toward the side opposite that which is being irrigated with cold water and is triggered by the cerebral cortex. The slow phase of nystagmus is caused by the oculovestibular reflex. In comatose patients with an intact response, cold water will turn both eyes slowly toward the side being irrigated. These movements are comparable with the slow phase of the nystagmus induced in normal individuals. Caloric-induced movements are absent when the midbrain or rostral pons is impaired and the oculovestibular path is no longer intact.

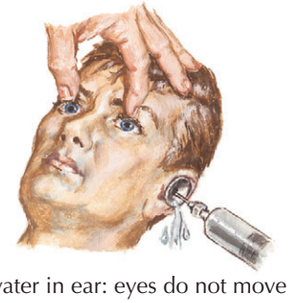


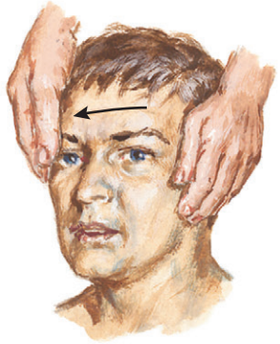
Coma; no response to voice, pain or other stimuli

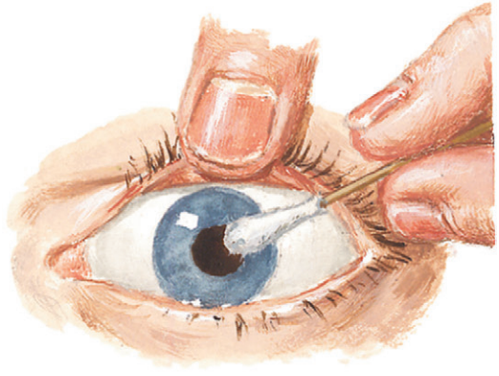


No spontaneous respiration


Pupils dilated, unresponsive to light


Ice water in ear: eyes do not move


"Doll's eyes": head turned sharply to side, eyes remain centered



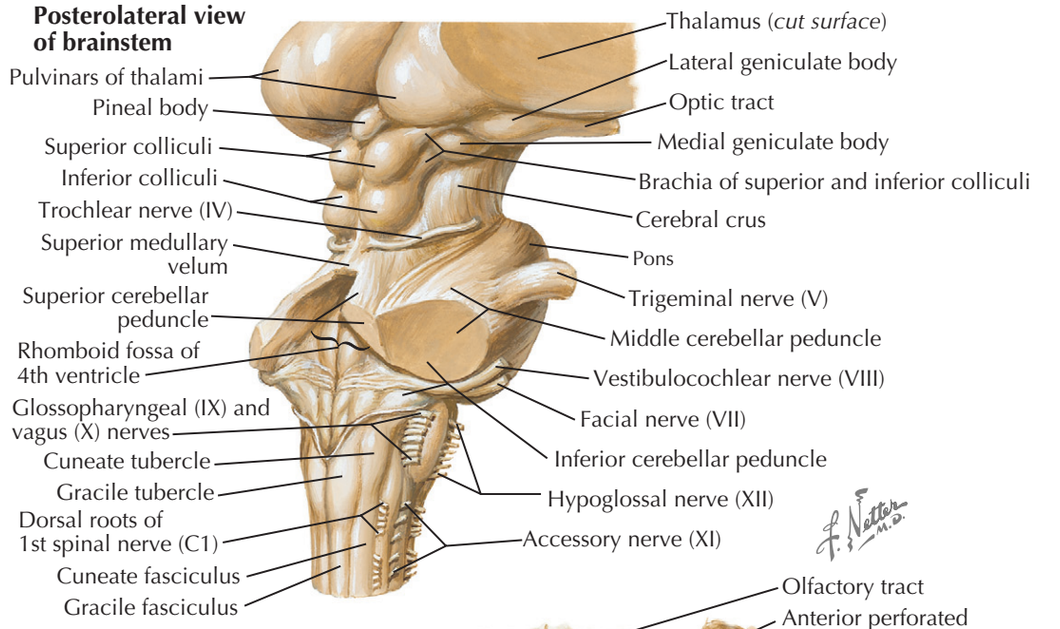
Corneal reflex lost

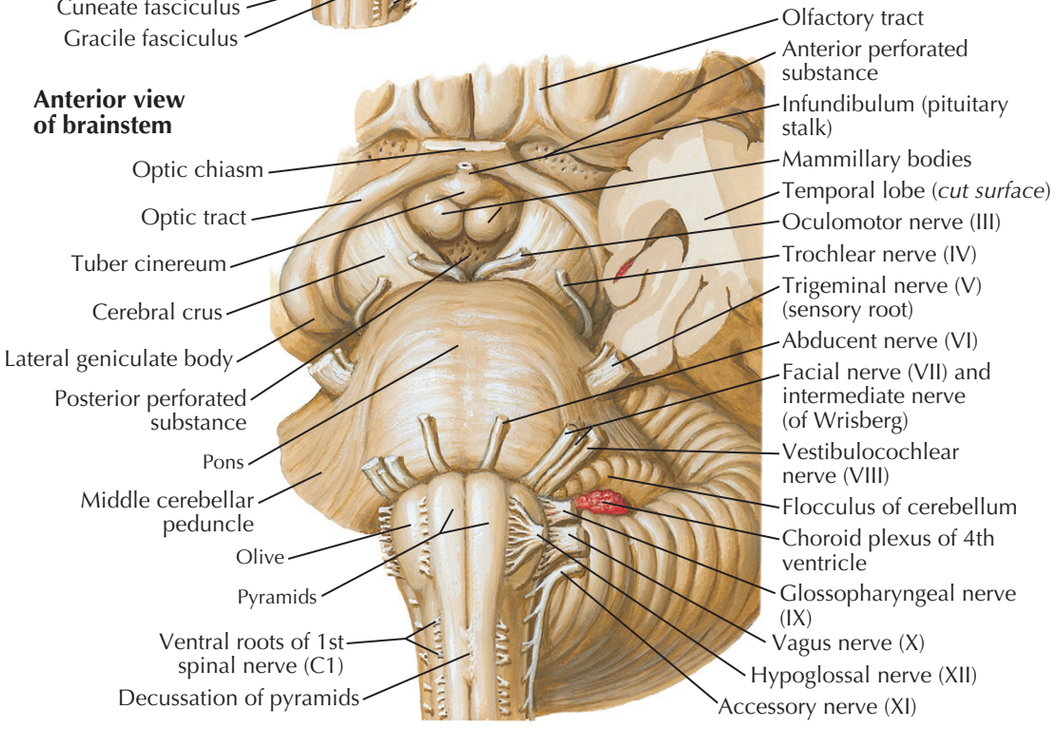
Ventilatory Patterns and the Apnea Test

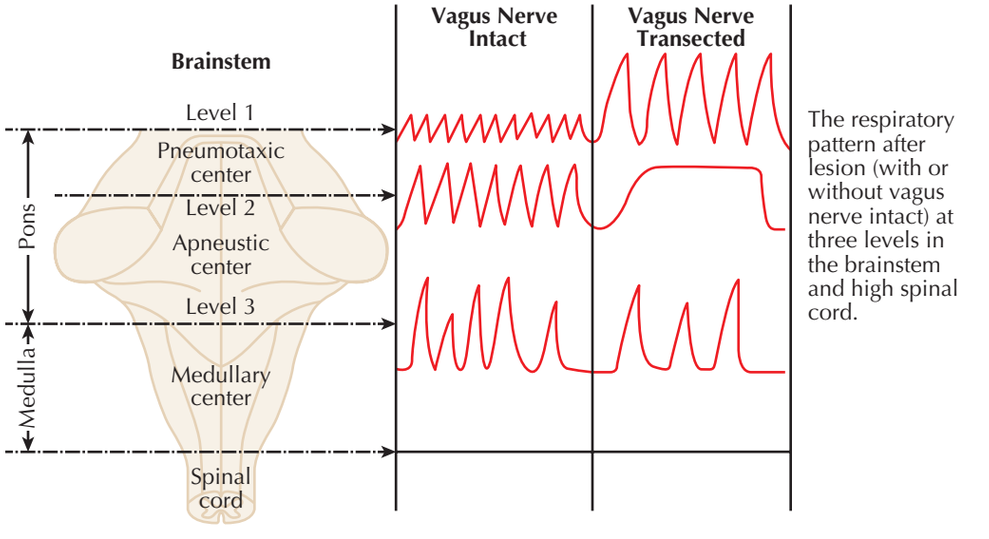
Central Pattern Generator for Breathing. In health, the anatomic origin of the cyclic pattern of breathing is the brainstem. Sectioning the brainstem above the pons leaves breathing unaffected when the *vagus nerve (cranial nerve X)* carrying afferent information from the lungs is intact. Vagotomy results in a reduction in the breathing frequency and an increase in tidal volume. Transection below the medulla results in complete cessation of breathing. Sectioning above the central medulla results in rhythmic but irregular breathing, with vagotomy slowing the irregular pattern. Transection at the level of the upper pons leads to a slowing of respiration and an increase in tidal volume. If both vagus nerves are cut, the result is the cessation of breathing at full inspiration (called *apneusis*), or inspiratory spasms interrupted by intermittent expirations (called *apneustic breathing*). The *central pattern generator for breathing* is located within the medullary center.

The areas of the brainstem that modulate ventilation are co-localized to the same structure containing the central pattern generator. The areas that are sensitive to changes in hydrogen ion concentration and blood composition of respiratory gases (*chemosensitive areas*) are localized to the ventral surface of the medulla, bilaterally, at the level of cranial nerve roots VIII to XI. These areas are very superficial, lying about 200 μM below the surface. Additional chemosensitive areas have also been found caudally in the area of the XII cranial nerve root (hypoglossal). All of these central chemoreceptors are sensitive to local changes in cerebrospinal fluid pH induced by rising $Paco_2$. Failure to respond to an adequate $Paco_2$ stimulus indicates a failure in the medullary respiratory centers.

The *apnea test* is performed if the brainstem reflexes are *all* absent, and it is a requirement of brain death testing (see Plate 6-8). There are a number of techniques that are used to perform this test in the intensive care unit. However, the essential feature in brain death is that the patient must have complete absence of respiratory effort by formal testing using the endogenous increase in arterial partial pressure of carbon dioxide ($Paco_2$) as the stimulus to breathing. At baseline, the patient should start with a $Paco_2$ of approximately 40 mm Hg. The stimulus to breathing is considered adequate when there has been a rise in $Paco_2$ by 20 mm Hg to some value greater than 60 mm Hg.





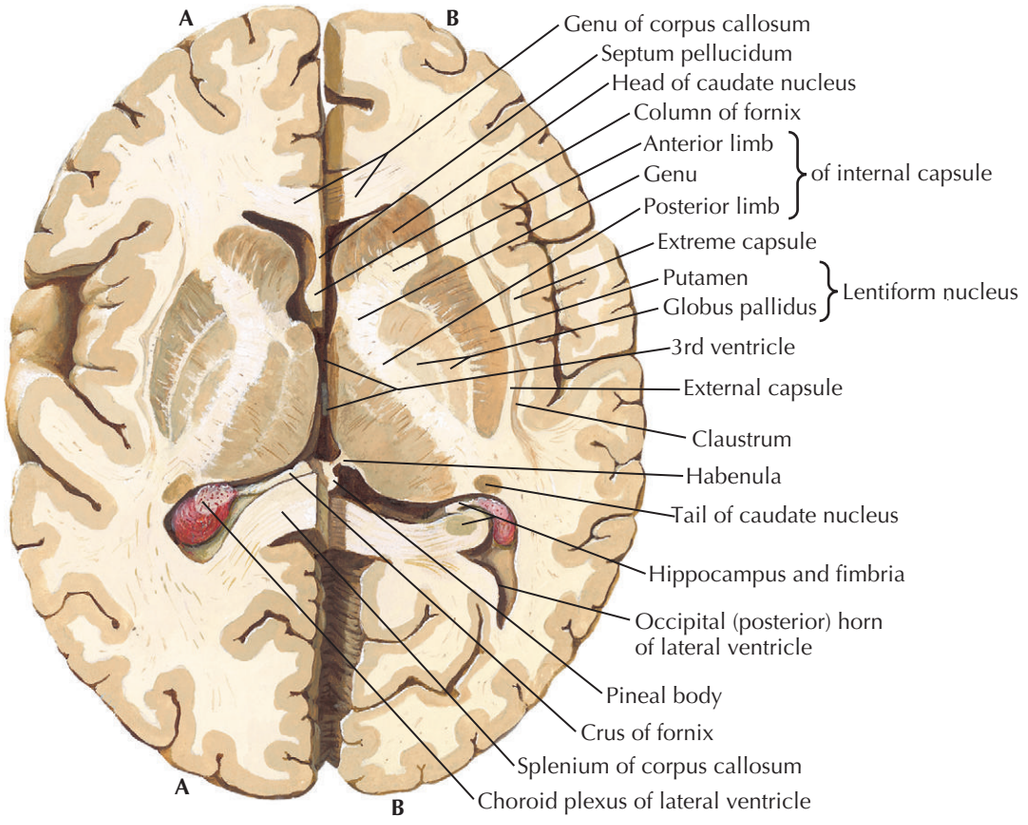


The respiratory pattern after lesion (with or without vagus nerve intact) at three levels in the brainstem and high spinal cord.

BASAL GANGLIA AND MOVEMENT DISORDERS

Basal Nuclei (Ganglia)

Horizontal sections through cerebrum



Anatomy of the Basal Ganglia and Related Structures

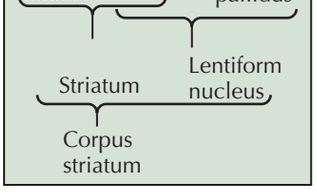
Overview of Movement Disorders

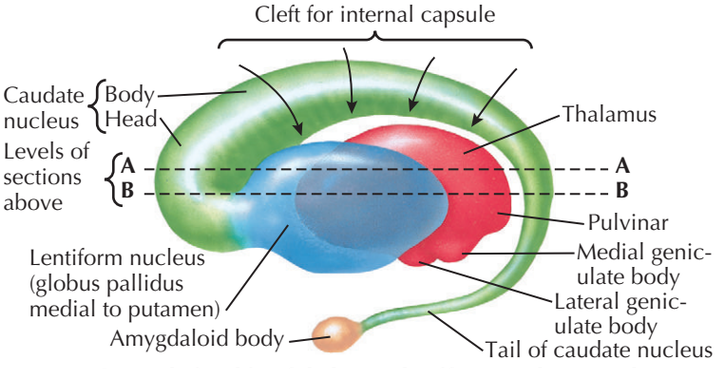
For the past 30 years, movement disorders have encompassed the study of a group of conditions characterized by poverty of movement, the *akinetic-rigid syndromes*, and those with excessive movements, the *hyperkinetic movement disorders* (tremor, dystonia, myoclonus, chorea/ballism, tics, and others). This traditional view, in which disorders of basal ganglia resulted in the aforementioned syndromes, has now expanded to include the *ataxias and disorders of gait and posture.* Advances in surgical techniques and imaging studies have broadened the clinical horizon and catchments of the movement disorders specialist. With the increasing indications for botulinum toxin therapy, *spasticity* and others disorders are now managed by many movement disorders neurologists.

Abnormal involuntary movements (AIMs) should be viewed as clinical signs with many causes. For example, parkinsonism may be the clinical manifestation of a variety of conditions with different or unclear etiologies. *Defining* the broad category of the movement disorder in a given patient *precedes* the classic approach to neurologic diagnosis: *localizing* the lesion and determining the *etiology* of the condition. A careful history with particular attention to family background, pregnancy, labor and delivery, early developmental milestones, trauma, infections, medical and psychiatric comorbidities, and use of illicit drugs and medications, especially neuroleptics, are particularly important when first evaluating a patient with abnormal involuntary movements and may suggest the underlying cause. A detailed general medical examination with emphasis on eye movements, presence of Kayser-Fleischer rings (suggesting Wilson disease), and funduscopic examination looking for retinopathy and optic nerve abnormalities (papillitis, papilledema, or optic nerve atrophy suggesting demyelinating diseases, metabolic disorders, or mitochondrial cytopathies); organomegaly (betraying metabolic or storage diseases); and skin discolorations or deposits (defining phakomatosis, xeroderma pigmentosum, vitaminosis, gastrointestinal disease, malabsorption, calcinosis, or cholesterol deposits, especially at the muscle tendons) may prove rewarding. Searching for additional clues, with a carefully performed neurologic examination, will help in the understanding of the patient's condition.

Once the abnormal movements have been classified, and the neurologic accompaniments documented and placed in context, the cause may become apparent and proper ancillary testing may be undertaken.

Organization of basal nuclei (ganglia)





Interrelationship of thalamus, lentiform nucleus, caudate nucleus, and amygdaloid body: left lateral view

Anatomy of the Basal Ganglia and Related Structures

Anatomically, the basal ganglia constitute a complex circuitry that includes neurons of the caudate nucleus, putamen, subthalamic nucleus (STN) globus pallidus,

Anatomy of the Basal Ganglia and Related Structures *(Continued)*

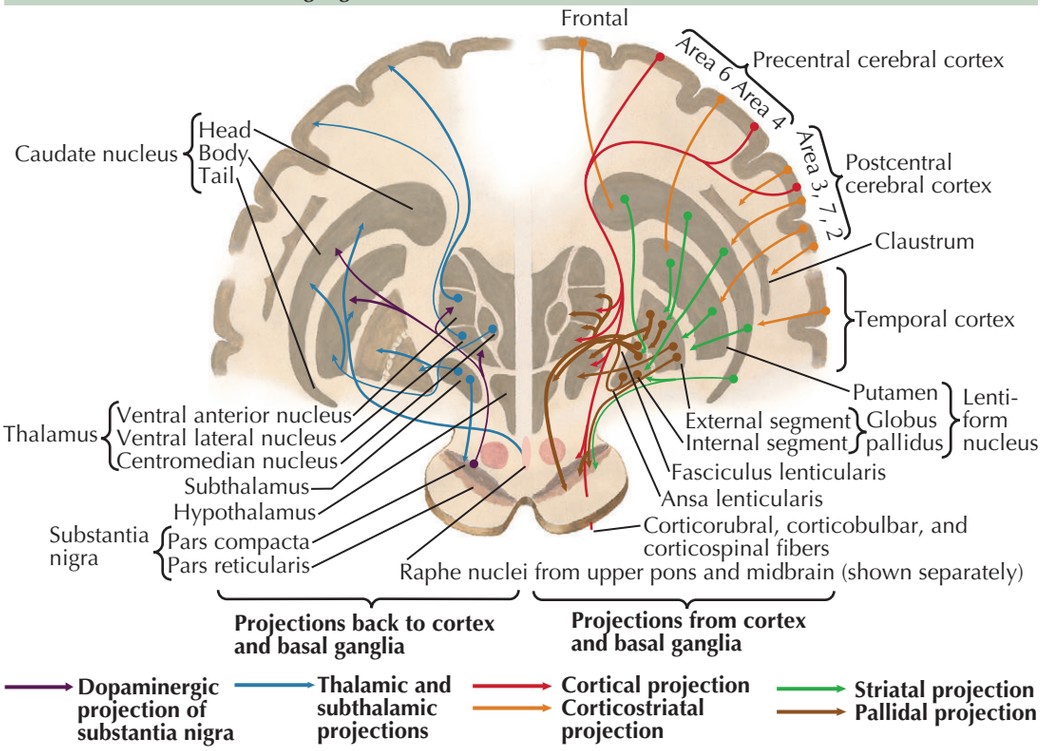
and substantia nigra (SN). The output of the basal ganglia is directed at the motor thalamus (and from there to the frontal cortex) and the pedunculopontine nucleus (PPN).

Globus Pallidus. Divided by the internal medullary lamina into an external (GPe) and internal (GPi) segments, the *globus pallidus* borders laterally with the putamen, dorsomedially with the internal capsule and optic tract and ventrally with the substantia innominata, which, in turn, contains three major functional anatomic systems: the ventral striatopallidal system, the extended amygdala, and the nucleus basalis of Meynert. The latter nucleus, with its cholinergic and γ-aminobutyric acid (GABA-ergic) projections, plays an important role in disorders of memory and the treatment of dementias. The GPi is a major efferent structure of the basal ganglia, using three major projection systems: the ansa lenticularis, the lenticular fasciculus, and the pallidotegmental tract. The ansa lenticularis sweeps ventromedially around the internal capsule, joining the lenticular fasciculus to form the thalamic fasciculus, which, in turn, projects to different thalamic nuclei, especially the ventral anterior (VA), ventral lateral (VL), centromedian, and parafascicular intralaminar nuclei of the thalamus. The pallidotegmental tract terminates in the pedunculopontine nucleus.

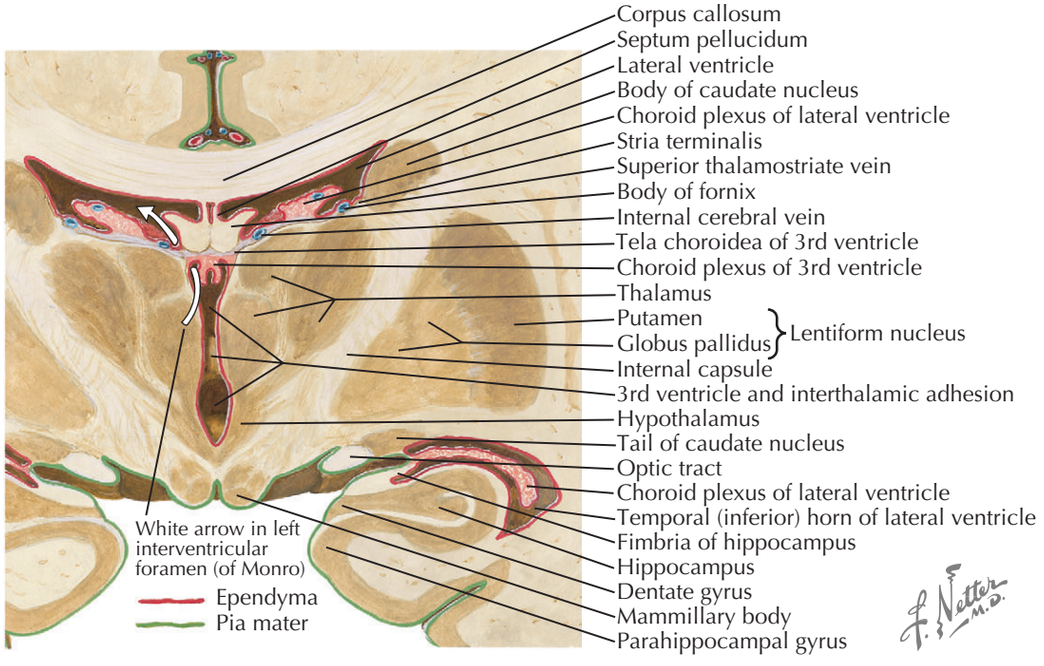
Caudate Nucleus. The caudate nucleus resembles an elongated and curved exclamation mark. Its main part is an expanded head directly continuous with a smaller and attenuated body that merges into an elongated tail. The *head* bulges into the anterior horn of the lateral ventricle and forms its sloping floor. The caudate nucleus is separated from the lentiform nucleus by the anterior limb of the internal capsule, but the separation is incomplete because the head of the caudate nucleus and the putamen are connected, especially anteroinferiorly, by bands of gray matter traversing the white matter of the anterior limb. This admixture of gray and white matter produces the striated appearance that justifies the term "corpus striatum" applied to these nuclei.

Basal Ganglia and Related Structures

Connections of the basal ganglia



Coronal section of brain: posterior view

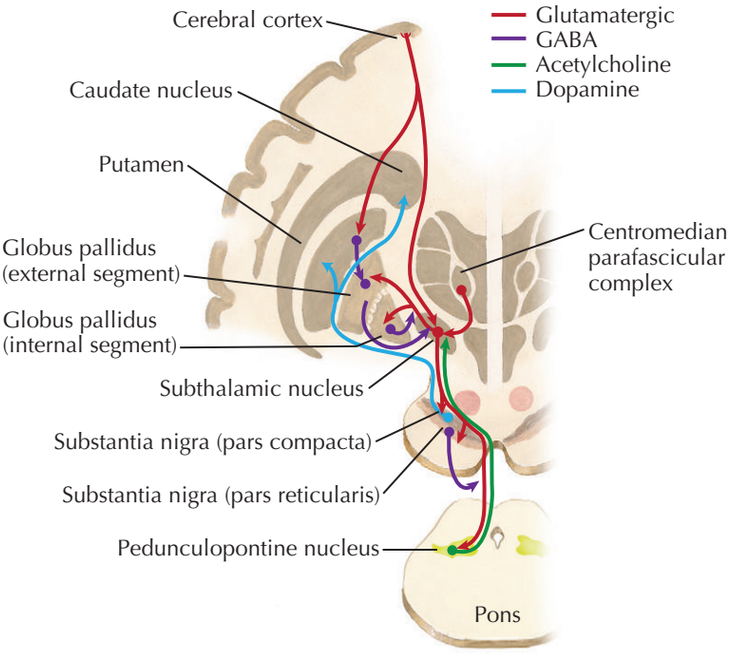


The head tapers into the narrower *body* that lies in the floor of the central part of the lateral ventricle, lateral to the superior surface of the thalamus and separated from it by a shallow sulcus lodging the stria terminalis and thalamostriate vein. The *tail* turns downward along the outer margin of the posterior surface of the thalamus, with the stria terminalis still lying in a slight groove between them. It then curves forward into the roof of the inferior horn of the lateral ventricle, where it separates from the thalamus and lentiform nucleus by the inferior part of the internal capsule and by fibers (including some from the anterior commissure) that spread into the temporal lobe.

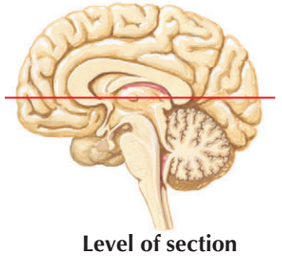
Amygdaloid Body. The tail of the caudate nucleus ends in a small, almond-shaped expansion, the amygdaloid body, which is a complex of several small nuclei located in the forepart of the roof of the inferior horn of the lateral ventricle. The *stria terminalis* issues from

Schematic and Cross Section of Basal Ganglia

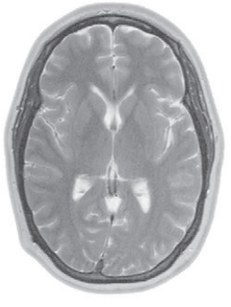
Simplified schematic diagram of basal ganglia circuitry

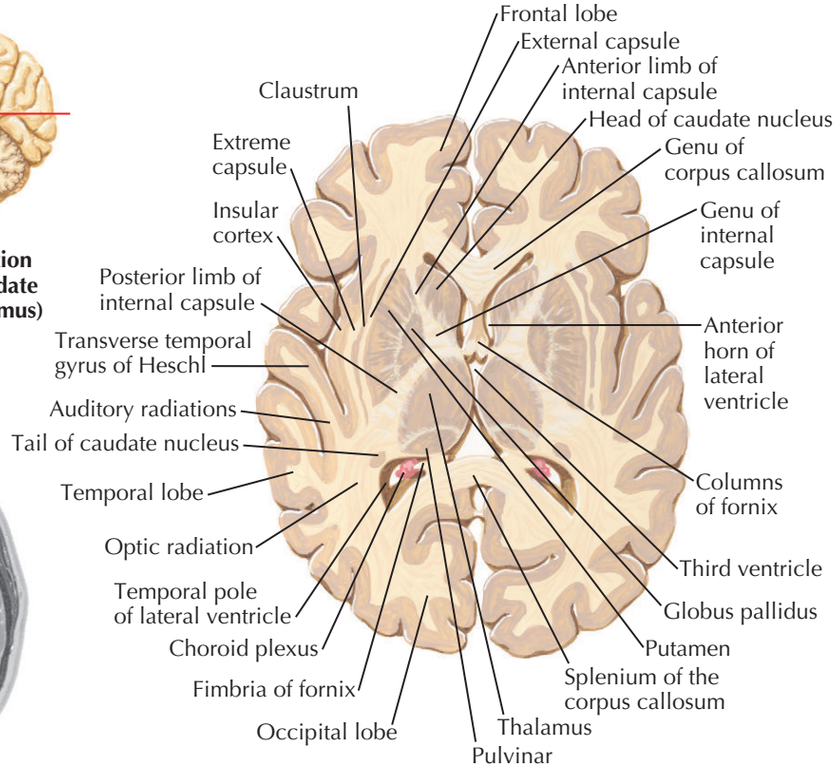


Axial (horizontal) sections through the forebrain



Level of section (head of caudate and midthalamus)





Anatomy of the Basal Ganglia and Related Structures *(Continued)*

the amygdaloid body and runs along the medial side of the caudate nucleus until it reaches the vicinity of the ipsilateral interventricular foramen. Here, some of its fibers join the anterior commissure, others pass to the "septal" region adjacent to the lamina terminalis, and the remainder descends to the hypothalamus and anterior perforated substance.

A nuclear midbrain complex, the *substantia nigra (SN)*, is divided into a pigmented and dopamine-containing pars compacta (SNc) and a cell-poor, pigment-free pars reticularis (SNr). Most dopaminergic projections go to the striatum, while a smaller proportion of SNc axons terminate in the prefrontal cortex. The SNr is a major primary efferent structure of the basal ganglia, along with GPi. SNr goes primarily to thalamus, PPN, and the superior colliculus.

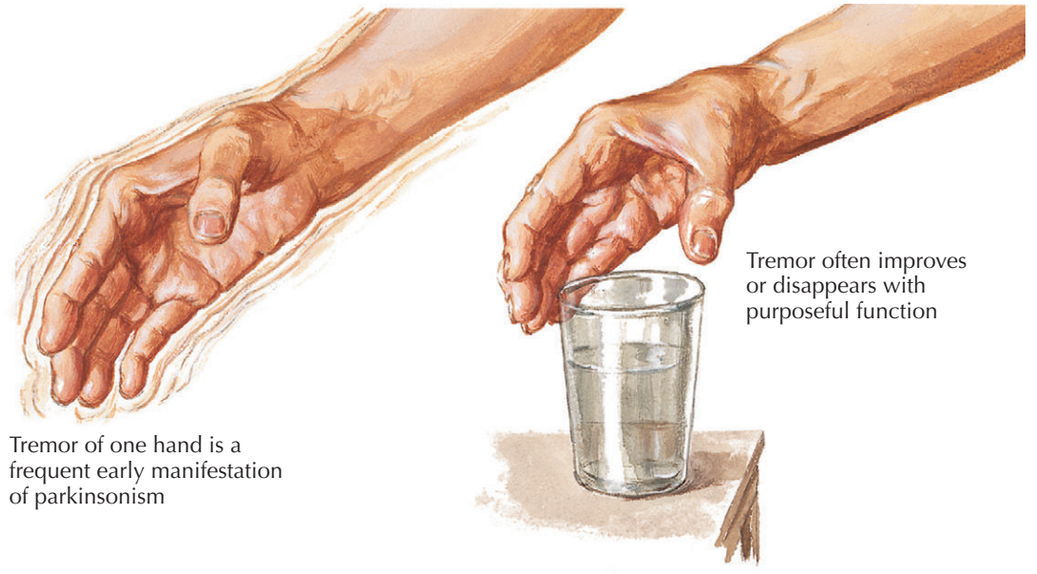
A biconvex structure, the *subthalamic nuclei (STN)* receives glutamatergic inputs from the cerebral cortex, GABA inhibition from the GPe, and provides glutamatergic innervations to the GPe, GPi, SN, and PPN. The STN has become a structure of interest because of its pivotal role in our understanding of basal ganglia function.

The postsynaptic dopamine receptors are divided into two major broad categories, D1/D5 and D2, D3, D4 family of receptors, segregated into two main pathways. The *direct pathway*, subserved by D1 dopamine receptors, sends its projections to the subthalamic nuclei via the GPi, and the *indirect pathway*, via the D2 family of receptors, influences the STN via the GPe.

Recently, the excitatory-inhibitory interplay between the direct and indirect pathways has been conceptualized as focused selection and tonic inhibition (surround inhibition hypothesis). By suppressing excitability in an area that is surrounding an activated neural network, neuronal activity focuses *to select* desired responses. Simultaneously, other pallidal neurons projecting to the thalamus, act *to permit* desired movements. By decreasing their discharge, through focused striatal output chiefly via the direct pathway, tonic inhibition to the thalamus is removed, releasing the cortical generators for normal or desired movement to occur. Therefore the presence of abnormal involuntary movements results from either *failure of inhibition or excessive excitation of the surrounding structures.*

Based on the models discussed above, it is important to recognize the pallidum as the major outflow structure of the basal ganglia. Most fugal pathways pass throught the fields of Forel. Presently, the STN is the preferred target for the surgical treatment of idiopathic Parkinson disease (iPD), the ventral intermediate (VIM) thalamus for the treatment of essential and certain other types of tremor, and the GPi for dystonia, with deep brain stimulation (DBS) being the favored surgical procedure.

Parkinsonism: Early Manifestations



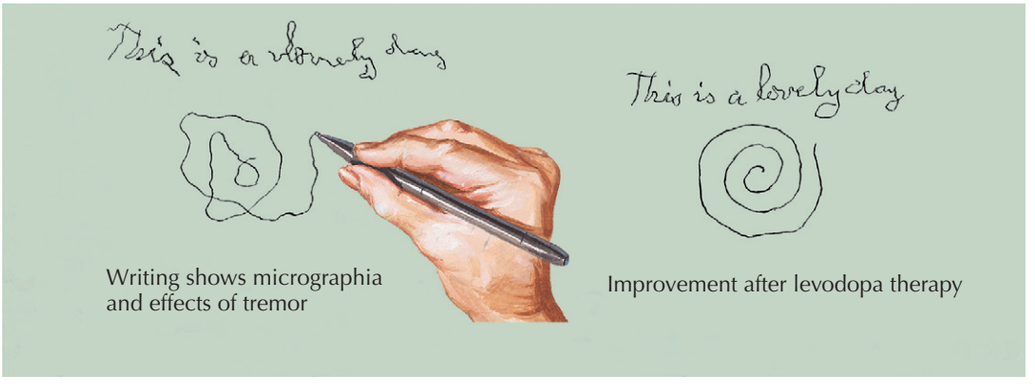
Tremor of one hand is a frequent early manifestation of parkinsonism

Tremor often improves or disappears with purposeful function

Akinetic-Rigid Syndrome, Parkinsonism, or Parkinsonian Syndrome

The parkinsonian syndrome is operationally defined by the presence of *T*remor, *R*igidity, *A*kinesia, and *P*ostural/gait disturbances (pneumonic: TRAP). The diagnosis of parkinsonism is readily made if a given individual has two of the four cardinal features at the time of presentation. Although there are many causes for the parkinsonian syndrome, idiopathic Parkinson disease is by far the most common cause, affecting 1% of the population older than 50 years. It has an insidious onset and progresses slowly at a variable rate for 10 to 20 years or more before culminating in severe disability.

Difficulty in performing simple manual functions may be initial symptom



Writing shows micrographia and effects of tremor

Improvement after levodopa therapy

Idiopathic Parkinson Disease

Idiopathic Parkinson disease is characterized by the presence of tremor, rigidity, or bradykinesia early in the course of the illness, with postural and/or gait disturbances usually developing late in the course of the disease. The presence of atypical symptoms and the rate of progression of the disease are important in distinguishing Parkinson disease from other parkinsonian syndromes. For example, early-onset postural instability, falls, and gait disturbances characterize progressive supranuclear palsy (PSP); marked autonomic disturbances, such as erectile dysfunction in men or urinary bladder incontinence in women may herald the onset of multiple system atrophy (MSA). Stooping, a masked facies, decreased blinking, micrographia, and hypophonia, are common features of parkinsonism but are not unique to Parkinson disease and may be present in other parkinsonian syndromes. Severe anterocollis and camptocormia (bent spine) are more likely to be due to MSA or paraspinalis muscle fatty atrophy/myopathy rather than Parkinson disease (see Plate 7-5). Excessive neck rigidity, primarily when accompanied by marked oculomotor disturbances, such as hypometric slowed saccades in downward gaze or a clear defect of voluntary ocular excursion to command or pursuit but a normal excursion on the doll's eye maneuver, particularly in the vertical plane, suggest PSP. Other oculomotor disturbances, such as saccadic intrusions (principally square wave jerks or ocular flutter), nystagmus, or ocular impersistence, may be present in PSP, MSA, corticobasal degeneration (CBD), Huntington disease (HD), and the cerebellar ataxias in variable combinations and degrees of severity.

It is estimated that approximately 80% of the dopaminergic neurons in the substantia nigra have been lost by the time that Parkinson disease is first diagnosed; hence the initial degenerative process leading to parkinsonism begins several years before the clinical diagnosis. Although it is usually difficult to diagnose Parkinson disease in the preclinical (premotor) stage, anosmia, constipation, and mood and personality changes may precede the onset of motor symptoms by a few years. For most patients, the onset of motor symptoms is subtle and may be obvious first to family members or coworkers.

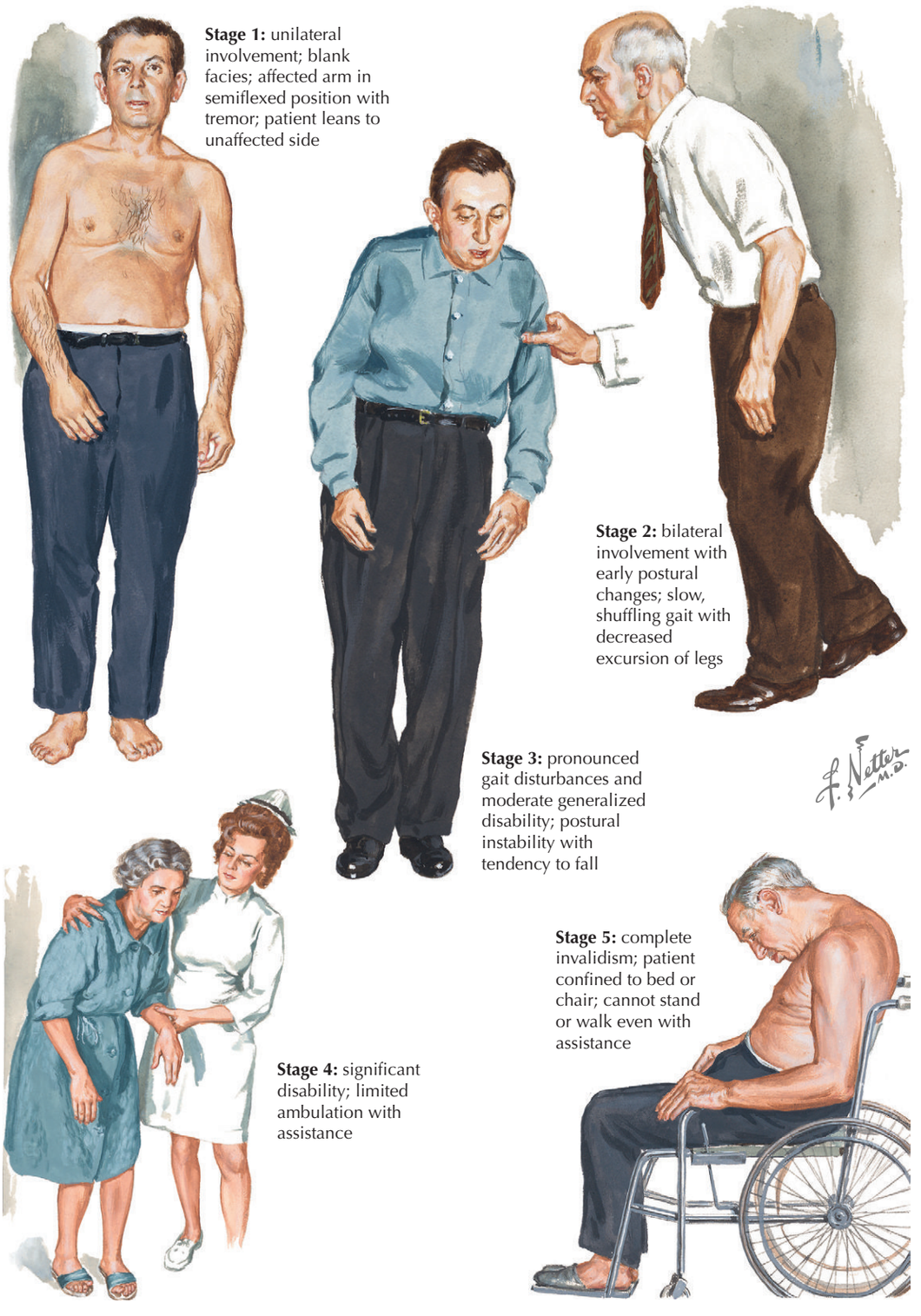
Dopamine deficiency is responsible for the pathophysiology of motor symptoms in Parkinson disease.

Akinetic-Rigid Syndrome, Parkinsonism, or Parkinsonian Syndrome
(Continued)

Although symptoms improve with dopaminergic replacement therapy, tremor and postural and gait disturbances tend to have only a partial response to treatment, particularly in the later stages of the disease, suggesting the substrate of such symptoms may lie somewhere else along the central nervous system. Indeed, it has been shown that the pedunculopontine nuclei (PPN), a cholinergic structure closely linked to the striatonigral system, may play a major role in gait control. In addition, preliminary studies using PPN-targeted neuromodulation have shown mild improvements in gait difficulties and freezing in some patients, although the final outcomes in such studies are unclear at this time.

Tremor is a classic feature of parkinsonism. Typically, it is a rest tremor, disappearing with movement but resuming when a static posture is achieved, and has a 3-Hz frequency. Although it is most commonly seen in Parkinson disease, it may occur in other parkinsonian conditions, such as MSA and in those states induced by dopamine-blocking or dopamine-depleting medications. Its origin is not clear, but some evidence suggests that the inferior olives or the cerebellum act as the central oscillators, driving tremor by using the cerebellothalamocortical loop as a reverberating system.

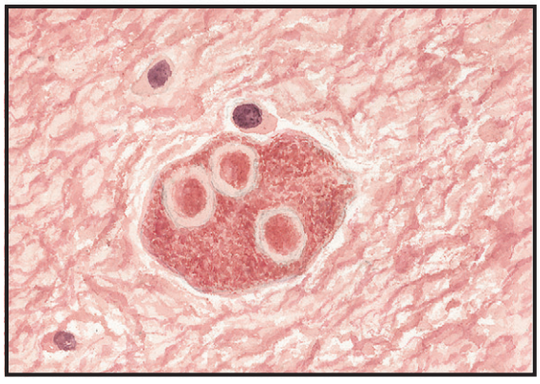
Untreated Parkinson disease may be divided into five stages. *Stage 1* is characterized by mild unilateral disease. Tremor may be the only visible sign but other subtle findings, including slowness or rigidity, may be noted on examination. Gait is usually normal, but there may be mild decrease in arm swing on the most symptomatic side, and the upper limb may be carried slightly abducted at the shoulder and flexed at the elbow. Diminished facial expression, hypophonic speech, reduced manual dexterity, impaired rapid alternating movements, and micrographia with poorly formed letters may be present. As the disease advances to *stage 2*, there is bilateral involvement with postural changes. In this stage, the more classic phenotype is observed, with reduced facial mobility, stooped posture when standing, reduced arm swing on walking, and en bloc turning, Rapid alternating movements are impaired. Movements become slow and deliberate, and patients may complain of fatigue and weakness. Fatigue may be disabling in up to 75% of patients. The hand assumes the so-called striatal posture with dorsiflexed wrist, adducted fingers, flexed metacarpophalangeal and distal interphalangeal joints, and extended proximal interphalangeal joints. In some patients, a "striatal foot" may be present consisting of a varus position with clawing of toes. In *stage 3* disease, retropulsion and propulsion reflect increasing impairment of postural reflexes and righting responses. Gait is festinating and shuffling. In this stage, the symptoms become increasingly pronounced, and the patient may require assistance in the activities of daily living. With further progression, a more advanced stage is reached (*stage 4*), with severe disability, rigidity, bradykinesia, and gait disturbances. Standing is unsteady; a slight push precipitates severe retropulsion, culminating in a fall if the patient is not caught or is left unattended. Eventually, the patient



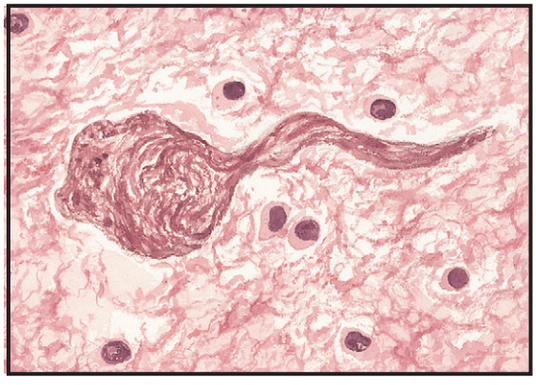
Neuropathology of Parkinson Disease

Normal: section through cerebral peduncles and substantia nigra

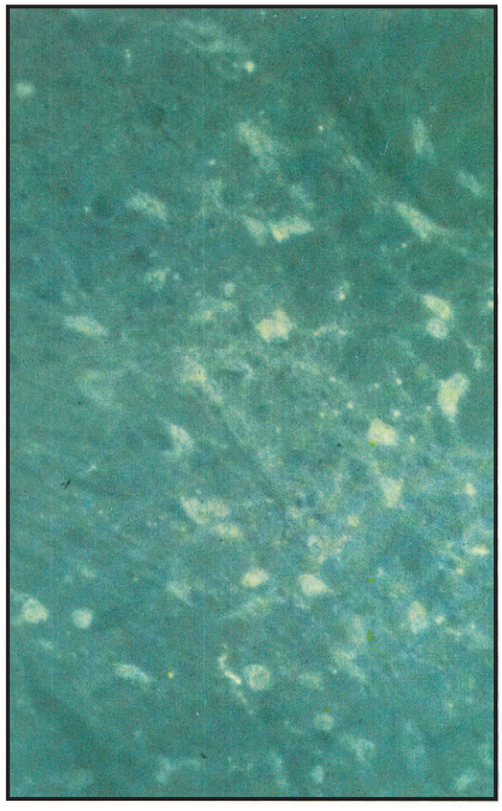
Parkinson disease: substantia nigra depigmented



Lewy inclusion bodies in cell of substantia nigra in Parkinson disease; may also appear in locus ceruleus and tegmentum, cranial motor nerve nuclei, and peripheral autonomic ganglia



Neurofibrillary tangle in nerve cell of substantia nigra as seen in postencephalitic parkinsonism, progressive supranuclear palsy and parkinsonism-dementia complex



Section of substantia nigra of normal animal: treatment of section with formaldehyde vapor causes formation of polymers with monoamines (dopa and norepinephrine) that fluoresce to bright green under ultraviolet light

Akinetic-Rigid Syndrome, Parkinsonism, or Parkinsonian Syndrome

(Continued)

becomes markedly bradykinetic, rigid, and confined to a wheelchair or bed (*stage 5*). Drs. Melvin Yahr and Margaret Hoehn studied the natural progression of patients suffering with Parkinson disease and developed a staging scale that bears their names. This classification, known as the Hoehn and Yahr staging scale, emphasizes the disease by progression of symptoms; it is arbitrarily divided into five stages of disease progression, and although widely used, it provides only a crude estimate of disease severity.

PATHOLOGY

The pathologic hallmark of Parkinson disease is the loss of pigmentation of the substantia nigra, decreased neuromelanin-containing neurons, and deposition of a Lewy body in the motor nucleus of the vagus, locus ceruleus, and substantia nigra (see Plate 7-6). The Lewy body is an intracytoplasmic, eosinophilic inclusion composed primarily of ubiquitin, neurofilaments, and alpha-synuclein, an important component protein normally found throughout the brain, particularly at the synapse. The role that alpha-synuclein plays in the pathogenesis of Parkinson disease is not well understood. Point mutations, duplications, or amplifications in the region of chromosome 4q21 containing the gene encoding for alpha-synuclein have been found in some familial, early-onset cases. Excessive alpha-synuclein leads to protein aggregation and clumping. Other mutations affecting the genes encoding for parkin, an important protein of the ubiquitin/proteasome system (*DJ-1* and *PINK1*), may affect mitochondrial function leading to impaired free radical handling and energy production. The high concentration of iron in the substantia nigra and striatum increases cell vulnerability to oxidative stress. Recently, the progression of Parkinson disease and Lewy body deposition with degeneration have been conceptualized as beginning in the olfactory bulb and lower brainstem, progressing over time to the diencephalon, amygdala, and entorhinal and neocortex.

An example of a fully developed clinical syndrome due to generalized diffuse Lewy deposits is diffuse Lewy body disease/dementia complex.

MULTIPLE SYSTEM ATROPHY

In *multiple system atrophy (MSA)*, the unifying pathologic feature is the oligodendroglial cytoplasmic inclusion bodies (GCIs), which are present in striatonigral degeneration (SND), sporadic olivopontocerebellar atrophy (OPCA), and Shy-Drager syndrome, nosologic entities once considered unrelated disorders but now grouped under the rubric of MSA. The autonomic abnormalities that characterize Shy-Drager syndrome are found eventually in both disorders. Thus MSA is divided in two major groups, MSA-C (cerebellar) and MSA-P (parkinsonism). Other pathologic features include variable neuronal cell loss with gliosis in the putamen and, to a lesser degree, the pallidum, brainstem (particularly the basis pontis and inferior olive), cerebellum, intermediolateral columns of the spinal cord, and peripheral nerves. When OPCA/MSA-C is

Akinetic-Rigid Syndrome, Parkinsonism, or Parkinsonian Syndrome
(Continued)

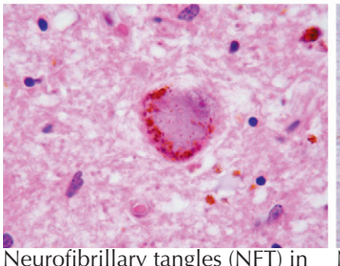
present, atrophy is predominant in the pons, cerebellum, and medullary olives. Tau and alpha-synuclein are the predominant components of GCIs. The MRI appearance is sometimes characteristic (see Plate 7-8).

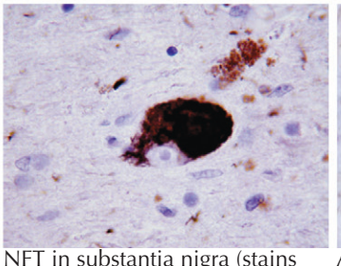
PROGRESSIVE SUPRANUCLEAR PALSY (PSP)

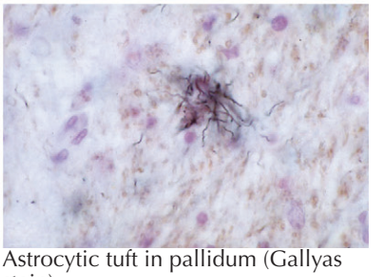
Progressive supranuclear palsy (PSP) is characterized by oculomotor disturbances, parkinsonism, and gait disturbances with postural instability, the latter a common early manifestation of the disease, preceding in most cases the typical downward gaze and horizontal paresis characteristic of the disease (see Plate 7-7). Pathologically, there is neuronal cell loss and gliosis in the periaqueductal gray with deposition of tau-containing globose neurofibrillary tangles with ubiquitin immunoreactivity, atrophy of diencephalon, globus pallidus, subthalamic nucleus, and mesencephalon. This atrophy leads to the "Mickey Mouse" midbrain sign on axial views or the penguin or hummingbird sign on sagittal views in brain magnetic resonance imaging.

CORTICOBASAL DEGENERATION (CBD)

Corticobasal degeneration (CBD) is characterized by asymmetric cortical atrophy, neuronal cell loss, gliosis, and ballooned neurons in the central sulcus region (primary motor/primary sensory cortex), with achromatic intracytoplasmic neuronal inclusions similar to the Pick bodies seen in Pick disease/frontotemporal dementia and primary progressive aphasia. These inclusions with corresponding neuronal cell loss are found predominantly in the diencephalon, thalamus, substantia nigra, locus ceruleus, and cerebral cortex. Tau protein, ubiquitin, phosphorylated neurofilaments and, to a lesser degree, alpha-synuclein are components of such inclusions, sharing immunoreactive properties similar to that found in Pick bodies. CBD (see Plate 7-8) is characterized clinically by asymmetric dystonic posturing with superimposed stimulus-sensitive and action-induced myoclonus, giving the affected hand or limb a tremulous appearance, and by the alien limb phenomena, limb apraxia, parkinsonism, and gait and postural instability, with dementia and oculomotor disturbances manifesting later in the course of the disease.


Neurofibrillary tangles (NFT) in substantia nigra (stained with hematoxylin and eosin)


NFT in substantia nigra (stains with tau)


Astrocytic tuft in pallidum (Gallyas stain)

LEWY BODY DISEASE

Lewy body disease, also known as *dementia with Lewy bodies*, operationally may be viewed as typical dopa-responsive parkinsonism with early-onset dementia, fluctuating alertness and attention, confusion, sleep disturbances, marked sensitivity to neuroleptic or dopamine-blocking agents, and vivid and well-formed visual hallucinations. In most autopsy series, Lewy body dementia is second after Alzheimer disease as the cause of dementia, with vascular dementia a close third. The Lewy body, which is structurally and morphologically similar to that found in idiopathic Parkinson disease, is found throughout the cerebral cortex to a variable degree and in the substantia nigra. Ubiquitin, neurofilament protein, and alpha-synuclein are components of Lewy bodies. In the nucleus basalis and hippocampal formation, scattered senile plaques and neurofibrillary

Akinetic-Rigid Syndrome, Parkinsonism, or Parkinsonian Syndrome *(Continued)*

tangles are found with granulovacuolar degeneration simulating that observed in Alzheimer disease.

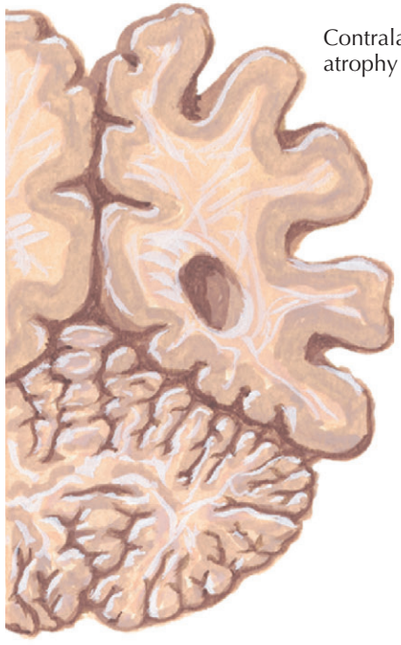
DRUG-INDUCED PARKINSONISM (DIP)

Although not a degenerative disorder of the basal ganglia, drug-induced parkinsonism can mimic idiopathic Parkinson disease and may be difficult to differentiate in a given individual. Therefore the clinician should have a high index of suspicion and must perform a thorough drug history. DIP is discussed here due to the importance in making the diagnosis. Treatment is readily available, and in most instances, identifying the offending medication(s) is all that is needed to explain the symptoms and proceed with treatment. At the most basic level, DIP results from either dopamine receptor blockade, such as that observed with neuroleptic medications, metoclopramide, or certain calcium channel blockers (flunarizine, cinnarizine), or when using dopamine-depleting agents (reserpine, tetrabenazine). Atypical neuroleptics (clozapine, olanzapine, risperidone, quetiapine, ziprasidone), once believed to be free of "extrapyramidal side effects," are now clearly implicated in some cases of DIP. Interactions with dopaminergic (D1, D2), histaminergic, muscarinic, alpha-adrenergic, and serotonergic receptor binding may account for the phenomenology observed. Selective serotonin reuptake inhibitors, the most commonly prescribed antidepressants, may result in DIP by serotonergic down-regulation of dopamine synthesis. Other medications, such as valproic acid and lithium, may result in DIP by mechanisms not well understood. Elimination of the offending agent, dose adjustments, or identification of drug-interactions (effect potentiation) may result in symptom improvement. Patients should be educated on the side effects of medications, particularly when parkinsonism may result as a consequence of their use.

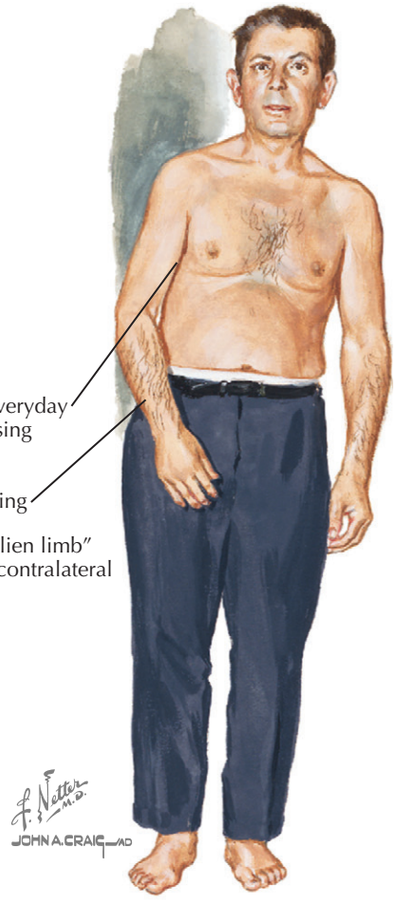
TREATMENT

Current treatment of parkinsonism centers on administration of levodopa. Despite recent advances in our understanding of the chemical and pathologic changes and development of novel therapies for PD, levodopa continues to be the gold standard (see Plate 7-9). Orally administered levodopa is absorbed into the circulation principally from the proximal small intestine. It may be detected in blood for several hours following its administration, reaching maximum peak levels in 2 to 3 hours after ingestion. Rapidly converted to dopamine by the enzyme dopa decarboxylase (DDC; L-amino-acid decarboxylase), approximately 1% of the oral dose penetrates the cerebral capillaries to diffuse through the brain parenchyma, where it is picked up and converted to dopamine in the remaining dopamine-producing cells. Once secreted into the synaptic cleft, dopamine is rapidly deactivated, principally to homovanillic acid by the enzymes catechol-*O*-methyltransferase (COMT) and monoamine oxidase (MAO). To increase available levodopa and to diminish unwanted peripheral dopamine side effects (nausea, vomiting,

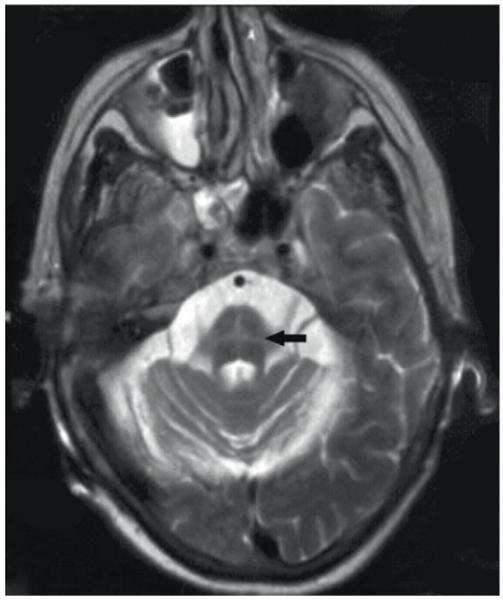
Corticobasal Degeneration



Contralateral asymmetric atrophy of parietal lobe



Multiple System Atrophy

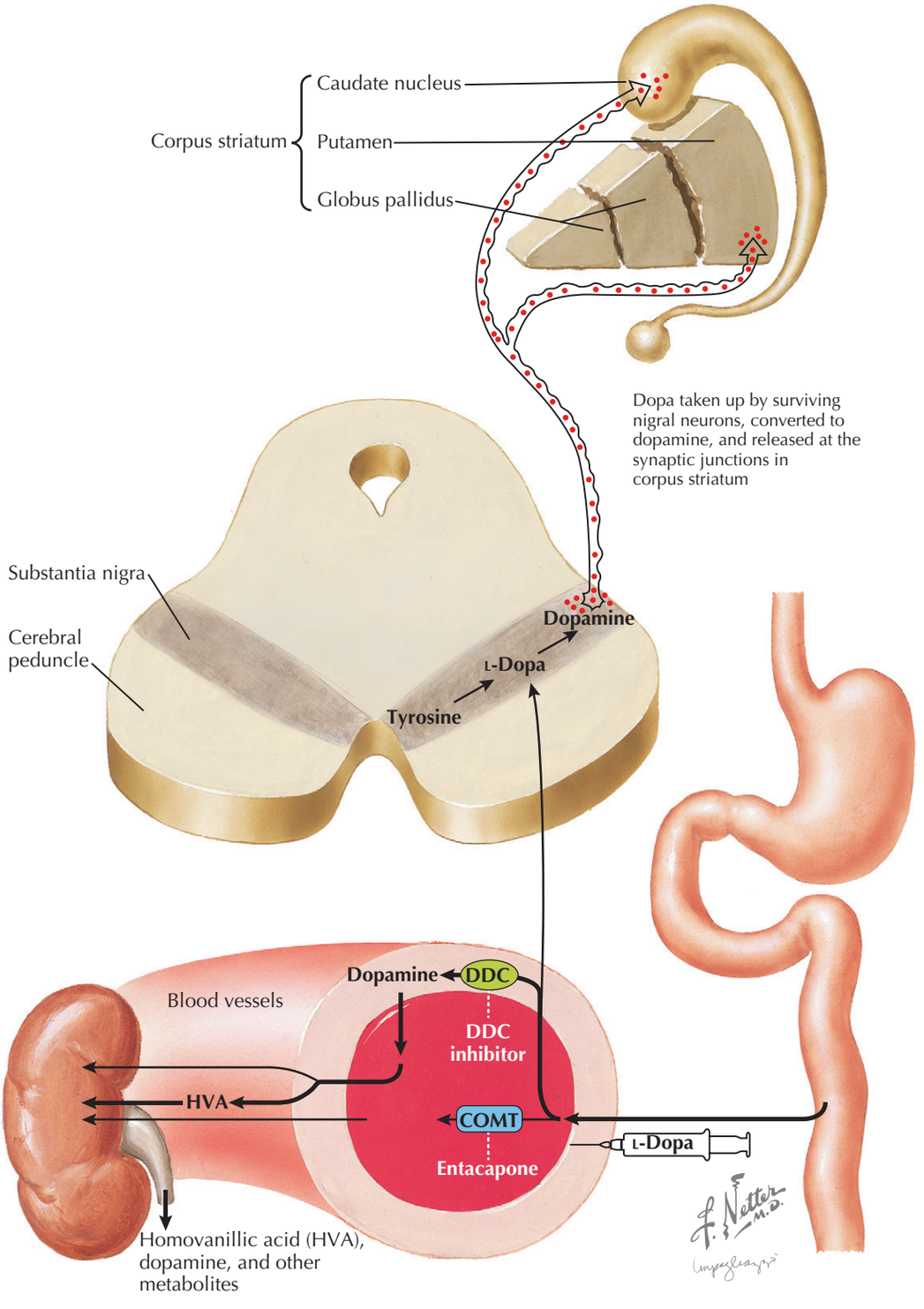


"Hot cross bun" sign typical for MSA

Akinetic-Rigid Syndrome, Parkinsonism, or Parkinsonian Syndrome
(Continued)

arterial hypotension), dopa decarboxylase is inhibited peripherally with carbidopa. The inhibition markedly reduces the conversion of levodopa to dopamine in the medullary vomiting center or trigger zone, preventing its activation. With long-term levodopa use, coupled with the intrinsic pathologic changes occurring in parkinsonism, late motor complications develop in approximately 75% of patients, particularly after 10 years of illness. Wearing off, freezing of gait, unpredictable responses, and levodopa-induced abnormal involuntary movements or dyskinesias may complicate medical management. Certain agents, namely dopamine agonists (ropinirole, pramipexole, rotigotine, pergolide, cabergoline, and bromocriptine) have been developed in hopes of eliminating or delaying the need for levodopa. These agents stimulate dopamine receptors and thus act like dopamine. A dopamine agonist may provide symptomatic improvement and may delay the development of motor complications, chiefly by delaying the need to introduce levodopa. Nonetheless, most patients will require levodopa at one point in the course of their disease. Another strategy has been the use of catechol-*O*-methyl transferase (COMT) enzyme inhibitors to block COMT. Consequently, dopamine remains at the synaptic cleft, leading to increased duration of on-time (time during which clinical benefit is obtained from levodopa) by 1 to 2 hours and stable plasma levodopa levels. With progressive loss of neurons and its attendant decline in buffering capacity, plasma levodopa levels become the primary driver of the clinical response and motor complications. Of the two currently available COMT inhibitors, entacapone, a peripheral COMT inhibitor, is the most commonly used. Unfortunately, the use of tolcapone, a peripheral and central COMT inhibitor, has been hampered by concerns of severe and potentially fatal liver failure. The latter is an idiosyncratic reaction that is difficult to predict, complicating tolcapone use.

The hope of "neuroprotective treatments," that is, treatments to slow disease progression, have been marred by controversies and methodologic flaws in most studies performed to date. Interpretation of the data has been conflicting; instruments used for data collection have proven insensitive, and results of studies in animal models have correlated poorly with findings in humans. Therefore, at the present time, no clear indication and consensus exists for the use of MAO inhibitors, such as rasagiline or selegiline, vitamins, such as vitamin E, or other elements (coenzyme Q10). Rasagiline, selegiline, and amantadine are agents producing mild symptomatic improvement in some patients, and thus may allow a delay in levodopa use.



Surgery

By the middle of the 20th century, a handful of surgical procedures had been developed for the treatment of Parkinson disease and other movement disorders (see Plate 7-10). Cortical excisions, capsulotomies, caudotomies, ansotomies, pedunculotomies, and pyramidotomies, were performed with variable results; unfortunately, most procedures were fraught with severe side effects and terrible outcomes. In 1952, while performing a

Akinetic-Rigid Syndrome, Parkinsonism, or Parkinsonian Syndrome *(Continued)*

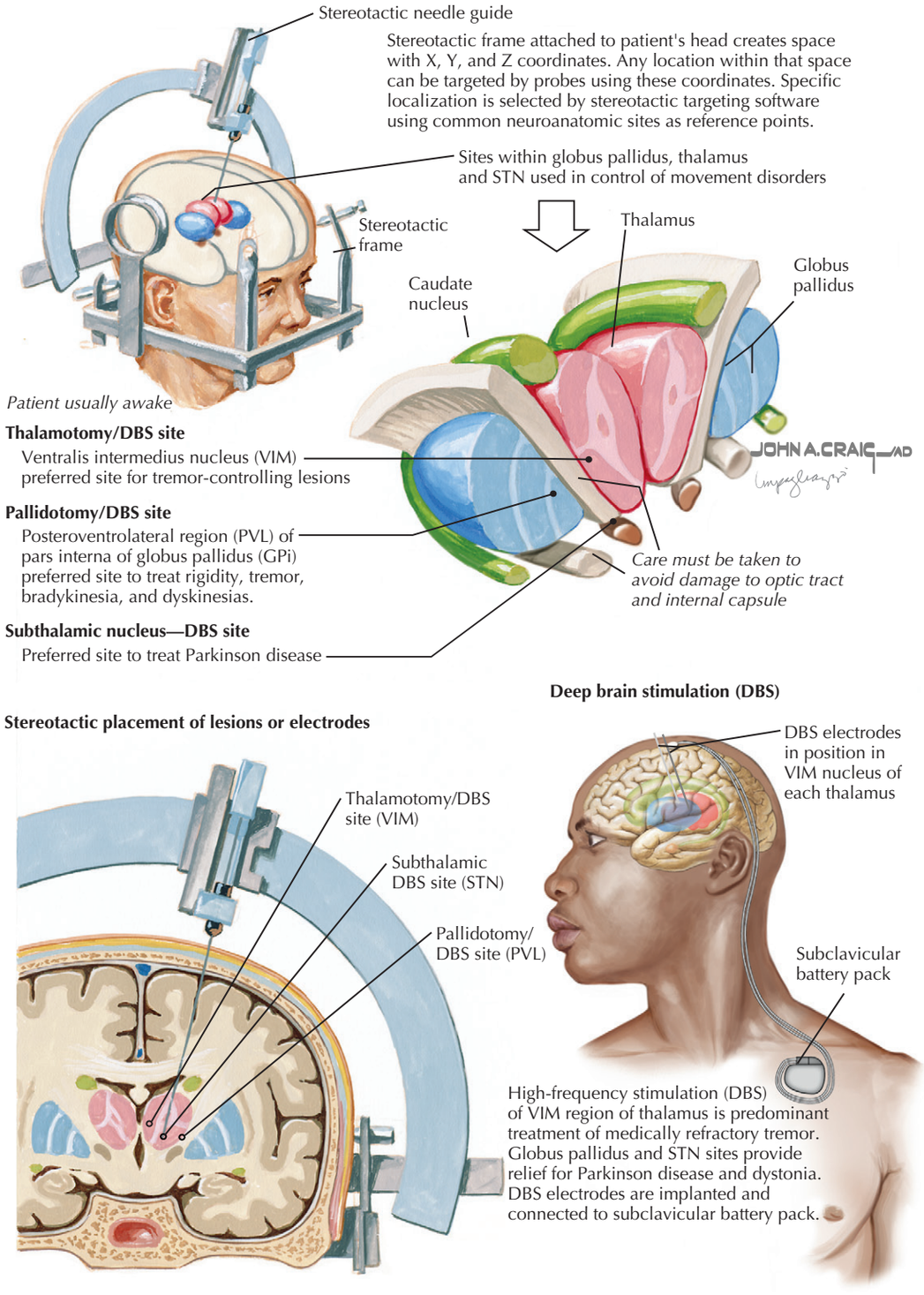
planned pedunculotomy on a 39-year-old patient with postencephalitic parkinsonism, Irving Cooper, a New York neurosurgeon, accidentally ligated the anterior choroidal artery (this type of insult results in a medial globus pallidus infarction). To Cooper's amazement, the patient survived with resolution of the incapacitating tremor and rigidity that had hampered his quality of life up to that point. This event led to an interest in the pallidum as a surgical target. It was not until advances had occurred in the understanding of the physiology of the basal ganglia in health and disease, in surgical and imaging techniques, and in intraoperative recording devices that the current era of lesioning and later neuromodulation techniques developed.

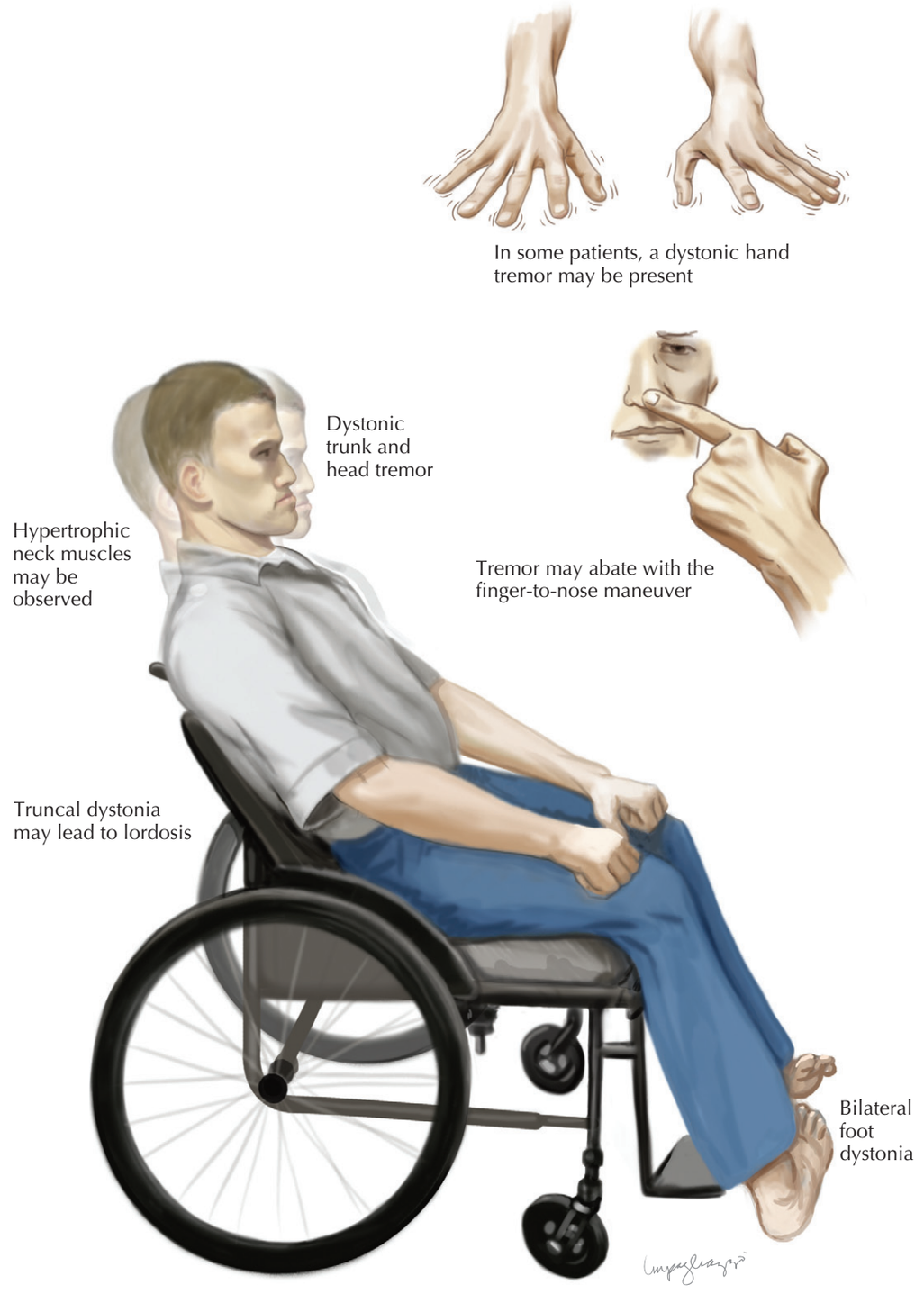
Deep Brain Stimulation (DBS) and Lesioning Procedures. With few exceptions, lesioning procedures such as pallidotomies or thalamotomies, are now rarely performed. These have been replaced by DBS using implantable quadripolar brain electrodes, particularly, in three main targets, namely the medial globus pallidus (GPi), subthalamic nucleus (STN), and ventral intermediate nucleus of the thalamus (VIM nucleus). Although STN is the preferred DBS target for the surgical treatment of Parkinson disease, there is no conclusive evidence that STN-DBS is superior to GPi-DBS.

DBS does not improve symptoms that are resistant to levodopa and, consequently, careful documentation of an adequate response to levodopa is important in surgical candidates. A positive symptomatic benefit from levodopa exposure predicts a better surgical outcome than otherwise. There is no clear age cut-off for the procedure. Octogenarians undergoing the procedure have done well. In general, surgery is reserved for those with a confirmed clinical diagnosis of idiopathic Parkinson disease who have developed motor fluctuations and drug-induced dyskinesias despite optimal medical therapy. Patients should have no general medical contraindications to surgery and should be without dementia or psychiatric comorbidities. In patients with atypical symptoms or a Parkinson-plus syndrome, a poor response to levodopa, dementia, or marked psychiatric disease, DBS is associated with an increased risk for poor outcome and is generally contraindicated. All parkinsonian symptoms improve with surgery, particularly tremor and medication-related abnormal involuntary movements on the side contralateral to the procedure. Rigidity and bradykinesia respond well but to a lesser degree. Postural instability and gait disturbances are less likely to respond.

It is not clear how DBS works. What is evident is that DBS provides a nondestructive and reversible means by which to disrupt neuronal function. DBS continues to evolve as an important and established treatment for neurologic diseases, with new indications being added continuously. A multidisciplinary approach to management provides the best chances for a good outcome in those who are candidates for surgery.

Surgical Management of Movement Disorders





Hyperkinetic Movement Disorder

DYSTONIA

Dystonia is a disorder characterized by sustained muscle contractions causing twisting and repetitive movements or abnormal postures. Dystonia may be a symptom, a syndrome, or a disease and may be classified by distribution, age at onset, and etiology. By definition, no cause for the dystonia is apparent in primary dystonia. In a small proportion of patients with dystonia, genetic and chromosomal abnormalities have been identified.

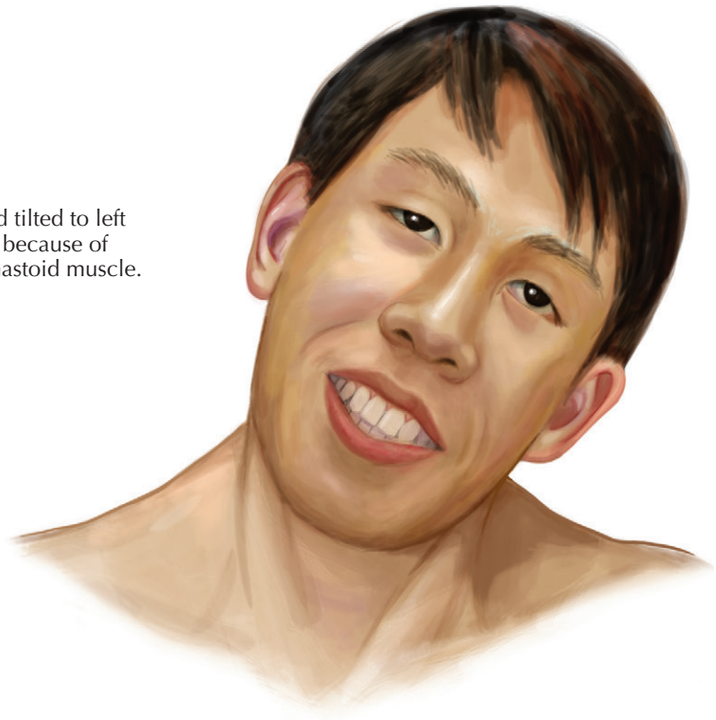
Childhood-onset primary generalized dystonia, also known as Oppenheim dystonia or idiopathic torsion dystonia, is characterized by involuntary, repetitive, sustained muscle contractions or postures, beginning in the foot and leg during childhood and progressing to a more generalized distribution by the second decade of life (see Plate 7-11). It was first described in Ashkenazi Jews expressing the DYT1 mutation on chromosome 9. A GAG deletion mutation in the *DYT1* gene, which encodes for the protein torsin A, has been associated more frequently with the disease. The estimated prevalence is 3.4 per 100,000 individuals. This mutation is also found in non-Ashkenazi individuals throughout the world.

Other genetic mutations causing childhood-onset generalized dystonia have been described more recently. Next to *DYT1*, perhaps the most important is *DYT6*, which is associated with a mutation in the *THAP1* gene.

Adult-onset primary dystonia is usually focal or segmental in distribution and may be a forme fruste of idiopathic generalized dystonia. It may develop in susceptible individuals who perform repetitive tasks, such as instrumentalists, typists, dental hygienists, and writers, or it may appear without known precipitating factors. Examples of *focal dystonia* are writer's cramp, cervical dystonia (spasmodic torticollis), blepharospasm (bilateral, involuntary, synchronous, forceful eye closure), oromandibular dystonia (forceful involuntary jaw opening or closure), spasmodic dysphonia (adductor or abductor dysphonia), and musician's dystonia. In *segmental dystonia*, characteristically there is involvement of two or more adjacent body parts. *Hemidystonia* involves an arm and leg on the same side of the body. *Axial dystonia* affects midline structures (trunk and neck muscles) and may cause speech and swallowing difficulty or arching of the back or neck. *Multifocal dystonia* refers to abnormal posturing affecting two or more nonadjacent body parts. Involvement of both legs and at least one arm, or axial involvement in combination with at least one affected limb is usually observed in *generalized dystonia*. Deep tendon reflexes may be normal or exaggerated, particularly in patients with a secondary cause or in patients with cervical dystonia who developed a compressive myelopathy as a consequence of severe and often early degenerative spine disease. In some patients, a "*dystonic tremor*" or myorrhythmia may be noted.

In *secondary dystonias*, a cause is identified, such as cerebral infarction, tumors, brain trauma, infections, and medication exposure, particularly to dopamine-blocking agents (neuroleptics, metoclopramide). Secondary dystonia can be focal, likely contralateral to the

Cervical Dystonia



Young man with torticollis. Head tilted to left with chin turned slightly to right because of contraction of left sternocleidomastoid muscle.

Hyperkinetic Movement Disorder *(Continued)*

Untreated torticollis in middle-aged woman. Thick, fibrotic, tendon-like bands have replaced the sternocleidomastoid muscle, making head appear tethered to clavicle. Two heads of left sternocleidomastoid muscle are prominent.

lesion, or may be due to minor peripheral trauma such as that resulting from the severe causalgia-dystonia syndrome. It may be hemidystonic or segmental when two or more contiguous body parts are affected, or generalized when the trunk and two other contiguous body parts are involved. Secondary generalized dystonia may result from trivial trauma or, in the appropriate setting, psychogenic factors may be the sole cause. Dopamine receptor–blocking medications, such as neuroleptics and phenothiazine-based antiemetics, can produce *acute dystonia* after a single dose or *tardive dystonia* after chronic usage.

Cervical dystonia, probably the most common focal dystonia, results in involuntary contraction of the neck muscles, causing chin deviation, anterocollis or retrocollis, lateral flexion, and, in many patients, shoulder elevation (see Plate 7-12). The continuous activity may result in muscle hypertrophy, particularly the sternocleidomastoid and neck flexors. Many patients may notice that specific sensory stimuli or sensory tricks, the "*geste antagoniste*," transiently suppress or attenuate spasms. Examples of sensory tricks include touching the face, chin, or elsewhere on the head with a hand, finger, or object. For many years, this phenomenon and the higher prevalence of cervical dystonia in women were mistakenly taken to support the belief that the disorder is psychogenic in nature. In approximately 75% of patients, pain is the most prominent feature. Degenerative cervical spine disease is a common complication and is occasionally associated with a compressive myelopathy.

Dystonia-plus syndromes include dystonia accompanied by other neurologic findings on examination. *Dopa-responsive dystonia (DRD)*, an autosomal dominant condition with incomplete penetrance, is due to a defect in chromosome 14 encoding for the guanosine triphosphate (GTP)-cyclohydrolase enzyme responsible for the biosynthesis of tetrabiopterin, which, in turn, is an essential cofactor in the production of dopamine by tyrosine hydroxylase. Tyrosine hydroxylase is the rate-limiting step in the synthesis of dopamine and other catecholamines. Dopa-responsive dystonia, also known as Segawa disease, typically manifests in the first decade of life as a gait disorder, mimicking cerebral palsy in some patients. In adolescents, the dystonia is characterized by diurnal symptom fluctuations and can be accompanied by mild parkinsonism, tremor, spastic or scissoring gait, and scoliosis. One key feature in the clinical examination of adolescents or young adults with DRD is the marked loss of postural stability noted when performing the pull-push test. The disorder has an excellent response to levodopa, which is the treatment of choice.

CHOREA/BALLISM

Chorea is characterized by random jerky movements jumping from one body part to another. They are irregularly timed, nonrepetitive, and abrupt in character, varying in severity. In mild cases, they may lead to restlessness, intermittent exaggeration of facial expression, or fidgetiness of the hands or toes. In more severe cases, the gait has a dancing quality and limbs exhibiting violent and ballistic movements. It can involve proximal and distal muscles. Patients often attempt to mask such movements by incorporating them into voluntary activities. *Ballism* can be conceptualized as a severe form of chorea affecting the proximal limb muscles, giving a "throwing" character to the movement. The most common form of ballism is seen in parkinsonian patients with severe levodopa-induced abnormal involuntary movements (dyskinesias) or in patients with contralateral subthalamic lesion (infarct, demyelination). Patients may have difficulties maintaining a sustained posture. When asked to grip the examiner's hand, pressure cannot be sustained, resulting in the "*milkmaid's grip*"; when asked to protrude the tongue, the tongue will pop out, resulting in the "*catch fly sign*" *or* "*harlequin's*" *tongue* The bon-bon sign may be present (the tongue moves involuntarily inside the mouth, hitting the inside wall of the cheeks). This latter sign is particularly prominent in patients with drug-induced orolingual chorea (neuroleptic-induced tardive dyskinesia).

There are many causes of chorea, such as pregnancy *(chorea gravidarum)*, *Huntington disease*, *benign hereditary chorea*, neuroacanthocytosis, *Sydenham chorea*, systemic lupus erythematosus, focal vascular lesions, medications (particularly the chronic use of neuroleptics and oral contraceptives), various metabolic and endocrine disorders (hyperthyroidism, hypoparathyroidism, or hyperparathyroidism and hypoglycemia or hyperglycemia), and others.

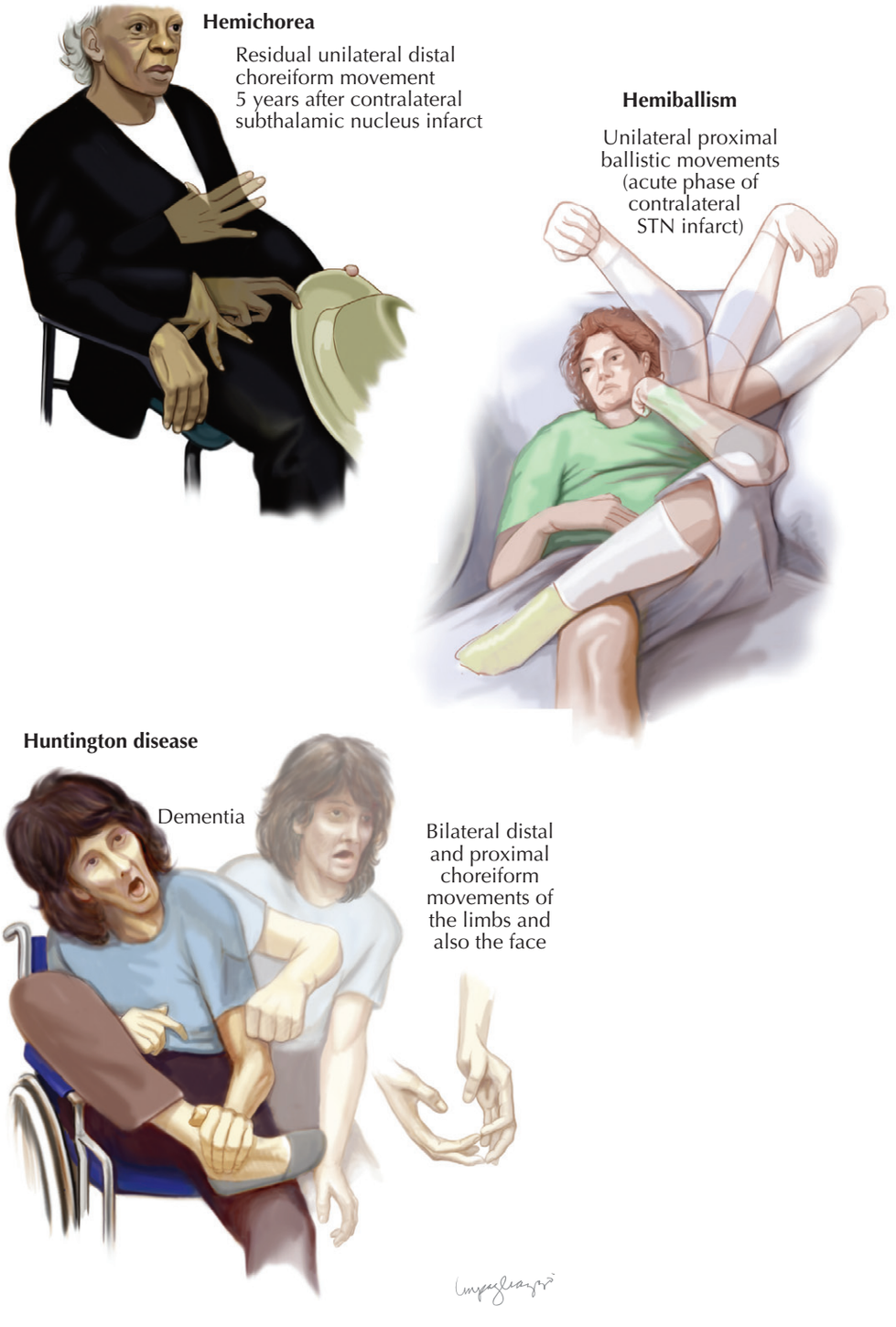
In adults, the most common cause of chorea is medication, especially the use of levodopa in Parkinson patients or the long-term use of neuroleptic drugs or metoclopramide, which causes tardive dyskinesia. In children, Sydenham chorea remains the most common cause.

The second most common cause of chorea in adults is *Huntington disease* (HD). First described by George Huntington in1872, this autosomal dominant neurodegenerative disorder, with a 100% penetrance, has an abnormal trinucleotide (CAG) gene expansion, with the defective gene located in the short arm of chromosome 4. The disorder is characterized by choreiform movements and dementia or behavioral changes. In the United States, the estimated prevalence is 5 to 10 cases per 100,000 people. Age at onset is in the fifth to sixth decades of life, with duration of illness of 15 years in the adult and 8 to 10 years with the Westphal variant. Because of its insidious onset, the onset of symptoms is often not recognized, and abnormal movements are erroneously attributed to anxiety. Patients often have personality and behavioral changes early in the disease and these may be the initial manifestation in more than 50% of cases. Eventually, symptoms become prominent and disabling. Speech becomes dysarthric. Oculomotor alterations, such as impaired saccade initiation, particularly an inability to initiate saccadic eye movement without blinking or head thrusts, are common. Loss of optokinetic nystagmus can occur after some years. The only laboratory study available to confirm the diagnosis is genetic testing. In early stages of the disease, brain magnetic resonance imaging (MRI) may show nonspecific changes in the neostriatum, caudate, and putamen; striatal atrophy, most notably the caudate head, occurs later in the disease.

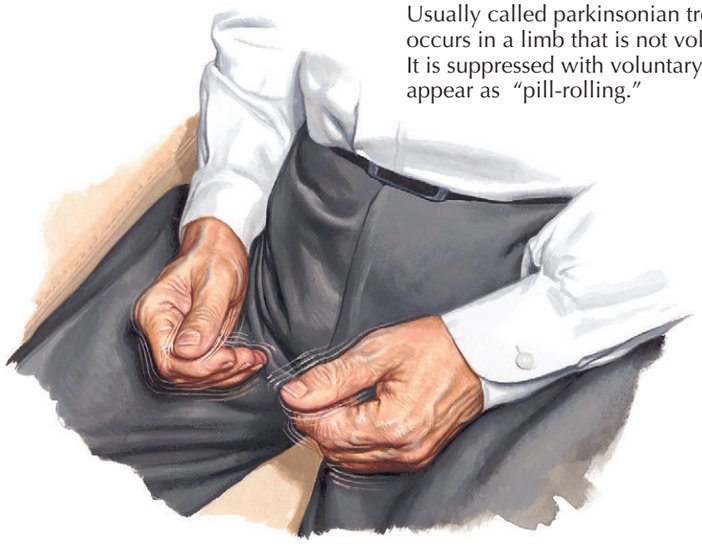
Benign hereditary (familial) chorea, an autosomal dominant disorder, begins early in childhood. Mild generalized chorea, affecting the distal extremities more than the proximal muscle groups, is the characteristic movement disorder; when present, minor neuropsychiatric features, such as mildly lower scores on cognitive tests, complete the clinical picture. Benign hereditary chorea has been associated with mutations in the *TITF-1* gene.

Sydenham chorea is a manifestation of acute rheumatic fever. It is also called "*St. Vitus's dance*," acute chorea, chorea minor, or rheumatic chorea. Although more common in adolescent girls, it is also seen in adults. The clinical features of chorea are similar to those described for Huntington disease. Obsessive-compulsive and impulsive disorders and emotional lability may also occur. Prophylaxis with antibiotics is recommended until adulthood for children with Sydenham chorea because rheumatic fever recurs in up to one third of patients.

Athetosis is a slow writhing movement of the fingers and toes, seen most often in patients with cerebral palsy, particularly when excited or when trying to communicate. Dystonic posturing, tremor, ataxia, or scissoring gait usually accompanies athetotic movements.



Rest tremor



Usually called parkinsonian tremor, rest tremor occurs in a limb that is not voluntarily activated. It is suppressed with voluntary movement. It may appear as "pill-rolling."

TREMOR

Tremor is a rhythmic, oscillatory, involuntary movement caused by the alternating activation of agonist and antagonist muscles. The etiology of tremor is diverse and includes *hereditary* (familial tremor), *degenerative* (Parkinson disease), *metabolic* (thyroid, parathyroid, or hepatic disorders and hypoglycemia), *toxins* (nicotine, mercury, lead, carbon monoxide, manganese, arsenic, toluene), *illicit drug use or medication-induced* (neuroleptics, tricyclics, lithium, cocaine, alcohol, adrenaline, bronchodilators, theophylline, caffeine, steroids, valproate, amiodarone, thyroid hormones, vincristine), *peripheral neuropathies* (Charcot-Marie-Tooth disease, Roussy-Levy syndrome, complex regional pain syndrome), and *psychogenic disorders*.

Tremor may be classified as *rest*, *postural*, *and intentional*, according to its relation to activity. Rest tremor is best seen when the limbs are relaxed, resting in the patient's lap; when necessary, mental exercises may help to "bring out" the dyskinesia. A 3- to 5-Hz rest tremor is a characteristic feature of Parkinson disease ("pill-rolling" tremor), in which it often starts asymmetrically. One important feature of this type of tremor is its disappearance or improvement with limb movement. Although the tremor may become bilateral with disease progression, it commonly remains more severe on the initially affected side.

Postural tremor is seen when the limbs are actively maintained in a particular posture against gravity and disappears when the limbs are at rest. Examples of postural tremors are *essential tremor*; drug- or toxin-induced tremor, metabolic conditions, and alcohol withdrawal states. *Physiologic tremors* are also postural in nature and are seen in all individuals at a frequency of 8 to 12 Hz. They are enhanced by caffeine, fear, or anxiety.

Essential tremor is a sporadic condition, but in approximately 50% of those affected, a family history may be elicited *(familial tremor)*. Typically, a 5- to 8-Hz tremor is present bilaterally in the hands or arms. A tremor of the head or vocal cords is also common. Patients often noticed an improvement in tremor after having a sip of alcohol. Most cases are mild and do not require treatment, but when necessary, propranolol, primidone, or certain antiepileptic drugs may be effective.

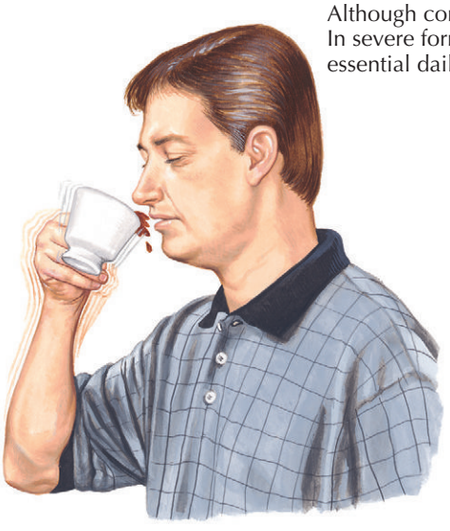
Intention tremor is the tremor most commonly associated with disease of the cerebellum and its associated pathways, but it may be seen in patients with advanced essential or familial tremor. The tremor, which occurs during movement, can be unilateral or bilateral, depending upon the cerebellar lesion, and may affect upper and lower limbs. It has a frequency of 2 to 4 Hz and characteristically worsens as the limb approaches its target (end-point accentuation). Another term used for cerebellar outflow tremor is rubral tremor. We discourage the use of such a term because these are not specific for lesions found only at the red nucleus. We prefer the term *cerebellar outflow tremor* to describe intention, rubral, or cerebellar tremor.

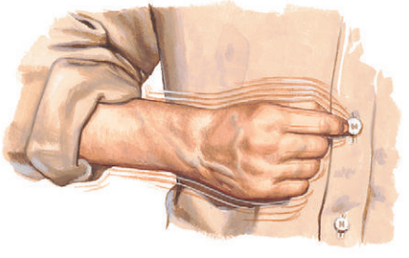
A "*wing beating*" tremor has been described in patients with Wilson disease and in patients with multiple sclerosis or stroke involving the superior cerebellar peduncular region. In these patients, the tremor is most prominent when flexing the forearms at the elbows and elevating the shoulders laterally to reach a 90-degree angle in the fully abducted position. This "phenomenology" is similar to that in cerebellar outflow tremor, particularly when severe, and probably represents involvement of cerebellothalamofugal pathways.

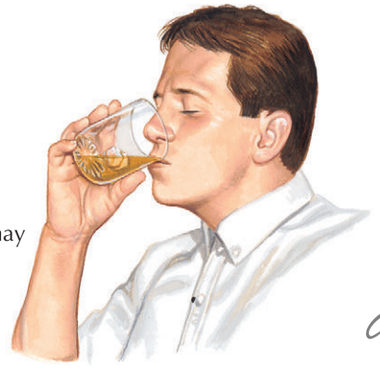
Action tremor (example: essential tremor)

Typically bilateral, essential tremor is the most common movement disorder. It may be accentuated with goal-directed movement of the limbs. Essential tremor affects the hands and cranial musculature (in this order of prevalence). Most common presentation is the association of hand tremor and a tremor in the cranial musculature (leading to a nodding or no-no head tremor).

Although considered benign, it can become incapacitating. In severe forms the patient may not be able to perform essential daily activities, such as drinking from a cup or dressing.







A useful clinical clue is that alcohol may temporarily alleviate symptoms.

C. Machado M.D.

Tics and Tourette Syndrome

Tics involving the eyes, such as eye-blinking, are the most common tic in childhood-onset tic disorders. Patients with tic disorders frequently develop other motor tics of the head and neck, including grimacing and frowning.

Tics are sudden, rapid, stereotyped, repetitive, nonrhythmic movements or vocalizations affecting discrete muscle groups. Most experts agree and clinical experience dictates that tics are preceded by a sensory component, described by patients as an "urge." When patients are asked to prevent movements from occurring, an uncomfortable inner sensation builds and an urge to "release" develops, resulting in expression of the tics.

The spectrum of tics includes *transient tics of childhood* when present for less than 1 year, *chronic motor or vocal tics* when tics are present for more than 12 months, and *Tourette syndrome*, defined by the presence of both motor *and* vocal tics for more than 12 months.

Tics may be classified according to complexity of symptoms as *simple motor or vocal tics* when involving only a few muscles or simple sounds, such as eye blinking, shoulder shrugging, facial grimacing, whistling, grunting, throat clearing, snorting, chirping, or sniffing. Many such youngsters are initially mistakenly diagnosed as having chronic rhinitis or "allergies," or punished unnecessarily for loud behaviors. Once considered rare, schoolteachers now easily identify tics and may be the first to call attention to a child's unique behavior. In *complex motor or vocal tics*, multiple muscle groups are recruited in orchestrated bouts of involuntary movements or utterances of words and sentences or phrases. Examples include hand gestures, jumping, touching, pressing, shouting words, or speech blocking. Some individuals may exhibit *copropraxia*, the sudden performance of obscene gestures or *echopraxia*, the involuntary spontaneous imitation of someone else's movements.

Tourette syndrome (TS) is characterized by multiple motor *and* vocal tics. In many TS patients, obsessive-compulsive behaviors and attention deficit disorder, or both, may be present. Anxiety, depression, and self-injury behaviors may complicate the clinical picture.

Tics may be primary or "idiopathic" or *secondary*, in which a definable cause is found. Primary tics are by far the more common in children and adolescents, with secondary disorders in that age group being rare. In adults, trauma, encephalitis, stroke, carbon monoxide poisoning, neurosyphilis, Creutzfeldt-Jakob disease, and central nervous system (CNS) injury from hypoglycemia may result in tics or Tourettism. Some genetics disorders in which tics have been described include Huntington disease, neuroacanthocytosis, neuroferritinopathy (Hallervorden-Spatz disease), dystonia with tics, tuberous sclerosis complex, and some cases of Duchenne muscular dystrophy. A few patients with Down syndrome, Asperger/autism spectrum, and fragile X-tremor syndrome have also been reported to have tics. The use of illicit drugs or medications may result in tics, Tourettism, or punding, particularly the use of cocaine, amphetamines, and antiepileptic medications (phenobarbital, phenytoin, and carbamazepine). Less commonly, opioids, lithium, levodopa, and antidepressants may induce or worsen tics.

The substrate for tics and Tourette syndrome seems to reside in the basal ganglia and related structures. Supporting evidence for this concept includes the clinical observation of tic improvement when patients are treated with dopamine-blocking or dopamine-depleting agents. Other evidence comes from functional imaging studies demonstrating volumetric striatal changes and, in some, increased dopamine synaptic content. Recently, deep brain stimulation has demonstrated improvement of tics when stimulating different targets of the corticostriatothalamic and limbic pathways/structures.

The goal of treatment of tics and Tourette syndrome is to relieve some of the more pressing symptoms. For some affected persons, tics may be the most bothersome aspect of their illness. For others, obsessive-compulsive behaviors, attention deficit with hyperactivity, anxiety, or depression may be more distressing. There is no general agreement as to the best treatment for tics. Most authors recommend alpha-2 agonists, such as guanfacine or clonidine, as first-line therapy. Dopamine-blocking agents are the most potent anti-tic medications but are also associated with a high incidence of side effects. Tetrabenazine, a dopamine depletor, may be useful in some cases. A stimulant such as methylphenidate does not worsen tics as previously thought. It can therefore be safely used in those with tics and attention deficit disorder. The serotonin reuptake inhibitors are helpful in treating anxiety, depression, or obsessive-compulsive disorder in patients with tics or Tourette syndrome. Botulinum toxin therapy has proven to be of some value when used in patients with dystonic tics. A behavioral therapeutic approach using habit reversal therapy at its core has been shown to be effective in a recent large multicenter study. Thalamic or pallidal deep brain stimulation is a promising strategy in refractory cases.

MYOCLONUS

Myoclonus is a brief, shocklike muscle jerk, which may be classified according to *origin*, (cortical, subcortical, brainstem, and spinal myoclonus) and *distribution* (focal, segmental, multifocal, or generalized). Cortical myoclonus may be epileptic (as in Baltic myoclonus or progressive myoclonic epilepsy, photosensitive myoclonus, epilepsia partialis continua) or part of a neurodegenerative disorder (corticobasal degeneration, Alzheimer dementia, diffuse Lewy body disease, and others). Myoclonus can be classified according to *etiology* as idiopathic/genetic (familial myoclonus, myoclonus-dystonia), physiologic (hypnic jerks or diaphragmatic myoclonus/hiccups) or secondary/symptomatic when a cause for the myoclonus is clearly identified. Examples of the latter group may include encephalitis, hypoxia, toxins, storage diseases, and basal ganglia degenerations, as in Huntington disease, Wilson disease, and certain other disorders). Myoclonus may be *positive* due to a brief muscle contraction or *negative* when muscle tone is briefly lost, as in asterixis.

Anoxic brain injuries may result in myoclonus, which, in turn, may be *cortical*, *diencephalic*, or *reticular in origin; stimulus sensitive* or *action induced;* and *segmental*, *generalized*, or *multifocal in distribution*. This type of myoclonus may be focal, preferentially affecting the distal limb muscles, or multifocal with spontaneous, reflexive or stimulus-sensitive jerks accentuated by movement. Frequently, anoxic-induced myoclonus is accompanied by secondary seizures, particularly after cardiopulmonary arrest. Status epilepticus is found in 32% of postanoxic patients, and in many, *multifocal myoclonus* alone or in combination with generalized tonic-clonic seizures is frequently observed. The incidence of myoclonic seizures is bimodal, with the majority of them occurring within 12 hours after cardiopulmonary resuscitation and the remaining occurring several days later. Electroencephalography (EEG) is useful when evaluating these patients, particularly when status epilepticus is suspected. The most frequent EEG findings include diffuse slowing with or without spike or polyspike complexes that are sometimes time locked to the myoclonic jerks. A burst-suppression EEG pattern, when recorded, has a poor prognostic significance. Magnetic resonance imaging of the brain may show diffusion restriction in the cortical and subcortical gray matter between 24 hours and 13 days. Isolated myoclonus generally does not require treatment unless it interferes with mechanical ventilation or nursing care. Myoclonus status is refractory to treatment, may require multiple antiepileptic drugs, and, when accompanied by convulsive status epilepticus, is best controlled with deep anesthesia.

Electrophysiologically, myoclonus is characterized by a muscle bursts that are less than 75 msec in duration. When the cerebral cortex is affected, a "giant" somatosensory evoked cortical response time locked to the onset of the jerk in back-averaged EEG may be obtained.

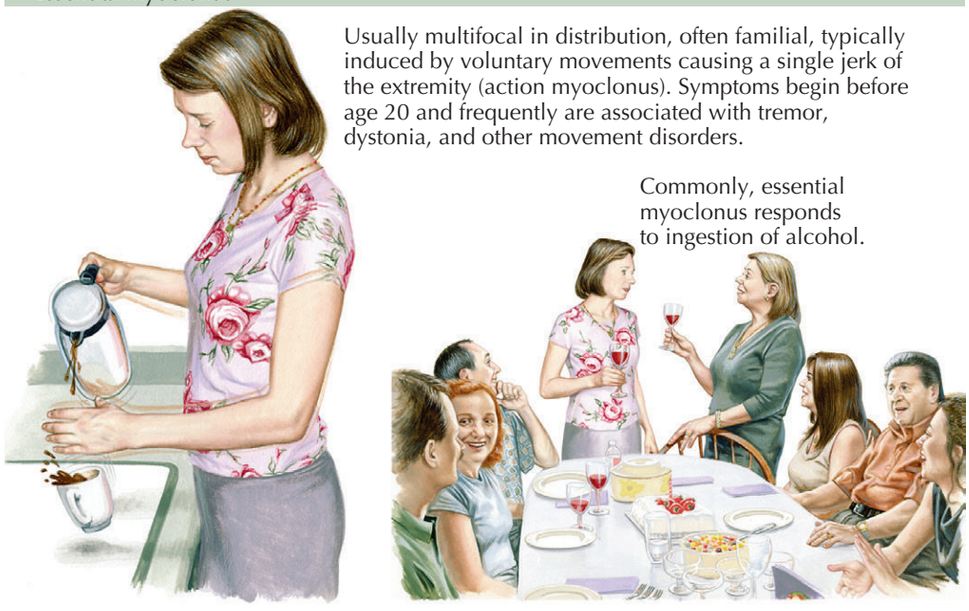
POSTANOXIC MYOCLONUS

In 1963, James Lance and Raymond D. Adams reported the first series of patients with the syndrome of intention or action myoclonus as a sequel to hypoxic encephalopathy. In *postanoxic myoclonus*, axial and proximal muscle groups are particularly affected, the myoclonus often occurring when patients perform an action, such as standing or reaching for an object (action myoclonus). Limb and truncal ataxia, cerebellar outflow tremor, and dysarthria are other common accompaniments. The exact substrate of postanoxic myoclonus generation is not clear. Postanoxic myoclonus may be the result of cortical or subcortical injury or be due to alterations in brainstem serotonergic pathways. The serotonergic raphe nuclei have frequently been implicated.

Some forms of myoclonus, particularly those of subcortical origin, are believed to arise from the reticular system primarily from the *nucleus reticularis gigantocellularis*. This *reticular reflex myoclonus* is characterized by a brief electromyographic burst lasting 10 to 30 msec, with generalized bilateral synchronous activation of muscles following a distribution suggesting spread up the brainstem and down to the cord.

Essential myoclonus may be idiopathic or familial, beginning in the first to second decade of life. In patients with essential myoclonus, the neurologic examination fails to demonstrate other deficits. In a few families, lower verbal scores have been reported and occasionally mental retardation. Similar to essential tremor, alcohol may help to ameliorate the symptoms, but the incidence of alcoholism is increased. In patients with *myoclonus-dystonia*, there is an autosomal pattern of inheritance, men are more affected than women, and there is a higher incidence of alcoholism and behavioral disturbances.

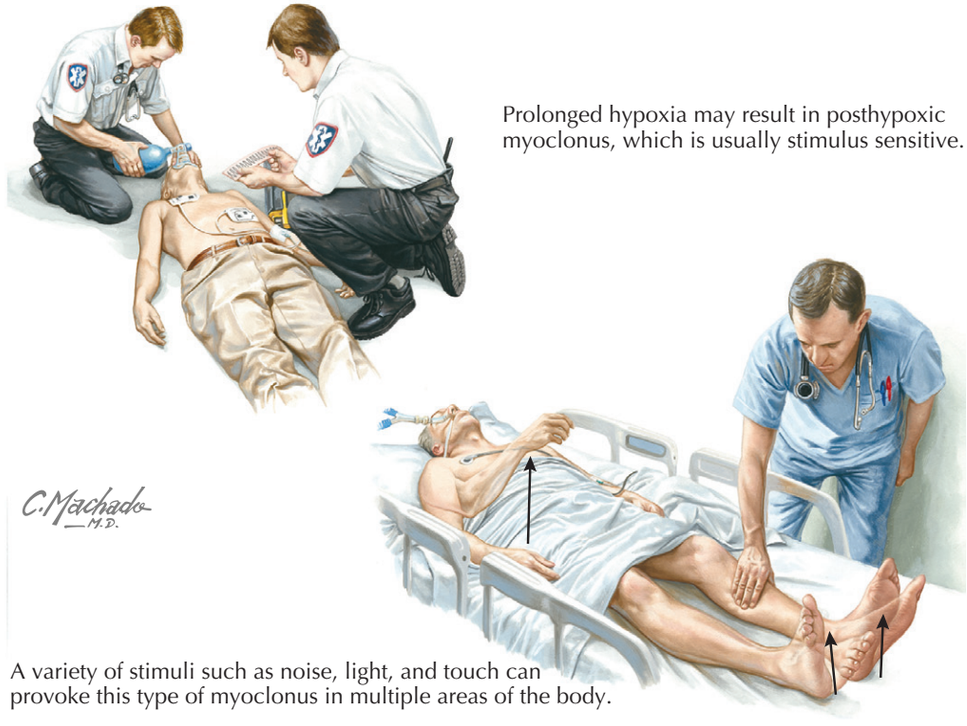
Essential myoclonus



Usually multifocal in distribution, often familial, typically induced by voluntary movements causing a single jerk of the extremity (action myoclonus). Symptoms begin before age 20 and frequently are associated with tremor, dystonia, and other movement disorders.

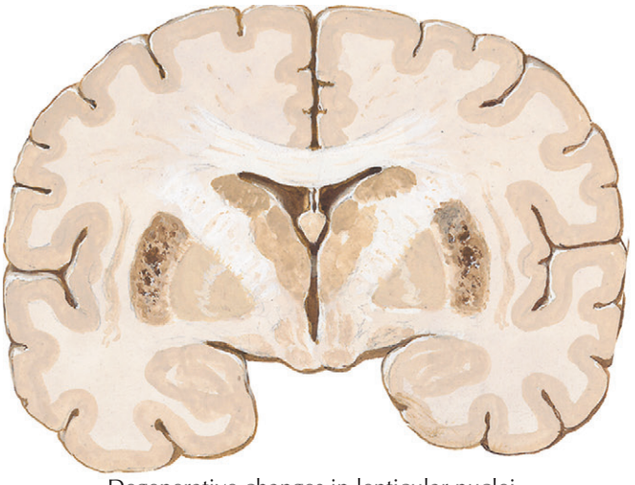
Commonly, essential myoclonus responds to ingestion of alcohol.

Lance-Adams syndrome (posthypoxic myoclonus)



Prolonged hypoxia may result in posthypoxic myoclonus, which is usually stimulus sensitive.

A variety of stimuli such as noise, light, and touch can provoke this type of myoclonus in multiple areas of the body.

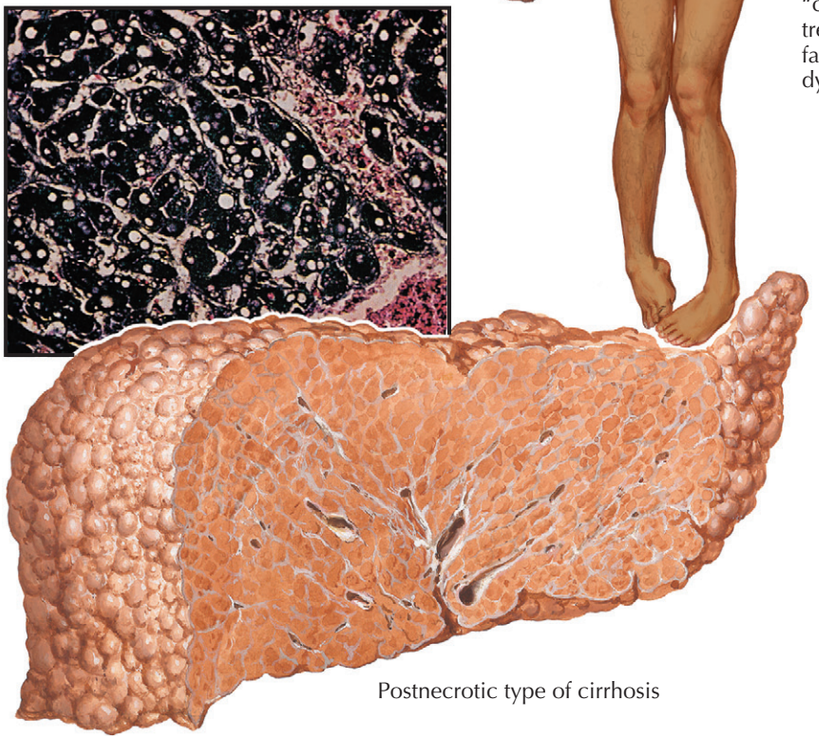


Degenerative changes in lenticular nuclei

Kayser-Fleischer ring

Adolescents more likely have generalized dystonia, with involvement of neck (torticollis) and face (grimacing), occasionally focal; hypertonicity and choreoathetosis may coexist.

Adults more likely have coarse, proximal "wing beating" or "chest beating" tremor, masked facies, and dysarthric speech.



Postnecrotic type of cirrhosis

Wilson Disease

Also known as hepatolenticular degeneration, Wilson disease is an autosomal recessive disorder that occurs in 1 of 30,000 individuals. The abnormal gene, the *ATP7B* (adenosine triphosphate) gene, is located on chromosome 13. The defective protein, adenosine triphosphatase (ATPase), is involved in the transport and incorporation of copper into ceruloplasmin and the vesicular compartment near the canalicular membrane for further bile excretion.

Although a neurologic disorder, it affects multiple organs, with the liver being the most common and earliest affected. Approximately 40% of newly diagnosed cases have hepatic involvement. Neurologic manifestations include dysarthria, dystonia, rigidity, *wing beating* tremor, and choreoathetosis. Children younger than 10 years rarely present with neurologic involvement. Progressive dementia, antisocial behavior, impulsivity, and decreased intellectual performance further complicate the disease and are important manifestations. The *Kayser-Fleischer ring*, the classic ophthalmologic sign of the disease, is a yellow-brown discoloration of the Descemet membrane, best demonstrated by slit-lamp examination. In addition, sunflower cataracts may be noted. Careful bedside ophthalmologic evaluation may reveal Kayser-Fleischer rings in suspected cases. Other features include hemolytic anemia, renal failure with tubular dysfunction, nephrolithiasis, cardiomyopathy, hypoparathyroidism, amenorrhea, and testicular atrophy.

Diagnosis requires a strong index of suspicion and should be considered in all patients, particularly those younger than 40 years, presenting with abnormal involuntary movements, and those presenting with abnormal liver function. Although not specific, 24-hour urinary copper excretion and serum copper and ceruloplasmin levels are useful screening tests. The single best confirmatory test for the diagnosis is elevated hepatic copper levels, but this requires a liver biopsy; this is performed only in cases in which the diagnosis is unclear but the index of suspicious is high. On neuroimaging, a brain MRI shows atrophy of cerebrum, brainstem, and less commonly cerebellum. The *face of the giant panda sign* (globus pallidus hypointensity) is a characteristic MRI finding on T2-weighted imaging seen in 34% of cases.

The copper-chelating agent D-penicillamine has been considered the gold standard of therapy. In patients who cannot tolerate penicillamine, trientine, another copper-chelating agent, has been used. In patients with cirrhosis or fulminant hepatic failure, liver transplantation is the only option.

Psychogenic Movement Disorders

Psychogenic (also called hysterical or functional) movement disorders are disorders without evidence of an organic etiology and for which an underlying psychiatric illness is held responsible. Perhaps one third of patients diagnosed with *psychogenic disorders* eventually are found to have an organic neurologic illness, although this may not necessarily relate to the movement disorder itself. A movement disorder must not be attributed to psychogenic causes simply because the clinician cannot arrive at a definitive organic diagnosis. It is important for the evaluating physician to await developments if a diagnosis is not immediately obvious. With time, new features may suggest the correct diagnosis or the acquisition of more information from the patient or family may suggest the relevance of psychogenic factors.

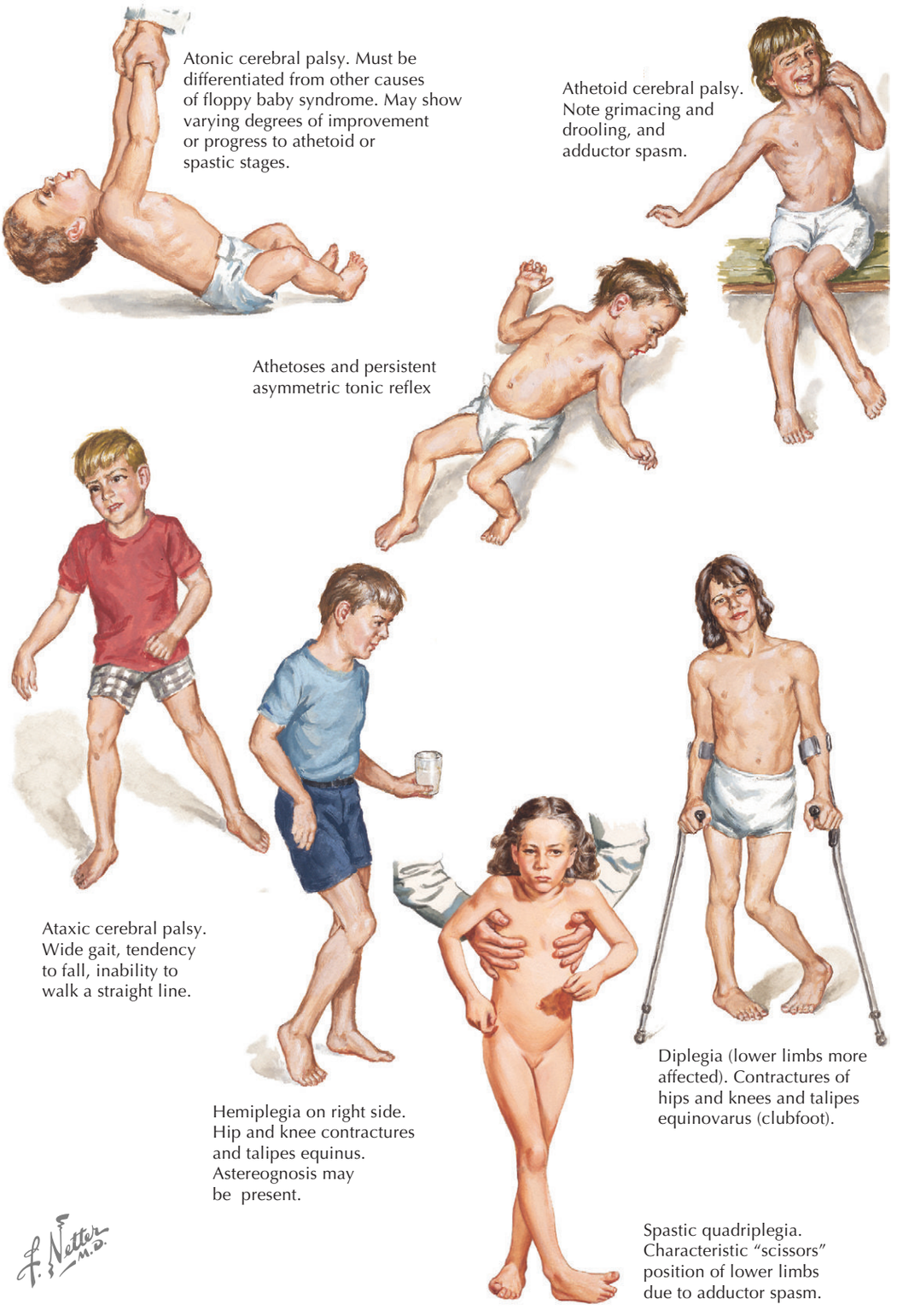
Certain features may suggest a nonorganic basis for the movement disorder. Features in the history that raise this possibility are the abrupt onset of symptoms and their marked variability in nature or severity over short periods of time. In addition, there is often a marked disparity between symptom severity and the functional limitation to which they reportedly lead. Patients may report that they are unable to work because of their abnormal movements, and yet they can perform the activities of daily living, such as using a personal computer, shopping, cooking, and the like. In other words, any disability is selective. It is also important to enquire about a past history of psychiatric or psychogenic illness and to seek any possible secondary gain, as from pending litigation or workers' compensation, which may result from the current symptoms.

The examination findings may also be helpful, especially the general appearance and affect of the patient. There may be a combination of different dyskinesias that vary markedly in nature and distribution over time and worsen when formally examined. Other signs of nonorganic neurologic deficits may be present, such as a nonanatomic sensory loss or a lurching unsteady gait that never results in falls.

Psychogenic tremor is typically of variable frequency and can be entrained by such maneuvers as foot tapping. With mental distraction, tremors or other *hyperkinetic movement disorders* may become more intermittent, variable, or irregular. During skilled movements with the affected limb, they may cease. Loading the limb with weights may increase rather than diminish tremor amplitude. Patients with *psychogenic dystonia* sometimes report that their symptoms are especially troublesome at rest, whereas organic dystonia is often more conspicuous with volitional activity. In a *psychogenic gait disorder*, the gait is often very slow, with excessive gesturing and sometimes wild or bizarre motor activity. It typically is quite variable in severity, lessening with distraction and worsening when the patient is observed overtly.

No anatomic correlation can be made, and the neurochemical basis of the movement disorder is unknown. Patients with psychogenic movement disorders typically are unresponsive to appropriate medications, but remission may occur with treatment of the underlying psychiatric disorder. The psychiatric diagnosis may include various somatoform and factitious disorders, depression, anxiety, and histrionic personality disorders. A specific psychiatric diagnosis cannot always be made despite a high index of suspicion for psychogenicity, and the neurologist and psychiatrist may differ in their assessments of the underlying problem.

Investigations may be required to exclude possible organic causes for the patient's symptoms. Symptoms may have developed on an organic basis and then been perpetuated and elaborated psychogenically. Studies may include brain MRI; serum copper and ceruloplasmin levels and 24-hour urine copper excretion, thyroid function studies, and other tests based on clinical suspicion. The diagnostic evaluation may also include a trial of medications typically used for various organic movement disorders, depending on the patient's clinical state. Psychiatric referral is then required, with careful follow-up of the patient. Prognosis is variable. Features suggesting a good prognosis are acute onset, short duration of symptoms, healthy premorbid functioning, absence of other organic or psychogenic disorders, and presence of an identifiable precipitant.



CEREBRAL PALSY

Cerebral palsy (CP) is the term applied to a group of slow or nonprogressive motor impairment syndromes resulting from a variety of lesions or congenital brain anomalies. Although the initial lesion may be fixed, the clinical pattern of presentation might vary with growth and development. Its incidence is 2 to 2.5 per 1,000 live births. The causes are diverse. Approximately 75% of cases are due to prenatal injury, with less than 10% due to birth trauma or asphyxia. Low birth weight and prematurity are important risk factors for the occurrence of cerebral palsy. Other risk factors include chorioamnionitis, teratogenic exposures, hyperbilirubinemia, and hypoglycemia. Cerebral palsy has a higher incidence in twins and triplets than in singletons.

Cerebral palsy is a clinical diagnosis. Delays in developmental milestones are usually the earliest clue. Milestones acquired do not show regression. Other early signs include hand preference, prominent fisting, persistence of neonatal reflexes, and delay in emergence of protective and postural reflexes.

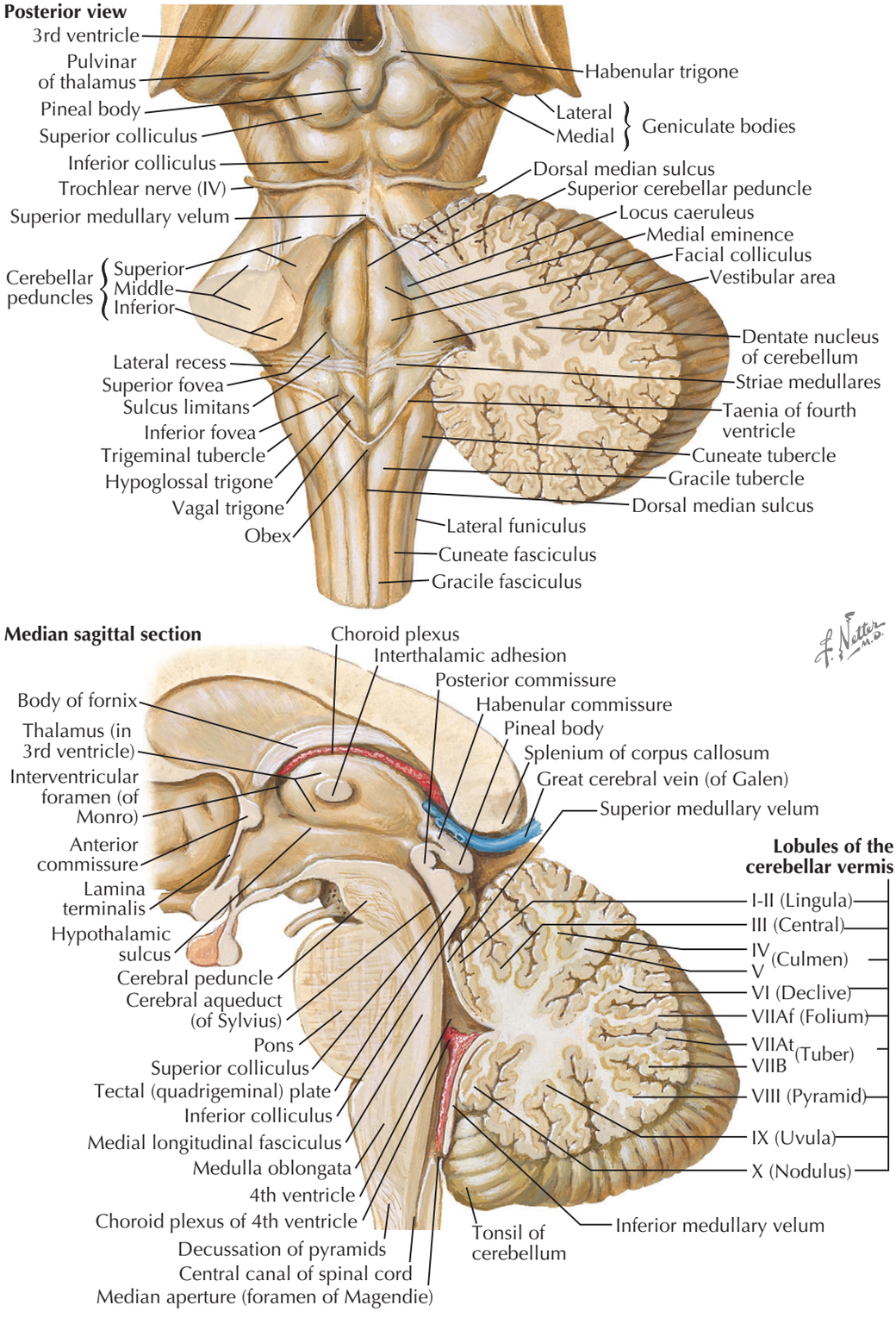
Topographic classification of CP includes *monoplegic*, *diplegic*, *hemiplegic*, and *quadriplegic*. Cases can also be classified into *spastic*, *dyskinetic*, *ataxic*, *hypotonic*, and *mixed*. Of these, spastic cerebral palsy with diplegia of the lower extremities and scissoring gait is the most common, accounting for 70% to 75% of cases. Imaging demonstrates *periventricular leukomalacia* around the lateral ventricles, with ischemia as the most common pathologic finding. Mild cases manifest with toe walking, whereas severe cases have flexion of the hips, knees, and elbows.

In hemiplegic cerebral palsy, the upper limb is predominantly affected. Palmar grasp reflexes may be present and can persist for years. Quadriplegic cerebral palsy, the most severe form, is characterized by polyporencephaly, polymicrogyria, and schizencephaly on neuroimaging studies. Pseudobulbar signs and optic atrophy is usually present in up to 50% of affected children.

Mental retardation (60%), visual impairment, and oculomotor impairments are common. In those children who develop cerebral palsy as a consequence of kernicterus, deafness, dystonia, choreoathetosis and, to a lesser extent, ataxia are the most common clinical findings, in addition to corticospinal tract involvement in a smaller proportion of patients. These are key points to remember when assessing adults who come for an evaluation of a new movement disorder and have a history of neonatal hyperbilirubinemia. Among children with cerebral palsy, 35% to 60% will have some form of epilepsy. Feeding difficulties, swallowing dysfunction, and drooling may complicate the clinical picture.

CEREBELLUM AND ATAXIA

CEREBELLUM AND THE FOURTH VENTRICLE



The *fourth ventricle* lies posterior to the *pons* and upper half of the *medulla oblongata* and anterior to the *cerebellum* (see Plate 8-1). Its upper and lower ends become continuous, respectively, with the *cerebral (sylvian, or mesencephalic) aqueduct* and the *central canal* of the *spinal cord* in the lower half of the medulla. On each side, a narrow prolongation, the *lateral recess*, projects outward from its widest part and curves around the brainstem above the corresponding *inferior (caudal) cerebellar peduncle*; its lateral aperture (*foramen of Luschka*) lies below the *cerebellar flocculus* and behind the emerging rootlets of the *glossopharyngeal (IX) and vagus (X) nerves*. The fourth ventricle has lateral boundaries, a roof, and a floor.

The lateral boundaries are formed on each side from above down by the superior cerebellar peduncle, the inferior cerebellar peduncle, and the cuneate and gracile tubercles.

Roof of Fourth Ventricle. The upper and lower parts of the V-shaped roof are formed by the superior and inferior medullary vela, which are thin laminae of white matter between the superior and inferior cerebellar peduncles. The lower part of the inferior velum has a median aperture (foramen of Magendie); cerebrospinal fluid escapes through this opening and the lateral aperture (foramina of Luschka) into the subarachnoid space. Because these are the only communications between the ventricular and subarachnoid spaces, their blockage can produce hydrocephalus.

The lower part of the roof and the posterior walls of the lateral recesses are invaginated by vascular tufts of pia mater, which form the T-shaped choroid plexus of the fourth ventricle.

The floor of the fourth ventricle is rhomboid shaped and is divided into symmetric halves by a vertical median sulcus. Its upper (pontine) and lower (medullary) parts are demarcated by delicate transverse strands of fibers, the striae medullares of the fourth ventricle.

On each side of the median sulcus is a longitudinal elevation, the medial eminence, lateral to which runs the sulcus limitans. Its superior part is the locus ceruleus, colored bluish-gray from a patch of deeply pigmented nerve cells. Also lateral to the upper part of the medial eminence is a slight depression, the superior fovea, and just below and medial to this fovea is a rounded swelling, the facial colliculus, which overlies the nucleus of the abducens (VI) nerve and the facial (VII) nerve fibers encircling it; the motor nucleus of the facial nerve lies more deeply in the pons. Inferolateral to the superior fovea is the upper part of the vestibular area, which overlies parts of the nuclei of the vestibulocochlear (VIII) nerve.

The lower (medullary) part of the medial eminence overlies the twelfth cranial nerve nucleus and is termed the hypoglossal trigone. Lateral to it is a slight depression, the inferior fovea, which, together with the neighboring vagal trigone, overlies parts of the dorsal nuclei of the glossopharyngeal and vagus nerves. Lateral to the inferior fovea is the lower part of the vestibular area, overlying parts of the vestibular nuclei of the vestibulocochlear nerve. On a deeper plane, parts of the trigeminal, solitary tract, and ambiguus nuclei also underlie the floor of the fourth ventricle. Some of the nuclei mentioned, such as the dorsal vagal and ambiguus nuclei, as well as others located in the nearby reticular formation, are concerned with cardiovascular, respiratory, metabolic, and other important functions, and are regarded as vital centers. Any lesion in this relatively small area of the brain may produce disastrous results.

Cerebellum Gross Anatomy

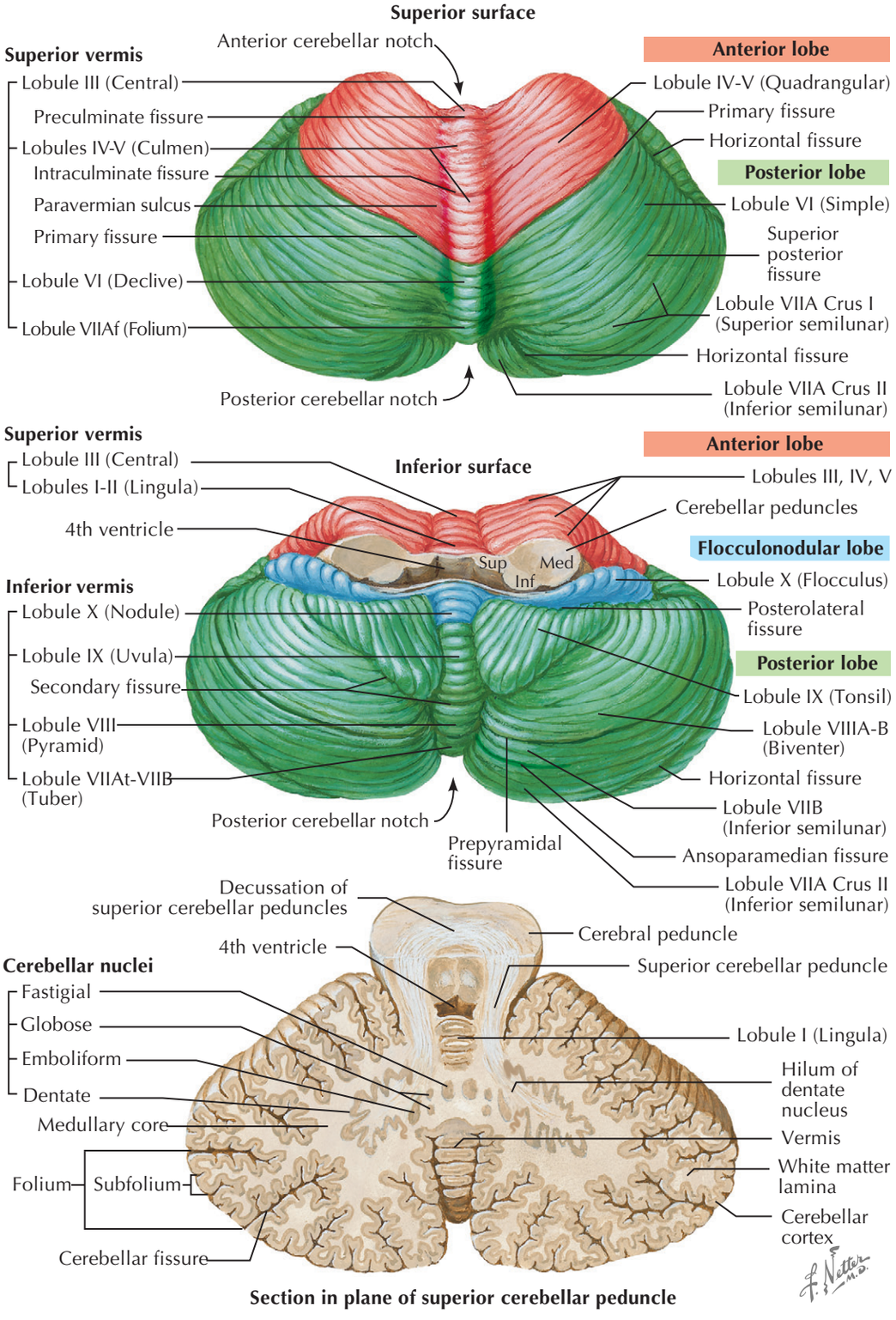
The cerebellum, from the Latin meaning *little brain*, is the largest part of the hindbrain occupying most of the posterior fossa. In the adult human brain, the cerebellum's volume is about 144 cm^3, weighing 150 grams (10% total brain weight). However, its surface area is 40% of the cerebral cortex, containing half the total number of intracerebral neurons. The cerebellum, consisting of two *hemispheres* situated contiguously with the midline *vermis*, is separated from the overlying cerebrum by the *tentorium cerebelli*. The vermis (i.e., from the Latin, meaning *worm*) is visible posteriorly and inferiorly in the *vallecula*, the deep groove separating the two cerebellar hemispheres. Superiorly, in contrast, the vermis appears as a low ridge straddling the midline, extending up 10 mm bilaterally.

A wide hollow within the anterior cerebellum is occupied by the pons and upper medulla oblongata, which are separated from the cerebellum by the fourth ventricle. Posteriorly, there is a narrow median notch, lodging the falx cerebelli. The cerebellum is connected to the brainstem by three white matter tracts: the superior, middle, and inferior cerebellar peduncles (described more fully in Plate 8-3). The cerebellum's *superior* and *inferior surfaces* meet within the caudal aspect of lobule *crus I*. The cerebellum forms a sphere, and therefore the vermal lobule I/II is separated anteriorly from lobule X by the fourth ventricle.

The *cerebellum surfaces* include numerous narrow folia separated by parallel, curved, deeply penetrating fissures. Each folium further consists of multiple, small subfolia. The folia are grouped into ten lobules divided by named fissures. These ten lobules form three lobes: the *anterior*, *posterior*, *and flocculonodular lobes*. *Lobules I to V are the anterior lobe*, *lobules VI to IX are the posterior lobe*, *and lobule X is the flocculonodular lobe*, including the *flocculus*, which is a small, semidetached portion lying close to the middle cerebellar peduncle. Earlier cerebellum nomenclatures were not uniform (one version is in the diagrams for comparison). These are replaced by a simplified, coherent numeric system existing across different species' brains. All lobules are identifiable at the vermis; lobules III to X are continuous across the hemispheres.

The *primary fissure* separating the anterior from the posterior lobe is deepest and most evident in the midsagittal plane but not as readily identifiable externally. The *superior posterior fissure* separating lobule VI from lobule VII is well seen on the posterior superior surface. The *horizontal fissure*, prominent on the posterior, inferior, and lateral hemisphere aspects divides lobule VIIA into two major components: lobule VIIAf at the vermis/crus I in the hemisphere, and lobule VIIAt at the vermis/crus II in the hemisphere. The *paravermian sulcus* on each side of the superior cerebellum surface is an indentation formed by the superior cerebellar artery medial branch. The *retrotonsillar groove* at the inferior and medial aspect of the cerebellum is caused by the rim of the foramen magnum and delineates the *tonsil*, a gross morphologic feature comprising lobule IX and part of lobule VIIIB that becomes clinically relevant with *herniation syndromes*.

The interior of the cerebellum contains a central mass of white matter, the medullary core, surrounded by the deeply folded cerebellar folia. The relationship of the folia to the white matter has a tree branch appearance, hence *arbor vitae*. The *white matter* core extends into the folia as narrow laminae, surrounded by the three-layered cerebellar cortex. The white matter consists largely of *mossy* and *climbing fibers* entering the cerebellum, and axons of *Purkinje cells* leaving the cerebellar cortex to the nuclei. There are no association fibers in the cerebellum linking cerebellar cortical areas with each other. The *cerebellar nuclei* within the *medullary core* include, medial to lateral, the *fastigial*, *globose*, *emboliform*, *and dentate*. These nuclei, together with other minor nuclei in the medullary core and vestibular nuclei in the posterior pons and medulla, are linked with the cerebellar cortex serving as the cerebellum's functional unit, namely, the *corticonuclear microcomplex*. Except for the vestibulocerebellum, these nuclei are the primary source of cerebellar efferents. These have highly organized connections with extracerebellar structures. The large, folded *dentate nucleus* is U-shaped. Its open end, or hilus, points medially, conveying fibers that, together with those from the *fastigial*, *globose*, *and emboliform* nuclei, form the superior cerebellar peduncle.



Section in plane of superior cerebellar peduncle

Cerebellar Peduncles

The cerebellum is linked with the spinal cord, brainstem, and cerebral hemispheres by three major fiber tracts—the inferior, middle, and superior cerebellar peduncles. These convey axons into the cerebellum (afferent) or away from it (efferent).

The *inferior cerebellar peduncle (ICP)* has two components. The larger is the *restiform body*, a purely afferent system, whereas the smaller *juxtarestiform body* carries both afferent and efferent fibers.

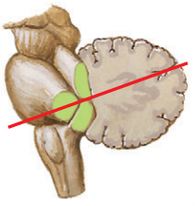
The *restiform body* (or ICP proper) is located in the dorsolateral medulla, lateral to the vestibular nuclei. Entering the cerebellum, it is situated medial to the middle cerebellar peduncle, conveying *uncrossed mossy fiber* afferents to cerebellum from the ipsilateral spinal cord and brainstem, and *crossed climbing fiber* inputs from the contralateral inferior olivary nucleus. Spinal cord inputs in the ICP are from the *dorsal (posterior) spinocerebellar tract (DSCT)*, conveying information from the trunk and lower limbs. The *rostral spinocerebellar tract* carries information from the upper limbs and the *central cervical tract* arising from upper cervical segments. From the brainstem, the ICP conveys the *cuneocerebellar tract* arising in the external cuneate nucleus (also known as the lateral or accessory cuneate nucleus), which conveys information from the upper limb and the reticular formation (reticulocerebellar fibers), the trigeminal principal sensory nucleus (trigeminocerebellar fibers), and the midline raphe. Climbing fibers arise in the inferior olive, cross in the medulla, and course within the ICP to reach the contralateral cerebellar hemisphere.

The *juxtarestiform body* is a small aggregation of fibers situated medial to the restiform body that enters the cerebellum passing through the vestibular nuclei. It conveys afferent fibers to vermal lobule IX (uvula) and lobule X (the flocculonodular lobe). Primary vestibular afferents arise from the vestibular sense organs (the saccule and utricle) and terminate ipsilaterally; secondary vestibular fibers from the vestibular nuclei terminate bilaterally. Efferent fibers in the juxtarestiform body arise from the cerebellar cortex and fastigial nucleus. Cerebellar cortical axons in the juxtarestiform body emanating from Purkinje cells in the vestibulocerebellum (part of lobule IX, and lobule X) terminate in Deiters lateral vestibular nucleus, and, together with efferents from the anterior vermis, are the only instance of projections from cerebellar cortex bypassing the deep cerebellar nuclei to terminate on a target outside the cerebellum. Juxtarestiform body fibers arising from the fastigial nuclei lead to the vestibular and the reticular nuclei. Axons from the rostral half of the fastigial nucleus course to the ipsilateral brainstem in the *fastigiobulbar tract*. Axons from the caudal half of the fastigial nucleus cross to the contralateral cerebellum in the *uncinate bundle*, that is, the hook bundle of Russell, before traveling to the brainstem in the contralateral juxtarestiform body (see Plate 8-10).

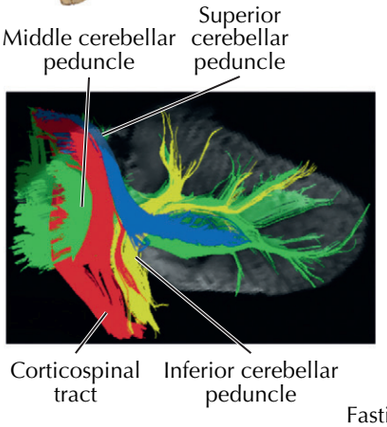
The *middle cerebellar peduncle (MCP)* is a massive tract situated at the lateral aspect of the basis pontis. Axons leave the pontine nuclei, cross to the opposite side of the pons, and course in the contralateral MCP to the cerebellum. The pontine nuclei are an obligatory intermediate link between the ipsilateral corticopontine input via the cerebral peduncle and the contralateral pontocerebellar projections by way of the MCP. A minor projection from cerebellar nuclei back to the pons is also present.

The *superior cerebellar peduncle (SCP)* transmits efferents from and afferents to the cerebellum. It lies within the posterolateral wall of the fourth ventricle, ascends as the *brachium conjunctivum* to the midbrain, where it decussates and continues rostrally, carrying ascending projections from the cerebellum to the reticular nuclei in the pons and midbrain, red nucleus, hypothalamic area, and thalamus. The hilus of the dentate nucleus is continuous with the SCP, but there are also axons in the SCP arising from the fastigial, globose, and emboliform nuclei. A descending branch of the SCP leaves the larger ascending component in the rostral pons, descends in the pontomedullary tegmentum, and crosses obliquely to the opposite side of the ventral medulla to terminate in the inferior olive (the cerebello-olivary projection). Afferents to the cerebellum coursing in the SCP arise in the spinal cord and brainstem. These include crossed ventral (anterior) spinocerebellar tract fibers conveying information concerning the contralateral trunk and lower limbs, and both crossed and uncrossed fibers in the central cervical tract. Ipsilateral afferents include tectocerebellar projections from the superior and inferior colliculi in the midbrain, trigeminocerebellar fibers from the trigeminal mesencephalic nucleus, and coeruleocerebellar projections from the locus coeruleus in the pons.

The three peduncles are differentially affected by ischemic, compressive, demyelinating, neurodegenerative, and other disorders. Clinically, peduncle lesions manifestations are heterogeneous, reflecting the wide range of functions subserved by the information they convey between the cerebellum and the remainder of the neuraxis.

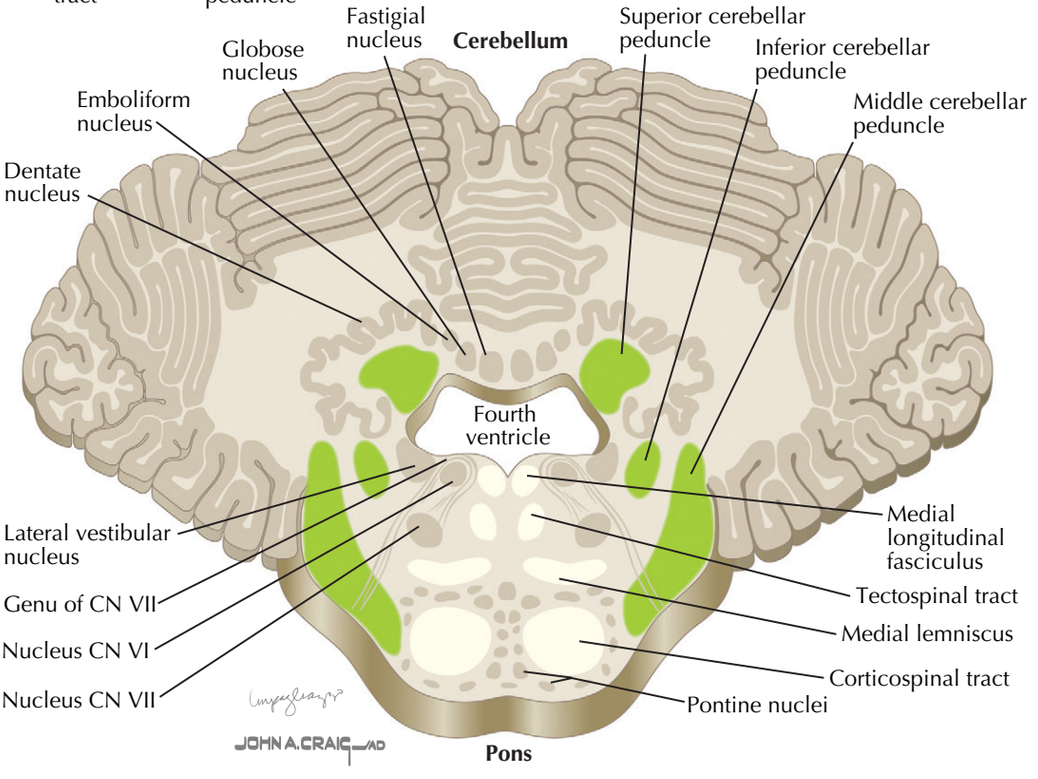


Level of section



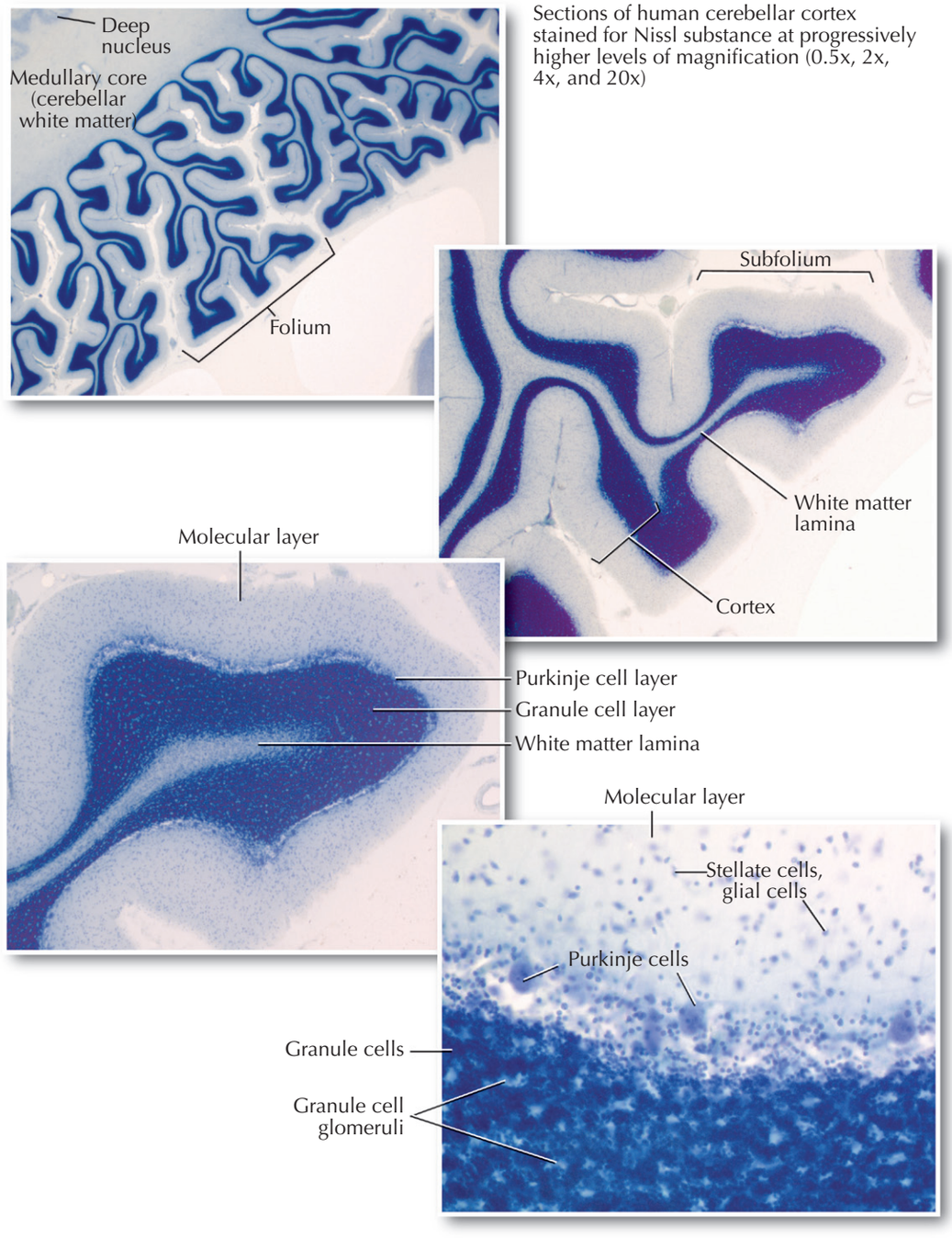
Peduncle	Input (afferents)	Output (efferents)
Inferior (restiform body)	Spinocerebellar Dorsal Rostral Cuneocerebellar Olive-cerebellar Reticulocerebellar Trigeminocerebellar Raphe-cerebellar	Fastigiobulbar, Uncinate fasciculus → To vestibular and reticular nuclei Direct cerebellovestibular (to LVN)
Juxtarestiform body	Vestibulospinal (primary, secondary)	
Middle (brachium pontis)	Pontocerebellar	
Superior (brachium conjunctivum)	Ventral spinocerebellar Trigeminocerebellar Tectocerebellar Superior colliculus Inferior colliculus Coeruleo-cerebellar	Dentatothalamic Dentatorubral Dentatoreticular Interpositus-rubral connections (globose, emboliform)

Reprinted with permission from Takahashi E, Song JW, Folkerth RD, Grant PE, Schmahmann JD. Detection of Postmortem Human Cerebellar Cortex and White Matter Pathways Using High Angular Resolution Diffusion Tractography: A feasibility study. NeuroImage, in press.



Cerebellar Cortex and Nuclei

Cerebellar Cortex and Nuclei: Neuronal Elements



Sections of human cerebellar cortex stained for Nissl substance at progressively higher levels of magnification (0.5x, 2x, 4x, and 20x)

The histology of the cerebellar cortex differs fundamentally from that of the cerebral cortex in that it has essentially the same paracrystalline structure throughout. The trilaminate cortex, the *Purkinje cell layer* lying between the innermost *granular layer* and the outermost *molecular layer*, is apposed on each side of a white matter lamella conveying fibers to and from the cortex (see Plates 8-4 and 8-5).

The Purkinje cell (PC) layer is a monolayer composed entirely of PCs, a 100 µm-thick sheet of 15 million neurons situated between the molecular and granular layers. The PC is the defining neuron of the cerebellum. It is among the largest cells in the nervous system, with a pear-shaped soma (35 × 70 µm) and a fanlike appearance of its dendritic tree. The proximal dendrite divides into two major dendrites that branch multiple times to form a flattened plate (400 × 20 µm) in the parasagittal plane oriented perpendicular to the long axis of the folium. Each PC has over 150,000 spines, with a density 25 times higher on distal dendrites, where parallel fibers (PFs) synapse, than on proximal dendrites, where climbing fibers (CFs) synapse. The PC is the *only neuron with axons leaving the cerebellar cortex*. The axon descends through a constricted region surrounded by the pinceau of basket cell axon terminals, acquires a myelin sheath, and descends to the deep cerebellar nuclei or vestibular nuclei. Recurrent collaterals course back toward the molecular layer, inhibiting interneurons as well as the soma and proximal dendrites of neighboring PCs.

The molecular layer is 300 µm thick. It contains *granule cell* axons and PFs, dendritic arborizations of PCs and *Golgi interneurons*, and cell bodies of *basket*, *stellate*, *and supporting glial cells*.

Parallel fibers are formed when the granule cell axon ascends through the PC layer into the molecular layer and branches in the shape of a T to form the PF, one of the thinnest vertebrate axons. It travels parallel to the long axis of the folium for 1 to 3 mm in the rat and cat, and possibly 6 to 8 mm in primates.

The basket cell lies in the lower third of the molecular layer just above the PCs. Its dendrites extend up into the molecular layer in a fan-shaped field 30 µm wide in the parasagittal plane (the same plane as the PC dendritic tree), giving off relatively few branches, interdigitating with the dendritic fields of the PCs, and contacted by the PFs. Its axon courses in the parasagittal plane among the lower dendrites of 9 or 10 PCs. It emits a succession of descending branches that envelope the PC somata in an axonal sheath with numerous synaptic contacts, giving the basket cell its name. Terminal axonal branches surround the initial segment of the PC axon in a dense fiber plexus with the appearance of an old paintbrush (French, *pinceau*). This axo-axonic complex is unique in the mammalian nervous system. Sparse ascending collaterals from the basket cell axon synapse on secondary and tertiary PC dendrites.

Stellate cells are small, 5 to 10 µm in diameter, with short, profusely branching dendrites contacted by parallel fibers and axons that terminate on PC dendrites. *Superficial stellate cells* in the upper molecular layer have short axons oriented in the parasagittal plane. *Deep stellate cells* in the middle part of the molecular layer have long axons up to 450 µm in the parasagittal plane, providing ascending and descending collaterals early in their course, but they rarely enter the pericellular PC plexus and do not participate in the pinceau.

The granular layer is 200 µm to 300 µm deep and contains granule, Golgi, Lugaro, and unipolar brush cells. G*ranule cells* number about 50 billion, 3,000 per single PC. They have minimal cytoplasm, are among the smallest neurons in the brain (6-8 µm diameter), and are the most numerous. Their density renders the granule cell layer a deep blue on stains such as Nissl, which label nuclear material. The granule cell has three to five clawlike branched dendrites that participate in the granule cell glomerulus, pale islands between the granule cells containing a complex articulation between terminal rosettes of mossy fiber afferents, arborizations of granule cell dendrites, and Golgi cell axons. The granule cell axon ascends into the molecular layer where its PFs provide excitatory input to the PCs.

Golgi cells are irregularly rounded or polygonal inhibitory interneurons numbering approximately 1 per 1.5 PCs. In contrast to the PC, basket, and stellate cells, the Golgi cell dendritic tree has a three-dimensional configuration. Large Golgi cells, 10 to 24 µm in diameter, lie in the upper half of the granular layer, their dendrites arising as one or two main trunks with subsidiary branches that ascend to the outer zone of the

CEREBELLAR CORTEX AND NUCLEI *(Continued)*

molecular layer. Smaller Golgi cells, 9 to 18 µm, are in the depths of the granular layer, with dendrites that radiate out from the soma. One to three axons emerge from the Golgi cell body or from proximal dendrites and divide repeatedly, resulting in a multitude of fine branches that form an elaborate, dense plexus extending throughout the granular layer and participating in the granule cell glomerulus.

The *Lugaro cell* is a fusiform inhibitory interneuron measuring 10 × 30 µm, lying horizontally or obliquely in the outer third of the granular layer. Its dendrites originate from the tapering extremities at the two poles and extend horizontally for up to 600 µm at the level of the PC bodies in the infraganglionic plexus formed by the PC recurrent axon collaterals. It receives excitatory input from the granule cell axon and serotoninergic modulation acting through volume transmission. Its axon arises from the cell body or large proximal dendrite, forming two types of axonal plexuses. One parasagittal axon contacts the soma and dendrites of stellate and basket cells in the molecular layer; the other is transverse and contacts Golgi cells in the granular layer.

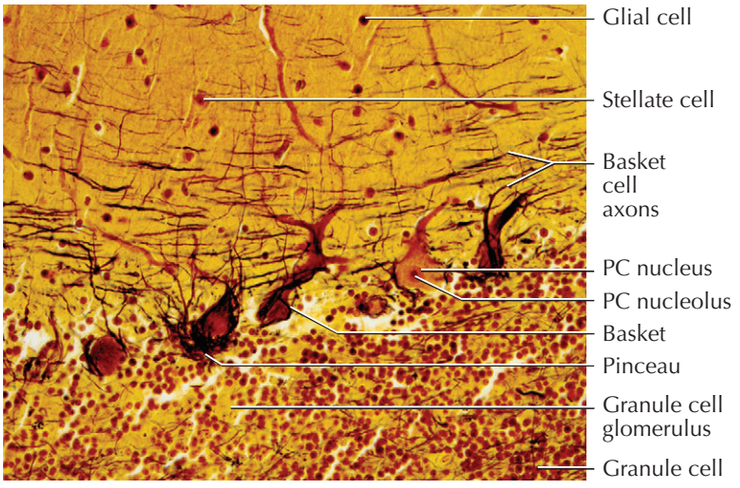
The *unipolar brush cell* (UBC) is the only excitatory interneuron in the cerebellum. The soma is 9 to 12 µm in diameter, with a single dendrite ending in a tight brushlike tip of dendrioles that have extensive synaptic contact with the mossy fiber rosette. Its axon synapses on granule and Golgi cells. The UBC is found in the vestibulocerebellum, vermis, and dorsal cochlear nucleus, and it is thought to amplify vestibular signals and provide feed-forward excitation to granule cells.

Glial cells in the cerebellum include protoplasmic astrocytes that envelope the PC perikaryon in a neuroglial sheath; Bergmann glial cells in the PC layer that are involved in neural migration and development of the cerebellar cortex, and that play a role in regulating glutamatergic neural transmission in the mature cerebellum; and oligodendroglia in cerebellar white matter and in the granular layer.

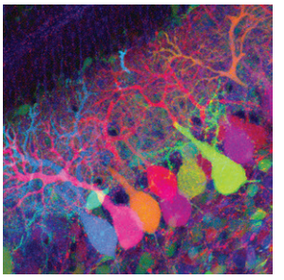
CEREBELLAR NUCLEI

The fastigial, globose, emboliform, and dentate nuclei are together termed the deep cerebellar nuclei (DCN) to differentiate them from the precerebellar nuclei. The fastigial nucleus is the homologue of the medial nucleus in lower primates, whereas the posterior and anterior interpositus nuclei are homologous with the globose and emboliform nuclei, respectively. Among the cerebellar nuclei, the dentate, or lateral nucleus in lower vertebrates, has evolved most. The posterior (dorsal) part with small narrow folds (microgyric) contains large cells and is phylogenetically older. The macrogyric anterior (ventral) and lateral part contains smaller neurons and has expanded greatly in concert with the association cortex of the cerebral hemispheres. This is important from the perspective of anthropology as well as cognitive neuroscience and behavioral neurology. Deiters lateral vestibular nucleus is located in the dorsal medulla. It receives PC axons directly from the vestibulocerebellum and part of the anterior vermis and is equivalent to a deep cerebellar nucleus.

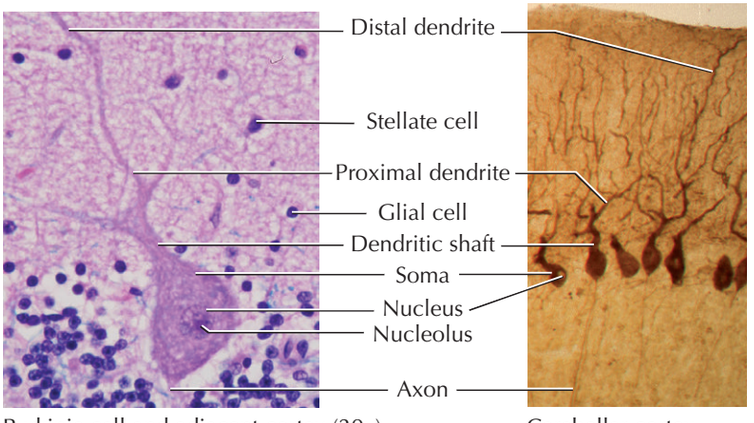
CEREBELLAR CORTEX: NEURONAL ELEMENTS



Cerebellar cortex studied with Bielschowsky silver stain (20x)
Courtesy Dr. Matthew P. Frosch.

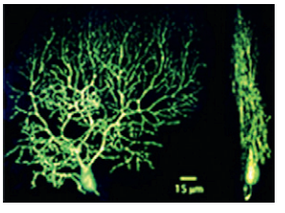


Brainbow image of Purkinje cells and granule cells in mouse, derived by mapping the differential expression of multiple fluorescent proteins in individual neurons Courtesy of Tamily Weissman, PhD. The Brainbow mouse was produced by Livet J, Weissman TA, Kang H, Draft RW, Lu J, Bennis RA, Sanes JR, Lichtman JW. *Nature* 2007;450:56-62.



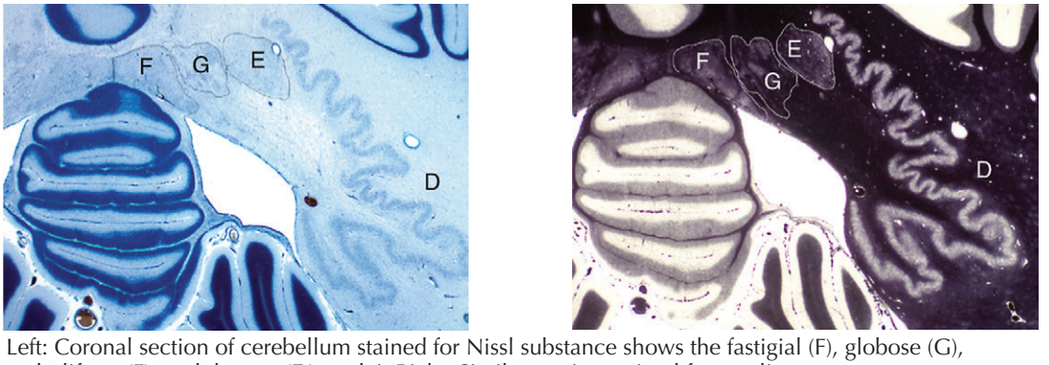
Purkinje cell and adjacent cortex (20x) stained with hematoxylin and eosin
Courtesy Dr. Matthew P. Frosch.

Cerebellar cortex immunostained with calbindin (10x)



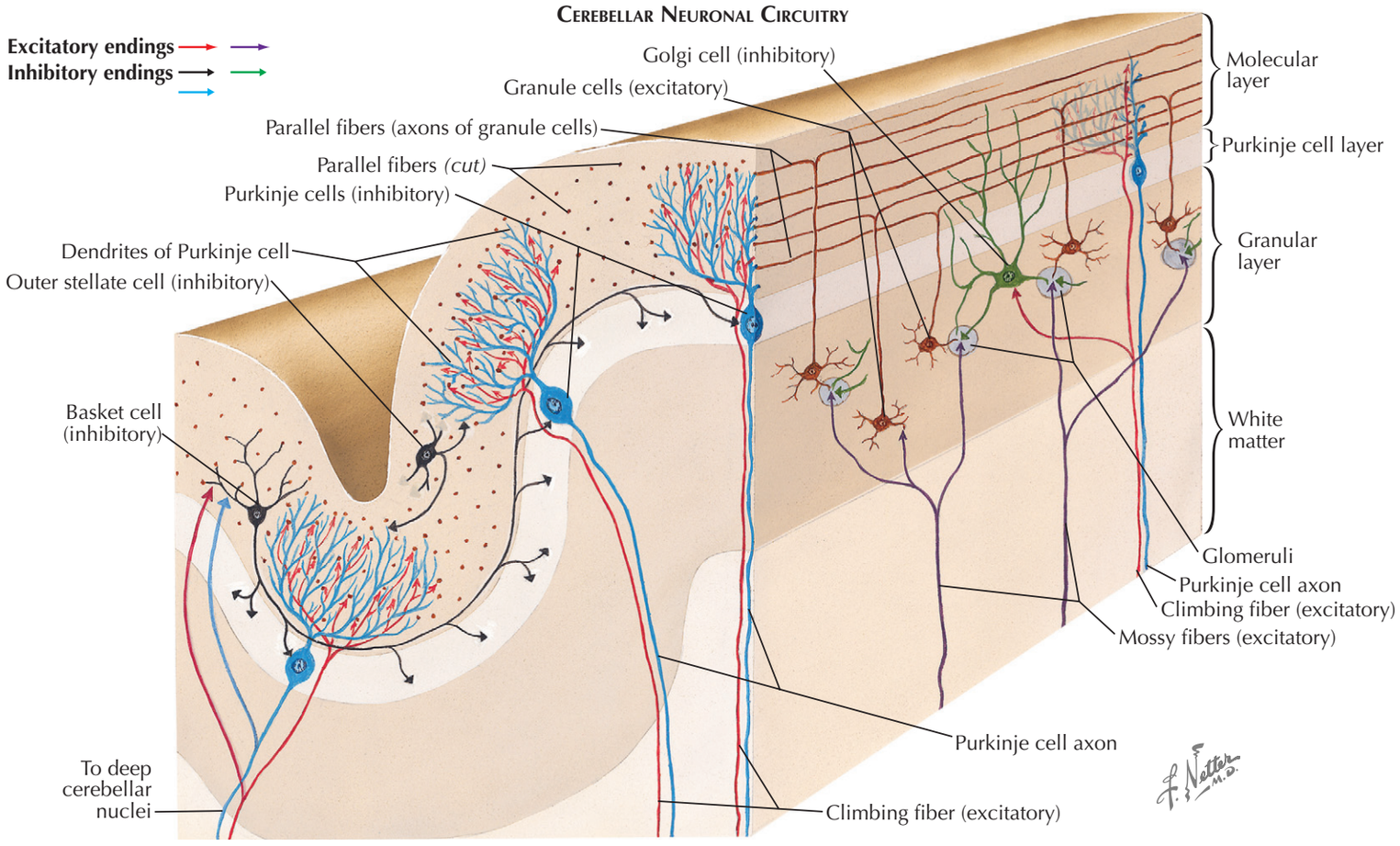
3D reconstruction of Lucifer yellow-filled PC viewed perpendicular to (left) and parallel to (right) the long axis of the folium. Reprinted with permission from Rossi DJ, Alford S, Mugnaini E, Slater NT. Properties of transmission at a giant glutamatergic synapse in cerebellum: the mosssy fiber-unipolar brush cell synapse. *J Neurophysiol* 1995;74:24-42.

CEREBELLAR NUCLEI



Left: Coronal section of cerebellum stained for Nissl substance shows the fastigial (F), globose (G), emboliform (E), and dentate (D) nuclei. Right: Similar section stained for myelin. Reprinted with permission from Schmahmann J, Doyon J, Toga A, Petrides M, Evans A. *MRI atlas of the human cerebellum.* San Diego: Academic Press, Elsevier; 2000.

The neurons of the DCN are outnumbered by the PCs of the cerebellar cortex by about 26 to 1. Each PC contacts approximately 35 nuclear neurons, and each DCN neuron receives inputs from more than 800 PCs. The cytologic features of the DCN suggest anatomic subdivisions that may have connectional and functional relevance, but these are not sufficiently definitive to formally subdivide the nuclei further. Neurons in the DCN are of three types. *Large glutamatergic neurons convey* excitatory output to the thalamus and brainstem, and nucleocortical projections back to the cerebellar cortex; *small γ-aminobutyric acid (GABA)ergic neurons* are inhibitory to the inferior olivary nucleus; and *small glycinergic neurons* in the DCN are thought to be inhibitory intranuclear interneurons. It is now possible to identify the DCN on magnetic resonance imaging (MRI) by taking advantage of their iron content, although detailed organization is not apparent with available technology.



Cerebellar Cortical and Corticonuclear Circuitry

The neurons of the cerebellar cortex and nuclei are linked together in multiple repeating anatomic microcircuits—corticonuclear microcomplexes—that serve as the essential functional unit of the cerebellum. The key to their elucidation is the dual nature of the cerebellar inputs—the mossy fiber and climbing fiber systems. Monoaminergic fibers from the brainstem are an additional minor source of cerebellar afferents.

Climbing fibers (CFs) arise exclusively from the *inferior olive*. Axons of olivary neurons branch to form 7 to 10 CFs. Each CF provides extensive *excitatory* synaptic contact with the dendritic tree of a single PC (between 1,000 and 1,500 synaptic contacts between a CF and its PC). Climbing fibers enter the cerebellum through the inferior cerebellar peduncle (ICP), branch in the white matter, where they emit collaterals to the deep cerebellar nuclei (DCN), and ascend to the molecular layer. In the lower two thirds of the molecular layer the CF is tightly wound around the trunk and major proximal branches of the PC dendritic tree. Each varicosity of a CF synapses with several dendritic spines arising from the same dendritic branch. Fine tendrils that branch off from the CF in the molecular layer synapse with ascending branches of the basket cell axon and with the dendritic trees of stellate and Golgi cells. The olivocerebellar projection is organized according to a strict mediolateral parasagittal zonal pattern (see Plate 8-12).

Mossy fibers (MFs) are named for their thickened terminals that have thick, short, divergent, varicose branches resembling moss. Their synaptic arborizations are termed rosettes, have a variety of shapes, and are located along the course of the MF in the granular layer at the branch points and at their sites of terminations. MFs are heavily myelinated and convey *excitatory afferents* to the cerebellar cortex from the spinal cord, brainstem (except the olive), and the cerebral hemispheres. They enter through all three cerebellar peduncles, giving off 20 to 30 collateral branches in the white matter of the folium as they course toward the granular layer. They also provide collaterals to the deep cerebellar nuclei. Many MFs terminate bilaterally in the cerebellum after crossing in the cerebellar white matter. Unlike the CF, the MF provides excitatory input to the PC indirectly. The MF rosette is the central component of the granule cell glomerulus, the complex articulation between MF rosettes and the terminal arborizations of granule cell dendrites. Each MF rosette makes excitatory synaptic contact with 50 to 100 dendritic terminals from up to 20 granule cells and receives inhibitory feedback from the descending axons of Golgi cells. The granule cell axon ascends toward the molecular layer, making synaptic contact with dendrites of Golgi cells in the granular layer and spines of the proximal dendrites of PCs in the molecular layer. Upon reaching the molecular layer, the granule cell axon divides to form parallel fibers (PFs), the two branches traveling in opposite directions along the folium. The PFs make synaptic contact with one or two spiny branchlets on intermediate and distal regions of the dendritic trees of up to 300 PCs along the folium.

Each PC receives synaptic inputs from approximately 200,000 parallel fibers. In addition to excitatory inputs to the PCs from MFs and CFs, the PCs participate in a bidirectional corticonuclear projection, receiving excitatory feedback back from those regions of the DCN and vestibular nuclei to which the PC inhibitory projection is directed. The PCs receive inhibitory inputs from interneurons in the molecular layer—stellate cells, basket cells, and Lugaro cells, all of which receive excitatory afferents from the ascending granule cell axon and the PFs. Recurrent axon collaterals of the PCs are also inhibitory. The dendrites of the unipolar brush cell (UBC) in the vestibulocerebellum, the only excitatory cerebellar interneuron, receive MF inputs within the granule cell glomerulus. The *net effect of these finely balanced interactions* is that inputs to cerebellum are excitatory, output from the cortex via the PC is inhibitory, and output from the cerebellum via the DCN is excitatory to thalamus and brainstem but inhibitory to the inferior olive.

Cerebellar Cortical and Corticonuclear Circuitry
(Continued)

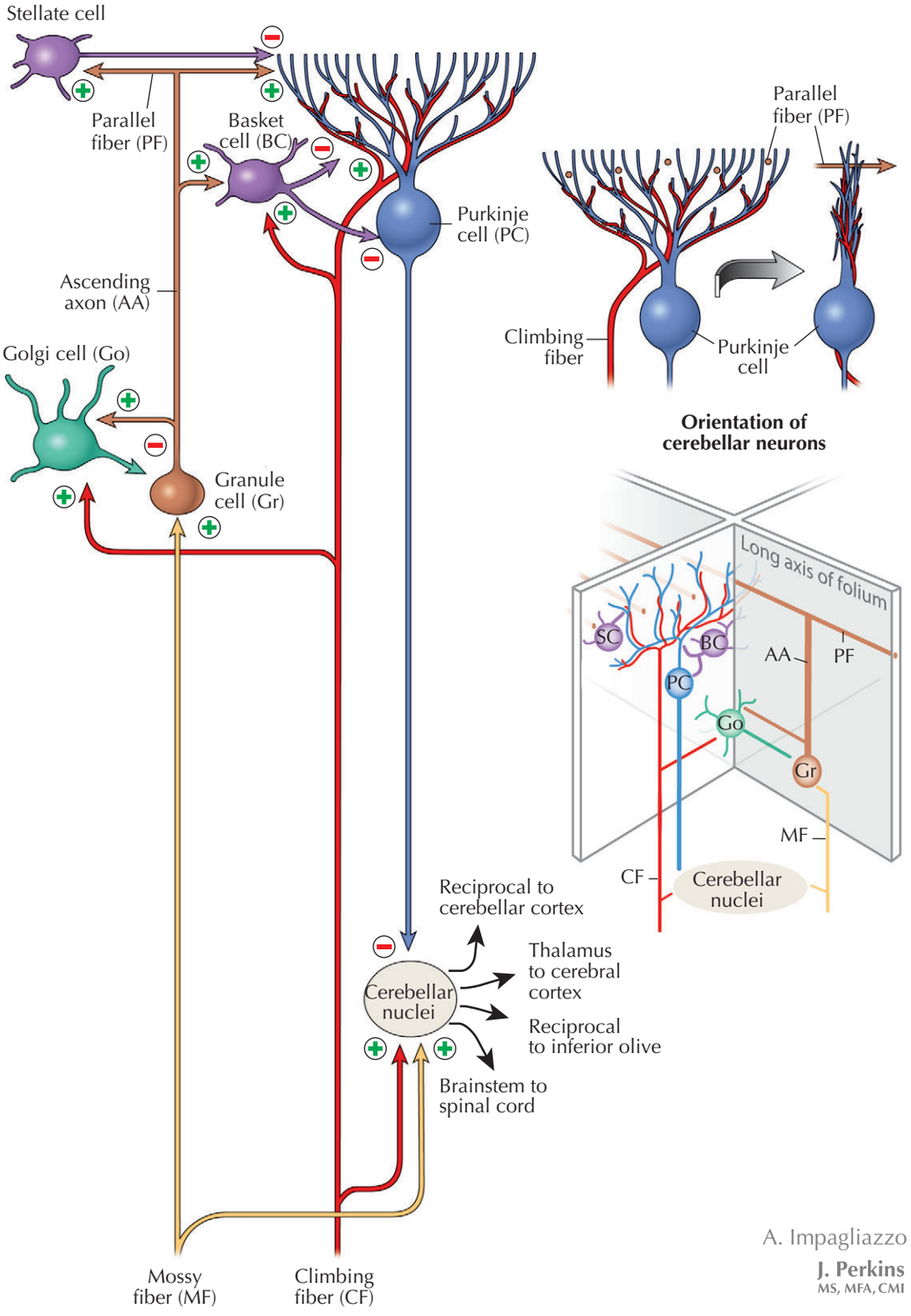
The output from the cerebellar cortex is derived exclusively from PCs, precisely organized, and directed toward the DCN and precerebellar nuclei. PCs in each lobule project to those parts of the deep cerebellar nuclei closest to them. Thus the vermis projects to the fastigial nucleus, the intermediate cortex to the globose and emboliform nuclei, and much of the lateral hemispheres project to the dentate nucleus. More detail on cerebellar corticonuclear circuits, modules, and microzones is presented in Plate 8-12.

The two major neurotransmitters in the cerebellum are glutamate and γ-aminobutyric acid (GABA). *Glutamate is excitatory* and is found in the MFs, PFs, CFs, UBCs, and deep cerebellar nuclear neurons that project to thalamus, brainstem, and cerebellar cortex. GABA is inhibitory and is utilized by the PCs, all remaining cerebellar interneurons (stellate, basket, Golgi, Lugaro), and the DCN neurons that project to the inferior olive. *Glycine is present in inhibitory interneurons* in the DCN. A number of other peptide neurotransmitters are present also in the afferent fibers and neurons of the cerebellar cortex.

The PC generates two different classes of action potentials in response to its principal afferents. The input of hundreds of MFs produces a brief burst of repetitive simple spikes, 50 to 150 per second. The *inhibitory basket and stellate cell interneurons produce inhibition of PCs* locally and for some distance lateral to the longitudinal strip of active parallel fibers. Therefore MF-induced PC activity consists of a brief burst of action potentials along the course of active parallel fibers, surrounded by a band of inhibited cells. PC excitation is further restricted by *Golgi cells*, which receive excitatory PF synapses on their apical dendrites and provide a mostly *tonic inhibitory input* to the glomerulus, decreasing the excitability of granule cells to MF afferents. PF input is thought to provide information about incoming signals, such as direction and speed of limb movement. *In the cognitive domain, the PF may provide the PC with the context in which behaviors occur.*

Climbing fiber input to the PC induces a complex spike with the very low frequency of 0.5 to 2 spikes per second, the same rate of firing as the olivary neurons from which the CF originates. The CF input to the PC is thought to signal the occurrence of errors. The *MF-CF inputs* to the PC are relevant to *synaptic plasticity involved in learning and memory. Long-term depression (LTD)* is characterized by the persistent depression of synaptic transmission from PFs to the PC that occurs when parallel and climbing fiber activation are concurrent. *Long-term potentiation (LTP)* has also been described. The balance of LTD and LTP enables the cerebellar cortex to adapt to errors by regulating cortical output either down or up.

Circuit Diagram of Afferent Connections in the Cerebellum



A. Impagliazzo
J. Perkins
MS, MFA, CMI

These corticonuclear circuits and physiology are the basis of theories that the *cerebellum functions as an adaptive filter, utilizing internal models to maintain behaviors around a homeostatic baseline, and optimizes cerebellar influence upon motor, cognitive, or limbic behaviors* appropriate to the prevailing context. The *paracrystalline structure* of cerebellar cortical architecture and organization has led to the idea that it has a *general signal-transforming ability, a universal cerebellar transform*, which is *applied to multiple domains of neurologic function*. The *role of the cerebellum in the nervous system* is a result, then, of the combination of the uniform cerebellar structure and function and the complex and varied connections of the cerebellar microcircuits, with extracerebellar areas conveyed by the mossy and climbing fiber inputs and the corticonuclear outputs.

Cerebellum Subdivisions and Afferent Pathways

The cerebellum is divided into three lobes: anterior, posterior, and flocculonodular (see also Plate 8-2). It is also divided into three mediolateral subregions on the basis of phylogeny and function. The *archicerebellum*, or vestibulocerebellum, includes vermal and hemispheric parts of lobule X (flocculonodular lobe), parts of vermal lobule IX (uvula), and lobule I/ II (lingula); it is linked with the vestibular nuclei and is concerned with eye movements and equilibrium. The *paleocerebellum*, or spinocerebellum, in vermal and paravermal lobules III through VI and lobule VIII, receives cutaneous and kinesthetic afferents from spinal cord, brainstem, and cerebral hemispheres. The *anterior vermis* is linked with the *rostral fastigial nucleus*, influences the medial motor system through brainstem vestibulospinal and reticulospinal projections, and controls trunk and girdle muscles enabling balance and gait. *Paravermal areas* are linked with the interpositus nuclei, the posterior part of the dentate nucleus, red nucleus, and primary motor cortex, influencing descending lateral motor systems and controlling distal limb movements. The *neocerebellum* (pontocerebellum) includes lobules VI and VII at the vermis and hemispheres. It receives afferents from cerebral cortex through the pons. Lateral *cerebellar hemispheres* project via the ventral dentate nucleus to thalamus and cerebral association areas; the *posterior vermis* is linked through the caudal fastigial nucleus with limbic areas. It appears that the neocerebellum is involved in cognition and emotion.

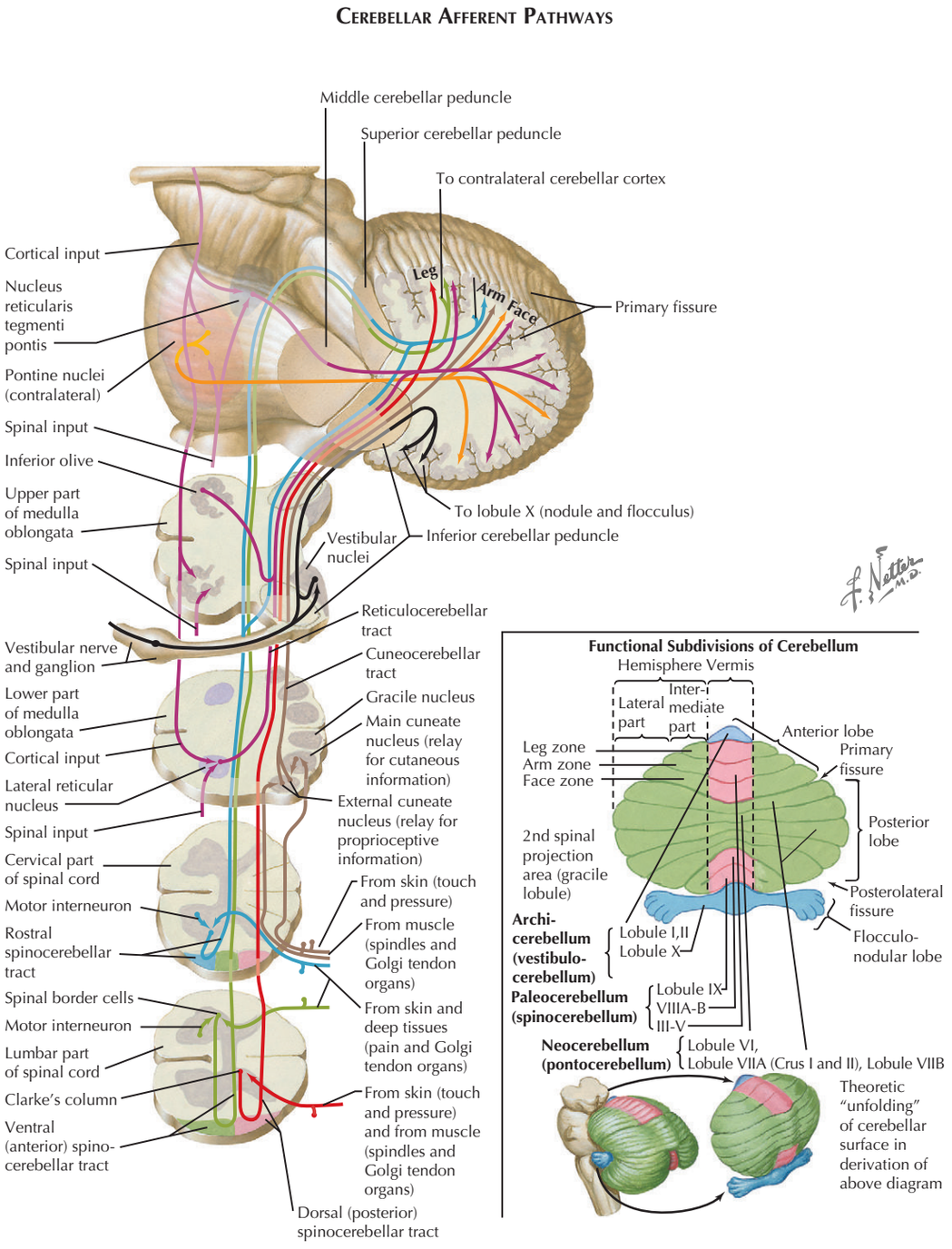
Knowledge of cerebellar connections with extracerebellar structures is critical to understanding the diverse roles of the cerebellum and the consequences of cerebellar injury. Afferents to cerebellum are conveyed predominantly by *mossy fibers* and *climbing fibers* that are organized in a fundamentally different manner (see Plates 8-6 and 8-7).

Mossy Fiber Pathways

Spinocerebellar Pathways. Sensory afferents from the spinal cord terminate in a somatotopic fashion in the primary sensorimotor representation in lobules III through V and the secondary sensorimotor representation in lobule VIII, with collateral inputs to the deep cerebellar nuclei (DCN). The trunk and lower limbs are subserved by the dorsal and ventral spinocerebellar tracts, and the head, neck, and upper extremities by the cuneocerebellar, rostral spinocerebellar, and central cervical tracts. These are all uncrossed, ascending in the ipsilateral spinal cord, except for the ventral (anterior) spinocerebellar tract (VSCT), which decussates and ascends on the contralateral side.

The *dorsal (posterior) spinocerebellar tract (DSCT)* and the *cuneocerebellar tract (CCT)* convey analogous proprioceptive and exteroceptive information from the hindlimb and forelimb, respectively. Both enter cerebellum via the inferior cerebellar peduncle (ICP). *Proprioceptive* information comes from (1) *muscle spindle afferents* that signal *muscle length* (groups Ia and II fibers) and (2) *Golgi tendon organs* that signal *muscle tension* (group Ib fibers). DSCT or CCT neurons convey information regarding closely related muscles; some relay information from joint receptors. *Exteroceptive* signals provide the cerebellum with cutaneous afferents originating from touch and hair-movement receptors in small areas of skin. The DSCT in the posterolateral funiculus conveys proprioceptive and exteroceptive afferents from the trunk and legs, arising in *Clarke's column* in lamina VII of the dorsal horn at spinal segments C8 to L3. It terminates in hindlimb projection areas in the intermediate part of the ipsilateral anterior lobe and lobule VIII. The CCT ascends from the medulla, conveying *proprioceptive* afferents from the arms, originating in the external cuneate nucleus, and *exteroceptive* fibers from the main cuneate nucleus.

The *ventral (anterior) spinocerebellar tract* and *rostral spinocerebellar tract (RSCT)* convey information to cerebellum regarding complex motor repertoires. Afferents arise from (1) interneurons within spinal motor centers controlling the hindlimbs (VSCT) and forelimbs (RSCT), (2) group I muscle afferents from Golgi tendon organs in groups of muscles involved in synchronized movements, and (3) multisynaptic spinal pathways activated by cutaneous and high-threshold muscle afferents. The *VSCT* originates from spinal border cells, mostly in Rexed lamina VII at the posterolateral aspect of the anterior horn of the lumbosacral spinal cord. It decussates close to the cell bodies, ascends in the contralateral anterolateral funiculus, and enters the cerebellum through the superior cerebellar peduncle (SCP). Most of its fibers cross to the other side, hence the double crossing. It terminates in longitudinal zones in the hindlimb representations in the anterior lobe and, to a lesser extent, in lobule VIII. The *RSCT* originates from neurons at the base of the posterior spinal horn in Rexed lamina VII at spinal cord levels C4 to C8, ascends in the ipsilateral posterolateral funiculus, and enters the cerebellum via both the ICP and SCP, terminating bilaterally in primary and secondary forelimb sensorimotor representations. The



CEREBELLUM SUBDIVISIONS AND AFFERENT PATHWAYS *(Continued)*

corticospinal system facilitates excitatory or inhibitory effects of cutaneous and muscle afferent fibers in the VSCT and RSCT, whereas the reticulospinal system inhibits them. The rubrospinal and propriospinal pathways produce excitation independent of spinal afferents.

Sensory afferents from C1 through C4 are conveyed in the *central cervical tract* (CCT). This arises in the *central cervical nucleus* in Rexed layer VII, which integrates information related to head rotation, such as group I afferent input from neck muscles and vestibular input from semicircular canals. The CCT carries information via the ICP and SCP to the anterior lobe and lobule VIII.

Trigeminocerebellar projections from the principal trigeminal sensory nucleus travel in the ICP to the face representation in caudal lobule V and lobule VI; in contrast, cerebellar projections from the *mesencephalic trigeminal nucleus* travel in the SCP. The *tectocerebellar* tract from the superior and inferior colliculi bilaterally projects to lobules VIII and IX (the posterior, or dorsal, paraflocculus and uvula), and the vermal visual area in lobule VII.

Reticulocerebellar projections act over wide areas of the cerebellum and DCN. They originate from the *lateral reticular nucleus* (LRN) and *paramedian reticular nucleus* in the medulla, the *nucleus reticularis tegmenti pontis* (NRTP) in the pons, and the *medial (magnocellular) reticular formation*. Feedback projections arise from the DCN, particularly the fastigial nucleus.

The *NRTP* receives cerebral cortical afferents from sensorimotor, frontal lobe, and superior parietal regions, and subcortical afferents from vestibular and visual- or eye-movement–related nuclei, including the superior colliculus. Inputs from limbic-related structures include the cingulate gyrus and mammillary bodies. NRTP fibers enter cerebellum through the middle cerebellar peduncle and project widely, with a focus in vermal lobules VI and VII, and lobule X. The NRTP is involved in ocular vergence and accommodation and the visual guidance of eye movements. The limbic relay provides cerebellum with emotionally salient information (see Plate 8-15).

The *lateral reticular nucleus* (LRN) receives inputs from the spinal cord, lateral vestibular nucleus, red nucleus, superior colliculus, and cerebral cortex. Its fibers enter the cerebellum through the ipsilateral ICP; many cross to the contralateral side, providing collaterals to the DCN and terminating in multiple parasagittal zones. LRN connections are somatotopically arranged: the ventrolateral parvicellular region conveys afferents from the lumbar cord to primary and secondary hindlimb representations bilaterally; the dorsomedial, magnocellular part conveys inputs from the cervical cord to cerebellar forelimb regions. LRN neurons resemble VSCT or RSCT neurons but lack group I muscle input, are excited by descending vestibulospinal fibers, and respond to stimulation of larger body surface areas.

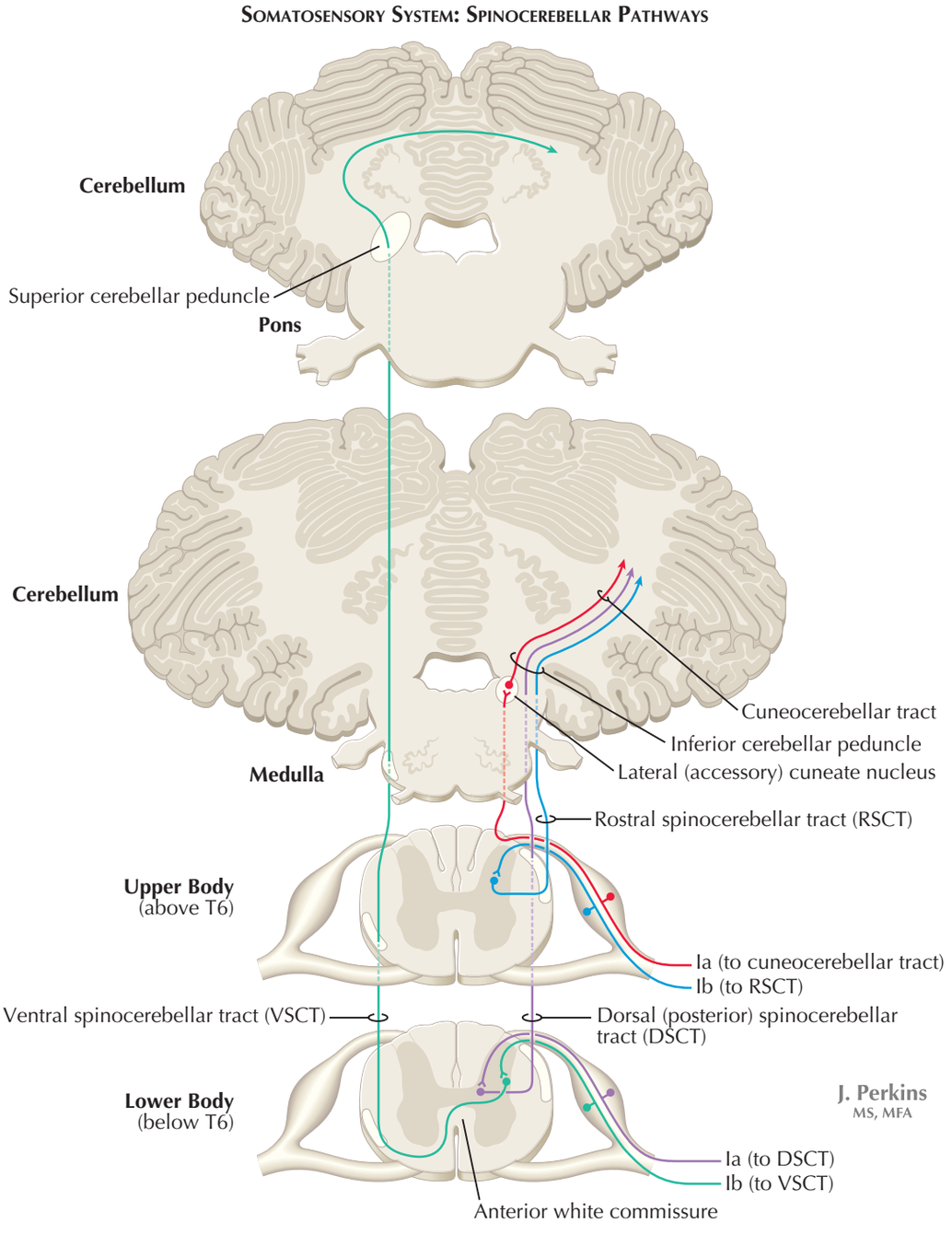
The *paramedian reticular nucleus* in the medulla receives afferents from the vestibular nuclei and somatosensory regions of the cerebral cortex and projects through the ICP to the vermis.

Perihypoglossal Nuclei. These medullary nuclei related to the control of extraocular muscles receive vertical and horizontal gaze information from midbrain and pontine nuclei and face regions of the sensorimotor cortex. They are reciprocally interconnected with vermal and hemispheric components of cerebellar lobule X (nodulus and flocculus) and the fastigial and interposed nuclei.

Arcuate Cerebellar Tract. Fibers from the arcuate nucleus in the ventral medulla form the *striae medullares* visible on the posterior surface of the medulla. They enter cerebellum via the ICP and terminate in ipsilateral hemispheric lobule X. The arcuate nucleus is involved in central reflex chemosensitivity and cardiorespiratory activity.

Vestibulocerebellar Pathways. Vestibular input to cerebellum arises from primary vestibular afferent fibers and projections of neurons in the vestibular nuclei. These fibers carry information from receptors of the vestibular labyrinth, which signal the position and motion of the head in space (see Plate 8-11).

Pontocerebellar Pathways. Basis pontis neurons receive input from multiple areas of the cerebral cortex and project as pontocerebellar fibers via the contralateral MCP to the cerebellar cortex. The organization, somatotopy, and functional relevance of the corticopontocerebellar system are considered in Plate 8-13.

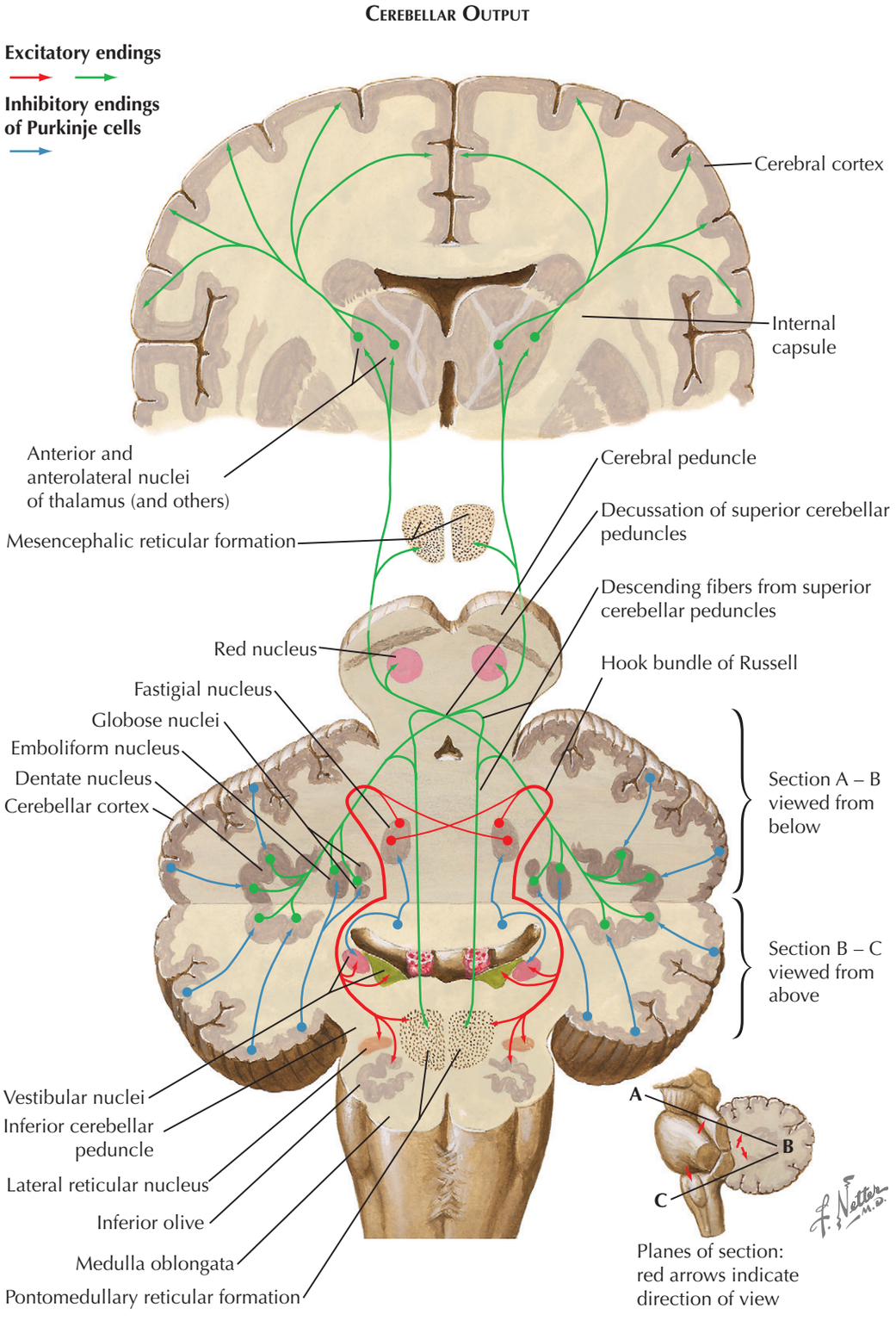


CLIMBING FIBER PATHWAYS

Climbing fibers from the inferior olives project via the contralateral ICP to the cerebellar cortex. Climbing fiber anatomy, connections, and physiology are shown in Plates 8-6 and 8-7.

MONOAMINERGIC FIBERS

Minor dopaminergic inputs to cerebellum arise in the substantia nigra—noradrenergic inputs from the locus coeruleus project diffusely to the vermis and lateral hemispheres, and serotonergic fibers from raphe nuclei project diffusely to most regions of cerebellar cortex.



Cerebellar Efferent Pathways

Efferent pathways from cerebellum originate in *Purkinje cells* (PCs) that project to the *deep cerebellar nuclei* (DCN). DCN neurons then convey efferents from cerebellum to extracerebellar areas in the spinal cord, brainstem, and cerebral hemispheres. DCN neurons receive inhibitory inputs from the PCs and from DCN interneurons, and excitatory input from collaterals of mossy fibers and climbing fibers on their way to the cerebellar cortex. The nature of DCN efferents is determined by the interaction of excitation and inhibition governed by the arrival of information in cerebellar afferent pathways and by the processing of that information by the cerebellar cortex. *Glutamatergic projection neurons* of the DCN are excitatory to all extracerebellar areas, whereas γ-aminobutyric acid *(GABA)-mediated DCN projection neurons* to the inferior olive are inhibitory. The PC-DCN interaction is the basis of the corticonuclear microcomplex, the essential component of the parasagittal zones that form cerebellar cortical modules (see Plate 8-12). The reciprocal nucleo-olivary connections are organized with exquisite precision in a closed-loop circuit. The PC-DCN corticonuclear microcomplex receives input from and sends DCN output to essentially the identical cluster of neurons within the inferior olivary complex. The exact pattern of thalamic terminations varies according to the cerebellar module of origin, but the thalamocerebellar projections conform to a general arrangement, whereby focal areas within the DCN project to rod-shaped aggregates of thalamic neurons situated within curved, longitudinally oriented, onion-like lamellae stacked in a mediolateral direction.

The exception to the PC-DCN projection pattern throughout the cerebellum is the vestibulocerebellar cortex (vermal part of lobule IX [uvula], vermal [nodulus], and hemispheric parts [flocculus] of lobule X), which has direct reciprocal connections with vestibular nuclei. In addition, PCs in zone B of the anterior vermis commit their axons directly to the *lateral vestibular nucleus*, the source of the *lateral vestibulospinal tract*, by which the cerebellum regulates the activation of descending spinal motor systems (see Plates 8-11 and 8-12).

Fastigial Nucleus

Corticonuclear projections from the cerebellar vermis are directed to the fastigial nucleus. It has *rostral and caudal parts* with different connections and functional significance. The *rostral* part of the *fastigial nucleus* sends

CEREBELLAR EFFERENT PATHWAYS *(Continued)*

efferents in the *ipsilateral juxtarestiform body* to the same side of the *brainstem*. Axons from its caudal part cross to the contralateral cerebellum in the *hook bundle of Russell (the uncinate fasciculus*) and project either to the contralateral brainstem in the juxtarestiform body or to the contralateral cerebral hemisphere in the superior cerebellar peduncle (SCP).

Both the rostral and caudal divisions of the fastigial nucleus project to nuclei of the *pontomedullary reticular formation* from which they receive inputs (see Reticular Afferents, Plate 8-9). They also both project to the *vestibular nuclei;* projections from the rostral fastigial nucleus are largely bilateral, those from the caudal fastigial nucleus are mostly contralateral. There are small, crossed projections from the caudal part of the fastigial nucleus to neurons in the posterolateral region of the basis pontis and to the medullary perihypoglossal nuclei. Crossed fastigiospinal projections terminate on motor neurons in the upper cervical spinal cord.

Crossed axons from the caudal division *of the fastigial nucleus* ascend *in the superior cerebellar peduncle* and terminate in the *pretectal*, *superior colliculus*, *and posterior commissure midbrain nuclei* concerned with oculomotor and visual control. Connections with *periaqueductal gray*, *anterior tegmental*, *solitary tract*, *and interpeduncular as well as parabrachial nuclei* impact autonomic, nociceptive, and limbic functions. Fastigial efferents also target the hypothalamus. Thalamic terminations occur in motor-related anterolateral/anterior posterolateral nuclei, the diffusely projecting midline nuclei, and the intralaminar nuclei (central lateral and centromedian). Earlier physiologic and anatomic studies pointed to *fastigial nucleus connections with the septal region*, *hippocampus*, *and amygdala*.

The fastigial nucleus *connections with the contralateral inferior olivary nucleus* are in the caudal part of the medial accessory olive.

Fastigial nucleus efferents influence multiple functional domains: *axial and limb girdle musculature* (medial motor system) via the vestibular and reticular nuclei; *oculomotor systems*, including vertical and horizontal gaze centers in the midbrain and pons; *autonomic centers* through connections with brainstem and hypothalamus; and *emotional modulation* through links with limbic-related circuits.

GLOBOSE AND EMBOLIFORM NUCLEI

These nuclei are referred to in lower mammals as the nucleus interpositus posterior (NIP) and nucleus interpositus anterior (NIA), respectively. They provide cerebellar efferents in the superior cerebellar peduncle from the predominantly motor-related spinocerebellum that receives proprioceptive and exteroceptive inputs from the spinal cord and brainstem, and sensorimotor information from the cerebral cortex. Fibers leave the interpositus nuclei and travel in the superior cerebellar peduncle (SCP), also known as the brachium conjunctivum, crossing to the contralateral side in the SCP decussation to course through the red nucleus, providing somatotopically arranged terminations in its caudal, magnocellular part. This red nucleus sector provides the origin for *rubrospinal fibers* that act on the spinal motor apparatus, particularly arm and hand flexor muscles.

Multiple other brainstem connections of the interpositus nuclei include (1) the lateral reticular nucleus and medullary reticular formation giving rise to *reticulospinal tracts*, (2) the vestibular nuclei as source for *vestibulospinal tracts*, (3) the superior colliculus giving rise to the *tectospinal tract*, (4) the oculomotor nuclei (prepositus hypoglossi, Darkschewitsch, and posterior commissures), (5) the sensory (lateral/external cuneate nucleus), and (6) the nociceptive systems (periaqueductal gray, medullary raphe). These rostrally directed fibers from the interpositus nuclei continue to the hypothalamus and zona incerta before reaching the thalamus. Here they provide heavy terminations to nuclei linked with the precentral motor cortex, notably the ventral posterolateral pars oralis (VPLo) and ventrolateral pars caudalis nuclei (VLc), and to the central lateral nucleus, which has widespread connections beyond motor areas. Efferents from the interpositus nuclei coursing within the descending limb of the SCP project back to the contralateral nucleus reticularis tegmenti pontis and to the dorsal and peduncular nuclei of the basis pontis.

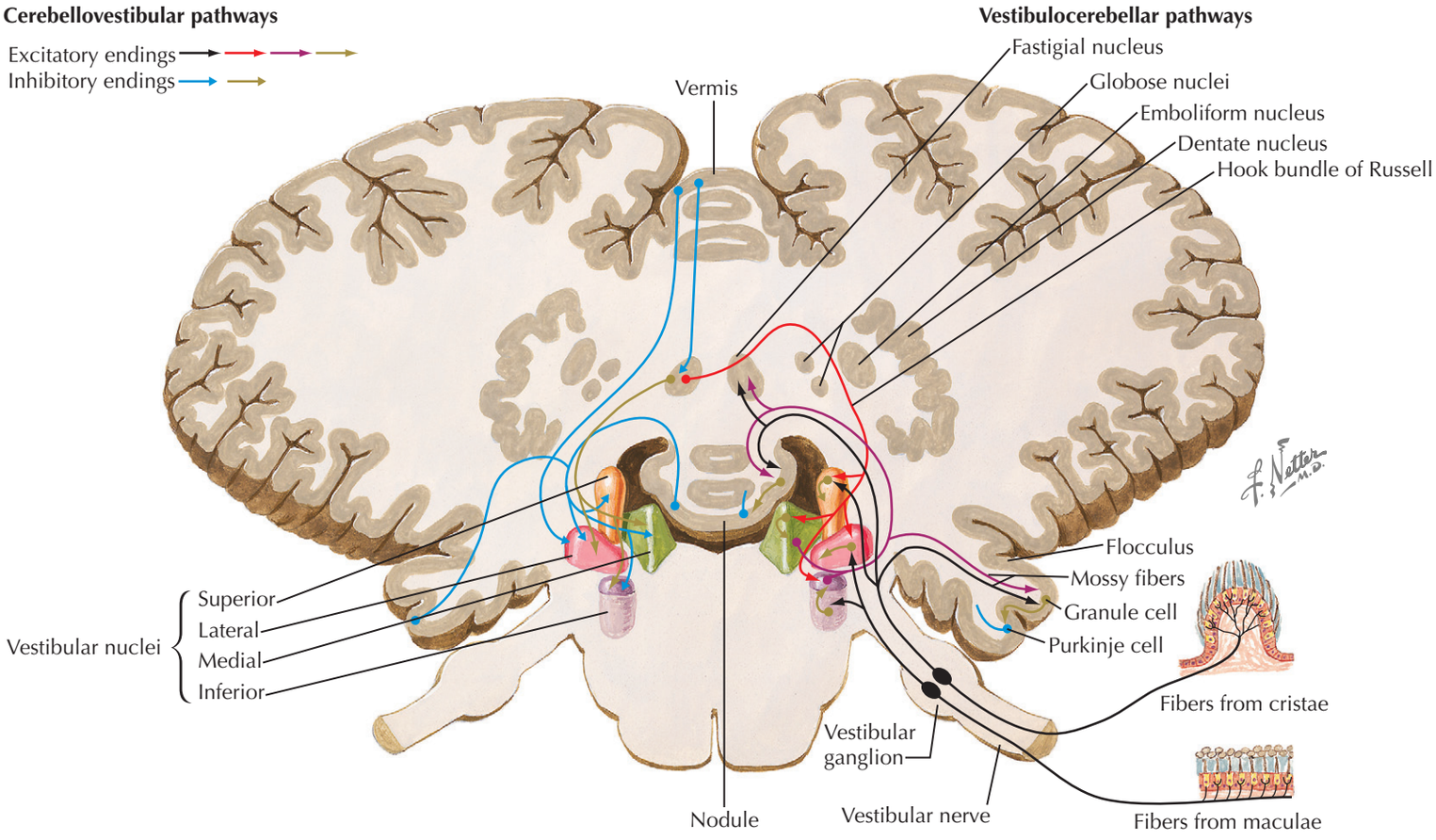
The globose nucleus (NIP) is reciprocally linked with the rostral half of the contralateral medial accessory olive, and the emboliform nucleus (NIA) with the rostromedial part of the dorsal accessory olive.

DENTATE NUCLEUS

The large and multiply folded dentate nucleus is the most lateral of the four major DCN. It is divided into a dorsal part with closely packed folds (polymicrogyric) and a ventral part that is less folded (macrogyric). The dorsal part (paleodentate, because of its relationship to the paleo-, or spinocerebellum) is linked with motor regions of the cerebral cortex. The ventral part (neodentate, interconnected with the more recently evolved neocerebellum) is linked with cerebral association areas. Axons from dentate neurons course in the white matter hilum, enter the SCP, cross to the other side in the decussation of the brachium conjunctivum, and terminate in the thalamus. Dorsal dentate nucleus fibers terminate in motor-related thalamic nuclei, including the ventroposterolateral and ventral lateral nuclei, that then project to the primary motor and premotor cerebral cortex. Middle and caudal thirds of the dentate nucleus are linked via the ventral anterior nucleus of thalamus with the premotor cortex and with the frontal eye fields engaged in saccadic eye movements. Ventral and lateral parts of the dentate nucleus project via the dorsal sector of the ventral lateral nucleus and the medial dorsal nucleus to dorsolateral prefrontal, posterior parietal, and other cerebral association areas. Dentate nucleus projections to thalamic intralaminar nuclei provide widespread influence on cerebral cortical areas. These intralaminar nuclei also project to the striatum, providing an indirect link between cerebellum and basal ganglia. The dentate nucleus also projects to the small-celled (parvicellular) part of the red nucleus that feeds back through the central tegmental tract to the inferior olive, which, in turn, is linked with the cerebellum. Lesions in this triangle of Guillain and Mollaret result in palatal tremor. Dentate fibers in the descending limb of the superior cerebellar peduncle (SCP) terminate in reticular nuclei in the pons.

The rostral and dorsomedial parts of the dentate nucleus (the paleodentate) project to the dorsal lamina and bend of the principal olive. The ventral and caudal parts of the dentate nucleus (the neodentate) project to the ventral lamina of the principal olive.

The complex and varied destinations of the projections from the DCN and vestibular nuclei underscore the role of the cerebellum in multiple domains of neurologic function. Lesions of these different pathways produce a wide array of impairments, motor and otherwise. Damage to the DCN superimposed upon cerebellar cortical dysfunction appears to have adverse consequences on long-term recovery, as exemplified in patients with cerebellar stroke or tumor.



Cerebellovestibular Pathways

The vestibular system is closely related to vermal lobule IX (uvula), vermal and hemispheric parts of lobule X (nodulus and flocculus, respectively), and vermal lobule I/II (lingula)—phylogenetically ancient regions that are therefore referred to both as archicerebellum and vestibulocerebellum. The vestibular system is also related to the paleocerebellum (spinocerebellum) through its connections with anterior lobe vermis and the fastigial nucleus.

VESTIBULOCEREBELLAR PROJECTIONS

There are five peripheral vestibular end organs; the cristae in the three orthogonally oriented semicircular canals detect movement in the sense of angular rotation in the horizontal, pitch, and roll planes, and the maculae in the two otoliths that sense the effect of the linear acceleration of gravity during roll-tilt (utricle) and pitch (saccule).

Vestibular afferents from these end organs combine in the vestibular nerve. One branch terminates in the ipsilateral cerebellar cortex, providing profuse primary vestibular afferents from otoliths to vermal lobule IX and from semicircular canals to vermal lobule X. The other branch terminates with varying degrees of intensity in different subregions of all four vestibular nuclei: medial, lateral, superior, and inferior. These nuclei, with the exception of the posterior part of the lateral vestibular nucleus (Deiters nucleus), provide cholinergic secondary vestibular afferents bilaterally to the vermal and hemispheric regions of lobules IX and X and to the anterior vermis. Together with the perihypoglossal nucleus, they also project to the fastigial nucleus as collaterals of vestibulocortical fibers. Axons of both pathways terminate as diffusely projecting mossy fibers in granule cell glomeruli within the cerebellar cortex. Tertiary vestibular afferents reach vermal lobules IX and X as climbing fibers derived from subregions of the medial accessory olive (beta subnucleus and dorsomedial cell column). These olivary nuclei receive inhibitory input from the parasolitary nucleus that, in turn, receives projections from the labyrinth. The olivocerebellar terminations are arranged in discrete parasagittal zones, relaying information from the vertical and anterior semicircular canals.

CEREBELLOVESTIBULAR PROJECTIONS

Projections from vermal and hemispheric parts of lobules IX and X are directed to all the vestibular nuclei. The anterior lobe vermis projects to the fastigial nucleus, and in addition, Purkinje cells in zone B of the anterior vermis project directly to the part of the lateral vestibular nucleus that is devoid of vestibular afferents and gives rise to the lateral vestibulospinal tract. Strong topographically arranged projections to the vestibular nuclei are also derived from the fastigial nucleus. The rostral fastigial nucleus, linked with the spinal recipient anterior vermis, projects to the medial, superior, and perihypoglossal nuclei. The caudoventral region of the fastigial nucleus, devoted to oculomotor control, projects to the inferior vestibular nucleus and to the part of the lateral vestibular nucleus that receives zone B cortical inputs. The projections of the rostral portion of the fastigial nucleus are ipsilateral, whereas fibers from the caudal fastigial nucleus cross in the hook bundle of Russell to excite contralateral vestibular neurons. Thus Purkinje cells of the cerebellar vermis can depress the activity of neurons in the vestibular nuclei either by direct inhibition or by inhibiting the discharge of neurons in the fastigial nucleus, thereby decreasing the excitatory activity reaching vestibular neurons via fastigiovestibular pathways, an example of disfacilitation.

FUNCTIONAL CONSIDERATIONS

The vestibular system is critical for the control of eye movements for orientation in intrapersonal and extrapersonal space and for control of the axial musculature, essential for balance. Vestibulocerebellar connections provide the cerebellum with a topographic map of space, serving as an anatomic substrate for modulation of postural reflexes evoked by vestibular and optokinetic stimulation. The vestibulocerebellum predicts spatial environments and, by modulating the amplitude of movements produced by reflexes such as the vestibulo-ocular reflex, compensates for head movements to optimally guide behavior. The clinical relevance of these vestibulocerebellar circuits is exemplified by the loss of plastic changes in the horizontal vestibulo-ocular reflex in individuals with damage to lobule X (flocculus) and by the inability to remember postural adjustments to a previously maintained head position in space after damage to the vermal lobules IX and X. Acute injury to the vestibular system produces violent nausea, vomiting, and vertigo. The paleocerebellum receives a modest amount of vestibular afferent input but extensive input from spinocerebellar tracts. The principal action of the paleocerebellum on the vestibular system is to regulate vestibular activity in relation to proprioceptive and exteroceptive information about the head, trunk, and extremities. This is critical for posture, balance, and equilibrium.

Cerebellum Modular Organization

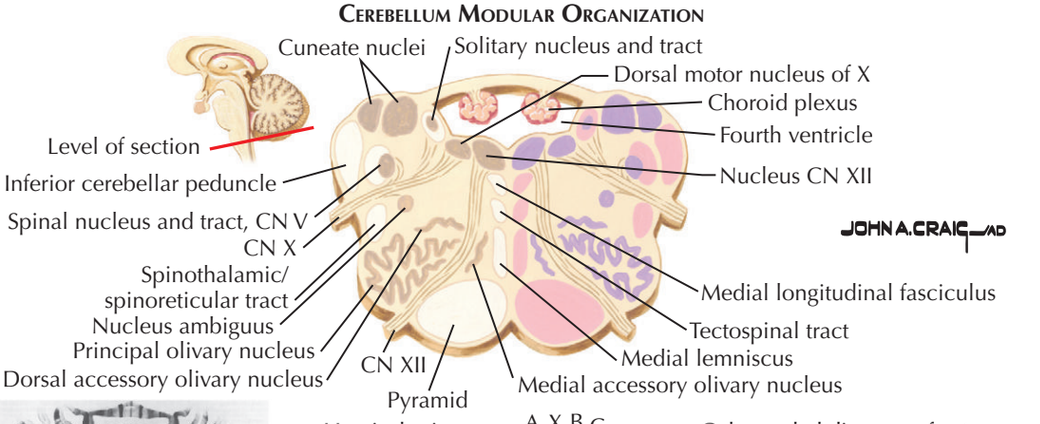
The cerebellar cortex and deep cerebellar nuclei (DCN) are linked anatomically in multiple repeating, parasagittally arranged, and histochemically identifiable *corticonuclear microcomplexes*. These channel Purkinje cell (PC) axons from longitudinal PC zones to focal regions within the DCN. The zonal organization is reflected also in the connections of the inferior olive with the cerebellar cortex and DCN. *Cerebellar zones* are further divided into microzones about 0.5 mm wide (four to five PCs), extending many millimeters rostrocaudally. Monoclonal antibody stains show alternating *zebrin*-positive and -negative stripes in the cortex that correlate with corticonuclear and olivocerebellar connections.

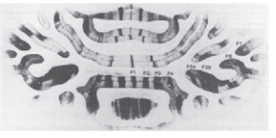
Cerebellar Corticonuclear Projection

Output from the cerebellar cortex to the DCN is derived exclusively from PCs and is inhibitory. The vermis projects to the fastigial nucleus, the intermediate cortex project to globose and emboliform nuclei, and lateral hemispheres project to the dentate nucleus (DN). There is a reciprocal excitatory projection of the DCN neurons back onto the PCs (Plate 8-5).

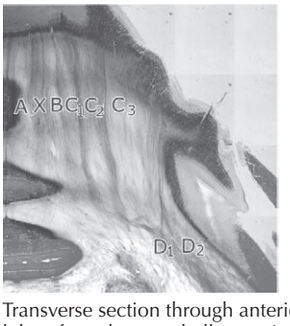
Inferior Olivary Nucleus

This nuclear complex is a folded sheet of 1.5 millions neurons in the medulla, situated between the pyramidal tract and the lateral reticular nucleus. The medial accessory olive (MAO) and the dorsal accessory olive (DAO) each have rostral and caudal components. The principal olive (PO) has dorsal, lateral, ventral, and medial lamellae. Other subnuclei include the beta cell group, dorsomedial cell column (DMCC), and dorsal cap of Kooy. Proximal dendrites of olivary neurons have appendages that form the central core of a complex synaptic structure, the olivary glomerulus. These have gap junctions enabling electrotonic coupling between groups of olivary neurons. Each olivary axon provides 7 to 10 climbing fibers to the cerebellar cortex and DCN; one CF per PC (see Plate 8-6).

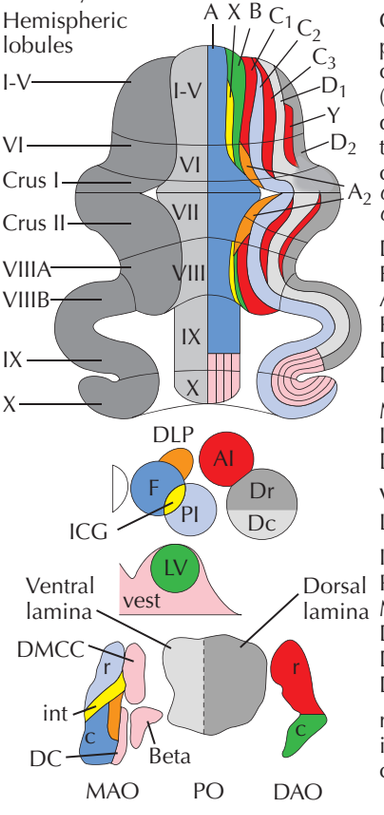




Coronal section through adult rat cerebellum immunostained for zebrin I shows Purkinje cells aligned in parasagittal bands in vermis and hemispheres Reprinted with permission from Leclerc N, Doré L, Parent A, Hawkes R. The compartmentalization of the monkey and rat cerebellar cortex. *Brain Res* 1990;506:70.



Transverse section through anterior lobe of monkey cerebellum stained for acetylcholinesterase shows parasagittal compartments within the white matter, from zone A medially to zone D2 most laterally Reprinted with permission from Voogd J, Paxinos G, Mai JK. *The human nervous system.* London: Academic Press; 1990.



Color-coded diagram of cat parasagittal zonal arrangement of cerebellar cortical connections (zones A through D2) with the deep cerebellar nuclei and with the inferior olivary nuclear complex. Adapted from Voogd J. *Cerebellar zones - a personal history. Cerebellum 2001;* 10: 334-350.

Deep cerebellar nuclei:
F (fastigial)
AI (anterior interposed)
PI (posterior interposed)
Dr (rostromedial dentate)
Dc (caudoventral dentate)

Minor nuclei:
ICG (interstitial cell group)
DLP (dorsolateral protuberance)

Vest (vestibular nuclei)
LV (lateral vestibular nucleus)

Inferior olivary nuclear complex:
PO (principal olive)
MAO (medial accessory olive)
DMCC (dorsomedial cell column)
DC (dorsal cap)
DAO (dorsal accessory olive)

r: rostral
int: intermediate
c: caudal

Olivary Afferents and Projections to Cerebellum

The olive receives multiple excitatory afferents, sends excitatory CFs to discrete longitudinally oriented parasagittal microzones in the cerebellar cortex, and sends collaterals to focal areas within the DCN that are linked to PCs in that cortical microzone. Olivary neurons receive inhibitory feedback projections from those DCN neurons to which they project, forming a closed-loop system.

Spinal cord projections are conveyed directly to the MAO and DAO in the crossed ventral spino-olivary tracts (SOT) and indirectly in the dorsal SOT that ascends in the ipsilateral dorsal column, synapses in the gracile and cuneate nuclei, decussates to the contralateral olive, and decussates again in the olivocerebellar projection, terminating in the cerebellum ipsilateral to its spinal cord origin. Spino-olivary fibers terminate in primary and secondary arm and leg representations in the spinocerebellum (zones A through C3).

The *trigeminal sensory nucleus* projects to the caudal MAO and rostromedial DAO; these project to lobule VI in zones C1 and C3, with collaterals to the emboliform nucleus.

Cerebral cortex projections are conveyed to the olive and cerebellum via the parvocellular component of the red nucleus *(RNpc)*. Primary motor and premotor cerebral cortex are linked somatotopically with the caudolateral *RNpc;* this projects to the PO dorsal lamina and bend, which sends efferents to the lateral cerebellar D2 zone and dorsomedial dentate nucleus (paleodentate) and to the rostral MAO that targets cerebellar zone C2 and the globose nucleus. Frontal eye fields, premotor, and prefrontal areas project via the dorsomedial RNpc and the PO ventral lamina to the medial cerebellar D1 zone and the caudoventral dentate nucleus (neodentate).

Optokinetic information from pretectal nuclei, including the nucleus of the optic tract and accessory optic nuclei, is conveyed to the dorsal cap and the ventrolateral outgrowth, and relayed to lobule X (flocculonodular lobe).

Vestibular information is conveyed to vestibular nuclei, including the parasolitary nucleus, which project via DMCC and nucleus β to vermal and hemispheric regions of lobules IX (uvula, paraflocculus) and X (nodulus and flocculus).

Visual information from superior colliculus is relayed through the caudal MAO to the vermal visual area in lobule VII and fastigial nucleus. Other afferents originate in midbrain regions concerned with oculomotor control (nuclei of Darkschewitsch, Cajal, Edinger-Westphal, perihypoglossal) and are conveyed to vermal lobules IX and X. The lateral reticular nucleus, periaqueductal gray, and zona incerta convey motor, nociceptive/autonomic, and associative information to the olive.

Together with their connections with the inferior olive, the corticonuclear microcomplexes comprise cerebellar modules that are also linked with pontine and other afferents and efferents. The paracrystalline architectural uniformity of the modules likely supports a *neural computation*, the *universal cerebellar transform*, common to all cerebellar areas, which can be applied to multiple domains of neurologic function by virtue of the precise connections of each module with extracerebellar structures.

Cerebrocerebellar Connections

There are massive, reciprocal, topographically arranged connections between the cerebral cortex and the cerebellum. Each cerebral hemisphere communicates predominantly with the contralateral cerebellar hemisphere. The cerebrocerebellar circuit has a two-stage feedforward limb and a two-stage feedback limb. Ipsilateral corticopontine projections originate in cortical layer Vb in sensorimotor areas as well as association and limbic-related cortices concerned with cognition and emotion (posterior parietal, superior and middle temporal, dorsolateral and medial prefrontal and cingulate areas, and posterior parahippocampal gyrus). Corticopontine projections terminate around neurons in the basis pontis. Pontocerebellar pathways decussate in the middle cerebellar peduncle, conveying corticopontine afferents to the contralateral cerebellum. Feedback to cerebral cortex is via crossed cerebellothalamic projections in the superior cerebellar peduncle, and ipsilateral thalamocortical projections to cortical areas from which the feed-forward projections arose, thereby completing the closed-loop systems.

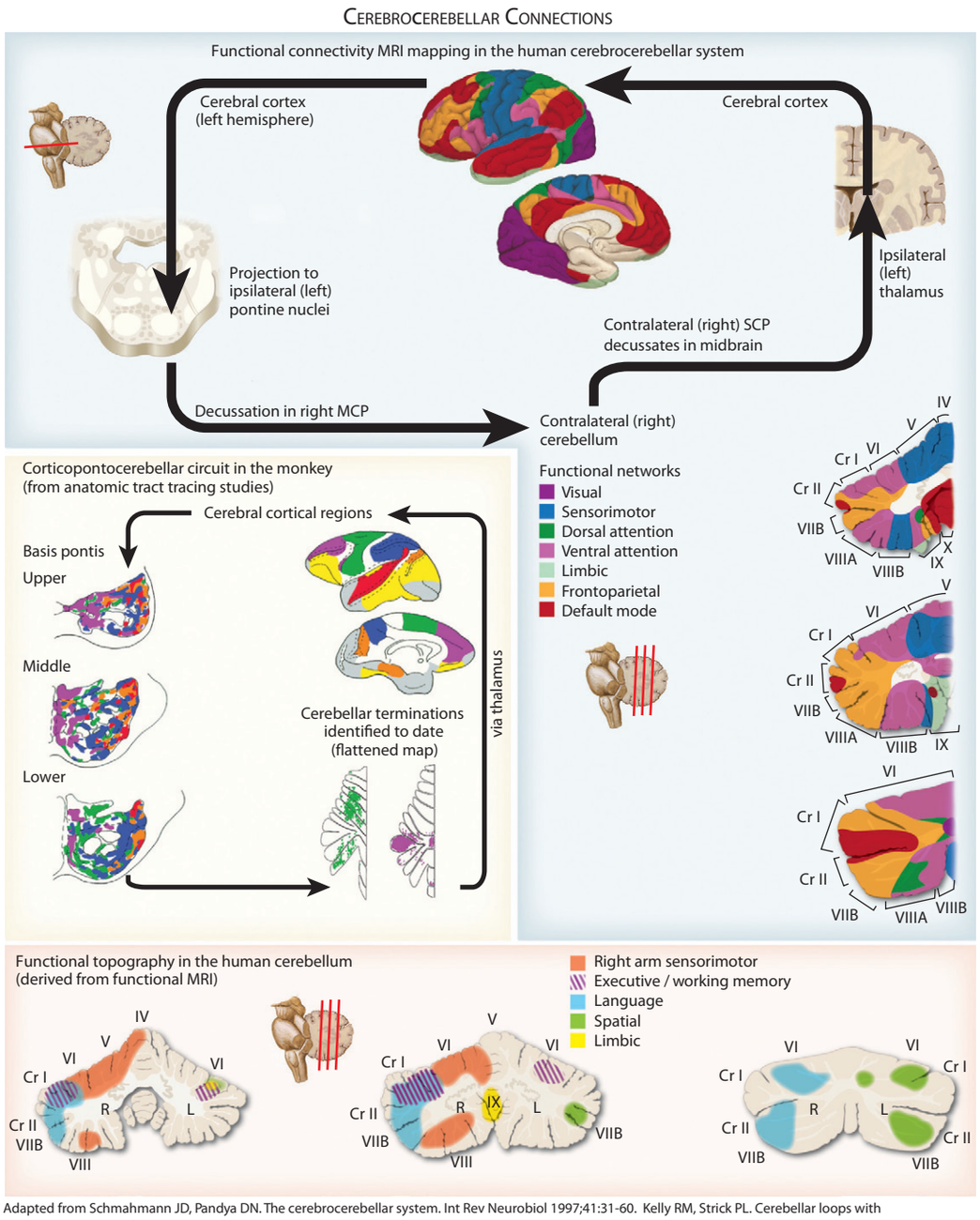
In the *cerebral peduncle*, prefrontal fibers are most medial, sensorimotor fibers intermediate, and fibers from the parietal, temporal, and occipital lobes are lateral. In the monkey, terminations in the pons from motor and association areas are topographically arranged. The *caudal pons* preferentially receives sensorimotor inputs and projects mostly to the cerebellar anterior lobe and lobule VIII, containing primary and secondary sensorimotor representations, respectively. *Dorsolateral pons* projects to visual areas in the vermal and hemispheric lobule IX. *Medial parts of the rostral pons* project to crus I. *Medial, anterior, and lateral pons* project to crus II. By way of these projections, lobules III through V of the anterior lobe and lobule VIII receive sensorimotor afferents. In contrast, much of lobule VI, crus I and crus II of lobule VIIA, and lobule VIIB receive inputs from association areas and limbic-related regions of the cerebral cortex.

Clinicopathologic studies in patients show that *speech* is represented medially in the rostral pons, *hand coordination* medially and anteriorly in the rostral and midpons, the *arm* anteriorly and laterally to the hand, *leg coordination* mostly laterally in the caudal pons, and *gait* is distributed in medial and lateral locations throughout.

In the *feedback system*, *primary motor cortex* receives projections via thalamus from dorsal parts of the dentate nucleus and caudal portions of the anterior interpositus nucleus, where neurons activate with arm movement. *Premotor cortex* receives input from midrostrocaudal dentate nucleus. Frontal eye field–projecting neurons are in the caudal third of the dentate nucleus activated by saccadic eye movements. The *dorsolateral prefrontal cortex* (areas 46 and 9 lateral) receives projections from the ventral dentate. *Projections to parietal, temporal, and cingulate association areas* also appear to arise in ventral and lateral parts of the dentate nucleus. *Fastigial nucleus projections* to intralaminar thalamic nuclei appear to have *widespread influence* on the cerebral hemisphere.

These connectional patterns are matched by magnetic resonance imaging studies in humans using resting state functional connectivity and experiments performed while subjects are actively engaged in tasks. The *cerebellum, like the cerebral cortex, is topographically arranged into functional domains.* The *primary sensorimotor cerebellum* is in lobules III, IV, and V of the anterior lobe and adjacent parts of lobule VI; the secondary sensorimotor representation is in lobule VIII. The *motor cerebellum* is functionally coupled with sensorimotor cerebral areas and engaged in motor tasks: leg and foot are in lobules II, III, and VIII; hand representation in lobules IV, V, and VIII; and orofacial movements in paravermal anterior lobe and medial lobule VI. The *supramodal, or cognitive, cerebellum* is linked with cerebral association cortices but not with sensorimotor areas. These posterior lobe regions are lobule VI, lobule VIIA at the vermis and in crus I and crus II in the hemispheres, and lobule VIIB. The *cognitive cerebellum* is differentially *linked with* the various subdivisions of the *prefrontal cortex* and other cerebral association areas. *Lobules VI, crus I and crus II, and lobule IX also correlate with an executive control network* in the cerebral hemispheres; lobule VI with a salience network; and lobule IX with the default network. *Working memory and executive functions* engage lobules VI and VII, *language recruits* posterolateral cerebellum on the right, and *spatial tasks* recruit it on the left. *Affective/emotional processing and pain and autonomic functions* involve lobules VI and VII in the vermis more than the hemispheres. The anterior lobe is not engaged in cognitive tasks; the posterior lobe is not involved in motor tasks, with the exception of parts of lobule VI and the second sensorimotor representation in lobule VIII.

These anatomic and imaging findings demonstrate a high degree of functional topography in cerebrocerebellar loops, and they provide the anatomic and functional foundations for the cerebellar modulation of sensorimotor, cognitive, and limbic domains.



Adapted from Schmahmann JD, Pandya DN. The cerebrocerebellar system. Int Rev Neurobiol 1997;41:31-60. Kelly RM, Strick PL. Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. J Neurosc 2003;23:8432-8444. Middleton FA, Strick PL. Cerebellar output channels. Int Rev Neurobiol 1997;41:61-82. Buckner RL, Krienen FM, Castellanos A, Diaz JC, Yeo BT. The organization of the human cerebellum estimated by intrinsic functional connectivity. J Neurophysiol 2011;106:2322-2345. Stoodley CJ, Schmahmann JD. Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. NeuroImage 2009;44:489-501. Stoodley CJ, Valera EM, Schmahmann JD. Functional topography of the cerebellum for motor and cognitive tasks: an fMRI study. NeuroImage 2012;59:1560-1570.

Cerebellar Motor Examination

Cerebellar incoordination is characterized by disturbed rate, rhythm, and force of movements. This manifests as impaired oculomotor control; articulation (dysarthria); stance, equilibrium, and gait (ataxia); and motion of the limbs (dysmetria). Severity of involvement can be graded using ataxia rating scales.

Eye Movements. Cerebellar lesions produce unsteady ocular fixation in *primary position*, *microsaccadic oscillations*, *square wave jerks*, *ocular flutter*, *ocular bobbing*, and *opsoclonus*. *Pursuit eye movements* show saccadic intrusions—jerkiness following a moving target. *Volitional gaze (saccades)* is hypermetric (overshoot) or hypometric (undershoot/catch-up). Gaze-evoked, direction-beating nystagmus has a fast phase in the direction of eccentric gaze and slow phase in the opposite direction. *Downbeat nystagmus* in primary gaze points to lesions of the cervicomedullary junction, *upbeat nystagmus* to midline lesions or drug toxicity.

The *vestibulo-ocular reflex (VOR)* maintains visualized image stabilization on the retina during head movement. With passive trunk and head rotation while focusing on his or her own hand, the patient's eyes should not move relative to the head. Failure of this VOR cancellation from lesions of the vestibulocerebellum manifests as saccadic eye movements.

Slowing of eye movements leading to ophthalmoplegia occurs in spinocerebellar ataxias and mitochondrial disorders. Patients with *oculomotor apraxia* cannot direct gaze voluntarily and perform head thrusts to initiate these movements.

Speech/Swallowing. Cerebellar dysarthria is described as "*scanning speech*." Syllables are poorly articulated, cadence is slowed and irregular, and rapid or alternating buccal, palatal, and lingual consonants are degraded. Dysarthria is compounded by deficient volume control. Ataxic respiration affects quality of speech. Impaired control of muscles of deglutition leads to dysphagia and aspiration risk.

Motor Control. Resting tone in pure cerebellar disease is generally decreased, or *hypotonic*. There may be a spastic catch or frank spasticity when spinal cord pathology is also present in some inherited ataxic disorders. Cerebellar lesions do not produce weakness, but there may be slowed initiation and generation of force. *Truncal ataxia* occurs with midline lesions, including *titubation*, that is, oscillations of the head and trunk. The patient has a *widened stance* and is unable to stand in tandem position or on one foot. *Cerebellar ataxic gait* is staggering, uneven, irregular, and veers from side to side. Unilateral lesions cause stumbling toward the affected side.

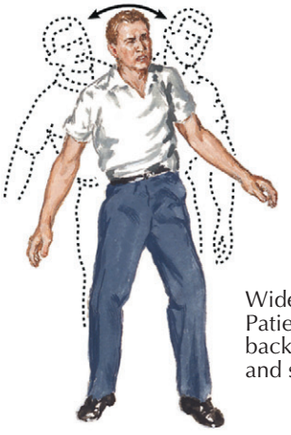
Coordination of Arms and Legs. *Dysmetria* (Greek *dys*, and *metron* [measure]) is the disordered ability to regulate, judge, and control behavior, both with motor and cognitive domains (see Plate 8-15). The cerebellar motor syndrome causes difficulty judging distances, trajectory of intended movements, and force required for movements. *Compound movements* (across more than one joint) are particularly affected. Visual guidance improves outcome minimally.

Postural tremor is assessed with arms extended in pronated position. *Rebound* is tested by the examiner displacing the arm downward, observing for overshoot above the starting point. *Dysmetria* characteristics include end-point tremor, overshooting targets (hypermetria) or undershooting (hypometria), and oscillation at the elbow. These are assessed with *finger-to-nose testing*; the patient brings the index finger to his/her nose and then to the examiner's finger held steady at arm's length. Tremor increases with proximity to the target; tremor direction is generally perpendicular to direction of movement. The *finger chase/mirror test* measures *overshoot/undershoot*. The patient points to the examiner's finger held at arm's length, following his/her sequential moves horizontally and vertically. *Dysdiadochokinesia* is degradation of rapid alternating movements, tested by forearm pronation/supination. Tapping the index finger on the crease of the thumb assesses fine motor control. *Dysrhythmia* is an inability to generate normal rhythms, assessed by rapidly tapping the hand on a surface or the heel on the ground.

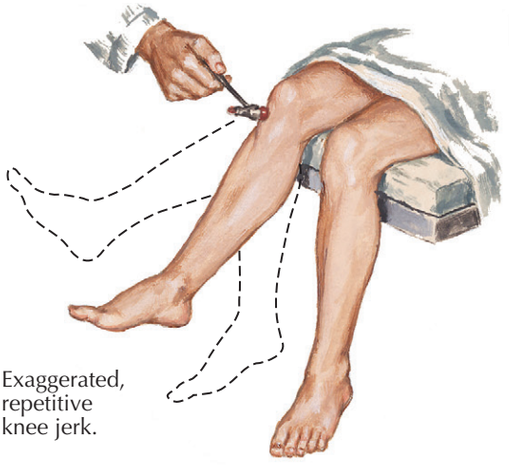
The *heel-to-shin test*, performed with the patient supine, assesses leg coordination. The heel is placed on the opposite knee and moved down the shin. In wheelchair-bound patients, the heel is brought to the knee of the opposite leg held parallel to the ground. Proximal overshoot occurs as the heel is placed on the knee, and tremor occurs as the heel is maintained in that position. Slowing, jerking, or side-to-side movements are noted as the heel moves down the shin. In the draw-a-circle test, the supine patient traces a circle in the air; decomposition manifests as irregular or chaotic motions.

Cerebellar tremor is large amplitude, 2 to 3 Hz, and may involve many body parts. *Rubral tremor* from red nucleus lesions and its connections involves multiple joints, direction changes, and is frequently *rotatory*. *Palatal tremor* is slow and semirhythmic, resulting from Guillain-Mollaret myoclonic triangle lesions of this neuronal brainstem/cerebellum network (dentate nucleus to red nucleus and inferior olivary nucleus).

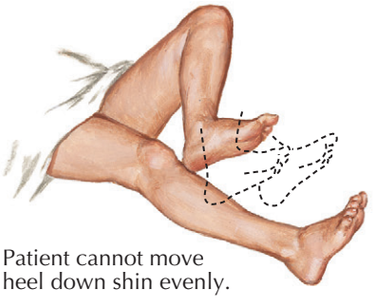
Brainstem and/or cerebellar manifestations



Wide-based gait. Patient teeters back and forth and sideways.

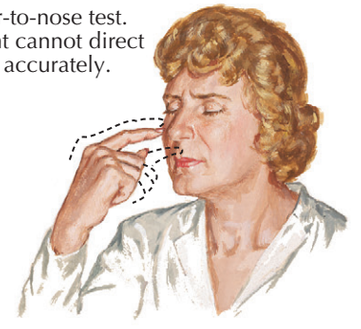


Exaggerated, repetitive knee jerk.



Patient cannot move heel down shin evenly.

Action tremor. Hand unsteady on attempting to hold glass, write, etc.



Finger-to-nose test. Patient cannot direct finger accurately.

Acute cerebellar lesions produce headache, nausea, vomiting, and vertigo, along with gait ataxia, dysarthria, and sometimes diplopia. Hiccups and tinnitus may also occur.

Cerebellar Cognitive Affective Syndrome

The cerebellum is organized into a primary sensorimotor region in the anterior lobe and adjacent part of lobule VI and a second sensorimotor region in lobule VIII. Current evidence indicates that *cognitive and limbic regions are in the posterior lobe* (lobule VI, lobule VIIA [which includes crus I and crus II], and lobule VIIB); lobule IX may also be part of this network. *Cognitively relevant areas are situated more laterally* in these lobules, whereas the limbic cerebellum is represented in the vermis. Lesions of the sensorimotor cerebellum result in the cerebellar motor syndrome (see Plate 8-14). Lesions of the cognitive and limbic cerebellum lead to the *cerebellar cognitive affective syndrome* (CCAS). This constellation of deficits is characterized by impairments in (1) executive function, (2) visual spatial processing, (3) linguistic deficits, and (4) affective dysregulation. The CCAS occurs in adults and children after many types of injury. It can be prominent after acute lesions, including stroke, hemorrhage, and infectious or postinfectious cerebellitis but relatively subtle in late-onset hereditary ataxias.

Executive function deficits include problems with working memory, as tested with reverse digit span; mental flexibility is tested using tasks of set shifting; and perseveration is demonstrated using bedside tests of mental control. Patients may have concrete thinking, poor problem-solving strategies, and impaired ability to multitask, with trouble planning, sequencing, and organizing their activities.

Mental representation of visual spatial relationships can be impaired. Visuospatial disintegration is apparent when attempting to copy or recall visual images. Identification of multiple features within a complex diagram (*simultanagnosia*) is difficult.

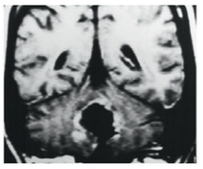
Expressive language can be abnormal, characterized by long response latency, brief responses, reluctance to engage in conversation, and word-finding difficulties. *Verbal fluency* is decreased affecting phonemic (letter) more than semantic (category) naming. *Mutism* occurs postoperatively for vermis tumors, particularly in children but also in adults subsequent to cerebellitis, infarction, and hemorrhage. Speech may have *abnormal syntax*, resulting in agrammatism. Degraded control of volume, pitch, and tone can produce *high-pitched*, *hypophonic speech*.

Short-term memory impairments include difficulty learning and spontaneously recalling new information, reflecting deficient strategies for organizing verbal or visual-spatial material for encoding, and difficulty locating information in memory stores. Successful recall is aided by a structured approach to the task, using clues and other prompts. Conditional associative learning is degraded, as shown in studies of classic conditioning in cerebellar patients (as well as in animals). Mental arithmetic is impaired. Ideational apraxia and hemiinattention have been reported.

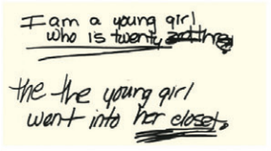
The *affective component* of the CCAS occurs when lesions involve the *limbic cerebellum* in the vermis and fastigial nucleus. Patients exhibit *difficulty modulating behavior and personality style*, have flattened affect or disinhibition manifesting as overfamiliarity, and flamboyant or impulsive actions. Behavior may be regressive and childlike, sometimes with obsessive-compulsive traits. Patients can be irritable, with labile affect and poor attentional and behavioral modulation. *Acquired panic disorder* is described in this setting as well.

Cerebellar Cognitive Affective Syndrome

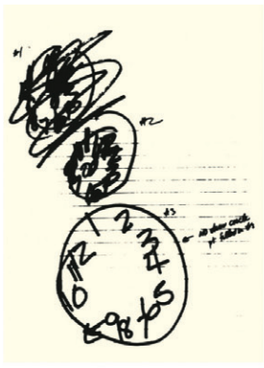
CCAS Following Tumor Resection in Adult



MRI after resection of ganglioglioma

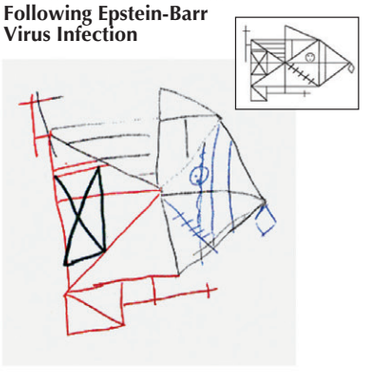


Patient writing sample demonstrates agrammatism ("twenty 3rd"), perseveration ("the the"), and disinhibition (underlining)



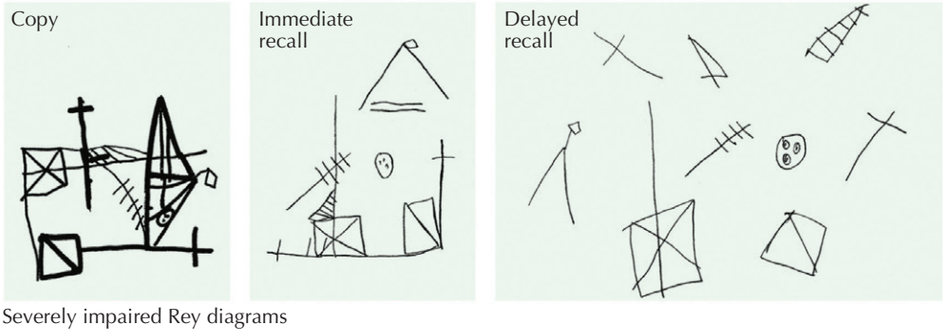
Patient clock drawing reveals impaired visual-spatial strategy and execution

Post-Infectious Cerebellitis Following Epstein-Barr Virus Infection



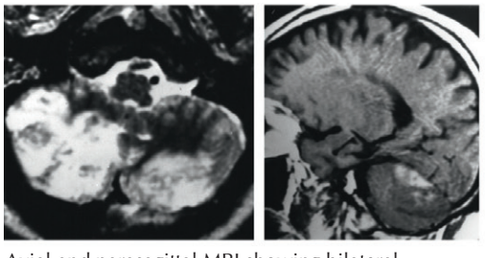
Patient's copy of Rey diagram showing poor visual-spatial planning

CCAS Following Resection of Left Cerebellar Cystic Astrocytoma in Child

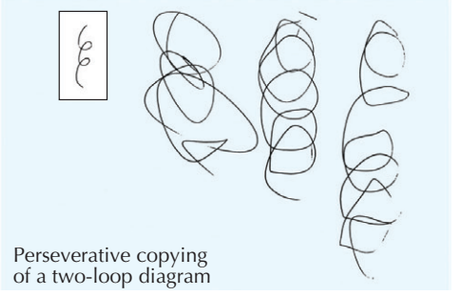


Severely impaired Rey diagrams

CCAS Following Cerebellar Infarction



Axial and parasagittal MRI showing bilateral PICA and left SCA infarcts respectively



Perseverative copying of a two-loop diagram

From Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. *Brain* 1998;121 (Pt 4): 561-579; and Levisohn L, Cronin-Golomb A, Schmahmann JD. Neuropsychological consequences of cerebellar tumour resection in children: cerebellar cognitive affective syndrome in a paediatric population. *Brain* 2000;123 (Pt 5):1041-1050.

Early evidence indicates that there are five domains of *behavioral dysregulation* caused by cerebellar damage. These are impairments of attentional control, emotional control, autism spectrum disorders, psychosis spectrum disorders, and difficulties with the social skill set. Within each of these domains, there are hypometric/diminished behaviors and hypermetric/exaggerated behaviors, consistent with the dysmetria of thought theory of the cerebellar role in nervous system function.

The intellectual and emotional impairments from damage to the cognitive and limbic posterior lobe of the cerebellum may be more disabling than motor deficits, and when the anterior lobe is spared, these occur in the absence of the motor syndrome. Recognizing the nonmotor manifestations of cerebellar lesions can lead to earlier diagnosis of cerebellar damage and facilitate treatment of cognitive emotional consequences of disrupted cerebellar modulation of higher function. The nature of these deficits provides new avenues for conceptualizing mental illnesses, including autism, schizophrenia, bipolar disorder, attention deficit disorder, and dyslexia. Appreciating the role of the cerebellum beyond motor control therefore has implications for understanding and improving neuropsychiatric disorders. This represents a radical departure from our previous understanding of the functions of the "little brain" and is an area of active investigation in neuroscience. The neural substrates that support this nonmotor cerebellar role are discussed in Plate 8-13.

CEREBELLAR DISORDERS—DIFFERENTIAL DIAGNOSIS

Diagnosing the cause of a cerebellar disorder can be straightforward or require sleuthing and special tests. The following principles guide the approach: (1) recognize symptoms and signs of cerebellar disease; (2) determine whether peripheral nerves, spinal cord, brainstem, or cerebral hemispheres are also affected; (3) characterize the timing of onset and progression, that is, the temporal profile; (4) search for risk factors, that is, toxins and drugs, recent infections, and systemic features of neoplasms; (5) document family history and country of origin, a critical feature when considering hereditary disorders; (6) brain magnetic resonance imaging is essential; and (7) laboratory data may clinch the diagnosis.

ACUTE—MINUTES TO HOURS

Ischemic stroke and hemorrhage start abruptly. Both worsen clinically over hours if cerebellar edema develops. Note the *"posterior fossa mantra" of acute cerebellar and brainstem injury*—headache, nausea, vomiting, and vertigo, *with or without ataxia*, dysarthria, diplopia, and nystagmus. Neurologic examination lateralizes to side of injury.

Acute cerebellitis occurs more commonly in children than adults, starting more abruptly than postinfectious cerebellitis; both produce a *pancerebellar syndrome*.

Thiamine deficiency produces *Wernicke encephalopathy*, a triad of ataxia, confusion, and oculomotor disturbances that is a medical emergency requiring immediate repletion of vitamin B_1.

SUBACUTE—DAYS TO WEEKS

Paraneoplastic immune-mediated Purkinje cell attack from remote tumors (lung, breast, ovary) may develop acutely over days, producing a pancerebellar syndrome.

Cerebellar tumors (benign or malignant) worsen over weeks to months but occasionally present acutely with obstructive hydrocephalus.

Other focal lesions include abscesses, multiple sclerosis, progressive multifocal leukoencephalopathy (PML), and rhombencephalitis. Alcoholic cerebellar atrophy (anterior superior vermis) may present subacutely, as can cerebellar leukoencephalopathy from inhaled solvents and heroin, and Creutzfeldt-Jakob disease, with ataxia, dementia, and myoclonus.

INSIDIOUS, CHRONIC PROGRESSION—MONTHS TO YEARS

Neurodegenerative disorders start insidiously, progressing over years or decades. Autosomal dominant (AD) ataxic disorders pass down through generations. AD spinocerebellar ataxias (SCAs) typically manifest during adulthood. SCA 1 and SCA 3 have extrapyramidal, corticospinal and peripheral nerve lesions. SCA 2 has slowed eye movements, and extrapyramidal features in younger patients. SCA 3 is prevalent in Portuguese Azorean communities; younger patients have dystonia. SCA 5 and 6 are purely cerebellar. SCA 7 has visual failure from rod-cone macular dystrophy. SCA 8 includes mild chorea. SCA 10 occurs associated with epilepsy in families with Native American ancestry. SCA 17 resembles Huntington disease, with cognitive failure and choreoathetosis. Dentatorubropallidoluysian atrophy causes myoclonus, dystonia, and cognitive decline; it is uncommon outside Japan. Currently, there are more than 35 SCAs (NIH website - GeneTests, www.ncbi.nlm.nih.gov/sites/GeneTests).

Episodic ataxias (EA) are AD. *EA1*, a *potassium channelopathy* starts in childhood, producing brief duration ataxic episodes and myokymia. *EA2* is a *calcium channelopathy*; attacks last for days, sometimes with migraine. The gene causing EA2 is associated with familial hemiplegic migraine and SCA6. Both EAs improve with acetazolamide.

Autosomal recessive disorders (AR) manifest in one generation, usually in childhood. Parents are asymptomatic; nonsibling family history is unrevealing. *Friedreich ataxia* is the most common AR cerebellar disorder, with ataxia, peripheral neuropathy, cardiomyopathy, scoliosis, and diabetes. Hearing and visual impairment occur late. Occasionally, it begins in adulthood, resembling SCAs. *Ataxia telangiectasia* often manifests before telangiectasias develop; features include recurrent infections from immunoglobulin IgA deficiency and radiation sensitivity with risk of neoplasia. *Ataxia with oculomotor apraxia* types 1 and 2 include peripheral neuropathy, choreiform movements, and cognitive difficulties. *French Canadians* experience *AR cerebellar ataxia (ARCA) type 1* progressing over decades and *AR spastic ataxia of Charlevoix-Saguenay* starting in childhood. ARCA-2 (ataxia with *coenzyme Q10 deficiency*) and ataxia with *vitamin E* deficiency are treatable.

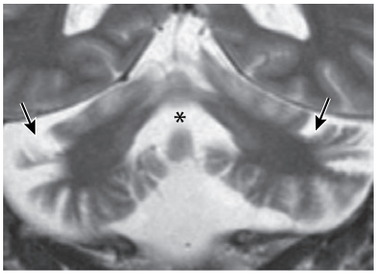
Hereditary spastic paraplegias are AD or AR. Myelopathy may be accompanied by ataxia and dysmetria.

Mitochondrial encephalomyopathies cause ataxia and complex clinical constellations. Most are AR or obey mitochondrial maternal inheritance. *Mitochondrial recessive ataxia syndromes (MIRAS)* caused by mutations in *polymerase gamma* cause ataxia, neuropathy, and hearing loss, particularly in Scandinavian families. *Fragile X–associated tremor ataxia syndrome* is an X-linked polyglutamine disorder causing ataxia, tremor, cognitive failure, and erectile dysfunction.

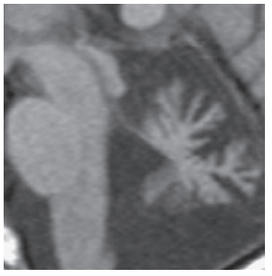
Sporadic ataxias include *multiple system atrophy*, a *synucleinopathy* with cerebellar ataxia or parkinsonism, autonomic dysfunction (postural hypotension, erectile dysfunction, urinary incontinence), and rapid eye movement (REM) sleep behavior disorder. *Idiopathic late-onset cerebellar ataxia* (ILOCA) describes adults older than 50 years with isolated cerebellar degeneration.

Isolated downbeat nystagmus points to lesions at the cervicomedullary junction or lobules IX/X. Rarely, this heralds a neurodegenerative disorder. *Palatal tremor* occurs with SCA 20.

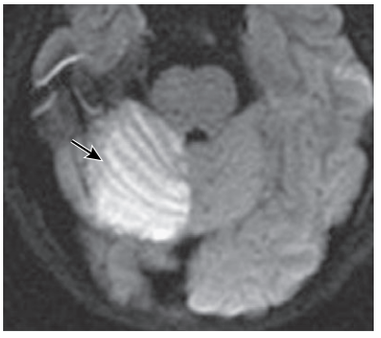
Many disorders of infancy and childhood have cerebellar malformations or disruptions—hypoplasia, agenesis, megacerebellum, Chiari, and Dandy-Walker malformations.



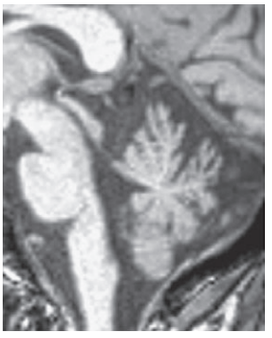
Cerebellar hypoplasia. Underdeveloped cerebellum seen on T2-weighted coronal MRI, with prominent fissures (arrows) and fourth ventricle (asterisk).



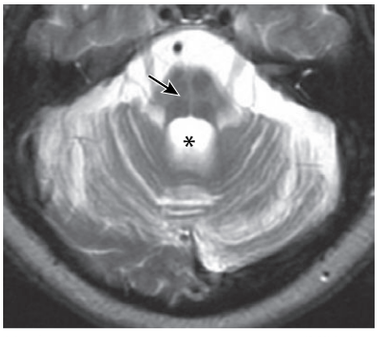
Idiopathic late onset cerebellar ataxia. Cerebellar volume loss with small vermis and prominent fissures seen on mid-sagittal T1 MRI. The pons is largely spared.

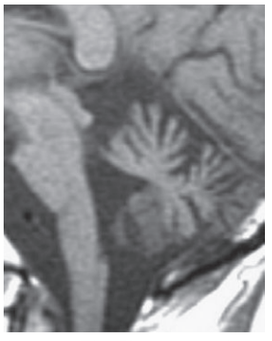


Cerebellar stroke. Acute infarction (arrow) in the territory of the superior cerebellar artery seen on axial diffusion-weighted MRI.

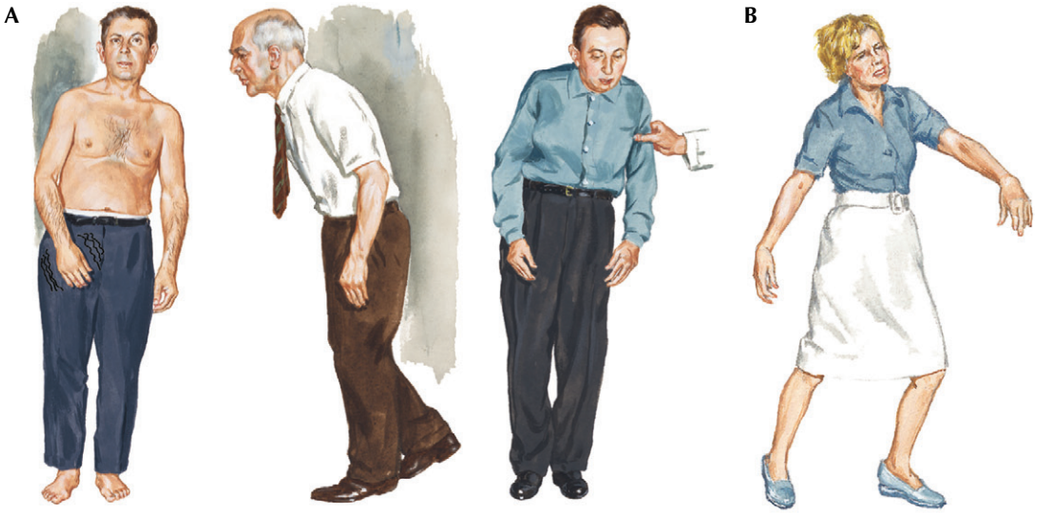


Spinocerebellar ataxia type 2. Cerebellar volume loss and mild pontine volume loss seen on mid-sagittal T1 MRI.





Multiple system atrophy, cerebellar type (MSAc). Axial T2 (left) and mid-sagittal T1 MRI (right), showing prominent cerebellar volume loss including the white matter, enlarged fourth ventricle (asterisk), and marked pontine volume loss with hot-cross-bun sign (arrow).



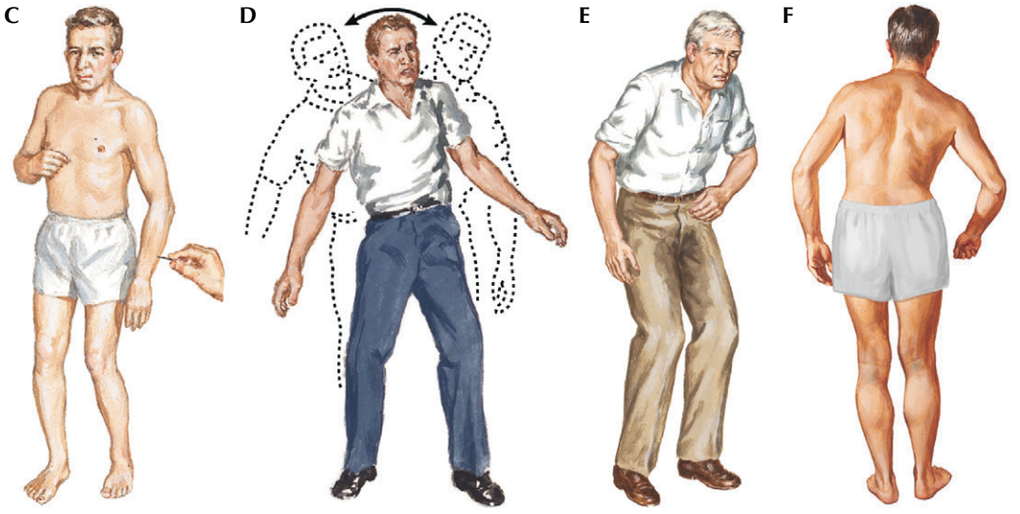
Stage 1 Parkinson disease: unilateral involvement; blank facies; affected arm in semiflexed position with tremor; patient leans to unaffected side

Stage 2 Parkinson disease: bilateral involvement with early postural changes; slow, shuffling gait with decreased excursion of legs

Stage 3 Parkinson disease: pronounced gait disturbances and moderate generalized disability; postural instability with tendency to fall

Typical wide-based gait of alcohol intoxication

Gait Disorders—Differential Diagnosis



Left hemiparesis with decreased arm swing sometimes associated with limited sensation secondary to a corticospinal tract lesion

Wide-based gait of midline cerebellar tumor or other lesion

Apraxic gait of normal-pressure hydrocephalus

Characteristic posture in left-sided lower lumbar disc herniation

Gait is a complex neurologic function that can be degraded by lesions at multiple points in the nervous and musculoskeletal systems. Identifying the location of pathology is essential to establishing the diagnosis. Elicitation of the history is followed by observation of the gait, which facilitates hypothesis-driven examination. Focused imaging and laboratory investigations confirm or refute the clinical impression.

Muscle. Myopathy is proximally predominant in inflammatory myopathies, steroid myopathy, and Duchenne and limb girdle dystrophies. Waddling gait results from dropping of the pelvis. Patients have difficulty ascending stairs, arising from chairs, or arising from a seated position on the floor.

Neuromuscular Junction (NMJ). Of the various NMJ disorders Lambert-Eaton myasthenic syndrome (LEMS) is most likely to present with a gait disorder. Climbing stairs and arising from a chair is impaired. Typically, myasthenia gravis presents with ocular symptoms; gait dysfunction usually does not occur until generalization later in the course. Both NMJ disorders worsen with exertion.

Peripheral Nerve. Peroneal nerve palsy produces foot drop because of tibialis anterior muscle weakness. The leg is lifted high; the foot does not dorsiflex and is slapped down with the ball of the foot hitting the ground first. Femoral neuropathies affect the quadriceps muscles, causing weakness or buckling when navigating stairs, particularly descending as the quadriceps needs to lock to support the after-coming leg.

Generalized peripheral neuropathies are symmetric and length dependent, causing foot slapping because of distal weakness and sensory deafferentation, particularly proprioceptive impairment. The proprioceptive loss contributes to increased difficulties in darkness; the Romberg test is positive. Muscle stretch reflexes are diminished or absent. Lumbosacral polyradiculopathies or plexopathies produce weakness in multiple myotomes, unilaterally or bilaterally, affecting walking.

Spinal Cord. With myelopathies, lower-extremity hypertonicity causes spastic gait, scissoring (legs tending to cross each other), stiff-legged motions, minimal knee flexion, and circumduction. Strength may be preserved. Reflexes are exaggerated with extensor plantar responses, but the jaw jerk is normal.

Cerebellum. Cerebellar gait is wide based, veers from side to side, with a lurching, irregular cadence, and extra steps when turning or making sudden moves. The earliest sign is inability to walk in tandem. Late-stage cerebellar disease destroys truncal stability, making gait impossible without a walker or bilateral support. Unilateral cerebellar lesions produce stumbling and/or ipsilateral falling. Strength is preserved.

GAIT DISORDERS—DIFFERENTIAL DIAGNOSIS *(Continued)*

Brainstem. Ataxic hemiparesis results from lesions in the basis pontis, midbrain, thalamus, and corona radiata, involving corticospinal and cerebrocerebellar circuits. Mild weakness is accompanied by true cerebellar dysmetria and dysrhythmia. The affected leg circumducts, with inaccurate foot placement.

Basal Ganglia. Extrapyramidal movement disorders affect gait, depending on the interplay of inhibition and disinhibition within the basal ganglia circuitry. Parkinsonian syndromes characteristically have small shuffling steps at initiation of stride and through all gait phases, stooped posture, and festination, with the anteriorly displaced center of gravity pulling the patient forward. The patient festinates from one stationery object to another to prevent escalation of speed. Resting tremor occurs in Parkinson disease (see Plate 7-4), anteflexed neck in multiple system atrophy, absent vertical gaze in progressive supranuclear palsy (see Plate 7-7), and limb apraxia in corticobasal degeneration (see Plate 7-7). Chorea, dystonia, and athetosis characterize Huntington disease (see Plate 7-13); dyskinesias occur with dopaminergic excess in treated Parkinson patients; hemiballism is seen after subthalamic lesions and in Tourette syndrome.

Cerebral Cortex and White Matter. *Frontal lobe gait disorders (gait apraxia)* secondary to subcortical small vessel lacunar disease are characterized by a magnetic quality, as if glued to the floor, or slipping clutch. Patients have difficulty initiating stride, taking small repetitive steps before launching a gait that looks almost normal. After stopping, the attempt to restart reproduces the pattern. Confined spaces are particularly troublesome.

Normal-Pressure Hydrocephalus (see Plate 8-17). Normal-pressure hydrocephalus produces a similar gait disorder, together with urinary dysfunction, cognitive decline, and ventriculomegaly on imaging. *Hemiparesis* from *upper motor neuron lesions* produces increased tone in the contralateral limbs, with the leg maintained in extension and the arm in flexion. The leg circumducts because of poor flexion at the hip and knees. The plantar-flexed foot may have clonus, producing a bouncing quality to the gait.

Non-neurologic Disorders. *Elderly persons* sometimes have a slow cautious gait, reflecting slowing of neural conduction and concern to prevent falls. Non-neurologic disorders producing limp or insecure gait include arthritis, trochanteric bursitis, lumbosacral spine or disc disease, and podiatric conditions (bunions, tenosynovitis, neuromas).

Gait is sometimes irregular in *primary psychiatric disorders*, with stereotypies and mannerisms or extrapyramidal features from chronic psychotropic medications. Psychogenic gait disorders (*astasia-abasia*) are varying and inconstant, contravening recognized neurologic patterns; this diagnosis is best made by neurologists after careful investigation.

G Patient walks gingerly due to loss of position sense and/or painful dysesthesia

H Patient with lumbar spinal stenosis with forward-flexed gait

I Patient with peripheral neuropathy and loss of proprioception

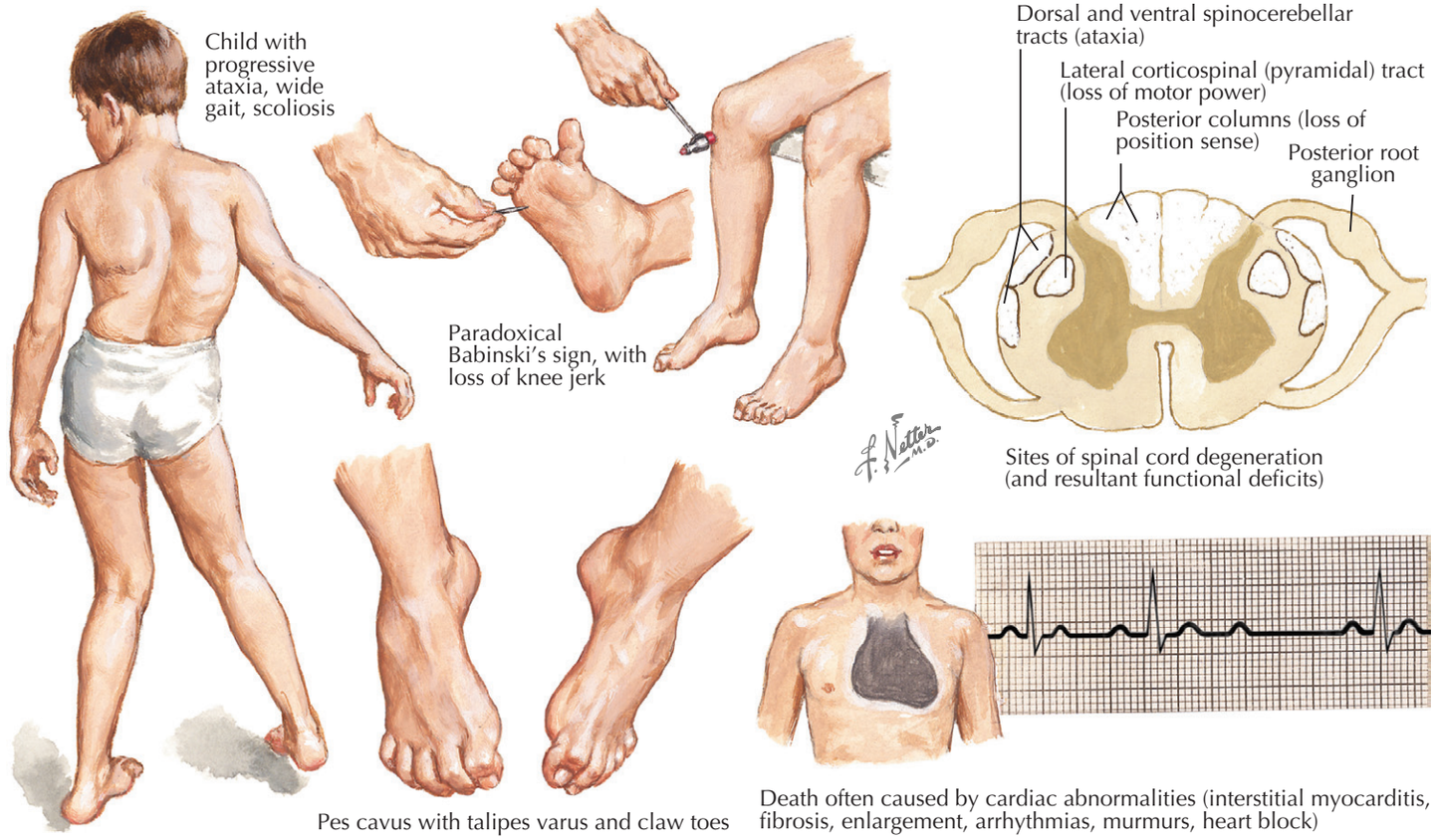
J Typical spastic gait, scuffing toe of affected leg

K Severe myopathy or NMJ lesion with proximal weakness

L Sudden occurrence of foot drop while walking (peroneal nerve)

M Sudden buckling of knee while going down stairs (femoral nerve)

N Muscle cramps from defect in energy metabolism (McArdle disease)



Friedreich Ataxia

Friedreich ataxia (FRDA; [Online Mendelian Inheritance in Man {OMIM}: phenotype 229300; gene/locus 606829]) is a unique disorder involving expansion of a trinucleotide repeat (GAA) in the first intron of the relevant gene, frataxin (*FXN*), leading to loss of function in the unstable frataxin protein. FRDA is autosomal recessive unlike other trinucleotide repeat disorders, which are typically autosomal dominant or X-linked. It differs from CAG repeat disorders (Huntington disease, the spinocerebellar ataxias, and Kennedy disease), wherein expansion occurs in the coding region, leading to toxic gain of function by increasing content of glutamine in the relevant protein.

FRDA is a progressive spinocerebellar disorder typically having prepubertal onset between ages 5 and 15 years, although exceptions occur, with up to 25% having delayed onset into adulthood. Because of spinal cord, peripheral nerve, and, to a lesser extent, cerebellar atrophy, the initial signs are principally ataxia involving gait and limb function (spinocerebellar tracts) and muscle weakness followed by progressive loss of muscle stretch reflexes at the knees and ankles, contrasting with spasticity and extensor plantar responses (pyramidal tracts). In addition, progressive diminution of proprioception and vibratory sensation (posterior columns) occurs. With steady progression of gait and lower limb dysfunction with foot deformities, that is, equinovarus, pes cavus, and clawed toes, wheelchair dependency occurs as early 10 years after onset.

Progressive dysarthria is typical. Abnormal visual and auditory function occurs, particularly in later stages. Abnormal oculomotor function is quite common; optic atrophy occurs in 25%. Although cognitive function is not affected overall, the speed of information processing is often slowed, with increasing difficulty in complex reasoning. Scoliosis is present in virtually all individuals, requiring constant surveillance for progression, bracing to retard progress, and surgical intervention in up to 20%.

Systemic involvement is also prominent in the form of cardiomyopathy and progressive cardiac conduction defects (arrhythmia and heart block), representing the most common cause of death. In addition, diabetes mellitus and glucose intolerance, requiring glucose monitoring, occur in at least one third of patients.

Assessment of neurologic function involves neuroimaging, clinical electrophysiology (electromyography [EMG]), radiologic evaluation for scoliosis, and testing for visual and audiometric function. Magnetic resonance imaging (MRI) of cerebral hemispheres is normal, but atrophy of the spinal cord, brainstem, and cerebellum are progressive. Motor nerve conduction velocities are generally normal, but sensory nerve studies reveal reduced or absent function. Electrocardiogram (ECG) is recommended at diagnosis and annually thereafter, and echocardiography is recommended with onset of cardiomyopathy.

FRDA has an incidence in Indo-European populations of approximately 1:50,000, although isolates have been described at 1:25,000. Lower frequencies are reported in Native Americans and residents of sub-Saharan Africa and Southeast Asia.

The normal range of GAA repeats in *FXN* is 5 to 33, with greater than 80% having less than 12. Affected individuals have at least 70 GAA repeats, although expansions up to 1,700 are described. Most commonly, repeat length is 600 to 1,200. The intermediate range is regarded as a premutation, although the percentage of affected individuals is less than 1%. In the 25% with delayed FDRA onset, the GAA expansion is generally smaller (100-600 repeats), but factors such as genetic background and environmental influences are important variables. FRDA is due to abnormal expansion (equal or different lengths) in both alleles of *FXN* in approximately 98% of cases. The remainder represents individuals with abnormal expansion in one allele and a point mutation or deletion inactivating the gene in the other allele. No individual has been described lacking an expansion in at least one *FXN* allele.

Diagnosis of FDRA depends on assessment of *FXN* in blood by deoxyribonucleic acid (DNA) sequencing methodology capable of detecting GAA expansion and direct assessment of inactivating mutations of nonexpanded regions for the small percentage with a point mutation or deletion. Carrier detection and prenatal diagnosis is recommended for individuals in a family with known disease-producing expansion. Frataxin is a relatively small (210 amino acids) protein that is prevalent in the inner mitochondrial membrane. Required in the formation of iron-sulfur clusters that occur in respiratory chain complexes I to III and aconitase, frataxin deficiency results in defective mitochondrial function, increased mitochondrial free iron, and abnormal energy production in spinal cord and skeletal and cardiac muscle. Differential diagnosis includes peripheral neuropathy (Charcot-Marie-Tooth), spinocerebellar ataxia, ataxia telangiectasia, abetalipoproteinemia, mitochondrial DNA mutations (myoclonus epilepsy with ragged-red fibers [MERF]), and late-onset hexosaminidase deficiency.

In general, survival is significantly shortened in FRDA, with an average longevity of 30 to 40 years after onset. Although no cure exists at present, a number of pharmacologic agents are under investigation. Specific gene therapy is not currently available.

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CEREBROVASCULAR CIRCULATION AND STROKE

Overview and Approach to Stroke Patient

Arterial Supply to the Brain and Meninges

Overview and Cervical Segments

The brain and meninges are supplied by branches that originate from the aorta. The brachiocephalic trunk (or *innominate artery*) divides behind the right sternoclavicular joint into a right common carotid artery (CCA) and a right subclavian artery that supplies the arm. The next aortic branches are the left common carotid artery and the left subclavian artery, arising directly from the aortic arch. The vertebral arteries are early branches of the subclavian arteries of each side. The common carotid arteries bifurcate in the neck, usually opposite the upper border of the thyroid cartilage, most often at the level of the body of the fourth cervical vertebra, into the internal carotid arteries, which are direct (nearly 180-degree extensions of the common carotid artery) and the external carotid arteries (ECAs), which course more anteriorly and laterally and supply branches to the face and its structures.

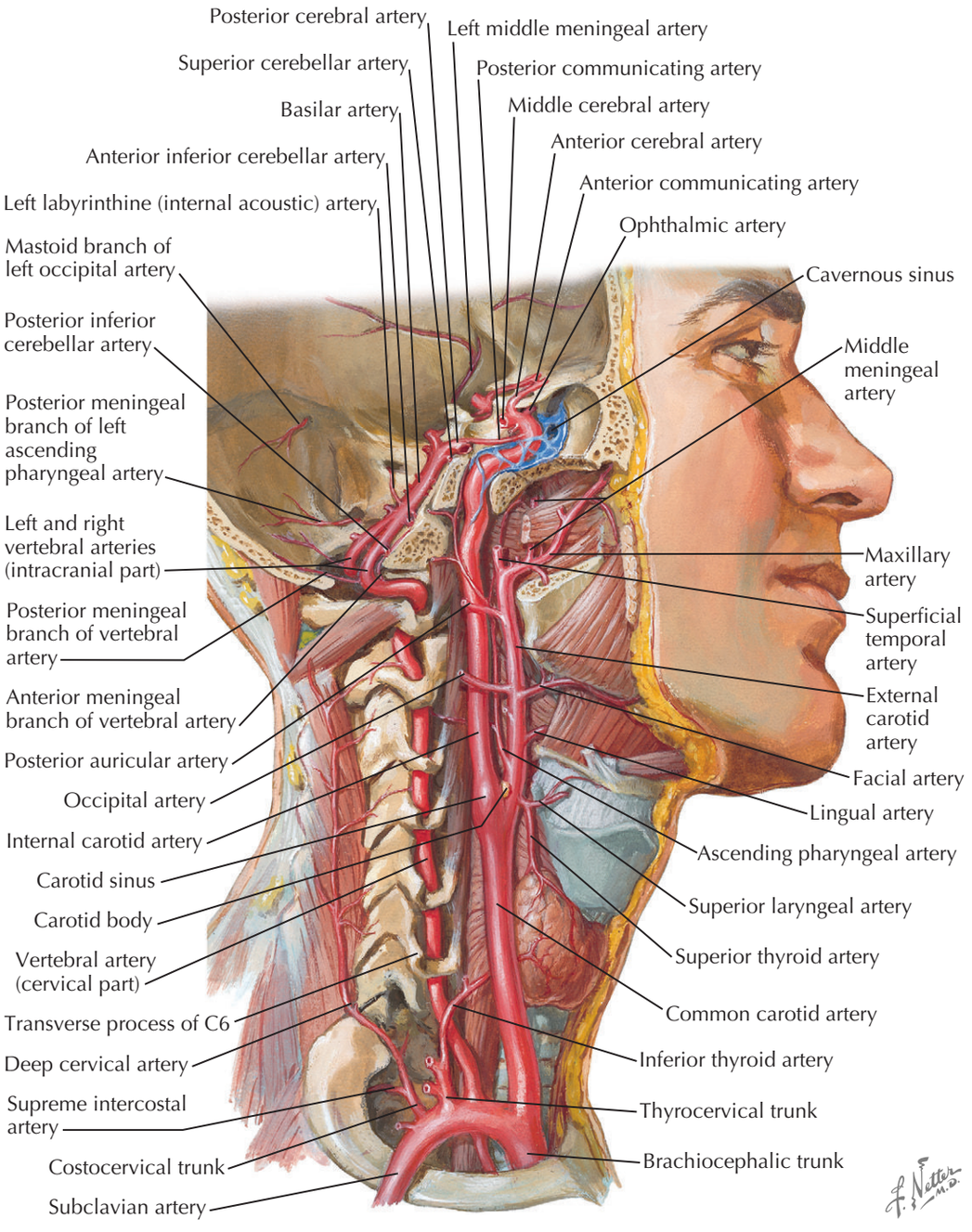
Internal Carotid Artery

The internal carotid arteries (ICAs) ascend vertically in the neck, posterior and slightly medial to the external carotid artery. These arteries are positioned medial to the sternocleidomastoid muscle and travel behind the faucial pillars of the pharynx until they reach the carotid canal at the skull base. They have no branches within the neck. At the skull base, the carotid arteries lie adjacent to the 9th to 12th cranial nerves, which exit the skull from the jugular and hypoglossal foramina. The arteries then enter the skull through the carotid canal within the petrous bone and form an S-shaped curve. The portion of the internal carotid arteries within this curve is referred to as the *carotid siphon*. There are three divisions of the internal carotid arteries within the siphon: an intrapetrous portion, an intracavernous portion within the cavernous sinus, and a supraclinoidal portion.

Branches. Two branches arise from the *petrous segment*: the caroticotympanic artery supplying the tympanic cavity and the artery of the pterygoid canal (vidian artery) supplying the pharynx and the tympanic cavity. The *cavernous segment* gives off the meningohypophyseal trunk supplying branches to the pituitary gland and meninges and the anterior meningeal artery. Within the cavernous sinus, the internal carotid artery lies in close relationship to the nerves that control eye movement (III, IV, and VI) and the ophthalmic and maxillary divisions of V. Soon after leaving the cavernous sinus, medial to the anterior clinoid process, the internal carotid artery gives off the *ophthalmic artery*. The ophthalmic artery passes through the optic canal into the orbit just below and lateral to the optic nerve.

The internal carotid arteries penetrate the dura mater, forming the *supraclinoid segment*. They ascend slightly posteriorly and laterally, passing between the oculomotor and optic nerves. The branches of the proximal supraclinoid region are the *anterior choroidal, superior hypophyseal, and posterior communicating* arteries, which arise and course posteriorly. The termination of the intracranial internal carotid arteries (the so-called T portion because of its shape) is the bifurcation into the *anterior cerebral* arteries, which course medially, and the *middle cerebral* arteries, which course laterally.

Arteries to Brain and Meninges



Vertebral Artery Extracranial

Segments. The first branch of each subclavian artery is the vertebral artery (VA). The *thyrocervical and costocervical* trunks originate from the subclavian arteries just after the vertebral artery and can serve as collateral channels when the vertebral artery becomes occluded. The vertebral arteries course upward and backward during their first segment (V_1) until they enter the transverse foramina of the sixth or fifth cervical vertebra. Then the artery ascends as the second segment (V_2), which courses within the intravertebral foramina, exiting from the transverse process of the atlas. The third segment (V_3) passes posteriorly behind the articular process of the atlas; it lies in a groove on the upper surface of the posterior arch of the atlas, behind the atlas, before piercing the dura mater to enter the foramen magnum. The intracranial portion (V_4) ends at the medullopontine junction, where the two VAs join to form the basilar artery.

Branches. The cervical portion of the vertebral arteries gives rise to many muscular and spinal radicular branches. The spinal branches pass through the intervertebral foramina and enter the spinal canal to supply the cervical portion of the spinal cord and the periosteum and bodies of the cervical vertebra. A small anterior and larger posterior meningeal artery originate from the distal extracranial segments (V_2, V_3). The intracranial vertebral arteries give off *posterior and*

Overview and Approach to Stroke Patient *(Continued)*

anterior spinal artery branches, *penetrating arteries to the medulla*, and the large *posterior inferior cerebellar* arteries.

External Carotid Artery

The external carotid arteries give off many branches that supply structures within the face and neck. They extend from the upper border of the thyroid cartilage to the neck of the mandible, where they divide into temporal and maxillary arteries. There are eight major branches. The superior thyroid, lingual, and facial arteries arise from the anterior aspect of the ECAs and course medially. The occipital and posterior auricular arteries arise from the posterior aspect of the artery. The temporal and mandibular artery branches arise behind the neck of the mandible. There are the deep and *superficial temporal* branches of the temporal artery.

The ECAs have two branches that supply the face and can provide collateral blood flow to the ICA system: the *facial* arteries, which course along the cheek toward the nasal bridge, where they are termed the angular arteries, and the preauricular arteries, which terminate as the superficial temporal arteries. The *internal maxillary* artery and ascending pharyngeal branches of the ECAs also can contribute to collateral circulation when an ICA occludes. The internal maxillary arteries give off the *middle meningeal* artery branches, which penetrate into the skull through the foramen spinosum. Another important arterial supply of the face involves the *frontal and supratrochlear* branches that originate from the ophthalmic arteries that supply the medial forehead above the brow. When an ICA occludes, these ECA branches can be important sources of collateral blood.

Anomalous Origins

The right common carotid artery and right subclavian arteries may arise as separate branches directly from the aortic arch. The right vertebral artery may arise directly from the brachiocephalic trunk instead of the right subclavian artery. The left vertebral artery may also arise from the brachiocephalic trunk. The right subclavian artery can arise from the aortic arch distal to the left subclavian artery, in which case it then crosses to the right side. Sometimes the left common carotid and the left subclavian arteries arise from a common (left brachiocephalic) trunk. Rarely, a VA can arise from a common carotid artery.

Supratentorial Arteries to the Brain

The internal carotid (anterior) circulation supplies the anterior and most of the lateral portions of the cerebral hemispheres, while the vertebrobasilar (posterior) circulation supplies the brainstem, cerebellum, and the posterior portion of the cerebral hemispheres. About 40% of the brain's blood flow comes through each internal carotid artery, while 20% flows through the vertebrobasilar arterial system.

Circle of Willis

This anastomosis at the base of the brain (more a hexagon than a circle) serves to connect the major arteries of the anterior and posterior circulations, and the arteries from both sides. The horizontal portions of the *anterior cerebral* artery branches of the internal carotid arteries are connected to the *anterior communicating* artery, forming the anterior portion of the circle. The *posterior communicating* artery branches of the internal carotid arteries on each side connect to the *posterior cerebral* artery branches of the *basilar* artery, forming the lateral sides and posterior portion of the "circle."

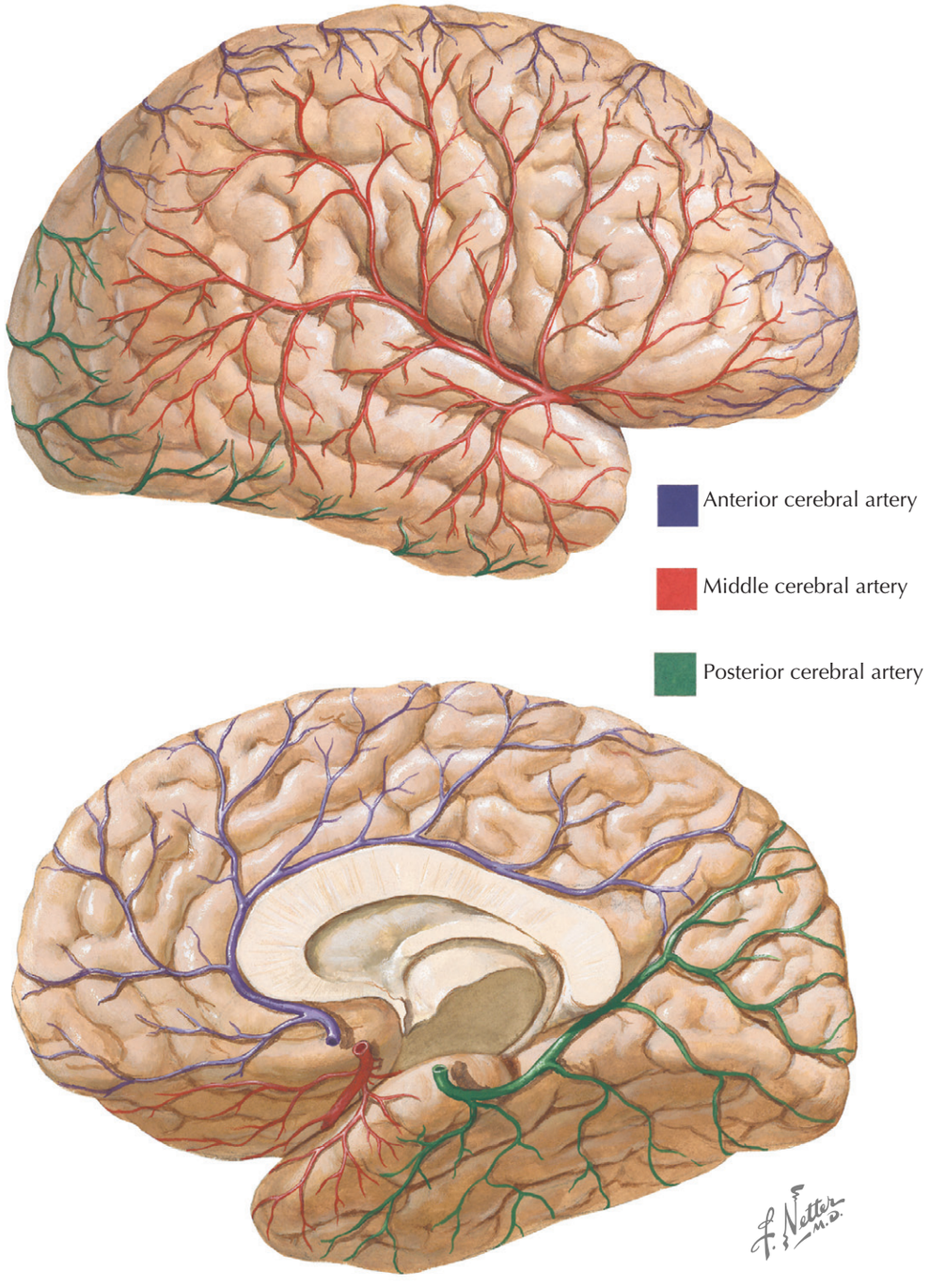
The superior hypophyseal arteries arise as the first branches of the supraclinoid portion of the internal carotid arteries, giving off branches to the optic chiasm and participating in an anastomosis that supplies the pituitary gland, which is composed of arterial branches from each side and branches of the right and left meningohypophyseal trunk.

The posterior communicating artery (about 1.5 cm in length) proceeds posteriorly and medially to join the posterior cerebral arteries on each side about 1 cm from their origins from the basilar artery. Small branches feed the optic tract and the posterior portion of the optic chiasm, the posterior hypothalamus, and the walls of the third ventricle. The *tuberothalamic* (polar) artery most often arises from the middle third of the posterior communicating artery but may also arise from the proximal segment of the posterior cerebral artery. The polar artery supplies the anteromedial and anterolateral portions of the thalamus.

Basilar Artery

The basilar artery is formed by the union of the two intracranial vertebral arteries at the medullo-pontine junction. It courses rostrally in a groove closely applied to the anterior surface of the pons, where it is located

Territories of the Cerebral Arteries



Overview and Approach to Stroke Patient *(Continued)*

within the prepontine cistern behind the clivus. The distal segment enters the interpeduncular cistern, where it is often separated from the basal surface of the brainstem. The distal portion of the artery lies between the cerebral peduncles and ends at the pontomesencephalic junction, just after passing between the two oculomotor nerves, by dividing into the two posterior cerebral arteries. The basilar artery is often curved and tortuous and may deviate from the midline. The basilar artery averages about 33 cm in length, and the diameter usually is between 4 and 4.5 mm. The main branches of the artery are the anterior inferior and superior cerebellar arteries, paramedian arteries that penetrate directly into the pons, and short circumferential arteries that course around the pons and give off lateral basal and lateral tegmental penetrating arteries.

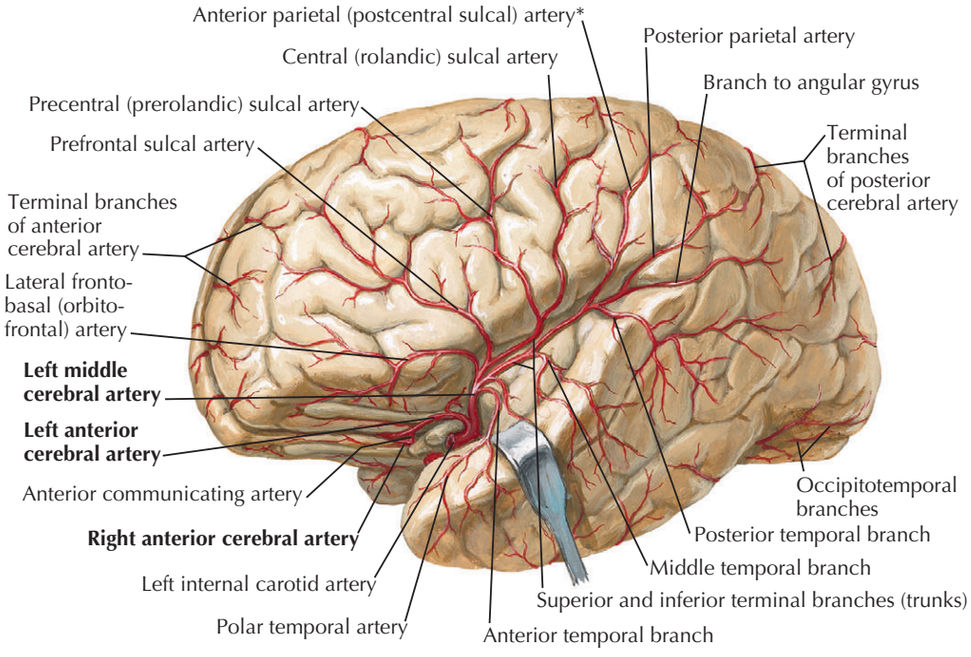
Posterior Cerebral Arteries

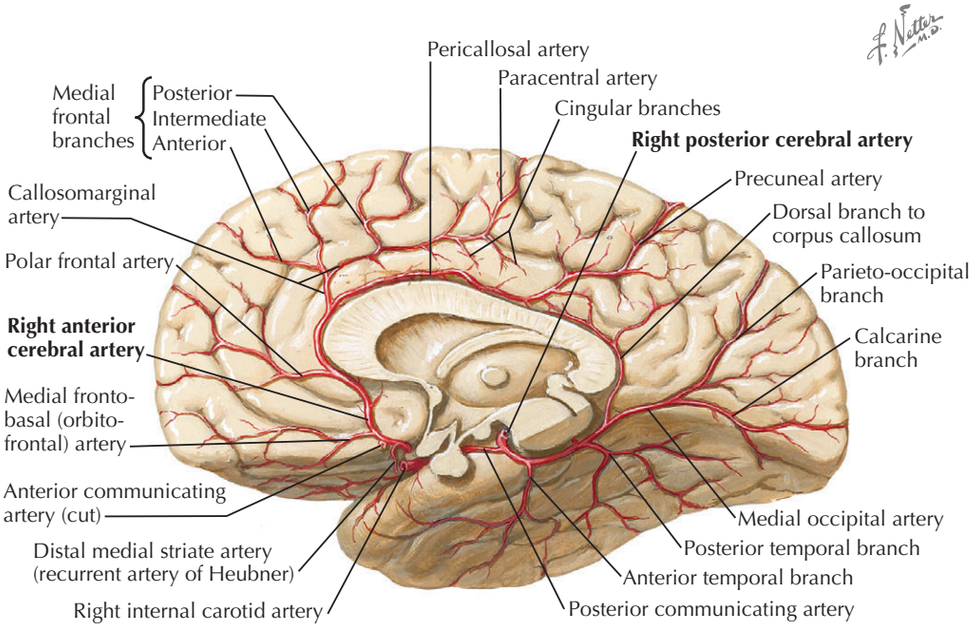
The posterior cerebral arteries originate from the terminal bifurcation of the basilar artery rostral to the third cranial nerves and then encircle the midbrain above the level of the tentorium cerebelli. As the posterior cerebral arteries course the dorsal surface of the midbrain, they divide into cortical branches. The arteries are divided into peduncular, ambient, and quadrigeminal segments, named after the cisterns through which they pass. The proximal portion of the arteries, before the posterior communicating artery branch, is referred to as the precommunal, P1 segment, or the mesencephalic artery.

Branches that supply the midbrain and thalamus arise from the proximal peduncular and ambient segments. *Paramedian mesencephalic* arteries arise from the first 3 to 7 mm of the arteries. The thalamic-subthalamic arteries (also called *thalamoperforating*) also arise proximally to supply the paramedian portions of the posteromedial thalamus. The *medial posterior choroidal* arteries also arise proximally from the peduncular segments and supply the quadrigeminal plate in the midbrain and the choroid plexus of the third ventricle. More distally, the *peduncular perforating* and *thalamogeniculate* arteries originate from the ambient segments. These supply the basolateral midbrain and the anterolateral thalamus, respectively. Each consists of a fan of parallel arteries.

Further in their course, after the posterior cerebral arteries have circled the midbrain, the *lateral posterior choroidal* artery branches arise, which will supply the pulvinar, dorsal thalamus, and the lateral geniculate bodies as well as the choroid plexus of the temporal horns of the lateral ventricles. There are four main cortical branches of the posterior cerebral arteries: the anterior temporal, posterior temporal, parieto-occipital, and calcarine arteries. The *anterior temporal* arteries arise first from the ambient segments, usually as single arterial trunks or as multiple branches to supply the inferior portion of the temporal lobe. The *posterior temporal* arteries course posteriorly on the inferior parietal and occipital lobes. The *parieto-occipital and calcarine* arteries are more variable, usually arising independently from the ambient segments and supplying the occipital and medial inferior parietal lobes. The *posterior pericallosal* arteries that circle the posterior portion of the corpus callosum to anastomose with the anterior pericallosal artery branches of the anterior cerebral arteries usually arise from the parieto-occipital arteries within the quadrigeminal cisterns.

Arteries of Brain: Lateral and Medial Views





*Note: Anterior parietal (postcentral sulcal) artery also occurs as separate anterior parietal and postcentral sulcal arteries.

Ophthalmic, Anterior Choroidal, and Posterior Communicating Arteries

The *anterior choroidal arteries* are relatively small arteries that originate from the internal carotid arteries after the origins of the ophthalmic and posterior communicating arteries. The *ophthalmic* artery projects anteriorly into the back of the orbit, whereas the *anterior choroidal* and *posterior communicating* arteries project posteriorly from the internal carotid artery. The *anterior choroidal* arteries course posteriorly and laterally, running along the optic tract. They first give off penetrating artery branches to the globus pallidus and posterior limb of the internal capsule and then supply branches that course laterally to the medial temporal lobe, and branches that course medially to supply a portion of the midbrain and the thalamus. The anterior choroidal arteries end in the lateral geniculate body, where they join with lateral posterior choroidal artery branches of the posterior cerebral arteries and in the choroid plexus of the lateral ventricles near the temporal horns.

Anterior Cerebral Arteries

The *anterior cerebral arteries* are the smaller of the two terminal branches of the internal carotid arteries. They course medially until they reach the longitudinal fissures and then run posteriorly over the corpus callosum. The first portion of the ACA is sometimes hypoplastic on one side, in which case the ACA from

Overview and Approach to Stroke Patient *(Continued)*

the other side supplies both medial frontal lobes. The *anterior communicating* artery connects the right and left anterior cerebral arteries and provides potential collateral circulation from the anterior circulation of the opposite side.

The horizontal segment of the anterior cerebral artery gives rise to multiple branches. Some course inferiorly to supply the upper surface of the optic nerves and the optic chiasm. Dorsally directed branches penetrate the orbital brain surface to supply the anterior hypothalamus, the septum pellucidum, the medial part of the anterior commissure, the columns of the fornix, and the basal frontal lobe structures (called the anterior perforated substance or substantia innominata). The largest horizontal segment branch is called the *recurrent artery of Heubner*. It most often arises from the anterior cerebral artery near its junction with the anterior communicating artery. Most often "Heubner's artery" is a group of parallel small arteries rather than a single vessel. They supply the anteromedial portion of the caudate nucleus and the anterior inferior portion of the anterior limb of the internal capsule.

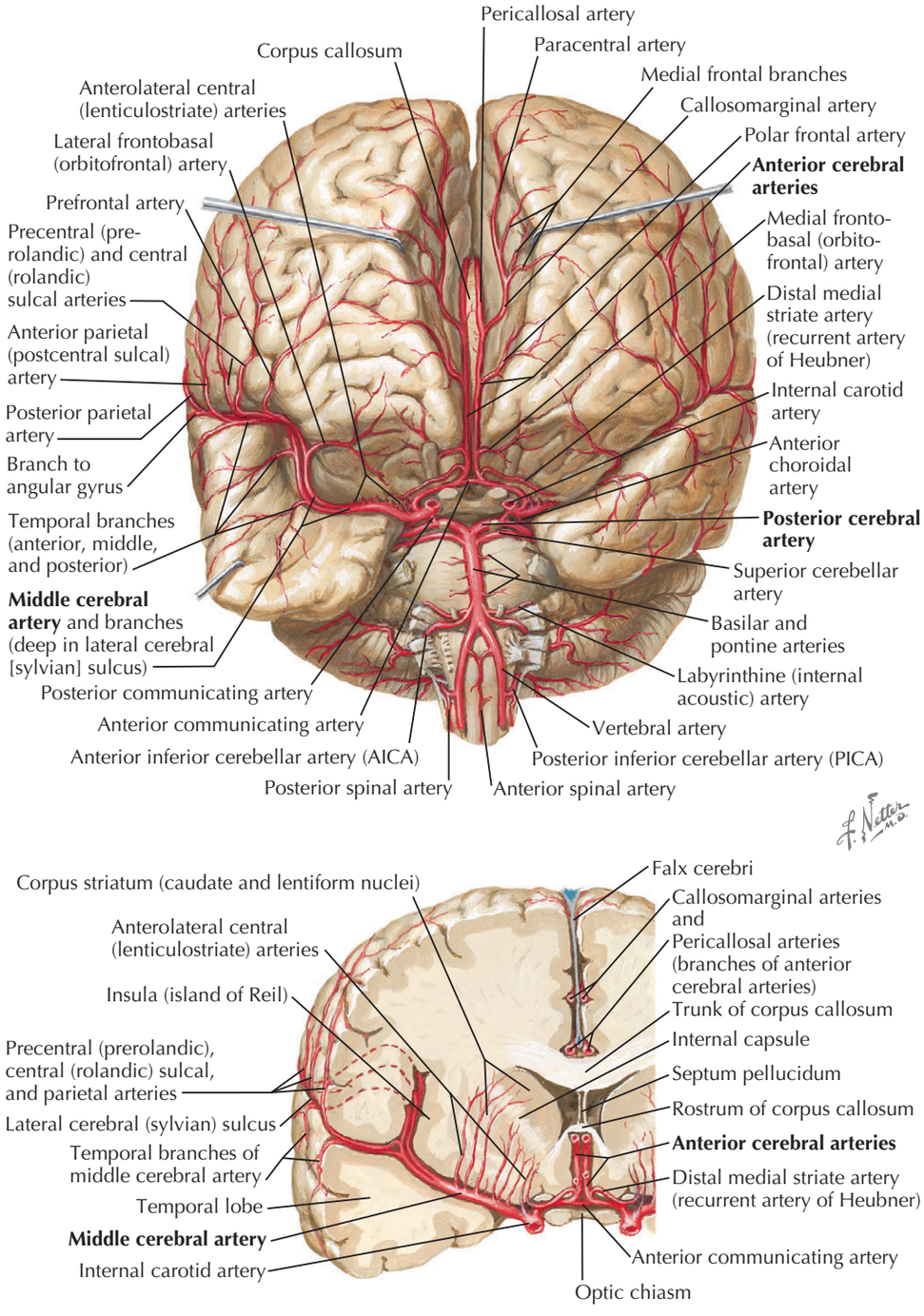
The proximal interhemispheric portions of the anterior cerebral arteries have medial orbitofrontal branches that travel anteriorly along the gyrus rectus to supply the medial part of the orbital gyri and the olfactory bulbs and tracts, and frontopolar artery branches to the superior frontal gyri. The anterior cerebral artery then passes around the genu of the corpus callosum and, in that general location, divides into callosomarginal and pericallosal branches. The *callosomarginal* artery passes over the cingulate gyrus to course posteriorly within the cingulate sulcus. It supplies anterior, middle, and posterior branches to the medial frontal lobes. The *pericallosal* artery courses posteriorly, below and parallel to the callosomarginal artery, in a sulcus between the corpus callosum and the cingulate gyrus. It supplies branches to the precuneus and medial superior parietal lobes. The pericallosal artery anastomoses with the pericallosal branch of the posterior cerebral artery variably, usually near the splenium of the corpus callosum.

Middle Cerebral Arteries

The *middle cerebral arteries* arise from the internal carotid artery bifurcation just lateral to the optic chiasm. The "mainstem" (M1) portion of the arteries courses horizontally in a lateral direction to enter the sylvian fissure. Three to six medial and lateral lenticulostriate arteries arise from the mainstem middle cerebral artery and penetrate the anterior perforated substance to supply the basal ganglia and deep portions of the cerebral hemispheres. The *medial lenticulostriate* arteries supply the outer portion of the globus pallidus and the medial parts of the caudate nucleus and putamen. The *lateral lenticulostriate* arteries supply the lateral portion of the caudate nucleus, the putamen, the anterior portion and genu of the internal capsule, and the adjacent corona radiata. Anterior temporal and frontopolar branches arise from the mainstem middle cerebral artery after the lenticulostriate origins.

As they near the sylvian fissures, the middle cerebral arteries divide into large superior and inferior divisions (referred to as M2 portions). The superior division supplies the lateral portions of the cerebral hemispheres above the sylvian fissures, and the inferior division supplies the temporal and inferior parietal lobes below the sylvian fissures. These main divisions turn upward around the inferior portion of the insula of Reil to continue upward and backward in the deepest part of the sylvian fissure between the outer surface of the insula and the medial surface of the temporal lobe. The superior division of the middle cerebral artery has lateral orbitofrontal, ascending frontal, rolandic, and anterior and posterior parietal branches. When the mainstem of the middle cerebral artery is short, the lenticulostriate branches may arise from the proximal portion of the superior division. The inferior division provides posterior temporal and angular branches to supply the lateral portions of the cerebral hemispheres below the sylvian fissures.

Arteries of Brain: Frontal View and Section



Meningeal Arteries

The meningeal arteries and veins are located along the outer portion of the dura, grooving the inner table of the skull. They supply the dura, the adjacent bony structures, and form anastomoses across both sides of the skull and with cerebral arteries. Their major clinical importance is (1) injuries to the skull, especially fractures, can cut across meningeal arteries, leading to epidural hemorrhages that require urgent drainage, and (2) meningiomas are often fed by meningeal arteries. Contrast opacification of meningeal arteries is often diagnostic in confirming that lesions are meningiomas, and interventional blockage of these feeding arteries can lead to shrinkage of a meningioma.

Overview and Approach to Stroke Patient *(Continued)*

The *middle meningeal artery*, originating from the external carotid system via the external maxillary artery, is the largest of the meningeal arteries. It supplies the major blood supply to the dura mater and arises from the maxillary artery and ascends just lateral to the external pterygoid muscle to enter the calvarium through the foramen spinosum. The middle meningeal artery then passes forward and laterally across the floor of the middle cranial fossa and divides into two branches below the pterion. The *frontal (anterior) branch* climbs across the greater wing of the sphenoid and parietal bone, forming a groove on the inner table of the calvaria and then dividing into two branches that supply the outer surface of the dura from the frontoparietal convexity to the vertex and as far posteriorly as the occiput. The smaller *parietal (posterior) branch* curves backward over the temporal region to supply the posterior part of the dura mater.

The *accessory meningeal artery* may also arise from the maxillary artery or from the middle meningeal artery. It ascends through the foramen ovale to supply the trigeminal ganglion and the adjacent dura within the middle cranial fossa.

The bone and dura of the posterior fossa are supplied by (1) the *meningeal branches of the ascending pharyngeal artery*, which pass through the jugular foramen, foramen lacerum, and the hypoglossal canal; (2) the *meningeal branches of the occipital artery*, which pass through the jugular foramen and the condylar canal; and (3) the small *mastoid branch of the occipital artery*, which passes through the mastoid foramen.

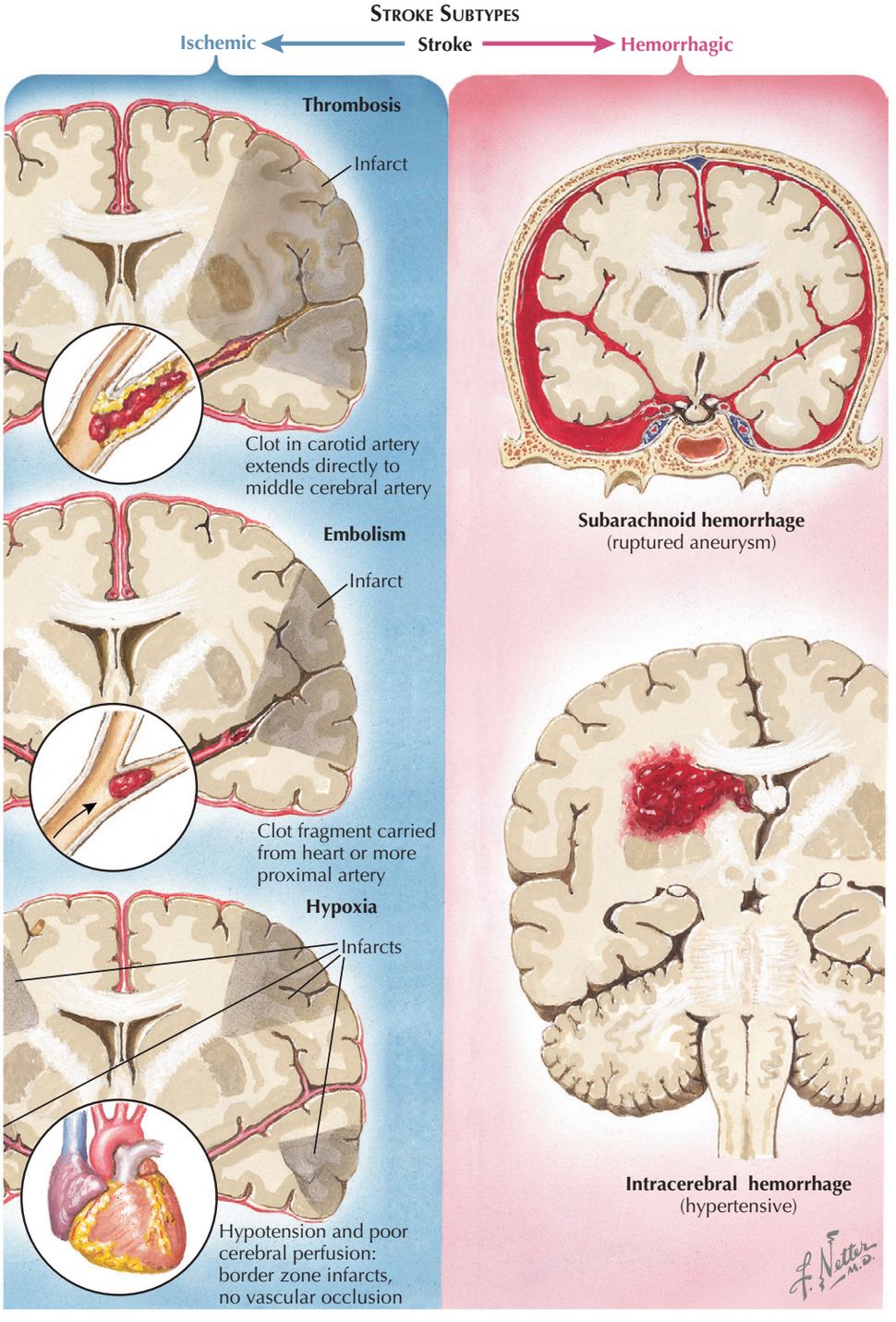
Branches of the Internal Carotid System. The meningohypophyseal trunk has three major branches. The *tentorial branch* enters the tentorium cerebelli at the apex of the petrous bone, supplying the anterolateral free margin of the tentorial incisura and the base of the tentorium near the attachment to the petrous bone. A *dorsal branch* supplies the dura mater of the dorsum sella and clivus, sending small twigs to supply the dura around the internal auditory canal. The *artery to the inferior portion of the cavernous sinus* originates from the lateral aspect of the cavernous segment of the internal carotid artery.

An *anterior meningeal artery* arises from the anterior aspect of the cavernous carotid artery and passes over the top of the lesser wing of the sphenoid to supply the dura of the floor of the anterior fossa.

As the *ophthalmic artery* passes medially and then above the optic nerve, it gives off a *lacrimal branch*. The *recurrent meningeal artery* arises from this branch and passes through the superior orbital fissure to supply the dura of the anterior wall of the middle cranial fossa.

The ophthalmic artery also provides several ethmoidal branches. The *posterior ethmoidal artery* leaves the orbit to supply the posterior ethmoid air cells and the dura of the planum sphenoidale and the posterior half of the cribriform plate. The *anterior ethmoidal artery* passes through the anterior ethmoidal canal to supply the mucosa of the anterior and middle ethmoidal air cells and the frontal sinus. It then enters the cranial cavity, where it gives off an *anterior meningeal branch* (*anterior falx artery*) to the dura mater and the anterior portion of the falx cerebri.

Branches of the Vertebral Artery. The meningeal branches enter the skull through the foramen magnum. The *anterior meningeal branch* originates from the distal part of the second segment of the vertebral artery just before its lateral bend at the level of the atlas. It ascends and passes anteromedially to supply the dura of the anterior margin of the foramen magnum. The *posterior meningeal branch* arises from the third segment of the vertebral artery between the atlas and the foramen magnum. It passes between the dura and the calvaria, supplying the posterior rim of the foramen magnum, the falx cerebelli, and the posteromedial portion of the dura of the posterior fossa.



TYPES OF STROKE

Strokes are divided into two broad categories: hemorrhage and ischemia. *Hemorrhage* refers to bleeding inside the skull into the brain or cerebrospinal fluid or membranes surrounding the brain. Brain *ischemia* refers to insufficient blood flow. Hemorrhage and ischemia are polar opposites. Hemorrhage is characterized by too much blood inside the skull, and in ischemia, there is not enough blood supply to allow continued normal functioning of the effected brain tissue. Brain ischemia is much more common than hemorrhage. About four fifths of strokes are ischemic.

Hemorrhage

The four designations of hemorrhage are named for their locations. Hemorrhages within brain substance (inside the pia mater) are called *intracerebral hemorrhages*;

Overview and Approach to Stroke Patient *(Continued)*

those between the pia mater and arachnoid are labeled *subarachnoid hemorrhages*. Hemorrhages outside the arachnoid but inside the dura mater are called *subdural hemorrhages*, and hemorrhages outside the dura mater but inside the skull are called *epidural hemorrhages*. The different sites of bleeding have different causes.

Intracerebral hemorrhages develop gradually and are located between normal brain tissues. The bleeding is due to rupture of small blood vessels, arterioles, and capillaries within the brain substance. The bleeding is most often due to uncontrolled hypertension. Bleeding disorders, vascular malformations, and fragility of blood vessels, for example, due to infiltration with amyloid in cerebral amyloid angiopathy, are other common causes. The blood usually oozes into the brain under pressure and forms a localized *hematoma*. The hematoma separates normal brain structures and interrupts brain pathways. Hematomas also exert pressure on brain regions adjacent to the collection of blood and can injure these tissues. Large hemorrhages are often fatal because they increase pressure within the skull compressing the brainstem.

Subarachnoid hemorrhages are usually caused by rupture of an *aneurysm* that breaks, spilling blood instantly into the spinal fluid. The sudden release of blood under arterial pressure increases intracranial pressure, causing severe sudden-onset headache, often with vomiting and often a lapse in brain function so that the patients may stare, drop to their knees, or become confused and unable to remember. The symptoms in patients with subarachnoid hemorrhage relate to diffuse abnormalities of brain function because usually there is no bleeding into one part of the brain. In contrast, in patients with intracerebral hemorrhages, the hematoma is localized and causes loss of function related to the area damaged by the local blood collection.

Subdural and epidural hemorrhages are most often caused by head injuries that tear blood vessels. In *subdural hemorrhages*, the bleeding is usually from veins located between the arachnoid and the dura mater. In *epidural hemorrhages*, the bleeding most often results in tearing of meningeal arteries. The tear is often caused by a skull fracture. Arterial bleeding develops faster than venous bleeding so that symptoms develop sooner after head injury in patients with epidural hemorrhages. In subdural hemorrhages, the bleeding can be slow so that symptoms may be delayed for weeks after head injury.

Brain Ischemia

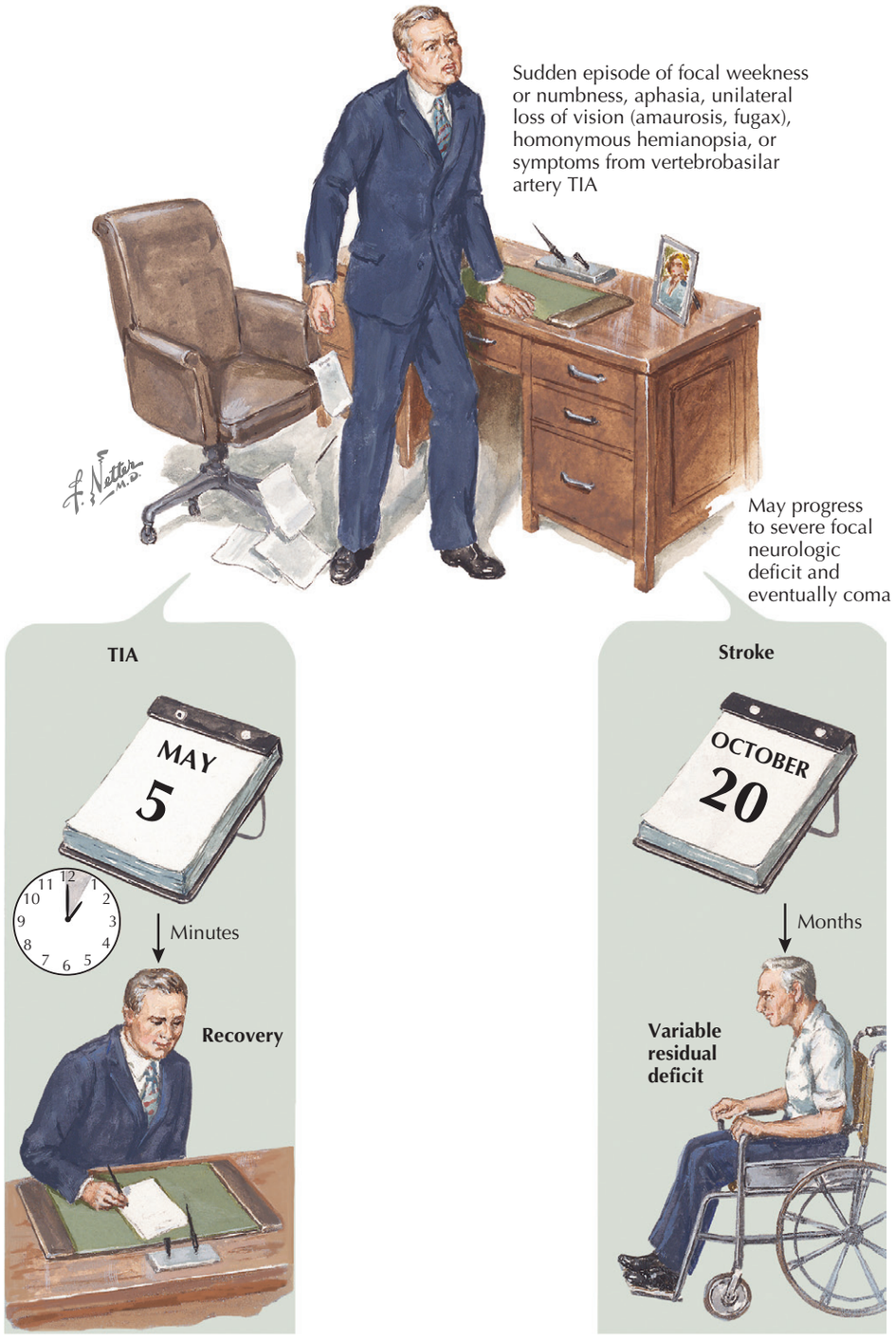
Insufficient blood supply to the brain is called ischemia. When ischemia is prolonged, it leads to death of tissue—*infarction*.

There are three different major categories of brain ischemia—*thrombosis*, *embolism*, *and systemic hypoperfusion;* each indicates a different mechanism of blood vessel injury or reason for decreased blood flow. The difference between these mechanisms is easiest to understand by using an analogy to house plumbing. Suppose, turning on the faucet in the second floor bathroom results in no flow, or instead, water dribbles out. The malfunctioning could be due to a local problem, such as rust buildup in the pipe supplying that sink. This is analogous to *thrombosis*, a term used to describe a local problem that involves an artery supplying the brain. Atherosclerosis or another condition often narrows the arterial lumen. When the lumen becomes very narrow, blood flow is severely reduced, causing localized stagnation of the blood column. This change in flow causes blood to clot, resulting in total arterial occlusion. This is a local problem in one pipe; a plumber would try to fix the damaged blocked pipe. Similarly, treating physicians could try to open or bypass a stenotic or occluded artery.

Alternatively, blockage of that second floor sink pipe could be due to debris in the water system that came to rest in that pipe rather than a local problem that began within the pipe. A neck or cranial artery supplying the brain can become blocked by thrombi or other particulate matter that breaks loose from a downstream site. The source could be from the heart, the aorta, or from a major artery in the neck or head located before the blocked artery along the same circulatory pathway. The process of particles breaking loose and blocking a distant artery is known as *embolism*. The source of the material is called the *donor site*, and the receiving vessel is called the *recipient site*. The material is called an *embolus*, and the process is called *embolism*. Treatment of embolism could involve unblocking the recipient artery but also trying to prevent further embolization.

Another reason for poor flow in the second floor sink might be a general problem with the water tank, water pump, or water pressure. In that case, flow through all

Temporal Profile of Transient Ischemic Attack (TIA) and Completed Infarction (CI)



Overview and Approach to Stroke Patient *(Continued)*

pipes in the house should be affected. Turning on the faucets elsewhere in the house will reveal the nature of the problem. In the body, this type of problem is called *systemic hypoperfusion*. Abnormal cardiac performance could lead to low pressure in the system. Abnormally slow or fast heart rhythms, cardiac arrest, and failure of the heart to pump blood adequately can all lead to diminished brain perfusion. Hypotension and hypoperfusion due to an inadequate amount of fluid in the vascular compartment of the body are other causes. Bleeding, dehydration, and shock all lead to inadequate brain perfusion. This would be akin to having a very low water tank.

In patients with brain embolism and thrombosis, one artery is usually blocked, leading to dysfunction of the part of the brain supplied by that blocked artery. This causes *focal* abnormalities of brain function, such as aphasia or hemiparesis. These abnormalities are similar to those found in patients with local brain hematomas. In contrast, systemic hypoperfusion leads to more diffuse abnormalities, such as light-headedness, dizziness, confusion, dimming of vision and hearing, and so forth. Patients appear pale and generally weak. These symptoms are attributable to a generalized reduction in blood flow and not to loss of function in one local brain region.

Timing and Evolution

In intracerebral hemorrhage patients, symptoms and signs gradually develop over minutes or hours. Improvements and fluctuations do not occur during this time. In aneurysmal subarachnoid hemorrhage, symptoms begin instantaneously. In ischemia, the severity of the decreased perfusion, the ability of collateral circulation to accommodate for blockages, and the vulnerability of various brain structures vary greatly. Arteries bring oxygen, sugar, and other nutrients necessary for survival of the brain. The underperfusion can be temporary, resulting in a focal deficit that lasts only a few minutes; these episodes are referred to as *transient ischemic attacks (TIAs)*. At times the ischemia is sufficient to cause more persistent symptoms and signs but not sufficient to cause brain infarction. Brain tissue is *stunned* but can recover if the supply of nutrients is restored soon enough. In ischemic patients, the time course varies and can fluctuate with periods of improvement, worsening, and stabilization.

Transient ischemic attacks are very important to recognize. Many studies show that patients with TIAs have a high risk of having a stroke during the succeeding hours and days. TIAs demand urgent diagnosis and management of the cause. TIAs provide a window of opportunity for clinicians to intervene before a stroke happens, and strokes do happen often in patients who have had TIAs. Most TIAs are very brief, lasting minutes and usually less than an hour. Recent magnetic resonance imaging (MRI) studies of patients with clinical TIAs who have no residual symptoms or signs shows that many actually have had brain infarcts—strokes. The distinction between TIAs and strokes is blurred and has been overemphasized in the past. Many clinicians now prefer the term *acute ischemic cerebrovascular syndrome*, which includes both TIAs and acute strokes. Management depends on the nature, location, and severity of the causative cardiocerebrovascular-hematologic cause of the brain ischemia. Finding the cause and treating it is much more important than characterizing the time course.

Therapeutic strategies relate to four different time epochs. *Prevention* involves strategies of identifying and controlling potential risk factors before a stroke occurs. Strategies during acute ischemia involve *reperfusion* of the ischemic area and *neuroprotection* (rendering the ischemic area more resistant to infarction). After a stroke, *recovery* and *rehabilitation* are facilitated.

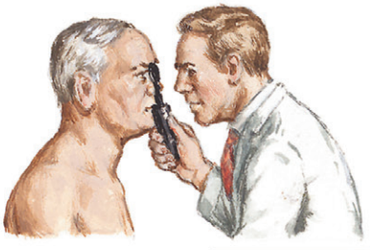
Clinical Evaluation and Treatment of Stroke

The most important diagnostic information is gained from a thorough history from the patient and sometimes a loved one or a colleague, with subsequent thoughtful vascular and neurologic examinations. The history is directed to answering *what* (the cause of the condition—the pathology and pathophysiology) and *where* (brain and vascular location) queries. The neurologic symptoms and signs and vascular examinations yield information about the *where* question. The differential diagnosis of the *what* question depends on information from the history about (1) the time and activity at and before the onset of symptoms; (2) the course of the symptoms—transient, gradually progressive, remitting, fluctuating, and so forth; (3) the past and present known medical and surgical conditions, especially hypertension, diabetes, heart disease, smoking, excess alcohol intake, drug use, peripheral

Clinical Evaluation and Therapeutic Options in Stroke

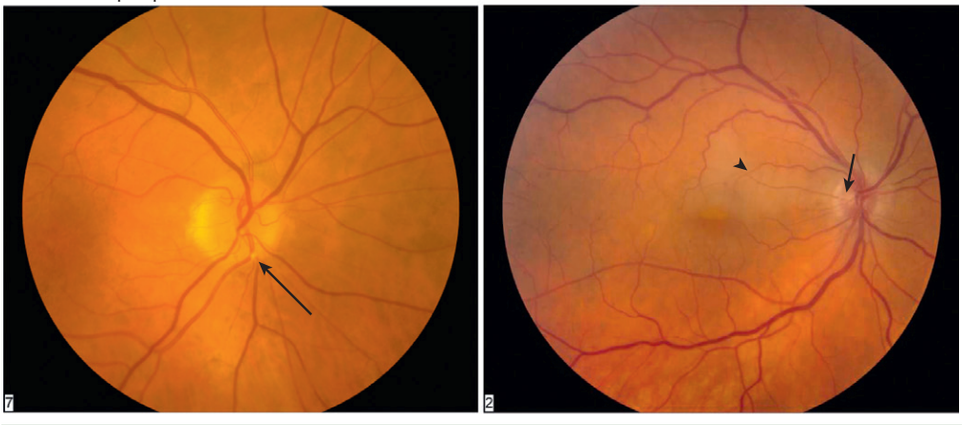
History (from patient and family, with emphasis on onset and timing)

Fundoscopic examination



Hollenhorst plaque *(arrow)*

Platelet fibrin emboli *(arrow)* with retinal ischemia *(arrowhead)*



Auscultation

Overview and Approach to Stroke Patient *(Continued)*

vascular disease, and obesity; (4) past strokes; (5) the presence, nature, and timing of any transient ischemic attacks; (6) headache before, at, or after stroke onset; and (7) the occurrence of a seizure, vomiting, or change in level of consciousness.

All stroke suspects require blood tests with brain and vascular imaging. A complete blood count (CBC), including platelet count, blood sugar, blood urea nitrogen or creatinine with a glomerular filtration rate, and a prothrombin time or international normalized ratio (INR) are obtained. The brain and the arteries that supply it and the veins that drain it can be imaged using either computed tomography (CT) or MRI. The questions to be answered by brain and vascular imaging are (1) Is/are the brain lesion(s) caused by ischemia or hemorrhage, or is it related to a nonvascular stroke mimic? (2) Where is/are the brain lesion(s), and what is/are its/their size, shape, and extent? (3) What are the nature, site, and severity of the vascular lesion(s), and how does/do the vascular lesion(s) and brain perfusion abnormality(ies) relate to the brain lesion(s)?

CT is readily available in most hospitals and reliably demonstrates the presence or absence of intracerebral hemorrhage. Immediately after the onset of bleeding, intracerebral hematomas (ICHs) are seen on CT as well-circumscribed areas of high density with smooth borders. Edema develops within the first days and is seen as a dark rim around the white hematoma. Subarachnoid bleeding is demonstrated by a high-density signal within the cerebrospinal fluid and brain cisterns. Early signs of brain infarction include obscuring of the basal ganglia density, blurring of the distinction between the grey matter of the cerebral cortex and the underlying white matter, and loss of definition of the insular cortex. Later, infarction appears as a low-density lesion. Specific vascular abnormalities include hyperdense arteries, indicating thrombosis or slow flow and calcific emboli within arteries. The signs of infarction on CT scans are often subtle when images are taken within several hours of the onset of symptoms. Viewing images on a computer with the ability to vary the contrast helps identify subtle abnormalities and asymmetries.

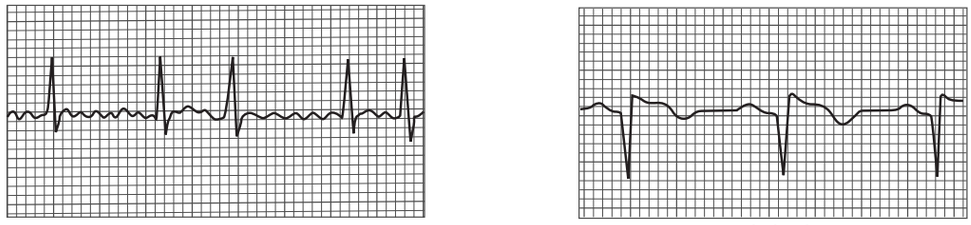
Diffusion-weighted MRI images (DWI) and fluid-attenuated inversion recovery (FLAIR) images are particularly useful and sensitive for detection of acute brain infarcts. Infarcted areas appear bright on DWI and dark on apparent diffusion coefficient (ADC) images. The location, pattern, and multiplicity of DWI ischemic lesions help to suggest the most likely causative stroke mechanism. DWI positivity wanes during the first 7 to 10 days after stroke onset. Lesions seen on DWI images (and confirmed by ADC) usually, but not always, correspond to areas of infarction. T2-weighted scans show established infarcts as bright. MRI can also accurately show ICH, especially when echo-planar gradient-echo susceptibility-weighted images (T2*) are performed. These T2*-weighted (susceptibility) images can also show thrombi within intracranial arteries and dural sinuses and veins.

Vascular imaging can be performed using CT (CT angiography [CTA]) or MR (MR angiography [MRA]), or by using ultrasound. CTA and MRA images can be obtained concurrently with the respective primary brain imaging. CTA requires intravenous dye infusion. The neck and intracranial arteries and veins can be shown well by either technique. Duplex ultrasound, which includes a B-mode image combined with a pulsed Doppler spectrum analysis, can accurately show occlusive lesions within neck arteries. Transcranial Doppler ultrasound (TCD) involves insonation of intracranial arteries by measuring blood flow velocities using a probe placed on the orbit, temporal bone, and foramen magnum. Areas of narrowing or occlusion can be detected; these probes also provide a means to monitor for embolic materials passing under them. Dye contrast digital angiography shows neck and intracranial arteries in more detail than CTA and MRA and is now used to clarify vascular lesions not shown well by these screening techniques; it is also pursued at the time of intravascular interventions, such as coiling of aneurysms, stenting, and intra-arterial thrombolysis or mechanical clot extraction. In patients in whom strokes cause seizures, electroencephalography (EEG) can be helpful.

Treatment of acute stroke patients depends heavily on the type and cause of the stroke. In *subarachnoid hemorrhage* patients, aneurysms and vascular malformations can be controlled by cranial surgical clipping or coiling through an intravenous interventional approach. The vasoconstriction that follows bleeding and surgery also is a target for therapy. In patients who have had an *intracerebral hemorrhage*, blood pressure control, reversal of bleeding diatheses, and drainage of space-taking hematomas, especially those that are lobar and near the surface, are the major therapeutic strategies.

Clinical Evaluation and Therapeutic Options in Stroke (continued)

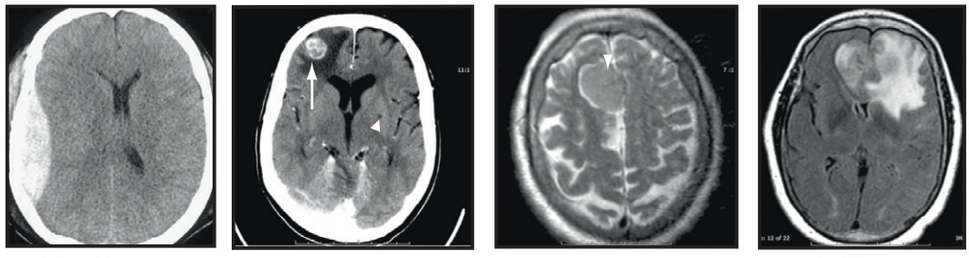
Electrocardiogram



Atrial fibrillation

Myocardial infarction

MRI and CT scans (to rule out other diseases)



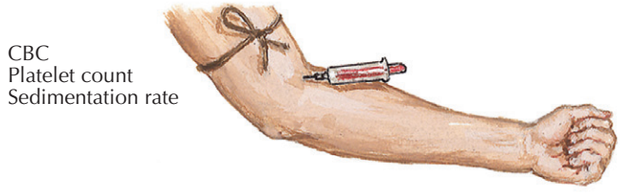
Subdural hematoma

Metastatic cancer

Meningioma

Glioblastoma

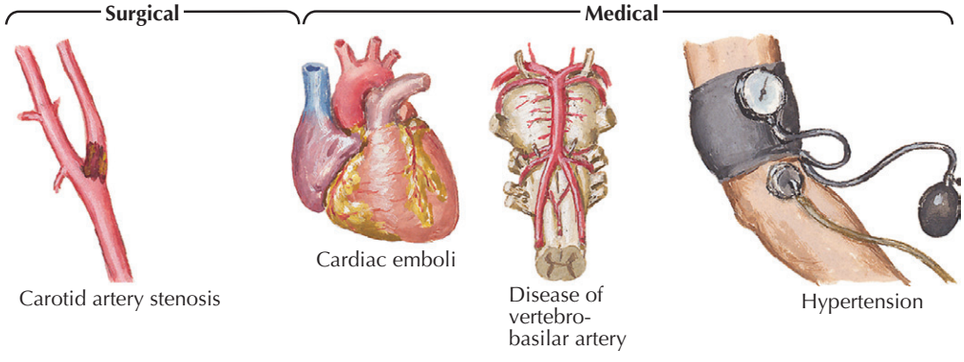
Blood analysis followed by angiography



CBC
Platelet count
Sedimentation rate

Glucose level
Calcium level
Serologic test for syphilis

Therapeutic options



Carotid artery stenosis

Cardiac emboli

Disease of vertebro-basilar artery

Hypertension

Overview and Approach to Stroke Patient *(Continued)*

In patients with acute brain ischemia, attention is directed toward reperfusing ischemic zones. When a thromboembolus blocks an artery, intravenous or intra-arterial thrombolysis can be pursued; alternatively, mechanical devices or stenting of blocked arteries can also lead to recanalization. Maximizing collateral blood flow by attention to blood pressure and blood volume can augment perfusion of the ischemic zone. Anticoagulants (heparins, warfarin, and direct thrombin antagonists and factor X inhibitors) can be given to prevent propagation and embolization of clots.

In addition to treating the acute stroke, attention must be directed toward *prevention* of future strokes. Identifying and modifying potential risk factors is essential. Pharmacologic treatment using antihypertensives, statins, and agents that alter platelet function are the mainstays of prophylaxis of brain ischemia. In those patients who have residual deficits after stroke, *recovery* and *rehabilitation* are optimized.

UNCOMMON ETIOLOGIC MECHANISM OF STROKE

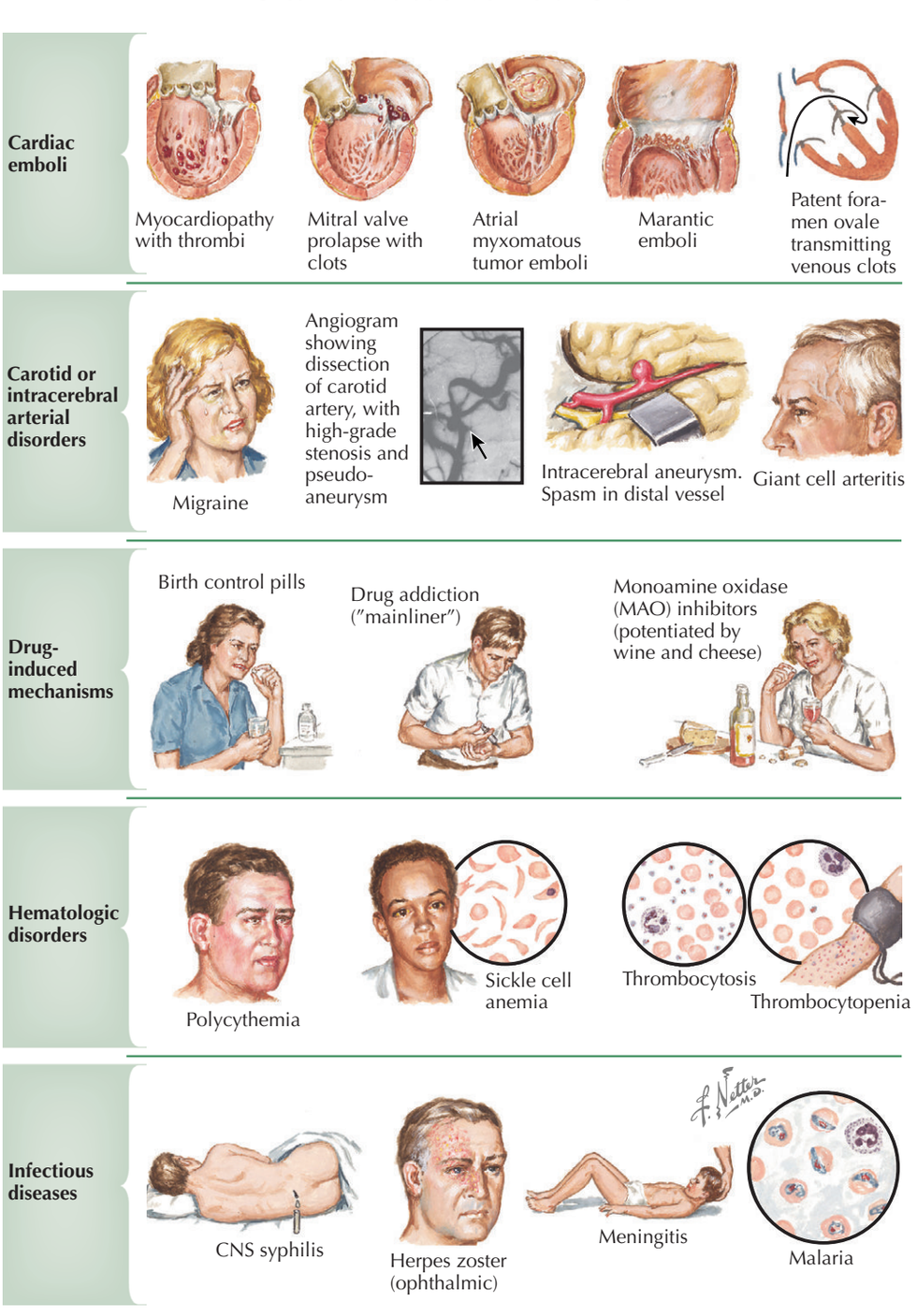
Although atherosclerotic abnormalities of brain supplying arteries are the most frequent causes of stroke, many other etiologies need consideration, especially in young individuals and those who do not have risk factors for atherosclerosis. Evaluation of the heart, neck and intracranial arteries and veins, and the blood are important in all patients with stroke and transient ischemic attacks. The most common conditions are brain embolism arising from the heart, especially in patients with arrhythmias and valvular disease; dissections of neck and intracranial arteries; emboli from aortic plaques, various vascular anomalies and malformations, and blood disorders that promote excess clotting or bleeding. A partial list of conditions follows.

Cardiac. A variety of different heart conditions serve as donor sources for brain embolism. Cardiac pump failure can lead to ischemic brain damage through systemic hypoperfusion. Other cardiac lesions cause strokes by providing a source of embolism to the brain: *valvular conditions*—rheumatic, calcific, infectious endocarditis, and noninfective fibrotic lesions (Libman-Sacks endocarditis associated with systemic lupus erythematosus and similar valvular lesions in patients with cancer and antiphospholipid antibodies), mitral annulus calcifications, and artificial surgically implanted mechanical and biological valves; *myocardial abnormalities*—myocardial infarcts, myocarditis, myocardiopathies; *arrhythmias*—atrial fibrillation, sick sinus syndrome; *neoplasms*—myxomas, fibroelastomas; and *septal abnormalities*—atrial septal defects, patent foramen ovale.

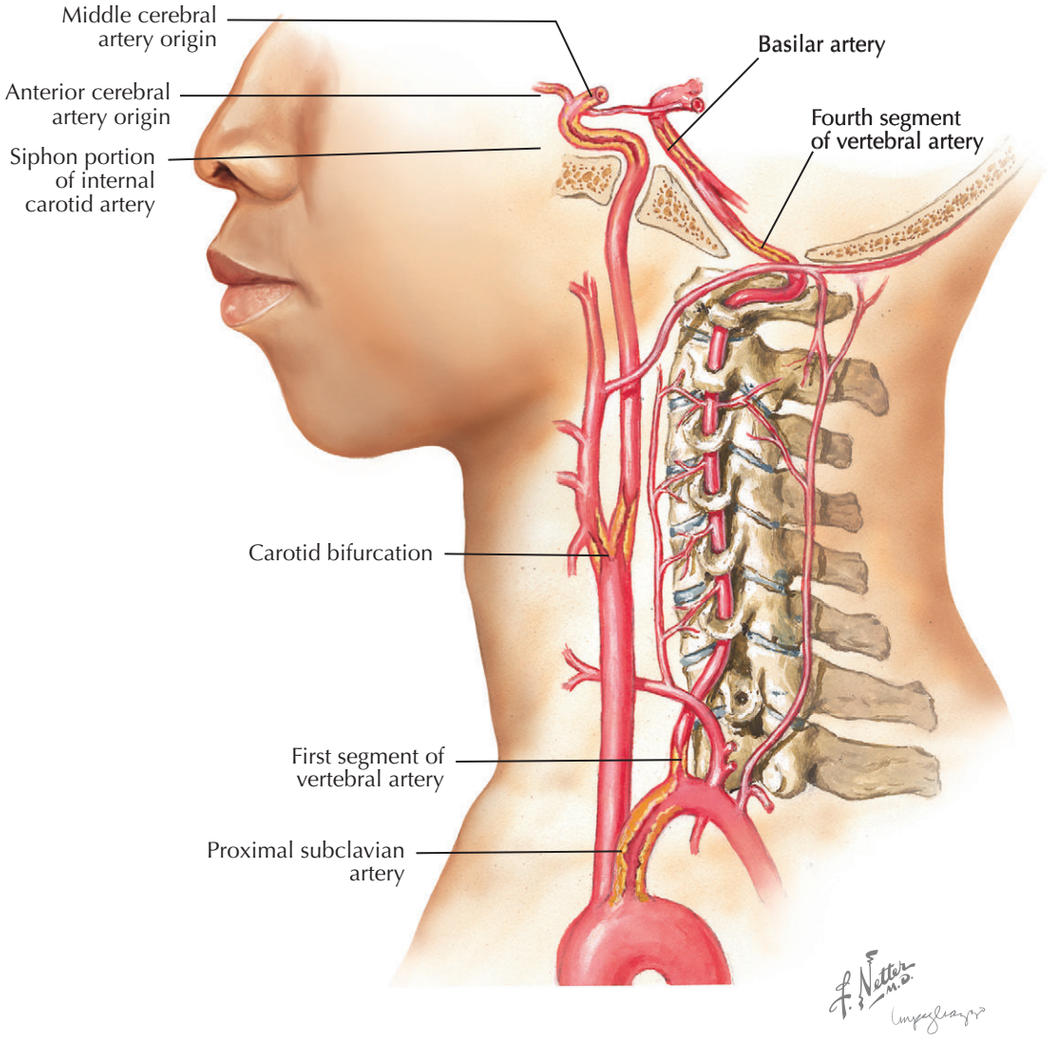
Arteries. Vascular conditions can also predispose to artery-to-artery embolism as well as causing localized ischemia due to decreased perfusion. Some vascular lesions promote bleeding. Aortic atheromas, especially those that are mobile and protruding, may on occasion lead to a stroke. Arterial dissection in either the carotid or vertebral artery system requires careful consideration. These often occur related to seemingly benign problems, such as a paroxysm of vomiting, or athletic injuries, such as from wrestling, skiing accidents, falls from horses, and so forth. Other unusual primary vascular lesions include fibromuscular dysplasia, arteritis, moyamoya syndrome, Takayasu arteritis, and severe migraine. Certain quite rare genetic conditions require consideration in the differential diagnosis of stroke. These include CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), Ehlers-Danlos syndrome, pseudoxanthoma elasticum, progeria, and cerebral amyloid angiopathy. *Vascular malformations*—aneurysms, arteriovenous malformations, cavernous angiomas, developmental venous anomalies, varices—predispose to bleeding. Infections, such as with herpes zoster varicella virus, can invade blood vessels and cause stroke. Meningitis sometimes causes arterial inflammation and strokes.

Hematologic. *Increase in coagulability* is seen due to decreased amounts of usual inhibitors: protein S, protein C, antithrombin, activated protein C–resistance, sickle cell disease, and other hemoglobinopathies; severe anemia; thrombocythemia; thrombocytosis; and *bleeding disorders*—thrombocytopenia, hemophilia, and prescription of antithrombotic agents.

Veins. Thrombosis of the dural sinuses, especially the superior sagittal sinus and the lateral sinus, are often associated with brain infarction, brain edema, and brain hemorrhage. Occlusion of deep veins is an important cause of stroke in the young. Occlusion of veins on the surface of the brain can also cause infarction and seizures.



Common Sites of Cerebrovascular Occlusive Disease



Anterior Circulation Ischemia

Etiology

The most common etiology of internal carotid artery disease is atherosclerosis, predominantly occurring in Caucasians and the elderly. Other etiologies include arterial dissection, fibromuscular dysplasia, and giant cell arteritis.

Atherosclerosis causes stenosis or occlusion of extracranial and intracranial arteries and is directly responsible for a significant percentage of cerebral ischemic events. Atheroma formation involves the progressive deposition of circulating lipids and ultimately fibrous tissue in the subintimal layer of the large and medium arteries, occurring most frequently at branching points. Plaque formation is enhanced by blood-associated inflammatory factors as well as increased shear injury from uncontrolled blood pressure. Intraplaque hemorrhage, subintimal necrosis with ulcer formation, and calcium deposition can cause enlargement of the atherosclerotic plaque with consequent worsening of the degree of arterial narrowing.

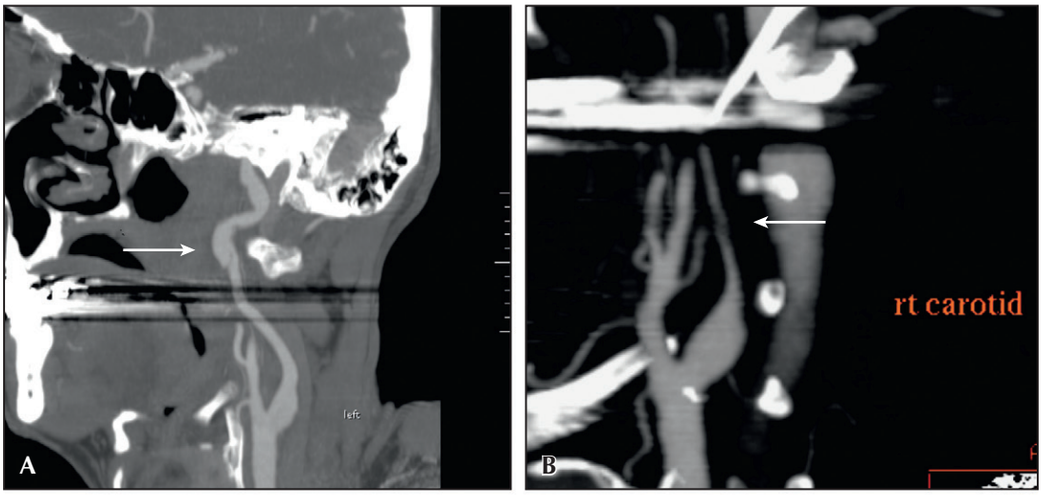
Disruption of the endothelial surface triggers thrombus formation within the arterial lumen through activation of nearby platelets by the subendothelial matrix. When platelets become activated, they release thromboxane A_2, causing further platelet aggregation. The development of a fibrin network stabilizes the platelet aggregate, forming a "white thrombus." In areas of slowed or turbulent flow within or around the plaque, the thrombus develops further, enmeshing red blood cells (RBCs) in the platelet-fibrin aggregate to form a "red thrombs." This remains poorly organized and friable for up to 2 weeks and presents a significant risk of propagation and embolization. Either the white or red thrombus, however, can dislodge and embolize to distal arterial branches.

The main risk factors for *carotid artery atherosclerotic disease* are arterial hypertension, diabetes, hypercholesterolemia, and smoking. Frequent sites for anterior circulation atherosclerosis are the origin of the internal carotid artery (ICA) , the carotid siphon, and the mainstems of the middle cerebral artery (MCA) and anterior cerebral artery (ACA) (see Plate 9-10). The internal carotid artery at or around the bifurcation is usually affected in Caucasians, whereas in Asian, Hispanic, and African-American populations, intracranial atherosclerosis is more common than carotid artery disease in the neck.

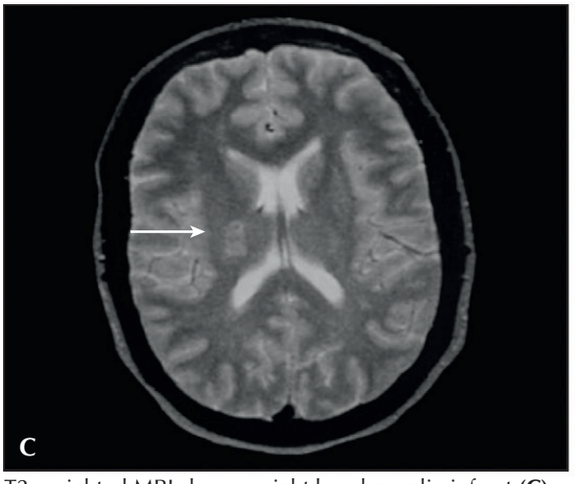
Dissection of the extracranial ICA usually occurs in patients between age 20 to 50 years and commonly involves its pharyngeal and distal segments. Dissection occurring between the intima and media usually causes stenosis or occlusion of the affected artery, whereas dissection between the media and adventitia is associated with aneurysmal dilation (see Plate 9-11, *A* and *B*). Congenital abnormalities in the media or elastica of the arteries as seen in Marfan syndrome, fibromuscular dysplasia, osteogenesis imperfecta, and cystic medial necrosis can predispose patients to arterial dissection. Although often associated with acute trauma, arterial dissection may result from seemingly innocuous incidents, such as a fall while hiking or skiing, sports activities (particularly wrestling or diving into a wave), and paroxysms of coughing that stretch the artery.

Spontaneous *intracranial ICA dissections* are uncommon when compared with dissections of its cervical portion. Although early reports described a very poor prognosis with extensive strokes and very high

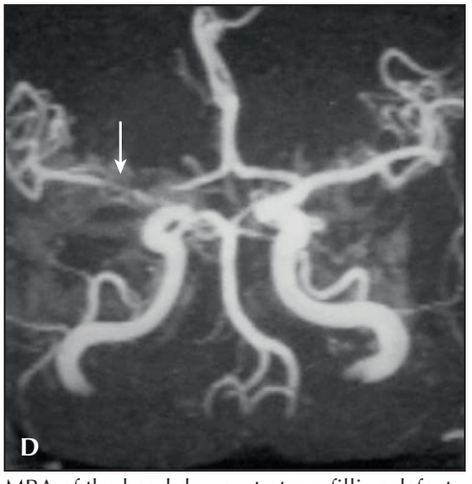
Other Etiologies of Carotid Artery Disease



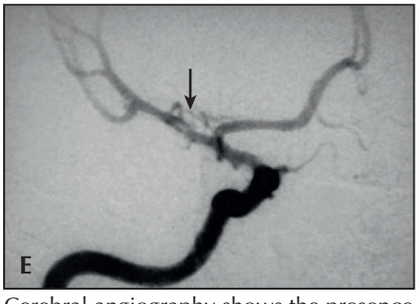
CTA of the neck shows a pseudoaneurysm **(A)** and a string sign of the internal carotid artery **(B)**

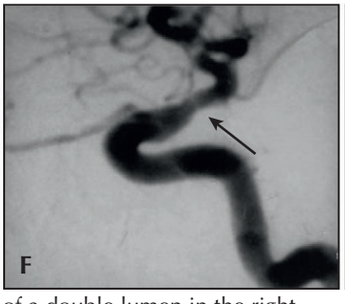


T2-weighted MRI shows a right basal ganglia infarct **(C)**

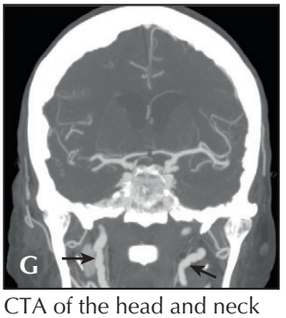


MRA of the head demonstrates a filling defect in the distal portion of the right ICA and proximal MCA stem **(D)**





Cerebral angiography shows the presence of a double lumen in the right MCA stem **(E)** and narrowing of the supraclinoid portion of the right ICA, suggestive of intracranial dissection **(F)**



CTA of the head and neck demonstrates areas of fibromuscular dysplasia in both internal carotid arteries **(G)**

Anterior Circulation Ischemia *(Continued)*

mortality, more recent studies have shown a relatively better outcome, with patients surviving with few or moderate deficits. Imaging studies usually show narrowing of the supraclinoid ICA, with extension to the MCA or ACA and, less commonly, aneurysm formation (see Plate 9-11, *C* to *F*).

Fibromuscular dysplasia is a nonatherosclerotic noninflammatory angiopathy characterized by fibrodysplastic changes of unclear etiology. It occurs predominantly in women of childbearing age and often affects the neck arteries, most often the pharyngeal portion of the internal carotid artery. Intracranial disease is much rarer. The lesions have a characteristic beaded appearance that can be detected on magnetic resonance angiography (MRA), computed tomography angiography (CTA), or conventional angiograms (see Plate 9-11, *G*). Fibromuscular dysplasia is a predisposing factor for spontaneous cervical carotid dissections and consequent strokes; however, strokes can also be caused by thromboembolism secondary to the fibromuscular dysplasia.

Giant cell arteritis is a common form of systemic vasculopathy affecting patients older than 50 years. Although it typically involves the temporal, maxillary, and ophthalmic arteries, it can rarely affect the siphon of the internal carotid artery, sometimes producing bilateral stenosis.

Clinical Manifestations

TIAs in patients with carotid artery disease usually precede stroke onset by a few days or months. TIAs caused by intra-arterial embolism from a carotid source are not stereotypical, and symptoms vary depending on which ICA branch is involved. In contrast, hemodynamic "limb-shaking" TIAs are often stereotypical and posturally related and are usually seen in patients with high-grade ICA stenosis or occlusion. In this classic example of hemodynamic ischemia, patients have recurrent, irregular, and involuntary movements of the contralateral arm, leg, or both, usually triggered by postural changes and lasting a few minutes.

Another important clue to ICA disease is the development of episodes of transient monocular blindness (TMB) (see Plate 9-12). TMB refers to the occurrence of temporary unilateral visual loss or obscuration that is described by careful observers as a horizontal or vertical "shade being drawn over one eye," but most frequently as a "fog" or "blurring" in the eye lasting 1 to 5 minutes. It often occurs spontaneously but at times is triggered by position changes. Positive phenomena, such as sparkles, lights, or colors evolving over minutes, are typical of migrainous phenomenon and help to differentiate such benign visual changes from the more serious TMB, a frequent harbinger of cerebral infarct

Anterior Circulation Ischemia *(Continued)*

within the carotid artery territory. Rarely, with critical ipsilateral internal carotid stenosis, gradual dimming or loss of vision when exposed to bright light, such as glare from snow on a sunlit background, can be reported and is due to limited vascular flow in the face of increased retinal metabolic demand.

Strokes from intra-arterial embolism from ICA disease are usually cortically based (see Plate 9-12). Symptoms depend on whether branches of the MCA, ACA, or both are involved (see Plate 9-13). The posterior cerebral artery (PCA) territory may rarely be affected by intra-arterial emboli from ipsilateral ICA stenosis or occlusion in patients with a persistent fetal PCA originating from the ICA.

Neurologic findings vary by the location of the occlusion and the adequacy of collateral circulation. A large MCA territory stroke is usually seen in patients with MCA mainstem occlusion without good collateral flow, whereas deep or parasylvian strokes are the most common presentation when enough collateral flow is present over the convexities. Contralateral motor weakness involving the foot more than the thigh and shoulder, with relative sparing of the hand and face, is the typical manifestations of distal ACA branch occlusion. Conversely, prominent cognitive and behavioral changes associated with contralateral hemiparesis predominate in patients with proximal ACA occlusions, due to involvement of the recurrent artery of Huebner.

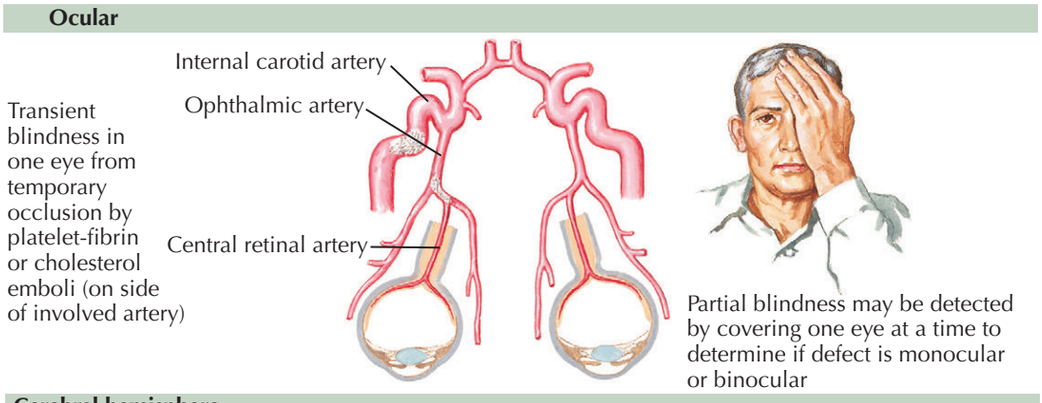
Hemodynamic strokes usually involve the border zone territory between ACA and MCA (anterior border zone), MCA and PCA (posterior border zone), or between deep and superficial perforators (subcortical border zone) and cause the typical clinical symptoms outlined in Plate 9-12.

Although TIAs can occur in intrinsic occlusive disease of the MCA and ACA , they are not as common as in patients with ICA disease and usually occur over a shorter period of hours or days. When strokes occur, initial symptoms are typically noticed on awakening and often fluctuate during the day, supporting a hemodynamic mechanism.

Isolated infarction of the anterior choroidal artery territory is not common. The classic clinical presentation includes hemiplegia, hemianesthesia, and homonymous hemianopsia, but incomplete forms of this syndrome are more frequently seen. Left-sided spatial neglect and mild speech difficulties may accompany right- and left-sided lesions, respectively. Small vessel disease is the most common mechanism of anterior choroidal strokes; however, large strokes in this territory have also been associated with cardioembolism and ipsilateral intracranial carotid artery disease.

Ipsilateral pain involving the eye, temple or forehead, and ipsilateral Horner syndrome secondary to

Clinical Manifestations of Carotid Artery Disease



Clinical symptoms in patients with border zone strokes

Stroke location	Clinical symptoms
Anterior border zone	Contralateral weakness (proximal > distal), sparing face, transcortical motor aphasia (left-sided infarcts), mood disturbances (right-sided infarcts)
Posterior border zone	Homonymous hemianopsia, lower-quadrant anopsia, transcortical sensory aphasia (left-sided infarcts), hemineglect, and anosognosia (right-sided infarcts)
Subcortical border zone	Brachiofacial hemiparesis with or without sensory loss, subcortical aphasia (left-sided infarcts)

Anterior Circulation Ischemia *(Continued)*

involvement of sympathetic fibers along the wall of the internal carotid artery are common in patients with extracranial carotid dissection, and its presence helps with the clinical diagnosis. TIAs and/or strokes usually occur several days after onset of symptoms and are usually caused by intra-arterial embolism.

Severe retro-orbital or temporal headaches are also frequent in patients with intracranial dissections; however, the neurologic signs, most commonly a contralateral hemiparesis, tend to follow almost immediately the headache's onset. Neurologic deficits tend to fluctuate within the first two weeks of onset of symptoms, probably reflecting cerebral hypoperfusion.

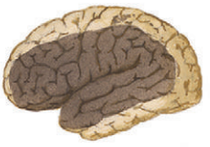
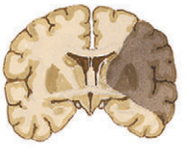
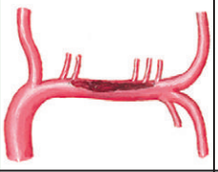
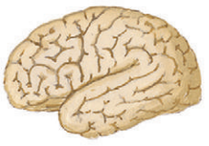
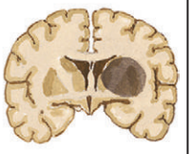
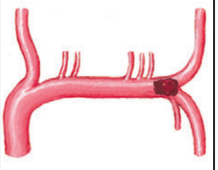
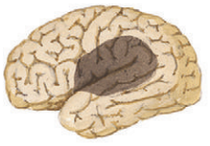
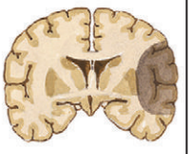
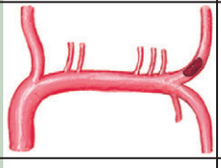
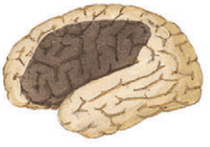
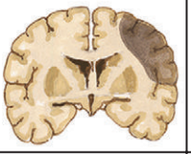
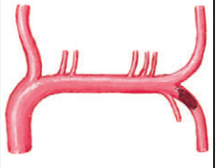
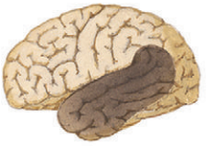
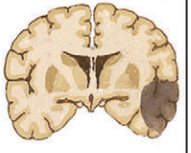
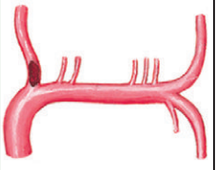
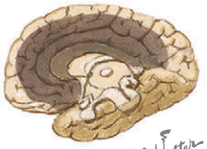
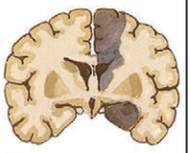
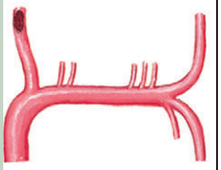
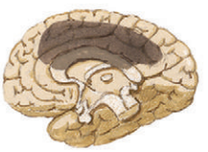
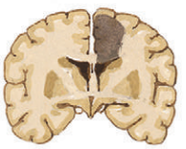
DIAGNOSIS

The diagnosis of anterior circulation ischemia is often made by noninvasive methods, including ultrasound techniques, computed tomography, and magnetic resonance imaging techniques (see Plates 9-14 and 9-15). Digital subtraction angiography remains the gold standard for the evaluation of the supra-aortic vasculature. However, due to its potential risks of neurologic complications, this technique is usually reserved for select patients when the diagnosis is still not clear after noninvasive testing.

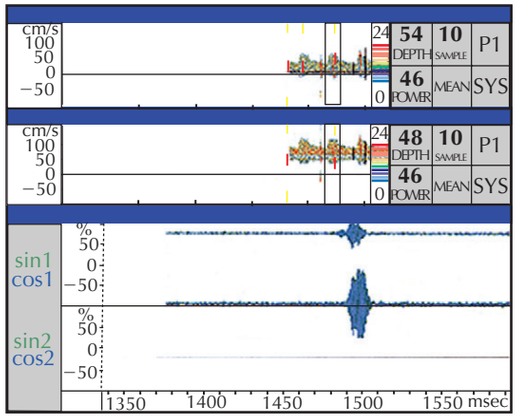
Ultrasound of the carotid arteries at their bifurcation in the neck can determine the presence of critically stenotic extracranial artery disease as well characterization of carotid plaques as "soft," consisting of cholesterol deposits and clot. "Soft" plaques are more prone to ulcerate and cause artery-to-artery emboli. "Hard" plaques are those that have fibrosed and calcified over time; they are a less common source of emboli. The role of ultrasound in detection of internal carotid artery dissection, fibromuscular dysplasia, or giant cell arteritis is more limited because lesions often occur on its pharyngeal portions or distal to it, and only indirect signs of a distal carotid occlusion are found. Transcranial Doppler can assess the patency of the intracranial arteries; patterns of collateral flow through the circle of Willis also can be used for emboli monitoring (see Plate 9-14).

Advances in both CTA and contrast-enhanced MRA have allowed assessment of the entire supra-aortic tree, from the aortic arch to the circle of Willis. Each of these techniques is extremely valuable in the evaluation of the degree of stenosis in patients with extra- and intracranial atherosclerotic disease as well as with plaque characterization (see Plates 9-14 and 9-15). Recent studies have shown that multidetector CTA has

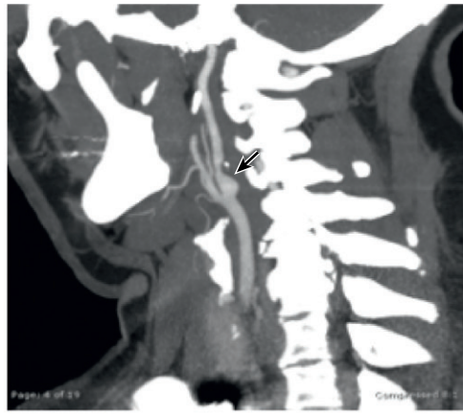
Occlusion of Middle and Anterior Cerebral Arteries

	Lesion	Artery occluded	Infarct, surface	Infarct, coronal section	Clinical manifestations
Middle cerebral artery	Entire territory	Anterior cerebral; Superior division; Lenticulostriate; Medial Lateral; Middle cerebral; Inferior division; Internal carotid			Contralateral gaze palsy, hemiplegia, hemisensory loss, spatial neglect, hemianopsia Global aphasia (if on left side) May lead to coma secondary to edema
	Deep				Contralateral hemiplegia, hemisensory loss Transcortical motor and/or sensory aphasia (if on left side)
	Para-sylvian				Contralateral weakness and sensory loss of face and hand Conduction aphasia, apraxia, and Gerstmann syndrome (if on left side) Constructional dyspraxia (if on right side)
	Superior division				Contralateral hemiplegia, hemisensory loss, gaze palsy, spatial neglect Broca aphasia (if on left side)
	Inferior division				Contralateral hemianopsia or upper quadrant anopsia Wernicke aphasia (if on left side) Constructional dyspraxia (if on right side)
Anterior cerebral artery	Entire territory				Incontinence Contralateral hemiplegia Abulia Transcortical motor aphasia or motor and sensory aphasia Left limb dyspraxia
	Distal				Contralateral weakness of leg, hip, foot, and shoulder Sensory loss in foot Transcortical motor aphasia or motor and sensory aphasia Left limb dyspraxia

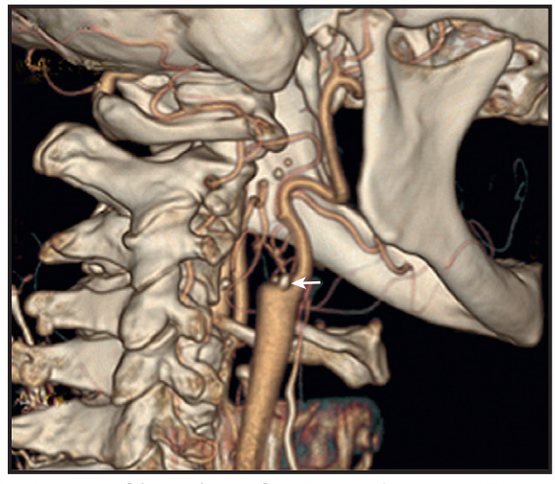
Diagnosis of Internal Carotid Disease



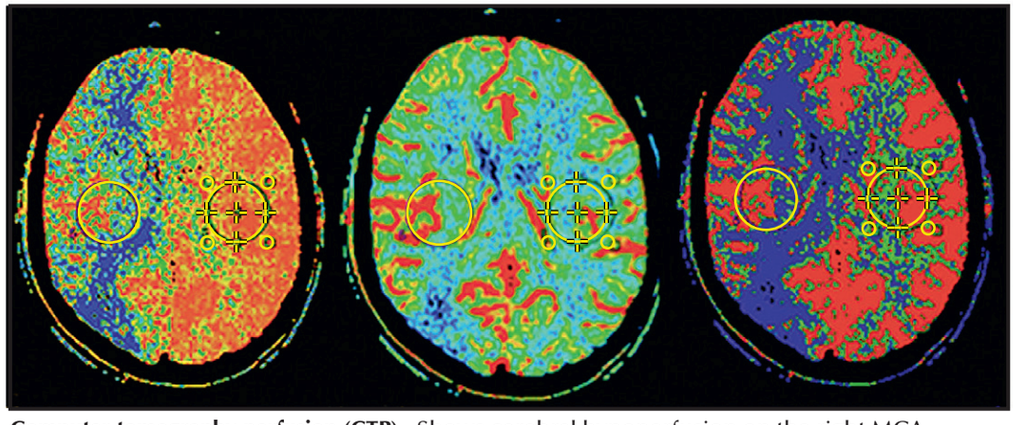
Transcranial Doppler (TCD). Shows intra-arterial embolism in a patient with carotid artery stenosis.



CTA of the head demonstrates an ulcerated plaque



Computer tomographic angiography (CTA). Shows an ICA occlusion.



Computer tomography perfusion (CTP). Shows cerebral hypoperfusion on the right MCA territory in a patient with severe right internal carotid artery (RICA) stenosis.

Anterior Circulation Ischemia *(Continued)*

a sensitivity of 98% to 100% and specificity of 96% to 100% for detection of severe carotid stenosis compared with angiography, whereas contrast-enhanced MRA has a sensitivity of 93% to 98% and a specificity of 96% to 100%. Regarding plaque characterization, MRI is able to qualitatively and quantitatively define carotid plaque morphology as well as identify vulnerable plaque features, such as intraplaque hemorrhages, whereas CTA is able to identify with precision the presence of plaque calcification and ulcerations.

In patients with anterior circulation dissection, MRI and MRA of the neck can provide morphologic details as well as document intraluminal blood flow, respectively, and is frequently the first choice of imaging studies in the workup. The typical MRI appearance of a dissected artery in cross section is an increased diameter of the artery with an eccentric narrowed lumen caused by the presence of an intramural hematoma. The hematoma can be detected on spin-echo T1- and T2-weighted images and fat-suppressed T1-weighted techniques (see Plate 9-15). The lumen containing a flow void, indicating patency, is usually the true lumen. Three-dimensional time-of-flight MRA can show the presence of a double lumen, string sign, wall irregularity, and aneurysmal dilation. Artifacts from swallowing, the patient's movement, tendency to overestimate the degree of stenosis, and difficulties distinguishing slow flow and intraluminal thrombus are the main limitations of this technique. CTA is another noninvasive alternative for the diagnosis of arterial dissection, and because it is independent of flow phenomena, even a small residual lumen and pseudoaneurysms causing slow or turbulent flow can be detected (see Plate 9-11, *A* and *B*). However, subtle intimal flaps and intramural thrombi can escape detection with CTA.

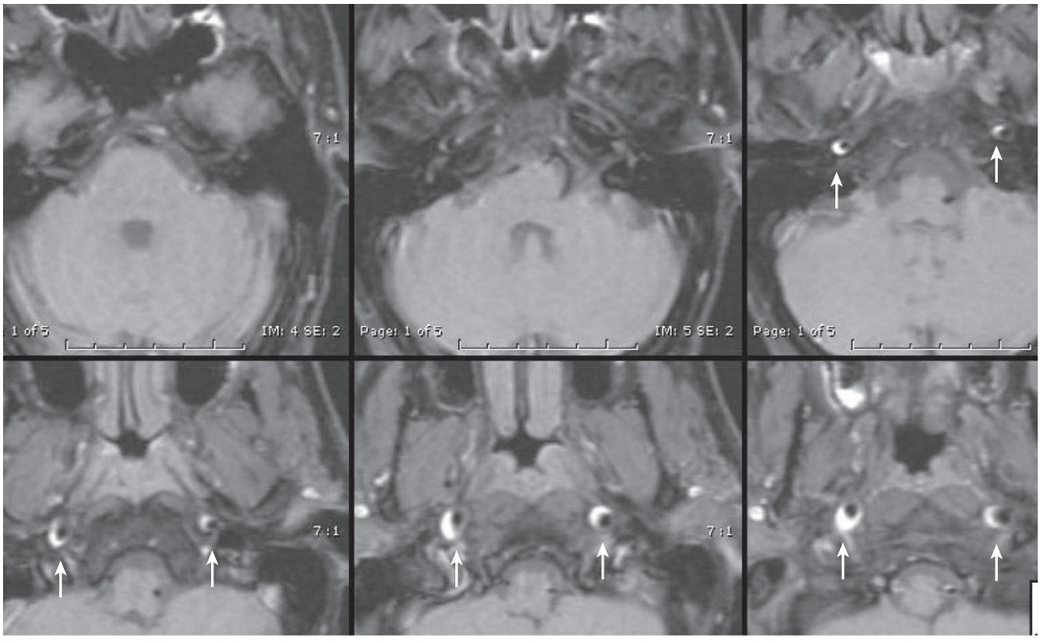
The presence of pacemaker devices and renal failure limit the imaging studies performed in patients with ICA disease. MRIs cannot be performed in patients with pacemakers, and renal failure is a contraindication for both CTA and MRA with gadolinium. Gadolinium-based contrast agents have been linked to the development of nephrogenic systemic fibrosis and nephrogenic fibrosing dermopathy, often with serious and irreversible skin or organ pathology in patients with moderate to end-stage renal disease.

TREATMENT

Carotid Artery Atherosclerotic Disease

All patients with carotid artery atherosclerotic disease, should be screened for modifiable risk factors, such as hypertension and diabetes, and appropriately treated according to the 2011 AHA/ASA (American Heart Association/American Stroke Association) guidelines, which include dietary changes, increased physical

Diagnosis of Carotid Artery Disease



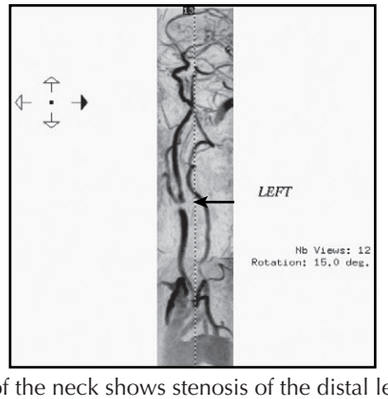
Fat-suppressed T1-weighted imaging showing eccentric narrowed lumen and the presence of an intramural hematoma in both distal ICAs suggestive of bilateral ICA dissection

Anterior Circulation Ischemia *(Continued)*

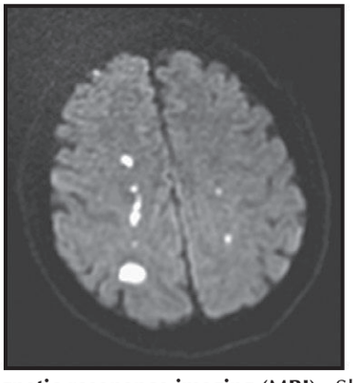
activity, and pharmacologic treatment. Smoking cessation is recommended, and avoidance of environmental tobacco smoke for stroke prevention should be considered in all patients. Statins have been approved for prevention of ischemic strokes in hypercholesterolemic patients with coronary artery disease and, more recently, since the publication of the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial, recommended by the 2011 AHA/ASA for patients with atherosclerotic ischemic stroke or TIA without known coronary heart disease to reduce the risk of both subsequent stroke and cardiovascular events. This trial showed a 5-year absolute risk reduction of 2.2% for the combination fatal and nonfatal stroke and of 3.5% absolute risk reduction for major cardiovascular events in patients receiving 80 mg of atorvastatin compared with placebo.

Antiplatelet treatments, such as aspirin, clopidogrel, and a combination of aspirin and dipyridamole, are often used for TIA and stroke prevention in patients with nonsignificant stenosis of the carotid arteries. Both clopidogrel (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events trial [CAPRIE]) and the combination between aspirin and dipyridamole (European Stroke Prevention Study 2 [ESPS-2]) have been shown to be superior to aspirin for prevention of recurrent cerebral ischemia, whereas no statistical difference was seen between clopidogrel and the combination of aspirin and dipyridamole (Prevention Regimen for Effectively Avoiding Second Strokes trial [PROGRESS]).

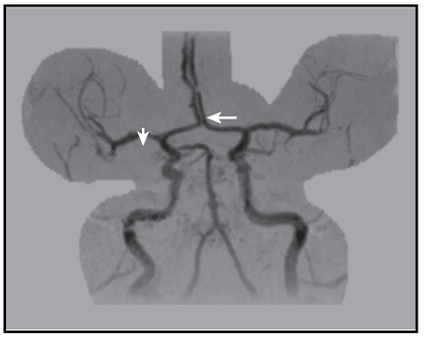
Carotid endarterectomy (CEA) for prevention of ischemic stroke has been performed since the early 1950s (see Plate 9-16), but it was only in the 1990s that several large-scale trials were performed comparing this type of surgery against best medical treatment in patients with asymptomatic and symptomatic internal carotid artery stenosis.



MRA of the neck shows stenosis of the distal left CCA just proximal to ICA and ECA bifurcation



Magnetic resonance imaging (MRI). Shows anterior border zone strokes, right greater than left, in a patient with bilateral carotid artery disease



MRA of the head demonstrates stenosis of the right MCA and left ACA

For patients with asymptomatic internal carotid artery stenosis from 60% to 99%, evidence from the Asymptomatic Carotid Atherosclerosis Study (ACAS) and Asymptomatic Carotid Surgery Trial (ACST) showed a modest benefit favoring CEA, with an absolute stroke risk reduction at 5 years of 5.9% and 5.4%, respectively. The stroke risk reduction was more prominent in men and independent of the degree of stenosis or contralateral disease. Therefore it was concluded that CEA should be considered for patients with asymptomatic stenosis of 60% to 99% if the patients have a life expectancy of at least 5 years and the rate of perioperative stroke or death for the institution or particular surgeon can be reliably kept to less than 3%. Since then, further studies have shown that more intensive medical treatment can decrease the ipsilateral stroke risk to less than 1%. It is possible that the absolute benefit from carotid endarterectomy is even smaller

Anterior Circulation Ischemia *(Continued)*

than reported by the above trials. A subgroup of patients with asymptomatic carotid artery disease and microembolism on transcranial Doppler monitoring or imaging markers of a vulnerable plaque or reduced cerebral blood flow reactivity may potentially benefit from vascular intervention; however, further studies will be required to answer this question.

For patients with symptomatic internal carotid artery disease, evidence from the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) support CEA for severe stenosis (70%–99%) over best medical treatment. The NASCET showed an absolute stroke risk reduction at 2 years of 17%, whereas the ECST showed an absolute benefit from surgery of 11.6%. For symptomatic patients with stenosis between 50% and 69%, CEA is moderately useful and can be considered in selected patients. The NASCET showed a 5-year rate of ipsilateral stroke of 15.7% in the surgical group compared with 22.2% among those treated medically in this subgroup of patients. CEA is not indicated for patients with stenosis less than 50%.

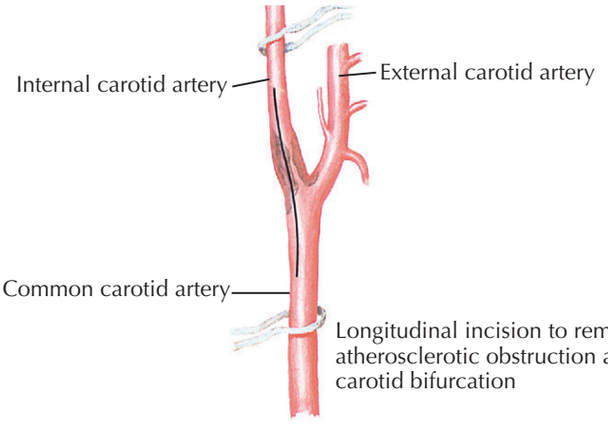
Stenting (see Plate 9-17) has been investigated as an alternative therapy for patients with carotid artery disease. Two multicenter studies, the International Carotid Stenting Study (ICSS) and the North American Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), have compared the efficacy of carotid endarterectomy versus carotid stents in patients with symptomatic and asymptomatic carotid artery disease and showed somewhat different results.

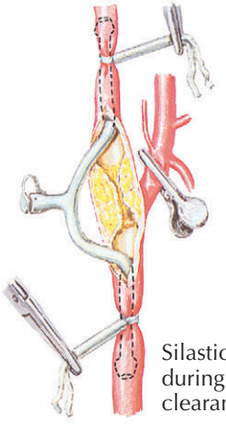
The ICSS was the first randomized trial for symptomatic patients with at least 50% internal carotid stenosis. This study showed that the risk of stroke, death, and myocardial infarction (MI) in the carotid artery stenting group was significantly higher than in the surgical arm (8.5% versus 5.2%, $P = .006$) with a major difference in the occurrence of minor strokes. This finding was also supported by the results of a MRI substudy showing more diffusion-weighted imaging lesions in patients submitted to a carotid stent than to a CEA.

The CREST enrolled symptomatic patients with at least 50% stenosis on angiography or 70% by ultrasound as well as asymptomatic ones with at least 60% stenosis by angiography or 70% stenosis by ultrasound. This trial showed no difference between the risks of stroke, death, and MI in patient treated with a stent or CEA; however, periprocedural strokes and death in symptomatic patients were significantly higher in patients treated with stents (6%) versus CEA (3.2%, $P = .02$), whereas MI was more frequent in patients treated with CEA.

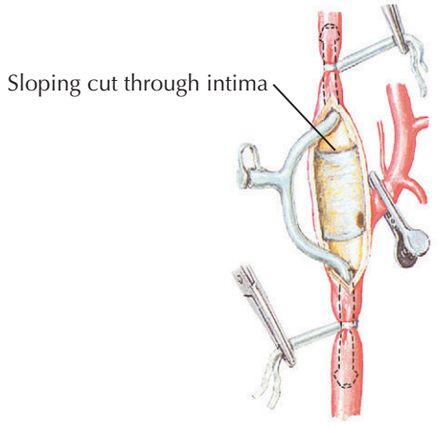
Stricter practitioner credentialing requirements and inclusion of lower-risk asymptomatic patients in the

Carotid Endarterectomy

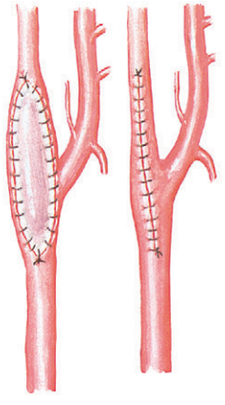




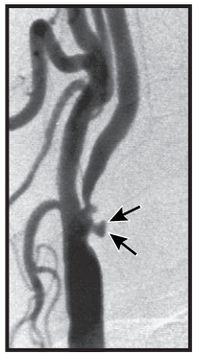
Silastic tube inserted for shunt during endarterectomy. T permits clearance of air from tube.



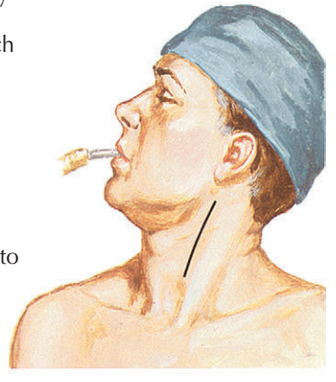
Endarterectomy performed



Vein graft or Dacron velour patch used to widen vessel if necessary. Arteriotomy closed by direct suture.

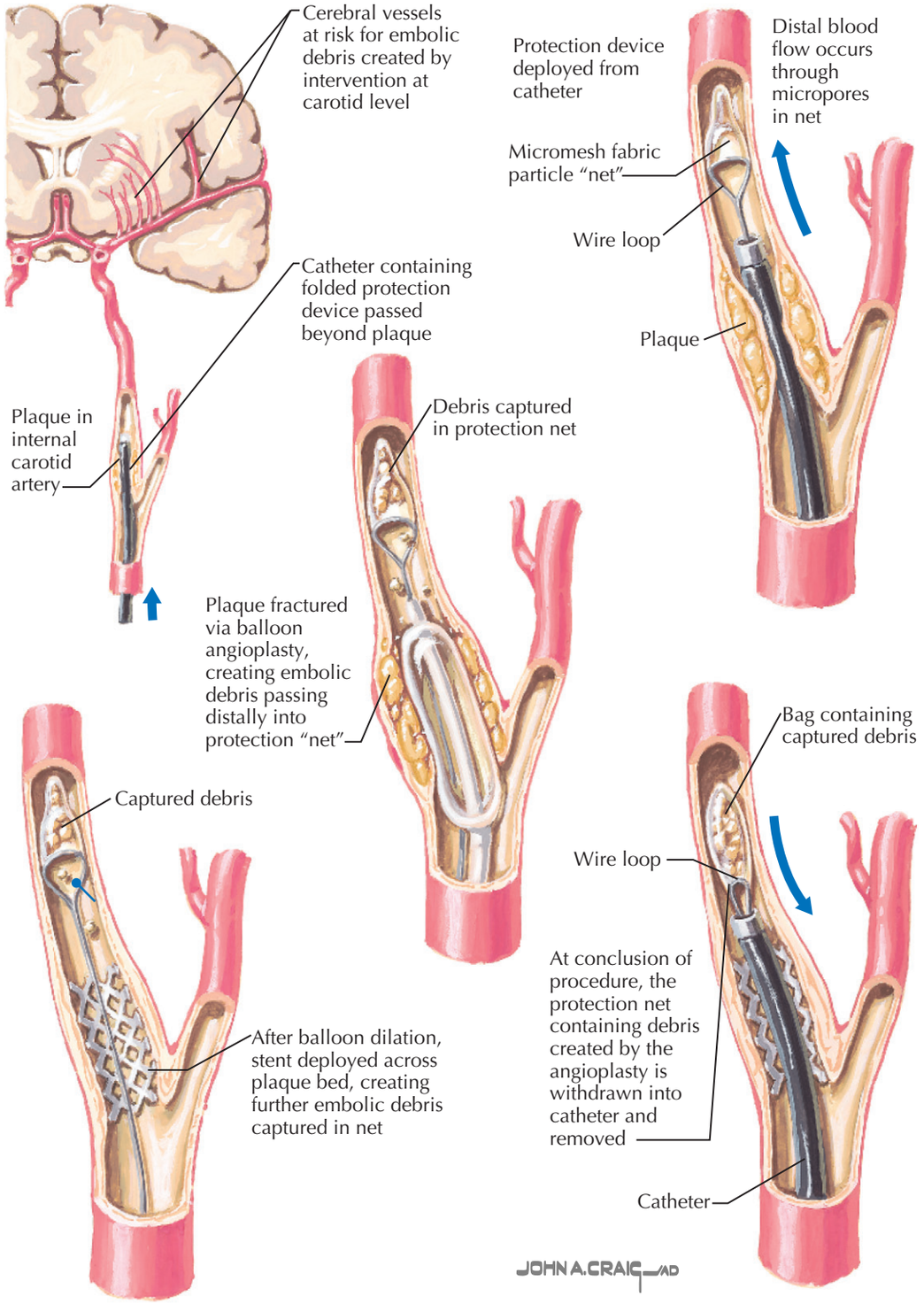


Angiogram (lateral view) showing moderately severe stenosis at origin of left internal carotid artery, with ulceration indicated by protrusion of contrast medium *(arrows)*. Such a case is suitable for endarterectomy.



Patient's head turned to side; incision along anterior margin of sternocleidomastoid muscle

Endovasular ICA Angioplasty and Stenting Using a Protective Device



Anterior Circulation Ischemia *(Continued)*

CREST probably explain some of the different results between these two trials. Until further studies are done, carotid endarterectomy is still the treatment of choice for patients with symptomatic carotid artery disease.

Intracranial ACA/MCA Atherosclerotic Disease

Warfarin has showed no advantage over aspirin for prevention of ischemic stroke or vascular death in patients with symptomatic intracranial artery stenosis (Warfarin-Aspirin Symptomatic Intracranial Disease [WASID] trial) and was associated with significantly higher rates of adverse events. The current guidelines from the Consensus Conference on Intracranial Atherosclerotic Disease recommend aspirin monotherapy, the combination of aspirin and extended-release dipyridamole, and clopidogrel monotherapy as acceptable options in patients with noncardioembolic ischemic stroke and TIA. Aggressive treatment of atherogenic risk factors is also beneficial in this group of patients.

The prospective randomized study SAMMPRIS (*S*tenting and *A*ggressive *M*edical *M*anagement for *P*reventing *R*ecurrent Stroke in *I*ntracranial *S*tenosis) showed that aggressive medical management was superior to stenting, both because the risk of early stroke after stenting was high and the risk of stroke with aggressive medical therapy alone was lower than expected.

Nevertheless, intracranial angioplasty, with or without stent placement, may still be considered for a select group of patients with high-grade stenosis, recurrent ischemia, and medication failure.

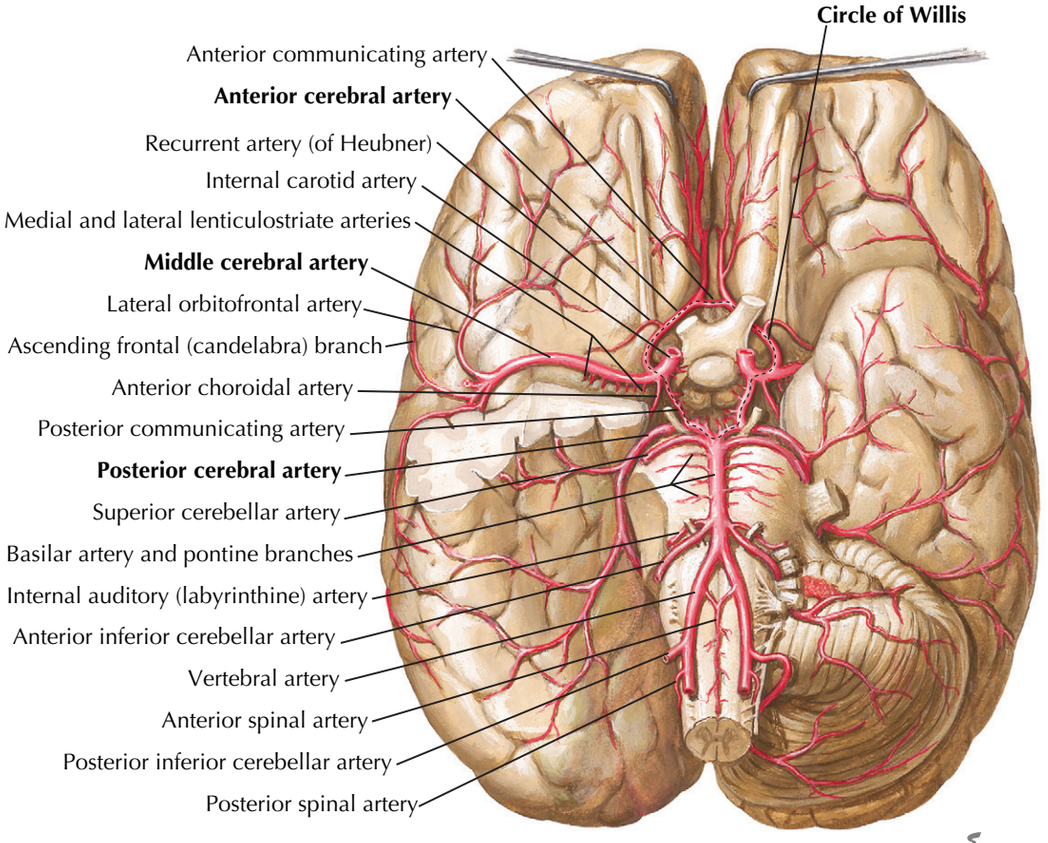
Anterior Circulation Dissection

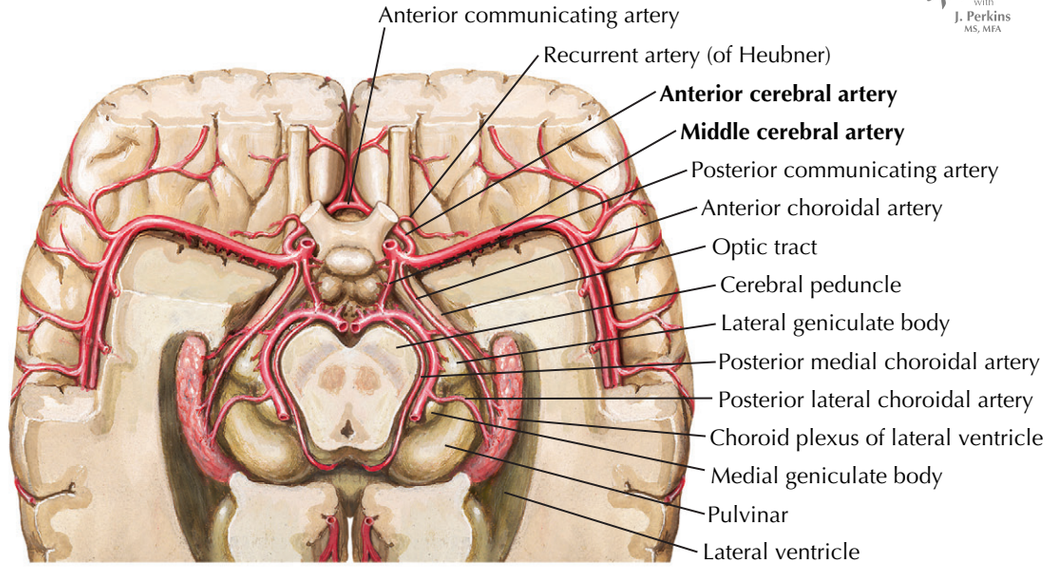
The best treatment for stroke prevention in patients with extracranial or intracranial artery dissections in the anterior circulation remains unclear. The 2011 AHA/ASA guidelines recommend the use of antithrombotic treatment for 3 to 6 months as a reasonable option but acknowledge that the relative efficacy of antiplatelet therapy compared with anticoagulation is unknown for these patients.

Even though most cases of carotid artery dissection have a good prognosis with conservative management, a small proportion of patients can develop fluctuating or progressive neurologic deficits secondary to hemodynamic insufficiency and may require more aggressive treatment with stent placement.

Although the number of reported patients with intracranial dissections treated with anticoagulation or antiplatelet treatment is too small for any type of conclusion, both treatments seem to be relatively safe in patients with intracranial dissections without subarachnoid hemorrhage.

Arterial Distrubution to the Brain: Basal View





Vertebral Basilar System Disorders

Subclavian and Innominate Arteries

The left subclavian artery is usually the last brachiocephalic branch of the aortic arch, while the right subclavian artery originates from the innominate artery. Subclavian or innominate artery occlusive lesions before the vertebral artery origins can cause altered vertebral artery blood flow. In the *subclavian steal syndrome*, obstruction to the proximal subclavian artery causes a low-pressure system within the ipsilateral vertebral artery and in blood vessels of the arm. Blood from a higher-pressure system, the contralateral vertebral artery and basilar artery, is diverted and flows retrograde down the ipsilateral vertebral artery into the arm. *In most patients, occlusive subclavian artery lesions are asymptomatic.* When symptoms occur, they most often relate to the ipsilateral arm and hand. Coolness, weakness, and pain on use of the arm are common but may not be severe. When there is decreased antegrade flow or retrograde vertebral artery flow, patients may describe spells of dizziness, diplopia, decreased vision, oscillopsia, and staggering occur. These attacks are brief and may be provoked by exercising the ischemic arm. In most patients, exercise of the ischemic limb does not induce neurologic symptoms or signs. *Innominate artery* occlusive lesions are uncommon. When present, they can cause both carotid and vertebral artery ischemic attacks and strokes.

Vertebral Arteries in the Neck

Atherosclerosis

The origin of the vertebral arteries is the most common location for atherosclerotic disease in the vertebral system. Atheromas often begin in the subclavian arteries and spread to the proximal few centimeters of the vertebral arteries. Disease at this site is often accompanied by internal carotid artery origin occlusive lesions. Risk factors for proximal vertebral artery atherosclerosis are hypertension, smoking, coronary artery, and peripheral vascular occlusive disease.

The most frequently reported symptom during transient ischemic attacks is dizziness. In at least some attacks, dizziness is accompanied by other signs of hindbrain ischemia, such as diplopia, oscillopsia, weakness of the legs, hemiparesis, or numbness. Vertebral artery origin lesions seldom cause chronic, hemodynamically significant hypoperfusion of the vertebrobasilar system. When one vertebral artery occludes, the other takes up the slack. There are also potential collateral blood vessels that originate from the subclavian and external carotid arteries that can reconstitute the distal vertebral artery when the proximal portion occludes. The most important morbidity of vertebral artery occlusive lesions is embolism to the intracranial vertebrobasilar arterial system. In patients with cerebellar and posterior cerebral artery territory infarcts, occlusion of the vertebral arteries in the neck has led to artery-to-artery embolism.

Vertebral Artery Dissection

The most important lesion of the more distal extracranial portions of the vertebral arteries is *arterial dissection*. Dissections usually involve portions of arteries that are mobile and rarely occur at the origins of arteries. The extracranial vertebral arteries are anchored at their origin from the subclavian artery and during their course through bone within the intervertebral foramina (V_2 portion), and by the dura at the point of intracranial penetration. The short movable segments between these anchored regions are most vulnerable to tearing and stretching. Dissections can involve the proximal (V_1) portion of the arteries above their origins before they enter the intervertebral foramina at C5 or C6. The

Arteries of Posterior Cranial Fossa

Vertebral Basilar System Disorders *(Continued)*

distal extracranial portion (V_3) is the most common location for dissection. This segment is relatively mobile and so vulnerable to tearing by sudden motion and stretching as might occur during chiropractic manipulation. Distal vertebral artery dissections may extend into the intracranial vertebral artery. The symptoms and signs are attributable to lateral medullary and cerebellar ischemia and are the same as those found in patients with intracranial vertebral artery occlusive disease. Distal extracranial vertebral artery dissections are often bilateral.

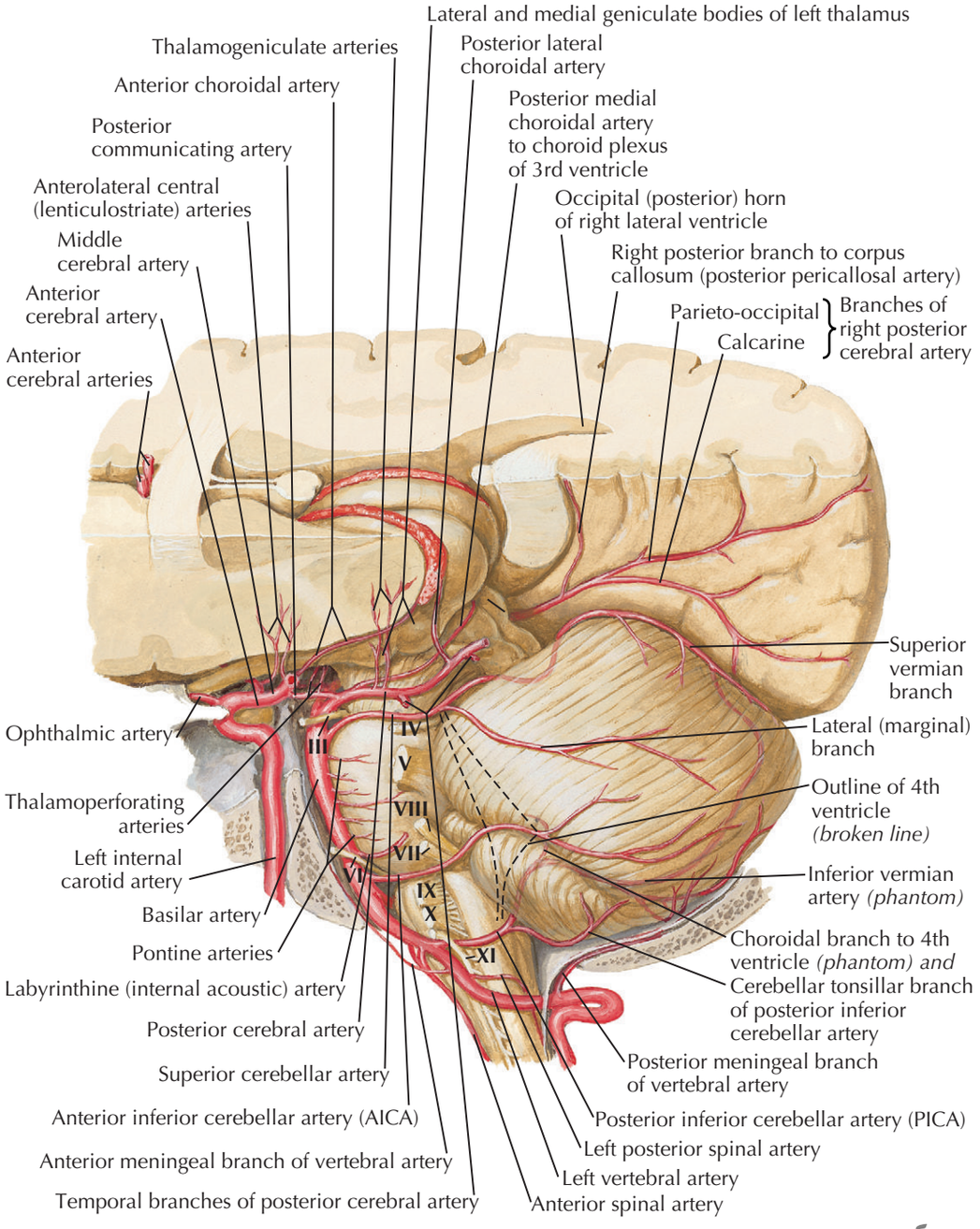
INTRACRANIAL VERTEBRAL ARTERY DISEASE

There are three specific intracranial vertebral artery syndromes.

Lateral Medullary Syndrome

Atherosclerosis of the intracranial vertebral arteries is most severe in the distal portion of the arteries, often at the vertebral-basilar artery junction, sometimes extending into the proximal basilar artery. Stenosis is also common just after dural penetration. Most often, patients with proximal intracranial vertebral artery occlusive disease present with features of the *lateral medullary syndrome*. The findings are understood best by reviewing the structures in the lateral medullary tegmentum that are specifically involved.

1. ***Nucleus and descending spinal tract of V.*** Sharp jabs of pain are found in the *ipsilateral eye and face, and numbness of the face;* examination confirms decreased pinprick and temperature sensations on the ipsilateral face.
2. ***Vestibular nuclei*** *and their connections.* Feelings of dizziness or instability of the environment may be present; examination shows nystagmus with coarse rotatory eye movements when looking to the ipsilateral side and small-amplitude faster nystagmus when looking contralaterally.
3. ***Spinothalamic tract.*** There is decreased pinprick and temperature sensation in the *contralateral limbs and body*; a sensory level may be present on the contralateral trunk with pain and temperature loss on the trunk below that level and in the lower extremity. The pinprick and temperature loss can extend to the contralateral face when the crossed *quintothalamic* tract that appends itself medially to the spinothalamic tract is involved. Rarely, the loss of pain and temperature sensation is totally contralateral and involves the face, arm, trunk, and leg.
4. ***Inferior cerebellar peduncle.*** There is veering or leaning toward the side of the lesion and clumsiness of the ipsilateral limbs; examination shows hypotonia and exaggerated rebound of the ipsilateral arm. On standing or sitting, patients often lean or tilt to the side of the lesion.
5. ***Autonomic nervous system nuclei and tracts.*** *Descending sympathetic system axons* traverse the lateral medulla in the lateral reticular formation; dysfunction causes an ipsilateral Horner syndrome. The dorsal motor nucleus of the vagus is sometimes affected, leading to tachycardia and a labile increased blood pressure.
6. ***Nucleus ambiguus.*** When the infarct extends medially, it often affects this nucleus, causing hoarseness and dysphagia. The pharynx and palate are weak on the side of the lesion, sometimes causing patients to retain food within the piriform recess of the pharynx. A crowlike cough represents an attempt to extricate food from this area.
7. At times, there is also ipsilateral facial weakness, perhaps related to ischemia of the *caudal part of*



VERTEBRAL BASILAR SYSTEM DISORDERS *(Continued)*

the seventh nerve nucleus, just rostral to the nucleus ambiguus, or involvement of corticobulbar fibers going toward the seventh nerve nucleus.

8. Abnormal respiratory control may also be found, especially in *bilateral lateral medullary lesions*. Hypoventilation is probably related to involvement of the nucleus of the solitary tract, nucleus ambiguus, nucleus retroambiguus, and nuclei parvocellularis and gigantocellularis.

Cerebellar Infarction

The other common clinical syndrome is *cerebellar infarction* in the distribution of the posterior inferior cerebellar artery, a branch of the intracranial vertebral artery. Cerebellar infarction is often difficult to diagnose. Symptoms can resemble labyrinthitis and can appear deceptively slight. Gait ataxia and vomiting are often accompanied by dizziness.

Medial Medullary Infarction

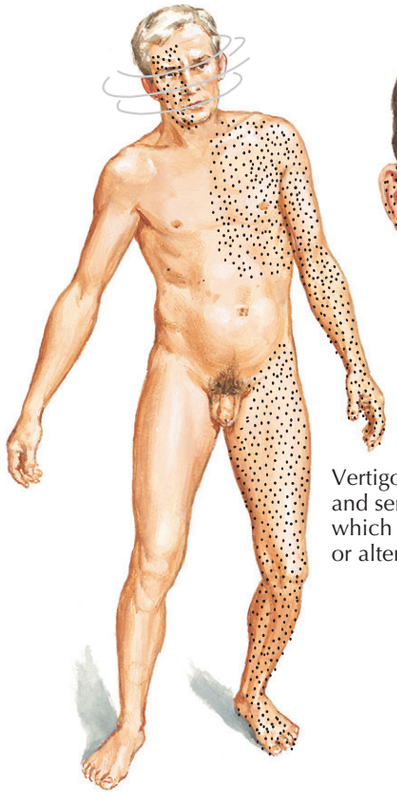
This third syndrome is much less common. The anterior spinal artery supplying the medial medulla arises from the distal intracranial vertebral artery. The medial medullary syndrome is characterized by a hemiparesis that affects the contralateral arm and leg attributable to ischemia of the medullary pyramid, and ipsilateral weakness of the tongue and contralateral loss of position sense explained by involvement of the hypoglossal nerve and the medial lemniscus. In some patients with intracranial vertebral artery occlusion, ischemia of the medial medulla accompanies lateral medullary infarction, forming a *hemimedullary syndrome*. This occurs when an intracranial vertebral artery occlusion is extensive and both the lateral medullary penetrators and the anterior spinal artery branches are concomitantly involved. Rarely, medial medullary infarction is bilateral and can extend caudally into the rostral spinal cord, causing a syndrome of quadriparesis difficult to separate from basilar artery occlusion with pontine infarction.

PROXIMAL AND MIDBASILAR ARTERY OCCLUSION

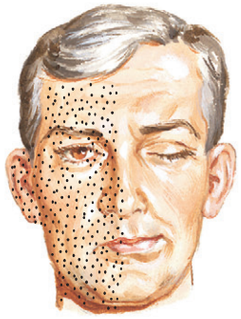
The basilar artery forms after merging of the two intracranial vertebral arteries at the medullo-pontine junction. The basilar artery ends at the junction of the pons and midbrain. The major territory of supply of the basilar artery is the pons, especially the basis pontis. The tegmentum of the pons has a rich collateral supply of blood vessels. The superior cerebellar arteries at the distal end of the basilar artery provide much supply to the pontine and midbrain tegmentum. Occlusion of the basilar artery often causes ischemia in the pontine base bilaterally, sometimes extending into the medial tegmentum on one or both sides. The most important neurologic signs and symptoms that accompany basilar artery occlusion are:

1. ***Limb paralysis.*** Limb paralysis is usually bilateral but often asymmetric; stiffness, hyperreflexia, and extensor plantar reflexes are found when examining the weak limbs. Some patients present with a hemiparesis, but examination shows weakness and reflex changes in the contralateral limbs.
2. ***Bulbar or pseudobulbar paralysis.*** Infarction may affect cranial motor nuclei, causing paralysis of the face, palate, pharynx, neck, or tongue on one or both sides. The 9th- to 12th-nerve nuclei are located within the medullary tegmentum, which is usually below the level of infarction. Weakness of the cranial musculature innervated by these nuclei causes dysarthria, dysphonia, hoarseness, dysphagia, and tongue weakness. The pontine

CLINICAL MANIFESTATIONS OF VERTEBROBASILAR TERRITORY ISCHEMIA

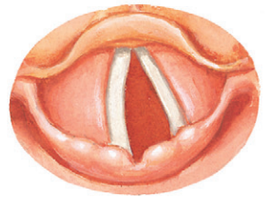


Vertigo, ataxia; motor and sensory deficits, which may be unilateral, or alternating



Motor and sensory deficits in face (cranial nerves V and VII); unilateral, bilateral, or alternating (cranial nerves V and VII)

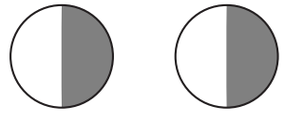
Dysphagia (cranial nerves IX and X)



Dysphonia (cranial nerve X)

Headache, vomiting

Abnormal eye movements (cranial nerves III, IV, and/or VI). Horner syndrome may be present.



Hemianopsia (bilateral occipital lesions—cortical blindness and Balint syndrome)

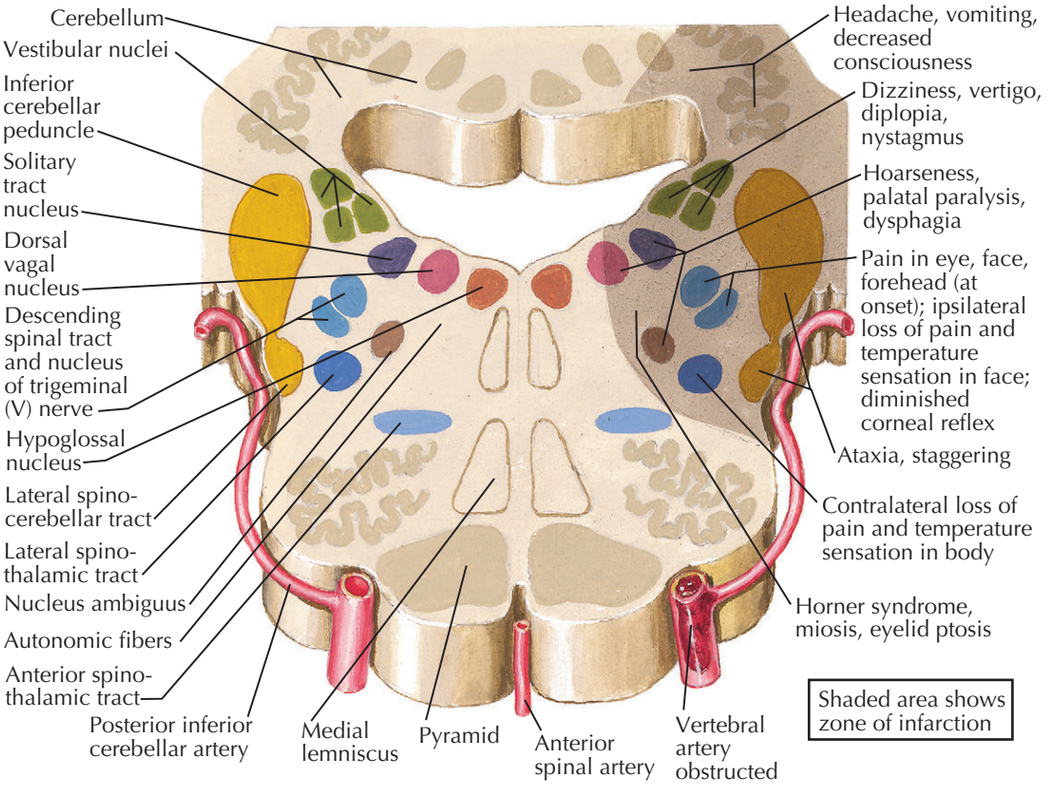
Altered consciousness (partial or complete) may be fleeting, transient, or of long duration

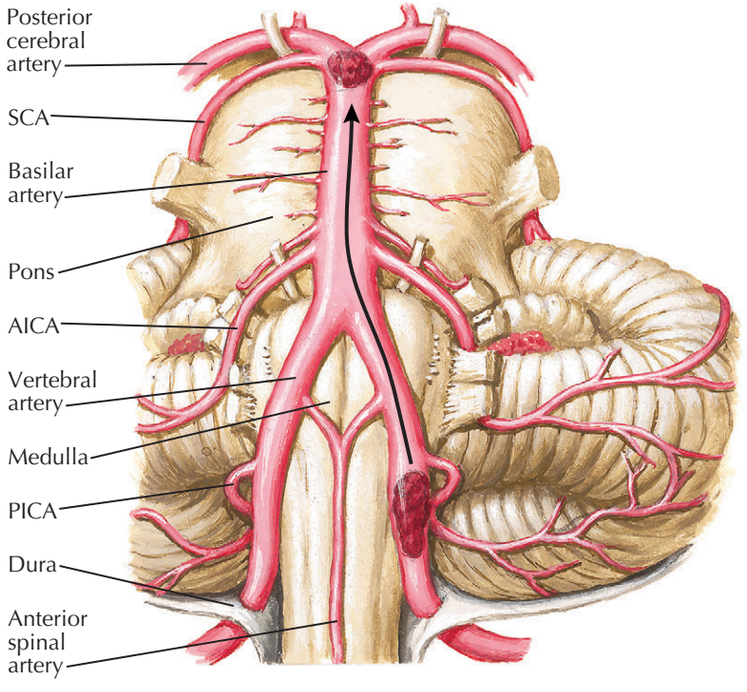
VERTEBRAL BASILAR SYSTEM DISORDERS *(Continued)*

lesion interrupts corticofugal descending fibers destined for these cranial nerve nuclei. The resulting weakness is referred to as pseudobulbar because it involves the descending pathways controlling the bulbar nuclei rather than the nuclei themselves. Exaggerated jaw and facial reflexes, increased gag reflex, and easily induced emotional incontinence with excessive laughing and/or crying are found. The limb and bulbar paralysis may be so severe that the patient cannot communicate verbally or by gesture. Such patients have been referred to as having the *locked-in syndrome* because of their loss of motor function.

3. ***Eye movement abnormalities.*** The sixth-nerve nuclei, medial longitudinal fasciculi (MLFs), and pontine lateral gaze centers are located in the paramedian pontine tegmentum, and are vulnerable to ischemia in this region. Lesions of the sixth nerve or nucleus cause paralysis of abduction of the eye. A MLF lesion results in loss of adduction of the ipsilateral eye on gaze directed to the opposite side and nystagmus of the contralateral abducting eye. This syndrome, called an internuclear ophthalmoplegia, can be bilateral. Lesions of the paramedian pontine tegmentum may also affect the paramedian pontine reticular formation (PPRF), the so-called pontine lateral gaze center that mediates gaze to the same side. A lesion of this region causes an ipsilateral conjugate-gaze paresis. A unilateral lesion can affect both the PPRF and the MLF on the same side, resulting in the *one-and-a-half syndrome* because only one half of gaze (scoring 1 for gaze to each side) is preserved. *Nystagmus*: the vestibular nuclei and their connections are also often affected, causing vertical and horizontal nystagmus. *Other eye signs*: ptosis, small pupils, and ocular skewing are also often found.
4. ***Coma.*** When the reticular formation is affected bilaterally in the medial pontine tegmentum, coma results. Sensory and cerebellar abnormalities are absent or slight because the infarct usually affects the midline and paramedian structures in the basis pontis, sparing the spinothalamic tracts and the cerebellum. Collateral circulation is mainly through the circumferential vessels, which course around the lateral portions of the brainstem to nourish the lateral base, tegmentum, and cerebellum. The cerebellar hemispheres are mostly nourished by the posterior inferior cerebellar artery that originates before the basilar artery, and the superior cerebellar artery (SCA), which is preserved when the basilar artery clot does not extend to the distal basilar artery.

INTRACRANIAL OCCLUSION OF VERTEBRAL ARTERY
Posterolateral medullary infarction and clinical manifestations





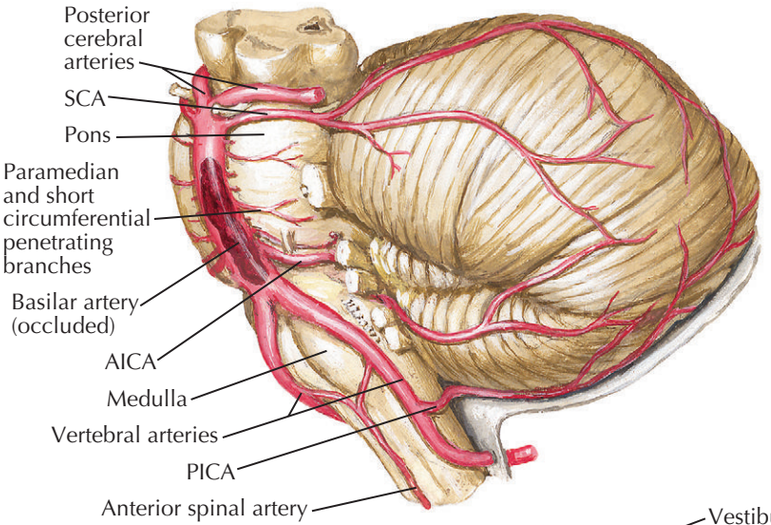
Intracranial obstruction of vertebral artery proximal to origin of posterior inferior cerebellar artery (PICA) may be compensated by preserved flow from contralateral vertebral artery. If PICA origin is blocked, lateral medullary syndrome (shown above) may result. Clot also may extend to block anterior spinal artery branch, causing hemiplegia, or embolization to basilar bifurcation may cause "top of basilar" syndrome.

TOP-OF-THE-BASILAR ARTERY EMBOLISM

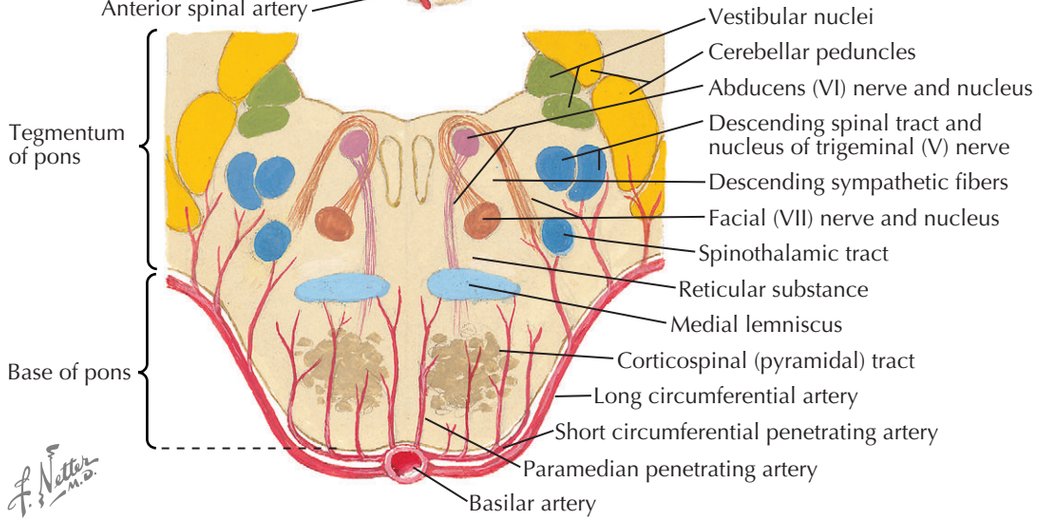
Occlusion of the distal basilar artery is most often caused by embolism from the heart or the proximal vertebral artery system. Emboli small enough to pass through the vertebral arteries seldom lodge in the proximal basilar artery, a vessel larger than each intracranial vertebral artery, but reach the distal basilar artery or its terminal branches. The distal basilar artery supplies the midbrain and diencephalon through small vessels that pierce the posterior perforated substance. The findings in patients with top-of-the-basilar embolism include

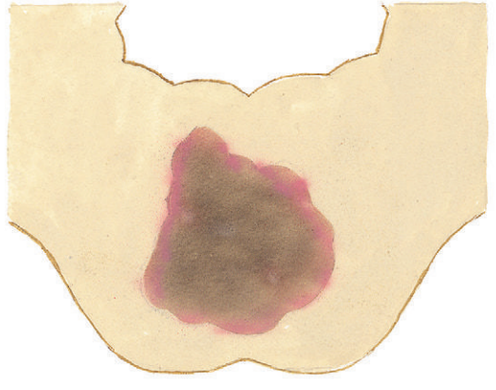
1. ***Pupillary abnormalities.*** The lesion often interrupts the afferent reflex arc by interfering with fibers going toward the Edinger-Westphal nucleus. The third-nerve nucleus can also be involved, as well as the rostral descending sympathetic system. The pupils are usually abnormal

Occlusion of Basilar Artery and Branches

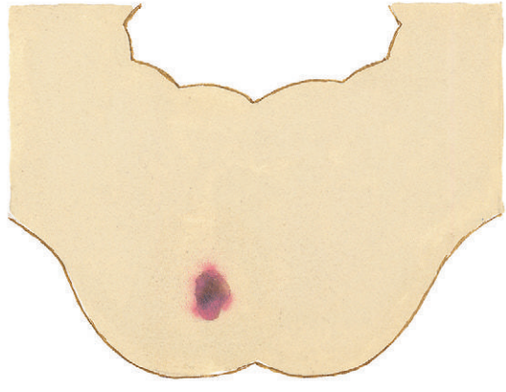


Collateral circulation via superior cerebellar (SCA), anterior inferior cerebellar (AICA), and posterior inferior cerebellar (PICA) arteries may partially compensate for basilar occlusion. Basilar artery has paramedian, short circumferential and long circumferential (AICA) and (SCA) penetrating branches. Occlusion of any or several of these branches may cause pontine infarction. Occlusion of AICA or PICA may also cause cerebellar infarction.





Large pontine infarction, resulting in pupillary and other ocular abnormalities, facial weakness, quadriplegia, and coma



Small infarct in the left base of the pons causing a right hemiparesis

Vertebral Basilar System Disorders *(Continued)*

and can be small, midposition, or dilated, depending on the level and extent of the lesion. Decreased pupillary reactivity and eccentricity or an oval shape of the pupil is also found.

2. ***Eye movement abnormalities.*** Paralysis of upward or downward gaze is common. The eyes may also be skewed and deviated at rest, most often downward and inward. Hyperconvergence, retractory nystagmus, and pseudo–VI-nerve paresis are other oculomotor abnormalities noted. Reduced ocular abduction in patients with pseudo-VI paresis is explained by hyperadduction of the eye. The adduction vector neutralizes the abduction motion, and so abduction is incomplete. The lesion is far rostral to the sixth nerve nucleus or fibers.
3. ***Decreased alertness.*** Hypersomnolence or frank coma can result from bilateral paramedian rostral brainstem dysfunction. After the acute phase, the patient may remain relatively inert and apathetic. Some patients sleep many hours a day unless stimulated or coaxed into activities.
4. ***Memory loss.*** Patients are unable to form new memories and may not be able to recall events just preceding their stroke. There often are other behavioral abnormalities, including agitation, hallucinations, and abnormalities that mimic lesions of the frontal lobe.

THALAMIC INFARCTS

The thalamus is supplied by arteries that arise at or near the basilar artery bifurcation and from the proximal posterior cerebral arteries. The *tuberothalamic (polar) artery* arises on each side from the middle third of the posterior communicating artery and supplies the anteromedial and anterolateral thalamic nuclei. Unilateral anterolateral thalamic infarction in the distribution of the polar artery on either side usually causes abulia, facial asymmetry, transient minor contralateral motor abnormalities and, at times, aphasia (left lesions) or visual neglect (right lesions). Abulia, with slowness, decreased amount of activity and speech, and long delays in responding to queries or conversation, is the predominant abnormality. Memory may also be affected.

The *thalamic-subthalamic arteries* (also called thalamoperforating) originate from the proximal posterior cerebral arteries and supply the most posteromedial portion of the thalamus near the posterior commissure. The right- and left-sided arteries usually arise separately but can originate from a single unilateral artery or a common pedicle. Unilateral lesions are usually characterized by paresis of vertical gaze (upward or both upward and downward) and by amnesia. Motor and sensory signs and symptoms are absent. Memory loss may be severe, with profound difficulty in forming new memories and encoding recent events, particularly with bilateral lesions. The amnesia often improves within 6 months in patients with unilateral infarcts. Bilateral butterfly-shaped paramedian posterior thalamic infarction can result from a branch occlusion of a single supplying artery or pedicle and cause hypersomnolence and bilateral third-nerve palsies.

The *thalamogeniculate group of arteries* arises from the posterior cerebral arteries to supply the ventrolateral thalamus, an area that includes the somatosensory nuclei (ventral posterior lateral and ventral posterior medial) and the ventral lateral and ventral anterior nuclei. The findings in patients with lateral thalamic infarcts are contralateral hemisensory symptoms accompanied by contralateral limb ataxia. At times, hemichoreic movements of the contralateral arm develop, and the hand may assume a fisted posture. Some patients have a transient hemiparesis at onset that improves quickly.

VERTEBRAL BASILAR SYSTEM DISORDERS *(Continued)*

Occlusion of branches of the thalamogeniculate arteries supplying the somatosensory nuclei is responsible for most patients with *pure sensory stroke* (hemisensory symptoms or signs without other abnormalities). The infarcts are usually smaller than those found in patients with the lateral thalamic syndrome. Occlusion of thalamogeniculate branches occasionally causes a syndrome referred to as *sensory motor stroke* characterized by the sensory symptoms and signs of pure sensory stroke accompanied by paresis and pyramidal signs involving the same limbs.

The *posterior choroidal arteries* originate from the posterior cerebral arteries and course forward from caudal to rostral in the thalamus. The lateral posterior choroidal arteries supply mostly the pulvinar, a portion of the lateral geniculate body, and then loop around the superior portion of the thalamus to supply the anterior nucleus. The medial arteries supply the habenula, anterior pulvinar, parts of the center median nucleus, and the paramedial nuclei. Hemianopia, hemisensory symptoms, and behavioral abnormalities may occur in patients with posterior choroidal artery territory infarcts.

POSTERIOR CEREBRAL ARTERIES

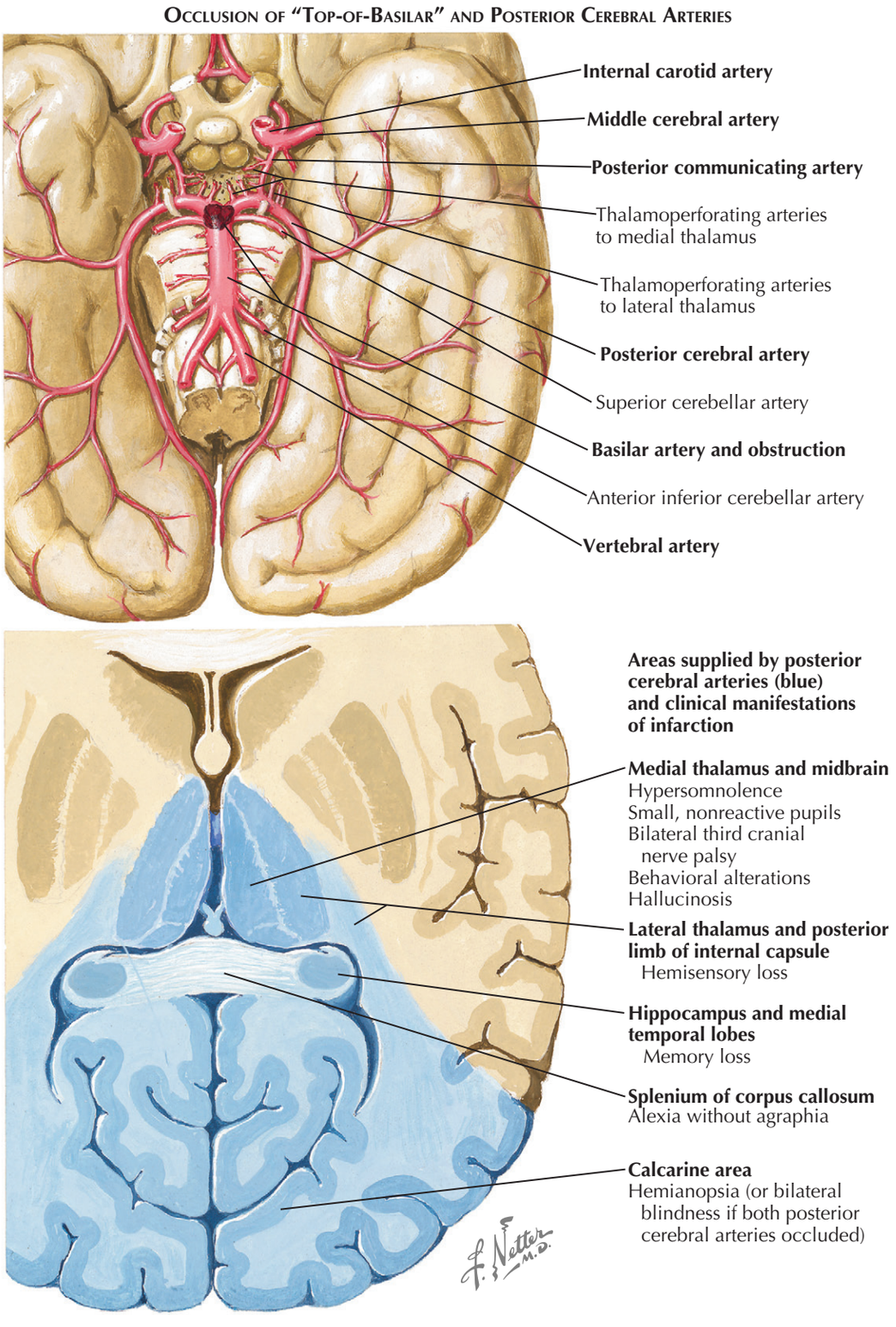
The posterior cerebral arteries are the main terminal branches of the basilar artery. Intrinsic atheromatous disease of the PCA most often affects the origin of the vessel. Most often, infarcts in the PCA territory are caused by emboli to the posterior circulation.

After giving off penetrating branches to the midbrain and thalamus, the posterior cerebral arteries supply branches to the occipital lobes and the medial and inferior portions of the temporal lobes. Infarction in the cerebral territories of the arteries most often affects vision and somatic sensation but seldom causes paralysis. *The most common finding is a hemianopia* caused by infarction of the striate visual cortex on the banks of the calcarine fissure or by interruption of the geniculocalcarine tract as it nears the visual cortex. If just the lower bank of the calcarine fissure is involved, the lingual gyrus, a superior quadrant-field defect, results. An inferior quadrantanopia results if the lesion affects the cuneus on the upper bank of the calcarine fissure. When infarction is restricted to the striate cortex and does not extend into the adjacent parietal cortex, the patient is fully aware of the visual field loss.

Somatosensory abnormalities are also common. The lateral thalamus is the site of the major somatosensory relay nuclei, the ventral posteromedial and lateral nuclei. Ischemia to these nuclei or white matter tracts carrying fibers from the thalamus to somatosensory cortex produces sensory symptoms and signs, usually without paralysis. Patients report paresthesias or numbness in the face, limbs, and trunk. The combination of hemisensory loss and hemianopia without paralysis is virtually diagnostic of infarction in the posterior cerebral artery territory. Rarely, occlusion of the proximal portion of the artery can cause a hemiplegia. Penetrating branches from the proximal posterior cerebral artery penetrate into the midbrain to supply the cerebral peduncle.

Cognitive and behavioral abnormalities are also common. When the left posterior cerebral artery territory is infracted, patients may lose the ability to read, although they retain the ability to write and spell. Anomic aphasia and memory loss are also common. When the right posterior cerebral artery territory is involved, disorientation to place may develop.

When the posterior cerebral artery territory is infarcted bilaterally, as may occur with emboli, the most common findings are cortical blindness, amnesia, and agitated delirium.



Brain Emboli

There are three main participants in the process of brain embolism: the *recipient artery* that catches and receives the embolic material even temporarily, the *embolic material* itself—the matter that makes up the emboli, and the *donor source* from which embolic material originates.

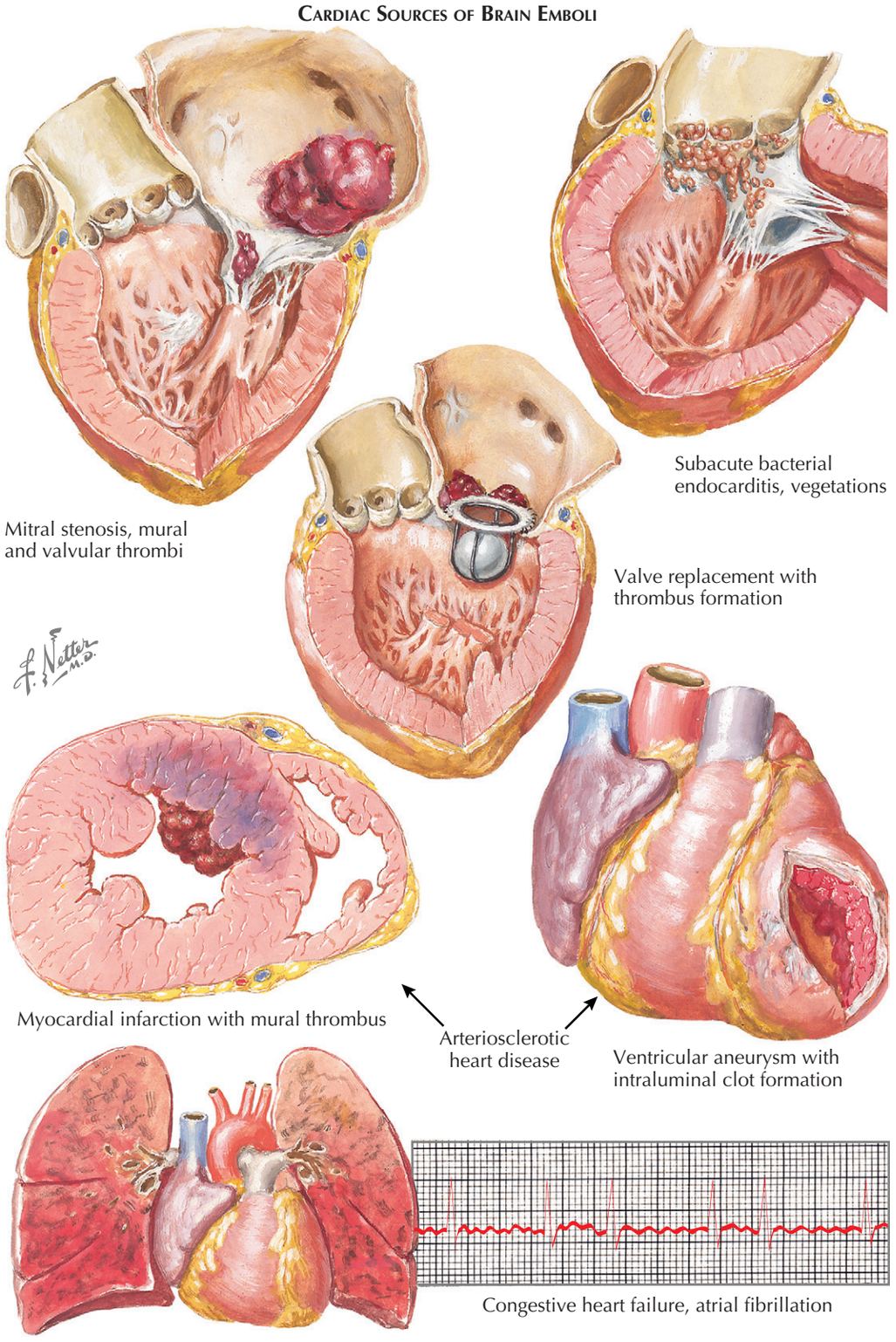
THE RECIPIENT ARTERIES

The recipient artery is the main determinant of the clinical symptoms and signs. When a recipient neck or intracranial artery is blocked, blood flow to the area of brain supplied by the blocked artery suddenly becomes insufficient and normal function stops. The neurologic symptoms that result from the arterial blockage depend on the area of brain that is underperfused. If an embolus blocks a posterior cerebral artery supplying the visual cortex, loss of vision in the opposite visual field might result. If an embolus blocks the left middle cerebral artery, the right limbs might become weak and numb, and the patient might become aphasic. An embolus to an intracranial vertebral artery might cause loss of cerebellar function and ataxia. The symptoms do not depend on the nature of the embolic material. The recipient artery cannot tell what is blocking it or where the material came from.

Whether the symptoms are transient or persist depends on the size and fate of the embolus. Emboli very often move through recipient arteries so quickly that no or very transient obstruction occurs. These passing emboli can be identified as so-called HITS (high-intensity transient signals) that pass quickly under an ultrasound probe monitoring an intracranial artery. Emboli can cause no symptoms, TIAs, or persistent infarction.

Most emboli that go into an internal carotid artery from the heart or aorta, or arise from the carotid artery, travel into the ipsilateral middle cerebral artery. The embolus might rest first within the carotid artery in the neck or head and then pass into the proximal middle cerebral artery or its superior or inferior divisions, or into one of the smaller cortical branches. Occasionally, the embolus might go into other branches of the intracranial carotid artery, the anterior cerebral artery, or the anterior choroidal artery.

If an embolus goes into a vertebral artery in the neck or arises from an extracranial vertebral artery most often it will travel rostrally into the ipsilateral intracranial vertebral artery or go even further to reach the basilar artery bifurcation or into one or both posterior cerebral arteries or the superior cerebellar arteries located at the top-of-the basilar artery. If the embolus is large enough it could obstruct the basilar artery itself, leading to severe brainstem ischemia or infarction. A shower of emboli can block multiple arteries simultaneously or sequentially.



DONOR SOURCES AND THEIR EMBOLIC MATERIALS

The nature of the embolic material determines the most likely prophylaxis and treatment.

Cardiac Sources. Emboli that arise from the heart often consist of *red erythrocyte-fibrin thrombi* that form in the atria or on the surface of myocardial infarcts or within ventricular aneurysms. The most common sources of embolism from the heart are *arrhythmias*, especially atrial fibrillation. Red thrombi form in the inefficiently contracting, dilated left atrium and left atrial appendage; *valvular diseases* are also common sources. *White platelet-fibrin thrombi* form along irregular valvular surfaces and prosthetic valves. Many times, white thrombi form the nidus for a superimposed red

Brain Emboli *(Continued)*

thrombus so that both are involved in the thromboembolism. In patients with systemic lupus erythematosus, antiphospholipid antibody syndrome, and cancer, a nonthrombotic fibrinoid valvulitis develops and serves as a nidus for white clots. *Calcium* present in *calcific aortic valves* and in *mitral annulus calcifications* can break loose and embolize to the brain. *Bacteria and fungi* engrafted upon valves in patients with *infective endocarditis* can travel into the bloodstream and into the cranium, causing meningitis, brain abscesses, and infarcts as well as infecting arteries, causing mycotic aneurysms. Tumor tissue present in *cardiac myxomas* and *fibroelastomas* can form the matter of emboli.

In some patients, red thrombi originate in veins of the limbs and pelvis and embolize to the right heart and then pass through atrial septal defects or patent foramen ovale into the left atrium. They then embolize to the brain. This process is called *paradoxic embolism*. A similar process of right-to-left shunting also occurs in patients with arteriovenous fistulas in the lungs.

Similarly emboli arising from the aorta are composed of different substances. *White platelet-fibrin thrombi* form in crevices and irregular surfaces. These white clots activate the coagulation cascade and promote *red thrombi* to form on their surface. Red thrombi often form within ulcers or regions of plaque rupture. Red and white thrombi often break off and reach the brain. Large protuberant and mobile plaques often contain red thrombi. *Cholesterol crystals* within aortic plaques or other *complex plaque constituents* themselves can travel to the brain. *Calcium* may also be a component of aortogenic emboli.

Artery-to-artery emboli have the same basic components as those that arise from the aorta: calcium, cholesterol fragments, red and white clots, and so forth. Occasionally air, fat, and foreign materials enter the bloodstream and embolize to the brain and other viscera.

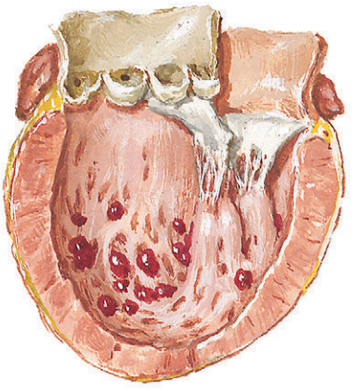
TREATMENT

Selection of treatment for acute embolic brain ischemia should consider the nature of the embolic material. Thrombolytic drugs, such as recombinant tissue plasminogen activator (rt-PA) can lyse red clots but are ineffective against white clots. Glycoprotein IIB/IIIA inhibitors that are active against platelet-fibrin bridges can potentially lyse white clots. These treatments are likely to be ineffective against calcium, cholesterol crystals, tumor fragments, infective agents, and foreign matter. Mechanical methods of retrieving emboli can snare different materials.

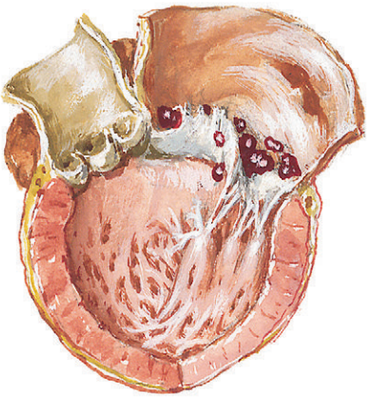
Similarly, prophylaxis against re-embolization (secondary prevention) must consider the nature of the embolic material. The most effective prophylaxes against embolism in patients with infective endocarditis are antibacterial and antifungal agents.

Secondary prevention also depends on the nature of the donor sources. Atrial fibrillation might respond to antiarrhythmics or cardiac conduction pathway ablation procedures. Intra-atrial septal abnormalities and defects can be repaired. Ventricular aneurysms can be resected. Abnormal valves can be repaired or replaced by prosthetic valves. Cardiac tumors can be removed. Surgeons have operated on protruding aortic atheromas, and in the future these lesions might be attacked by endovascular techniques. Arterial lesions are often repaired surgically or using endovascular technology in the form of angioplasty and/or stenting.

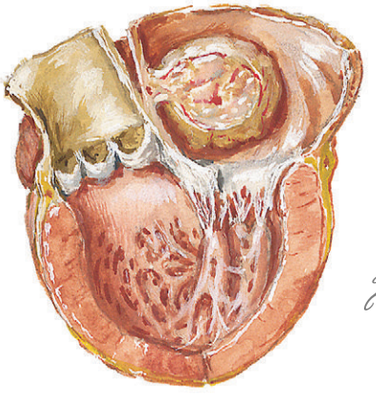
Uncommon Cardiac Mechanisms in Stroke



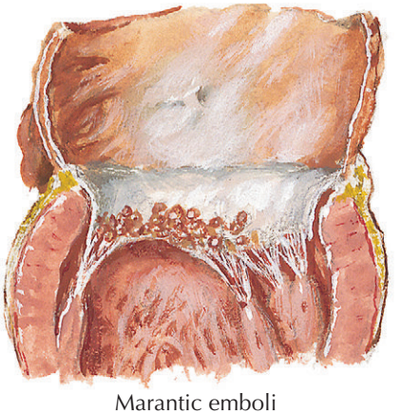
Myocardiopathy with thrombi



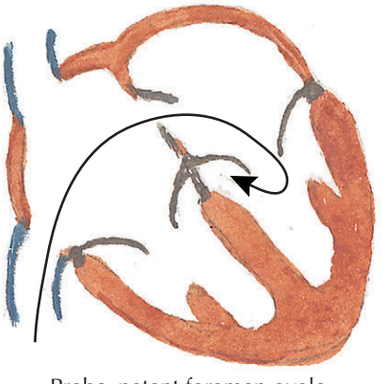
Mitral valve prolapse with clots



Atrial myxomatous tumor emboli



Marantic emboli



Probe–patent foramen ovale transmitting venous clots

Lacunar Stroke

Penetrating arteries are branches that supply the deeper portions of the brain. They take origin at nearly 90 degrees from their parent arteries. The most prominent of these vessels are: lenticulostriate branches of the middle cerebral arteries, Huebner's artery branches of the anterior cerebral arteries, thalamogeniculate branches of the posterior cerebral arteries, and paramedian basilar artery branches. These arteries bear much of the brunt of hypertension. Occlusion of these penetrating arteries causes lacunes—small deep infarcts.

Lacunar Infarcts

Lacunar infarcts are miniature, discrete lesions, ranging from 1 to 20 mm in size. The most common locations are the putamen and the pallidum, followed by the pons, thalamus, caudate nucleus, internal capsule, and corona radiata. Rarer are lacunes in the cerebral peduncles, pyramids, and subcortical white matter. Lacunes are not found in the cerebral or cerebellar cortices.

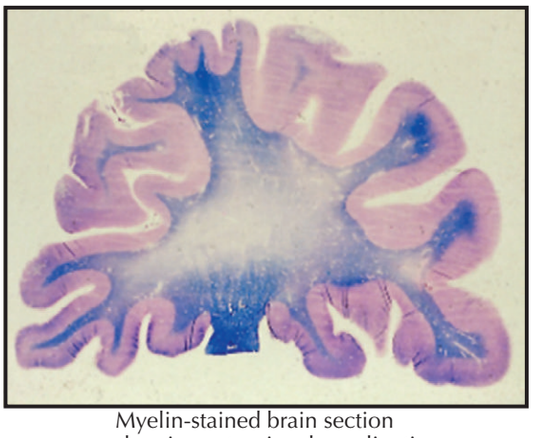
The two most common pathologies that affect penetrating arteries are *lipohyalinosis* and *atheromatous branch disease*. Serial sections of penetrating arteries that supply the territory of lacunar infarcts often have focal enlargements and small hemorrhagic extravasations through the walls of the arteries. Subintimal foam cells sometimes obliterate the lumens, and pink-staining fibrinoid material lies within vessel walls. Arterial segments are often replaced by whorls, tangles, and wisps of connective tissue that obliterate the usual vascular layers. This vascular pathology has been called segmental arterial disorganization, fibrinoid degeneration, and lipohyalinosis. Hypertension is the predominant pathophysiologic mechanism. The distribution of deep hypertensive hemorrhages is the same as the locations of lacunes (putamen, capsule, thalamus, and pons). Lipohyalinotic arteries could occlude, causing lacunar infarction, or rupture, causing intracerebral hemorrhage.

Intracerebral branch atheromatous disease also effects brain tissue supplied by penetrating arteries. In this condition, the orifices of penetrating arteries are blocked by atheroma in the parent artery. Atheroma could originate in the parent artery and extend into the branch, or microatheroma could arise at the origin of the branch itself. Thrombus is sometimes superimposed on the atheromas. This vasculopathy is sometimes referred to as microatheromatous disease. Pontine infarcts are the most frequent neuropathologic lesion found in necropsies of diabetics and, in most cases, are caused by atheromatous branch disease.

Two genetic conditions are also known to predominantly affect these small penetrating vessels: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and *COL 4*, *A1* mutations. In CADASIL, penetrating arteries contain a granular material in the media that extends into the adventitia. Smooth muscle cells in the media are swollen and often degenerated, and the endothelium may be absent and replaced by collagen fibers. This hereditary condition causes lacunar infarcts in the basal ganglia and cerebral white matter similar to those found in hypertensive patients.

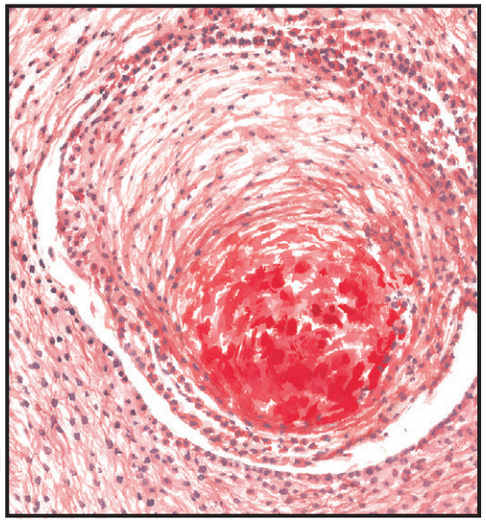
A hereditary angiopathic condition associated with mutations in a gene encoding procollagen type IV alpha 1 *(COL 4, A1)* effects small brain arteries as well as larger retinal and cerebral arteries. The clinical findings include perinatal hemorrhages and porencephaly, tendency to brain hemorrhage after trauma, retinal artery tortuosity, cerebral aneurysms, penetrating artery related infarcts, white matter gliosis, and kidney disease.

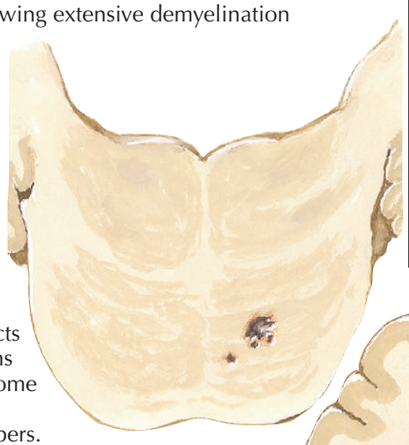
Lacunar Infarction



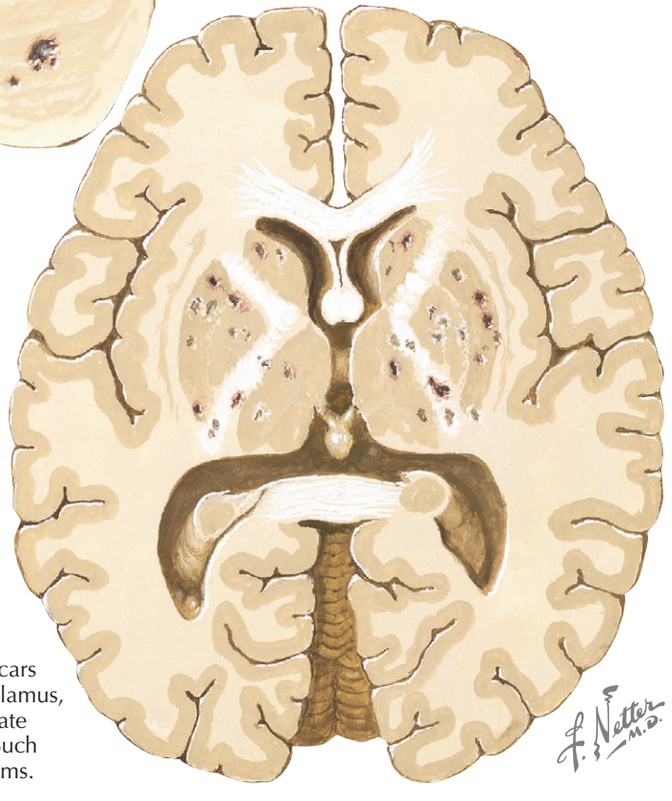
Myelin-stained brain section showing extensive demyelination

Small (100-μm) artery within brain parenchyma showing typical pathologic changes secondary to hypertension. Vessel lumen almost completely obstructed by thickened media and enlarged to about 3 times normal size. Pink-staining fibrinoid material within walls.





Lacunar infarcts in base of pons interrupting some corticospinal (pyramidal) fibers. Such lesions cause mild hemiparesis.



Multiple bilateral lacunes and scars of healed lacunar infarcts in thalamus, putamen, globus pallidus, caudate nucleus, and internal capsule. Such infarcts produce diverse symptoms.

LACUNAR STROKE *(Continued)*

Diagnosis. Intracerebral branch atheromatous disease can be imaged using high-resolution magnetic resonance imaging (MRI). Plaques in the middle cerebral artery and basilar artery can be shown to impinge upon or occlude penetrating branches by MRI techniques that show axial sections of the origins of branches from the parent arteries.

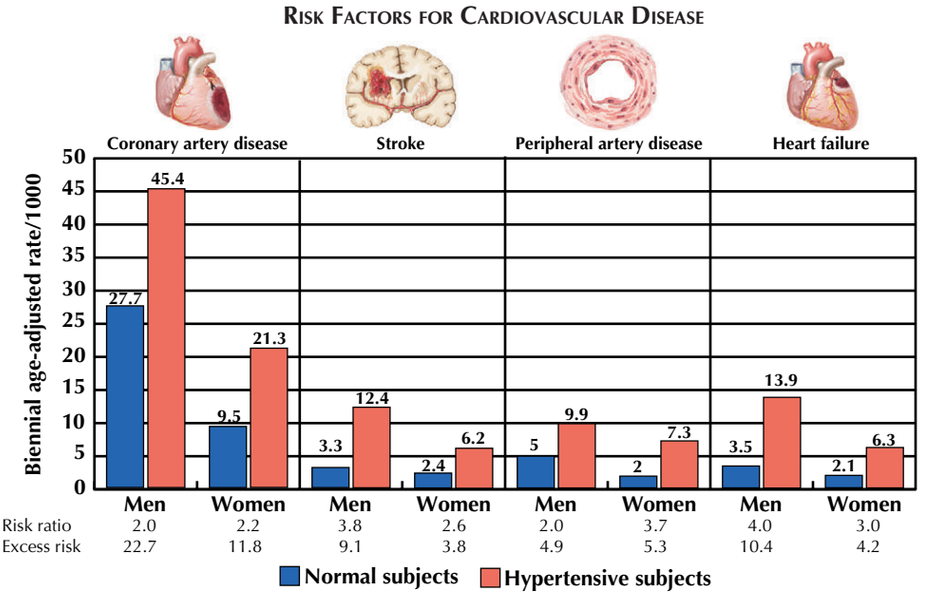
Differential. The major important condition to separate from these "micropathologies" is occlusion of parent arteries blocking flow in penetrating artery branches. In patients of Asian origin, especially Japan, Korea, and China, small deep infarcts are often caused by occlusive disease of the large intracranial parent arteries. When small deep infarcts are caused by severe occlusive disease of the intracranial large parent arteries, the infarcts are slightly larger, the neurologic signs are slightly worse, and recurrence is more common than in infarcts caused by intrinsic disease of the penetrating arteries.

Clinical Presentations. The most common clinical syndromes caused by lacunar infarction are *pure motor hemiparesis* (weakness of face, arm, and leg on one side of the body with no sensory, visual, or cognitive abnormalities; *pure sensory stroke* (hemisensory loss without other signs); *dysarthria–clumsy hand* syndrome; and *ataxic hemiparesis*.

CHRONIC SUBCORTICAL VASCULAR DISEASE

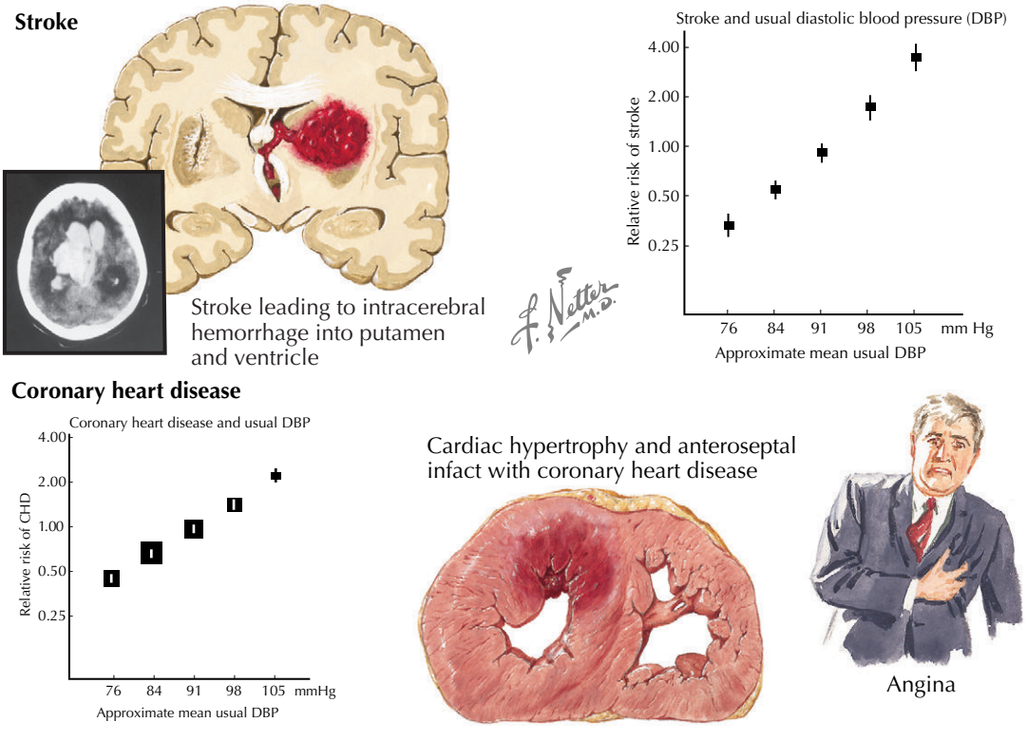
Multiple lacunes, white matter gliosis, and atrophy almost always occur together and are accompanied by widespread abnormalities of penetrating small arteries. When severe and clinically evident, this chronic microvasculopathy is often called Binswanger disease. In this condition, the cerebral white matter has confluent areas of soft, puckered, and granular tissue. These areas are patchy and predominate in the occipital lobes and periventricular white matter, especially anteriorly and near the ventricular surface. The cerebellar white matter is also often involved. The ventricles are enlarged, and at times, the corpus callosum is small. The volume of white matter is reduced, but the cortex is generally spared. There are nearly always some lacunes. Microscopic study shows myelin pallor. Usually, the myelin pallor is not homogeneous, but islands of decreased myelination are surrounded by normal tissue. Gliosis is prominent in zones of myelin pallor. The walls of penetrating arteries are thickened and hyalinized, but occlusion of the small arteries is rare. Occasional patients with Binswanger white-matter changes have had amyloid angiopathy and CADASIL as the underlying vascular pathology. In these patients, arteries within the cerebral cortex and leptomeninges are thickened and contain a congophilic substance.

The clinical picture in patients with Binswanger white matter abnormalities is variable. Most patients have abnormal cognitive function and behavior. Most become slow and abulic. Memory loss, aphasic abnormalities, and visuospatial dysfunction are also found. Pseudobulbar palsy, pyramidal signs, extensor plantar reflexes, and gait abnormalities are common. The clinical findings often progress gradually or stepwise, with worsening during periods of days to weeks. Often, there are plateau periods with relative clinical stability. Many patients also have acute lacunar strokes that present clinically with hemiparesis. MRI defines the full extent of white matter involvement and has spatial resolution that allows detection of small lacunar lesions. Diffusion-weighted imaging can show even small acute and subacute infarcts with great accuracy.



*According to hypertensive status in subjects 35–64 years of age from the Framingham at 36-year follow-up.
Adapted from Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. *JAMA* 1996; 275:1571–1576.

Level of blood pressure is associated with cardiovascular events in a continuous, graded, and apparently independent fashion**



** Relative risk of stroke and coronary heart disease as a function of usual diastolic pressure in 420,000 individuals 25 years or older with a mean follow-up period of 10 years. Adapted from MacMahon S, Peto R, Cutter S, et al. Blood pressure, stroke, and coronary heart disease: part one. *Lancet* 1990;335:765-767.

Hypertensive Encephalopathy

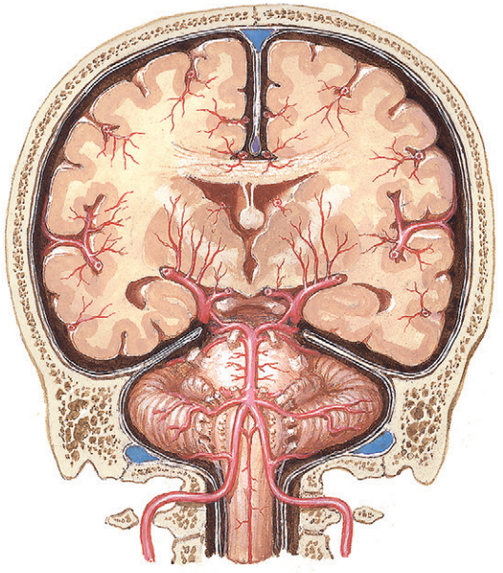
Hypertensive encephalopathy refers to the consequences for brain function associated with severe and acute rises in systemic blood pressure. The effects of severe hypertension involve a variety of clinical features, including generalized tonic-clonic seizures, decreased level of consciousness, cortical blindness, and the funduscopic features of hypertensive retinopathy or "malignant" hypertension. This clinical picture has an imaging correlate in computed tomography (CT) scan and, especially magnetic resonance imaging (MRI) in the form of abnormal signal that especially involves the white matter of the cerebral hemispheres, predominantly posteriorly; because these changes tend to be reversible after normalization of blood pressure, the initial imaging correlate of hypertensive encephalopathy was initially labeled the *posterior reversible leukoencephalopathy syndrome*.

The MRI features of the syndrome are characterized by vasogenic edema, which corresponds to bright signal on diffusion-weighted imaging (DWI) sequences as well as on apparent diffusion coefficient (ADC) maps, the latter differentiating vasogenic edema from infarction, because the latter is expected to show decreased signal to accompany the bright signal on DWI. These features are generally reversible, the same as the clinical manifestations, including cortical blindness. The features of the *posterior reversible leukoencephalopathy syndrome* demonstrate substantial variability, because the MRI changes can also have an *anterior location*, with *gray*, as well as white matter involvement, and there may be only *partial reversibility*.

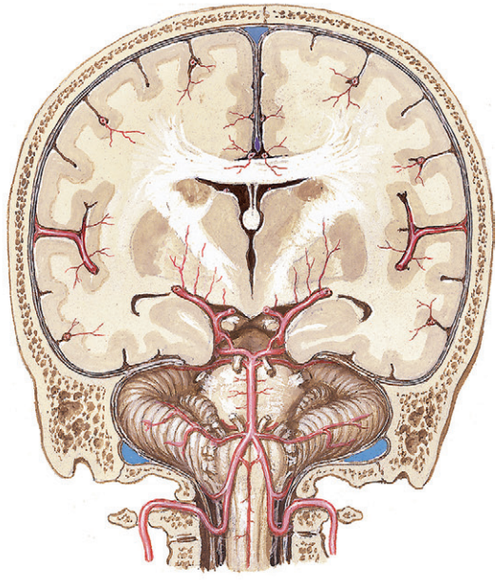
An important aspect of this disorder that needs to be emphasized is that hypertensive encephalopathy is not a function of the absolute levels of systemic blood pressure elevation but rather of the percentage increase in blood pressure based on the individual patient's baseline blood pressure. Thus a normotensive person can present with hypertensive encephalopathy after a modest blood pressure elevation, whereas a chronic hypertensive patient may require a severe blood pressure elevation in order to develop the syndrome. Although the majority of patients experience clinical recovery with concomitant resolution of the imaging changes after blood pressure control, there is the potential for persistent deficits to occur as a result of concomitant intracerebral bleeding into the areas of the brain affected by the encephalopathy.

There are a number of clinical as well as imaging variations in patients presenting with hypertensive encephalopathy. One that is occasionally seen is a syndrome predominantly affecting the brainstem and cerebellum, with presentation with headache, nausea, and vomiting, as well as mild and nonspecific brainstem signs, such as gait disturbance, in the setting of florid vasogenic edema, at times involving the whole extent of the brainstem. In some instances, the patient may actually not have any clinical signs of brainstem involvement while having florid vasogenic edema in that area; this highlights the fact that the imaging changes reflect edema, not infarction.

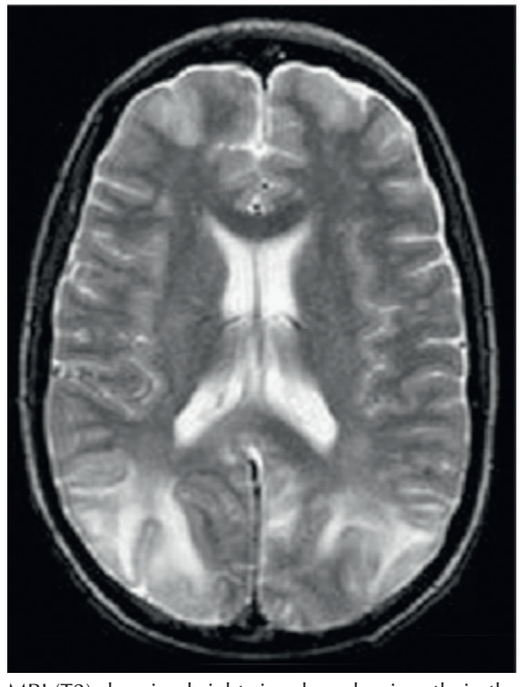
The pathogenesis of the clinical-radiologic syndrome of hypertensive encephalopathy is thought to reflect the effects of an acute increase in blood pressure, leading to fibrinoid necrosis of the arterial wall with increase in the permeability of the blood-brain barrier and loss of cerebral autoregulation, with the end result of formation of vasogenic edema. It is still unclear why most instances predominantly involve the posterior aspects of the cerebral hemispheres. The prevailing theory is that the posterior cerebral circulation has less sympathetic innervation than the anterior circulation, thus making it more prone to vasodilation with development of cerebral edema in the event of a sudden increase in systemic arterial pressure.



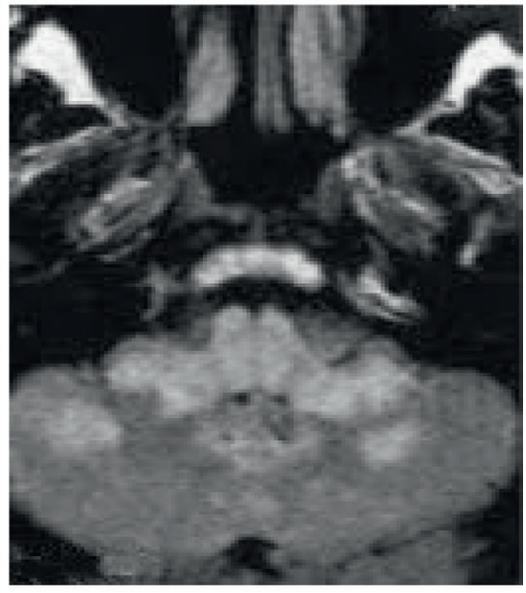
Normal brain



Hypertensive encephalopathy, with generalized constriction of cerebral arteries and their small branches



MRI (T2) showing bright signal predominantly in the white matter of the posterior aspect of both cerebral hemispheres in a patient with posterior reversible encephalopathy syndrome



Diffusely increased signal in MRI (FLAIR sequence) in medulla and cerebellum in patient with posterior reversible encephalopathy syndrome restricted to the posterior fossa structures. *Reprinted with permission from Karakis I, MacDonald JA, Stefanidou M, Kase CS. Clinical and radiological features of brainstem variant of hypertensive encephalopathy. J Vasc Interv Neurol 2009;2:172-176.*

Hypoxia

The brain is especially vulnerable to any decrease in its blood, oxygen, or fuel supply. Patients with hypotension or hypoxia often present to their physicians or the emergency room because of brain dysfunction. Most often, decreased brain perfusion is caused by cardiac disease, either arrhythmia or pump failure often caused by an acute myocardial infarction. Shock and hypovolemia also decrease whole brain perfusion. Because circulatory failure usually leads to hypoventilation, and hypoxia soon causes diminished cardiac function, hypoxia and hypoperfusion are usually combined. The general term hypoxic-ischemic encephalopathy reflects the dual nature of the central nervous system stress. Pulmonary embolism is another acute disorder that causes hypotension and diminished blood oxygenation. In some patients, decreased cerebral perfusion is caused by acute blood loss or hypovolemia, or shock related to sepsis.

Globally decreased cerebral perfusion causes generalized nonfocal brain dysfunction. Dizziness, lightheadedness, confusion, and mental concentration difficulty are common. Focal symptoms and signs, such as hemiplegia, hemianopia, and aphasia, are rarely present. At times, prior strokes or vascular occlusions may contribute to asymmetric signs. Patients with globally decreased cerebral perfusion often appear ill with sweating, tachycardia, and hypotension. Prolonged severe hypotension causes coma; initially, the patients often have no remaining brainstem reflexes (pupillary, corneal, oculovestibular).

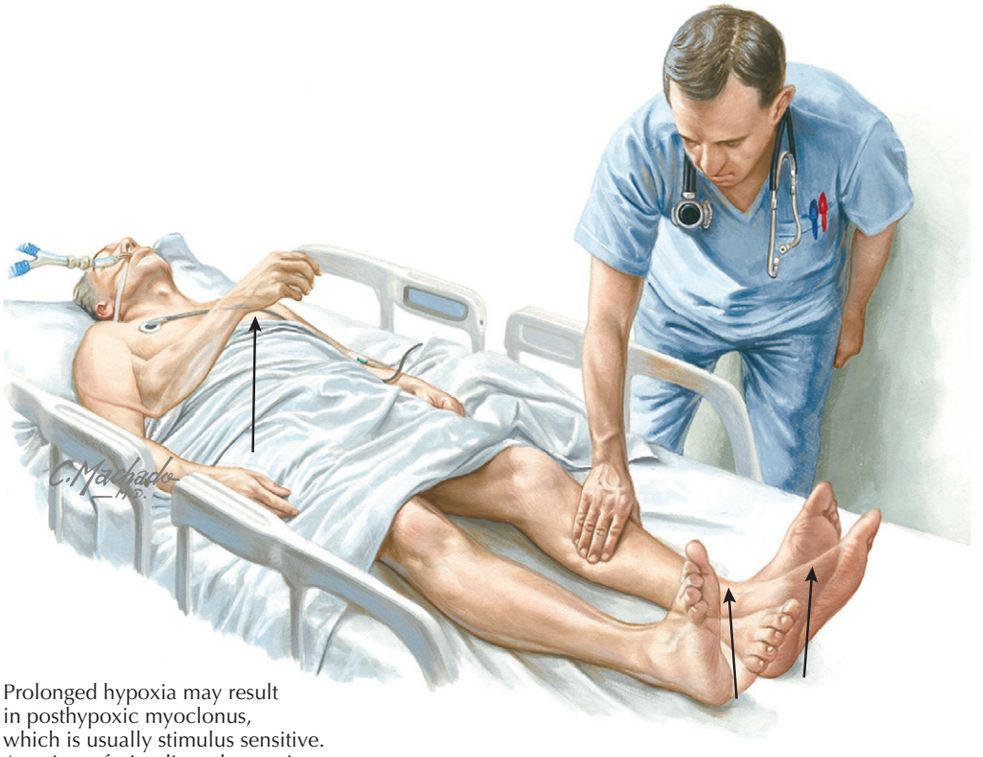
When and if coma clears, or hypotension is less severe, abnormalities of cortical function-memory, vision, and behavior predominate.

The hippocampi are particularly vulnerable to ischemia; therefore memory loss is particularly common. The border zone cerebral cortex located between the middle cerebral arteries and the anterior and posterior cerebral arteries are often rendered ischemic. The posterior border zone between the middle cerebral artery and the posterior cerebral arteries territories are most often involved, possibly because these regions are farthest from the heart.

Lesions in the posterior border zones can disconnect the preserved calcarine visual cortex in the occipital lobe from the more anterior centers that control eye movements. A visual problem called *Balint syndrome*, often results. Patients act as if they cannot see but sometimes surprisingly notice small objects. The features of *Balint syndrome* are (1) *asimultagnosia:* patients see things piecemeal that is, do not see all the objects in their field of vision at one time and may notice only parts of objects, (2) *optical ataxia:* patients cannot coordinate hand and eye movements and point erratically at objects; and (3) *gaze apraxia:* patients cannot direct their gaze where desired.

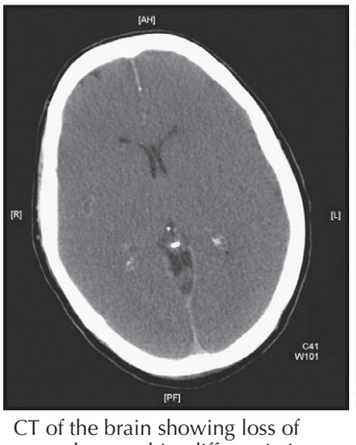
When hypotension is more severe, lesions can spread to the anterior border zones between the anterior cerebral artery and the middle cerebral artery. The areas of the motor homunculus most affected are those related to the shoulder, arm, and thigh. The face territory in the central portion of the middle cerebral artery territory and the foot region in the center of the anterior cerebral artery supply are spared. The distribution of weakness has been likened to a "man in a barrel." The frontal eye fields are also affected so that roving eye movements and hyperactive passive head movements (doll's eye reflexes) result. Stupor results from extensive bilateral border-zone ischemia.

Myoclonus status epilepticus

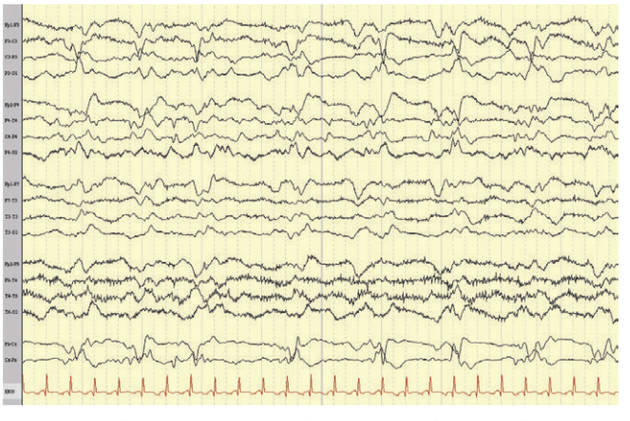


Prolonged hypoxia may result in posthypoxic myoclonus, which is usually stimulus sensitive. A variety of stimuli, such as noise, light, and touch, can provoke this type of myoclonus in multiple areas of the body. Therapeutic hypothermia is recommended after cardiac arrest.

Hypoxic-ischemic encephalopathy (HIE)



CT of the brain showing loss of normal gray-white differentiation



Electrocardiogram of the same patient showing rhythms, which are slow and disorganized

When hypoperfusion is severe and prolonged, diffuse anoxic damage to cerebral, brainstem, and cerebellar neurons occurs. The most severe damage may occur in the large cell regions of the cerebral cortex, producing a *laminar necrosis* pattern. Severe hypoxic-ischemic damage causes *coma* and *brain death*. In some patients, partial recovery leaves the patients in a *minimally conscious state* or a *persistent vegetative state* in which there is no or minimal communication.

Although hypoxic-ischemic cerebellar damage is often found at necropsy, clinical signs of cerebellar dysfunction are rare and are usually overshadowed by cerebral abnormalities. After cardiac arrest, some patients have spontaneous arrhythmic fine or coarse muscle jerking, markedly exaggerated when the limbs are used. This disorder of limb movements is usually referred to as *action myoclonus* or the *Lance-Adams syndrome* and is often accompanied by gait ataxia.

Very occasionally, a delayed progressive deterioration develops after a single hypoxic insult. In other rare instances, patients recover from coma without obvious cerebral damage but instead have paraplegia related to *hypoxic-ischemic damage to the spinal cord*. The most vulnerable spinal regions are the upper and lower thoracic and lumbar spinal cord segments. The cervical cord is usually not involved so that the arms are normal despite severe weakness of the lower limbs.

COAGULOPATHIES

ROLE OF PLATELETS IN ARTERIAL THROMBOSIS

Normal hemostasis depends on an intricate balance between prothrombotic and antithrombotic processes, with the goal of maintaining normal blood flow and the structural integrity of the vasculature. These processes are mediated by cellular components, soluble plasma proteins, and endothelium-derived factors. Any stimulus that perturbs the normally antithrombogenic nature of the vascular system, such as the rupture of an atherosclerotic plaque, exposes subendothelial tissue elements and initiates a hemostatic response. The first defense after vascular injury, denoted primary hemostasis, consists of platelet–blood vessel interactions that lead to physiologic platelet plug formation. Platelets are produced by multinucleated megakaryocytes in the bone marrow and released into the peripheral blood, where they exist for approximately 7 to 10 days. These non-nucleated, discoid cell fragments normally circulate individually and in an unactivated state. Platelet activation and aggregation are suppressed by products of the normal endothelium, mainly nitric oxide, prostacyclin, and the more recently described ecto-adenosine di(tri)phosphatase AD[T]Pase (CD39).

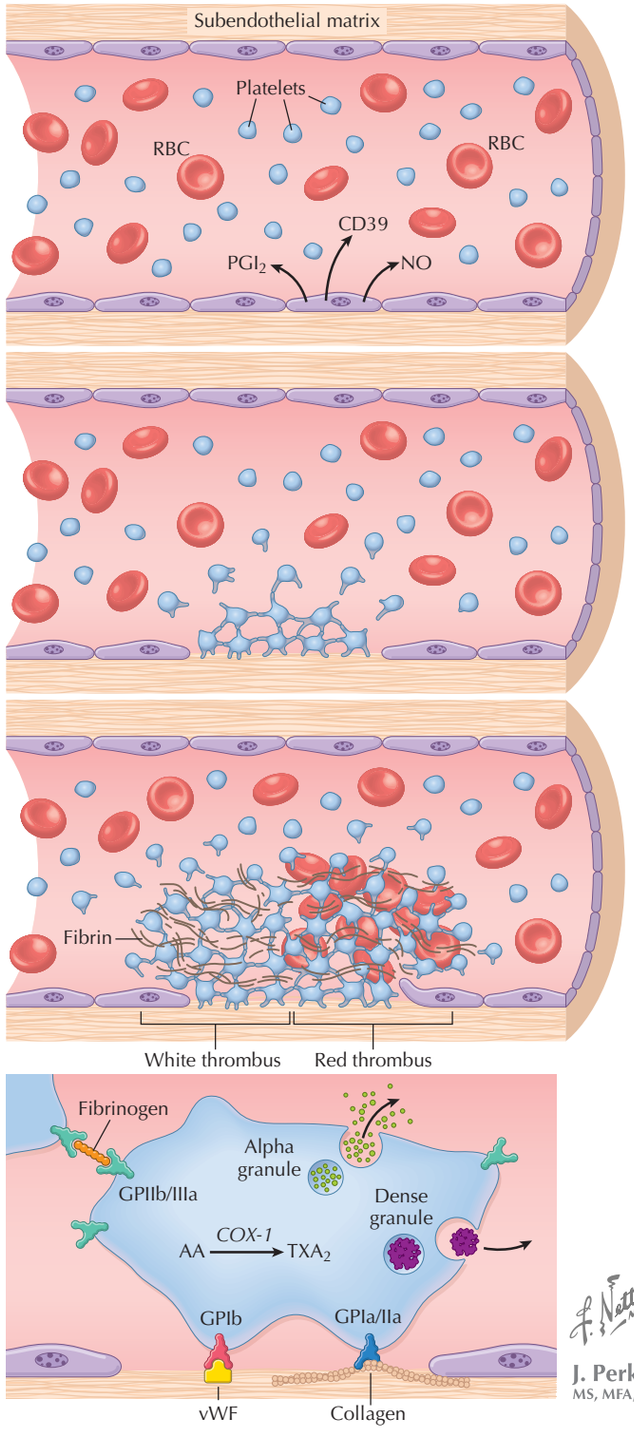
The exposure of subendothelial matrix leads to almost instantaneous adhesion of platelets to the site of vascular injury. Two molecules in the subendothelium are critical to this step: von Willebrand factor (vWF) and collagen. Platelets bind to vWF and collagen fibrils via the receptors glycoprotein (GP) Ib and Ia/IIa, respectively. This receptor-ligand interaction starts the process of platelet activation; it triggers a series of intracellular signaling events that result in cytoskeletal rearrangement, shape change, and release of alpha and dense granules. These storage granules contain substances, such as adenosine diphosphate (ADP), serotonin, fibrinogen, and thrombospondin, that promote aggregation and recruitment of additional platelets to the growing hemostatic plug. In addition, thromboxane A_2, formed after cyclooxygenase cleavage of arachidonic acid and released during platelet activation, is both a potent platelet agonist and vasoconstrictor.

The platelet receptor GPIIb/IIIa then undergoes a calcium (Ca^{++})-dependent conformational change that allows it to bind to additional vWF and circulating fibrinogen. GPIIb/IIIa is the most abundant glycoprotein on the platelet surface, with approximately 50,000 copies expressed on resting platelets, and additional GPIIb/IIIa receptors within the cytosol that are mobilized to the surface after activation. Fibrinogen can simultaneously bind two GPIIb/IIIa receptors, thereby linking neighboring platelets. This results in platelet aggregation, formation of a fibrin network, and ultimately stabilization of the mass into a *white thrombus*. Red blood cells eventually become enmeshed in the platelet-fibrin aggregate and produce a more fully formed *red thrombus*. Aggregated platelets then provide cell-surface phospholipid for the assembly of coagulation factor complexes, forming a link with the processes of secondary hemostasis.

Platelets are particularly relevant in the high-pressure arterial circulation, where minor vascular damage can rapidly lead to major hemorrhage. The hemostatic system must therefore promptly control bleeding. Platelets assume a critical role in this response, because they initially contain blood loss and, as a second step, provide an active surface for rapid fibrin and, ultimately, clot formation. In contrast, in the low-pressure venous circulation, platelets are less relevant as the pivotal reaction controlling hemostats is the rate of thrombin generation.

These pathophysiologic differences define the antithrombotic or anticoagulant agents used in each situation. Antiplatelet agents are the treatment of choice to prevent coronary artery disease or arterial ischemic stroke, whereas antithrombin-based interventions, such as heparin and warfarin, are used for prophylaxis and treatment of systemic and cerebral venous thrombosis. Aspirin is an irreversible inhibitor of platelet cyclooxygenase-1 (COX-1) activity, thereby blocking thromboxane A_2 formation for the lifetime of that platelet. Clopidogrel inhibits platelet activation and aggregation through the irreversible binding of its active metabolite to the ADP receptors on platelets, preventing activation of the GPIIb/IIIa receptor. Dipyridamole inhibits platelet phosphodiesterase, thereby raising cyclic adenosine monophosphate (cAMP) levels, thus interfering with platelet aggregation. Nonsteroidal anti-inflammatory drugs (NSAIDs) bind to COX-1 reversibly and competitively, and thus their effects are dependent on plasma levels of the drug, unlike aspirin.

ROLE OF PLATELETS IN ARTERIAL THROMBOSIS



Platelets circulate individually and in an unactivated form. The intact vascular endothelium produces nitric oxide (NO), prostacyclin, and CD39, substances that inhibit platelet activation and aggregation.

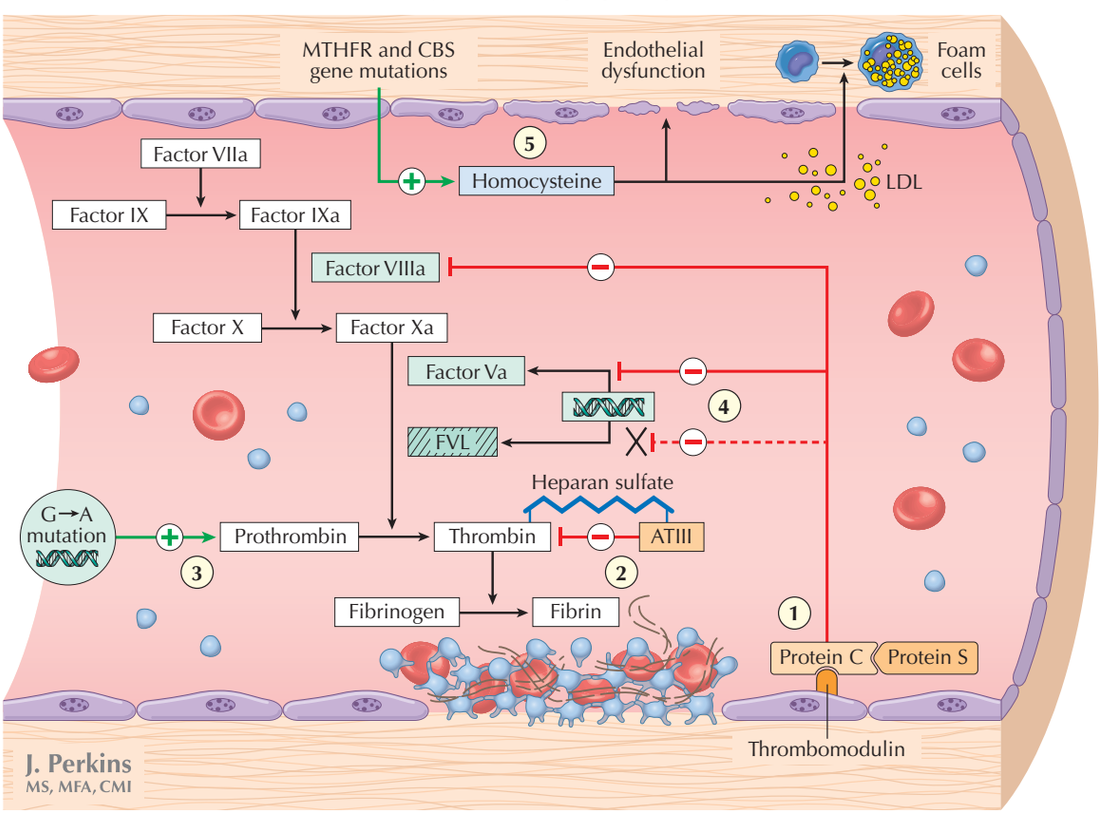
If endothelial integrity is interrupted, for example by atherosclerosis or trauma, exposure of subendothelial matrix triggers a hemostatic response with rapid adhesion of platelets to the injured vessel wall. Platelets then release thromboxane A_2 and products of their storage granules that lead to aggregation and recruitment of additional platelets.

As more platelets aggregate, a fibrin network develops and stabilizes the mass into a "white thrombus." If the thrombus develops further, red blood cells become enmeshed in the platelet-fibrin aggregate to form a "red thrombus," which can grow and block the vessel lumen. Either platelet-fibrin aggregates or more fully formed clots may break off, leading to embolization in distal arteries.

Platelets attach to the injured endothelium (adhesion) and to other platelets (aggregation) via specific surface glycoproteins. During platelet activation, cyclooxygenase converts arachidonic acid into thromboxane A_2 (TXA_2), a strong platelet agonist and vasoconstrictor. The content of alpha and dense granules is released, contributing to further growth of the platelet plug.

F. Netter M.D.

J. Perkins
MS, MFA, CMI



COAGULOPATHIES *(Continued)*

INHERITED THROMBOPHILIAS

Patients with unexplained arterial and venous thrombotic events require investigation for hypercoagulable states. Individuals with increased tendency to thrombosis are designated as having *thrombophilia*, either acquired (e.g., antiphospholipid antibody syndrome) or inherited due to genetic defects in protein compounds directly or indirectly involved with hemostasis. Clinically, inherited thrombophilia is characterized by one or more of the following: (1) thrombotic events occurring before age 45 to 50 years; (2) spontaneous, recurrent, or life-threatening events; (3) thrombosis occurring at unusual sites, including the central nervous system; and (4) family history of thromboembolic events.

Secondary hemostasis, or blood coagulation, is initiated by interaction of blood with vascular subendothelium or tissue factor exposed on cell surfaces after cellular injury. Intrinsic and extrinsic coagulation pathways converge through a series of steps to form a common pathway, ultimately leading to thrombin generation. The coagulation cascade rapidly transduces small initiating stimuli into large fibrin clots. Endogenous anticoagulant mechanisms offset the potentially explosive nature of this cascade by carefully regulating extent of coagulation serine protease generation. The natural anticoagulants permit coagulation to proceed locally while preventing it from becoming a systemic process. Congenital and acquired hypercoagulable states arise when imbalance develops between prothrombotic and anticoagulant plasma activities in favor of thrombosis. In most inherited thrombophilias, genetic variations of proteins regulating hemostasis ultimately lead to increased generation, or impaired neutralization of thrombin, predisposing to thrombotic events. Hypercoagulable states are more clinically relevant as causes of venous thromboembolism (VTE) than thrombotic arterial disease.

Antithrombin III, Protein S, and Protein C Deficiencies. These are the three most important natural anticoagulants. Antithrombin III (ATIII) inhibits the activity of several serine proteases of intrinsic and common coagulation pathways, particularly thrombin. In the presence of heparin sulfate, the rate of inactivation is increased by several 1000-fold. Protein C and protein S form the second regulatory system. When linked to the endothelial membrane protein thrombomodulin, thrombin activates protein C, which, in turn, cleaves factors VIIIa and Va. Protein S serves as a cofactor accelerating this reaction. Although gene mutations in these natural anticoagulants are uncommon, when present they lead to venous and arterial thrombosis in early adulthood. If these occur in homozygosity, severe thrombogenesis occurs during infancy and childhood that is often incompatible with life.

Factor V Leiden (FVL). This is the most common genetic defect related to venous thrombosis, present in 10% to 50% of affected individuals. Worldwide carrier frequencies range from 1% to 15%; it is highly prevalent among Caucasians. This point mutation in the coagulation factor V gene renders the mutant factor V resistant to proteolytic degradation by activated protein C, a characteristic denominated activated protein C resistance. This leads to increased thrombin generation and a procoagulant state. FVL heterozygosity increases VTE risk threefold to eightfold; homozygosity is associated with a 50 to 100 times higher risk. Its role in arterial thrombosis is debated. Because it interacts synergistically with smoking, oral contraceptives, and other inherited thrombophilias, it is a potential risk factor for ischemic stroke in young patients with additional vascular risk factors.

Prothrombin Gene Mutation. Prothrombin is a vitamin K–dependent zymogen that in its activated form (thrombin) converts fibrinogen into fibrin. A prothrombin gene G-to-A substitution in the 3′-untranslated region is associated with elevated plasma prothrombin levels and increased thrombotic risk. This is the second most common inherited thrombophilia; it leads to a twofold to fivefold increased VTE risk. The prevalence of heterozygosity is 2% in Caucasians. The relationship with arterial thrombosis and stroke remains controversial; although this mutation is associated with a moderate increase in arterial thrombotic disease, it assumes particular importance in certain subgroups, including young women taking oral contraceptives and children.

Hyperhomocysteinemia. Homocysteine is a sulfur-containing amino acid formed as an intermediary compound during methionine metabolism and metabolized by both remethylation and trans-sulfuration. Vitamins B_{12}, B_6, and folate are essential cofactors in these pathways. Plasma homocysteine elevations can be caused by genetic (mutations in the methylenetetrahydrofolate reductase [MTHFR] and cystathionine β-synthase [CBS] genes), nutritional (vitamin B and folate deficiencies), and acquired factors (e.g., renal failure). Deleterious effects of hyperhomocysteinemia include endothelial dysfunction, platelet activation, and arterial and venous thrombus formation. Nutritional factors and homozygosity of the MTHFR polymorphism lead to mild forms of hyperhomocysteinemia with modestly increased thrombotic risk. CBS gene mutations lead to severe hyperhomocysteinemia manifested clinically with premature, severe atherosclerosis, early thromboembolic events, mental retardation, skeletal deformities, and ectopia lentis.

COAGULOPATHIES *(Continued)*

ANTIPHOSPHOLIPID ANTIBODY SYNDROME

The antiphospholipid antibody syndrome (APS), also known as Hughes syndrome, is an acquired autoimmune prothrombotic condition characterized clinically by the presence of vascular thrombosis and/or recurrent fetal loss during pregnancy associated with laboratory evidence of antibodies directed against phospholipids or phospholipid-binding proteins. The most commonly detected subgroups of antiphospholipid antibodies are lupus anticoagulant (LA), anticardiolipin antibodies (aCL), and anti–β2-glycoprotein-1 (anti–β2-GP1). The disorder can be primary or secondary to another major autoimmune disease, most commonly systemic lupus erythematosus. This is one of few conditions that can manifest with both arterial and venous thromboembolism, and can affect both large and small vessels. Increasingly, microthrombotic disease is being recognized as a manifestation of APS, in particular in the form of renal thrombotic microangiopathy.

The cardinal features of APS include thrombotic manifestations, recurrent fetal loss, and thrombocytopenia. Cardiac valvular abnormalities, livedo reticularis, and hemolytic anemia are additional common findings. Patients are typically 35 to 45 years old when they develop their first thrombotic event. Men and women are equally affected. Almost two thirds of patients have thrombi limited to the venous system, 20% to 30% are arterial, and in 10% to 15% of individuals both circulations are affected. Most patients present with deep vein thrombosis of the lower extremities, up to half of whom subsequently develop pulmonary emboli. Thrombosis can also affect the superficial and deep cerebral venous system, and typically does so at a young age with relatively more extensive involvement.

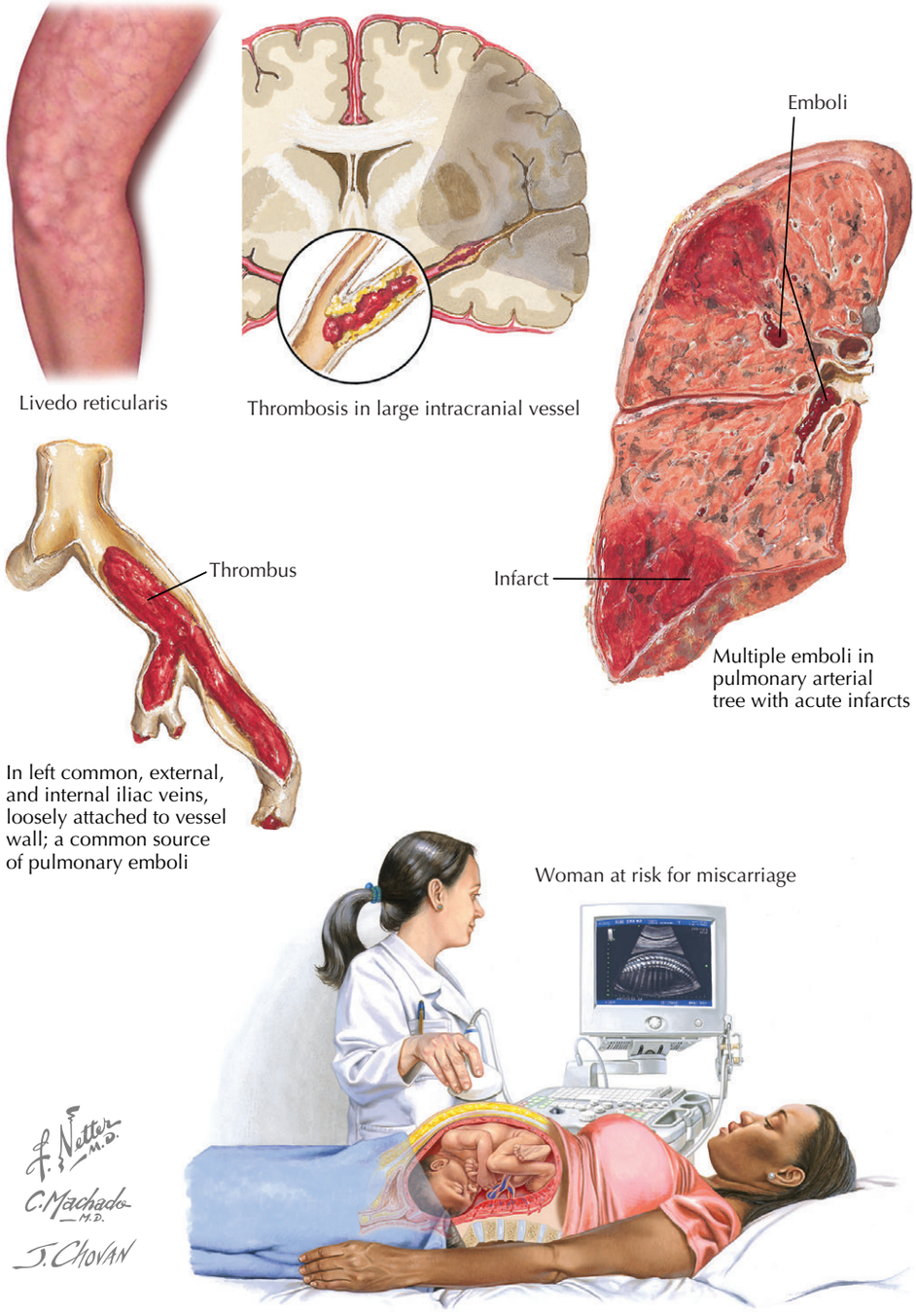
Ischemic stroke and transient ischemic attacks are the most common presentation of APS arterial disease. This occurs in approximately one fifth of patients, followed by myocardial infarction at about half this frequency. Most of these events are clinically indistinguishable from atherosclerotic or small vessel strokes, therefore requiring a high level of suspicion. The syndrome should be suspected in young patients with ischemic stroke whenever other atypical vascular beds are involved, particularly the subclavian, renal, or retinal arteries, or when a patient experiences recurrent thromboembolic events with no defined etiology. Of note, not all arterial episodes are thrombotic in origin. Emboli, especially from mitral valve or aortic valve vegetations, can lead to cerebral events. Paradoxic embolization through a patent foramen ovale may occur. The association of livedo reticularis with cerebral thrombosis characterizes the Sneddon syndrome. The most severe and fortunately infrequent form of APS is a catastrophic one wherein patients develop multiorgan failure subsequent to widespread thrombotic disease. The mortality rate is greater than 50%.

The mechanisms by which antiphospholipid antibodies induce thrombosis are not entirely appreciated. It is postulated that these antibodies interfere with endogenous anticoagulant pathways, bind and activate platelets, and lead to activation of the complement cascade. Thrombosis in APS may occur spontaneously or in the setting of predisposing factors, including smoking, oral contraceptive use, vascular stasis, surgery, or trauma. Women are at particularly high risk for venous thromboembolism during pregnancy and their postpartum period. Some patients, generally those with venous rather than arterial thrombosis, also have concurrent genetic thrombophilic conditions. There is no definitive association between specific clinical manifestations and particular subgroups of antiphospholipid antibodies. However, the risk for recurrence after a first episode of venous thromboembolism in the presence of aCL is particularly high (approximately 30%); this correlates with the antibody titer.

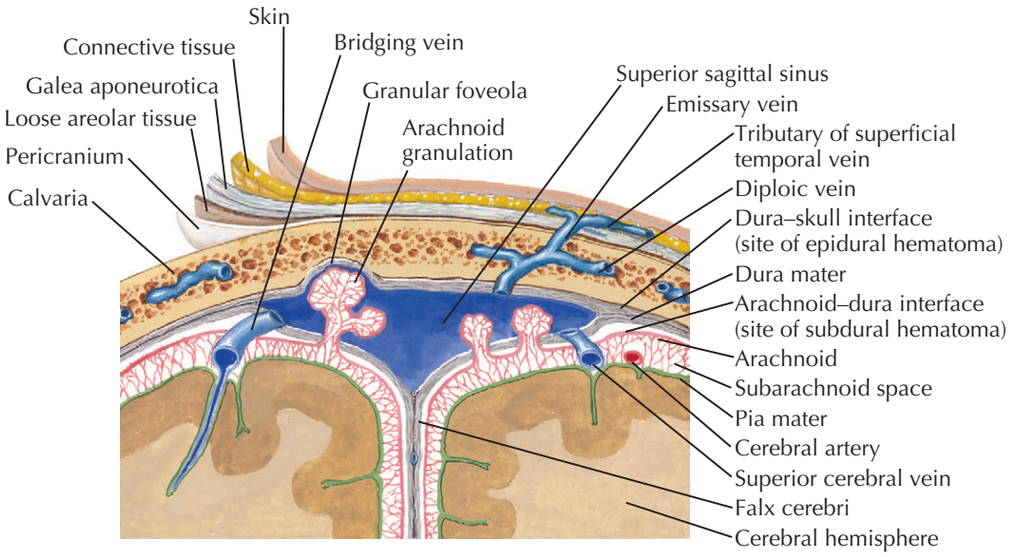
The diagnosis of APS is made by combining clinical features with laboratory evidence of medium- or high-titer circulating antiphospholipid antibodies that are identified to be present on two or more occasions at least 12 weeks apart. The antibodies can be of either IgG or IgM subtypes and are measured by a standard enzyme-linked immunosorbent (ELISA). The term lupus anticoagulant is a misnomer that resulted from the early observation that its presence can prolong the partial thromboplastin time (PTT). An abnormal PTT should not be used as a screening test for APS. However, patients with APS need to be screened for possible concomitant systemic lupus erythematosus (SLE).

Given the high risk of recurrent thromboembolism that characterizes this condition, the mainstay of treatment in patients with APS is antithrombotic therapy. Warfarin is the usual drug of choice, with the international normalized ratio (INR) often kept in the upper range for anticoagulation (i.e., INR 3.0-4.0). The addition of aspirin may also need to be considered. Because thrombocytopenia is a frequent finding in patients with APS, therapy must be carefully balanced against the bleeding risks associated with a low platelet count.

ANTIPHOSPHOLIPID ANTIBODY SYNDROME



Meninges and Superficial Cerebral Veins



Venous Sinus Thrombosis

Venous Sinuses of the Dura Mater

Located between the two layers of the dura mater, the venous sinuses are divided into a posterosuperior group within the upper and posterior skull and an anteroinferior group situated at the base of the skull, consisting of paired sinuses and plexuses.

Posterosuperior Group

Superior Sagittal Sinus (SSS). The superior sagittal sinus traverses the superior margin of the falx cerebri, gradually increasing in dimension as it passes posteriorly, receiving superior cerebral veins and veins from the pericranium, the diploe, and dura mater. Its anterior portion is occasionally absent, replaced by two veins converging behind the coronal suture. The SSS terminates near the occipital protuberance and joins the straight sinus to form the *confluence of sinuses* (*torcular herophili*).

Inferior Sagittal Sinus (ISS). The inferior sagittal sinus traverses the posterior two thirds of the lower falx cerebri margin; this becomes larger as it receives veins from the falx and cerebral hemisphere's medial surfaces to join the *great cerebral vein of Galen*, forming the straight sinus.

Straight Sinus. The straight sinus is located at the falx cerebri junction with the tentorium cerebelli, receiving superior cerebellar veins to terminate and join the confluence of sinuses. It is usually a single channel, although occasionally doubled or tripled.

Transverse Sinuses *(bilateral; usually of unequal size).* The transverse sinuses are at the internal occipital protuberance, where usually the right side is the direct ***SSS*** continuation, whereas the other derives from the *straight sinus.* Each becomes larger running anterolaterally within the tentorium cerebelli margin, receiving the *superior petrosal sinuses*, and inferior cerebral, cerebellar, diploic, condyloid, and mastoid veins. These leave the tentorium, entering the jugular foramen as the *sigmoid sinus.*

Sigmoid Sinuses. Sigmoid sinuses are continuations of the *transverse sinuses* situated over the temporal mastoid bones. These terminate at the jugular foramens, draining into the internal jugular veins.

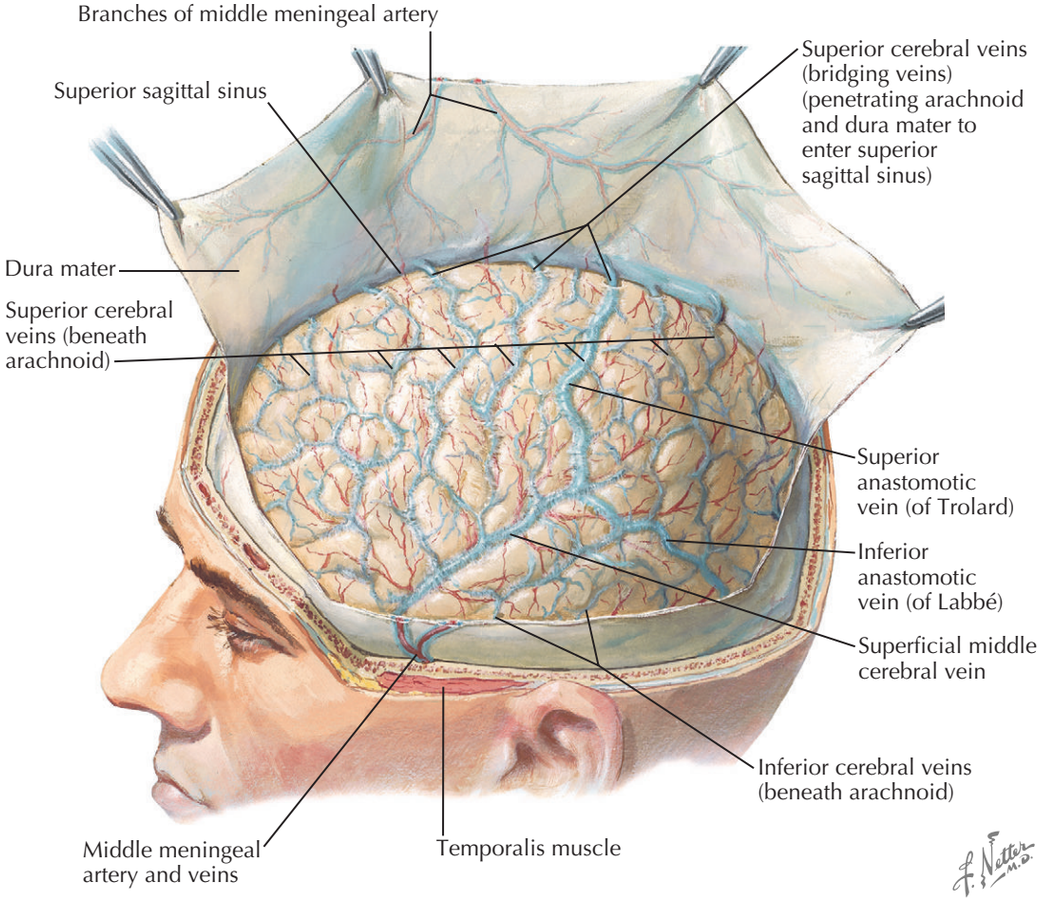
Occipital Sinus. The occipital sinus is the smallest, usually single, sinus, originating from small venous channels at the foramen magnum, communicating with the transverse sinus, and terminating at the confluence of the sinuses.

Anteroinferior Group

Cavernous Sinuses. Cavernous sinuses are irregular networks of communicating venous channels beginning at the superior orbital fissures and extending to the petrous apex of the temporal bones. The internal carotid artery, carotid plexus, and abducens nerve lie on its medial wall, whereas oculomotor, trochlear, and ophthalmic/maxillary divisions of trigeminal nerves traverse the lateral wall. Each sinus receives ophthalmic (superior and inferior) and middle cerebral veins and the small *sphenoparietal sinus*, and it communicates via the *intercavernous sinuses*. These drain into the *transverse sinuses* via the *superior petrosal sinuses*, the *internal jugular veins* via the *inferior petrosal sinuses*, the plexus of veins on the internal carotid artery, and the *pterygoid venous plexus.*

Intercavernous Sinuses. Anterior and posterior sinuses connect the two cavernous sinuses, forming a venous circle around the pituitary stalk.

Sphenoparietal Sinuses. They course along the undersurface of the lesser wing of the sphenoid bone and drain into the cavernous sinuses.



Venous Sinus Thrombosis
(Continued)

Petrosal Sinuses. (1) *Superior petrosal sinuses* receive blood from cerebellar, inferior cerebral, and tympanic cavity veins; traverse the tentorium cerebelli; and connect the cavernous and transverse sinuses. (2) *Inferior petrosal sinuses* originate within inferior petrosal sulcus at junction of the petrous temporal and basilar occipital bones and the jugular foramen. These receive blood from the internal auditory veins, medulla, pons, and cerebellum and connect the cavernous sinus with the *internal jugular vein* bulb.

Basilar Plexus. The basilar plexus consists of interlacing venous channels over the basilar occipital bone; it connects the *inferior petrosal sinuses* while also draining the anterior vertebral venous plexus.

CEREBRAL VENOUS SYSTEM

The cerebral veins are best considered as being related to either superficial or deep brain structures.

Superficial Group

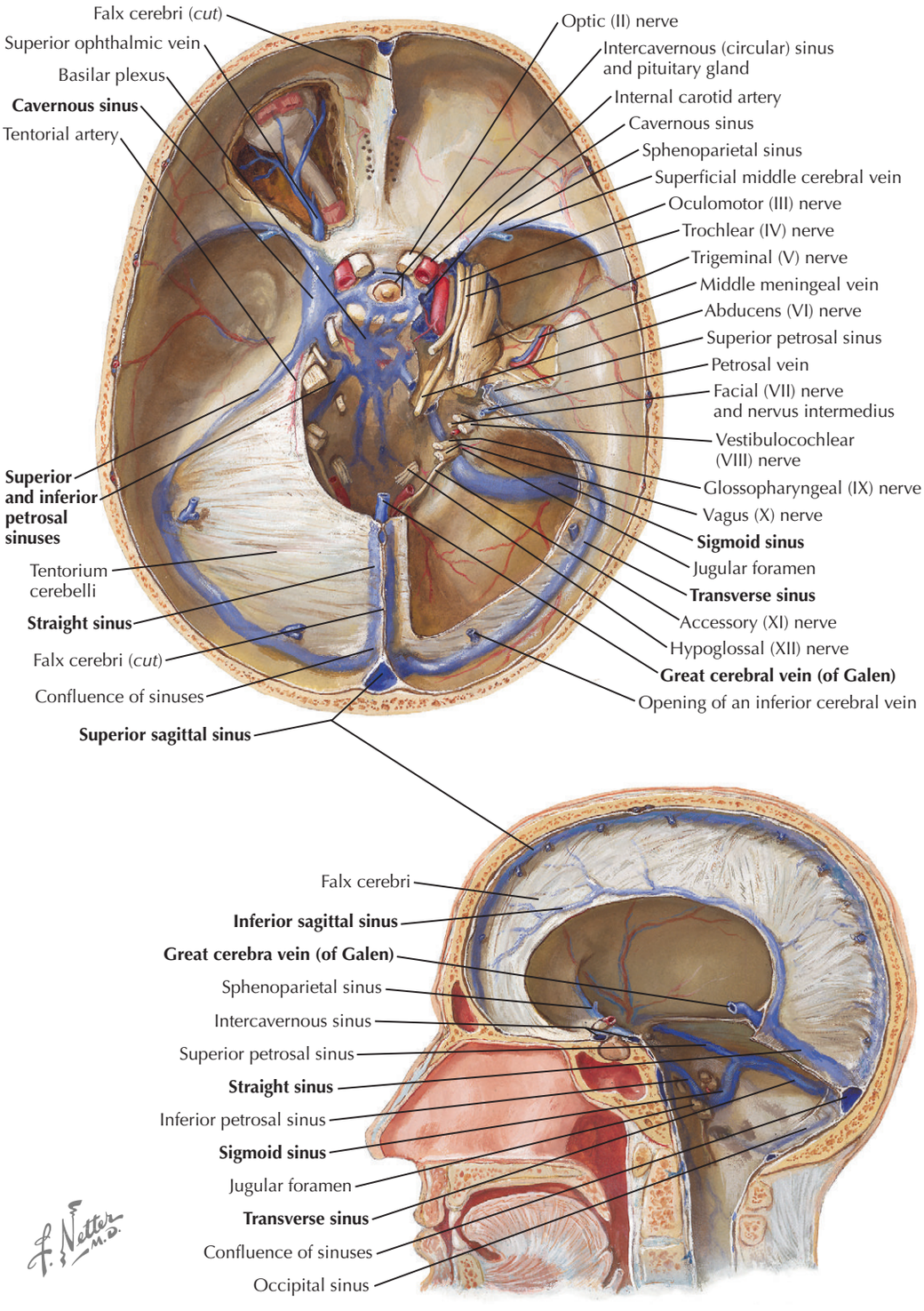
These veins drain the cerebral cortex and subcortical white matter to drain into the superior sagittal, straight, transverse, and cavernous sinuses. These include the following: (1) the *great anastomotic vein of Trolard*, connecting the middle cerebral veins to the superior sagittal sinus; (2) the *vein of Labbé*, connecting the middle cerebral veins with the transverse sinuses; (3) the *middle cerebral veins*, receiving communicating branches from the veins of Trolard and Labbé and draining into cavernous sinuses.

Veins of the posterior fossa, draining the cerebellum and brainstem, are divided into (1) the superior (Galenic) vein, including precentral, superior cerebellar, superior vermian, posterior mesencephalic, lateral mesencephalic, quadrigeminal, and anterior pontomesencephalic veins that drain the superior portion of the cerebellum and upper brainstem into the vein of Galen; (2) the anterior (petrosal) vein, including petrosal, anterior medullary, cerebellar hemispheric, and lateral medullary veins, each draining into the petrosal sinuses; and (3) the posterior (tentorial) vein, including the inferior vermian and some cerebellar bihemispheric veins, these draining into the confluence of the sinuses and neighboring transverse sinuses.

Deep Group

These veins drain the deep central white matter and basal ganglia to empty into the subependymal veins of the lateral ventricles. The major subependymal veins include (1) *septal veins* draining frontal horns of the lateral ventricles near the septum pellucidum, the corpus callosum, and deep frontal white matter; uniting with (2) the *thalamostriate veins* formed by the anterior caudate and terminal veins. These run in the floor of the lateral ventricle and drain into (3) the *internal cerebral veins*; each receiving blood from the thalamostriate, choroidal, septal, epithalamic, and lateral ventricular veins and situated within the roof of the third ventricle. Both internal cerebral veins unite beneath the splenium of the corpus callosum to merge with (4) the *basal veins of Rosenthal* arising within the sylvian fissure. These receive blood from the anterior cerebral, deep middle cerebral, and inferior striate veins and then course around the cerebral peduncles and midbrain tectum to form *the great cerebral vein of Galen*. This curves around the splenium in the quadrigeminal cistern, terminating near the tentorial apex, where it joins the *inferior sagittal sinus* to form the *straight sinus*.

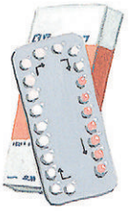
Intracranial Venous Sinuses



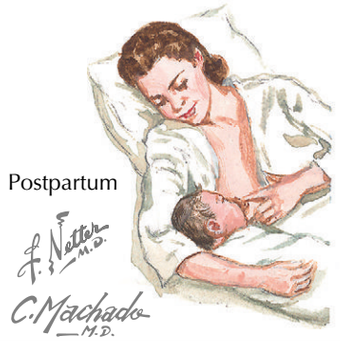
Diagnosis of Venous Sinus Thrombosis

Causes of venous sinus thrombosis

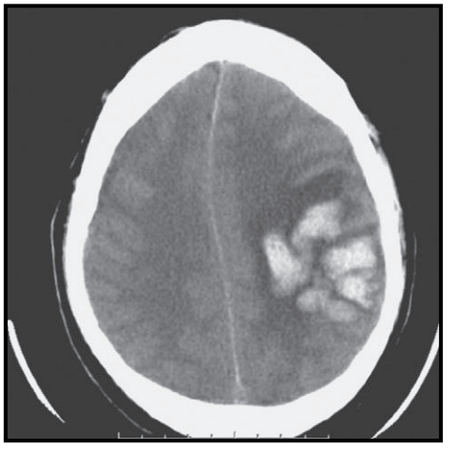
Lack of sleep



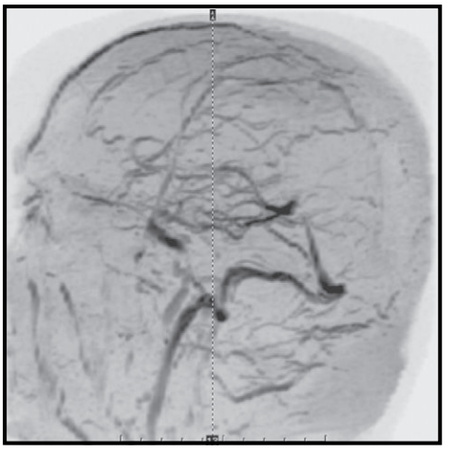
Oral contraceptives



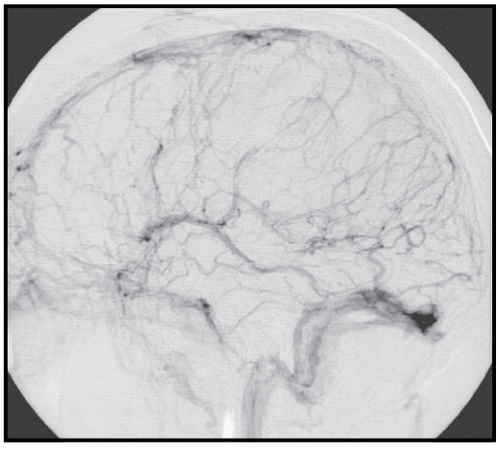
Diagnosis of sinus thrombosis



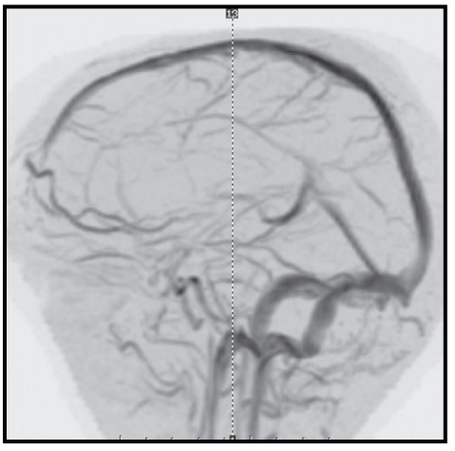
A. CT 2 days after admission showing left posterior frontal parietal patchy hemorrhage within the ischemic region



B. Magnetic resonance venography (MRV) demonstrates absence of flow in posterior sagittal sinus and some cortical veins



C. Digital angiogram, venous phase confirms the MRV findings



D. Normal MRV for comparison

Venous Sinus Thrombosis

(Continued)

Diagnosis and Treatment of Cerebral Venous Sinus Thrombosis

Infections and increased coagulability are the main causes of dural and venous sinus occlusions. Many instances occur during pregnancy and the puerperium. The sagittal and lateral sinuses are most often involved. The main symptom is headache, and it may be the only symptom. Brain edema, infarction, and hemorrhage can develop in the brain regions drained by the occluded veins. In these patients, focal neurologic deficits and seizures often occur. In some patients, dural sinus occlusion leads to a *pseudotumor cerebri syndrome* of increased intracranial pressure.

In most patients, the D-dimer level in the blood is increased, reflecting increased blood clotting. Radiologic brain imaging studies are required to establish the diagnosis of cerebral venous sinus thrombosis, suspected on clinical grounds. Direct visualization of the thrombosed sinus or vein conclusively confirms the definitive diagnosis.

Initial evaluation commonly uses plain computerized axial tomography (CT) scanning of the brain. Plain CT may show evidence of brain swelling and edema, or venous infarctions, which tend to be hemorrhagic with large surrounding edema and not conforming to well-defined arterial vascular territories (see Plates 9-13 and 9-21 to 9-23). However, plain CT scan may only show subtle and nonspecific abnormalities in the absence of venous infarction. Contrast administration may increase the sensitivity of CT scan in diagnosing cerebral venous sinus thrombosis. Magnetic resonance imaging (MRI) is superior to CT scan and is the imaging modality of choice.

The major cerebral sinuses and veins can be reliably imaged by magnetic resonance venography (MRV), CT venography (CTV), or conventional catheter-based angiography. Plate 9-35, *D* depicts a normal MRV showing all major sinuses and veins, whereas Plate 9-35, *B* depicts MRV showing absence of flow in the posterior portion of the *superior sagittal sinus* and some of the neighboring cortical veins. Conventional angiography with a prolonged venous phase is the gold standard for diagnosing cerebral sinus or vein thrombosis (see Plate 9-35, *C*), and its use is usually reserved for cases with high suspicion where MRV and CTV are negative or equivocal.

The specific treatment of cerebral venous sinus thrombosis depends on the underlying etiology. Most patients without contraindications for anticoagulation are initially treated either with body weight–adjusted subcutaneous low-molecular-weight heparin or dose-adjusted intravenous heparin and transitioned to oral anticoagulation to avoid thrombus extension and to prevent pulmonary embolism. The optimal duration of oral anticoagulation is uncertain and varies from 3 to 12 months in idiopathic cases or those provoked by thrombogenic drugs to lifelong anticoagulation in those with thrombophilia.

Local thrombolysis may be occasionally used in patients who deteriorate despite anticoagulation and in whom other causes of deterioration have been excluded. Symptomatic treatment includes the management of increased intracranial pressure, use of antiepileptic drugs, and analgesics for headache.

Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH) represents 10% to 15% of strokes. Its relative importance derives from the associated high mortality (35%-50% at 6 months) and the severity of the permanent sequelae in survivors: only 20% are independent at 6 months compared with 60% after ischemic stroke. The mortality and morbidity related to ICH are primarily dependent on location and hematoma size; the latter is known to increase substantially soon after ICH onset in almost 40% of patients. Hemorrhages less than 30 cm^3 generally have a good prognosis; 30 to 60 cm^3 may be more amenable to surgery and have a better outlook, whereas those greater than 60 cm^3 have a very poor outlook, particularly with a diminished level of consciousness. In contrast, hemorrhages due to rupture of small arteriovenous malformations may have a substantially better outcome.

The *risk factors* for ICH include hypertension, advancing age, vascular malformations, cerebral amyloid angiopathy, anticoagulant and fibrinolytic agents, brain tumors, sympathomimetic agents, and vasculitis. Hypertension is the primary risk factor across all ages, with the highest representation in those aged 40 to 69 years, whereas cerebral amyloid angiopathy is a more common risk factor in patients older than 70 years. In younger persons, sympathomimetic agents, especially cocaine, and vascular malformations are dominant factors. Brain tumors associated with ICH are typically the malignant varieties, either primary (particularly glioblastoma multiforme) or metastatic, including melanoma, choriocarcinoma, bronchogenic, renal cell, and thyroid carcinoma.

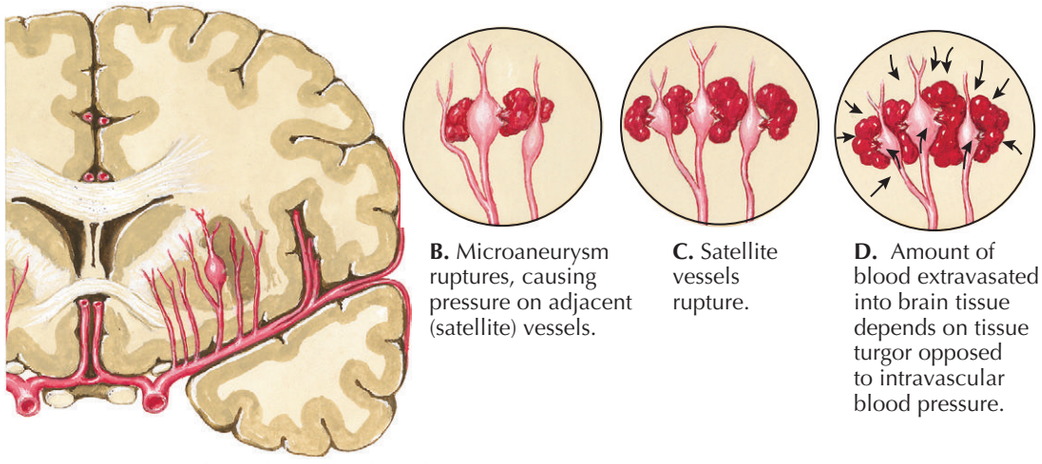
Warfarin-related ICH is an important group, particularly in senior or middle-aged individuals who are more likely to be taking this medication because of underlying atrial fibrillation; here a leading risk factor is excessive prolongation of the international normalized ratio (INR). This variety of ICH is associated with a particularly high mortality because of the generally large hematoma volumes that develop due to frequent enlargement of the hematoma within the initial hours after onset of symptoms. The ICHs that occur after treatment of acute ischemic stroke with thrombolytics are also generally large sized, tending to occur within hours of completion of the thrombolytic treatment, and typically are located in the area of the manifesting cerebral infarction.

The *locations* of ICH and their approximate frequency are putaminal (35%), lobar (25%), thalamic (20%), cerebellar (10%), pontine (5%), and caudate (5%) (see Plate 9-37). The predominant location of ICH in deep subcortical and brainstem locations reflects the anatomic distribution of chronic changes within the wall of deep small penetrating arteries subjected to chronic hypertension. In contrast, the more superficially-located lobar ICHs reflect the classic pathoanatomy related to cerebral amyloid angiopathy.

The *clinical presentation* of an ICH has a number of general features that are frequent with all topographic varieties and particularly reflect the clinical symptomatology that results from a rapidly expanding intracranial mass lesion. These include headache, vomiting, and depressed levels of consciousness. Although these are not constant features, their presence is virtually diagnostic of an ICH, in particular if a gradual decline in the level of consciousness occurs in parallel with a gradual increase in the severity of the presenting focal neurologic deficits. The specific findings on neurologic examination are related to the particular localization of the ICH within the brain.

Intracerebral Hemorrhage: Pathogenesis and Types

Pathogenesis

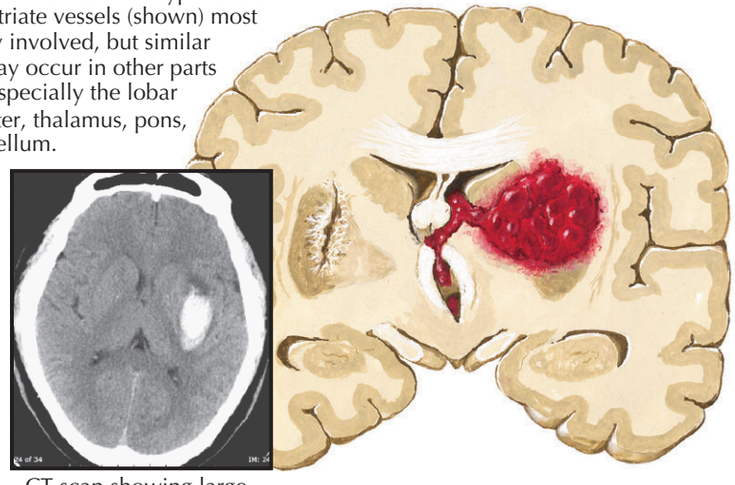


A. Microaneurysm formed in parenchymal artery of brain as result of hypertension. Lenticulostriate vessels (shown) most commonly involved, but similar process may occur in other parts of brain, especially the lobar white matter, thalamus, pons, and cerebellum.

B. Microaneurysm ruptures, causing pressure on adjacent (satellite) vessels.

C. Satellite vessels rupture.

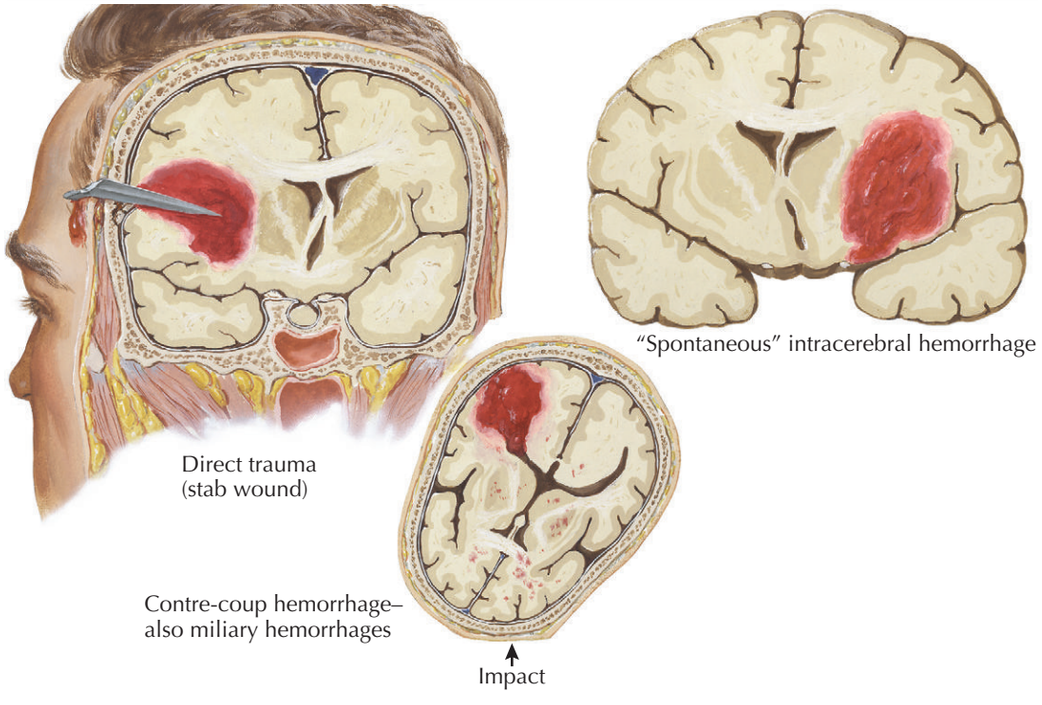
D. Amount of blood extravasated into brain tissue depends on tissue turgor opposed to intravascular blood pressure.



Moderate-sized intracerebral hemorrhage involving left putamen, with rupture into lateral ventricle; brain displaced to opposite side; scar of healed hemorrhage on right side.

CT scan showing large putaminal hemorrhage

Types



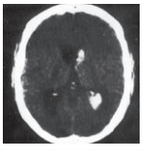
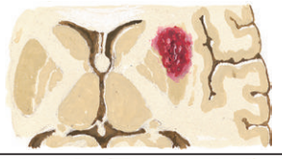
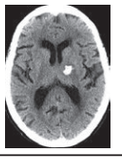
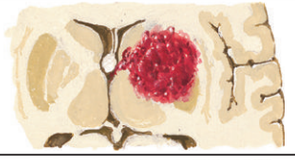
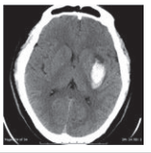
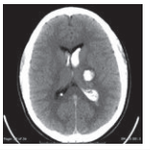
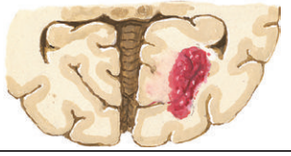
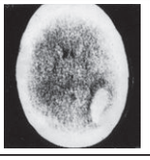
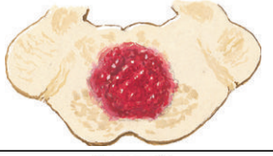
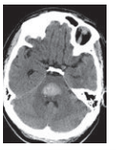
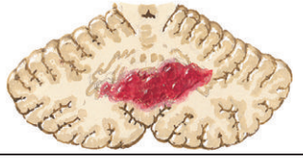
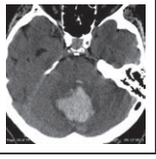
Direct trauma (stab wound)

"Spontaneous" intracerebral hemorrhage

Contre-coup hemorrhage–also miliary hemorrhages

Impact

Clinical Manifestations of Intracerebral Hemorrhage Related to Site

Pathology	CT scan	Pupils	Eye movements	Motor and sensory deficits	Other
Caudate nucleus (blood in ventricle)			Sometimes ipsilaterally constricted	Conjugate deviation to side of lesion; slight ptosis	Contralateral hemiparesis, often transient	Headache, confusion
Putamen (small hemorrhage)			Normal	Conjugate deviation to side of lesion	Contralateral hemiparesis and hemisensory loss	Aphasia (if lesion on left side)
Putamen (large hemorrhage)			In presence of herniation, pupil dilated on side of lesion	Conjugate deviation to side of lesion	Contralateral hemiparesis and hemisensory loss	Decreased consciousness
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)
Occipital lobar white matter			Normal	Normal	Mild, transient hemiparesis	Contralateral hemianopsia
Pons			Constricted, reactive to light	No horizontal movements; vertical movements preserved	Quadriplegia	Coma
Cerebellum			Slight constriction on side of lesion	Slight deviation to opposite side; movements toward side of lesion impaired, or sixth cranial nerve palsy	Ipsilateral limb ataxia; no hemiparesis	Gait ataxia, vomiting

Intracerebral Hemorrhage
(Continued)

The tendency of the hematoma to expand in the initial hours after symptom onset is a very important feature of ICH. This is common to all locations of ICH. More than one third of patients will have an increase in the ICH size within the first 3 hours, and most all who eventually develop mass effect will do so within 6 hours from symptom onset. This hematoma expansion is typically associated with deteriorating neurologic function. The risk factors for this occurrence are still not clearly identified, although uncontrolled hypertension is suggested by some; this underlies the need to stress the potential value of maintaining blood pressure control within the early hours subsequent to ICH onset. Another factor associated with a high frequency of early hematoma expansion is the occurrence of ICH in patients under warfarin anticoagulation, thus stressing the great importance of rapidly normalizing the elevated INR, with the combination of vitamin K, fresh frozen plasma, or prothrombin complex concentrate, possibly recombinant activated factor VII in instances when INR reversal is immediately needed before subjecting the patient to surgical drainage of the hematoma (because it is often indicated in instances of cerebellar ICH). The risk for hematoma expansion is correlated with the finding of the "spot sign" in computed tomographic angiography (CTA) at presentation with ICH. This finding on CTA consists in the presence of a dot of contrast within the hematoma, and it reflects active bleeding at the time of the intravenous (IV) contrast infusion during performance of CTA. The presence of the "spot sign" shows high correlation with subsequent hematoma enlargement.

Cerebellar Hemorrhage

Cerebellar hemorrhage represents about 5% to 10% of ICH cases, and despite its relatively low frequency, it is of great clinical importance because prompt diagnosis may lead to lifesaving emergency surgical intervention. The clinical presentation is typically with abrupt onset of vertigo, vomiting, headache, and inability to stand and walk. In those patients who are alert enough to undergo full neurologic examination, the classic findings include ipsilateral cerebellar ataxia, horizontal gaze palsy, and peripheral facial palsy as a triad that is highly suggestive of the diagnosis. Other signs of ipsilateral pontine tegmental involvement can be present, including trigeminal sensory loss, Horner syndrome, findings that occur in the absence of contralateral hemiplegia because the pressure effects of the cerebellar hematoma are exerted on the dorsal portion of the pons, sparing the basis pontis and the corticospinal tracts.

Intracerebral Hemorrhage
(Continued)

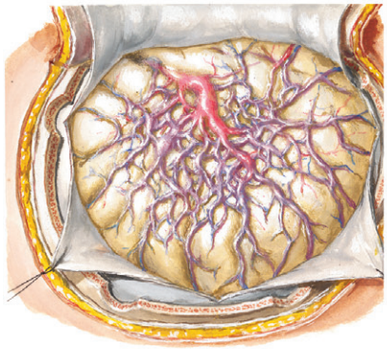
The clinical course in cerebellar hemorrhage is notoriously unpredictable because patients who are alert and responsive at presentation can suddenly deteriorate as a result of brainstem compression, rapidly leading to coma, respiratory depression, and death. This sudden change can occur without "warning," and this has resulted in a great deal of interest in documenting clinical and imaging features at presentation that may be predictive of this type of neurologic deterioration versus clinical stability. From a clinical standpoint, the presence of signs of compression of the pontine tegmentum at presentation (ipsilateral horizontal gaze palsy, facial palsy) calls for strong consideration of surgical evacuation of the hematoma, especially if associated with imaging features that have been found to correlate with potential for neurologic deterioration, including hematoma diameter of greater than 3 cm, supratentorial hydrocephalus, obliteration of the ipsilateral quadrigeminal cistern, and deformation/compression of the fourth ventricle. These imaging features have been correlated with high frequency of sudden neurologic deterioration requiring emergency surgical treatment, while their absence has been compatible with a more benign clinical course without need for surgical removal of the hematoma.

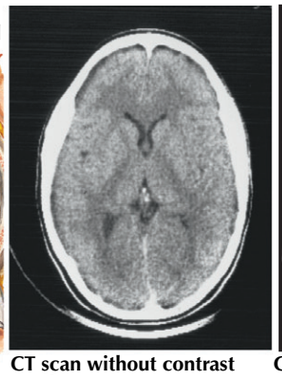
For these reasons, it is imperative that patients with cerebellar hemorrhage are assessed at presentation with the specific purpose of determining whether they should be subjected to surgical intervention in the early course of their illness, before neurologic deterioration. These considerations are based on the correlation between preoperative level of consciousness and surgical result: patients who are alert or obtunded preoperatively have a surgical mortality of approximately 15%, while those who have reached the stage of lethargy or coma have a surgical mortality of at least 75%. Once the decision has been made to subject the patient to surgery, an initial consideration is to whether an emergency ventriculostomy is required before performing the more definitive suboccipital craniectomy for hematoma evacuation. This procedure is indicated in patients with massive hydrocephalus whose level of consciousness has suddenly deteriorated and is used as an emergency temporizing procedure while arrangements are being made for the patient's transfer to the operating room for the more definite suboccipital craniectomy. Also in favor of this type of management of cerebellar hemorrhage is the fact that, despite an initially severely compromised neurologic condition, the successful removal of the cerebellar hematoma is generally followed by adequate functional outcomes because the initially severe ipsilateral limb ataxia and gait ataxia tend to gradually improve, at times leaving no long-term motor disability.

Hemorrhage into the cerebellar vermis is one variety of cerebellar hemorrhage that differs from the classic unilateral hemispheric type described above. This type of hemorrhage tends to be more severe in its initial manifestations and has less potential for benefit from surgery because of the generally early and bilateral compression of the tegmentum of the pons. This often results in severe compromise in the level of consciousness, with bilateral oculomotor deficits at presentation, at times with coma and bilateral ophthalmoplegia with miosis, a presentation that is clinically difficult to separate from primary pontine hemorrhage. Because of this early and bilateral compromise of the pontine tegmentum, and the localization of the hemorrhage in the midline of the cerebellum, the surgical option of hematoma evacuation is generally less successful than in the hemispheric variety of cerebellar hemorrhage, and most patients are only treated with ventriculostomy because they frequently have prominent supratentorial hydrocephalus as a result of fourth ventricular compression.

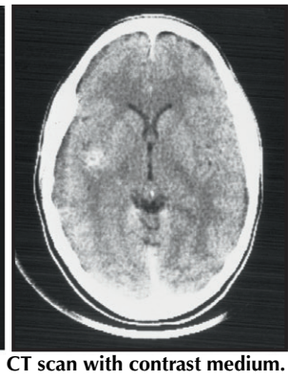
Vascular Malformations

Arteriovenous malformations. On surface of brain, covered by arachnoid

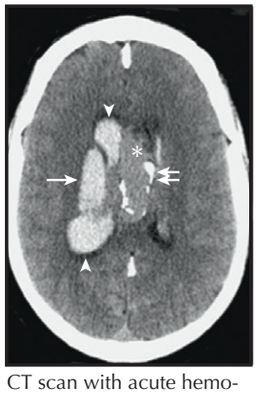




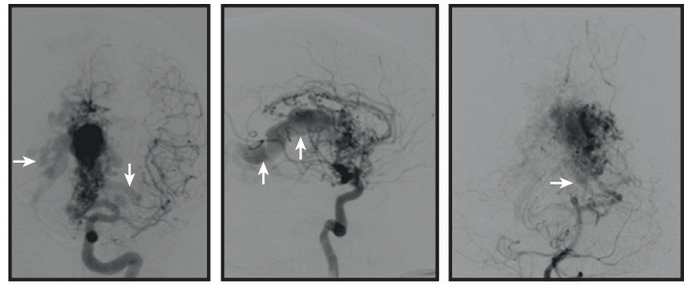
CT scan without contrast medium. Does not clearly demonstrate arteriovenous malformation.



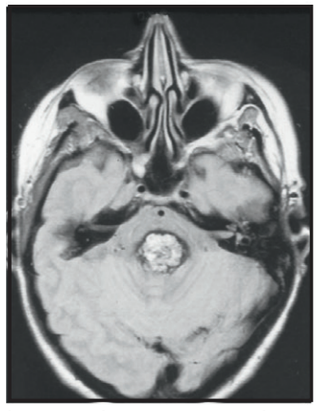
CT scan with contrast medium. Clearly demonstrates arteriovenous malformation (AVM).



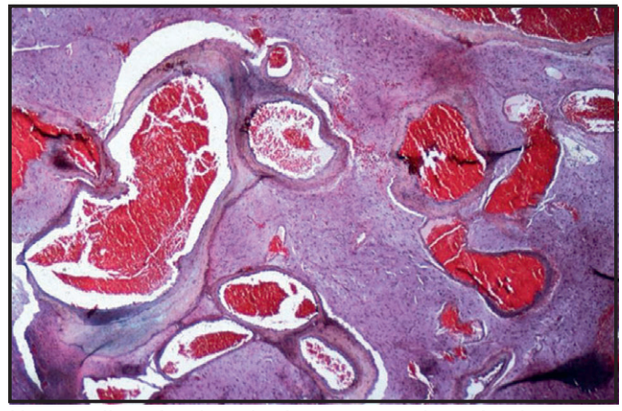
CT scan with acute hemorrhage in right hemisphere *(arrow)* and right lateral ventricle *(arrowheads)*, caused by ruptured AVM *(asterisk)*, surrounded by calcifications *(double arrows)*.



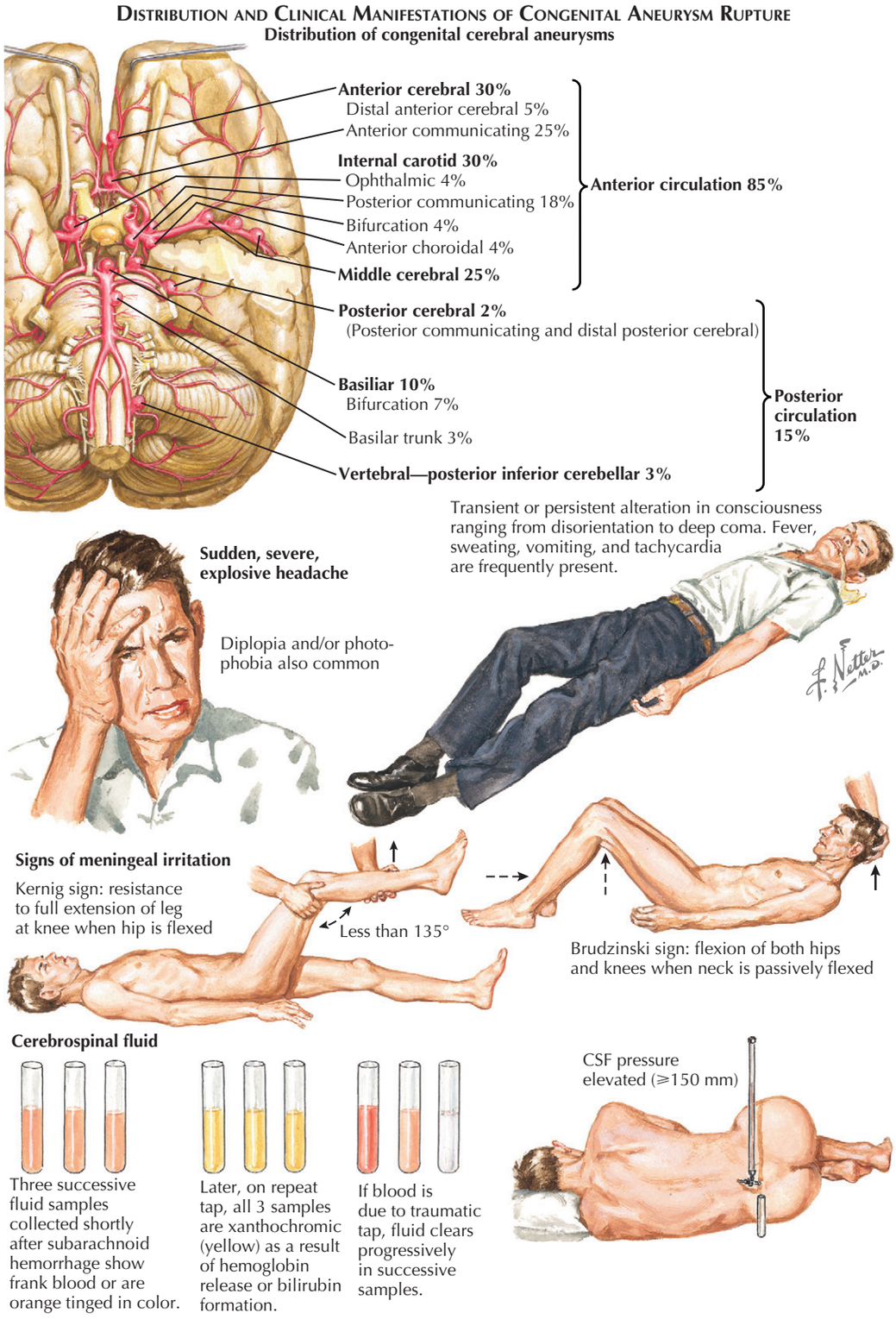
Contrast angiogram showing large midline AVM with arterial supply from left anterior cerebral artery branches (anteroposterior view; lateral view) and left posterior cerebral artery branches (anteroposterior view of vertebral artery injection). All views show, in addition to multivessel arterial supply of the AVM, prominent dilated draining veins *(arrows)*.



Large pontine cavernous angioma with central portion with mixed high and low signals and irregular margins ("popcorn" aspect), surrounded by black halo corresponding to old hemosiderin deposits.



Hemotoxylin and eosin–stained cavernous angioma showing characteristic aggregate of vascular structures of thin walls, without arterial or venous morphology, in a background of sclerotic tissue, without areas of intervening brain parenchyma among the vascular channels. Areas of calcification are shown in the lower right corner.



Subarachnoid Hemorrhage and Intracranial Aneurysms

Rupture of an intracranial aneurysm is the leading cause of nontraumatic subarachnoid hemorrhage (SAH), which accounts for approximately 5% of all cases of stroke. The incidence of SAH has not declined; it occurs in approximately 30,000 Americans annually. Besides bleeding in the subarachnoid space (SAH), a ruptured aneurysm also may produce intraventricular hemorrhage or intracerebral hemorrhage. Patients with SAH are critically ill, the 1-month mortality approaches 50%, and many patients die before reaching medical attention. Many survivors have serious neurologic sequelae, including cognitive impairments and a reduced quality of life.

Saccular (berry) aneurysms are the most common cause of spontaneous SAH. Nonsaccular aneurysms include fusiform (dolichoectatic), dissecting, infectious (mycotic), neoplastic, and post-traumatic lesions. The dolichoectatic and dissecting aneurysms that are associated with SAH are usually in the posterior circulation. Mycotic infectious and neoplastic aneurysms usually are found in distal branch arteries. Perimesencephalic hemorrhage, which is confirmed by the presence of blood in the spaces around the brainstem detected by computed tomography (CT), is an alternative diagnosis to a ruptured aneurysm.

Saccular aneurysms are found in approximately 2% to 5% of adults, and in most cases, persons live their entire lives without having symptoms secondary to these aneurysmal lesions. The locations of saccular aneurysms are at sites with a predilection for hemodynamic stress, namely at the bifurcations of major intracranial arteries. Approximately 85% of berry aneurysms arise adjacent to the circle of Willis; the most common locations are the anterior communicating artery, bifurcation of the middle cerebral artery, or the junction of the internal carotid artery and posterior communicating artery.

The absence of a second layer of internal elastic lamina in intracranial arteries probably plays a role in the evolution of the aneurysm. The wall of a saccular aneurysm contains intima, media, and adventitia, and the thickness of the wall may be very thin, particularly at the dome. Although the aneurysms often are quite large, the neck of the aneurysm (area adjacent to the parent artery) may be quite small. There is growth of the aneurysm during adulthood.

SAH and aneurysms affect men and women of all ethnic groups. The frequency of aneurysmal SAH is low in children. Although a ruptured aneurysm may cause SAH in adults of any age, the peak age for the illness is the sixth decade. The risk of subarachnoid

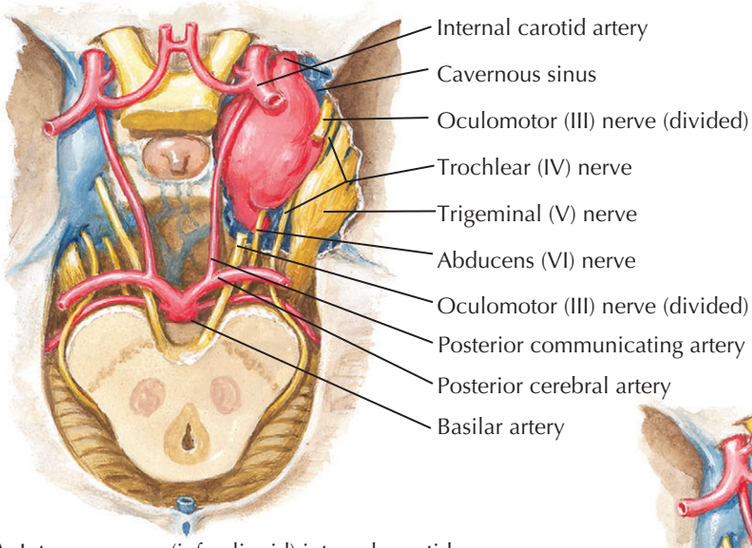
Subarachnoid Hemorrhage and Intracranial Aneurysms *(Continued)*

hemorrhage is increased in individuals who smoke or have hypertension; the smoking association is especially strong in women and in those taking oral contraceptives. The use of sympathomimetic drugs may incite rupture of the aneurysm, presumably through a sudden surge in blood pressure. The risk of SAH also may be increased during periods of increased physical activity or emotional stress. These globular shaped lesions are categorized as small (<10 mm in diameter), large (10-25 mm), or giant (>25 mm) (see Plate 9-40). The risk of hemorrhage increases with aneurysmal enlargement. Approximately 25% of patients will have more than one aneurysm.

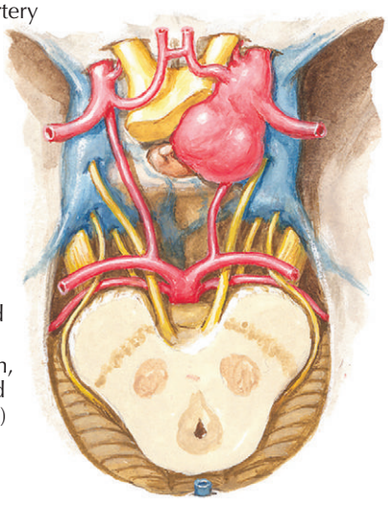
Approximately 10% of patients with SAH report a relative who has had the illness, and thus risk of hemorrhage is increased when there is a known family history of aneurysmal bleeds. Saccular aneurysms have significant concomitant clinical association with autosomal dominant polycystic kidney disease. Sometimes the presence of an aneurysm is associated with moyamoya disease/syndrome, coarctation of the aorta, fibromuscular dysplasia, cerebral vascular malformations, Ehlers-Danlos syndrome, and Marfan syndrome. Currently, studies are being directed to look for a genetic linkage predisposing individuals to development of intracranial aneurysms but, to date, no definite genetic locus is established. Such a finding would be helpful for screening of relatives. Because of the high prevalence of intracranial aneurysms in the general population, the current recommendation is to only perform hereditary screening (at present, magnetic resonance angiography [MRA] or computed tomographic angiography [CTA] vascular imaging) when at least two first-degree relatives have a history of aneurysms. The potentially affected patient needs to be counseled about the implications of detection of an otherwise asymptomatic intracranial aneurysm.

Although SAH is the most feared and common clinical presentation of a berry aneurysm, there are other settings wherein an aneurysm may come to medical attention. An asymptomatic lesion may be detected by brain or vascular imaging performed for another indication, for example, for assessment of chronic headaches. Rarely, a giant aneurysm may be a source of thrombi that migrate to a distal intracranial artery and cause an ischemic stroke or transient ischemic attack. Occasionally giant aneurysms may cause compression of adjacent neurologic structures; the most common clinical setting is compression of the oculomotor (III) nerve by an aneurysm located at the bifurcation of the basilar artery

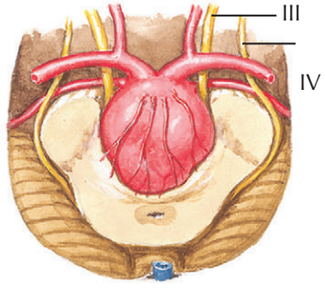
Giant Congenital Aneurysms



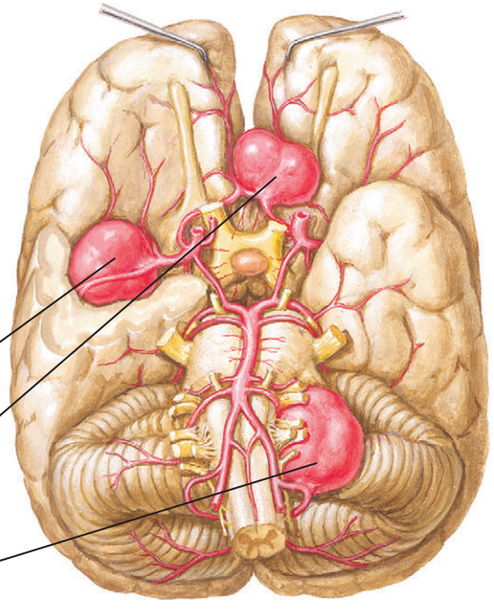
A. Intracavernous (infraclinoid) internal carotid aneurysm compressing abducens (VI) nerve. Oculomotor (III), trochlear (IV), and trigeminal (V) nerves may also be affected. Trigeminal involvement may cause facial pain.



B. Aneurysm of supraclinoid segment of internal carotid artery elevating optic chiasm, distorting infundibulum, and compressing oculomotor (III) nerve



C. Aneurysm of basilar bifurcation projecting posteriorly, invading peduncles and compressing cerebral aqueduct. Corticospinal tracts may be affected, resulting in paralysis or paresis.



D. Aneurysm of middle cerebral artery

E. Aneurysm of anterior cerebral-anterior communicating arteries

F. Aneurysm of posterior inferior cerebellar artery

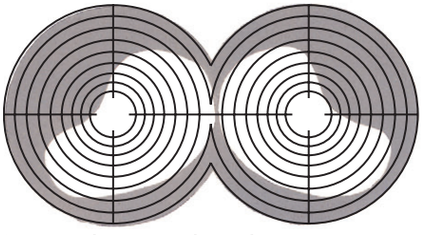
Ophthalmologic Manifestations of Cerebral Aneurysms

A. Cranial neuropathies

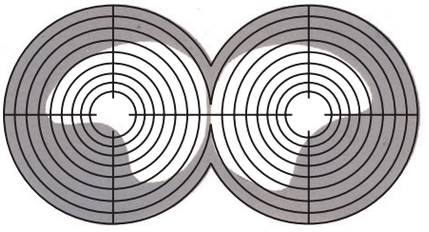
Abducens nerve palsy: affected eye turns medially. May be first manifestation of intracavernous carotid aneurysm. Pain above eye or on side of face may be secondary to trigeminal (V) nerve involvement.

Oculomotor nerve palsy: ptosis, eye turns laterally and inferiorly, pupil dilated. Common finding with cerebral aneurysms, especially carotid-posterior communicating aneurysms.

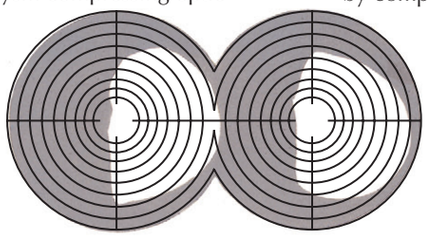
B. Visual field disturbances



Superior bitemporal quadrantanopia caused by supraclinoid carotid aneurysm compressing optic chiasm from below

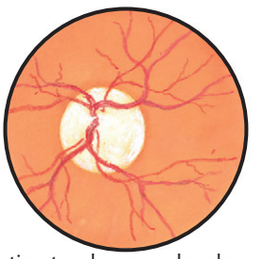


Inferior bitemporal quadrantanopia caused by compression of optic chiasm from above

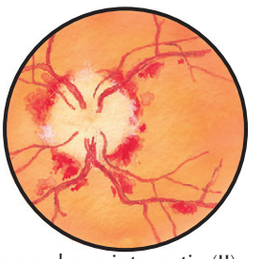


Right (or left) homonymous hemianopsia caused by compression of optic tract. Unilateral amaurosis may occur if optic (II) nerve is compressed.

C. Retinal changes



Optic atrophy may develop as result of pressure on optic (II) nerve from a supraclinoid carotid, ophthalmic, or anterior cerebral aneurysm



Hemorrhage into optic (II) nerve sheath after rupture of aneurysm may result in subhyaloid hemorrhage, with blood around disc

Subarachnoid Hemorrhage and Intracranial Aneurysms *(Continued)*

or the posterior communicating artery (see Plate 9-40). A giant intracavernous aneurysm may cause multiple cranial nerve palsies, causing an ipsilateral ophthalmoplegia and facial sensory loss.

Prompt recognition of SAH is crucial for successful management. Unfortunately, delays in diagnosis may occur in approximately 5% to 15% of cases, and such misdiagnoses are most common among the less seriously affected persons in whom prognosis is most favorable once diagnosed. Common alternative diagnoses include sinusitis, tension headache, migraine, viral meningitis, herniated cervical disk, drug or alcohol abuse, and ischemic stroke. Unfortunately, the subsequent delay in treatment has serious implications, including leaving the patient at risk for recurrent hemorrhage or other major neurologic complications. These delays in diagnosis occur despite a relatively stereotyped presentation.

A SAH usually is a very dramatic event. The cardinal symptom is the cataclysmic onset of an extremely severe headache, often described as absolutely the worst pain the patient has ever experienced (see Plate 9-39). Sometimes the headache is associated with transient loss of consciousness, seizures, or a prolonged period of unresponsiveness. Other symptoms include nausea, vomiting, photophobia, phonophobia, and neck pain. Some patients may appear mildly ill while they are complaining of severe headache. Other patients may appear critically ill. Often, the vital signs are unstable, with an irregular pulse and a volatile blood pressure. Focal neurologic impairments may be subtle, and in most cases, no localizing signs are found. An oculomotor (III) nerve palsy with a nonreacting pupil is the most common and clinically useful diagnostic sign (see Plate 9-41). Other ocular signs include intraocular (subhyaloid) hemorrhages, which are most commonly noted in seriously ill patients. The presence of intraocular hemorrhage in a comatose patient points to the diagnosis of an intracranial hemorrhage and, in particular, a ruptured aneurysm. If the aneurysmal bleed is associated with a large localized hematoma or intracerebral extension of the hemorrhage, the patient may have a paraparesis, hemiparesis, or aphasia. Although nuchal rigidity usually is found, it may take several hours for this sign to appear.

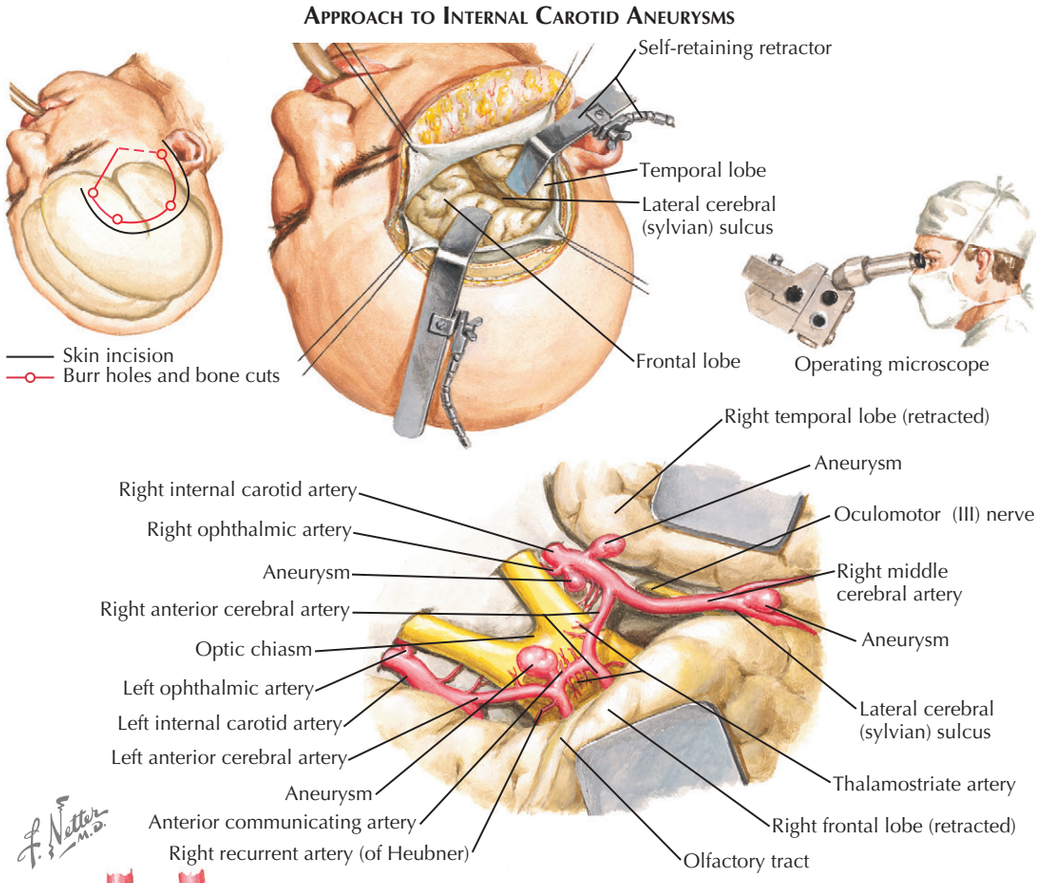
The advent of CT with its current widespread availability has revolutionized the evaluation of patients with suspected SAH; it is an extraordinarily sensitive diagnostic test. It is noninvasive and relatively inexpensive. The study will be abnormal in almost all SAH patients.

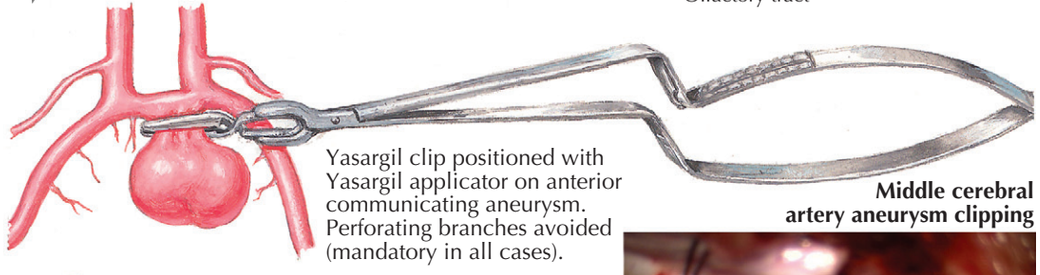
Subarachnoid Hemorrhage and Intracranial Aneurysms
(Continued)

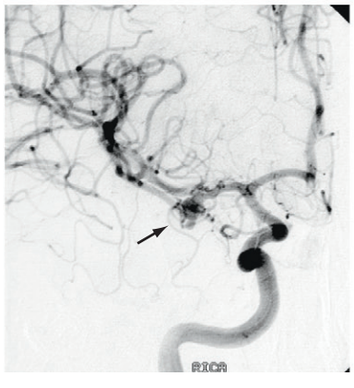
On rare occasion, a CT scan may not demonstrate a minor hemorrhage, particularly in an alert patient whose hemorrhage is restricted to the posterior fossa or in someone whose hemorrhage occurred days or weeks previously. The interval from SAH until the performance of the test also affects the yield; the scan will show subarachnoid blood in approximately 95% of cases scanned at the day of the event, but the frequency of detection of bleeding drops rapidly after a few days. Besides detecting blood in the subarachnoid space, CT also may demonstrate intraventricular or intracerebral hemorrhage, hydrocephalus, brain edema, or a mass effect. The location and pattern of hemorrhage may be helpful in determining the specific site of the ruptured aneurysm, and these findings may be used to predict the development of vasospasm. Whenever there is neurologic worsening, a second CT scan is indicated to screen for evidence of recurrent hemorrhage.

Magnetic resonance imaging also may be used to screen for SAH. Vascular imaging, such as CTA or MRA, is performed to show the arterial lesion. Digital subtraction angiography usually is performed to define the aneurysm and the adjacent vasculature, particularly to screen for the presence of vasospasm.

The role of lumbar puncture has declined with the advent of brain imaging. If the CT demonstrates a SAH, there is no need for cerebrospinal fluid (CSF) examination (see Plate 9-39). However, if the diagnosis of SAH is suspected and the CT is negative, CSF evaluation is definitely indicated. When a SAH develops, the CSF becomes bloody and its pressure is often elevated. With centrifugation, the CSF appears xanthochromic; this is an important study component because this finding helps differentiate a true SAH from a traumatic lumbar puncture. In the former, xanthochromia is evident; in the latter, there is no xanthochromia. Additional diagnostic studies include an electrocardiogram, coagulation studies, complete blood count, renal function studies, and electrolytes. These tests are done to screen for comorbid diseases or medical complications of the SAH.

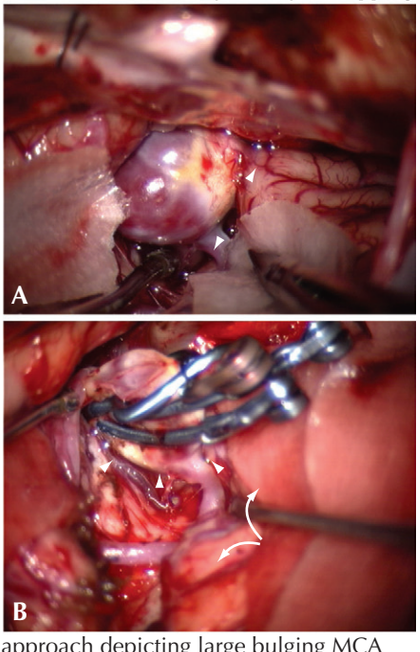






Right middle cerebral artery aneurysm
Frontal digital subtraction angiogram showing large right middle cerebral artery aneurysm *(arrow)*

Middle cerebral artery aneurysm clipping



Right-sided peterional approach depicting large bulging MCA aneurysm *(arrowheads)* before **(A)** and after **(B)** surgical clipping. Aneurysm has been decompressed with surgical clips at its base with preservation of the parent artery *(arrowheads)*.

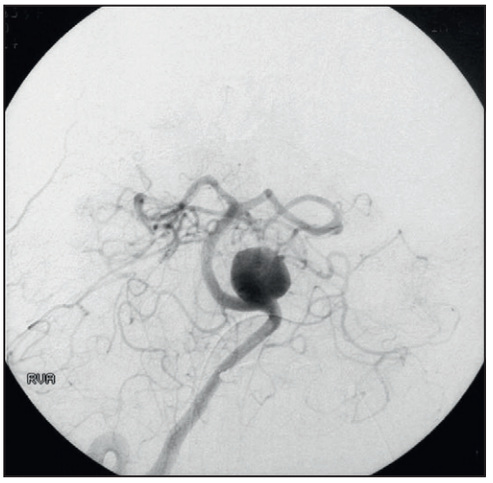
Subarachnoid Hemorrhage and Intracranial Aneurysms
(Continued)

Many of the causes of death or disability occur within the first days of the SAH, including the neurologic and medical consequences of the initial hemorrhage. Early complications include cardiac arrhythmias, pulmonary edema, electrolyte disturbances, acute hydrocephalus, and seizures. The risk of recurrent aneurysmal bleeding may be as high as 4% within the first 24 hours and 20% in the first 10 days. Recurrent hemorrhage has a major negative impact on prognosis. Vasospasm, which is a severe arterial constrictive syndrome that peaks at approximately 1 week after SAH and usually affects adjacent intracranial arteries, may cause secondary brain infarction.

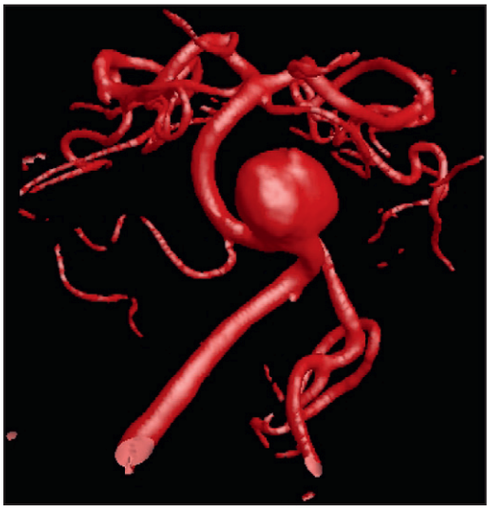
The early management of patients with SAH involves an integrated, multidisciplinary team of neurologists, neurosurgeons, neurointerventional physicians, and intensive care unit physicians. Patients should be hospitalized in a stroke unit or intensive care unit, with frequent monitoring of vital signs and neurologic status. Those individuals having a decline in consciousness or a compromised airway are intubated. Measures to prevent or treat cardiac arrhythmias, hypertension, electrolyte or metabolic disturbances, or other medical complications are instituted. Increased intracranial pressure is managed with placement of a ventricular drain or medications such as hypertonic saline or mannitol. Symptoms such as pain, nausea, vomiting, or agitation should be medically treated.

Either surgical clipping of the aneurysm or endovascular occlusion (placement of coils) is performed as soon as the patient's condition permits. The goal is to prevent recurrent hemorrhage. Nimodipine is approved for prevention of cerebral ischemia secondary to vasospasm. Patients who develop ischemic symptoms are treated with hypervolemic hemodilution and induced hypertension, intra-arterial administration of vasodilators, or angioplasty, depending on the severity of the vasospasm.

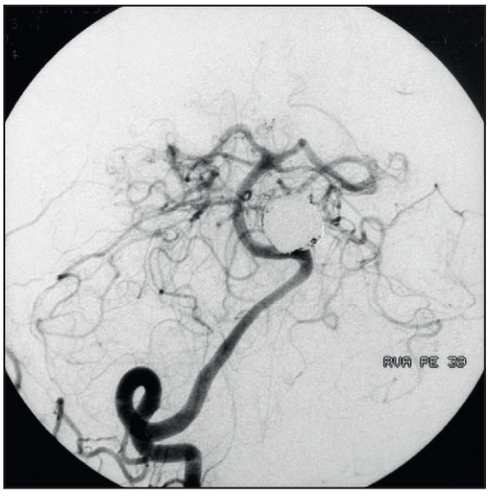
Interventional Radiologic Repair of Berry Aneurysms



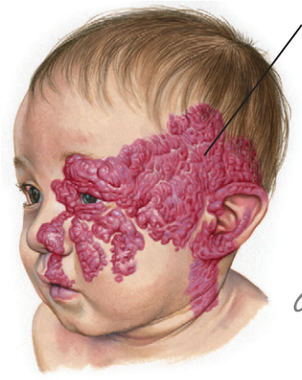
Large berry aneurysm at junction of vertebral and basilar artery

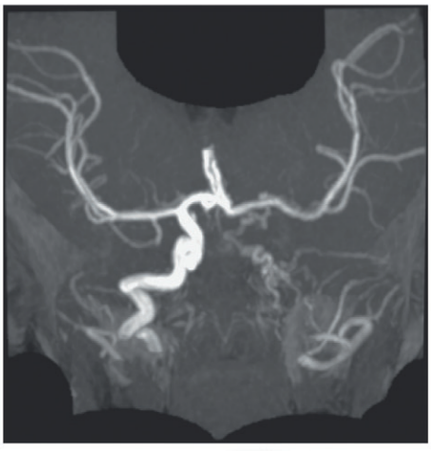


Three-dimensional reconstruction of a giant vertebrobasilar junction aneurysm



Total obliteration of the aneurysm with interventional radiology placement of coils within the aneurysm





This hypoplastic and tortuous internal carotid artery is one of the classic vascular abnormalities seen in **PHACE** syndrome

Pediatric Cerebrovascular Disease

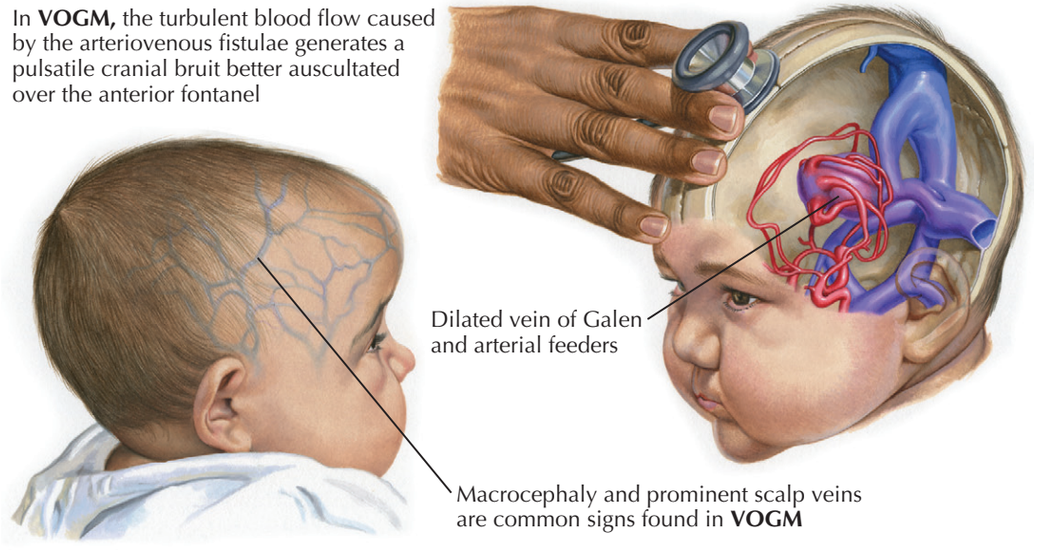
Every year in the United States, at least 5,000 children have a stroke; half of these strokes are hemorrhagic (intracerebral hemorrhage or subarachnoid hemorrhage). The causes of childhood stroke are diverse and heterogenous. Here we focus on three diseases that are particularly unique to childhood.

Moyamoya. Moyamoya is a progressive occlusive arteriopathy of the distal internal carotid arteries. The idiopathic form, also known as "primary moyamoya" or "moyamoya disease," occurs more commonly in children of Japanese or Korean descent, although it has been observed in all ethnicities. Secondary moyamoya, or "moyamoya syndrome," can develop after brain radiation for the treatment of childhood cancers, most commonly retinoblastoma, or can occur in genetic conditions, such as sickle cell disease, Down syndrome, neurofibromatosis type 1, and a rare form of primordial dwarfism. The name, Japanese for "haze" or "puff of smoke," comes from small collateral blood vessels that form near the site of occlusion and give a hazy appearance on conventional angiography. Moyamoya typically manifests with ischemic strokes or transient ischemic attacks in early to mid childhood. However, if a child develops enough collateral blood flow to preclude ischemic events, he or she may not present until young adulthood with a hemorrhagic stroke, typically due to rupture of the abnormal moyamoya collaterals. Surgical treatment of moyamoya includes a variety of revascularization procedures intended to bypass the internal carotid circulation and improve cerebral perfusion.

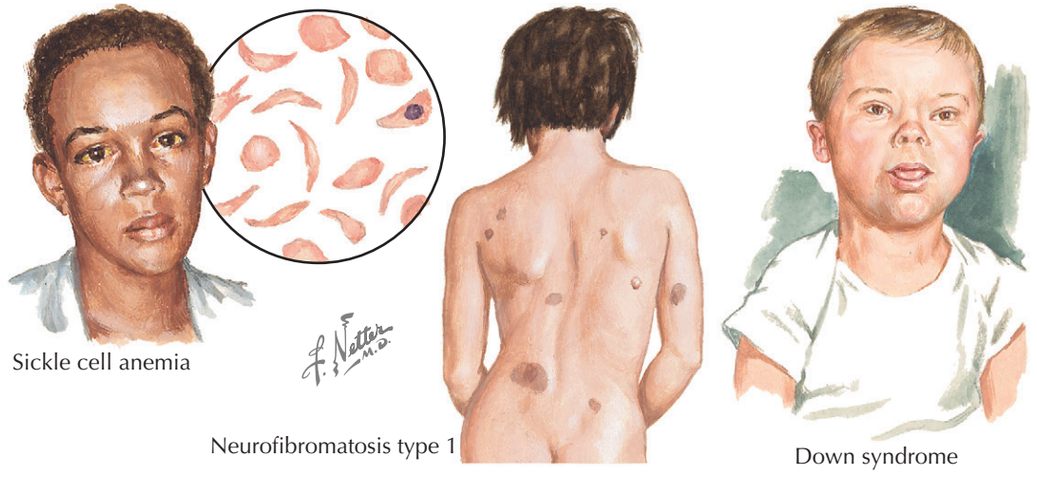
PHACE Syndrome. PHACE is a recently recognized neurocutaneous syndrome that includes *P*osterior fossa abnormalities, such as cerebellar hypoplasia or Dandy-Walker malformation; large, segmental cervicofacial *H*emangiomas; cervical and/or cerebral *A*rterial anomalies; *C*ardiac anomalies, such as coarctation of the aorta; and *E*ye abnormalities, such as optic nerve atrophy, congenital cataracts, and retinal vascular abnormalities. The skin hemangiomas seen in PHACE are considered infantile hemangiomas, defined as benign neoplasms of the vascular endothelium that display a characteristic natural history of being absent or minimally apparent at birth, growing rapidly during infancy, and then slowly regressing. The cerebrovascular anomalies vary widely from clinically insignificant "normal variants," such as a duplicated vessel or persistent fetal vessel, to severe hypoplasia of the internal carotid artery that can lead to ischemic stroke.

Vein of Galen Malformations. Vein of Galen malformations (VOGM) are congenital arteriovenous fistulas, or direct connections between arteries and veins, that drain into the developmental precursor of the vein of Galen, a midline vein that is part of the deep venous drainage system of the brain. VOGMs are easily detected on head imaging, even prenatal ultrasounds, as a large midline vascular structure. VOGMs can present in the neonatal period with high-output congestive heart failure, often with pulmonary hypertension. If the flow is not sufficient to lead to heart failure, they will often present later in infane with symptoms of hydrocephalus. VOGMs can injure the brain by causing venous ischemia (poor perfusion due to local high venous pressures), or, rarely, intraventricular or intracerebral hemorrhage. Findings on exam will include a pulsatile cranial bruit, macrocephaly, and prominent scalp veins. These lesions are treated with embolization, that is, endovascular placement of embolic material to close off the abnormal artery to vein connections. Although presentation during the neonatal period with congestive heart failure portends a poor prognosis, children whose VOGMs can be cured before the brain is injured can have a normal outcome.

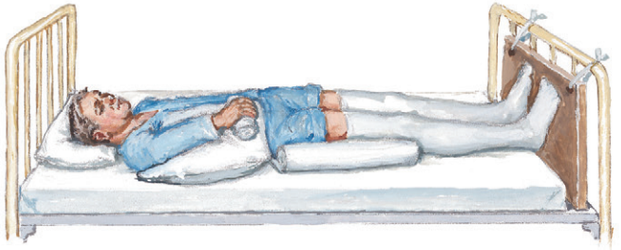
In **VOGM,** the turbulent blood flow caused by the arteriovenous fistulae generates a pulsatile cranial bruit better auscultated over the anterior fontanel



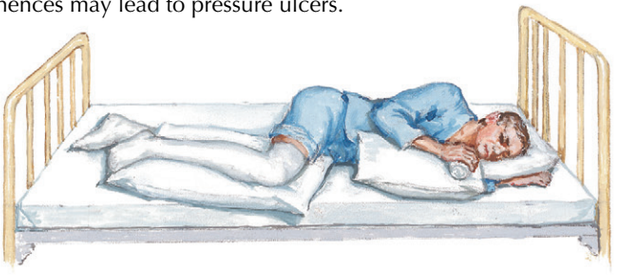
Children at risk for moyamoya syndrome



Positioning in bed after stroke



Supine position. Mattress firm, left flat. To avoid dependent edema, affected upper limb supported on pillow with shoulder abducted, hand slightly higher than elbow, and elbow slightly higher than shoulder. Small towel roll or orthosis used to maintain hand in functional position and minimize contractures of finger or wrist. Towel roll alongside trochanteric region and thigh (extending slightly under body to secure it) prevents external rotation of paretic limb. Foot board deters contracture of Achilles tendon and equinus of foot. Pressure stockings prevent deep vein thrombosis and thrombophlebitis, which may result in pulmonary embolism. Patient's position must be changed frequently because total immobility with continous pressure over bony prominences may lead to pressure ulcers.



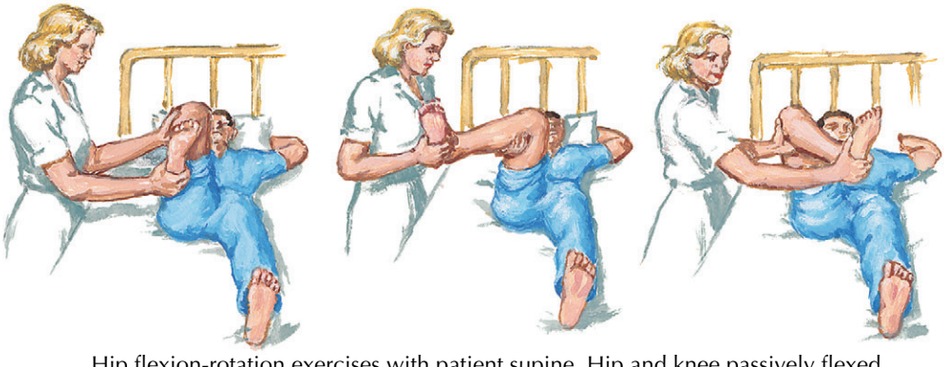
Side-lying position. Patient's forearm and hand suported on pillow. Another pillow placed under paretic lower limb, between knees and ankles. Note towel roll in hand and pressure stockings.

Passive range-of-motion exercises after stroke

With patient supine, therapist places one hand under knee; other hand grasps heel

Leg lifted, bending knee, then pushed toward patient's head as far as possible without causing pain

Leg passively extended, partially relaxing hip flexion. Limb then lowered to starting position.



Hip flexion-rotation exercises with patient supine. Hip and knee passively flexed, then limb rotated laterally and medially as pain permits.

Introduction and Initial Stroke Rehabilitation

Very few clinical events provide such a major challenge to the previously healthy and physically vigorous individual than the precipitous, absolutely unexpected, and emotionally devastating loss of focal neurologic function that occurs with a stroke. Whether the patient is literally struck down in the midst of a familiar, seemingly nonthreatening setting, or awakens from their sleep with an inability to speak and/or use his or her limbs, and/or sustains a significant loss of vision, or becomes comatose, the physicians, nurse, and rehabilitation therapist are responsible not only for finding the pathophysiologic mechanism leading to the event but also to plan for the patient's rehabilitation. Such a program is multidimensional and often instituted within the first 24 to 28 hours.

Positioning after stroke is carried out with goals of preventing joint contractures, edema of the paretic extremity, pressure ulcers over bony prominences, and aspiration. The patient can be positioned fully supine or at 30 degrees head elevation (depending on aspiration risk) on a firm pressure relief mattress with hips slightly abducted, toes pointing up with use of towel rolls along the outer thigh or resting lower extremity splints and heels kept off the bed using pressure relief boots or pillows under the calves. Ankle plantar flexion contractures can be prevented by using a footboard or resting splints and upper extremity edema minimized by elevating the paretic arm on a pillow. Patients need to be turned a minimum of every 2 hours if they are not able to do so independently with the most efficacious side-lying position set at 30 degrees, using pillows to support the paretic arm and leg.

Passive range-of-motion exercises help prevent contractures that can develop in muscles and tendons of paretic limbs. During these exercises, the limb should be fully supported and brought through as full a range of motion as possible without causing pain.

Transfer training begins early in rehabilitation of the patient with hemiplegia. Ability to maintain a sitting position with assistance and following directions are the minimal requirements. An assisted transfer can be performed using a slide board, lateral scoot technique, or a stand-pivot technique, where the clinician may need to block the knee and provide significant physical assistance to move the patient from one sitting surface to another. This is best illustrated on moving from bed to wheelchair; as the patient recovers, the degree or assistance provided decreases with the ultimate goal of full independence.

Depression is another expected complication of any major stroke. It is very important to keep this possibility under consideration at all phases of rehabilitation therapy. Initial family support and encouragement is essential if at all possible. The clinician must be alert to loss of interest in pursuing rehabilitation efforts as well as the potentially depressing setting once a recent stroke patient is transferred to a rehabilitative setting where he or she is exposed to individuals with similar or worse outcomes not seeming to respond to therapy. Judicious use of antidepressant agents, including tricyclics and selected serotonin and epinephrine reuptake blockers, may prove beneficial. Cognitive therapy with a supervising psychiatrist and psychiatric social worker may also prove to be beneficial.

Aphasia Rehabilitation

Approximately 90% to 95% of adults are right handed. Evaluation of stroke patients estimates that left-hemisphere language dysfunction occurs in more than 95% of right-handed individuals and in almost 20% of left-hand dominant persons. This has been further verified earlier on using intracarotid arterial amobarbital during investigations. More recently, functional magnetic resonance imaging (fMRI) has confirmed the presence of left brain language dominance.

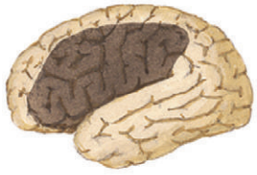
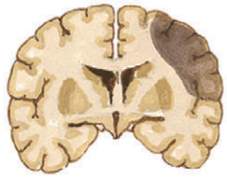
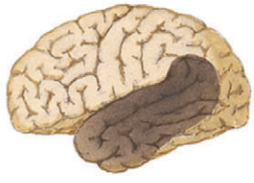
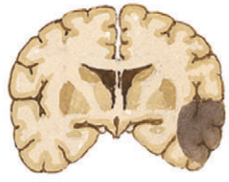
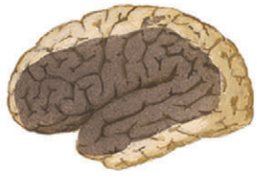
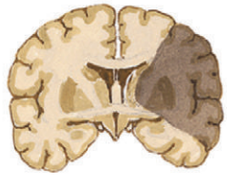
Broca aphasia is the classic form of frontal lobe language dysfunction with dominant hemisphere lesions. It is characterized by a *nonfluent*, *effortful*, *slow*, *and halting speech*. This language dysfunction is typically of reduced length, that is, few words with reduced phrase length, simplified grammar, and impaired naming. Repetition is characteristically intact. These individuals often have associated apraxia (buccofacial, speech, and of the nonparalyzed limb) and right-sided weakness of the face and hand.

Wernicke aphasia is the classic example of language dysfunction occurring with a left superior temporal gyrus stroke, often secondary to left middle cerebral artery emboli. Typically, such patients have *fluent* spontaneous speech with *phonemic* (mixed syllables) and *verbal* (incorrect words) *paraphasic* errors sometimes referred to as a *word salad*. Often these individuals exhibit naming and repetition problems associated with comprehension, reading, and writing impairments. Sometimes these patients are not completely aware of their various limitations; however, when they are cognizant of these same problems, this can be extremely frustrating, leading to emotional lability. Less commonly, the temporal lobe may be disconnected from other or both auditory cortices. This may result in certain circumscribed language function disorders referred to as a *disconnection syndromes*. *Pure word deafness* is defined as loss of pure language word recognition while retaining one's ability to normally hear and interpret meaningful nonverbal sounds such as a dog barking or a telephone ringing.

Global aphasia occurs with a more extensive dominant hemisphere cerebral infarction, leading to marked functional damage (see Plate 9-46). Here the patient may initially be unable to express any language function. As improvement begins, the damage may remain more pronounced in the frontal or temporal parietal cortex, with either a Broca- or Wernicke-type deficit emerging as the primary residual language impairment.

Prognosis for recovery from aphasia depends on the location and extent of lesion. Most patients improve to some extent, with greatest gains in the first few months, although there is significant treatment response with speech therapy regardless of the time postonset. Most communication therapy is provided through a multifactorial model and may include both context- and skill-based approaches combining multiple sensory stimuli, such as pictures and music, focus on semantics and repetition, and using emotional and social components in speech. Intensity of therapy, rather than the method, seems to be more important in the recovery response.

Constraint-induced aphasia therapy, a high-intensity treatment approach that restricts the use of nonverbal communication, has recently shown significant positive results in some patients with chronic aphasia. This rehabilitation language therapy is directed at a few individuals with a chronic aphasia entered into a group therapy program. These patients are encouraged to increasingly use verbal responses, emphasizing more expansive word output over time with hopes of maintaining these changes in treated individuals having chronic aphasia. Alternative compensatory means to attempt to communicate without language function are very much discouraged, for instance, writing, drawing, and various simple gestures during group therapy sessions. This modality demands a very significant daily time commitment of 2 to 3 hours per session, often taking place over a matter of months. The overall goal is to promote improved verbal language output. Initial reviews suggest that this very intensive therapeutic program is more effective for patients with nonfluent frontal Broca-type aphasias.

Infarct, surface	Infarct, coronal section	Clinical manifestations
		**Broca aphasia (if on left side)** Contralateral hemiplegia, hemisensory loss, gaze palsy, spatial neglect  Patient trying to find words but only producing nonfluent effortful, slow, halting speech
		**Wernicke aphasia (if on left side)** Contralateral hemianopsia or upper quadrantanopsia Constructional dyspraxia (if on right side)  Fluent phonemic mixed syllables verbally incorrect words (i.e., paraphrase errors/ "word salad")
 F. Netter M.D.		**Global aphasia (if on left side)** Contralateral gaze palsy, hemiplegia, hemisensory loss, spatial neglect, hemianopsia May lead to decreased consciousness and even coma secondary to edema  Right-handed patient with severe hemisphere deficit unable to utter any language or comprehend with hemiplegia individual

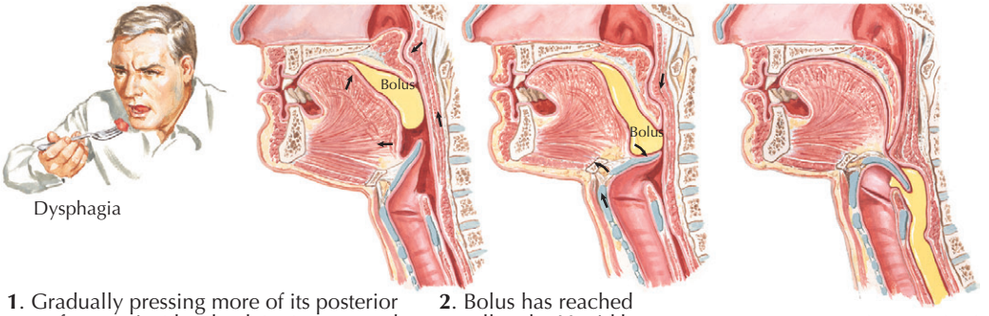
Other Rehabilitative Issues: Dysphagia/Gait Training/ Locked-in Syndrome

Dysphagia

A majority of stroke patients have dysphagia, typically the oral or pharyngeal swallowing phases. These symptoms can be variously related to differing anatomic area infarctions, predominantly brainstem and sometimes cortex or internal capsule. Symptoms relate to (1) poor food manipulation within the mouth, including bolus propulsion toward the oral pharynx; (2) incomplete bolus movement through the pharynx; (3) poor laryngeal epiglottic closure; and (4) difficult vocal cord closure, each increasing aspiration risk. Diagnosis and definition of dysphagia types is aided by a clinical speech swallowing therapist. Sometimes supplemental studies are helpful: videofluoroscopic modified barium study or a fiberoptic endoscopic evaluation of swallowing (FEES) test.

Dysphagia management is multidimensional, including emphasis on oral hygiene. Range-of-motion exercises, oral motor strength, and coordination, including lip, tongue, and jaw and respiratory muscles and vocal cord adduction, are performed 5 to 10 times per day. Compensatory strategies include head rotation to the weaker side, tucking the chin while swallowing, and performing dry swallows between boluses of food to reduce aspiration risk. These programs are initiated as soon as the patient is alert enough to understand instructions. Modern stroke therapy protocols emphasize these modalities to prevent aspiration pneumonias that prolong hospitalization, often requiring intensive care stays with increased fatalities.

Dysphagia



Dysphagia

1. Gradually pressing more of its posterior surface against hard palate, tongue pushes bolus backward into oral pharynx. Soft palate is drawn upward to make contact with Passavant ridge, closing off nasopharynx. Receptive space in oral pharynx forms by slight forward movement of root of tongue. Contraction of stylopharyngeus and upper pharyngeal constrictor muscles draws pharyngeal wall upward over bolus.

2. Bolus has reached vallecula. Hyoid bone and larynx move upward and forward. Epiglottis is tipped downward. "Stripping wave" on posterior pharyngeal wall moves downward.

3. "Stripping wave" has reached vallecula and is pressing out last of bolus from there. Cricopharyngeus muscle has relaxed, and bolus has largely passed into esophagus.

F. Netter M.D.

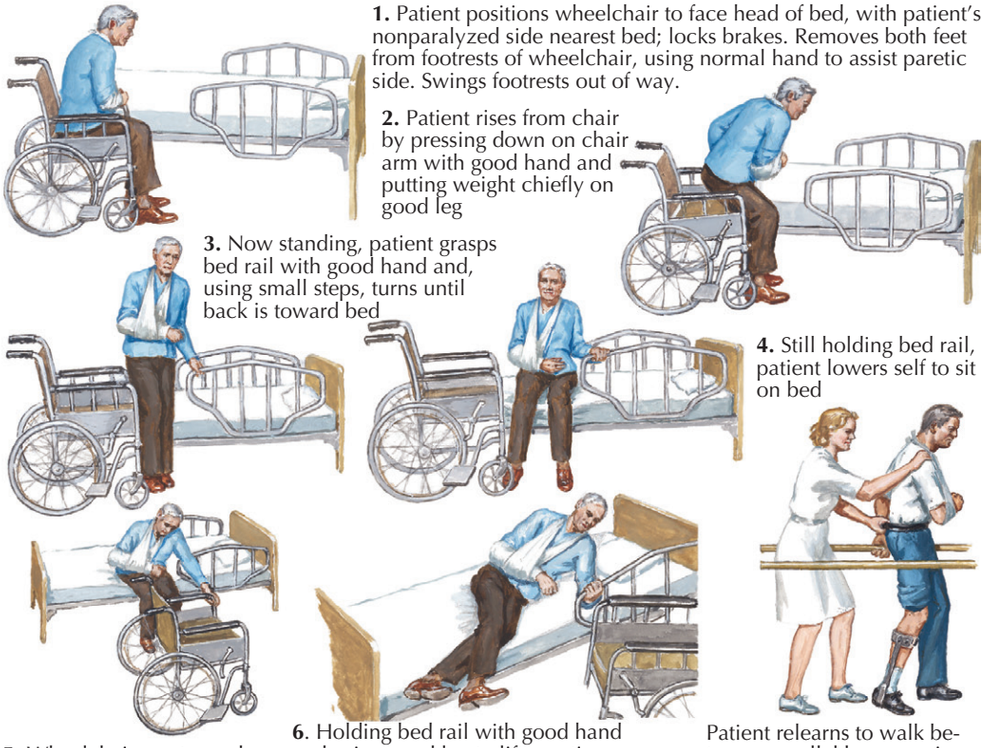
Gait Disorders

Therapeutic approaches to the patient with gait disorders after a stroke focus initially on proximal muscle stabilization, often using proprioceptive neuromuscular facilitation techniques to regain better distal extremity control. Therapy can use verbal or visual feedback for more symmetric foot placement with a narrower base of support and use a stepwise approach to improve balance and gait stability by working on turns, walking backward, or sideways, step ups and downs, and using progressive external perturbations. Strategies such as using weighted walkers for more external support and use of ankle weights to improve proprioceptive feedback have also been used with some success in patients with ataxic gait.

Gait training should be initiated when the patient has sufficient postural control to maintain an upright stance. Parallel bars and assistance from one or more therapists may be required in the early stages. *Ankle foot orthoses (AFO)* support paretic muscles and provide stability to the ankle and knee joints of patients with hemiplegia during transfer and gait training. New technologies that allow patients to begin gait training earlier and facilitate motor recovery include *partial weight support lower extremity robotic devices* and *functional electrical stimulation orthoses.*

Gait training in those with hemiplegia focuses treatment on the component parts of the gait cycle. The patient initiates gait by weight shifting toward the stronger leg in order to unweight the paretic one. The patient is then instructed to flex the paretic hip, minimizing external rotation and using the inertia of the leg to swing the leg toward a position slightly forward and lateral, ideally making contact at the heel rather than the forefoot. Toe clearance during swing phase of gait and heel strike is usually aided by an orthotic to assist with dorsiflexion. The patient is then told to contract the paretic side quadriceps and gluteals before shifting his or her weight to the paretic side in order to unweight and advance the stronger leg. More advanced hemiparetic gait training focuses on improving the symmetry of gait by working on hip flexion, weight shifting, stance duration, foot placement, and arm swing. However, patients often require other interventions, including pharmacologic means such as Botox or baclofen (a γ-aminobutyric acid [GABA] agonist), for tone management to significantly impact gait quality.

Gait disorders–transfer from wheelchair to bed after stroke



1. Patient positions wheelchair to face head of bed, with patient's nonparalyzed side nearest bed; locks brakes. Removes both feet from footrests of wheelchair, using normal hand to assist paretic side. Swings footrests out of way.

2. Patient rises from chair by pressing down on chair arm with good hand and putting weight chiefly on good leg

3. Now standing, patient grasps bed rail with good hand and, using small steps, turns until back is toward bed

4. Still holding bed rail, patient lowers self to sit on bed

5. Wheelchair must now be swung out of way and positioned for next use. May be done by patient or attendant.

6. Holding bed rail with good good hand and using good leg to lift paretic one, patient swings both feet onto bed and lies down on good side. May then roll onto back or to other position.

Patient relearns to walk between parallel bars wearing ankle-foot brace or orthosis. Support by attendant usually necessary at first.

Locked-in Syndrome

Patients with locked-in syndrome resulting from basilar thrombosis (see Plate 9-21) benefit from intensive rehabilitation. Although most patients remain locked in, some patients can regain motor function over time, occurring up to a year poststroke. Areas of focus are dysphagia therapy, communication, respiratory function, seating, mobility and, where able, activities of daily living. Augmentative communication devices triggered by sensitive switches or eye tracking systems can allow individuals to communicate, control their environment, and use computer-based entertainment.

MULTIPLE SCLEROSIS AND OTHER CENTRAL NERVOUS SYSTEM AUTOIMMUNE DISORDERS

MULTIPLE SCLEROSIS: OVERVIEW

In temperate climates, multiple sclerosis (MS) is the most common episodic neurologic illness of early adult years. The process begins as periodic and focal loss of central nervous system (CNS) myelin and the oligodendrocytes (OGCs) that synthesize myelin. Axons that have lost their myelin function imperfectly or not at all. Accordingly, symptoms ensue, and as episodes recur, disability accumulates.

MS is thought to be an autoimmune disease even though no antigens are identified, with certainty, against which a disease-relevant autoimmune response might be directed. As with other autoimmune entities, there is a genetically determined propensity to develop the illness. The strongest positive genetic association is with the class II major histocompatibility complex (MHC) antigen, that is, the human leukocyte antigen (HLA)-DRB1*15:01. HLA-DR alleles present antigenic peptides to $CD4^+$ T cells, pointing to a *major disease-promoting role for $CD4^+$ T cells* in MS. In contrast, HLA-A*02:01 expression is reduced in MS, indicating a protective role for this, the most commonly expressed class I allele in humans. The less prevalent HLA-A*03:01 class I allele doubles risk for developing MS. HLA-A alleles present antigenic peptides to $CD8^+$ T cells, indicating that *$CD8^+$ T-cell–mediated protection is suboptimal in MS. HLA-A*03:01 and HLA-DRB1*15:01 are independent risk factors*. Genome-wide studies have identified some 50 additional minor genetic associations. Most have a role in immune system function with a major enrichment in cell surface receptor genes implicated in T-cell activation and proliferation. One third of identified genomic loci overlap with regions associated with one or more other autoimmune diseases.

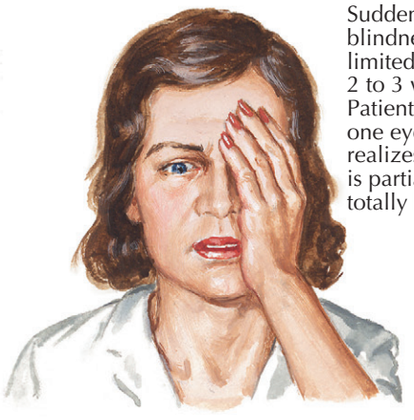
The prevalence of MS can be as high as 1 in 500 in the overall population. Twenty percent of patients have a blood relative with the disease. In siblings and in children of an affected parent, concordance for MS is 1% to 3%, ruling out simple dominant, recessive, or sex-linked inheritance. Siblings share half their genes. Yet, even among identical twins sharing all their genes, MS concordance is only 25%, indicating that environmental factors have a major role in determining risk for MS.

Epstein-Barr virus (EBV) is acquired in adolescence or early adult years in developed countries, where MS is encountered frequently and where EBV often causes infectious mononucleosis; in less-developed countries, where MS is uncommon, EBV is usually acquired asymptomatically in early childhood. Unlike controls, at diagnosis all MS patients test positive for prior contact with EBV, and a history of frank infectious mononucleosis (always before disease onset) is increased threefold over the general population. *EBV is at present the leading candidate environmental trigger* for propensity to develop MS. The presence of subnormal *vitamin D levels* is a possible additional putative environmental factor in MS. This vitamin is *an inflammatory response inhibitor* and an *enhancer of regulatory T-cell function*, coupled with the fact that MS is uncommon in regions with high sunlight exposure, the chief inducer of vitamin D synthesis.

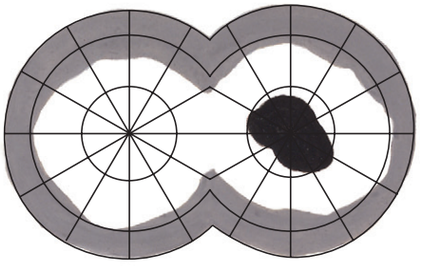
Clinical Course. MS usually begins in young adults; peak age at first attack is 30 years, but onset can occur before age 10 years or after age 50 years. MS is two to three times as frequent in women. Eighty-five percent of patients present with a clinically isolated syndrome characterized by subacute loss of neurologic function that will usually worsen over a week or more, stabilize for a time, and eventually recover partially or, quite often, completely. Subsequently, after highly variable intervals, additional episodes, known as relapses, develop. Relapses, having finite spans of a few weeks, are followed by recovery of variable extent and duration. Periods of seeming disease quiescence occur with remissions lasting for months or years. These patients are referred to as having relapsing-remitting multiple sclerosis (RRMS). Symptoms and signs vary from one relapse to the next as additional sites of myelin loss accumulate within the CNS white matter. Sites of myelin loss are called plaques; their locations determine symptoms.

After some years, the character of MS can change. Relapses diminish in frequency, ultimately cease, and are replaced by slow but steady worsening of nervous system impairment referred to as secondary progressive MS (SPMS), distinguishing it from the 15% of cases in which a primary progressive course is present from symptom inception. Primary progressive MS (PPMS) usually begins later in life than RRMS; a female preponderance is less evident. The usual presentation is a slowly progressive myelopathy evolving into paraparesis or paraplegia.

Visual manifestations

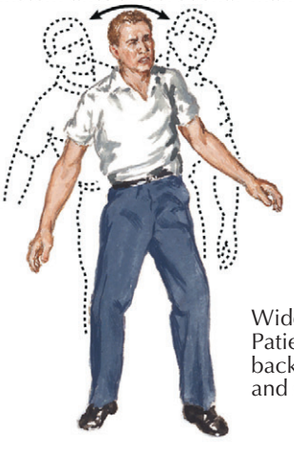


Sudden unilateral blindness, self-limited (usually 2 to 3 weeks). Patient covering one eye, suddenly realizes other eye is partially or totally blind.

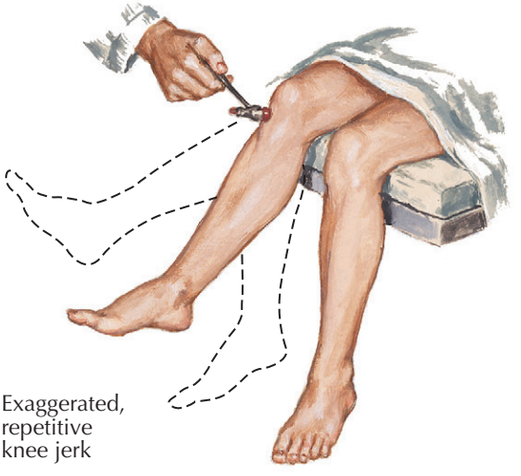


Visual fields reveal central scotoma due to acute retrobulbar neuritis

Brainstem and/or cerebellar manifestations



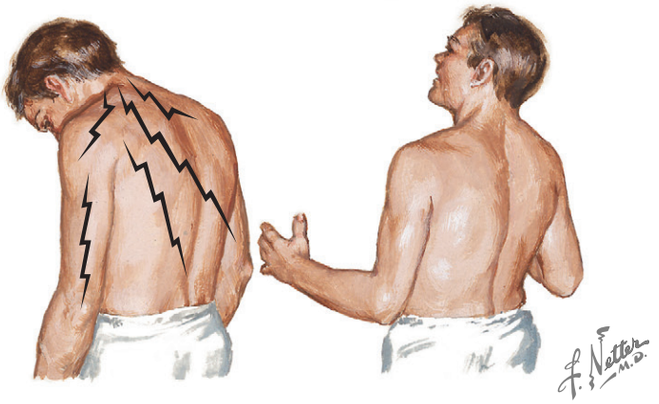
Wide-based gait. Patient teeters back and forth and sideways.



Exaggerated, repetitive knee jerk

Spinal cord manifestations

Spastic gait. Patient needs help walking.



Lhermitte sign: sudden sensation of electric shock down spine and along arms when patient flexes neck

Multiple Sclerosis: Clinical Manifestations

Symptoms and signs of MS vary with the locations of the plaques.

Optic Neuritis

Typically, patients experience relatively abrupt unilateral decrease in central or paracentral vision with pain on movement of the globe; this is a very common MS presentation. At times, symptoms are subtle, with brief episodes of decreased visual acuity provoked by exposure to heat, such as hot showers, followed by prompt resolution. Magnetic resonance imaging (MRI) may show a lesion in the affected optic nerve, and usually, if this is a first attack of MS, other lesions indicative of earlier clinically silent multiple sclerosis activity are seen on brain MRI. Optic neuritis without the concomitant presence of such MRI lesions is seldom an initial sign of MS. Optic disc pallor often develops during recovery.

Brainstem Lesions

These are common and tend to occur early. Diplopia is usually caused by a lesion affecting the abducens (VI) nerve. *Nystagmus* is a common sign but is usually asymptomatic. It is a particularly useful sign when it is pronounced in degree and especially when the primary component is vertical.

Internuclear ophthalmoplegia is a classic MS sign indicating involvement of the medial longitudinal fasciculus. Examination reveals paresis of adduction on lateral gaze and associated nystagmus in the abducting eye. Despite the unilateral loss of adduction on lateral gaze the ability to converge (i.e., bilateral adduction) may be preserved.

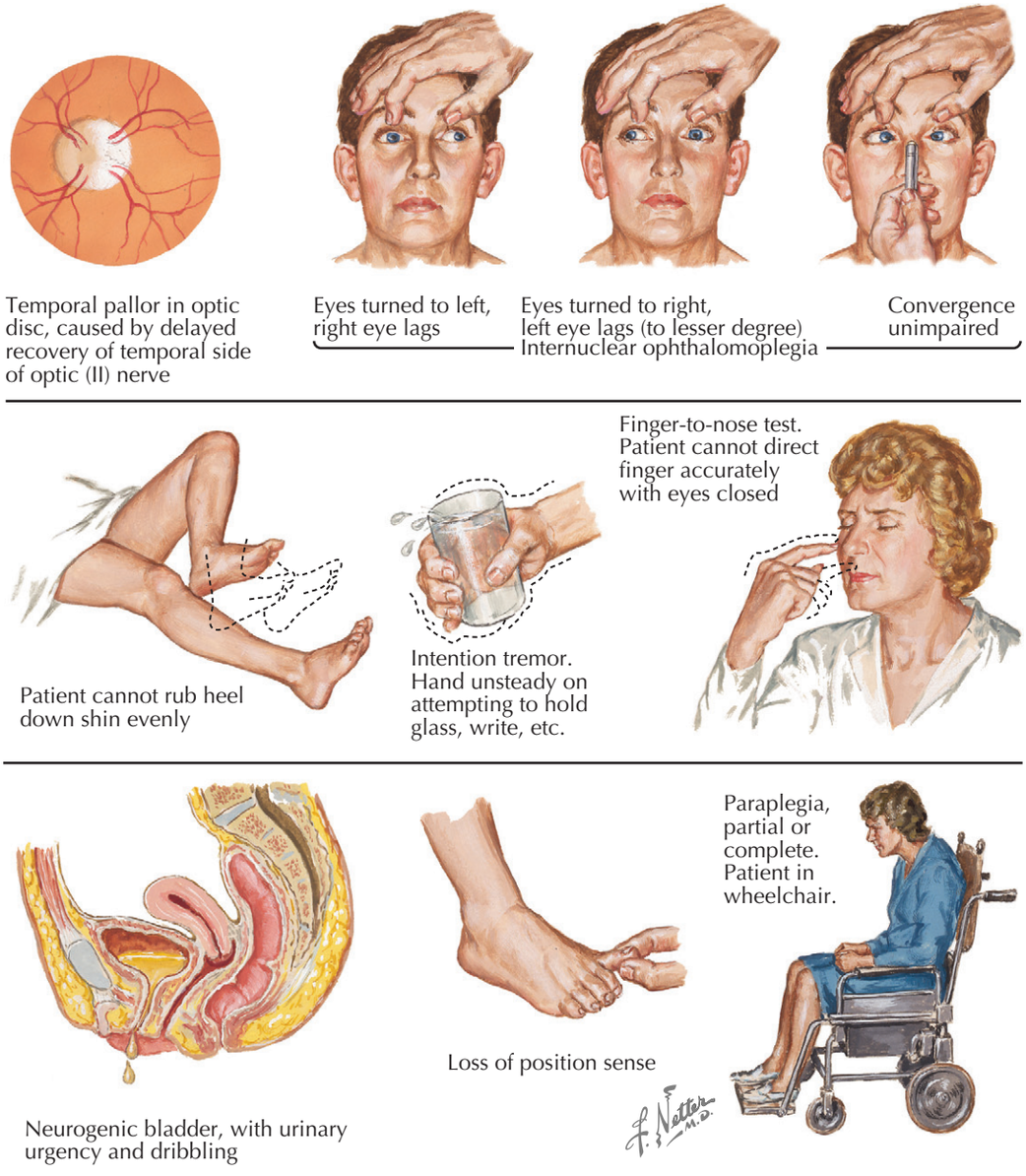
Vertigo may be difficult to differentiate from a benign labyrinthitis, although a finding of vertical nystagmus points to a CNS rather than a peripheral cause. *Trigeminal neuralgia* is sometimes confused with idiopathic tic douloureux, a disease primarily of senior adults. *Trigeminal neuralgia* occurring in young adults is highly suggestive of MS because it is otherwise most atypical in this age group. Similarly, facial weakness may be mistaken for *Bell palsy*.

Cerebellar Ataxia

This occurs in about 50% of patients. Symptoms include poor balance, intention tremor, dysarthria and, when ataxia is extreme, titubation. Cerebellar symptoms can be severely disabling.

Sensory Symptoms

Typically occurring early with paresthesias and dysesthesias, often described as constricting or swollen sensations, these symptoms indicate posterior column demyelination in the cervical spinal cord, an area that may be affected early in MS. A hemicircumferential bandlike patch of numbness, usually midtrunk, is frequent but can also be seen with transverse myelitis or spinal cord mass lesions. Often patients forget to mention a very important, clinically useful phenomenon, namely the Lhermitte sign. The physician needs to inquire about this symptom because patients seldom volunteer this information. The Lhermitte sign is typified by momentary electric shocklike sensations shooting or radiating down the arms, back, or legs, precipitated by neck flexion. However, the Lhermitte sign is not diagnostically specific; other posterior cervical spinal cord lesions can provoke it. Examination often reveals diminished vibration and position sense.



Corticospinal Tract Dysfunction

This causes muscle fatigue, stiffness, spasticity, and weakness. Hyperreflexia, clonus, and the Babinski sign are frequently elicited. *Clonus* is a form of movement marked by contractions and relaxations of a muscle occurring in rapid succession. Clonus is most often elicited at the ankle. The *Babinski sign* is an extension of the great toe and abduction, or fanning, of toes two to five instead of the normal flexion response to plantar stimulation.

Urinary frequency and urgency suggest a hyperreflexic neurogenic bladder. Constipation and sexual dysfunction are also frequent complaints.

Inordinate fatigability is common and can be overwhelming. Demyelinated axons require far more energy to conduct nerve impulses than properly insulated axons; thus conduction may fail with effort. For example, a limp may replace a seemingly normal gait after walking some distance, only to disappear after a rest period. The inefficiency of demyelinated axons worsens as body temperature rises, thus short-lived symptoms, including a transient limp, can be provoked by summer heat, taking hot showers, by fever, or may occur in the late afternoon, when the normally modest diurnal upward body temperature swing peaks, as does MS-related lassitude.

MS patients may experience ill-defined pain, presumably neuropathic in origin. However, one must always seek out other pathophysiologies before presuming that MS is the cause.

Depression

Occurring at some time in 50% of MS patients, episodes of depression sometimes antedate overt disease onset. The frequency of depression is threefold of that encountered in the overall population. Cardinal features are anger, frustration, irritability, anxiety, and frank panic attacks.

Cognition

Mildly deficient short-term memory frequently develops early. This can progress to substantial cognitive deficits in later years.

Multiple Sclerosis: Diagnosis

Magnetic Resonance Imaging (MRI)

Formerly, a firm diagnosis of MS required evidence of *dissemination* of *clinically detected deficits* in both space and time. This was achieved by documentation of two attacks, each lasting more than 24 hours (absent fever or infection), with each attack typical of an acute demyelinating event and with the requirement that there be objective clinical evidence of a lesion in the second episode at a site anatomically distinct from that documented in the first episode. Such a second event might not occur for years or even decades.

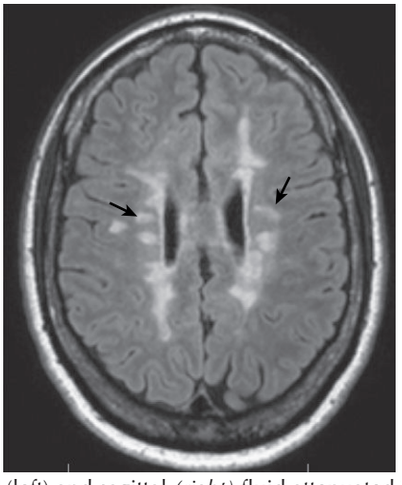
MRI has greatly enhanced the ability to establish a diagnosis early in the course of MS. This modality is noninvasive, reproducible, and sensitive to the presence or absence of disease and to both clinically evident and clinically silent changes in lesion burden. These features permit its use as a follow-up procedure to assess change.

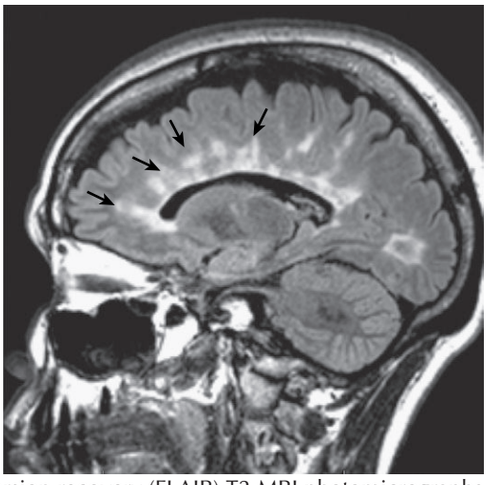
An MRI is highly sensitive for the presence of disseminated white matter lesions. Gadolinium (GD) enhancement provides insights into *active (enhancing) lesions* because GD crosses into the CNS parenchyma only at sites of *blood-brain barrier (BBB) leakage*, whereas established inactive lesions do not show GD enhancement. *New lesions* often have *central GD enhancement*, whereas a *ringlike* or arcuate enhancement may be seen with *reactivation* at the margin of an existing plaque.

MRI may permit diagnosis during an initial clinical occurrence if the study demonstrates evidence of one or more lesions with dissemination in space and time, as illustrated by the simultaneous presence of GD-enhancing and nonenhancing lesions of typical configuration and location (periventricular, juxtacortical, infratentorial, or spinal cord). Diagnosis can also be established if a new T2 or GD-enhancing lesion, often clinically silent, appears on a follow-up MRI.

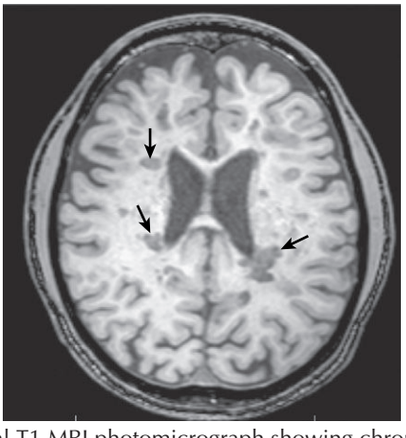
Classic MRI findings include so-called Dawson's fingers, consisting of multiple well-demarcated ovoid perivenular plaques with their long axes situated perpendicularly within the corpus callosum and extending upward from the roof of one or both lateral ventricles, often as a fore and aft row situated parallel to the midline. Additional preferential plaque location sites include subcortical white matter, the middle cerebellar peduncles, the pons, and the medulla beneath the floor of the fourth ventricle. Spinal cord plaques originate at the meningeal surface and expand inward. Spinal cord plaques, as with plaques elsewhere, need not be symptomatic. Gray matter lesions within the cerebral cortex can be abundant in MS but are usually underappreciated because they are poorly visualized by standard MRI techniques. Rarely, white matter lesions can be ominously large, so-called tumefactive MS, and may even on occasion require biopsy to exclude glioma.

Up to 40% of time-spaced serial MRI scans demonstrate new GD-enhancing lesions in untreated patients with RRMS. Most such lesions are clinically silent. The finding indicates a several-fold higher level of disease activity than can be appreciated by considering overt clinical relapses alone. In contrast, the majority (60% plus) of randomly obtained MRI scans do not show current activity; this illustrates the presence of relative disease quiescence much of the time. However, this clinically inactive hiatus is intermittently interrupted by episodic pulses of MRI-detected or clinical MS disease activity. The frequency of MRI-positive newly active lesions is reduced by up to 80% by current treatments. GD-positive lesions are uncommon in progressive MS.

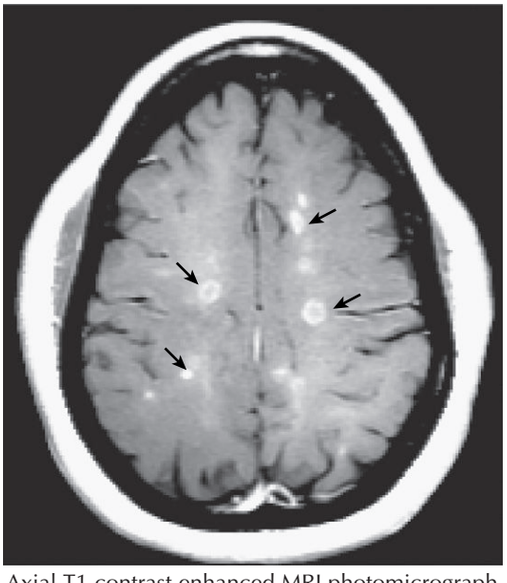




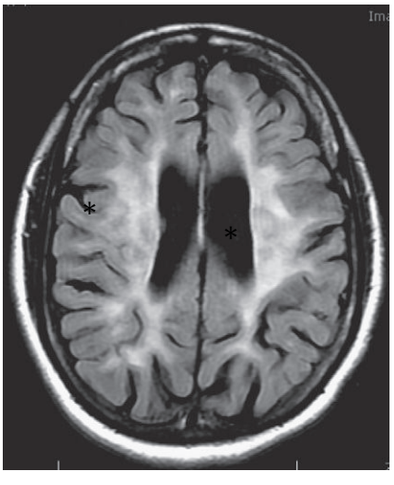
Axial (left) and sagittal *(right)* fluid attenuated inversion recovery (FLAIR) T2 MRI photomicrographs showing MS lesions radially distributed around the periventricular zone. The elongated lesions are referred to as Dawson fingers *(arrows)*, sites of prior perivenular demyelination.



Axial T1 MRI photomicrograph showing chronic scarring in the periventricular region *(arrows)*, which are referred to as T1 "black holes"



Axial T1 contrast enhanced MRI photomicrograph showing acute, inflammatory lesions in the brain *(arrows)*.



Axial FLAIR T2 MRI photomicrograph showing chronic stage of multiple sclerosis, with confluent T2 lesions and brain atrophy as evident by thinning of gyri, enlargement of sulci (asterisk), and ventricular dilatation.

The validity of a diagnosis of MS based on the MRI criteria described above is established for RRMS in adults in Western countries. Criteria for a diagnosis of PPMS still require at least 1 year of disease progression plus two of three of the following criteria: (1) evidence for dissemination in space (DIS) from spinal cord into the brain based on at least one T2 lesion, not necessarily new, in a location characteristic for MS; (2) evidence for DIS in the spinal cord based on two lesions in the spinal cord; and (3) cerebrospinal fluid positive for oligoclonal bands, a positive immunoglobulin G (IgG) index (see later), or both.

MS is uncommon in children, and diagnosis at present requires a second attack to distinguish it from acute disseminated encephalomyelitis (ADEM), a distinct demyelinating disorder that is almost always monophasic (see later). MRI features that strongly favor the likelihood that a first attack of demyelinating illness

Multiple Sclerosis: Diagnosis
(Continued)

will subsequently prove to be MS include presence of one or more T1-weighted hypointense lesions (black holes) indicative of prior CNS white matter damage or presence of one or more periventricular lesions. The likelihood for MS is further increased when both are present. In children younger than 11 years, MRI lesions are larger and more ill-defined than in teenagers or adults so that shape, size, and lesion frequency do not discriminate reliably between MS and ADEM, although a diffuse bilateral lesion pattern favors ADEM.

The reliability of MRI criteria currently accepted as valid in Western countries remains to be established in Asia and Latin America. The higher frequency of neuromyelitis optica (NMO) and NMO-spectrum disorders and the lower frequency of MS in these geographic regions raise concerns. Both NMO and MS usually relapse. Symptomatic brain lesions at disease onset do not exclude NMO (see later). It is important to clearly distinguish between MS and NMO because of their different clinical courses, prognoses, underlying pathophysiology, and the negative response of NMO patients to at least some of the MS disease-modifying therapies. Findings particularly suggestive of NMO are a myelopathy with MRI-detected spinal cord lesions that are central in location and span more than three spinal segments, and optic neuritis that is bilateral, severe, painless, and associated with a swollen optic disc or a chiasmal lesion. These findings warrant prompt testing for the aquaporin-4 autoantibody found in most patients with NMO, but by no means in all.

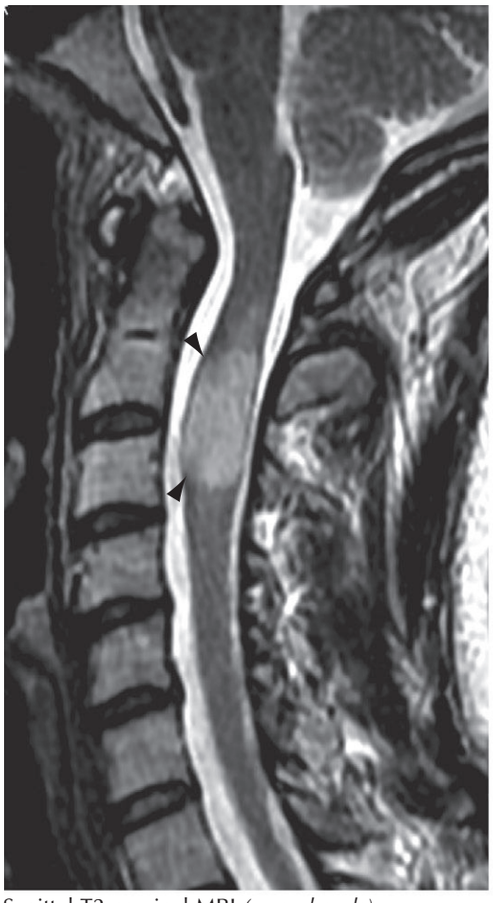
From time to time, lesions that appear to be typical for MS turn up unexpectedly on MRI scans of persons with no clinical symptoms suggestive of MS, no history of them, and no findings on examination. The MRI has usually been obtained for reasons unrelated to MS, such as headaches or head trauma. Several groups have followed such persons with this so-called radiologically isolated syndrome (RIS) for a decade or more. Many RIS cases have gone on to develop radiologic progression with new, enlarging, or GD-enhancing, but still asymptomatic, lesions. A smaller proportion have converted to clinically apparent MS. MS usually has a preclinical phase with asymptomatic lesions acquired in the past detected on MRI scans obtained at the time of a first clinical event. It is also agreed that treatment of a first MS attack is more effective than when treatment is delayed. As a counterbalance, it is well known that a forme fruste of MS exists. There are numerous reports of MS being found at autopsies of elderly persons with no known neurologic deficit during life.

Thus the conundrum: should one treat based on new asymptomatic lesions seen on an MRI scan? Can probability to develop overt MS be predicted? It has been proposed that presence of cervical spinal cord lesions shifts the odds for early appearance of clinically definite MS dramatically upward. If so, the absence of a cervical spinal cord lesion shifts the odds downward. The issue of when to treat remains open.

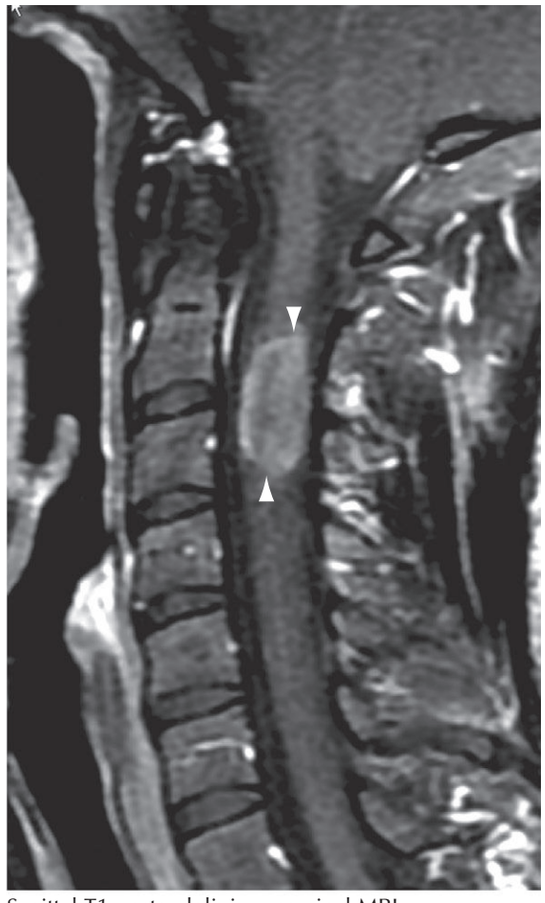
Tumefactive MS

One unusual radiologic imaging feature of MS is the presence of a large tumefactive lesion. Clinical features vary with the specific anatomic location of the lesion and may be atypical for MS. There may be cognitive abnormalities, mental confusion, aphasia, agnosia, seizures, ataxia, hemiplegia, and visual field defects. Median age at onset is about 37 years (8-69), and there is a slight female preponderance. Tumefactive lesions may be found in patients with an established diagnosis of MS, but when they present as a single, ominous-appearing, space-occupying lesion in patients experiencing a first neurologic event, there may be considerable diagnostic difficulty. Tumefactive lesions are larger than 2 cm in diameter, with an open-ring–enhancing edge, an edematous surround, and frequently, depending on their size, a mass effect. These imaging features may mimic a brain tumor, an abscess, other inflammatory disorders, vasculitis, or granulomatous disease and may lead to brain biopsy. Histologic examination reveals hypercellularity, confluent demyelination, foamy macrophages full of myelin debris intermingled with reactive large-bodied astrocytes, relative axonal preservation,

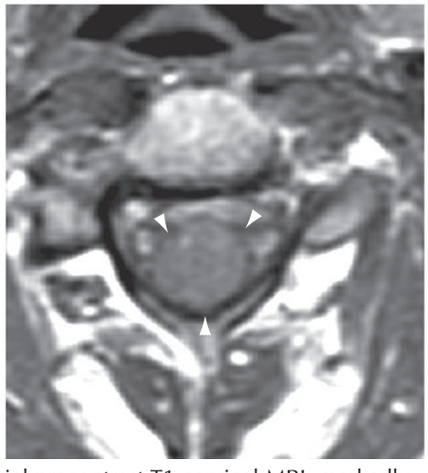
Spinal Cord MRI in Multiple Sclerosis



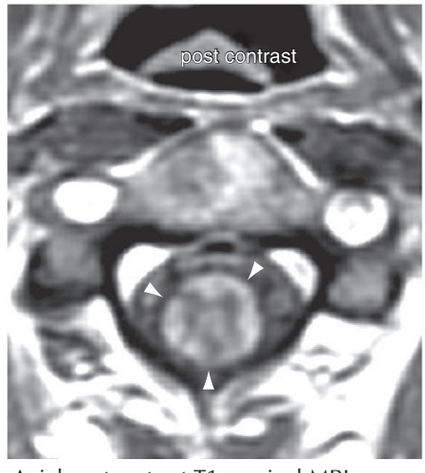
Sagittal T2 cervical MRI *(arrowheads)*



Sagittal T1 postgadolinium cervical MRI: large expansile hyperintense upper cervical cord plaque *(arrowheads)*



Axial precontrast T1 cervical MRI: markedly expanded cervical spinal cord *(arrowheads)*



Axial postcontrast T1 cervical MRI: expansile peripherally enhancing plaque *(arrowheads)*

Visual Evoked Response and Spinal Fluid Analysis

Multiple Sclerosis: Diagnosis
(Continued)

and variable perivascular and parenchymal lymphocytic infiltration.

Tumefactive lesions are commonly treated with intravenous methylprednisolone. Most patients respond favorably with substantial, and sometimes dramatic, contraction of lesion size over time. Solitary tumefactive lesions are usually a herald of MS. In one large series of cases, 70% of patients with tumefactive lesions developed definite MS, but the median interval to a second event was much delayed compared with the overall MS population, suggesting a favorable prognosis.

Cerebrospinal Fluid (CSF) Analysis

A spinal tap is performed less often today than formerly but may be helpful when the diagnosis is in doubt or to satisfy diagnostic criteria. Total white cell count is elevated in about 25% of MS patients, but rarely above 25 mononuclear cells per mm^3. The total protein concentration is slightly elevated in 40% of patients but is seldom greater than 75 mg/dL. In 40% to 60%, the γ-globulin (IgG) fraction is elevated above 15% of the total CSF protein, reflecting an increased production of IgG within the CNS. The IgG index provides a more precise estimate of IgG synthesis within the CNS. It is calculated as the ratio of IgG in CSF/IgG in serum divided by albumin in CSF/albumin in serum. A value greater than 0.7 is taken as abnormal and is found in 70% of MS patients. Unfortunately, the IgG index is not entirely specific for MS. Oligoclonal bands in the IgG sector of the protein isoelectric focusing pattern or immunofixation pattern, but not found in blood, are detected in more than 90% of cases and in fewer than 5% of controls once CNS infections are excluded. CSF pressure and glucose content are normal.

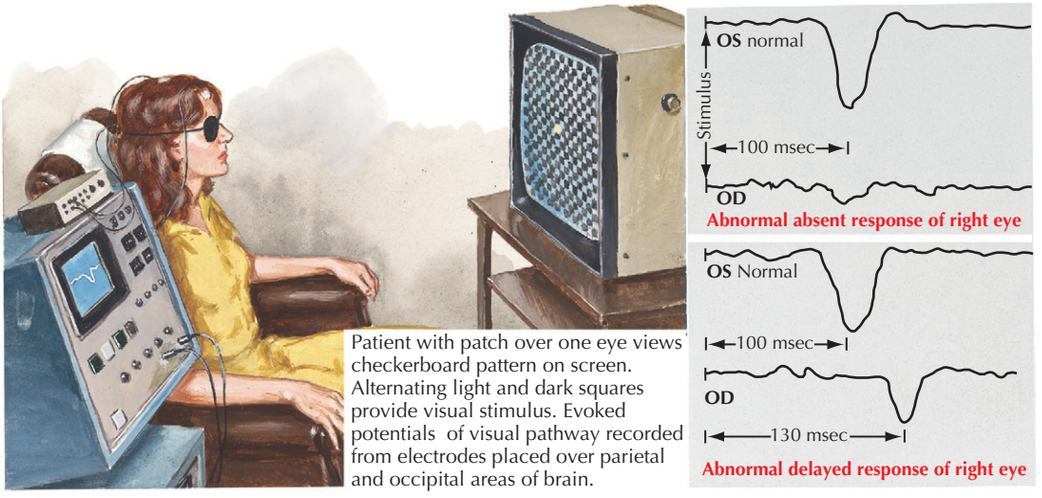
Evoked Potentials (EPs)

These neurophysiologic studies permit an objective analysis of the integrity of neuronal pathways in the CNS. Before the ready availability of MRI, EPs were widely used to identify subclinical CNS disease. Testing is easily performed and requires minimal patient cooperation, particularly when testing the visual pathways by means of visual evoked responses (VERs). In centers where MRI is at hand, brainstem and somatosensory EPs are seldom required today to confirm a tentative diagnosis of MS.

Today the primary value of EP testing occurs when a patient presents with an acute, seemingly monophasic myelopathy plus a normal brain MRI and one wishes to determine whether there might be dissemination of disease in space and time. Some patients may have had an earlier subclinical optic neuritis. Others may have either forgotten a prior episode of visual loss or offer an uninterpretable history of earlier visual disturbance now recovered. In such instances, VER testing may establish or exclude the presence of prior damage to visual pathways. The combination of an abnormal VER and a myelopathy is essentially confined to MS or neuromyelitis optica.

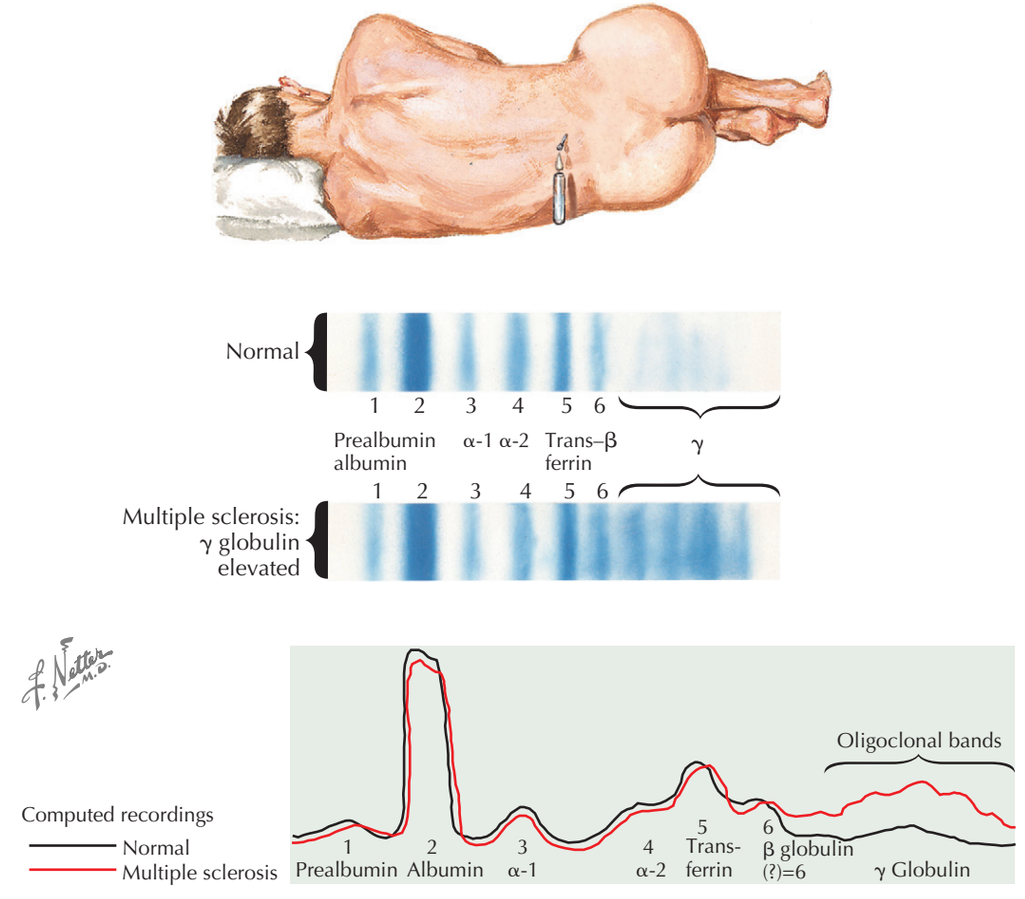
With VERs, a retinal stimulus, typically a reversing high-contrast checkerboard pattern, provides a means to study the integrity of the visual system. Response latencies provide objective data regarding the ability of the nervous system to transmit impulses efficiently from the optic nerve to the occipital cortex. If absence or delay of conduction is unilateral, one can conclude that there is slowed conduction between the retina and the optic chiasm typical for unilateral optic neuritis. VERs are most helpful when patients have fully regained their vision. Remyelination is never perfect so that a VER-documented slowing of conduction velocity provides an indelible marker of prior damage. When delayed latencies, attenuated potentials, or conduction block are bilateral, the lesion cannot be localized precisely because it could be situated anywhere along the visual pathway.

Visual evoked response (VER)

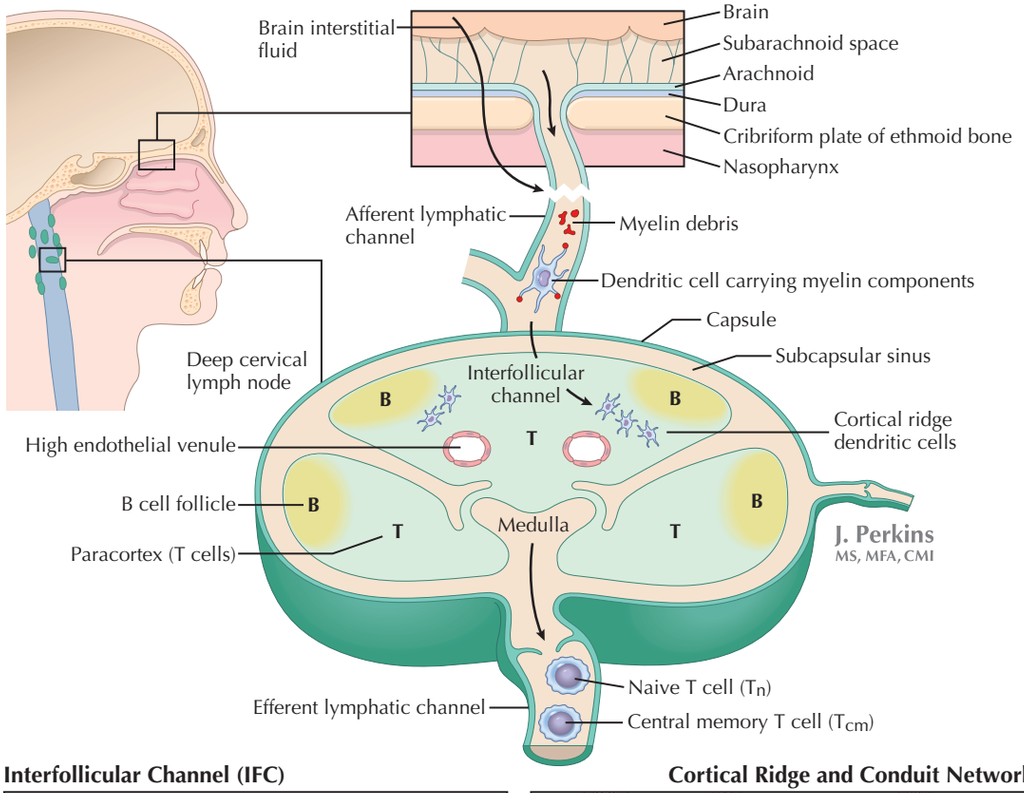


Patient with patch over one eye views checkerboard pattern on screen. Alternating light and dark squares provide visual stimulus. Evoked potentials of visual pathway recorded from electrodes placed over parietal and occipital areas of brain.

Cerebrospinal fluid electrophoresis



Deep Cervical Lymph Node – Multiple Sclerosis in Remission



Multiple Sclerosis: Pathophysiology

Peripheral Events That Precede a Multiple Sclerosis Relapse

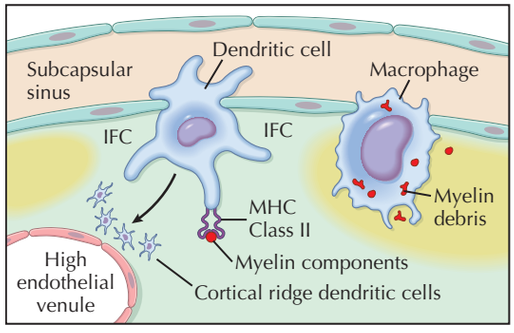
MS relapses evolve subacutely. The *accepted environmental antecedent for relapses* is an *upper respiratory viral illness*. Such illnesses activate the immune system, increasing relapse frequency two- to threefold, and leave behind greater deficits than relapses that occur without a history of a viral illness. Immune responses to viruses involve drainage of pathogenic antigens and antigen-presenting cells (APCs) along lymphatic channels to a regional lymph node (LN). Upper respiratory *viruses and viral antigens drain via nasal lymphatic channels into the subcapsular sinuses of the deep cervical LNs*. Immature dendritic cells (DCs) and monocytes lie beneath the subcapsular sinus and protrude processes into it, permitting them to sample newly arrived lymph and capture viral antigens. *Drainage of CSF and of brain parenchymal interstitial fluid occurs through the cribriform plate located below the olfactory bulb into nasal lymphatics and then into these very same deep cervical LNs.*

Immature DCs in the CNS subarachnoid space ingest myelin elements; after that, they may mature in situ. Mature DCs express the cell surface molecule C-C chemokine receptor 7 (CCR7), whereas endothelial cells in afferent lymphatic channels express chemokine ligand 21 (CCL21) counterligand. Ligation of CCR7 permits mature self-antigen–bearing DCs to migrate via afferent lymphatics to deep cervical LNs. Mature DCs are short lived and have lost their capacity to sample newly presented viral or other antigenic material, whereas long-lived immature DCs or macrophages can do so.

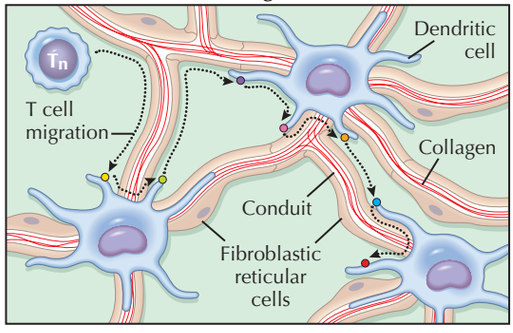
Extracellular debris, including myelin and its peptides, flows from a damaged CNS to deep cervical LNs where subcapsular macrophages and immature DCs capture it. Unlike controls, deep cervical LNs of MS patients with inactive disease contain numerous immature DCs and macrophages with ingested myelin and myelin proteins that can, under appropriate circumstances, be presented to T cells. Immature DCs and macrophages retain the capacity to respond to subsequently encountered viral antigens.

Naïve CD4⁺ T cells (T_N) move swiftly through LNs, making serial brief contacts with antigen-loaded DCs draped atop the fibroblastic reticular cells (FRC) that enwrap the collagen fiber structural backbone of the LN. Lymph is transferred from the subcapsular sinus to the medulla via the collagen-containing channels of the conduit network. DCs insert processes into the conduit channels to capture peptide elements contained therein, which they can then process and present to T cells. T_N cells seek that rare DC expressing the cognate antigen they are programmed to recognize. When a CD4⁺ T_N cell fails in its quest, as usually occurs, it migrates to the LN medulla and exits via efferent lymph. *Exit requires expression of the sphingosine-1-phosphate receptor-1 (S1P-1)* by migrating CD4⁺ T_N cells. This requirement has been exploited in MS therapy. CD4⁺ T_N cells pass from the efferent lymph

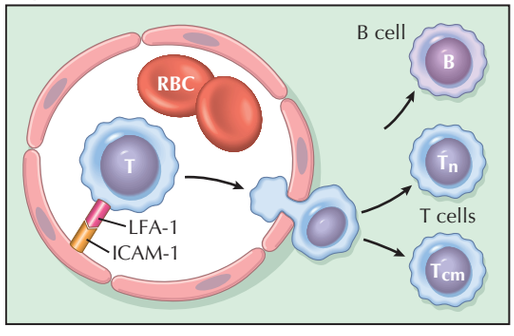
Interfollicular Channel (IFC)



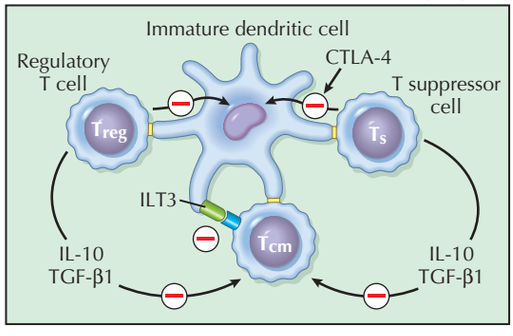
Cortical Ridge and Conduit Network



High Endothelial Venule



Tolerizing Signals



MULTIPLE SCLEROSIS: PATHOPHYSIOLOGY *(Continued)*

into the circulation and move on via the blood to sample another LN. They do not enter the tissues.

Circulating $CD4^+$ T_N cells express CCR7 and low levels of the adhesion molecule leukocyte function–associated antigen-1 (LFA-1). CCL21 and intercellular adhesion molecule-1 (ICAM-1), counterligands for CCR7 and LFA-1, respectively, are expressed by the high endothelial cells of venules sited in LN T-cell–dependent areas with a nearby cortical ridge that is enriched in DCs. CCR7 binding to CCL21 and LFA-1 binding to ICAM-1 enables $CD4^+$ T_N cells to cross from the blood via these venules into LNs passing either between LN endothelial cells or, intriguingly, as illustrated, through them.

When a $CD4^+$ T_N cell finally contacts a cognate antigen–expressing DC, it is either activated or tolerized. Both outcomes are germane to MS. Both require contact between the $CD4^+$ T_N cell receptor and an MS-relevant small peptide fragment cleaved from an ingested protein and inserted into a cleft in a human leukocyte antigen (HLA) molecule that then is expressed on the DC surface. Cognate antigen contact lasts longer than contact with DCs expressing irrelevant peptides, and contact is of even longer duration if the $CD4^+$ T_N cell is being activated rather than tolerized.

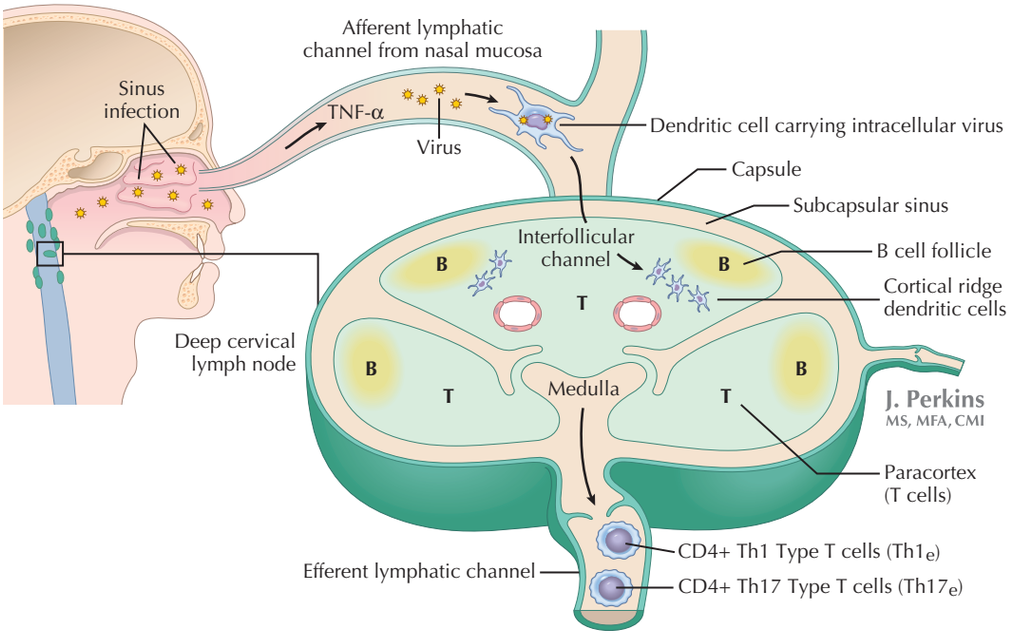
DC maturation is critical for activation of a $CD4^+$ T_N cell. Maturation involves increased expression of co-stimulatory molecules (e.g., CD80/86 and CD40) and reduced expression of tolerizing molecules (e.g., immunoglobulin-like transcript 3 [ILT3], transforming growth factor-beta 1 [TGF-beta1], and interleukin-10 [IL-10]). Full activation of $CD4^+$ T cells by DCs requires two signals. The first signal is delivered by T cell receptors following contact with their cognate antigen presented to them at an immunologic synapse by a MHC class II molecule. The second set of signals is delivered by a network of interactive costimulatory molecule pairs with CD80/86, expressed initially at low level by DCs, and CD28 expressed constitutively by T cells, providing one prototypic pair and CD40 expressed by DCs in the early stage of their activation and CD40 ligand (CD40L/CD154), induced on T cells in the early hours of their activation, providing a second.

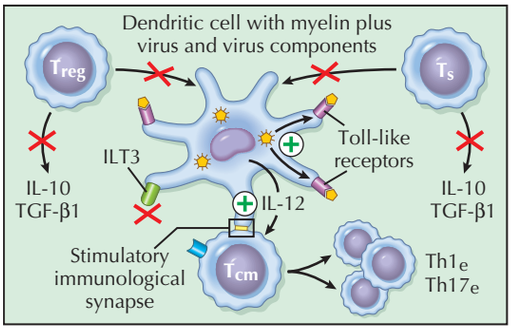
Both cross-communicating pairs upregulate synthesis of their counter ligand, and both pairs, acting in concert, transduce additional activating signals via intracellular second messengers. Each pair synergistically reinforces the actions of the other. CD28 is critical for the initiation of T cell activation, while CD40L has a key role in sustaining it. CD40L also promotes a Th1 cell bias and an even more marked Th17 cell bias. T cells, once activated, proliferate within the LN to generate an up to 10^4-fold increase of $CD4^+$ effector T cells (T_E cells).

Cytotoxic T lymphocyte antigen-4 (CTLA-4), a homologue of CD28, has a critical role in the prevention of autoimmunity. CTLA-4 is expressed by activated T cells and by regulatory T cells. CTLA-4 is focused at the immunologic synapse where it opposes CD28. Both CD28 and CTLA-4 bind CD80/86 but because of its higher affinity CTLA-4 can out-compete CD28 and reverse or blunt the T cell activating actions of CD28. DCs downregulate their expression of CD80/86 in response to the potent negative signal provided by CTLA-4 when it binds to CD80/86. In this way CTLA-4 promotes tolerance.

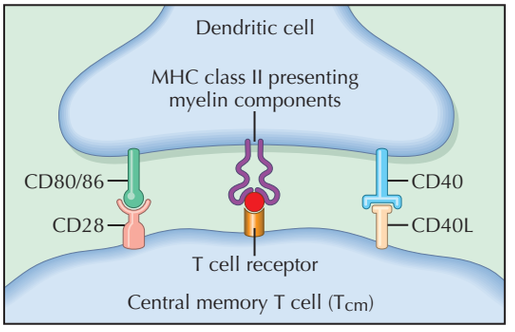
CTLA-4 is not expressed by resting T cells but comes to be expressed by activated T cells as an immune response evolves. CTLA-4 tempers what would otherwise be an excessive T cell expansion. CTLA-4 is constitutively expressed, and highly so, on the surface of regulatory T cells and, additionally, as a released biologically active soluble splice variant. Regulatory T cells have a major role in autoimmunity prevention. Even when prevention fails, as in MS, regulatory T cells can lessen MS relapse frequency and the severity of those relapses that do occur. Regulatory T cells also participate in the processes that end a relapse (see later). Agents that duplicate actions of CTLA-4 are of interest as MS treatments.

Deep Cervical Lymph Node – Immunostimulatory Events That Lead to a Relapse





Cortical Ridge - Stimulation and Loss of Inhibitory Signals



Simplified Stimulatory Immunologic Synapse

MULTIPLE SCLEROSIS: PATHOPHYSIOLOGY *(Continued)*

$CD4^+$ T_E cells are divided into subtypes known as Th1 cells, *Th17 cells*, and Th2 cells. Broadly viewed, *Th1 cells protect against intracellular organisms*, Th17 cells protect against fungi, whereas Th2 cells protect against helminths, certain other extracellular pathogens, and allergens. DCs, over the course of their activation of naïve T cells, can polarize T-cell development along paths that lead to the preferential expansion of a single Th-cell subset. Th-cell subsets interact; *Th2 cells inhibit Th1 cells and vice-versa*. *Th1 cells and Th17 cells cause damage in MS*, while *Th2 cells protect* because they inhibit Th1 and Th17 cells. Thus any drug (e.g., glatiramer acetate, teriflunomide) or mechanism that shifts polarization from a Th1 to Th2 dominance might be expected to prove beneficial in MS.

The $CD4^+$ T_E-cell population in MS contains both interferon-γ–secreting Th1 cells and interleukin-17–secreting Th17 cells. Deep cervical LN-generated MS-relevant $CD4^+$ T_E cells *migrate to the LN medulla*, express S1P-1, move via efferent *lymph into the blood and then to the CNS* to participate in an MS relapse (see later).

As a *relapse ends*, *most CNS-infiltrating Th1 and Th17 T_E cells die in situ by apoptosis*, *but perhaps 5% survive as T-effector memory (T_{EM}) cells that remain in the periphery to provide a prompt defense against a subsequent challenge*. An additional 5% to 10% remain as $CD4^+$ T central memory (T_{CM}) cells that express the same adhesion molecules as T_N cells so that they too reenter LNs via high endothelial venules, sample DCs, and recirculate via efferent lymph and then the blood to other LNs. Unlike T_N cells, MS-relevant T_{CM} cells also survey the tissues and other body compartments, including the CSF, seeking an APC loaded with the MS-relevant peptide they are programmed to recognize. T_{CM} cells outnumber T_N cells with the same specificity so that a secondary $CD4^+$ T_{CM}-cell response in a LN is usually more rapid and robust than a $CD4^+$ T_N-cell response. Activation of $CD4^+$ T_N cells requires peptide presentation by mature DCs, but requirements for $CD4^+$ T_{CM}-cell reactivation are less stringent; they can respond to some extent to antigenic peptide–presenting macrophages and to immature DCs. $CD4^+$ T_{CM}-cell reactivation leads to generation of a new $CD4^+$ T_E-cell population that again migrates to the circulation and then to the CNS.

Throughout MS remissions, myelin debris–laden immature DCs and macrophages in the cervical LNs of MS patients are thought to promote tolerance. Deep cervical LNs are favored sites for tolerance induction because they are continuously bathed with products released by the commensal biota of the nasal mucosa. The immune system is programmed to tolerate commensal organisms and to eliminate pathogens. Tolerance is mediated primarily by antigen-specific regulatory (suppressor) T cells that powerfully inhibit T-cell activation. For this reason, when antigen-specific regulatory T cells are deleted, overly robust T_E-cell responses ensue. The finding points to a ceaseless positive versus negative competition for control of DC function.

Multiple types of regulatory T cells are described. $CD4^+CD25^+$ T regulatory cells (T_{REGS}) and $CD8^+CD28^-$ T suppressor cells (T_S) are the most studied in MS. The role of $CD4^+CD25^+$ T_{REG} cells in MS remains unresolved. *$CD8^+CD28^-$ T_S-cell function is grossly defective during MS relapses*. $CD8^+CD28^-$ T_S-cell function reverts toward normal as relapses end and is restored, although not always fully, during remissions. Agents that augment $CD8^+$ $CD28^-$ T_S-cell function would be expected to be beneficial in MS.

$CD8^+$, $CD28^-$ T_S cells are antigen-specific. The $CD8^+$, $CD28^-$ T_S-cell receptor makes direct contact with its cognate antigen presented by an HLA class I allele expressed on a DC. Contact between them shunts the DC into a tolerizing mode with co-stimulatory molecule (e.g., CD86) expression reduced and tolerance-inducing molecule (e.g., ILT3) expression increased. In the obverse, when DC expression of ILT3 is silenced, proinflammatory cytokine synthesis up-regulates, and generation of disease-provoking T_E cells soars. ILT3 expression and $CD8^+$ $CD28^-$ T_S-cell function are reduced during MS relapses. Blood levels of type 1 interferons (IFN-α and IFN-β) are low in MS. IFN-β, widely used to treat MS, increases ILT3 expression and augments $CD8^+$ $CD28^-$ T_S-cell function.

A single DC can present multiple peptides to $CD4^+$ and $CD8^+$ T cells and can interact with up to 10 T cells, each with a different specificity, at any point in time. Likewise, a $CD8^+$ $CD28^-$ T_S cell can interact sequentially with several DCs, provided each expresses the antigenic peptide specific for that $CD8^+CD28^-$ T_S cell. It follows that several $CD4^+$ T cells with different specificities can be tolerized in a cascade by a single $CD8^+CD28^-$ T_S cell. Further, *as relapses recur* and additional DCs are driven to maturity, *new immune responses to recently captured self-antigens may be generated*. This process is known as *epitope spreading*.

Multiple factors released during viral infections can drive immature tolerance-inducing DCs to maturity and convert them into immune system activators. Reinforcing actions of several factors may be required to ramp up co-stimulatory molecule expression and ramp down tolerogenic molecule expression to extents that permit an override of $CD8^+CD28^-$ T_S-cell–mediated tolerance. Included are proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α) released at sites of inflammation and swept into LNs plus binding of virus components to Toll-like receptors (TLR) expressed by DCs and macrophages. *Viral infections commonly shunt MS-relevant peptide-loaded immature DCs and macrophages into a $CD4^+$ T-cell–activating mode*, *and in this way*, *they can provoke MS relapses*. This *disease-enhancing action of viruses is probably facilitated by an unmasking in MS of a defect in $CD8^+CD28^-$ T_S-cell function that is at least in part genetically determined.*

Mature DCs present antigen to T cells at the onset of an immune response, but their life span is short (only ≈3 days in mice). *During the later stages of an immune response*, *B cells often assume the dominant APC role*. B-cell receptors bind unprocessed antigen rather than the short peptide sequences recognized by T-cell receptors. Nonetheless, once an unprocessed antigen bound to a B-cell receptor has been internalized, B cells can process internalized antigenic material into small peptides, insert them into the clefts of major histocompatibility complex (MHC) class II molecules, and transfer MHC class II–processed peptide complexes to the cell surface for presentation to $CD4^+$ T cells.

B cells enter LNs via high endothelial venules in T-cell–dependent areas. *Most B cells move quickly from the T-cell–rich paracortex into B-cell zones called follicles*. Follicle entry occurs because follicle-destined B cells express the chemokine CXCR5 that binds to its CXCL13 counterligand expressed by follicular dendritic cells (FDC), a distinct population of follicle-confined stromal cells. Follicle-infringing subcapsular macrophages transport particulate material into the follicle and pass it along to FDCs that can then present it to B cells. In addition, soluble antigens percolate into the follicle, are captured by FDCs, and presented to B cells. Antigen-pulsed B cells next leave the follicle to form monogamous immunologic synapses with DC-primed $CD4^+$ T cells at the T-cell–B-cell boundary. Each B cell drags its T-cell partner along the border for a time, but the B cell then separates from its T-cell partner with the B cell moving back into the follicle, only to be followed much of the time by its prior partner T cell that has now come to express the CXCR5 chemokine, a marker for so-called follicular helper T cells (T_{FH}).

Bidirectional interactions between $CD4^+$ T_{FH} cells and B cells are important for (1) germinal center formation, (2) expansion of both populations, (3) hypermutation of B cells that diversifies their antigen receptors and permits affinity-driven clonal selection, (4) B-cell differentiation into long-lived plasma cells that secrete high-affinity antibody and confer long-lasting protection from secondary challenge and, (5) development of memory B cells.

Of importance, *T cells can shift lineages*. Antigen-presenting B cells may shift $CD4^+$ T_{FH} cells into $CD4^+$ T_{CM} cells, $CD4^+$ IFN-γ–secreting Th1 T_E cells and $CD4^+$ Th17 T_E cells in response to low doses of autoantigens. Thus B cells can contribute in a major way to MS relapse severity.

Multiple Sclerosis: Relapses

The initiation of MS relapses is thought to involve five sequential CNS-restricted steps. Much evidence to support this concept derives from study of experimental autoimmune encephalomyelitis (EAE), an inducible rather than a spontaneous animal model for MS. This raises concerns as to the validity of extrapolating findings from EAE to human disease. Even so, fundamental mechanisms, such as antigen recognition, are likely to be similar if not identical.

STEP ONE

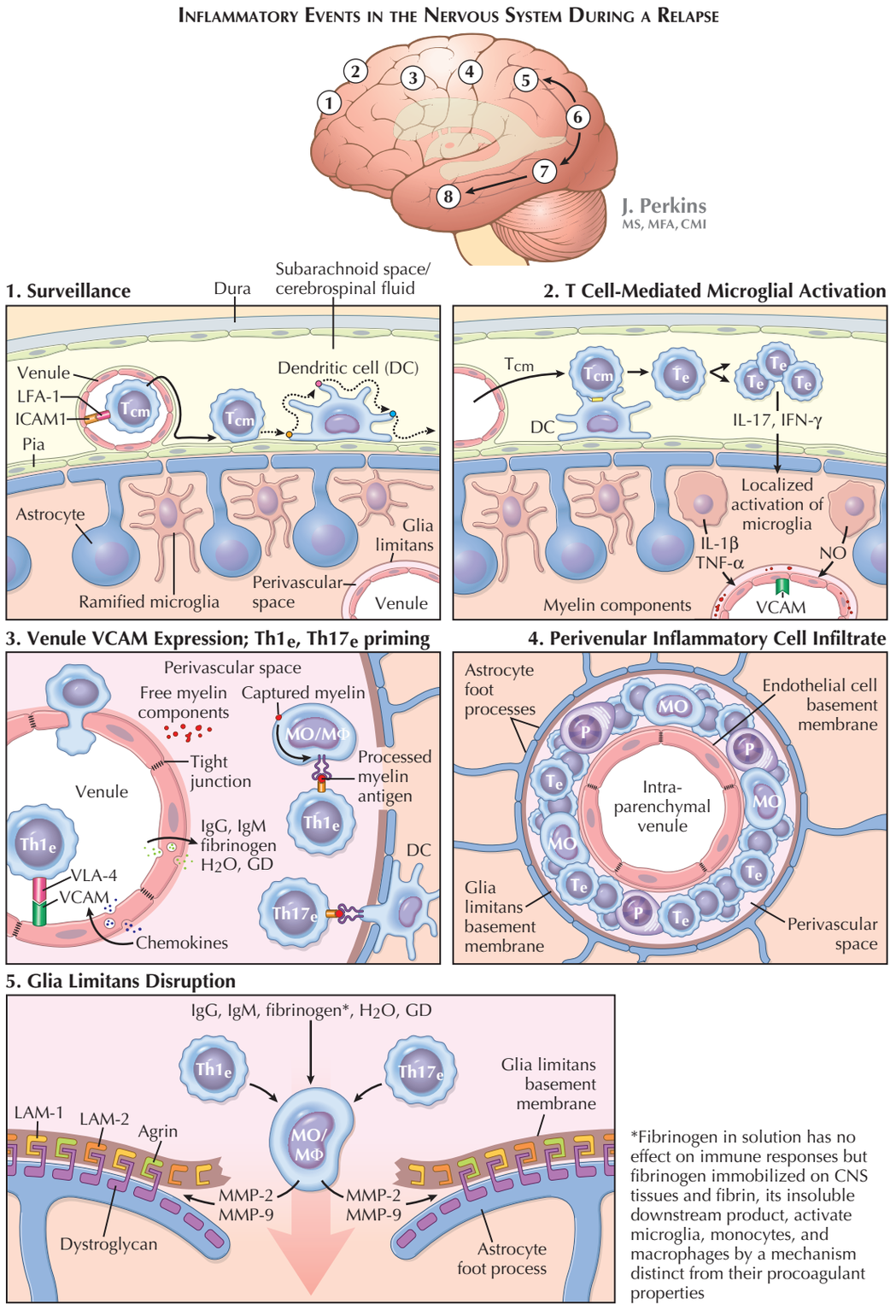
This is *clinically silent* and takes place in the subarachnoid space (SAS) and within the cerebral ventricles. Between 10^5 and 5×10^5 lymphoid cells are present in the noninflamed CSF of humans at any point in time. Eighty percent of these are $CD4^+$ T_{CM} cells in search of their cognate antigen, with lesser representations of $CD8^+$ T_{CM} cells and of $CD4^+$ T_E cells, these last probably derived from $CD4^+$ T_{CM} cells that have found their cognate antigen (see later).

Postcapillary venules on the pial surface and within the choroid plexuses express CCL21 and ICAM-1, whereas $CD4^+$ T_{CM} cells express CCR7, the counterligand for CCL21, and richly express LFA-1, the counterligand for ICAM-1. CCR7-CCL21 and LFA-1–ICAM-1 interactions permit $CD4^+$ T_{CM} cells to pass from postcapillary venules into the SAS and from choroid plexus venules into the ventricles. $CD4^+$ T_{CM} cells, once in the SAS, move first along the outer surface of meningeal vessels and then along the pial surface, searching for their cognate antigen. Should they encounter their cognate antigen, offered to them in processed form by an APC, a local immune response is initiated. Should surveillance of the SAS prove fruitless, $CD4^+$ T_{CM} cells return to the blood.

In humans, major histocompatibility complex (MHC) class II–expressing DCs with up-regulated co-stimulatory molecule expression are present in the CSF compartment. They are situated on the surface of meningeal microvessels and on pial and ependymal surfaces. Their numbers appear to be enriched in MS. Abundant myelin debris with contained protein antigens, residua of prior MS relapses, follows the established drainage paths of interstitial fluid through the ependyma into the ventricular CSF and via Virchow-Robin spaces into the SAS. Residual myelin particles are extracellular for the better part but are also detected within DCs and macrophages. Myelin debris is not found in controls.

$CD4^+$ T_{CM} cells prepare the terrain for the subsequent entry of T_E cells into the CNS parenchyma and the onset of the clinically evident component of a relapse. Adhesion molecules are not expressed by resting brain parenchymal endothelial cells, nor do meningeal vessels ordinarily express vascular cell adhesion molecule-1 (VCAM-1), the adhesion molecule required for $CD4^+$ T_E-cell exit from the blood. $CD4^+$ T_{CM} cells, having made synaptic contact with a DC, may undergo several cycles of division, still within the meninges or the ventricles to generate a small locally restricted $CD4^+$ T_E-cell cohort. Some members of this cohort cross the pia or ependyma to enter the subjacent CNS parenchyma. These pioneer $CD4^+$ T_E cells secrete interferon-γ (IFN-γ), as does a subpopulation of still SAS-confined $CD4^+$ T_{CM} cells that are perhaps transitioning into T_E cells.

Released IFN-γ diffuses from the pial and ventricular ependymal surfaces and from the immediately subjacent CNS parenchyma for a considerable depth into the CNS parenchyma, oozing preferentially along fiber tracts. In addition, the released IFN-γ activates intraparenchymal microglia as evidenced morphologically by retraction and thickening of their processes. Microglial



*Fibrinogen in solution has no effect on immune responses but fibrinogen immobilized on CNS tissues and fibrin, its insoluble downstream product, activate microglia, monocytes, and macrophages by a mechanism distinct from their procoagulant properties

Multiple Sclerosis: Relapses *(Continued)*

activation is essential for the subsequent invasion of the CNS parenchyma by T_E cells and by blood monocytes destined to become macrophages. Activated microglia secrete cytokines, and notably tumor necrosis factor-α (TNF-α), which activates nearby parenchymal postcapillary venules. These venules quickly come to resemble the high endothelial venules of LNs and, most important, now begin to express the adhesion molecules intercellular adhesion molecule-1 (ICAM-1) and VCAM-1.

STEP TWO

Expression of microglial-driven ICAM-1 and VCAM-1 by parenchymal venular endothelial cells permits very late antigen-4 (VLA-4)–expressing $CCR7^-$ $CD4^+$ Th1-type T_E cells and $CCR7^-$ $CD4^+$ Th17-type T_E cells to traverse CNS parenchymal venules and form perivascular inflammatory cuffs. Monocytes also express VLA-4 and interactions between VLA-4 and VCAM-1 are critical for their co-transmigration into perivascular cuffs and their subsequent disease-promoting activities. Cell passage across CNS venular endothelium is transcellular rather than intercellular. The tight junctions that join CNS endothelial cells to create the blood-brain barrier (BBB) are not disrupted during MS relapses. The perivascular space is bounded by an inner endothelial cell, laminin-containing, basement membrane in which pericytes and vascular smooth muscle cells are embedded. This endothelial cell basement membrane is permissive for T-cell and monocyte transmigration into the perivascular space and the formation of perivascular inflammatory cell cuffs. Of note, these perivascular cuffs are still silent clinically.

STEP THREE

Perivascular cuff monocytes function as APCs. They capture local antigenic material, process it, and present processed antigen in the context of surface-expressed MHC class II molecules so as to prime abutting $CD4^+$ T_E cells for full effector function. In addition, microglial-derived DCs, resident in the juxtavascular CNS parenchyma, extend processes between astrocyte foot processes and through the basement membrane of the glia limitans (see later), express MHC class II alleles, and likewise present antigen to perivascular T_E cells, further priming them in anticipation of their movement into the CNS parenchyma.

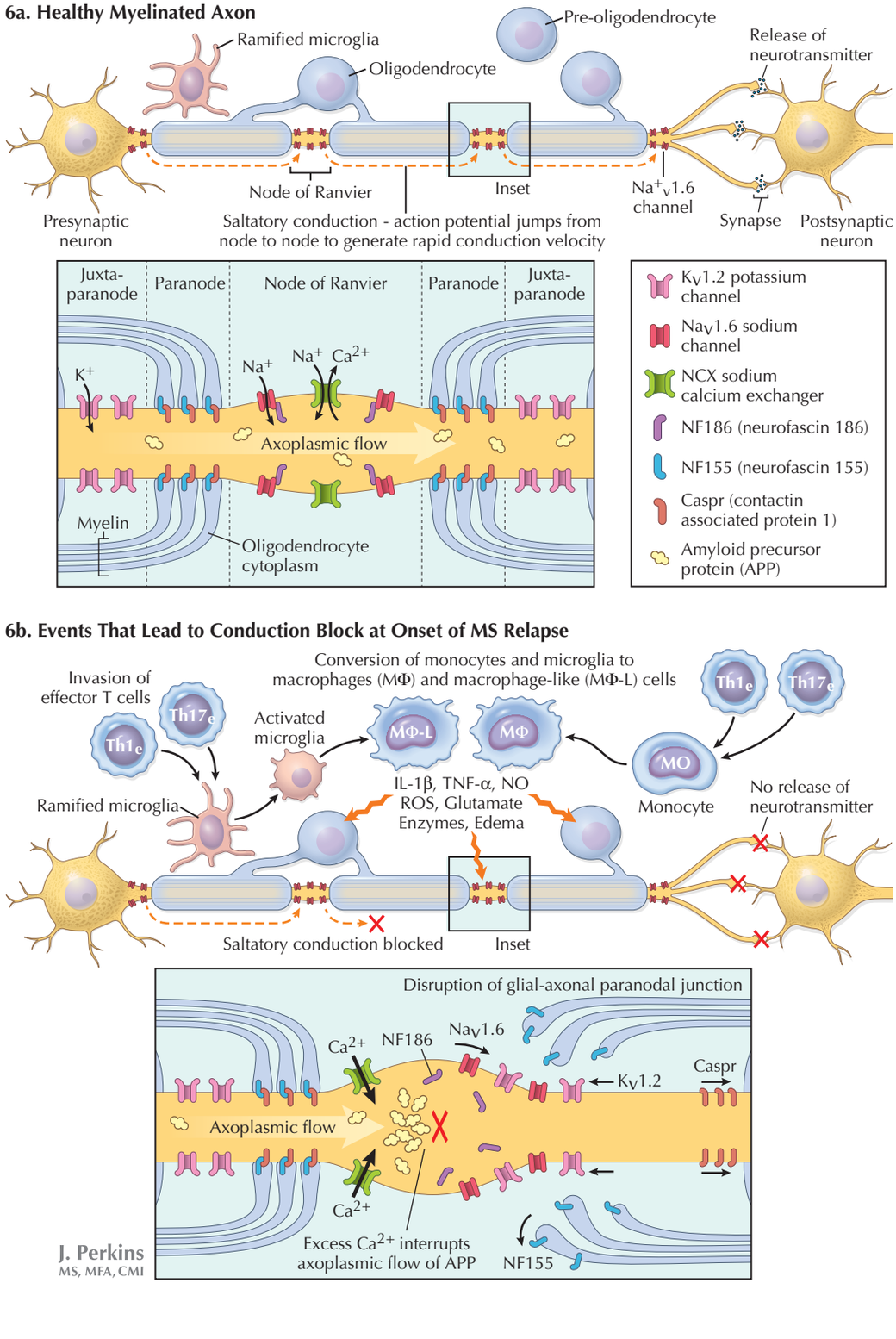
STEP FOUR

Plasma proteins leak into the CNS parenchyma at sites of acute MS disease activity. Plasma proteins, including fibrinogen and high-molecular-weight IgM, are carried across endothelial cells by an energy-requiring intracytoplasmic vesicular transport mechanism. Gadolinium (GD) is also transported into the CNS parenchyma in this same fashion, at least in guinea pigs with EAE. Transport is maximal across capillaries rather than across the postcapillary venules that CNS-invading immune system cells traverse. Most gadolinium positive lesions are silent clinically so that transendothelial cell transport of blood elements into the perivascular space need not, even when extensive, engender symptoms of an MS relapse.

STEP FIVE

Perivascular cuff T cells and monocytes must next cross the glia limitans (GL). The GL is composed of astrocytic end-foot processes and a basement

Inflammatory Events in the Nervous System During a Relapse (continued)



MULTIPLE SCLEROSIS: RELAPSES
(Continued)

membrane. It covers the entire surface of the brain and spinal cord, where it faces the SAS. Internally, the GL forms the outer barrier of the extravascular space. The laminins of this outer basement membrane (LAM-1, LAM-2) differ from those of the vascular basement membrane. The GL blocks T-cell transmigration. However, monocytes, co-migrants with T cells into perivascular spaces, secrete the matrix metalloproteinases (MMP)-2 and MMP-9 in response to the VLA-4–VCAM-1 interaction that permitted their diapedesis into a perivascular cuff. These proteases acting together, cleave the dystroglycan that anchors astrocyte end feet to the GL basement membrane so that dystroglycan no longer binds to LAM-1, LAM-2, or to agrin, a laminin stabilizer. As astrocyte foot processes retract, the GL opens. Products released from perivascular cells can now freely percolate into the CNS parenchyma, and T cells and macrophages can migrate into the CNS parenchyma and induce the neurologic deficits that characterize an MS relapse.

The preferred locations of MS plaques are probably to a considerable extent determined by the events described above. $CD4^+$ T_{CM} cells patrolling within the ventricles are likely to be attracted preferentially to nearby CCL21 chemokine gradients. For this reason, areas of intraparenchymal inflammation and maximal tissue damage are likely to be located close to the choroid plexuses, thus accounting for the frequency with which MS plaques are found in the corpus callosum, which sits immediately above the choroid plexuses of the lateral ventricles and along the floor of the fourth ventricle just beneath the choroid plexus of the fourth ventricle. $CD4^+$ T_{CM} cells also patrol the SAS. This may explain why plaques are often located juxtacortically in proximity to the meninges, and spread from the meningeal surface inward in the spinal cord.

Clinical Features of an MS Relapse: Events during the clinically apparent phase of a relapse, as with its prelude, involve a series of steps.

STEP SIX

Conduction Block. The symptoms of a relapse begin as $CD4^+$ T_E cells and macrophages move across the GL into the CNS parenchyma. MS relapses include inflammation, demyelination and reactive changes in astrocytes within MS plaques. The inflammatory infiltrate that was formerly purely perivascular now becomes largely intraparenchymal. Tissue-invading T cells, macrophages, and newly activated CNS-resident microglial cells release multiple proinflammatory cytokines, glutamate, reactive oxygen and nitric oxide intermediates, other free radicals, and proteolytic enzymes, including MMPs. Collectively, these elements damage axons as the initial clinically relevant event of an MS relapse. Early toxic damage is centered on nodes of Ranvier and abutting paranodes, with morphologic changes that provide markers of compromised axonal function. The initial event is a disruption of the coupling of glial end foot NF155 to axonal CASPR at the paranode with retraction of the end feet and their separation from one another. This is followed by an uncoupling of nodal $Na_v1.6$ sodium channels from their anchoring NF186. Saltatory conduction requires a complete separation of nodal sodium channels from juxtaparanodal potassium channels. As these channels intermingle nerve impulse conduction fails. Calcium entry at the node causes nodal swelling and axoplasmic flow ceases. This can be readily recognized by the development of amyloid precursor protein (APP)-containing spheroids that accumulate at those nodes of Ranvier where axoplasmic flow has been interrupted. Such spheroids are seen at sites of irreversible axonal severing, but only some axons that develop spheroids are doomed. As axoplasmic flow recovers, spheroids may regress and axonal conduction of nerve impulses may resume.

INFLAMMATORY EVENTS IN THE NERVOUS SYSTEM DURING A RELAPSE (CONTINUED)

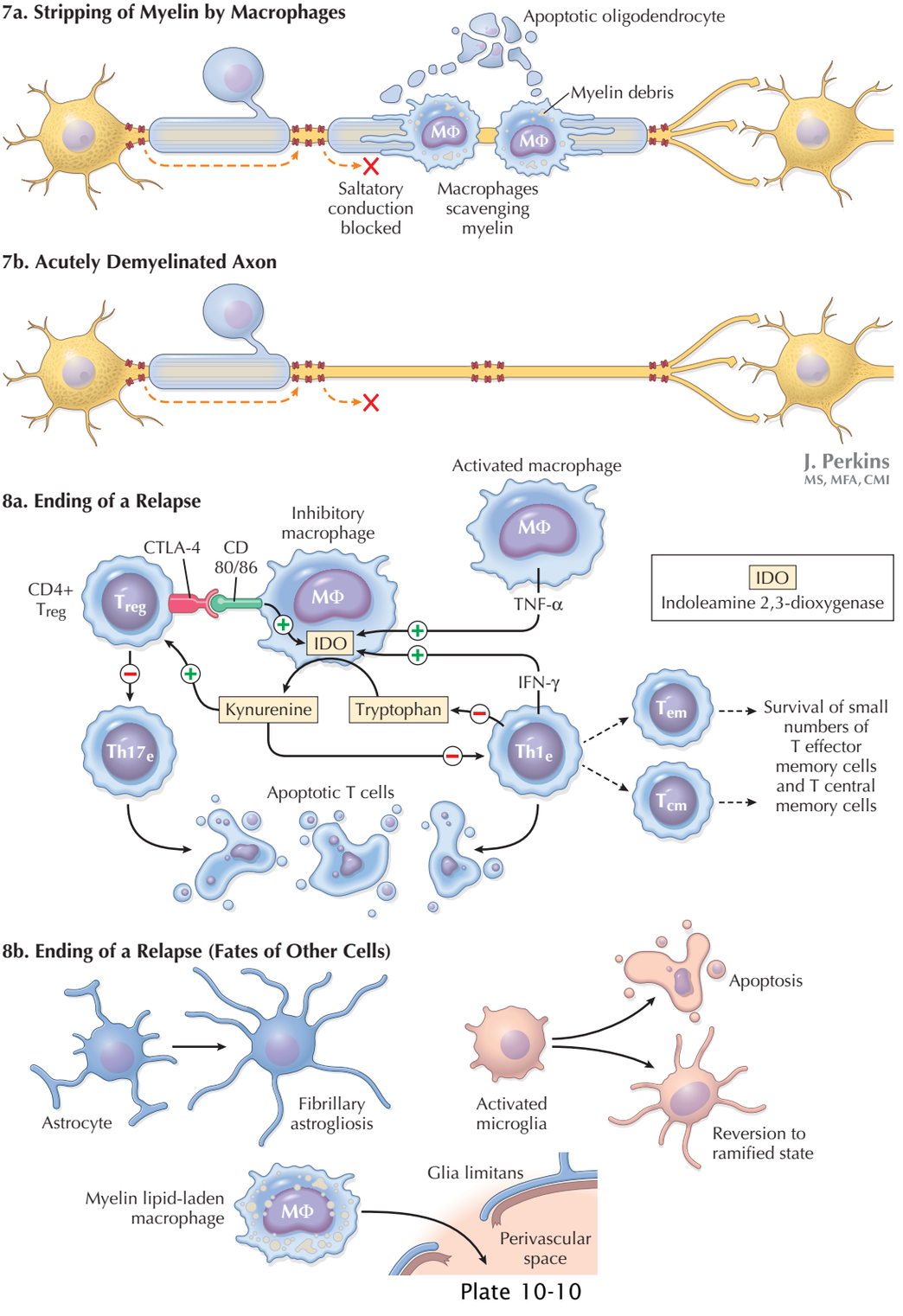
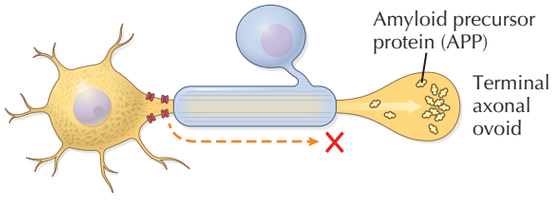


Plate 10-10

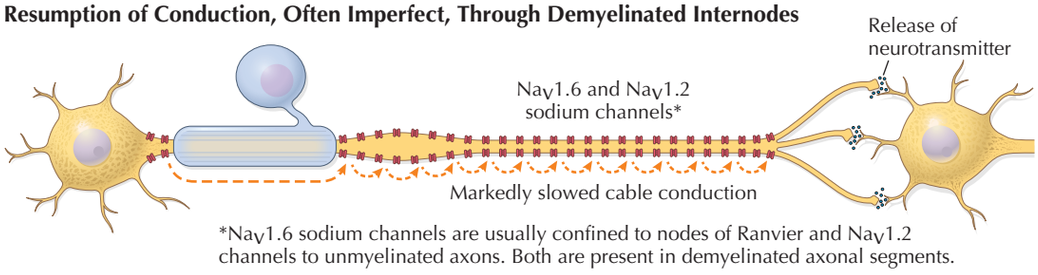
Consequences of a Multiple Sclerosis Relapse

Multiple Sclerosis: Relapses
(Continued)

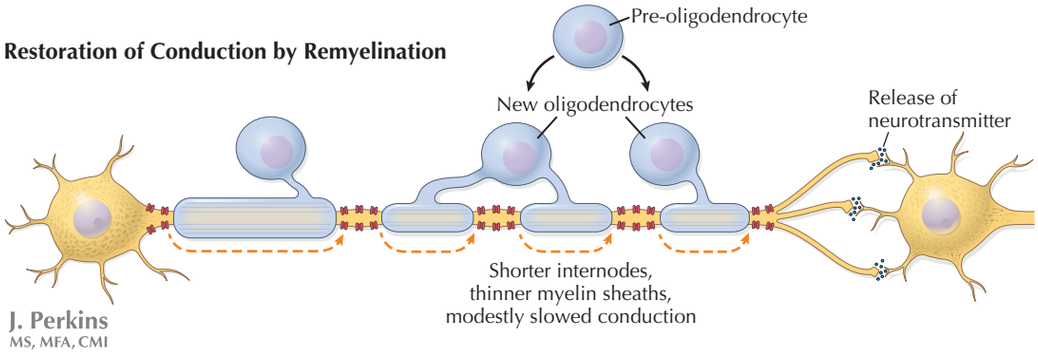
Irreversible Axonal Interruption



Resumption of Conduction, Often Imperfect, Through Demyelinated Internodes



Restoration of Conduction by Remyelination



J. Perkins
MS, MFA, CMI

STEP SEVEN

Demyelination. Macrophages remove damaged myelin. They may derive from infiltrating monocytes, and perhaps from CNS-resident activated microglia. Macrophage processes insinuate themselves between compromised myelin lamellae, physically remove myelin fragments, ingest them, and degrade them. So-called foamy macrophages, present in active plaques, contain the myelin degradation products and are stuffed with lipid droplets. Naked axons are left behind.

As noted, in myelinated axons *sodium channels cluster at nodes of Ranvier.* This ensures saltatory axonal conduction that jumps from one node of Ranvier to the next. Nerve impulse conduction across acutely demyelinated axonal segments fails. Compensation for demyelination and resumption of nerve impulse conduction requires a redistribution of sodium channels along myelin-denuded axonal segments so as to permit the slower and less efficient cable conduction that is normal for unmyelinated axons. Channel redistribution takes a week or two, sometimes longer. Until this occurs, conduction along a demyelinated segment cannot resume.

STEP EIGHT

The Ending of the Relapse. MS relapses have a finite duration. They are curtailed by a classic feedback loop in which the end product eliminates the originator. Most CNS-invading Th1 and Th17 T_E cells apoptose in situ. Apoptosis is facilitated by a cytokine-mediated induction of the macrophage/microglial enzyme indoleamine-2,3-dioxygenase (IDO). IFN-γ released by invading Th1 cells activates IDO, with synergistic support provided by macrophage-secreted TNF-α. IDO shunts tryptophan, an amino acid essential for cell growth and functioning, along a pathway that leads to kynurenine. IDO-mediated tryptophan starvation compromises immune cell function and initiates stress-induced apoptosis, chiefly of Th1 effector cells. In addition, catabolites derived from the kynurenine metabolic pathway are directly cytotoxic to Th1 effector cells.

Th17 effector cells are relatively insensitive to tryptophan starvation and kynurenine toxicity. However, $CD4^+$ regulatory T cells, now evident in the inflammatory infiltrates, further activate IDO-mediated production of kynurenine via a CTLA-4- CD80/86 interaction. Kynurenine then back-signals to these same regulatory T cells instructing them to send a pro-apoptotic message to Th17 effector cells. In addition, regulatory T cells up-regulate protective cytokines, including interleukin-10 (IL-10). All three mechanisms contribute to the ending of a relapse.

As a relapse is ending, some of the amplified activated microglia are culled by apoptosis, whereas others revert to their earlier ramified state. Astrocytes become gliotic, whereas lipid-laden macrophages make their way to the perivascular space and are thought to slowly exit the CNS.

STEP NINE

Repair. *Demyelinated segments may be remyelinated by preoligodendrocytes* that enter demyelinated plaques from surrounding areas. Remyelinated segments are readily recognized because internodal distances are shorter, and the myelin sheaths are thinner than their predecessors. Areas of remyelination are known as shadow plaques. Remyelination is spotty at best and becomes minimal as disease evolves. Remyelinated areas are seldom protected from demyelination in subsequent relapses. There is interest currently in neurotrophins as vectors for repair of tissue damage in MS (see later).

EVOLUTION OF THE MS PLAQUE

Pathologists have classified MS plaques in numerous ways. Perhaps the simplest has been to judge them as acute, chronic active, or chronic silent. *Acute plaques* are likely to be responsible for a new exacerbation. They manifest as regions of active demyelination with ill-defined boundaries, extensive inflammatory cell infiltrates throughout, perivascular cuffs, macrophages engaged in myelin stripping and removal, plus diffuse MHC class II–positive macrophages/microglia that release IL-1β, TNF-α, lymphotoxin (LT) and other cytokines, nitric oxide and other free radicals, proteolytic enzymes such as MMPs, and express surface-bound co-stimulatory molecules.

The chronic active plaque shows recent disease at its periphery, or parts of it, but chronic changes in its center. Ongoing demyelination is restricted to the plaque edge extending into the adjacent parenchyma in a centrifugal fashion, and there is a border of MHC class II positivity.[61] The *chronic silent plaque* has a marked down-regulation of MHC class II reactivity throughout, an absence of further demyelinating activity, and a sharp border. Astrocytes now take on a fibrillary morphology and express the sinuous processes of chronic gliosis. There may be clusters of demyelinated axons in a chronic silent plaque, but also clearly evident is axonal loss that is maximal centrally. OGCs are absent.

Enigma of Progressive Multiple Sclerosis

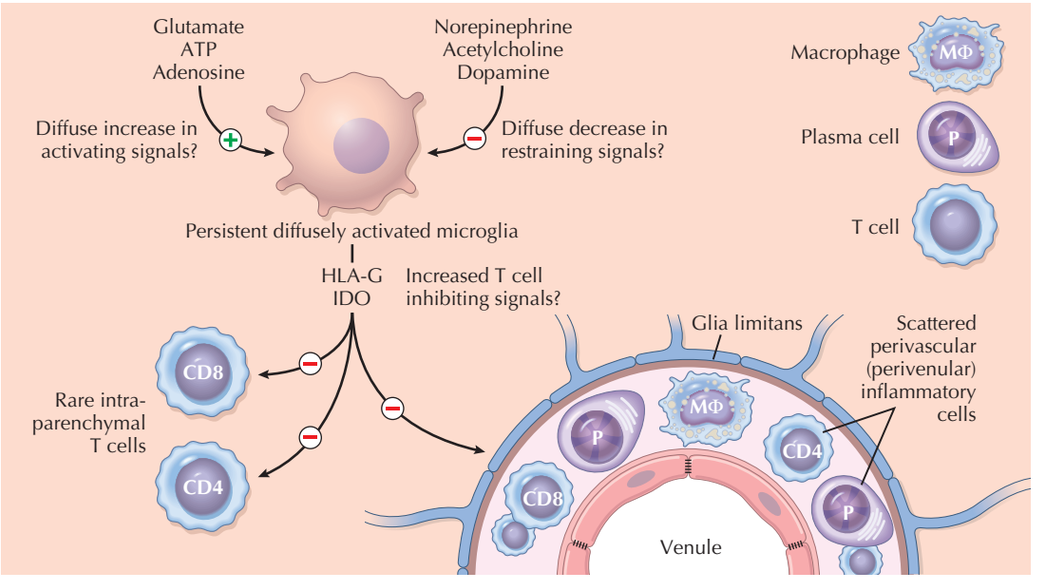
Relapses cease in secondary progressive MS and demyelination tempo slows markedly. GD-positivity on magnetic resonance imaging (MRI) also becomes rare. Current therapies that reduce the number and severity of MS relapses fail to slow disability progression in progressive MS. For the better part, these therapies are directed against T cells and the peripheral immune component. Their dismal record in progressive MS suggests a minor role, at best, for T cells acting within the CNS in late-stage disease. Rather, what characterizes primary progressive MS (PPMS) and secondary progressive MS (SPMS) is a global activation of MHC class II$^+$ microglia with thicker and shorter processes than observed in control microglia, a global decrease in axonal metabolism, in part ascribed to microglial cell–induced mitochondrial dysfunction documented by reduced levels of N-acetyl aspartate, widespread axonal severing, a progressive loss of brain volume, an inexorable worsening of gait linked to a selective loss of small fiber axons from the pyramidal tracts, and often a substantial cognitive decline.

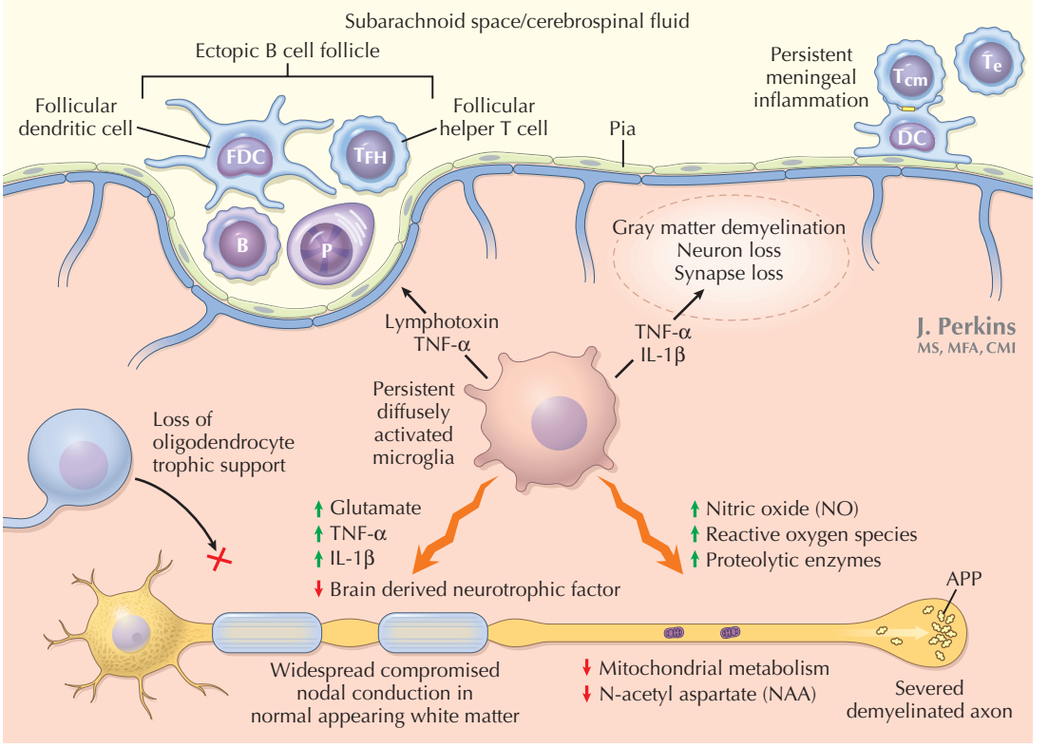
Careful examination of normal-appearing white matter in progressive MS reveals elongated paranodes with a disrupted profile, axonal swellings, and amyloid precursor protein accumulations. These correlate with the density of ramified activated (inducible nitric oxide synthase–positive) microglia but not with the limited presence of perivascular T-cell infiltrates or the limited number of CNS parenchyma-infiltrating T cells, most of which are now CD8$^+$ and of uncertain function. Gray matter lesions that contain few T cells become increasingly prominent with accompanying damage to cortical axons, to dendrites, and to neuronal cell bodies. Gray matter lesions in SPMS, as with axonal dysfunction in white matter, are strongly associated with activated microglia.

Of interest, activated T cells are still to be found in the meninges. Meningeal inflammation can be extensive and it has been suggested that it may somehow contribute to subpial cortical demyelinated plaques and an accelerated clinical course. Since T cells and macrophages are rare in cortical demyelinated regions and activated microglia are abundant, a microglia-activating signal delivered from a distance has been proposed. What prevents activated CD4$^+$ T cells from entering the CNS gray matter and white matter parenchyma in SPMS is not understood. One possibility is the release of human leukocyte antigen-G (HLA-G) by activated microglia in SPMS. HLA-G is a nonclassic HLA class I antigen first detected at the extravillous cytotrophoblastic fetomaternal interface where it provokes immune tolerance and potently protects the fetus from destruction by maternal T cells. HLA-G has subsequently been found at several immunologically privileged sites including the CNS. In RRMS, HLA-G levels in CSF are far lower when MRI scans are GD-positive, an indicator of T-cell activation within the CNS, than when MRI scans are GD-negative and disease is quiescent. Microglia in tissue sections from autopsied individuals with SPMS show markedly up-regulated expression of HLA-G.

It seems likely that products released from microglia, including nitric oxide and other free radicals; glutamate, known to be toxic in excess; and cytokines, including tumor necrosis factor-α (TNF-α) and lymphotoxin (LT) that are also toxic in excess, have a major role in the diffuse axonopathy and neuronal destruction of progressive MS. Loss of the trophic support to axons normally provided by oligodendrocytes may also contribute. Some MS patients with late-stage disease show meningeal plasma cell-containing lymph follicle-like structures chiefly deep in sulci and superimposed on extensive meningeal T cell and macrophage infiltrates. Paradoxically, TNF-α and LT, released in excess in progressive MS, may actually promote the development of these lymphoid follicle-like meningeal structures because TNF-α and LT are essential for development of LN follicles.

Presumably, in progressive MS microglia no longer receive those signals from neurons and astrocytes that, in homeostasis, hold them in quiescence. Among such signals are norepinephrine, acetylcholine, and dopamine. These neurotransmitters counteract activating signals provided by glutamate and by ATP, which attracts microglia to sites of damage, and adenosine, which holds them there. How to change this for the better remains a challenge.





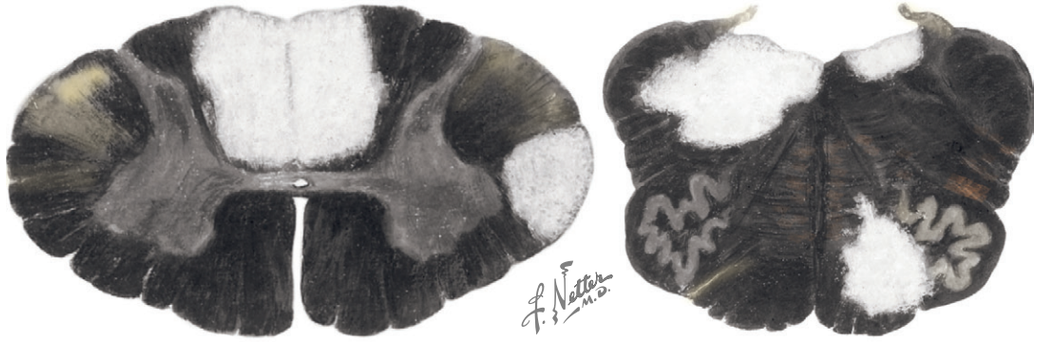
MULTIPLE SCLEROSIS: PATHOLOGY

GROSS CENTRAL NERVOUS SYSTEM PATHOLOGY

The *surface of the brain* in multiple sclerosis (MS) may show little on inspection, although there may be shrinkage of the cerebral hemispheres. The *third and lateral* ventricles may be enlarged, sometimes substantially, and particularly so in cases of long-standing MS. The *spinal cord* may show grayish areas on its surface, often unilateral and slightly depressed.

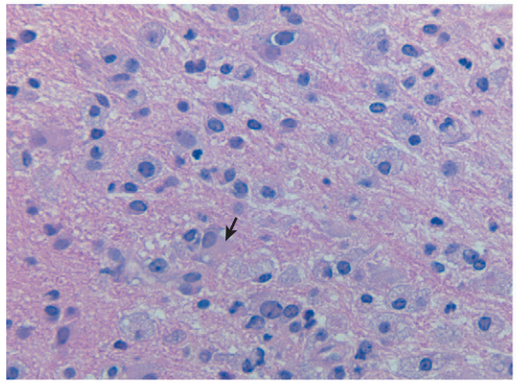
When the *cerebral hemispheres* are sectioned, the demyelinating lesions become obvious. These may be *numerous or scanty* and rounded (as illustrated), oval, or irregular. Recently acquired lesions are soft and pink, whereas lesions of long standing tend to be numerous, firm, and to have a grayish gelatinous appearance indicative of substantial gliosis. These lesions also tend to be *scattered asymmetrically through the gray and white matter*. Smaller lesions are spheric or oval. Larger lesions form by coalescence of smaller ones and by bouts of relapse-driven expansion at their edges. Large lesions usually have an irregular shape and a sharp outline, provided disease is inactive.

A favored site for plaque location is under the floor of the fourth ventricle, as illustrated, but plaques may occur in any location and spread from their origins at the pial and ependymal surfaces over a larger or smaller area. In the spinal cord, lesions are once again based on the pial surface and extend inward as hemispheric or conical areas. Histologically, plaques are most easily demonstrated in sections stained for myelin, where they appear as demyelinated areas.

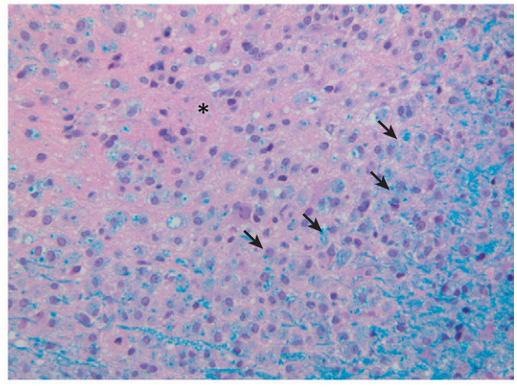


In cervical spinal cord

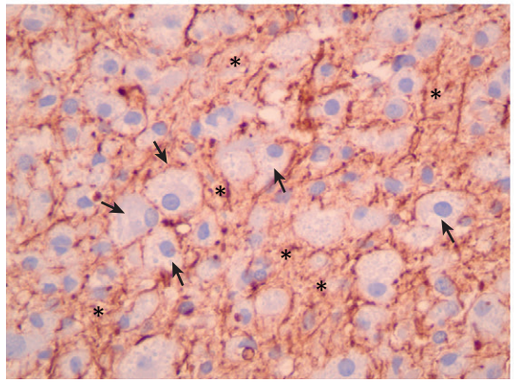
In medulla



Photomicrograph showing a reactive astrocyte (arrow) in an area of inflammation.



Photomicrograph showing an area of myelin loss (star) surrounded by healthy myelin stained with Luxol fast blue. The transition from the demyelinated area to intact myelin is demarcated by the arrows.



Photomicrograph showing foamy macrophages (arrows) surrounding axons stained with neurofilament antibody (asterisks), which is a marker for demyelinated and damaged axons. The prominent cytoplasm in the macrophages contains myelin debris.

HISTOPATHOLOGY OF MULTIPLE SCLEROSIS

Microscopic analysis demonstrates that many archetypical plaques have no relation to specific nerve tracts. Often the plaques have a perivenular and paraventricular distribution. Severe loss of oligodendrocytes within MS plaques is associated with the concomitant nonspecific finding of hypertrophic astrocytes. Pathologists classify MS plaques in numerous ways. Perhaps the simplest is to judge MS plaques as acute, chronic active, or chronic silent.

Acute plaques are likely to be responsible for a new exacerbation. They present as regions of active demyelination with ill-defined boundaries, extensive inflammation throughout, perivascular cuffs, and macrophages engaged in myelin stripping and removal. In addition, there are diffuse MHC class II–positive macrophages/microglia that release (1) IL-1β, TNF-α, and lymphotoxin (LT) among other cytokines, (2) nitric oxide and other free radicals, (3) *proteolytic enzymes* such as matrix metalloproteinases (MMPs), and (4) express surface-bound co-stimulatory molecules. Acute plaques contain myelin debris.

C*hronic active plaques* demonstrate recent disease at their periphery, or parts of it, but chronic changes within its center. Ongoing demyelination is restricted to the plaque edge, extending into the adjacent parenchyma in a centrifugal fashion, and there is a border of MHC class II positivity.

Chronic silent plaques demonstrate a marked down-regulation of MHC class II reactivity throughout, an absence of further demyelinating activity, and a sharp border. Astrocytes now take on a fibrillary morphology and express the sinuous processes of chronic gliosis. There may be clusters of demyelinated axons within a chronic silent plaque, but in addition, there is clear evidence of axonal loss that is maximal centrally. OGCs are absent.

Myelin loss from a nerve fiber is distinct and best defined by toluidine blue stains. Macrophage accumulation is a frequent accompaniment. Signs of leptomeningeal inflammation, not unlike that found in acute disseminated encephalomyelitis, may be evident. There is also a very significant component of axonal and neuronal damage in multiple sclerosis.

This is particularly relevant to the long-term outcome and eventual disability. One can find evidence of axonal injury early in the disease process. This is found both in areas of obvious demyelination as well as in areas of white and gray matter that appear normal to gross inspection. It is proposed that an antigen-specific destructive component related to both T cells and autoantibodies as well as nonspecific effects of activated macrophages and microglia can lead to very significant axonal damage, the latter particularly evident in SPMS. Mitochondrial function may also be impaired, perhaps by nitric oxide released by activated microglia, and further contribute to axonal loss.

Multiple Sclerosis: Treatment

Prognosis

Several agents lessen relapse frequency, reduce relapse severity, reduce gadolinium (GD)-positive lesions, and lower accumulating disease burden in RRMS. Nonetheless, MS relapses still occur. Relapses are often treated with intravenous (IV) glucocorticoids, particularly 1 g of IV methylprednisolone daily for 3 to 5 days. Steroid treatment often accelerates recovery from an MS relapse but not the magnitude of persisting deficit, nor do steroids favorably affect accumulating disability. Advent of MS immunomodulatory therapies has changed this scenario.

Interferon-β

Three *interferon-β (IFN-β)* formulations are approved for relapsing-remitting MS (RRMS). These are IFN-β-1b (Betaseron) subcutaneously every other day, IFN-β-1a (Rebif) subcutaneously three times weekly and IFN-β-1a (Avonex) intramuscularly weekly. The *earlier that treatment is initiated, the better the result.*

IFN-β is a hydrophobic short-range molecule; little crosses into the CNS. *Interferon-β* reduces MHC class II molecule and immune system–activating co-stimulatory molecule expression on dendritic cells (DCs) and monocytes/macrophages. These actions inhibit processing and presentation of antigen to $CD4^+$ T cells. IFN-β increases tolerance-inducing cytotoxic T lymphocyte antigen-4 (CTLA-4) and immunoglobulin-like transcript 3 (ILT3) production and restores deficient $CD8^+CD28^-T_S$-cell function. These actions further inhibit T-cell activation and proliferation within lymph nodes (LNs). In addition, IFN-β increases soluble vascular cell adhesion molecule-1 (VCAM-1) production. The very late antigen-4 (VLA-4) adhesion molecule expressed by $CD4^+$ T_E cells is captured by soluble VCAM-1 so that VLA-4 binding to endothelial cell surface–expressed VCAM-1 is reduced, and $CD4^+$ T_E-cell adhesion to cerebral venular endothelium and subsequent cell translocation across the blood-brain barrier (BBB) (step 2) is lessened. IFN-β inhibits matrix metalloproteinases (MMP) activity and hence leukocyte migration across the glia limitans into CNS parenchyma (step 5). IFN-β facilitates apoptosis of autoreactive T cells (step 8), down-regulates proinflammatory cytokine production by activated T cells, and up-regulates anti-inflammatory cytokine production by T cells and mononuclear cells, IFN-β modestly increases brain-derived neurotrophic factor (BDNF) production by immune system cells pointing to a putative neuroprotective role (step 9 of the MS relapse and see later).

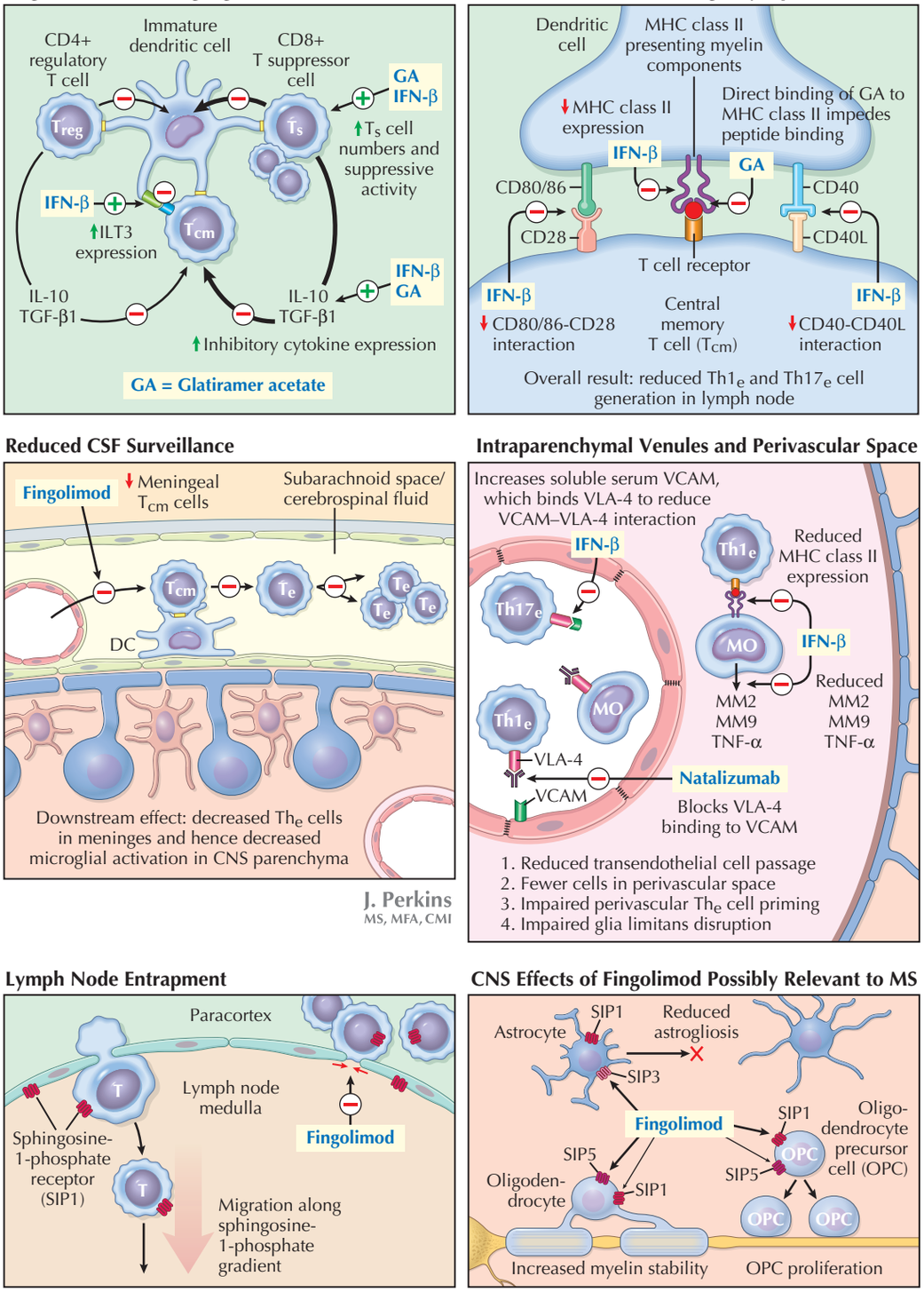
One third of patients receiving high-dose IFN-β subcutaneously develop neutralizing antibodies to the agent. Antibody positivity is transient in many patients but persists in others and more so in those with high-titer antibody. In two recent studies, high antibody titer was associated with increased magnetic resonance imaging (MRI) activity (i.e., with a deleterious impact on MRI outcomes), whereas in a seeming paradox, no discernable deleterious effect on any clinical outcome by any statistical analysis was detected.

Glatiramer Acetate

Glatiramer acetate (GA) (Copaxone) is approved for treatment of RRMS. How it acts is imperfectly understood. GA, a random polymer of glutamic acid, lysine, alanine, and tyrosine, is highly basic and does not cross the BBB. GA modulates antigen-presenting cells (APC) function such that T cells shift from the Th1 dominance of MS relapses to Th-2 dominance. Perhaps this is why attack frequency lessens.

GA reduces expression of APC-derived inflammatory mediators. APC-derived interleukin (IL)-12p70 drives proinflammatory IFN-γ production by Th1 cells. GA reduces IL-12p70 levels and reduces secretion of proinflammatory TNF-α while concomitantly increasing production of anti-inflammatory IL-10 and transforming growth factor-β (TGF-β). In addition, APC-derived IL-10 and TGF-β augment Th2 cell production of anti-inflammatory IL-4 and IL-10. Release of cytokines that participate in Th17 cell differentiation is also reduced. Although GA binds rapidly and efficiently to APC-expressed MHC class II molecules, its effect on the Th1 to Th2 shift appears to be independent of this binding.

Multiple Sclerosis Treatments and Immune Responses



MULTIPLE SCLEROSIS: TREATMENT *(Continued)*

GA stimulates polyclonal proliferation of $CD4^+$ T cells. Proliferation declines over time. In contrast, $CD8^+$ T-cell proliferative responses of patients, initially deficient, versus $CD8^+$ T cells of controls, rise over time on drug, and $CD8^+CD28^-$ T_S-cell function, also defective initially, corrects to levels observed in controls. The $CD8^+CD28^-T_S$-cell population is clonally restricted, indicating antigen specificity. Response is confined to antigen presented by HLA-E, an HLA class1 molecule with a limited antigenic repertoire. Of interest, $CD8^+$ T cells in MS brain parenchyma are likewise clonally restricted. Patients receiving GA invariably develop anti-GA antibodies. These antibodies do not appear to interfere with efficacy.

There is interest in a neuroprotective role for GA. Neurotrophins are polypeptide growth factors essential for development and maintenance of the vertebrate nervous system. BDNF, a neurotrophin that encourages neuronal and axonal survival and regulates neurotransmitter release, is made within the CNS chiefly by neurons but is also synthesized by stimulated T cells and monocytes/macrophages. BDNF is seen within invading cells in MS plaques, and its receptor is expressed by neurons and astrocytes in MS brain lesions. GA substantially increases BDNF production by immune system cells, and this action might favorably alter step 9 of MS relapses.

NATALIZUMAB

Natalizumab (Tysabri) is a humanized (>90% human components) monoclonal antibody (MAb) directed against the α4 subunit of VLA-4, an adhesion molecule expressed by T cells, B cells, and activated macrophages. Natalizumab blocks adhesion between VLA-4–expressing immune cells and VCAM-1 expressed by endothelial cells at sites of inflammation. Blocking of adhesion prevents immune cell extravasation across CNS parenchymal venules (step 2 of an MS relapse). VLA-4–mediated events help up-regulate monocyte-induced MMP expression so that natalizumab may also impede step 5 of an MS relapse.

Natalizumab is approved for treatment of RRMS. Natalizumab reduced MS relapse rate by 68% compared with placebo. Its ability to markedly reduce lymphocyte migration into the CNS is counterbalanced by a reduction in CNS surveillance and increased risk for progressive multifocal leukoencephalopathy (PML), a serious opportunistic infection caused by the JC virus that can kill. Natalizumab is generally reserved for patients who fail first-line therapies. The drug is administered monthly intravenously. The 10% of patients who develop antibodies to natalizumab lose efficacy. Natalizumab has a half-life of 11 days. Should PML be suspected, accelerated clearance of natalizumab via plasma exchange has been proposed as a way to accelerate restoration of immune function. Because 50% of MS patients test negative for anti-JC virus antibodies at screening, they may be at reduced risk for PML, but conversions to positivity during treatment do occur.

FINGOLIMOD

Fingolimod (Gilenya) is the first oral agent approved for treatment of MS; this reduces MS relapses by 53%. Fingolimod is a sphingosine-1-phosphate (S1P) receptor modulator that regulates lymphocyte trafficking and exerts pleiotropic actions on OGCs, other neural cells, and endothelium. Fingolimod is phosphorylated in vivo. Fingolimod-phosphate, the active moiety, binds to S1P receptors. When a recirculating $CCR7^+$ $CD4^+$ T_{CM} cell within a LN encounters an APC bearing its cognate antigen, the T cell stops moving. Shut-down requires internalization of S1P-1. Arrested T cells undergo clonal expansion, after which S1P-1 receptor expression is restored and movement resumes. LN exit requires signaling between newly restored S1P-1 receptor and its endogenous ligand S1P. Fingolimod-phosphate causes S1P-1 receptors to be internalized and degraded. Consequently, T cells are trapped in the LNs. Th1 and Th17 cells are trapped preferentially. $CD8^+$ T cells are largely spared because the circulating $CD8^+$ T-cell pool consists primarily of cells that do not enter LNs. $CD4^+$ T_{EM} cells also remain in the periphery. Fingolimod-phosphate does not interfere with T-cell function. Hence $CD4^+$ T_{EM} cell defense against previously encountered organisms remains largely intact. However, circulating $CD4^+$ T_N and $CD4^+$ T_{CM} cell numbers fall, and because T_{CM} cells initiate step 1 of an MS relapse, their entrapment in LNs lessens MS relapse likelihood. Circulating lymphocyte counts revert to normal within 4 to 8 weeks of stopping the drug.

Fingolimod crosses the BBB. Disturbed sphingolipid metabolism within normal-appearing white matter occurs in MS. Phospholipid content shifts upward and sphingolipid content downward. Such shifts should increase repulsive forces between apposed lipid bilayers and loosen myelin structure. Fingolimod accumulating within CNS white matter might, over time, correct this abnormality. Fingolimod lessens toxin-triggered CNS myelin breakdown, lessens toxin-induced injury to OGCs, and spares axons. Fingolimod also increases endothelial integrity, possibly lessening CNS vascular leakage.

Fingolimod has risks. Infections have included fatal herpes virus infections. Macular edema has occurred during early months on treatment. Bradycardia, possibly serious, can occur with the first dose.

TERIFLUNOMIDE

Teriflunomide (Aubagio), the second oral agent approved for treatment of MS, reduced relapse frequency by 31% at doses of 7 or 14 mg daily. GD-positive lesions were reduced by 57% (7 mg) and 80% (14 mg). Disability progression was reduced significantly at the higher dose.

Teriflunomide blocks dihydroorotate dehydrogenase (DHODH), the rate limiting enzyme for the de novo pyrimidine synthesis required for rapid clonal expansion of T and B cell blasts. Pyrimidine can be salvaged from food and by recycling. This DHODH independent path suffices for day to day needs. Thus the agent is highly specific for rapidly dividing immune system cells. Its antiproliferative effect is reversed by exogenous uridine.

Some actions of teriflunomide are not reversed by uridine. Included are impaired proinflammatory cytokine and surface molecule expression, deficient T cell migration, and reduced interactions of T cells with APCs or B cells. A Th1 to Th2 shift occurs with increased expression of antiinflammatory IL-10.

Side effects, seen in a minority of patients include GI upset, mild hair thinning that reverses spontaneously, asymptomatic liver enzyme elevations, and mildly elevated blood pressure. Discontinuation for these reasons is rare. The overall safety profile is favorable. A prodrug, with teriflunomide the active moiety, has been used to treat rheumatoid arthritis since 1998.

Teriflunomide has a long half-life, but because it recycles through the gut it can be cleared rapidly by oral polystyramine daily for 11 days. The drug is contraindicated in pregnancy, in which case clearance should be prompt.

MITOXANTRONE: (NOVANTRONE)

Mitoxantrone, a synthetic anthracenedione, intercalates into deoxyribonucleic acid (DNA), causing cross-linking and strand breaks that interfere with DNA repair. Mitoxantrone, primarily used as an antineoplastic agent, is approved for the treatment of secondary progressive MS (SPMS), progressive relapsing MS, and rapidly worsening RRMS. Mitoxantrone inhibits monocyte and lymphocyte migration, decreases secretion of proinflammatory cytokines, inhibits B-cell and DC-cell function and augments T_S-cell function. Mitoxantrone is usually given briefly to RRMS patients with overwhelming disease before introduction of a first-line anti-MS drug.

Complications include myelosuppression, cardiac toxicity (sometimes fatal), acute myelogenous leukemia (frequently fatal), and infertility. MS reactivates once drug is stopped.

DIMETHYL FUMARATE (BG-12)

This agent reduced MS relapse rate by 53%, disability by 38%, new GD-positive lesions by 90% and new/enlarging T2 lesions by 85%. Adverse events include early flushing and gastrointestinal upset. BG-12's mode of action is imperfectly understood; it may activate the nuclear factor (erythroid-derived 2)–like 2 (Nrf2) transcription pathway that has antioxidant effects, may have NF-κB–inhibiting effects that reduce levels of proinflammatory IL-1β, TNF-α, and IL-6 and may shift DC differentiation along a tolerance-promoting path.

ANTI–B-CELL AGENTS

Rituximab (Rituxan) is a chimeric (two thirds human and one third murine) anti-CD20 monoclonal antibody (MAb) approved for treatment of B-cell lymphomas and rheumatoid arthritis (RA). Ocrelizumab is a humanized (>90% human components) anti-CD20 MAb thought less likely than rituximab to provoke production of efficacy-blocking antibodies. In pilot trials in RRMS, both drugs reduced relapse frequency and the number of new GD-positive lesions. Neither is approved for treatment of MS, but data at hand indicate a clear-cut role for B cells in MS pathogenesis.

CD20 is expressed by mature naïve B cells and by memory B cells but not by the plasma cells that produce most of the antibody. Although CD20-positive cells are totally depleted within days of agent administration and remain so for 6 months, total immunoglobulin levels are little reduced, and most protective antibodies remain unchanged. B cells do not simply make disease-relevant antibodies in MS. Rather, a role in antigen presentation to T cells, at which B cells are highly efficient, seems likely. Several cases of PML in systemic lupus erythematosus (SLE) patients given rituximab, and opportunistic infections (some fatal) in rheumatoid arthritis patients given ocrelizumab are reported. To date, such infections have not been reported in MS.

Neuromyelitis Optica, Acute Disseminated Encephalomyelitis, and Acute Hemorrhagic Leukoencephalitis

Neuromyelitis Optica

Neuromyelitis optica (NMO), also known as Devic disease, is an autoimmune illness having selective spinal cord and optic nerve inflammation with sequelae of paralysis and blindness. Although initially considered an MS variant, there is evidence that NMO and MS are clinicopathologically very different. Diagnostic criteria for NMO are distinct from MS. Many NMO patients have elevation of antinuclear (ANA) or Sjögren syndrome A/B (SSA/B) autoantibodies. There is a 15-fold increased incidence of other autoimmune diseases in NMO, including Sjögren disease, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), mixed connective tissue disease, and myasthenia gravis (MG).

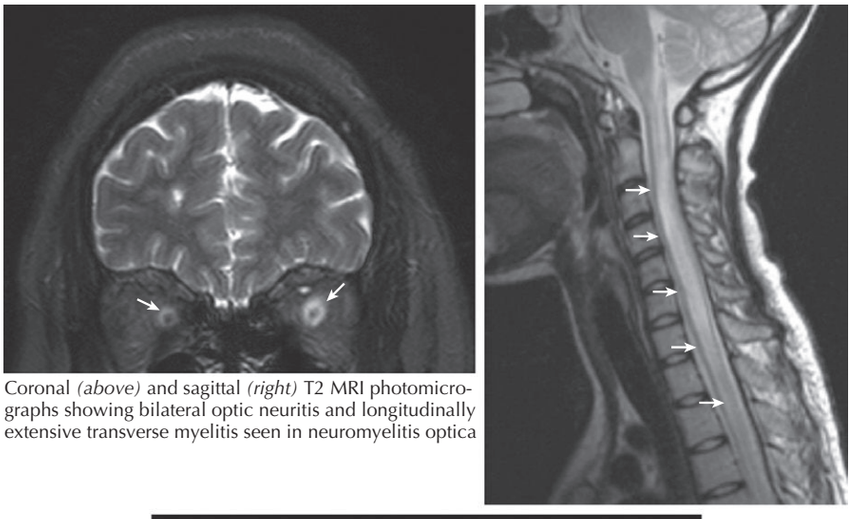
Recurrent spinal cord and/or optic nerve inflammation reminiscent of relapsing-remitting MS occurs in 80% of NMO patients. A monophasic course appears in 20%; visual and motor involvement is severe initially. However, recovery, although delayed, is usually substantial. In contrast, in patients with relapsing NMO, although less severely affected initially, progressive disability develops with recurrent attacks. Total blindness and quadriplegia sometimes result. A 30% incidence of upper cervical cord and medullary dysfunction leads to respiratory failure, usually fatal, in recurrent NMO.

Most NMO patients have elevated levels of an IgG antibody to a water channel called *aquaporin-4 (NMO-IgG)*. This antibody is considered pathogenic because it binds complement-causing tissue destruction. However, not all NMO patients have anti–aquporin-4 antibody. Other pathologic mechanisms must exist. T cells initially cause blood-brain barrier (BBB) perturbation, with subsequent anti–aquaporin-4 antibodies entering brain parenchyma with CNS destruction.

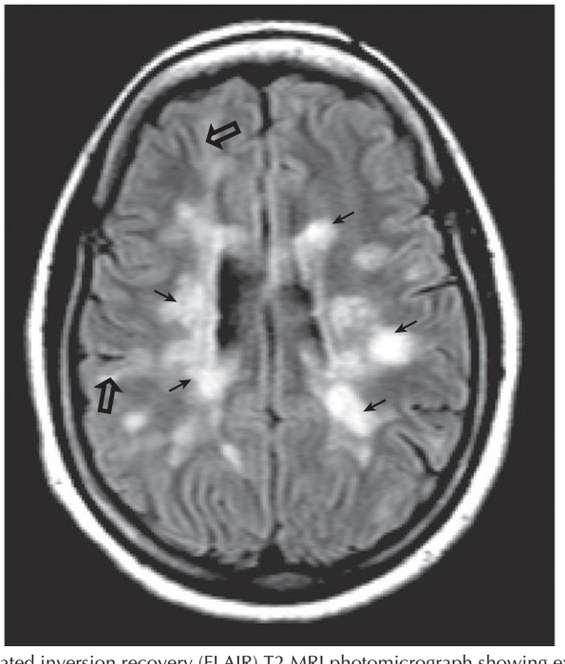
NMO lesions are distinct when compared with lesions of classic MS or acute disseminated encephalomyelitis (ADEM). Spinal cord lesions exhibit prominent vascular fibrosis and hyalinization involving gray and white matter with prominent necrosis, cavitation, and axonal loss. Extensive demyelination occurs, with extensive oligodendrocyte loss, prominent infiltration of neutrophils, eosinophils, and ringlike perivascular IgM and IgG deposits. Complement products are deposited in NMO lesions. Myelopathic lesions are primarily central in NMO rather than peripheral as in MS, with gray matter preferentially involved in NMO and white matter in MS. Spinal cord MRI demonstrates lesions of a greater longitudinal extent in NMO than those typically seen in MS.

Specific radiologic and laboratory criteria proposed to differentiate NMO from MS include (1) spinal cord MRI lesions extending contiguously over three or more vertebral segments (longitudinally extensive transverse myelitis [LETM]), (2) brain MRI not meeting MS diagnostic criteria, and (3) positive NMO-IgG aquaporin-4 antibody titer. Two of these three criteria are required for NMO diagnosis. In clinical practice, some patients present initially with LETM or severe optic neuritis having neither NMO-IgG antibodies nor brain lesions resembling MS. Some patients continue with recurrent attacks of LETM or ON with or without associated positive NMO-IgG. Such patients are considered to have *restricted forms of NMO or are classified as NMO spectrum of disease*.

Radiologic Findings



Coronal *(above)* and sagittal *(right)* T2 MRI photomicrographs showing bilateral optic neuritis and longitudinally extensive transverse myelitis seen in neuromyelitis optica



Axial fluid attenuated inversion recovery (FLAIR) T2 MRI photomicrograph showing extensive lesions in the deep white matter *(filled arrows)* and juxtacortical regions *(open arrows)* seen in ADEM

In general, patients presenting with acute optic neuritis or LETM receive urgent care. Attacks are often treated with high-dose systemic glucocorticoids. Methylprednisolone 1 g daily intravenously for 7 to 10 days, sometimes longer, is popular currently. Controlled trials are lacking, and whether lasting benefit accrues remains uncertain. Plasmapheresis and intravenous immunoglobulin as adjunctive therapies have their advocates but, again, whether meaningful benefit ensues remains cloudy. Prophylactic therapy aimed at lessening relapse frequency in those at high risk (positive NMO-IgG or a history of recurrences) has been attempted with an array of immunosuppressants including azathioprine, methotrexate, mitoxantrone, cyclophosphamide, mycophenolate mofetil, and even stem cell replacement regimens, among others. Their number alone argues for limited efficacy, at best, for any of them. Not one is without hazard.

Because it is easily administrated, rituximab is a popular NMO therapy used to chronically suppress B cells. This monoclonal antibody, directed against the CD20 protein expressed on B-cell surfaces potently depletes B cells for several months. It is often given twice a year and is generally well tolerated. Rituximab may be more effective than other immunosuppressive agents in preventing NMO relapses. However, rituximab may not be effective in all patients; breakthrough relapses sometimes occur. NMO is an aggressive disease; sometimes the most intense regimens do not produce favorable results. Long-term safety of rituximab in NMO or MS is not yet established; rituximab use sometimes is associated with progressive multifocal leukoencephalopathy (PML), a generally fatal disorder. Hence rituximab therapy for chronic NMO needs to be used cautiously.

Acute Disseminated Encephalomyelitis (ADEM)

Acute disseminated encephalomyelitis (ADEM) is an acute demyelinating monophasic central nervous system (CNS) disease that follows an infectious illness

Neuromyelitis Optica, Acute Disseminated Encephalomyelitis, and Acute Hemorrhagic Leukoencephalitis *(Continued)*

or immunization, usually within 6 to 8 weeks. Although described more often in children after measles infection, it can occur after any nondescript viral illness. Most ADEM cases develop in children. ADEM is seen in the adult population, but with lesser frequency. Because pediatric multiple sclerosis (MS) is rare, the higher occurrence of ADEM in children, as opposed to adults, suggests that ADEM constitutes a distinctive entity.

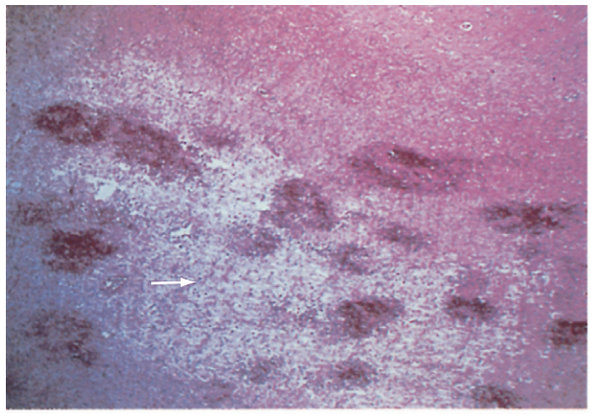
ADEM manifests abruptly and evolves rapidly. Headache, seizures, and delirium at onset are common in childhood cases but less so in adults. Onset is often polysymptomatic, usually presenting with motor, sensory, cerebellar, and brainstem disturbances. Multiple focal findings coincide with widespread magnetic resonance imaging (MRI) demyelination. Recurrences rarely occur and, if so, usually after a brief delay. In most instances, such recurrences typically develop subsequent to an inappropriately abbreviated initial treatment schedule wherein early improvement created a false sense of security for physicians.

ADEM results from an autoimmune attack triggered by infection or immunization against CNS myelin proteins. Thus ADEM closely resembles experimental allergic encephalomyelitis (EAE) induced in rodents by CNS myelin products. In ADEM, the white and gray matter of the brain and spinal cord characteristically demonstrate multiple foci of acute demyelination. These demyelinating foci contain T cells and macrophages. Most ADEM lesions develop over several weeks and are best demonstrated on MRI T2 and contrast-enhanced T1 images (see Plate 10-15). Scans performed soon after illness onset demonstrate that most ADEM lesions have contrast enhancement, implying simultaneous lesion development. ADEM can continue to evolve over several weeks. MRI scans obtained late in the course of the illness may contain both lesions of recent onset that enhance and mature lesions of longer duration that no longer do so. When primary evidence of T1 hypointense lesions occurs on noncontrast T1 images acquired at acute clinical presentation, a multiple sclerosis diagnosis is more likely. In addition, ADEM lesions are often much larger (1-2 cm) than typical MS lesions, and while white matter lesions predominate in ADEM, there may be substantial lesional involvement of the gray matter of the cortex, thalamus, basal ganglia, brainstem, and cerebellum.

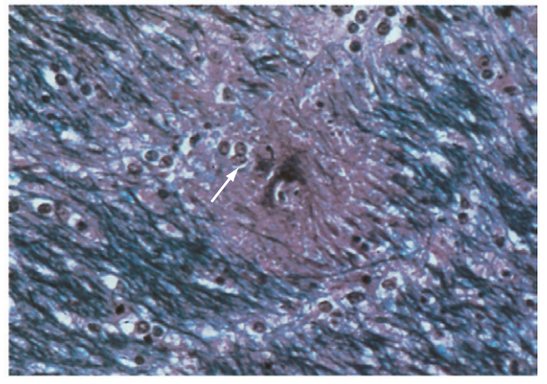
Compared with MS, CSF findings in pediatric ADEM include increased perturbation of the blood-brain barrier as measured by elevated CSF albumin to serum albumin ratio, lower positivity of CSF oligoclonal bands (10% vs. 83%), and in some cases, moderately high CSF lymphocytic pleocytosis (>20 cells/μl).

The prognosis of ADEM in earlier decades was relatively poor, with mortality rates of 20%, whereas 50% of survivors had serious neurologic deficits. Today prognosis is much more favorable when ADEM is adequately treated with intravenous methylprednisolone administered systemically for several days and then followed by an extended oral glucocorticoids taper over 6 to 8 weeks. Although controlled studies are lacking, relapses appear to occur less frequently with this regimen. The degree of remyelination during recovery from ADEM is more extensive than for MS patients, and many patients recover completely.

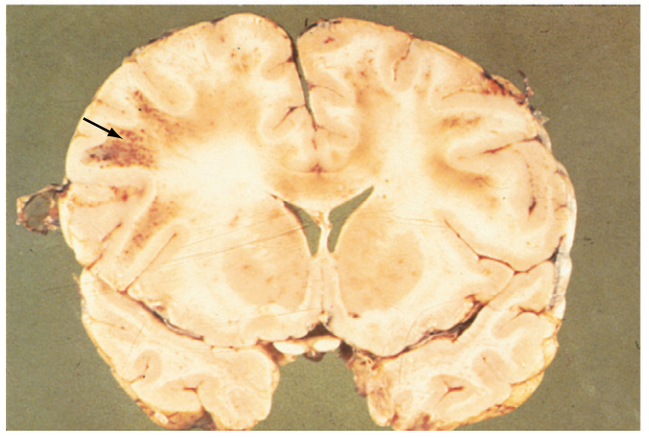
Histopathologic Findings



Cingulate gyrus white matter showing area of perivenous demyelination (Luxol fast blue Holmes, ×100)



Cerebral white matter with scattered deep hemorrhages in pale, edematous areas (H and E stain, ×10)



Coronal section of cerebral hemispheres at level of corpus striatum showing punctate hemorrhagic lesions in subcortical white matter

Acute Hemorrhagic Leukoencephalopathy (AHL)

First described by Hurst in 1941, AHL characterized by a fulminant clinical course is the most serious representative of the ADEM disease spectrum. It is also variably known as acute necrotizing hemorrhagic leukoencephalopathy or Weston-Hurst syndrome. It is a monophasic illness and very infrequent compared with ADEM. In contrast to ADEM's propensity to affect children, AHL occurs primarily in young adults, developing within days to a few weeks postinfection, usually respiratory, or after immunization.

Clinical presentation includes fever, headache, confusion, seizures, and weakness progressing rapidly to stupor and coma. Death can occur within days due to cerebral edema and hemorrhage. Most patients do not survive this illness; survivors sustain serious permanent deficits.

Pathologic features on computed tomography (CT) or MRI include cerebral edema with mass effect, tissue displacement, and frank or petechial hemorrhages. Cerebrospinal fluid (CSF) analysis, if available when intracranial pressure is not too elevated, typically shows elevated protein, polymorphonuclear pleocytosis, increased red blood cells, normal glucose level, and increased gamma globulins. In AHL, peripheral leukocytosis and an elevated erythrocyte sedimentation rate (ESR) is often seen.

Histopathologic analysis demonstrates hemorrhagic white matter lesions, perivascular polymorphonuclear cell infiltrates, necrosis, demyelination, and perivascular fibrin deposits. AHL requires urgent treatment with high-dose intravenous methylprednisolone and control of elevated intracranial pressure. Concomitant therapy with cyclophosphamide and plasma exchange may lead to a favorable outcome.

Other Neuroimmunologic Syndromes: an Overlap Between Primary and Paraneoplastic Processes

There is an ever increasing recognition of the role of immunologic mechanisms underlying many neurologic disorders. Clearly, multiple sclerosis is the primary central nervous system (CNS) model of a neuroimmunologic disorder. Acute hemorrhagic leukoencephalitis, acute disseminated encephalomyelitis, neuromyelitis optica, and the stiff-man syndrome are classic CNS examples. Other autoimmune disorders, such as *N*-methyl-D-aspartate (NMDA) encephalopathy, are increasingly recognized. Guillain-Barré syndrome and myasthenia gravis are the preeminent peripheral motor-sensory unit immunologically mediated disorders. Multifocal motor neuropathy (MfMN) is an increasingly recognized and important peripheral example of an autoimmune mediated syndrome. Although this disorder clinically mimics primary motor neuron disease, MfMN is very responsive to immunosuppressive therapy. This contrasts with the terrible prognosis of motor neuron disease; thus its recognition is of paramount importance to the patient.

The astute neurologist confronted with an unusual, seemingly idiopathic clinical disorder, always needs to be vigilant, asking whether a difficult diagnostic problem could also have a neuroimmunologic basis and eventual potential clinical responsiveness to an immunosuppressive therapy. The recently defined condition associated with exposure to pig brain is an example of an occupational, environmentally induced, previously unrecognized neuroimmunologic disorder. This disorder affected 21 workers in two meat processing plants. Each patient had exposure to aerosolized brain tissue at the time of hog slaughter. This rapidly developing disorder led to a subacute neurologic syndrome most often characterized by a painful, sensory predominant, polyradiculoneuropathy developing within just a 4-week period. Less commonly, central nervous system involvement developed, producing a meningoencephalitis or transverse myelitis syndrome.

Nerve conduction studies localized abnormalities to the most proximal and distal nerve segments. Quantitative sensory and autonomic testing demonstrated large and small sensory fiber involvement as well as autonomic dysfunction affecting sweat fibers. Magnetic resonance imaging confirmed prominent nerve root and dorsal root ganglia abnormalities. Nerve biopsies revealed mild demyelination, axonal degeneration and perivascular inflammation. Cerebrospinal fluid (CSF) protein was elevated in most patients; in contrast, there was no significant CSF pleocytosis except for those individuals presenting with central nervous system involvement.

Distinctive neural-reactive immunoglobulin G (IgG) occurred in the serum in all and in the CSF in a high majority. In addition, voltage-gated potassium channel (VGKC) IgG was identified in 79% and myelin basic protein-specific IgG in 75%. When the probable occupational exposure facilitating the neuroimmunologic mechanism was identified, the method of brain harvesting was discontinued, and this disorder no longer occurs. However, this experience serves as an important bellwether for the astute neurologist considering other mysterious ailments.

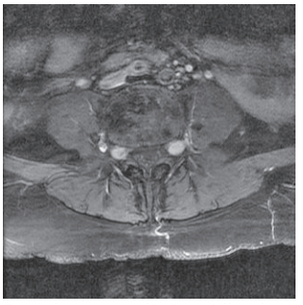
Sometimes patients may have underlying idiopathic systemic disorders wherein a sudden and overwhelming potentially life-threatening neurologic deterioration develops without any obvious inciting mechanism. One needs to consider the potential that neuroimmunologic factors are playing an important role. Sometimes empiric treatment with methylprednisolone, intravenous immunoglobulin (IVIG), and/or plasmapheresis (PPx) in these settings, even when no specific antibodies are identified, can occasionally prove to be lifesaving.

An example of this occurred with a colleague who had scleromyxedema, an unusual chronic dermatologic condition. Over a 72-hour period, he developed severe skeletal muscular pain involving his extremities and truncal musculature, including his abdomen, where there was initial concern about a surgical emergency. While this was under investigation, sudden respiratory and cardiovascular distress occurred, followed by an acute encephalopathy with confusion leading to coma. Intense therapy with high-dose corticosteroids and antibiotics was unsuccessful; he became moribund with decerebrate posturing. The emergent introduction of plasmapheresis therapy led to a remarkable improvement; eventually he returned to medical practice.

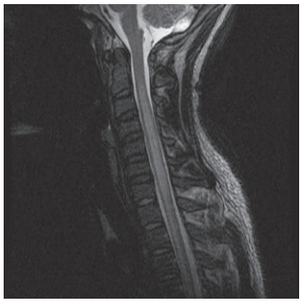
We were not certain what led to the acute crisis in this patient; however, response to immunotherapy clearly implicated an autoimmune mechanism. One needs to always consider such a possibility with seemingly indeterminate acute neurologic disorders; sometimes a trial of immunosuppressive therapy can be lifesaving even when there is no previous "evidence-based" experience.

Paraneoplastic autoimmune disorders are discussed in the subsequent four plates. Some syndromes initially recognized as having a paraneoplastic context sometimes do not always occur with an underlying cancer. The *Lambert-Eaton myasthenic syndrome* (LEMS) is an excellent example; although historically associated with small cell lung cancer, it is now recognized to occur not only in young adults who never subsequently develop a cancer, but even in children as young as 8 years. The inciting immunologic mechanism for these LEMS variants has yet to be elucidated. Nevertheless, these are eminently treatable patients. Therefore their recognition is of paramount importance.

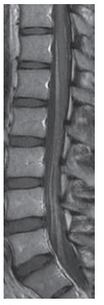
MRI



Dorsal root ganglia in midlumbar spine, asymmetric enlargement (left greater than right) and enhancement of nerve roots; axial T1-weighted spoiled gradient recalled imaging

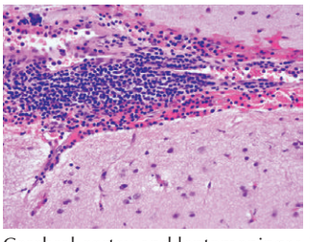


Magnetic resonance images: Cervical spinal cord, marked edema principally in central gray matter; sagittal T2-weighted (fast spin echo) with fat suppression

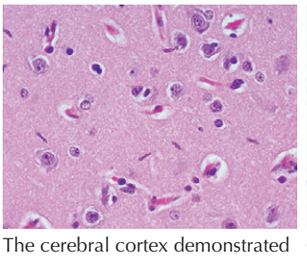


Midspine, pial enhancement of the anterior cord (after contrast administration), and enhancement and enlargement of cauda equina roots; sagittal T1-weighted (fast spin echo) with fat suppression

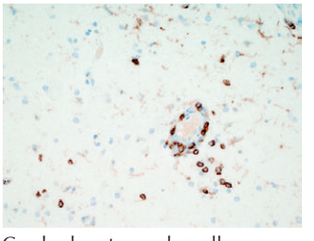
Brain biopsy



Cerebral cortex and leptomeninges demonstrating moderate, chronic leptomeningitis in association with an inflamed vessel

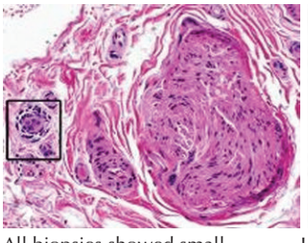


The cerebral cortex demonstrated generalized microglial proliferation

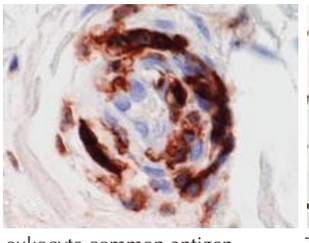


Cerebral cortex and small parenchymal vessels demonstrating numerous CD3-labeled T lymphocytes

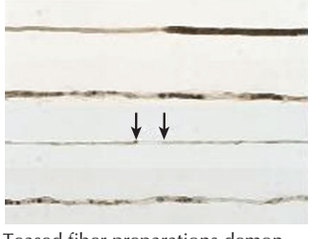
Nerve biopsy



All biopsies showed small collections of inflammatory cells surrounding outer layers of small epineural blood vessels adjacent to nerve fascicles (enlargement of area boxed) hematoxylin and eosin stain



Leukocyte common antigen (CD45). Segmental demyelination with low frequency of axonal degeneration shows occasional degenerating nerve fibers and evidence of remyelination (thinly myelinated profiles). Turnbull blue stain.



Teased fiber preparations demonstrates remyelination (top fiber), axonal degeneration (myelin ovoids, 2nd and 4th fibers from the top), and segmental demyelination (segment between arrows on 3rd fiber)

Stiff-Man Syndrome

Occasional patient with stiff person syndrome assumes hyperextended posture with increased lordosis.

Generalized stiff person syndrome with abdominal rigidity

INTRODUCTION

The stiff-man syndrome (SMS) is a chronic autoimmune disorder generally presenting in midlife with intermittent painful spasms and eventually severe rigidity primarily affecting paraspinal, abdominal, and leg musculature. Women are more commonly affected. Onset is insidious; a loud noise or sudden surprise can result in acute muscle spasms with inappropriate leg extension sometimes precipitating sudden falls.

SMS variants include stiff-limb syndrome, progressive encephalomyelitis with rigidity and myoclonus (PERM), and a paraneoplastic process associated with breast cancer. Idiopathic gait ataxias sometimes accompany SMS. There is one instance of tamilial SMS affecting a father and daughter with transplacental tranfer of antibodies to a granddaughter.

ETIOLOGY

Classic, primary autoimmune SMS is typically associated with rarely a glutamic acid decarboxylase (GAD-65) autoantibody, and rarely a paraneoplastic variant with antiamphiphysin antibodies. Other autoimmune disorders commonly associated with GAD-65 autoimmunity include type-1 diabetes mellitus, thyroiditis, vitiligo, and pernicious anemia. The antibody's precise pathophysiologic role is unclear. In classic SMS, the autoimmune process may be directed at inhibitory spinal interneurons producing γ-aminobutyric acid (GABA). GAD antibodies from stiff-persons' serum patients inhibit GAD and GABA synthesis in vitro.

CLINICAL PRESENTATION

Classic generalized SMS is characterized by paraspinal, abdominal, and leg rigidity with lumbar hyperlordosis as a key feature. Leg rigidity impairs walking. Superimposed painful spasms develop, sometimes precipitated by sudden noise, anxiety, or touch. The spasms are sometimes abrupt and powerful, leading to precipitous falls and agoraphobia with fear of falling in public. When the abdominal musculature is involved, the concomitant pain and rigidity can potentially mimic an acute abdomen.

Neurologic examination is often initially normal in patients just experiencing intermittent spasms; however, later with generalized SMS, concomitant paraspinal and abdominal musculature contraction is obvious, with lumbar hyperlordosis and lower limb rigidity. Some patients become extremely frightened of simply moving because that may precipitate severe painful spasms. Sometimes the examiner touching the patient causes a generalized opisthotonic spasm mimicking tetanus. Muscle stretch reflexes are normal to brisk, occasionally associated with Babinski signs.

Primary appendicular SMS variants present focally in a leg with rigidity and spasms; axial involvement is less prominent. Eventually abdominal and truncal muscle involvement develops if the SMS is not diagnosed and treated early.

SMS patients with *PERM* have associated *antiglycine receptor antibodies (GlyR-abs)*. One SMS syndrome is *paraneoplastic*, having various manifestations. It is often associated with *antiamphiphysin antibodies*, requiring search for underlying breast cancer; however, small cell lung cancer, colon cancer, and lymphoma are also associated. *Another idiopathic variant*, presumed autoimmune, is not associated with an identifiable autoantibody and may be rapidly progressive leading to severe disability and death.

DIFFERENTIAL DIAGNOSIS

SMS patients previously have had multiple nondiagnostic visits to physicians. Normal examination findings early on sometimes lead the unsuspecting physician to label these patients as hysteric or somatoform, leading to psychiatric evaluations. Other diagnostic considerations include lumbosacral disks, dystonia, multiple sclerosis, stroke, arthritis, myelopathy or basal ganglia disorders, Lyme disease, poliomyelitis, spinal myoclonus, tumors, and strychnine poisoning. In acute conditions, tetanus needs consideration because of the severe boardlike, stiffening, abdominal wall muscle spasms. Sparing of the jaw muscles and absence of trismus and risus sardonicus in SMS excludes tetanus. Two channelopathies with muscle rigidity, namely myotonia congenita and Isaac syndrome, are unlikely; these are not painful.

SMS is primarily a clinical diagnosis, and certain features should help alert the clinician to this diagnosis. These include painful muscle stiffness and rigidity, primarily axial but occasionally individual limbs; progressive involvement with abnormal axial posture; marked lumbar hyperlordosis; superimposed muscle spasms; and normal brainstem, extrapyramidal, and lower motor neuron evaluation.

Markedly elevated GAD-65 autoantibody titers in serum support the diagnosis. In classic SMS, 60% to 90% patients have very high serum GAD-65 titers, usually greater than 20 nmol/L. Lower GAD-65 antibody levels may occur with type 1 diabetes mellitus. Elevated amphiphysin antibodies suggest occult cancers, usually of the breast. PERM is associated with elevated anti–GlyR-ab titers.

Although electromyography (EMG) is often normal early in SMS, this must not dissuade the clinician from obtaining antibody studies in an appropriate clinical setting. EMG eventually reveals a characteristic concomitant and continuous firing of motor unit potentials in agonist and antagonist muscles.

TREATMENT

Diazepam is first-line symptomatic therapy. Benzodiazepines are $GABA_A$ receptor agonists inhibiting excessive motor-unit firing and thus painful muscle contraction. Baclofen, a $GABA_B$ receptor agonist, is also effective. Immunotherapy requires high-dose corticosteroid (e.g., prednisone 1 mg/kg/day or intravenous equivalent). Intravenous immunoglobulin (IVIG), plasma exchange and azathioprine are other options.

Paraneoplastic Immune-Mediated Disorders

Paraneoplastic disorders (PND) are cancer-associated conditions that cannot be explained by a tumor's direct invasion of tissue or by its treatment consequences. Most paraneoplastic neurologic disorders reflect specific nervous system autoimmunity. Typically, these subacute-onset, rapidly progressive syndromes precede initial tumor recognition or its recurrence. Some PND patients present with distinct syndromes; others develop complex clinical pictures with simultaneous central and peripheral nervous system involvement.

Immune-mediated paraneoplastic neurologic disease (PND) occurs as a consequence of the body's immune response to a neoplasm. This is a complex interaction evolving during tumor development, varying with tumor type, organ involvement, and the individual, per se. Autoimmunity, or organ-specific immune-mediated injury, is a consequence of loss of immune tolerance. Active primary immune responses combined with dysregulation of normal immune activation checkpoints, varying by organ system and certain individually inherent factors, provides the setting for specific immunologic-based injuries.

Autoantibody detection provides important markers to identify various PNDs. In the context of cancer, these are either consequences of specific tumor immune responses or less specific markers of autoimmunity subsequent to immune checkpoint dysregulation. An evolving spectrum of PND autoantibodies is increasingly recognized, associated with a broad spectrum of nervous system disorders. Thus their presence serves primarily as a predictor of an underlying neoplasm rather than a specific neurologic syndrome.

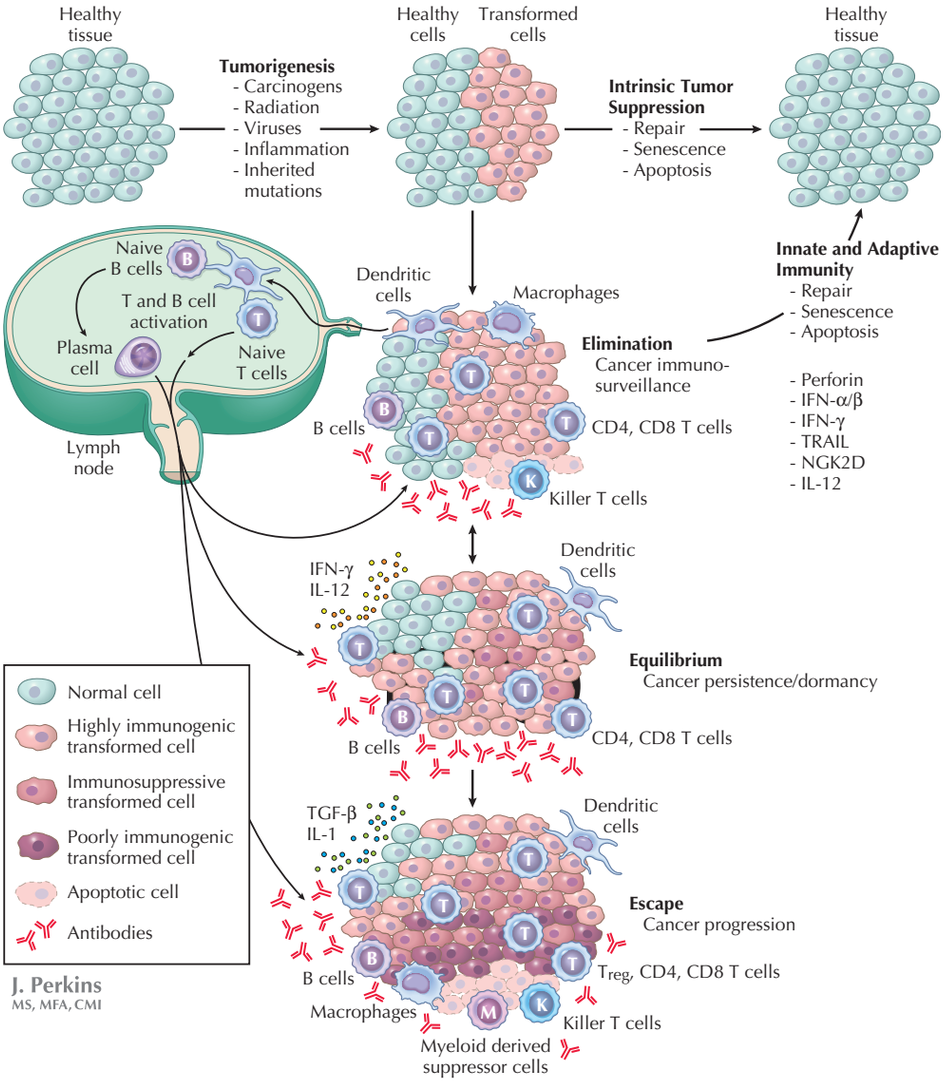
These PND autoantibodies, available for clinical measurement, most likely represent a subset of those generated by the body's immune response to the neoplasm. With respect to the associated neurologic autoimmunity, the antibodies may or may not represent actual mediators of tissue injury. When these antibodies are the mediators of neurologic disease, it is fortunate that they not only serve as specific markers for that disorder, but they can become therapeutic targets. Unfortunately, autoantibodies are often not either necessary or sufficient to express neurologic injury. Typically, neurologic lesions result from complex expressions of activated cellular elements, cytokines, and antibodies in concert with specific patterns of immune dysregulation and loss of tolerance.

This immune response, occurring throughout the neoplasm's life cycle, can be conceptualized as immunoediting (Schreiber 2011). A neoplasm likely arises through a complex set of germline variations, tissue-specific genetic mutation, and environmental interactions, resulting in a process of tissue transformation. Senescence, apoptosis, and innate and adaptive immune response elements may combine to restore that tissue to health, eventually eliminating the neoplasm. Alternatively, the neoplastic transformation continues to evolve, potentiating inherently immunogenic processes and an array of immune response elements that may successfully eliminate the neoplasm or successfully suppress it.

Clinically, such neoplasms may be undetectable, occult, or detectable, yet at limited early-stage disease causing no or very limited tissue-specific symptoms. Therefore some neoplasms exist in an undefined equilibrium with an immune response, failing to progress without any clinical effort (surgery, radiotherapy, chemotherapy) to suppress or remove it. Unfortunately, a neoplasm frequently continues on a path of genetic and epigenetic mutation and modification. Once it becomes less immunogenic, changing its relationship with the tissue microenvironment, it eventually becomes locally immunosuppressed. Once the tumor escapes immune control, it can then progress.

As a neoplasm evolves from potential elimination to an immunoequilibrium, and eventually to escape, immune responses to tumor-specific antigens are activated. These antigens represent unique cell surface components of the tumor, or intracellular components exposed to the local environment after apoptosis occurring in its natural evolution. Local tissue macrophages process these antigens, presenting them to cytotoxic T cells or to tissue dendritic cells migrating to regional lymph nodes, thereby activating T and B lymphocytes. The pattern of immune activation toward Th1, Th2, Th17, and T regulatory cells (Tregs), governed by the cytokine milieu, dictates the effects of the immune response.

The autoimmune expression within this immunoediting context of cancer is further regulated by multiple immune checkpoints. These include but are not limited to the status of regional and systemic Tregs, Th17 mediators, regulatory B cells (B10 via interleukin-10 [IL-10]), relative activation of STAT 4 versus STAT 6 transcription factors, genetic and epigenetic variation regulating any given individual's immune response and generation of tolerance, the status of important negative regulators of immune activation such as cytotoxic T-lymphocyte antigen-4 (CTLA-4), and programmed cell death 1 (PD-1) and its ligand B7-H1 (or PD-L1).



Immune Effectors
- Macrophages
- CD8 T cells
- CD4 T cells
- T_{reg}
- Killer T cells
- B cells
- Antibodies
- Cytokines

+

Immune Dysregulation
- Th17/IL-17, IL-22
- B10/IL-10
- CD4 CD25 FoxP3 T_{reg}
- STAT 4 vs. STAT 6
- Genetic/epigenetic variation
- CTLA4
- PD1/B7-H1 (PD-L1)

→

Nervous System Immune-Mediated Injury
- Mechnisms of immune effector access to specific nervous system targets largely unknown
- Specificity of nervous system targets likely related to molecular mimicry between nervous system antigens and tumor antigens processed via antigen-presenting cells
- Multiple levels of nervous system may be affected simultaneously or at different points in time
- Multiple autoantibody markers present simultaneously
- In some cases may be associated with better tumor prognosis
- In some instances autoantibodies may be directly involved in pathogenesis; better prognosis for immunotherapy
- Non-antibody immune-mediated tissue injury likely irreversible; early identification and intervention critical

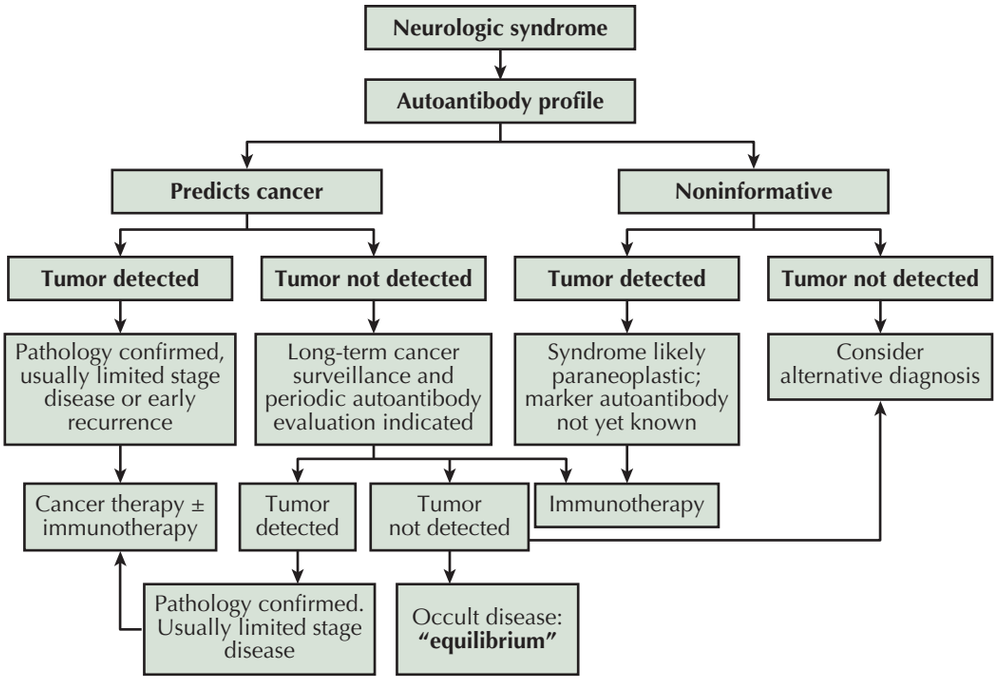
Paraneoplastic Immune-Mediated Disorders *(Continued)*

For example, blockade of CTLA-4 leads to development of autoimmunity within several organ systems. The expression of autoimmunity within the nervous system also relates to a host of additional factors, including regulation of immune effector access across the blood-brain barrier or blood–peripheral nerve barrier, as well as mechanisms of antigen presentation within the nervous system.

Paraneoplastic neurologic autoimmunity occurs within the context of an evolving immune response to a developing neoplasm, is expressed via a complex array or immune effectors, and is dependent on the status of numerous immune activation and injury regulators. Consequently, these disorders have unique attributes, not the least of which is their frequent association with an identifiable panel of autoantibodies potentially predicting the presence of a specific limited-stage cancer and possibly serving as a therapeutic target.

The evolution of our understanding of paraneoplastic autoimmunity began with descriptions of particular syndromes associated with specific cancers and subsequent individual autoantibody identification. *Antineuronal nuclear autoantibody type-1* (ANNA-1), also known as *anti-Hu*, was initially reported in patients with *sensory neuronopathies* related to small cell lung cancer (SCLC). *Purkinje cell cytoplasmic autoantibody-type-1* (PCA-1), also known as *anti-Yo*, was first recognized in women with cerebellar ataxia and *ovarian carcinoma*. *ANNA-2* (also known as anti-Ri) was initially reported in women with *opsoclonus/myoclonus* related to *breast carcinoma*. The *anti-amphiphysin antibody* was first reported in women with "*stiff-man*" *syndrome* related to *breast carcinoma*.

In contrast, most paraneoplastic autoantibodies are associated with a multifocal, variable neurologic presentation involving multiple neuroaxis levels in most patients. Moreover, patterns of involvement vary significantly from one patient to another despite the presence of the same autoantibody or autoantibody profile. When tabulating the patterns of nervous system dysfunction by reported associated autoantibody, it becomes clear that although given antibodies are associated with specific syndromic presentations, these are not uniquely associated with the autoantibody, per se, nor is the expression of autoantibodies uniquely associated with one level of nervous system disease. However, when tabulating known autoantibodies by predictive value for identifying underlying neoplasms, the antibody or pattern of antibodies primarily predicts the cancer and not specific neurologic disorders. Understanding that the immune response to a tumor is highly complex, and that the expression of autoimmunity is related to dysregulation of immune function at any number of potential checkpoints, the complexity and range of neurologic autoimmunity for given patients with specific malignancies becomes easier to comprehend.



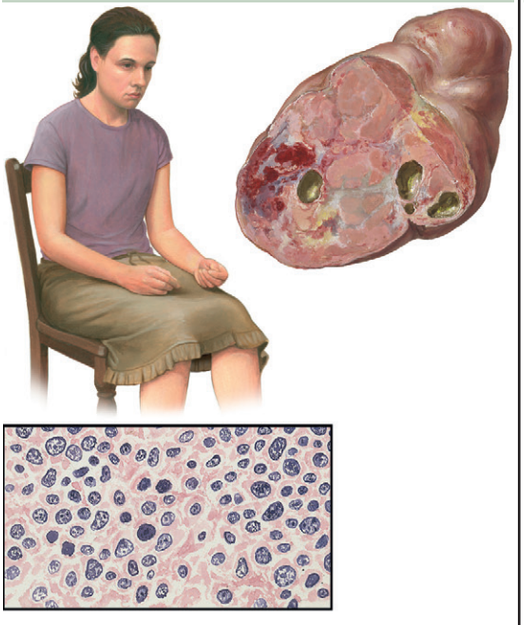
Antibody	Neoplasm Predicted by Seropositivity	Neoplasm Found (%)
ANNA-1 (anti- Hu)	SCLC, Neuroblastoma, thymoma	>81
ANNA-2 (anti-Ri)	Lung or breast carcinoma	86
ANNA-3	Lung or upper airway carcinoma	90
AGNA-1	SCLC	>90
Zic 4	SCLC	92
PCA-1 (anti-Yo)	Ovarian, fallopian, endometrial, breast carcinoma	90
PCA-2	SCLC	80
PCA-Tr	Hodgkin lymphoma	90
Amphiphysin	Breast or lung carcinoma	>80
CRMP-5-IgG	SCLC, thymoma, thyroid carcinoma	>80
Striational	Thymic tumors, carcinoma	uncertain
VGCC, N	Lung, breast or ovarian carcinoma	65
VGCC P/Q	SCLC, ovarian, breast	50
Ganglionic AChR	Thymoma, adenocarcinoma	90
Muscle AChR	Thymoma, carcinoma	*
VGKC	Thymoma, carcinoma	30
NMDAR	Teratoma	59 (female)

AChR, Acetylcholine receptor; *ANNA-I,* antineuronal nuclear antibody, type 1; *ANNA-2,* antineuronal nuclear antibody, type 2; *ANNA-3*, antineuronal nuclear antibody, type 1; *AGNA-1*, antiglial neuronal nuclear antibody, type 1; *CRMP-5*, collapsin response mediator protein; *IgG*, immunoglobulin G; *NMDAR*, *N*-methyl-D-aspartate receptor; *PCA-1*, Purkinje cell antibody, type 1; *PCA-2,* Purkinje cell antibody, type 2; *PCA-Tr,* Purkinje cell antibody, type Tr; *SCLC*, small cell lung cancer; *VGCC*, voltage-gated potassium channel; *Zic 4*, zinc finger protein 4. *May be up to 30%; varies by age, sex, and presence of coexisting antibodies.

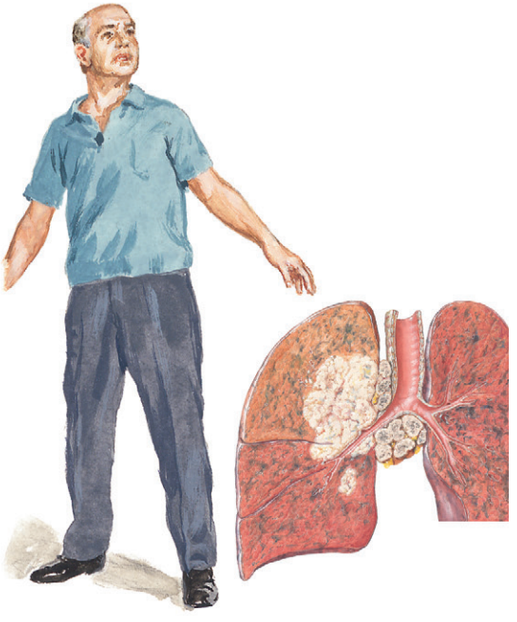
Cancers associated with paraneoplastic neurologic disorders are most often clinically asymptomatic and not defined, per se, until the appearance of the specific clinical syndrome dictates an evaluation for such, and that, per se, may not initially always lead to a diagnosis. Sometimes the cancer is not identified for months to years after the onset of the paraneoplastic neurologic syndrome. Taken together, the current appreciation of the pathophysiology of cancer-related autoimmunity, the understanding of autoantibodies as markers of a complex evolving immunoediting response, and knowledge that those antibodies are markers of the immune response to a specific cancer and not a specific neurologic syndrome, a diagnostic paradigm leading to a potentially specific diagnosis emerges. The specific neurologic disorder leads to an evaluation that includes a means to localize the disease, and exclude other diseases having a similar presentation. The suspicion of neurologic autoimmunity leads to testing for a panel of known paraneoplastic autoantibodies and search for an underlying cancer appropriate to age, sex, and risk factors such as tobacco abuse. Certain antibodies direct specific cancer investigations or, when unrevealing after an appropriately exhaustive search, a need for long-term surveillance. The need for immunotherapy is dictated by the severity of the underlying neurologic disorder, plans for treatment of the primary tumor, and previous experience with response to specific immunotherapeutic approaches for known conditions. There is always the inherent and paradoxical risk that initiation of immunomodulating therapy may suppress the body's ability to fight the cancer, allowing it to appear sooner than it might have, barring this therapeutic intervention.

Central Nervous System: Paraneoplastic

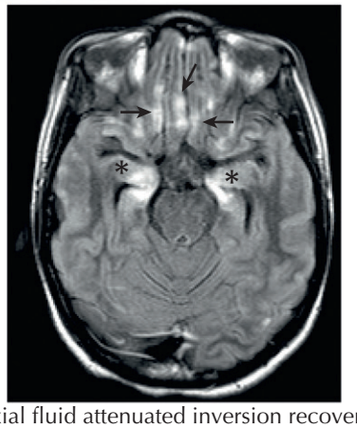
NMDA encephalitis, young woman with ovarian teratoma



Ataxic man with small cell lung cancer

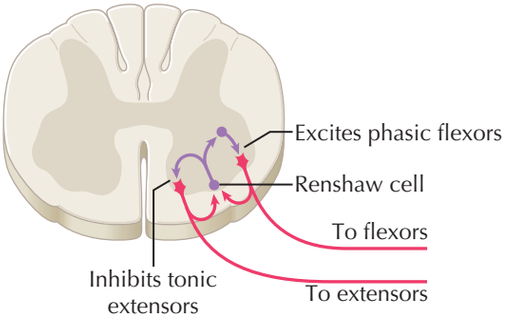


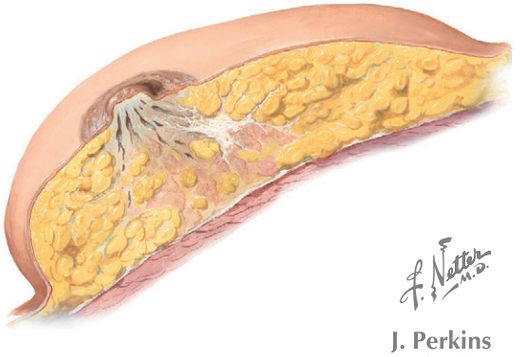
Limbic encephalitis with small cell lung cancer



Axial fluid attenuated inversion recovery (FLAIR) T2 MRI photomicrograph showing lesions in the bilateral hippocampus *(stars)* and orbitofrontal cortex *(arrows)* seen in limbic encephalitis

Spinal cord–stiff woman with breast cancer





J. Perkins
MS, MFA

Neuroimmunology: Paraneoplastic and Other Autoimmune Syndromes

Cerebral Cortex and Limbic System

N-methyl-D-aspartate receptor *(NMDAR) encephalitis* is characterized by an unusual psychiatric or neuropsychiatric presentation, often associated with seizures, evolving within a few weeks to decreased consciousness, occurs in association with antibodies to the NR1 subunit of the *NMDA receptor*. Patients are often female, notably young adults and children. Periods of catatonic-like akinesis alternate with agitation, paradoxic responses to stimuli, echolalia, dyskinesias (especially orofacial), and autonomic instability. Central hypoventilation, requiring prolonged ventilatory support, is common. Teratoma, particularly ovarian, including nervous system tissue reactive to patient sera and NMDA antibodies, occurs in nearly 60%. Diagnosis and immunotherapy can lead to dramatic improvement.

Limbic encephalitis is characterized by cognitive impairment, seizures, and behavioral abnormalities and may occur as a primary autoimmune or paraneoplastic condition. The most commonly associated neoplasm is small cell lung cancer (SCLC). Multiple autoantibody markers are associated with this syndrome; the specific serum autoantibody profile may predict a specific cancer risk. Other levels of the neuroaxis are frequently involved when associated with some paraneoplastic autoantibody markers, for instance, Ma2, antineuronal nuclear autoantibody type-1 (ANNA-1), antiglial neuronal nuclear antibody-1 (AGNA-1), whereas not so with others (voltage-gated potassium channels [VGKC], LGI1). Isolated paraneoplastic autoimmune cerebral cortex involvement is rare; current autoantibody markers are found infrequently. Instances of cortical encephalitis in association with neuronal acetylcholine receptor (AChR), and/or VGKC, collapsin response mediator protein-5 (CRMP-5), or glutamic acid decarboxylase (GAD-65) antibodies and thymoma are reported.

Diencephalon

Hypothalamic dysfunction with excessive sleepiness and some features of cataplexy occur in patients with Ma2 autoantibody. Cerebrospinal fluid (CSF) hypocretin levels are low or undetectable. Features of diencephalic involvement are also quite prominent in NMDA encephalitis.

Basal Ganglia and Extrapyramidal System

Paraneoplastic chorea occurs most commonly with SCLC in association with an antibody to *CRMP-5*. Variable movement disorders occur with *NMDA antibody*. *Orofacial dyskinesia* may occur with lung cancer and *ANNA-2*. *Myoclonus*, including *opsoclonus*, is the most frequent of the rare paraneoplastic movement disorders. It occurs with a number of different neoplasms, particularly childhood neuroblastoma; it lacks specific syndromic serologic markers. Anatomic localization is difficult; this potentially arises from the brainstem or spinal cord, as with *rigidity* manifesting dystonia and "stiff-person" phenomena.

Cerebellum

Subacute cerebellar ataxia is the most common manifestation in patients seropositive for *Purkinje cell*

Neuroimmunology: Paraneoplastic and Other Autoimmune Syndromes *(Continued)*

cytoplasmic autoantibody-type-1 (PCA-1) or PCA-Tr. This may occur with other antibody markers, including P/Q-type voltage-gated calcium channel antibody and AGNA-1. With PCA-Tr, Hodgkin lymphoma diagnosis has often preceded the cerebellar syndrome. Otherwise, the antibody profile directs the cancer search. PCA-1 highly suggests gynecologic sources, especially occult ovarian cancer; AGNA-1 strongly predicts SCLC.

BRAINSTEM

Subacute onset tremor, rigidity, opsoclonus, myoclonus, ophthalmoplegia, nausea, vomiting, vertigo, nystagmus, ataxia, or bulbar palsy may indicate brainstem inflammation. *Brainstem encephalitis* is frequent in association with ANNA-2 and Ma2, but less so with several other paraneoplastic autoantibodies and associated cancers.

CRANIAL NERVES

Paraneoplastic autoimmune vision loss–associated optic neuritis, retinitis, and vitreous inflammation is syndromic with CRMP-5 IgG and SCLC. Although *autoimmune retinopathy* lacks inflammatory infiltrates, visual loss can be severe. This may be paraneoplastic, notably associated with SCLC and melanoma, or idiopathic. Antibodies to *recoverin* and other retinal proteins are identified; however, the visual-loss pathophysiology is poorly understood.

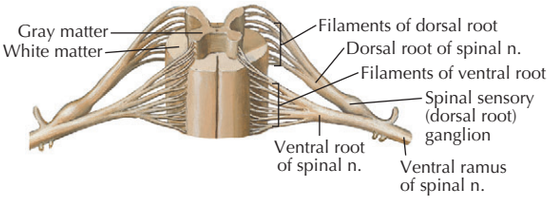
Multiple cranial neuropathies, including hearing loss, occur in a paraneoplastic context. Association with CRMP-5 IgG and SCLC is most frequent. Differentiating cranial nerve from brainstem pathology is difficult.

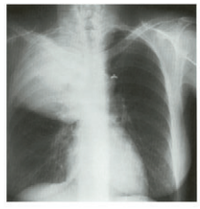
SPINAL CORD

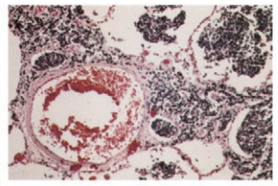
Subacute onset myelopathy is associated with several different cancers and cancer-specific autoantibodies. Clinically, it is typically symmetric, with longitudinally extensive long-tract or gray matter–specific magnetic resonance imaging (MRI) changes. Motor involvement can be severe, especially the necrotizing variant having a distinct cord level.

Peripheral Motor Sensory Unit: Paraneoplastic

Subacute sensory neuropathy





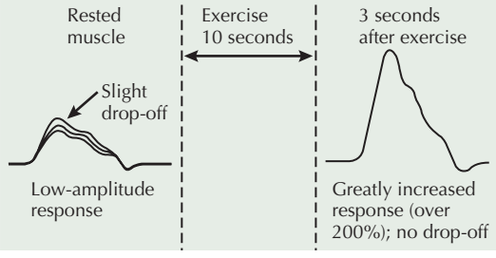


Intrapulmonary lymphatic spread of neoplasm

Lambert-Eaton in bronchogenic small cell carcinoma

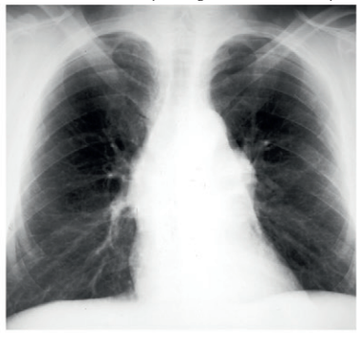
Lambert-Eaton syndrome; weakness of proximal muscle groups (often manifested by difficulty in rising from chair); compound muscle action potential facilitation with high frequency motor nerve stimulation

Electromyography with voluntary exercise
Each tracing represents 3 superimposed action potentials evoked by stimulation at 3/second

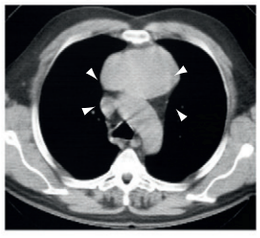


Myasthenia gravis thymoma

Thymus gland abnormality in myasthenia gravis

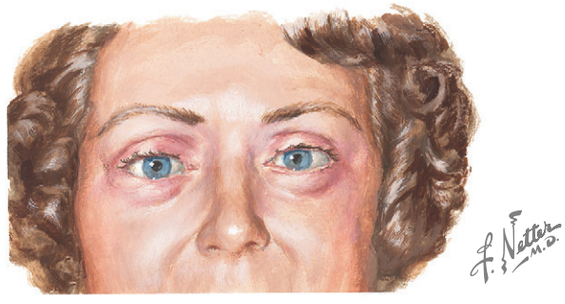


X-ray film shows large mediastinal tumor, which localized to anterior compartment (view not shown)



CT scan clearly demonstrates same large tumor anterior to aortic arch *(arrowheads)*

Dermatomyositis and typical rash



Edema and heliotrope discoloration around eyes a classic sign. More wisespread erythematous rash may also be present.

"Stiff-man" syndrome (SMS), Moersch-Woltman syndrome, typically has severe, painful, and progressive muscle rigidity or stiffness prominently affecting the paraspinal musculature and/or leg muscles, sometimes unilaterally. High-serum *GAD-65 autoantibody* levels (usually >>>> 20 nmol/L) aids nonparaneoplastic SMS diagnosis. Ironically, SMS rarely occurs with thymoma in contrast to myasthenia gravis. Lower-titer GAD-65 may be seen with Hashimoto thyroiditis, pernicious anemia, and type 1 diabetes.

Amphiphysin antibody is a paraneoplastic stiff-person (SPS) marker associated breast or lung cancer. Atypical nonparaneoplastic stiff-person syndromes, particularly progressive encephalomyelitis rigidity and myoclonus (PERM), occur with antibodies to *glycine* receptors (GlyR). SPS variants are difficult to distinguish from

NEUROIMMUNOLOGY: PARANEOPLASTIC AND OTHER AUTOIMMUNE SYNDROMES
(Continued)

other neuromuscular hyperexcitability, rigidity, or dystonia syndromes. Electrophysiologic testing is helpful. Concurrent involvement of multiple neuroaxis levels, and specific autoantibody profiles, that is, amphiphysin, identify paraneoplastic SMS patients.

MOTOR NEURON OR MOTOR NERVE SYNDROMES

These rarely occur in paraneoplastic contexts. Concurrent involvement of nonmotor neuroaxis regions and specific autoantibody profiles distinguish these *motor neuronopathies* from amyotrophic lateral sclerosis (ALS). However, ALS occasionally occurs coincident with neoplasms; no pathophysiologic relationship between the two is discernible. The clinical course is inexorably progressive, regardless of the neoplasm's prognosis.

In contrast, paraneoplastic *motor nerve* syndromes may slow or remit with treatment of the underlying neoplasm. It is important to distinguish demyelinating inflammatory neuropathic syndromes, for example, multifocal motor neuropathy with conduction block, because these are immunotherapy responsive, particularly with intravenous immunoglobulin (IVIG).

Mononeuropathy, plexopathy, polyradiculopathy, and small-fiber neuropathy occur in isolation or multifocal presentations with cancer. Paraneoplastic autoimmunity rarely explains these syndromes; it is important for the clinician to look for those conditions such as metastatic disease, radiotherapy effects, anatomic deformities, and toxic medication metabolic disorders that are more typically responsible.

SENSORY NEUROPATHIES

Subacute sensory neuronopathy affecting the dorsal root and autonomic ganglia is a prototypic neurologic SCLC manifestation with ANNA-1 autoimmunity. It is distinguished clinically by affecting face, trunk, and extremities in contrast to a classic distal-predominant sensory *peripheral neuropathy (PN)*. Associated large-fiber proprioceptive sensory deficits predispose to the sensory ataxia. Electromyography (EMG) demonstrates that *peripheral sensory nerve action potentials (SNAPs) are absent.*

Sensory neuropathy, distinguished from neuronopathy, is a painful and common paraneoplastic accompaniment. Concurrent motor involvement varies. Multiple autoantibodies occur, primarily related to the cancer. Many cancers are treated with peripheral neurotoxic chemotherapy. Furthermore, neuropathy patients often have multiple organ failures, making etiologic assignment problematic. EMG demonstrates low-amplitude SNAPs.

Myeloma and Waldenström macroglobulinemia are associated with monoclonal immunoglobulins. These entities have variable peripheral neuropathic presentations, sometimes severe, with distinct demyelinating features.

AUTONOMIC NERVOUS SYSTEM

Autonomic neuropathy or ganglionopathy usually occurs as a multifocal disorder associated with cancer, sometimes having multiple autoantibody markers. Orthostatic hypotension, anhidrosis, dry mouth, erectile dysfunction, impaired pupillary light response, fixed heart rate, and gastrointestinal dysmotility are variably present. Cancer-attributed symptoms, including cachexia, anorexia, early satiety, postprandial abdominal pain, and vomiting, may relate to gastroparesis or severe constipation.

Primary nonparaneoplastic autoimmune dysautonomias, associated with high titers for neuronal AchR antibodies, are often severe and disabling.

NEUROMUSCULAR JUNCTION

Lambert-Eaton myasthenic syndrome (LEMS) is a presynaptic peripheral cholinergic neuromuscular transmission disorder classically causing proximal limb weakness and sometimes bulbar and extraocular muscle dysfunction. Typically, weakness improves within seconds of voluntary muscle activation; symptoms often exceed physical examination findings. Electromyographic characteristics and seropositivity for neuronal calcium (Ca^{2+}) channel autoantibodies distinguish presynaptic LEMS from postsynaptic myasthenia gravis. The *P/Q-type Ca^{2+} channel antibody* is specifically pathogenic, mediating presynaptic surface channel loss that distinguishes LEMS from most paraneoplastic disorders where neuronal, glial nuclear, or cytoplasmic antibodies are serologic markers but not clearly pathogenic.

SCLC occurs in 60% of LEMS patients; LEMS clinically affects 1% to 2% of SCLC patients, although the frequency of *P/Q-type Ca^{2+} channel antibody* is higher. Other antibodies, especially *N-type calcium channel antibodies*, frequently coexist. Limited dysautonomia is characteristic. Profound dysautonomia, especially if gastrointestinal motility is impaired, usually indicates an additional concurrent immune-mediated paraneoplastic mechanism often associated with ANNA-1, amphiphysin, or CRMP-5–IgG.

Myasthenia gravis (MG) is a postsynaptic disorder of peripheral cholinergic neuromuscular transmission. Fatigable ptosis, diplopia, and bulbar/extremity muscles weakness are characteristic. Antibodies directed at the extracellular muscle AChR domain are pathogenic in MG. Thymoma occurs in 10% to 15%. Here antibodies modulating (internalizing) the AChR, as well as antibodies directed against striated muscle, GAD-65, VGKC, CRMP-5, and neuronal AChR, are sometimes also identified. MG rarely occurs with other neoplasms.

Neuromuscular hyperexcitability disorders, including *neuromyotonia, or cramp-fasciculation syndrome* often occur as acquired idiopathic autoimmune and, rarely, paraneoplastic disorders. VGKC or contactin-associated protein 2 (CASPR2) antibodies are frequently identified.

MUSCLE

Cancer coexists in 15% of dermatomyositis patients, less frequently in polymyositis. It can usually be identified at time of myopathy diagnosis. Symptoms and signs are indistinguishable in paraneoplastic and nonparaneoplastic forms, although necrotic skin lesions, rapid onset, and older age provide clues to paraneoplastic dermatomyositis; no autoantibody markers are identified.

Acute necrotizing myopathy is rarely associated with a variety of cancers. Coincidental association with statin use is important to recognize. There are no antibody markers in paraneoplastic varieties, but antibodies to signal recognition particle (SRP) are reported in idiopathic autoimmune variants.

INFECTIONS OF THE NERVOUS SYSTEM

Bacterial Meningitis

Pathophysiology. Bacterial meningitis is initially an acute purulent infection of the meninges and subarachnoid space that is followed by an inflammatory reaction in the subarachnoid space, the brain parenchyma, and the cerebral arteries (arteritis) and veins (dural sinus thrombosis and thrombophlebitis). Meningitis is most often the result of bacterial invasion of the subarachnoid space from hematogenous dissemination. Bacterial meningitis may be preceded by colonization of the nasopharynx by the organism or develop as a complication of pneumonia, acute otitis media, acute sinusitis, endocarditis, skull fracture, a neurosurgical procedure, or the use of a catheter to decrease intracranial pressure or administer chemotherapeutic or antimicrobial agents.

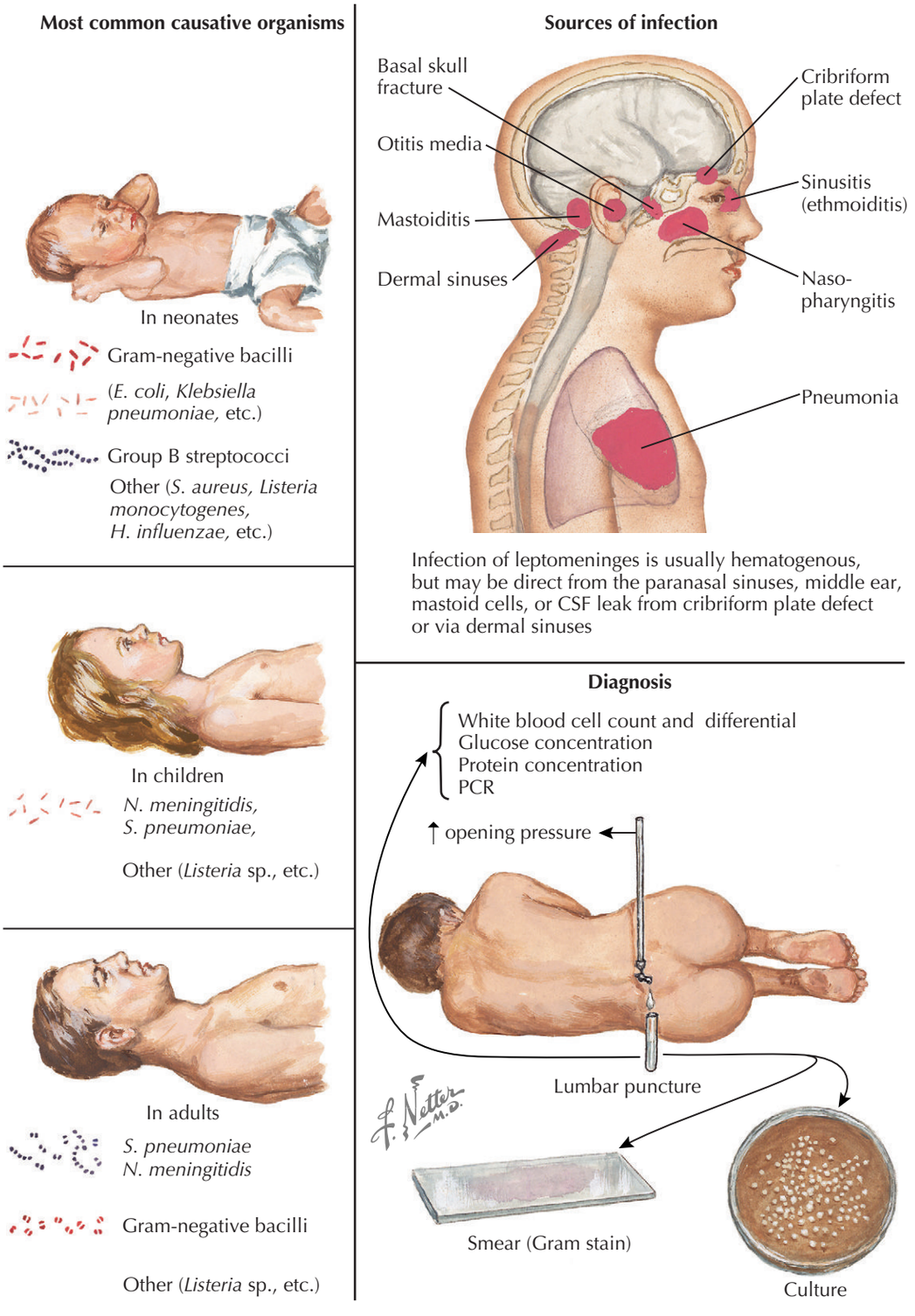
The meningeal pathogen can be predicted by the patient's age. In neonates, the most common pathogens are group B streptococci (*Streptococcus agalactiae*), gram-negative bacilli, and *Listeria monocytogenes*. In children, adolescents, and adults, the most common causative organisms of community-acquired bacterial meningitis are *Neisseria meningitidis* and *Streptococcus pneumoniae*. *Listeria monocytogenes* is a causative organism of meningitis in individuals with impaired cell-mediated immunity due to organ transplantation, chronic illness, pregnancy, acquired immunodeficiency syndrome, malignancy, immunosuppressive therapy, or age. When meningitis complicates acute otitis media, mastoiditis, or sinusitis, the causative organisms are *Streptococci* spp., gram-negative anaerobes, *S. aureus*, *Haemophilus* sp., or Enterobacteriaceae. Meningitis in the postneurosurgical patient and the patient with a ventriculostomy or other indwelling catheter may be due to staphylococci, gram-negative bacilli, or anaerobes.

Clinical Manifestations. The signs and symptoms of meningitis in the neonate include irritability, lethargy, poor feeding, vomiting, diarrhea, temperature instability, respiratory distress, apnea, seizures, and a bulging fontanel. The signs and symptoms of bacterial meningitis in children, adolescents, and adults include fever, vomiting, photophobia, headache, nuchal rigidity (meningismus), and a decreased level of consciousness ranging from lethargy to stupor, obtundation, or coma.

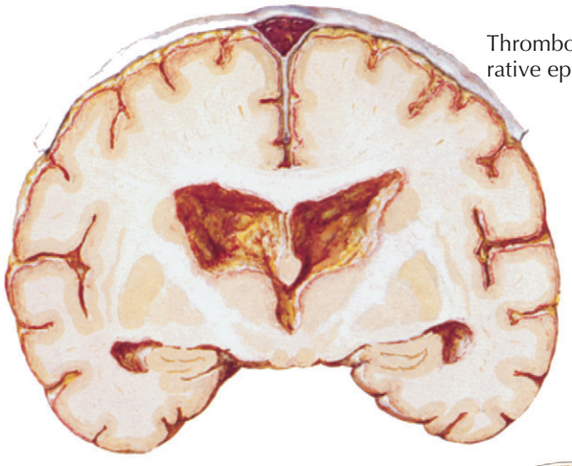
On physical examination, the classic sign of bacterial meningitis is meningismus, but this sign is not invariably present. The neck resists passive flexion. Kernig sign and Brudzinski sign are also signs of meningeal irritation (see Plate 11-2). Both signs are elicited with the patient in the supine position. To elicit Kernig sign, the thigh is flexed on the abdomen with the knee flexed. Attempts to passively extend the leg elicit pain and are met with resistance when meningeal irritation is present. Brudzinski sign is positive when passive flexion of the neck results in spontaneous flexion of the hips and knees. The presence of a petechial rash on the trunk and lower extremities, in the mucous membranes and conjunctiva, and occasionally on the palms and soles is typical of the rash of meningococcemia. A petechial rash is not seen in all cases of meningococcal meningitis, and a petechial rash is rarely seen in *H. influenzae*, pneumococcal, and staphylococcal meningitis. Patients with enteroviral meningitis may also have a rash, but this is an erythematous maculopapular rash that involves the face and neck early in infection.

Diagnosis. The gold standard for the diagnosis of bacterial meningitis is analysis of the cerebrospinal fluid. A computed tomography (CT) scan should be obtained in the patient with any of the following: an

Bacterial Meningitis—I

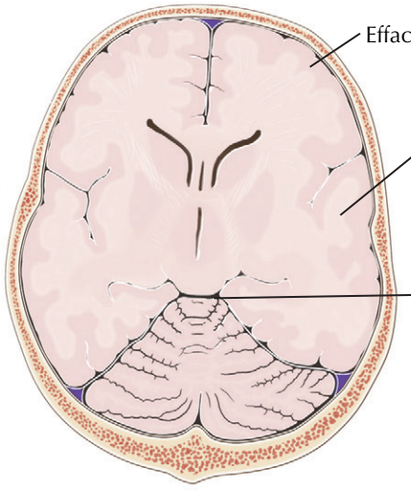


BACTERIAL MENINGITIS—II

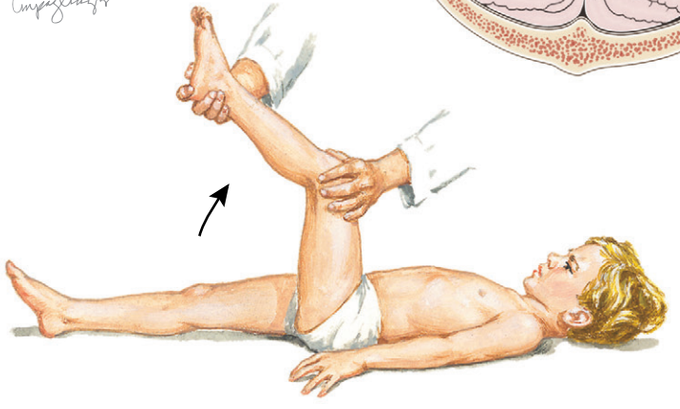


Thrombophlebitis of superior sagittal sinus and suppurative ependymitis, with beginning hydrocephalus

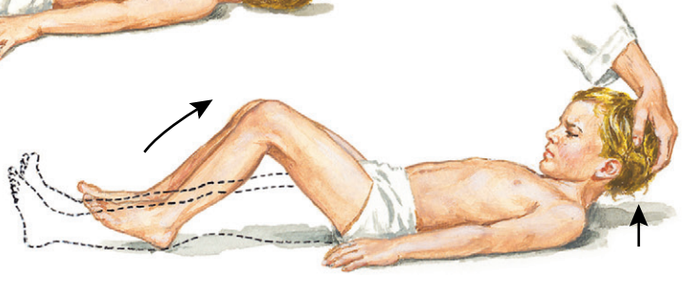
BACTERIAL MENINGITIS
(Continued)



Diffuse cerebral edema



Kernig sign. Patient supine, with hip flexed 90°. Knee cannot be fully extended.



Neck rigidity (Brudzinski neck sign). Passive flexion of neck causes flexion of both legs and thighs.

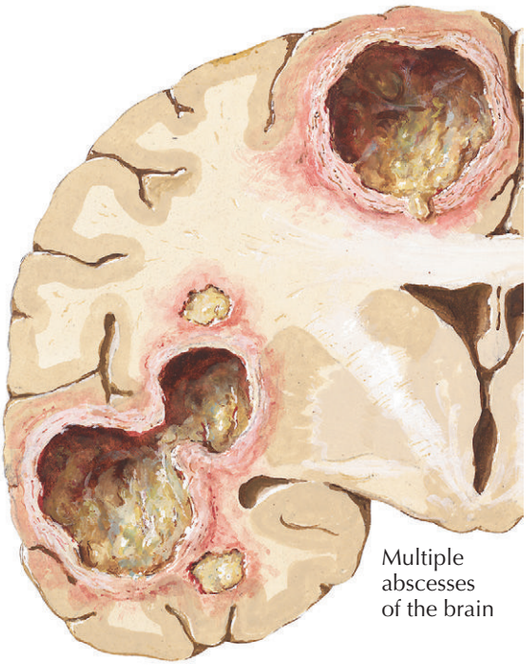
altered level of consciousness, papilledema, a focal neurologic deficit, new-onset seizure activity, immunocompromised state, a dilated or poorly reactive pupil, signs of a posterior fossa mass lesion (cranial nerve abnormalities, cerebellar deficit, and a wide-based ataxic gait), or a risk for neurocysticercosis. The classic abnormalities in bacterial meningitis on examination of the cerebrospinal fluid are the following: (1) an opening pressure greater than 180 mm H_2O, (2) an increased white blood cell count with a predominance of polymorphonuclear leukocytes, (3) a decreased glucose concentration (less than 40 mg/dL), (4) an increased protein concentration, and (5) a positive Gram stain and bacterial culture. Gram stain is positive in identifying the organism in 60% to 90% of cases of bacterial meningitis. The probability of detecting bacteria on a Gram-stained specimen depends on the number of organisms present. The cerebrospinal fluid (CSF) 16S ribosomal ribonucleic acid (rRNA) conserved-sequence broad-based bacterial polymerase chain reaction (PCR) detects bacterial nucleic acid in CSF. There are also meningeal pathogen–specific PCRs available to identify the nucleic acid of a specific meningeal pathogen. The PCR is most useful in rapidly distinguishing between bacterial and viral meningitis. The PCR will not replace bacterial culture because culture is essential for antimicrobial sensitivity testing.

The classic cerebrospinal fluid abnormalities in viral meningitis are (1) a normal opening pressure, (2) a lymphocytic pleocytosis, (3) a normal glucose concentration, and (4) a normal or slightly elevated protein concentration. Enteroviruses can either be isolated in CSF culture or detected in CSF by the reverse-transcriptase polymerase chain reaction (RT-PCR). Herpes simplex virus type-2 deoxyribonucleic acid (DNA) can be detected in CSF by PCR. Human immunodeficiency virus-1 (HIV-1) RNA can be detected and measured in CSF, and the virus can be cultured from CSF. Viral immunoglobulin M (IgM) antibodies can be detected in CSF.

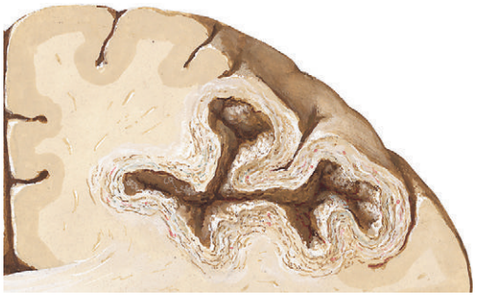
In patients with a clinical presentation of meningitis and a CSF lymphocytic pleocytosis with a decreased glucose concentration, fungal infections, *Mycobacterium tuberculosis*, sarcoidosis, and lymphoma/leptomeningeal metastases are in the differential diagnosis. A subarachnoid hemorrhage manifests with headache and a sudden transient loss of consciousness. Examination of the spinal fluid will reveal red blood cells and xanthochromia, although it may take several hours for xanthochromia to appear.

Treatment. When bacterial meningitis is suspected, dexamethasone and empiric antimicrobial therapy is begun immediately. The choice of empiric antimicrobial therapy depends on the suspected meningeal pathogen, which is determined by the age of the patient and predisposing or associated conditions. Once the organism is identified and the results of antimicrobial sensitivity testing are known, antimicrobial therapy is modified accordingly.

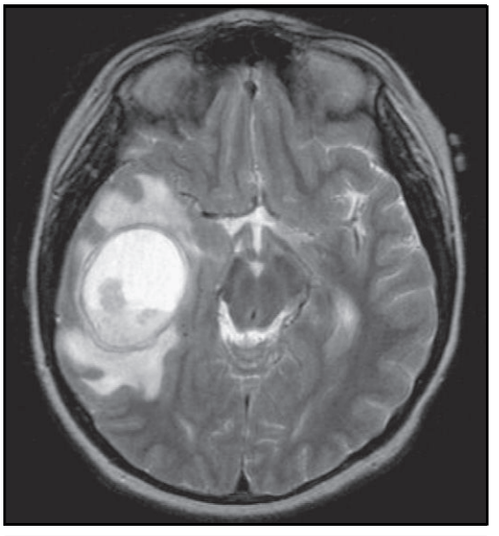
Complications. The major complications of bacterial meningitis are focal and diffuse brain edema, hydrocephalus, arterial cerebrovascular complications (ischemic and/or hemorrhagic stroke), septic sinus thrombosis with thrombophlebitis, hearing loss and vestibulopathy, and seizures. It is the complications of bacterial meningitis that cause the acute and chronic neurologic deficits.



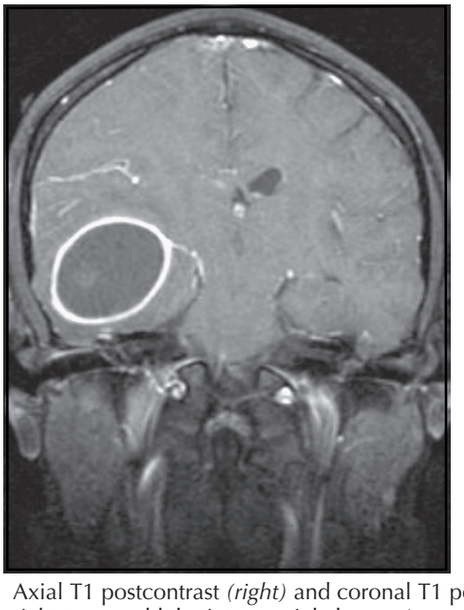
Multiple abscesses of the brain

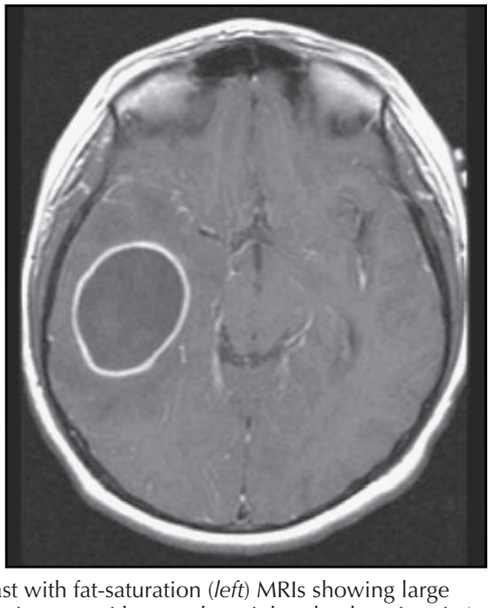


Scar of healed brain abscess, with collapse of brain tissue into cavity



Axial T2 MRI showing large right temporal lobe intracranial abscess (central T2 hyperintense internal debris, and peripherhal T2 hypointense capsule), with surrounding vagogenic edema





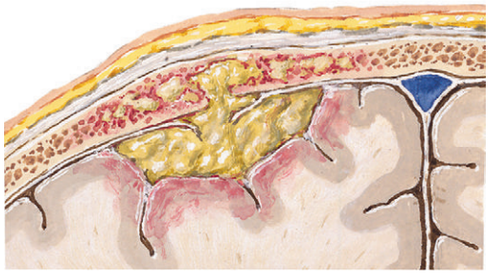
Axial T1 postcontrast *(right)* and coronal T1 postcontrast with fat-saturation (*left*) MRIs showing large right temporal lobe intracranial abscess (central T1 hypointense with smooth peripheral enhancing rim)

Brain Abscess

A brain abscess is a focal suppurative process that develops in the brain parenchyma in one of the following ways: (1) by direct spread from a contiguous cranial site of infection (paranasal sinusitis, mastoiditis, otitis media, or dental infections), (2) after cranial trauma, or (3) as a result of hematogenous spread from a remote site of infection (cyanotic congenital heart disease, endocarditis, lung abscess, intra-abdominal infection). The most common etiologic organisms of a brain abscess are streptococci, *Bacteroides* species, staphylococci (after trauma or craniotomy), *Fusobacterium* species, *Haemophilus* species, Enterobacteriaceae, and *Pseudomonas aeruginosa*. A brain abscess manifests with fever, headache, and a focal neurologic deficit. Headache is the most common symptom, but fever is not invariably present. As the area of cerebral edema surrounding the brain abscess increases, signs of increased intracranial pressure develop.

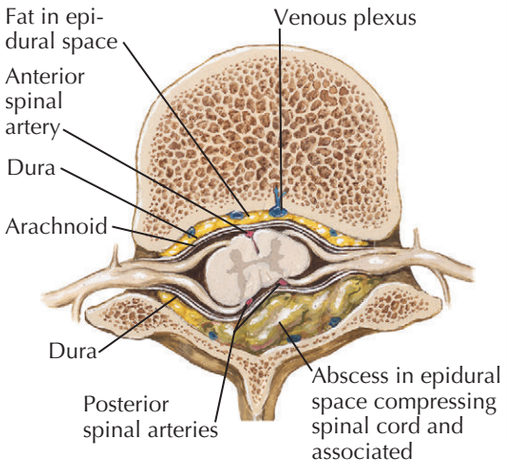
Magnetic resonance imaging (MRI) with contrast administration is the neuroimaging procedure of choice, because MRI is better able to demonstrate an abscess that is in the cerebritis stage than a cranial CT scan. On T1-weighted MRI after the administration of intravenous gadolinium, the abscess appears as a central area of hypointensity with a smooth peripheral enhancing rim. On T2-weighted MRI, the abscess appears as a hyperintense lesion surrounded by a hypointense capsule. A lumbar puncture is contraindicated. Aerobic and anaerobic blood cultures can be obtained, and a careful physical examination may identify the source of infection. Definitive diagnosis is made by CT- or MRI-guided stereotactic aspiration of the abscess for Gram staining and culture. Empiric antimicrobial therapy is typically started before the results of Gram stain and culture are known and is based on the possible causative organism if the source of infection is known. Empiric therapy is modified once the results of Gram stain and bacterial culture and antimicrobial sensitivity testing is known. Corticosteroids are recommended in patients with significant edema but only for a short period of time because they decrease antibiotic penetration into the abscess cavity. Prophylactic antiepileptic medications are recommended because a brain abscess is an epileptogenic focus.

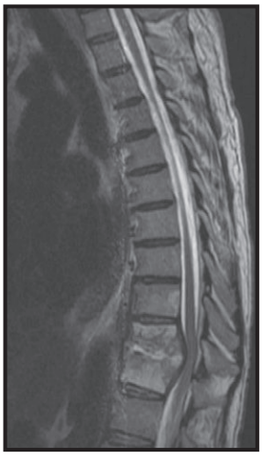
Subdural abscess



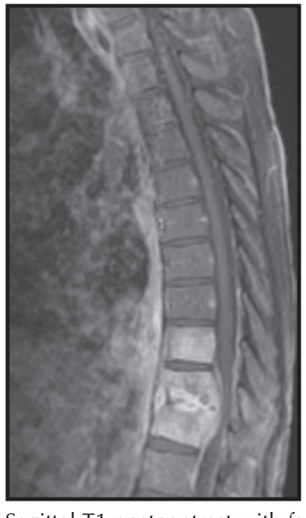
Osteomyelitis of skull, with penetration of dura to form subdural "collar button" abscess

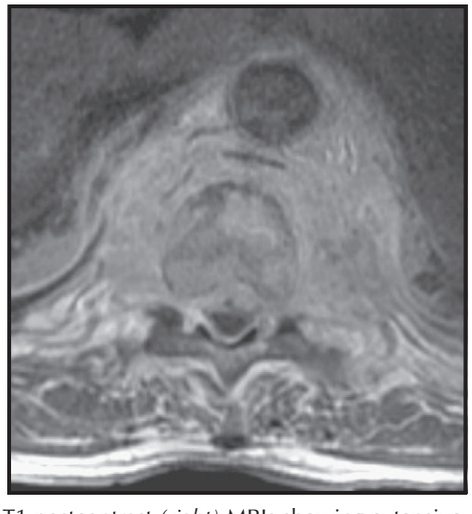
Epidural abscess





Sagittal T2 MRI showing extensive marrow edema, intervertebral disk space collapse, and cortical erosion at the T10-11 level, compatible with diskitis-osteomyelitis and associated ventral epidural abscess. Marked resultant mass effect and compression of the mildly edematous distal thoracic spinal cord. Abnormal edema is also present within the T9 vertebral body.





Sagittal T1 postcontrast with fat-saturation *(left)* and axial T1 postcontrast *(right)* MRIs showing extensive abnormal enhancement within the bone marrow, intervertebral disk space, and anterior epidural space at the T10-11 level, compatible with diskitis-osteomyelitis and associated ventral epidural abscess. Marked resultant mass effect and compression of the distal thoracic spinal cord. The sagittal view shows abnormal enhancement also present within the T9 vertebral body. The axial view shows significant associated paravertebral phlegmon.

Parameningeal Infections

Subdural Empyema

A subdural empyema is a collection of pus in the space between the dura and the arachnoid. Paranasal sinusitis is the most common predisposing condition associated with a subdural empyema, but otitis media, mastoiditis, and a neurosurgical procedure may also be complicated by a subdural empyema. A subdural empyema that is a complication of sinusitis, otitis media, or mastoiditis is usually due to aerobic, microaerophilic, or anaerobic streptococci. Subdural empyemas that are a complication of a neurosurgical procedure are often due to staphylococci. The initial signs and symptoms of a subdural empyema are due to increased intracranial pressure from an expanding infectious mass lesion. Headache and fever are the initial symptoms, followed by focal neurologic deficits, seizures, and a decrease in the level of consciousness. A subdural empyema is a life-threatening infection because patients may have a rapid progression of neurologic deficits and altered level of consciousness. A subdural empyema is readily imaged by computed tomography (CT) scan or magnetic resonance imaging (MRI) with contrast administration. The definitive step in the management of subdural empyema is surgical drainage and antimicrobial therapy. Empiric therapy with a combination of a third- or fourth-generation cephalosporin plus vancomycin and metronidazole is begun and then modified when the results of Gram's stain and bacterial cultures and sensitivities are known.

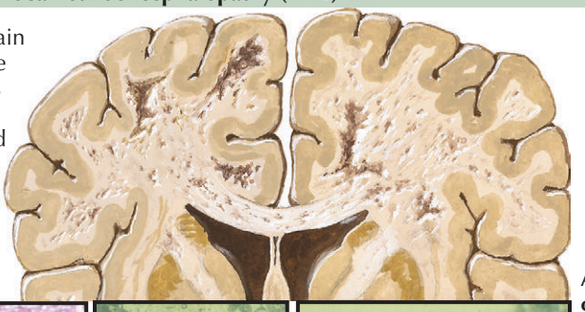
Spinal Epidural Abscess

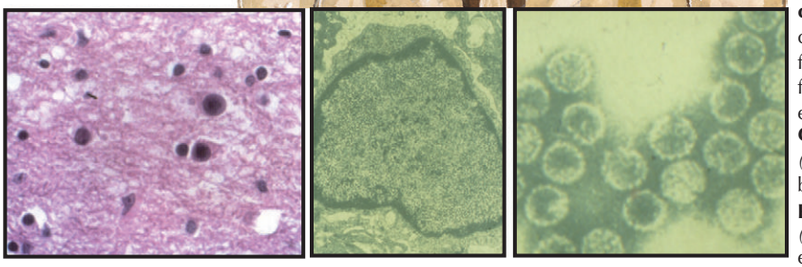
A spinal epidural abscess develops in the space outside the dura mater but within the spinal canal as a result of the hematogenous spread of infection from a remote site of infection or by direct extension from a contiguous infection, such as vertebral osteomyelitis, decubitus ulcers, or infected abdominal wounds. Neurologic deficits are the result of direct mechanical compression of the spinal cord and/or inflammatory thrombosis of the intraspinal vessels with subsequent ischemia and infarction. The initial symptom is back pain. Fever may be present. Back pain is followed by radicular pain, then weakness, and then paralysis of appendicular musculature, loss of sensation below the level of the lesion, and loss of bowel and bladder control. MRI is the procedure of choice to demonstrate a spinal epidural abscess and a contiguous area of infection when present. If there is evidence of compression of the spinal cord from the epidural abscess, an emergency decompression with evacuation of pus and granulation tissue is performed. This also allows for identification of the causative organism and guides antimicrobial therapy. Empiric antimicrobial therapy is directed at the most common causative organisms, which are staphylococci (*Staphylococcus aureus* and coagulase-negative staphylococci) and gram-negative bacilli.

Progressive Multifocal Leukoencephalopathy and Nocardiosis

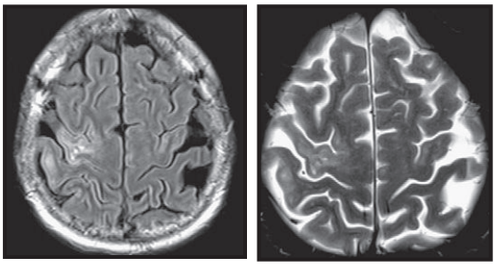
Progressive multifocal leukoencephalopathy (PML)

Coronal section of brain showing many minute demyelinating lesions in white matter, which have coalesced in some areas to form irregular cavitations



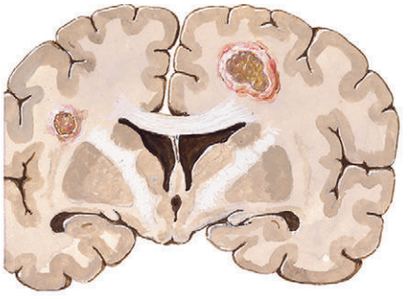


Abnormal oligodendrocytes *(left)* with large hyperchromatic nuclei section from edge of demyelinated focus (hemotoxylin and eosin stain)
Giant glial nucleus *(middle)* with inclusion bodies, electron micrograph
Papovirus virions *(right)* isolated from brain, electron micrograph

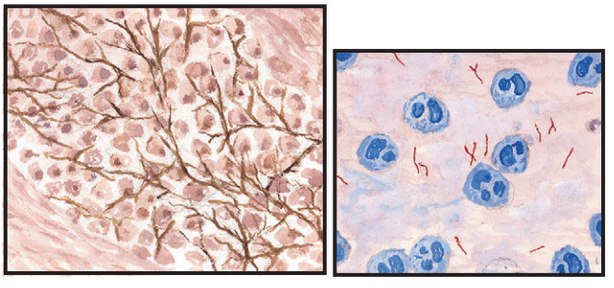


Axial FLAIR (left) and axial T2 *(right)* MRIs showing patchy abnormal hyperintense signal within the subcortical white matter of both (right > left) posterior frontal lobes (precentral gyri) and anterior right parietal lobe (postcentral gyrus), with characteristic sparing of the subcortical U fibers

Nocardiosis



Multiple nocardial abscesses in brain



Branching hyphae of *Nocardia asteroides* in brain abscess (methenamine-silver stain)

Modified acid-fast organisms as they may appear in pus, sputum, or tissues. They may be mistaken for tubercle bacilli, but are actually fragmented nocardial hyphae.

Infections in the Immunocompromised Host

There are four central nervous system (CNS) infections unique to the immunocompromised host. They are progressive multifocal leukoencephalopathy, a brain abscess due to *Nocardia asteroides*, meningitis due to *Listeria monocytogenes*, and toxoplasmosis.

Progressive Multifocal Leukoencephalopathy. Progressive multifocal leukoencephalopathy (PML) is a disease caused by the JC virus, a polyoma virus that is acquired in childhood, establishes latent infection in the kidneys and lymphoid organs, and reactivates in the setting of cellular immunosuppression. Because PML is a viral infection of oligodendrocytes causing focal areas of demyelination, the clinical presentation is that of focal or multifocal neurologic deficits, including hemianopsia, hemiparesis, or aphasia. On neuroimaging, the lesions are located in the subcortical hemispheric white matter, sparing the U fibers, and are typically not contrast enhancing and not surrounded by edema. The spinal fluid is similarly noninflammatory. There may be a slight increase in the white blood cell count and a mild elevation in the protein concentration. The diagnosis is made by demonstration of JC virus deoxyribonucleic acid (DNA) by polymerase chain reaction (PCR) of cerebrospinal fluid (CSF) or by brain biopsy. There is no specific antiviral therapy, and treatment is directed at reversing the immunosuppression.

Nocardiosis. *Nocardia asteroides* is a gram-positive bacterium that is found in soil and decaying vegetables. This bacterium is a causative organism of a brain abscess in individuals with impaired cell-mediated immunity. Risk factors include organ transplantation, immunosuppressive therapy, pulmonary alveolar proteinosis, sarcoidosis, and pregnancy. Unlike the primary management of the majority of bacterial brain abscesses by stereotactic aspiration guided by computed tomography (CT) or magnetic resonance imaging (MRI), a brain abscess due to *Nocardia asteroides* requires surgical excision through a craniotomy. These are thick-walled multiloculated brain abscesses. The infection is treated with trimethoprim-sulfamethoxazole or sulfonamide. Nocardial brain abscesses are relatively rare in human immunodeficiency virus (HIV)-positive individuals, because many HIV-positive individuals take trimethoprim-sulfamethoxazole to prevent *Pneumocystis carinii*.

Listeriosis. *Listeria monocytogenes* is a gram-positive bacterium that causes meningitis in immunocompromised individuals from organ transplantation, malignancies, chronic corticosteroid therapy, immunosuppressive therapy, diabetes mellitus, and pregnancy. Increasing age is also a risk factor for *Listeria monocytogenes* meningitis due to the natural decrease in cell-mediated immunity. Infection is acquired from soft cheeses, unpasteurized milk, hot dogs, deli meats, and cole

Infections in the Immunocompromised Host
(Continued)

slaw. In addition to meningitis, *Listeria monocytogenes* is one of the causative organisms of a brainstem encephalitis (rhomboencephalitis). Patients typically have headache, nausea, vomiting, and fever, followed by brainstem symptoms and signs, the most common of which is a unilateral facial nerve palsy. This is followed by dysarthria, vertigo, dysphagia, and hemiataxia. Spinal fluid analysis demonstrates a CSF pleocytosis with a predominance of neutrophils but also a mixture of lymphocytes and monocytes. The spinal fluid may also show a predominance of lymphocytes or monocytes. The glucose concentration may be decreased or normal. The organism can be grown in culture of CSF. In rhomboencephalitis, a lesion of increased signal intensity on T2-weighted and fluid attenuated inversion recovery (FLAIR) imaging can be seen in the pons and medulla. Therapy of meningitis due to *Listeria monocytogenes* is with ampicillin. In patients who are obtunded, gentamicin is added. Rhomboencephalitis is treated with a combination of ampicillin and gentamicin.

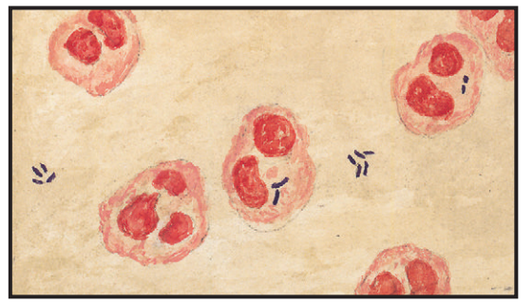
Toxoplasmosis. *Toxoplasma gondii* is a parasite that is acquired by ingesting the oocysts from contaminated soil, meat, or cat feces; however, *Toxoplasma* encephalitis is the result of reactivation of latent infection. HIV-infected individuals and patients receiving immunosuppressive therapy for lymphoproliferative disorders are at greatest risk for this infection. Patients present with headache, fever, an altered level of consciousness, focal neurologic deficits, and/or seizures. Neuroimaging demonstrates one or more focal or multifocal ring-enhancing lesions with edema. Diagnosis begins with serology for anti-*Toxoplasma* immunoglobulin G (IgG).

Listeriosis and Toxoplasmosis

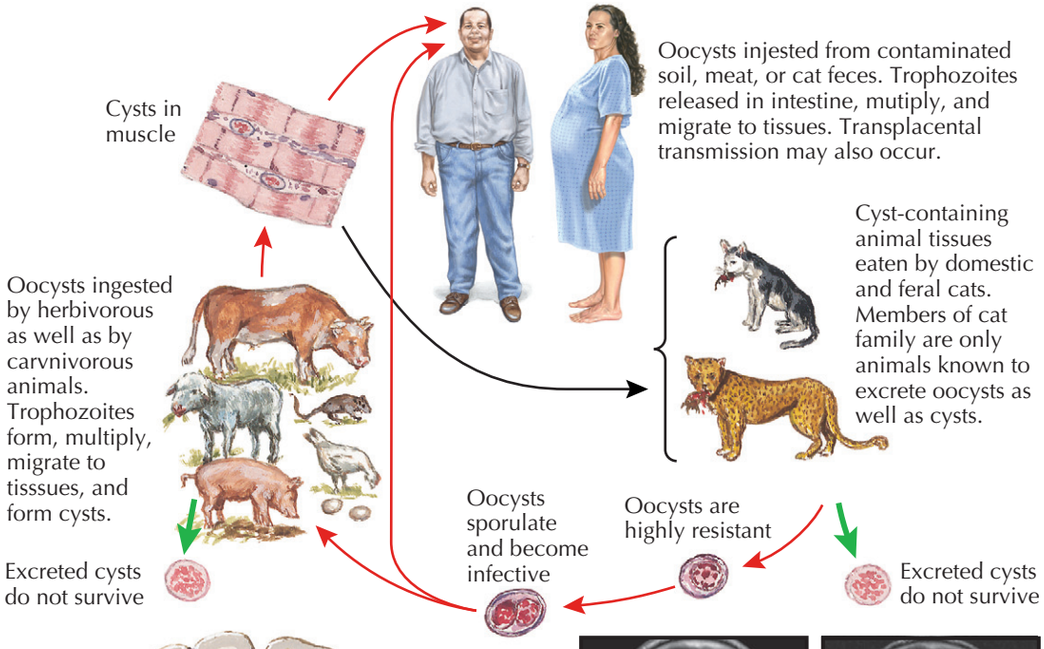
Listeriosis

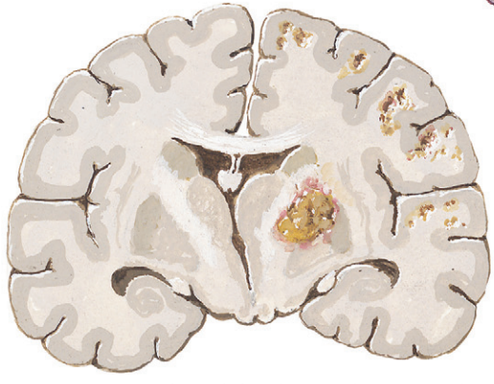
Smear of CSF showing white blood cells and *Listeria* organisms, which appear as gram-positive rods. They may be very short, resemble cocci, and they often orient in palisades suggestive of Chinese characters. They cause severe purulent meningitis, most commonly in immunocompromised patients or newborns.

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

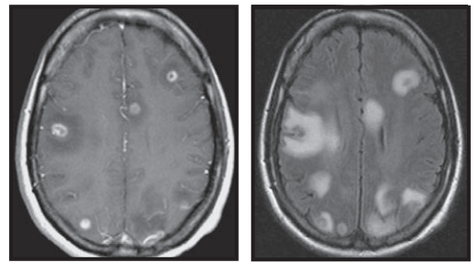


Toxoplasmosis





Brain section with nodule of *Toxoplasma gondii* in basal ganglia and necrotizing encephalitis in left frontal and temporal corticomedullary zones

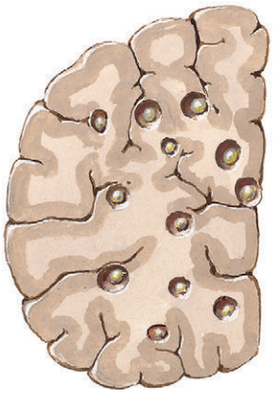


Axial T1 postcontrast MRI *(left)*. Multiple small rim-enhancing cystic lesions within the bilateral frontal and bilateral parietal juxtacortical white matter. **Axial FLAIR MRI** *(right)*. Significant vasogenic edema surrounding the multiple cystic lesions within the bilateral frontal and bilateral parietal juxtacortical white matter.

In an HIV-infected individual with multiple enhancing lesions with edema and a positive anti-*Toxoplasma* IgG, a treatment trial is often initiated with a combination of pyrimethamine and sulfadiazine. If clinical and radiographic improvement occurs with treatment, a presumptive diagnosis of *Toxoplasma* encephalitis is made. Clinical improvement is expected in 90% of patients by day 7 of therapy, and if this does not occur, additional diagnostic studies are warranted because primary central nervous system lymphoma and tuberculous abscesses may have a similar clinical and radiographic appearance in HIV-infected individuals. As primary central nervous system lymphoma is the leading disease in the differential diagnosis, cerebrospinal fluid can be sent for the detection of Epstein-Barr virus deoxyribonucleic acid (DNA) by PCR. If spinal fluid analysis is not safe due to the degree of edema, a stereotactic CT-guided brain biopsy is recommended.

Ovum of *Taenia solium* (pork tapeworm)

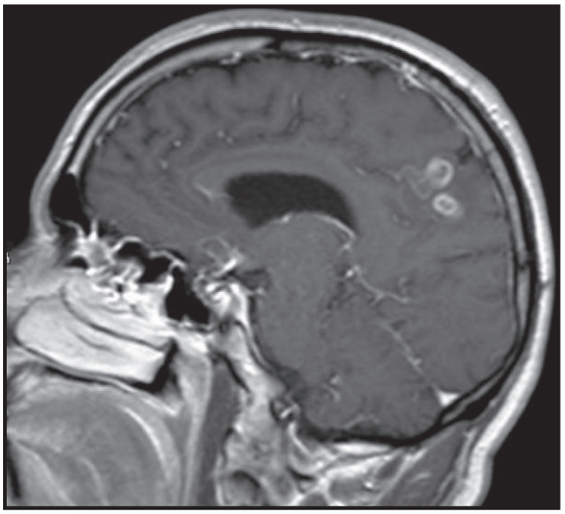
Cysticercus (larval stage) of pork tapeworm. Fluid-filled sac (bladder) containing scolex (head) of worm.



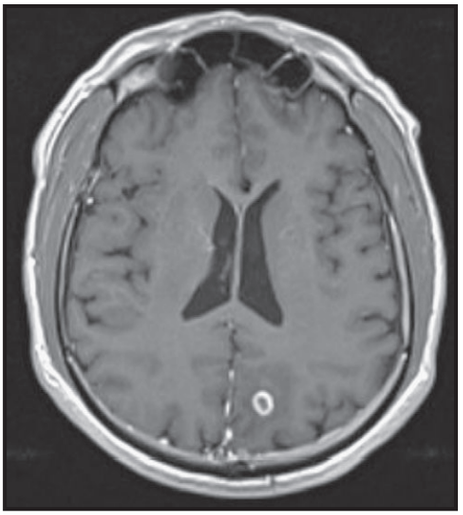
T. solium may produce a single cyst or multiple cysts in the brain

NEUROCYSTICERCOSIS

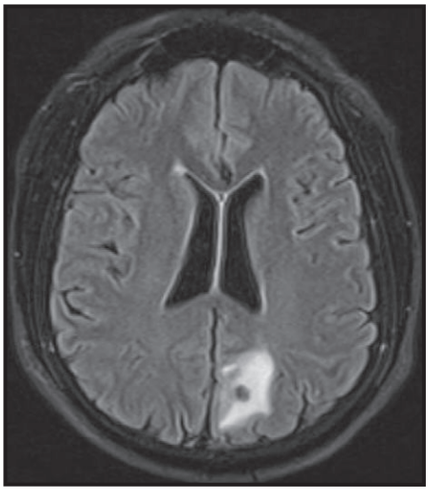
Neurocysticercosis is a parasitic infection of the central nervous system that is acquired by either the ingestion of undercooked pork contaminated by larva of the tapeworm *Taenia solium* or by fecal-oral transmission of the eggs of the tapeworm as a result of exposure to feces of asymptomatic *Taenia* carriers. The embryos of the eggs develop and hatch in the intestine and then enter the bloodstream. Larvae migrate to the central nervous system (CNS). The most common clinical manifestation is a seizure, and neurocysticercosis is the most common cause of acquired epilepsy in the developing world. The clinical presentation is affected by the number and location of cysts in the brain parenchyma, the basilar or perimesencephalic cisterns, and the subarachnoid space. Cysts may also be attached to the choroid plexus or the ventricular wall. As such, the presentation may be that of headache, signs of increased intracranial pressure, or focal neurologic deficits. Cysticercal cysts evolve through four stages: the vesicular stage, the colloidal stage, the granular stage, and the stage of calcification. The appearance of the cyst on computed tomography (CT) and magnetic resonance (MR) scan depends on the stage. In the vesicular stage, the cyst contains living larvae and has the appearance of a nonenhancing cystic lesion without edema. In the colloidal stage, the larva is degenerating, and a CT scan demonstrates a ring-enhancing lesion with edema. On CT scan, but better demonstrated on MR scan, cysts in the vesicular stage and those in the colloidal stage contain live active cysts that have the appearance of a nodule, which is the invaginated scolex. In the granular stage, the larva continues to degenerate and the cyst develops a ring enhancement. Finally, a calcified lesion is seen on neuroimaging. The most definitive neuroimaging evidence of neurocysticercosis is a cystic lesion showing the scolex. The diagnosis is supported by a serum immunoblot assay that detects anticysticercal antibodies. In every stage, with the exception of the vesicular stage, the parasite is in the process of dying. Patients most typically become symptomatic with a seizure when the cyst has evolved to a calcified lesion, but this stage does not require anticysticidal therapy. Patients may also become symptomatic in the earlier stages, when the parasite elicits an inflammatory response and the lesion becomes surrounded by edema. The decision to treat cysts in the other stages must take into account that during therapy with anticysticidal agents there is a risk of a strong inflammatory reaction, with an increase in cerebral edema. Prednisone is started either before or with the first dose of anticysticidal therapy and continued throughout the course of treatment. Cysticidal drug therapy appears to be most efficacious in patients with cysticerci in the colloidal and vesicular stages.



Sagittal T1 postcontrast MRI. Two subjacent small rim-enhancing cystic lesions within the left parietal juxtacortical white matter.

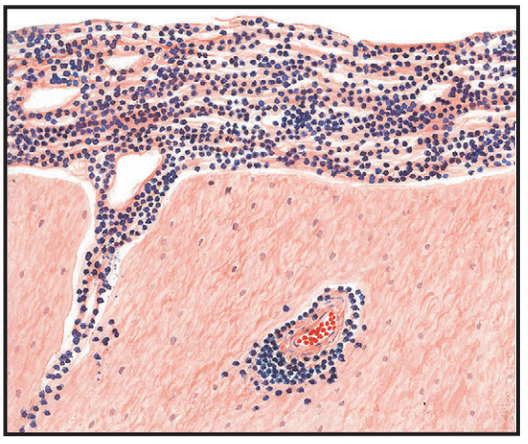


Axial T1 postcontrast MRI. Small rim-enhancing cystic lesion within the left parietal juxtacortical white matter.



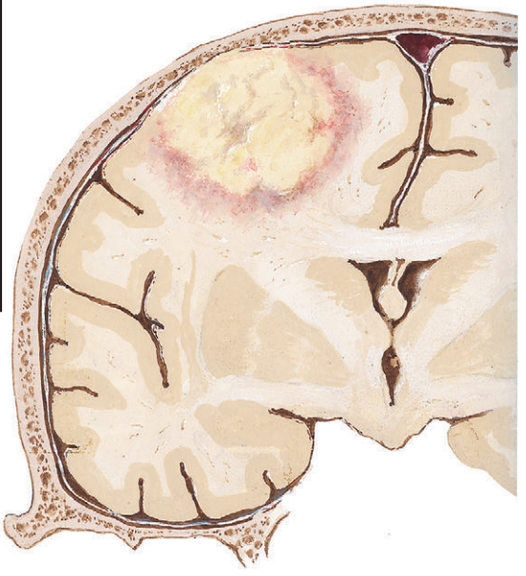
Axial FLAIR MRI. Significant vasogenic edema surrounding the cystic lesion within the left parietal juxtacorical white matter.

Neurosyphilis



Syphilitic meningoencephalitis with perivascular infiltration

Gumma with beginning erosion of skull



Spirochetal Infections

NEUROSYPHILIS

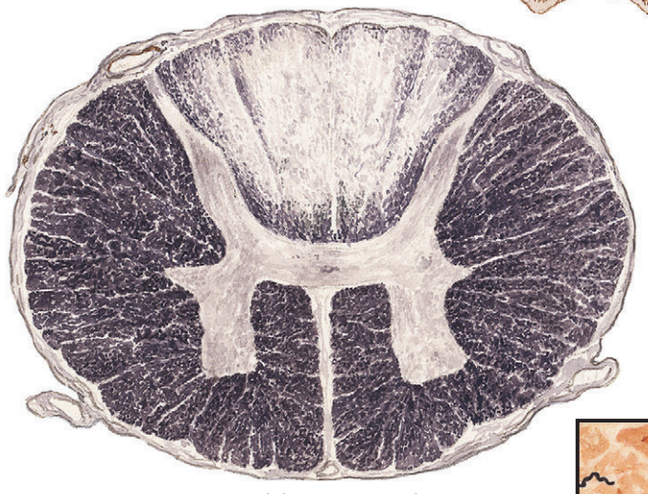
Neurosyphilis is the result of infection of the central nervous system (CNS) by the bacterium *Treponema pallidum*. There are several different forms of neurosyphilis, which can be divided into early and late neurosyphilis. Early neurosyphilis includes *asymptomatic neurosyphilis*, *syphilitic meningitis*, and *meningovascular syphilis*. The late forms of neurosyphilis are *tabes dorsalis* and *general paresis (dementia paralytica)*.

Asymptomatic neurosyphilis is defined by the presence of spinal fluid abnormalities in the absence of neurologic signs and symptoms.

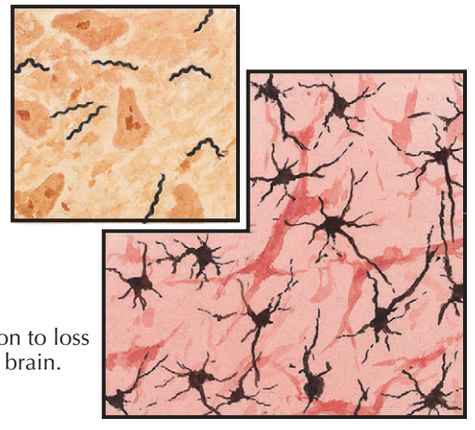
Syphilitic meningitis is defined by the appearance of meningeal signs and symptoms, including headache, nausea, vomiting, stiff neck, and cranial nerve abnormalities. Spinal fluid analysis in syphilitic meningitis reveals an increased opening pressure, a lymphocytic pleocytosis, a normal or slightly decreased glucose concentration, and an elevated protein concentration. The serum rapid plasma reagin (RPR) is usually positive.

Meningovascular syphilis is defined by the appearance of focal neurologic signs due to an inflammatory arteritis involving small and medium-size arteries in association with signs of meningeal inflammation. Vascular syphilis may also involve the arterial blood supply to the spinal cord.

General paresis (*dementia paralytica*) is a chronic progressive meningoencephalitis with a peak incidence 10 to 20 years after primary infection. Initially, there is a slow deterioration in cognitive functioning and personality changes, but as the disease progresses there is loss of appendicular strength, abnormality of the pupils, dysarthria, tremor, and loss of bowel and bladder control. *Tabes dorsalis* develops 10 to 20 years after primary infection and is characterized at onset by episodic lancinating pain in the lower extremities. As the disease progresses, there is loss of proprioceptive and vibratory sensation due to neuronal degeneration and infiltration of inflammatory cells in the dorsal column and posterior spinal nerve roots of the spinal cord. *Tabes dorsalis* is also characterized by loss of the pupillary reaction to light, with preservation of pupillary constriction to accommodation—the Argyll Robertson pupillary abnormality. Due to lumbosacral nerve root dysfunction, lower extremity areflexia, impotence, and loss of urinary continence may develop.



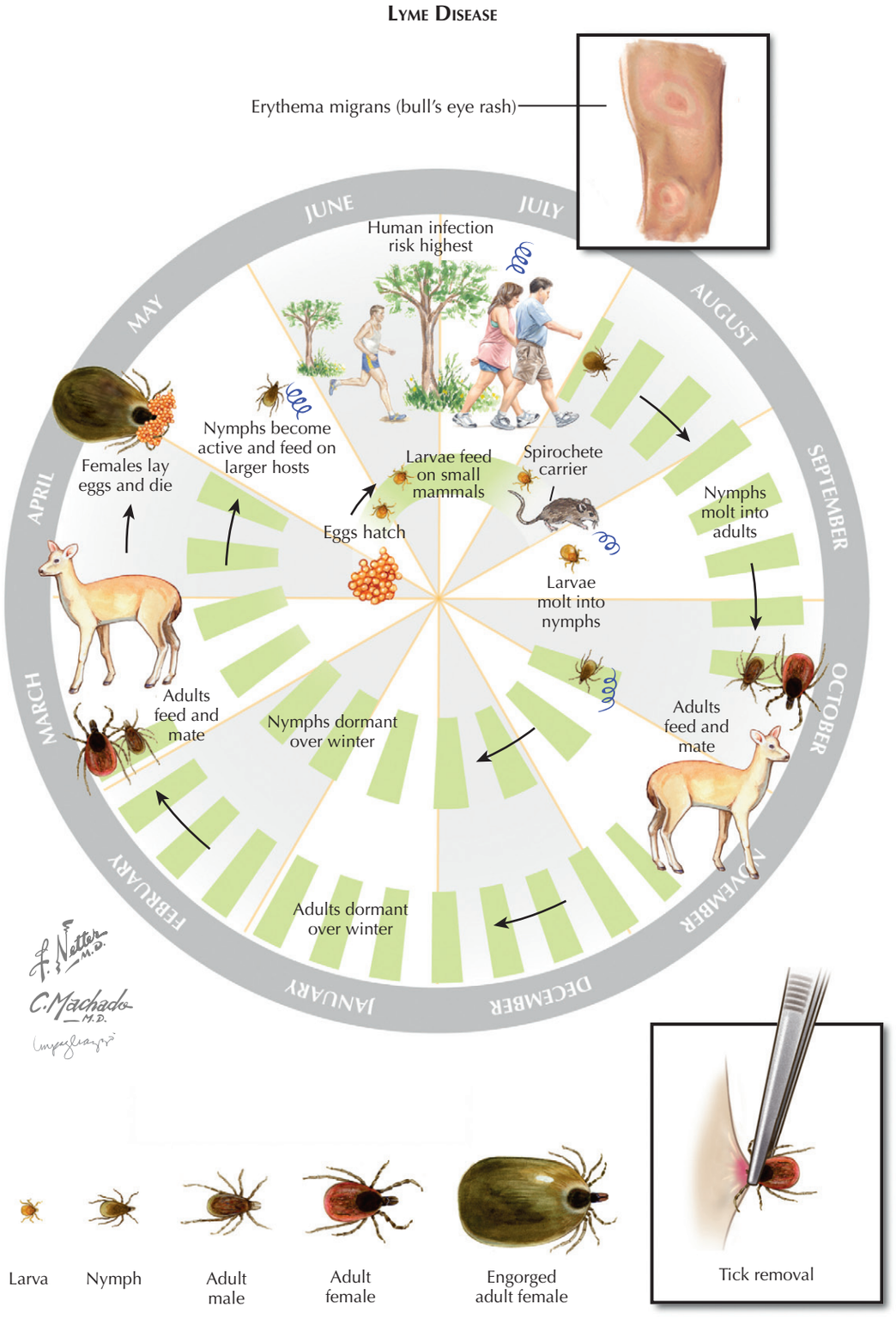
Section of thoracic spinal cord in tabes dorsalis



General paresis: astrocytosis in cortex in reaction to loss of nerve cells. Small inset shows spirochetes in brain.

Gummatous Neurosyphilis. CNS gummas are rare but present as space-occupying lesions.

The diagnosis of neurosyphilis is made by a combination of serologic tests and spinal fluid analysis. The serologic tests are typically the Venereal Disease Research Laboratory (VDRL) or the RPR although the *Treponema pallidum* hemagglutination assay is more specific. A diagnosis of neurosyphilis is made by the detection of a reactive CSF VDRL. When the CSF VDRL is nonreactive, but there is a positive serologic test and an elevated CSF white blood cell count and protein concentration, treatment for neurosyphilis is recommended. Neurosyphilis is treated with intravenous aqueous penicillin G.



SPIROCHETAL INFECTIONS
(Continued)

LYME DISEASE

Lyme disease is caused by the spirochete *Borrelia burgdorferi*. The endemic regions for Lyme disease in the United States are the east coast from New Hampshire to the District of Columbia, parts of Minnesota and Wisconsin, and areas of northern California. The infection can also be acquired in areas in Europe and Asia. Patients with meningitis due to *Borrelia burgdorferi* complain of headache and fatigue. A unilateral or bilateral facial nerve palsy may be present or a painful radiculopathy. In patients with cranial neuritis or radiculoneuritis who reside in or who have traveled to a Lyme endemic area, inquire about the lesion of erythema migrans. This lesion is an erythematous lesion that, as it expands, develops central clearing so that it has the appearance of a target lesion. Diagnosis begins with a serum enzyme-linked immunosorbent assay (ELISA) to measure antibody to *B. burgdorferi*. A positive result is confirmed with a Western blot. Examination of the CSF demonstrates a lymphocytic pleocytosis with a normal glucose concentration and a mild-to-moderately elevated protein concentration. The demonstration of anti–*Borrelia burgdorferi* antibodies in CSF should not be regarded as definitive evidence of neurologic Lyme disease because antibodies can be passively transferred from serum to CSF, and Lyme antibodies may persist in the CSF for years. To detect the intrathecal production of antibodies, an antibody index is recommended. The antibody index is the ratio of (anti–*Borrelia* IgG in CSF/anti–*Borrelia* IgG in serum) to (total IgG in CSF/total IgG in serum). The antibody index is considered positive when the result is greater than 1.3 to 1.5. Lyme meningitis, cranial neuritis, and radiculitis is treated with intravenous ceftriaxone for 2 to 4 weeks. Doxycycline is a reasonable option because it has been used successfully in Europe for the treatment of meningitis due to Lyme disease in adults and children 8 years of age or older.

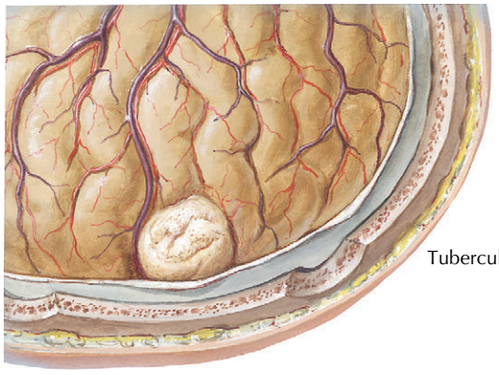
Tuberculosis of Brain and Spine

Mycobacterium tuberculosis central nervous system infections take a variety of forms, including an acute fulminant meningoencephalitis, a subacute meningitis, tuberculoma, and vertebral tuberculosis (Pott disease). Infection with *M. tuberculosis* is acquired by inhalation of aerosolized droplet nuclei. Tuberculous meningitis does not develop acutely from hematogenous spread of tubercle bacilli to the meninges. Rather, isolated miliary tubercles form in the brain parenchyma or the meninges during hematogenous dissemination of bacilli and subsequently enlarge and are usually caseating. Subependymal caseous foci may remain quiescent for months or years but then may discharge bacilli and tuberculous antigens into the subarachnoid space, causing meningitis. The neurologic complications of tuberculous meningitis are initiated by the intense inflammatory reaction to the discharge of tubercle bacilli and tuberculous antigens into the subarachnoid space. The inflammatory reaction leads to the production of a thick exudate that fills the basilar cisterns, obstructing the flow of cerebrospinal fluid (CSF) and surrounding the cranial nerves. Vasculitis typically involves the major blood vessels at the base of the brain, resulting in cerebral ischemia and infarction. Tuberculous meningitis may manifest as a subacute meningitis or as a fulminant meningitis, resembling bacterial meningitis. When the presentation is that of a subacute meningitis, headache, fever, and lethargy are often present for 4 weeks or longer before the patient presents for evaluation. Patients present for evaluation of unrelenting headache, night sweats, stiff neck, and lethargy. Cranial nerve abnormalities occur in approximately one fourth of patients.

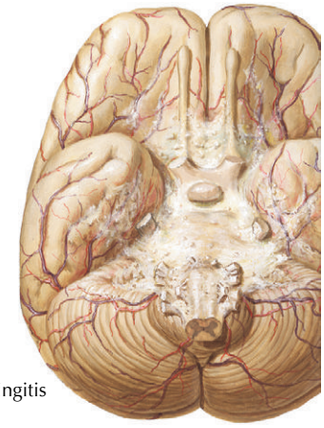
The diagnosis of tuberculous meningitis is made by examination of the spinal fluid. The classic spinal fluid abnormalities in tuberculous meningitis are as follows: (1) elevated opening pressure, (2) lymphocytic pleocytosis, (3) an elevated protein concentration in the range of 100 to 500 mg/dL, and (4) a decreased glucose concentration. A CSF glucose concentration between 45 and 35 mg/dL in combination with a lymphocytic pleocytosis and an unrelenting headache, stiff neck, fatigue, night sweats, and fever is highly suspicious for tuberculous meningitis. At an early stage in the clinical illness, polymorphonuclear leukocytes may predominate in the spinal fluid, but typically lymphocytes become the predominant cell type within 48 hours. The CSF glucose concentration is only mildly decreased. The last tube of fluid collected at lumbar puncture is the best tube to send for smear for acid-fast bacilli. Culture of CSF takes 4 to 8 weeks to identify the organism, except in cases of fulminant tuberculous meningitis where culture is often positive in 1 to 2 weeks. There is a polymerase chain reaction (PCR) available for *M. tuberculosis* ribosomal ribonucleic acid (rRNA). Neuroimaging abnormalities are nonspecific and include enhancement of the meninges postcontrast administration, communicating and/or obstructive hydrocephalus, and infarctions typically in the basal ganglia. Patients should have chest radiographs and intradermal tuberculin skin test. The tuberculin skin test may be negative because patients with central nervous system (CNS) tuberculosis are immunosuppressed. With treatment, the skin test may become positive. Treatment of tuberculous meningitis includes a combination of isoniazid, rifampin, pyrazinamide, ethambutol, and pyridoxine. Dexamethasone therapy is recommended for patients who develop hydrocephalus. This complication may also require a ventriculostomy or a ventriculoperitoneal shunt.

Tuberculomas manifest as space-occupying lesions. On computed tomography (CT) scan, they often have the appearance of a central nidus of calcification surrounded by a ring of enhancement and/or edema. Tuberculomas may develop during the course of therapy for tuberculous meningitis. The treatment of tuberculomas includes a three- or four-drug regimen similar to the treatment of tuberculous meningitis. Superficial tuberculomas can be surgically excised if they do not respond to antituberculous chemotherapy.

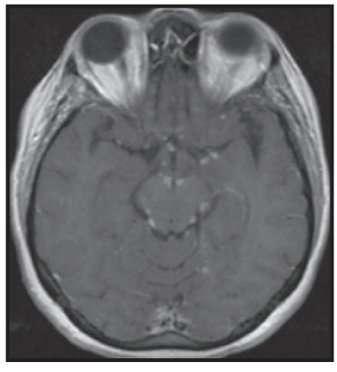
Pott disease refers to vertebral tuberculosis or tuberculous spondylitis. Two or more adjacent vertebral bodies are often involved, and infection can spread to the disk and/or the epidural space. The thoracic and lumbar spine are the most commonly affected areas, and thus the clinical presentation is with back pain in the thoracic or lumbar area and fever. When the epidural space is involved, signs and symptoms of progressive spinal cord compression can develop. Diagnosis is made by stereotactic aspiration of the lesion. Treatment includes antituberculous chemotherapy and surgical decompression if spinal cord compression is present.



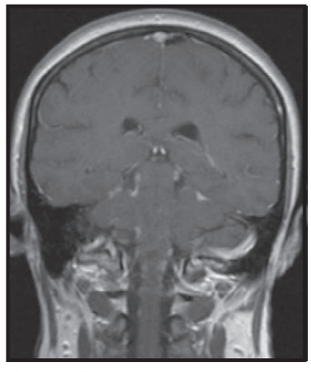
Tuberculoma



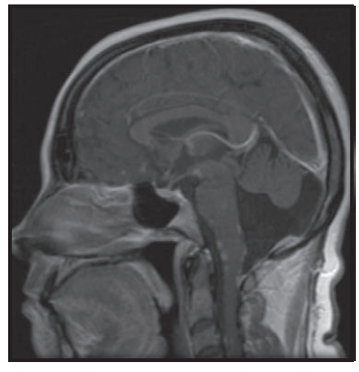
Tuberculous basilar meningitis



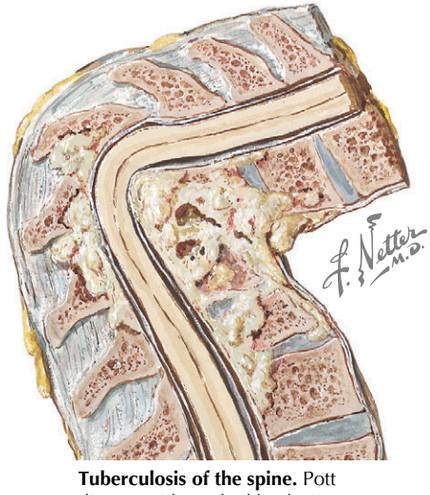
Axial T1 postcontrast MRI showing nodular leptomeningeal enhancement along the basifrontal lobes, perimesencephalic cisterns, interpeduncular cistern, and medial left temporal lobe



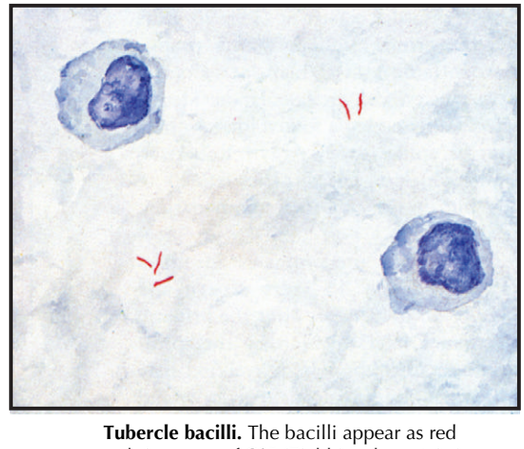
Coronal T1 postcontrast MRI showing nodular leptomeningeal enhancement along the perimesencephalic cisterns, medial temporal lobes, and lateral thecal sac at the craniocervical junction



Sagittal T1 postcontrast MRI showing nodular leptomeningeal enhancement extending along the basifrontal lobes, interpeduncular cistern, and ventral and dorsal thecal sac surrounding the lower brainstem and cervical cord. Note presence of incidental Dandy-Walker malformation.



Tuberculosis of the spine. Pott disease with marked kyphosis.

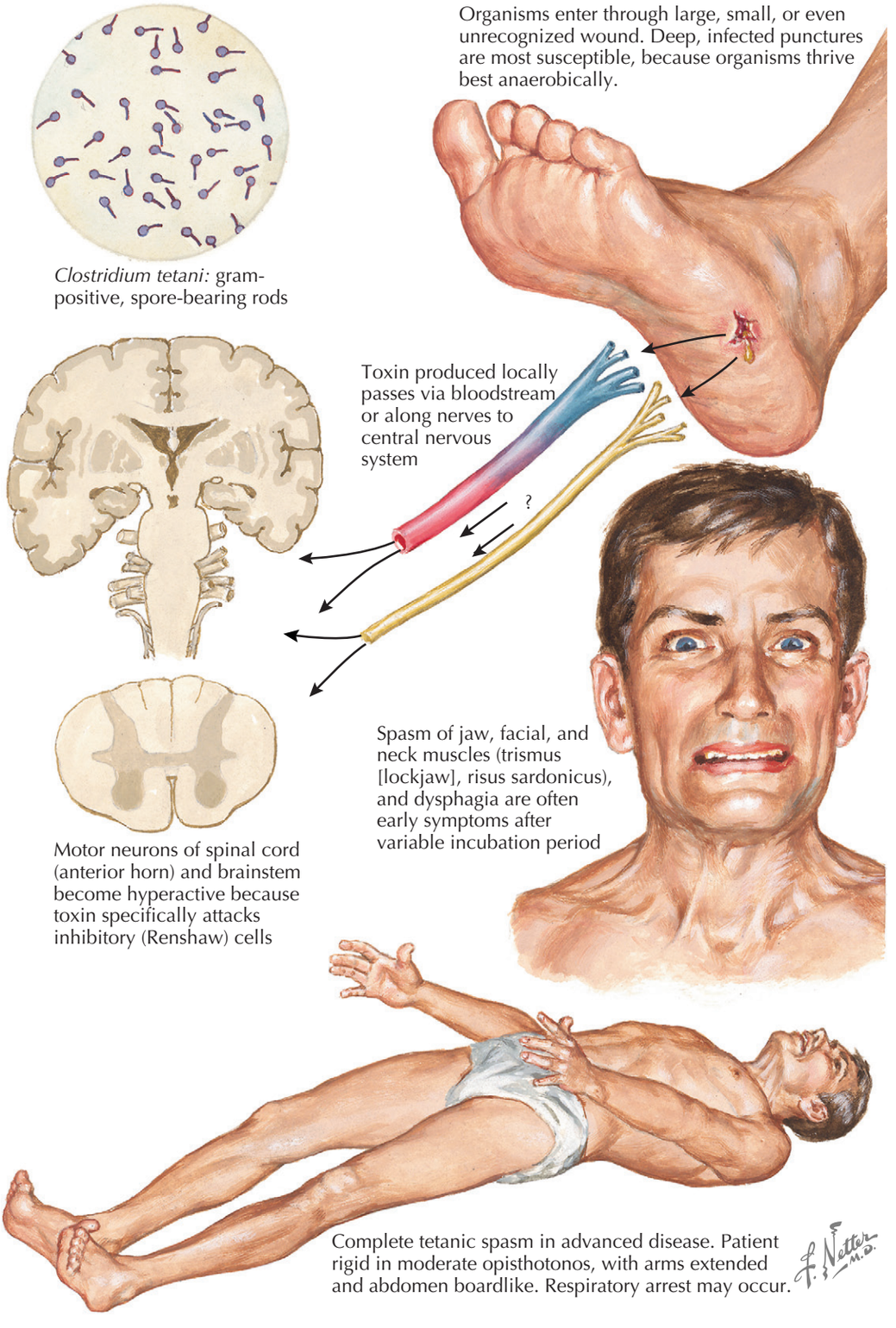


Tubercle bacilli. The bacilli appear as red rods in smear of CSF (Ziehl-Neelsen stain.)

TETANUS

The bacterium *Clostridium tetani* produces a neurotoxin tetanospasmin (tetanus toxin) in wounds it contaminates. Tetanus toxin enters the central nervous system by retrograde axonal transport in motor neurons from its site of formation in a wound to its site of action—the motor neuron cell bodies in the ventral gray of the spinal cord and brainstem.

Tetanus toxin produces spasticity by blocking the release of the inhibitory neurotransmitters, glycine and glutamic acid decarboxylase (GAD), from presynaptic nerve terminals that synapse on alpha motor neurons in the spinal cord and brainstem. With the loss of inhibitory input, the uninhibited lower motor neuron increases resting muscle tone, producing rigidity. Tetanus is divided into four clinical forms: localized, generalized, cephalic, and neonatal. The *incubation period* is defined as the time from inoculation with *C. tetani* spores to the appearance of the first symptom. The incubation period is followed by *the period of onset of tetanus*, which is defined as the interval from the first symptom to the first reflex spasm. Localized tetanus is limited to the extremity in which there is a contaminated wound, blister, or burn. The patient's initial complaint is stiffness of the muscles in the extremity with voluntary movement. This is followed by the development of a continuous spasm or rigidity in the group of muscles in close proximity to the wound. Local tetanus may remain restricted to the limb or may become generalized. In generalized tetanus, the usual manifesting sign is trismus (lockjaw), which is a rigidity of the masseter muscles, causing an inability to open the mouth to speak or to chew. Another early sign is risus sardonicus due to increased tone in the orbicularis oris, causing a sneering grin. The generalized spasm consists of opisthotonic posturing with flexion and adduction of the arms, clenching of the fists, and extension of the lower extremities. The spasms are often precipitated by external stimuli and are extremely painful. Sudden spasms of the muscles of respiration may stop respiration for 10 to 20 seconds, and laryngeal or pharyngeal spasms may obstruct the airway, compromising respiration. Cephalic tetanus involves the muscles supplied by one or more cranial nerves and almost always follows a head wound. The facial nerve is affected most often. Neonatal tetanus typically develops as a result of infection of the umbilical stump, and the usual manifesting symptom is poor feeding. The infant cannot suck, and when a finger is put into its mouth its jaw clamps tightly. This is followed by involvement of the muscles of facial expression, risus sardonicus, and then opisthotonos.



Tetanus is a clinical diagnosis. When tetanus is suspected, a careful immunization history should be obtained because tetanus is unlikely if the patient has received a complete primary series of toxoid injections with booster doses every 10 years. Diagnosis is dependent on ruling out the diseases that have an appearance similar to tetanus, including strychnine poisoning, a dystonic reaction secondary to a neuroleptic agent or a dopamine-blocking agent, and rabies. Dystonic reactions are quickly reversed with intravenous benztropine or diphenhydramine.

There are three goals of treatment in tetanus: (1) securing the airway and treating generalized spasms with benzodiazepines, (2) stopping production of the toxin by surgical debridement of the wound and antimicrobial therapy (the most frequently recommended antibiotic is metronidazole), and (3) passive immunization with human tetanus immunoglobulin (HTIG).

Aseptic Meningitis

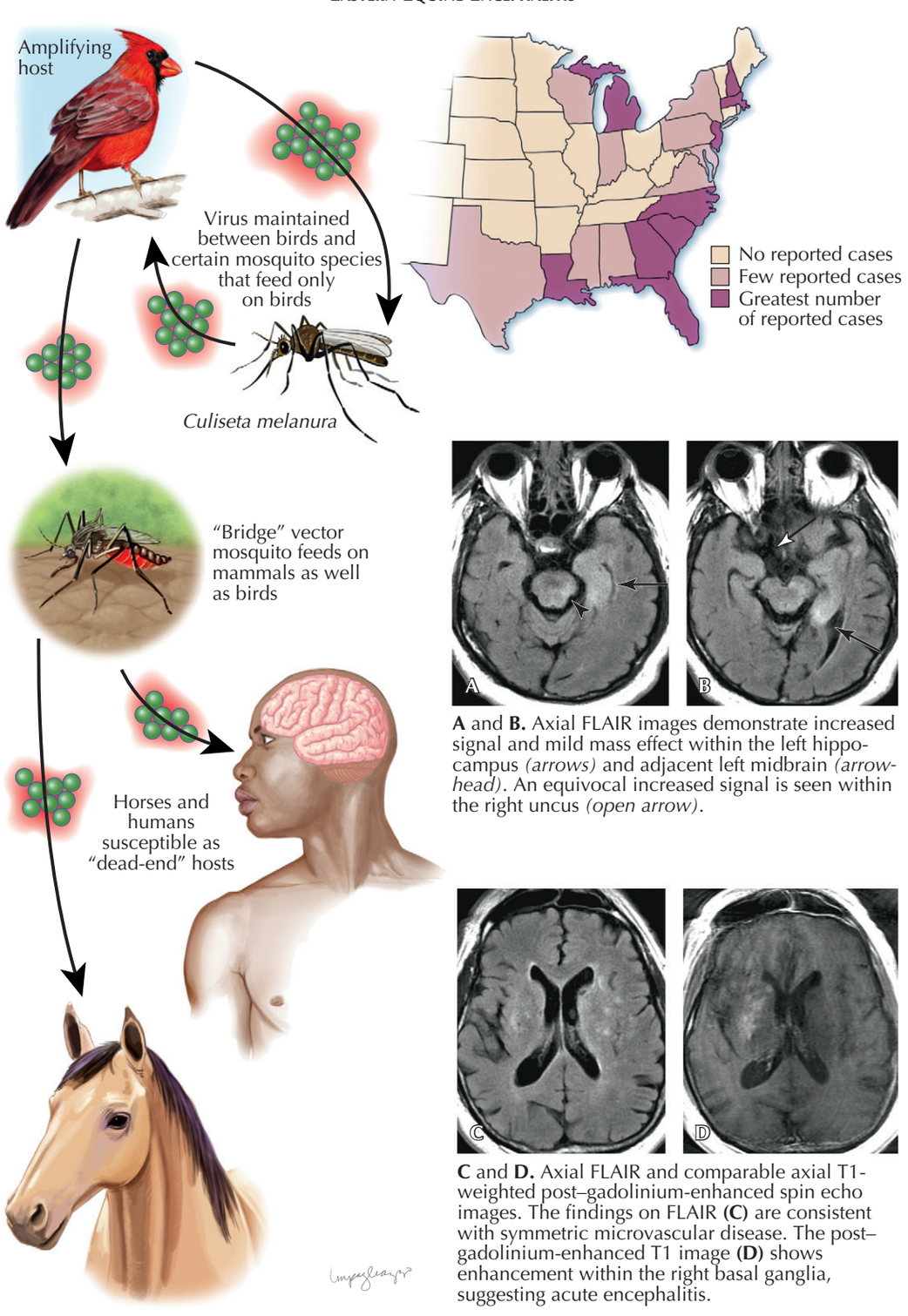
Aseptic meningitis is a disorder in which the characteristic symptoms and findings of meningeal irritation are present, and cerebrospinal fluid (CSF) analysis is suggestive of meningitis but without evidence of bacterial infection. In many instances, the cause is a viral; less often, mycobacterial, spirochetal, parasitic, or fungal infection is responsible. A similar syndrome can arise with sarcoidosis, various connective tissue diseases, neoplastic leptomeningeal involvement, or as a drug-induced complication. A sterile CSF with an increased cell count may also be found with parameningeal infections and partially treated bacterial meningitis. In addition to a spinal tap (with CSF analysis), Gram and other stains, culture, serology, cytology, and polymerase chain reaction (PCR), other investigations may include complete blood count, serologic studies, magnetic resonance imaging (MRI) of the brain and spine, chest radiography, blood cultures, and other studies, depending on the clinical evaluation. Treatment depends on the cause.

Select Arthropod-Borne Virus Infections

Various mosquito-borne viruses may cause an infectious encephalitis. Treatment is primarily symptomatic, making preventive strategies important, especially for arthropod-borne viruses *(arboviruses)*, such as eastern equine encephalitis virus and West Nile virus (WNV). The related St. Louis encephalitis virus is transmitted mainly in North America during late summer or early autumn and typically causes mild nonspecific symptoms but occasionally an encephalitic illness.

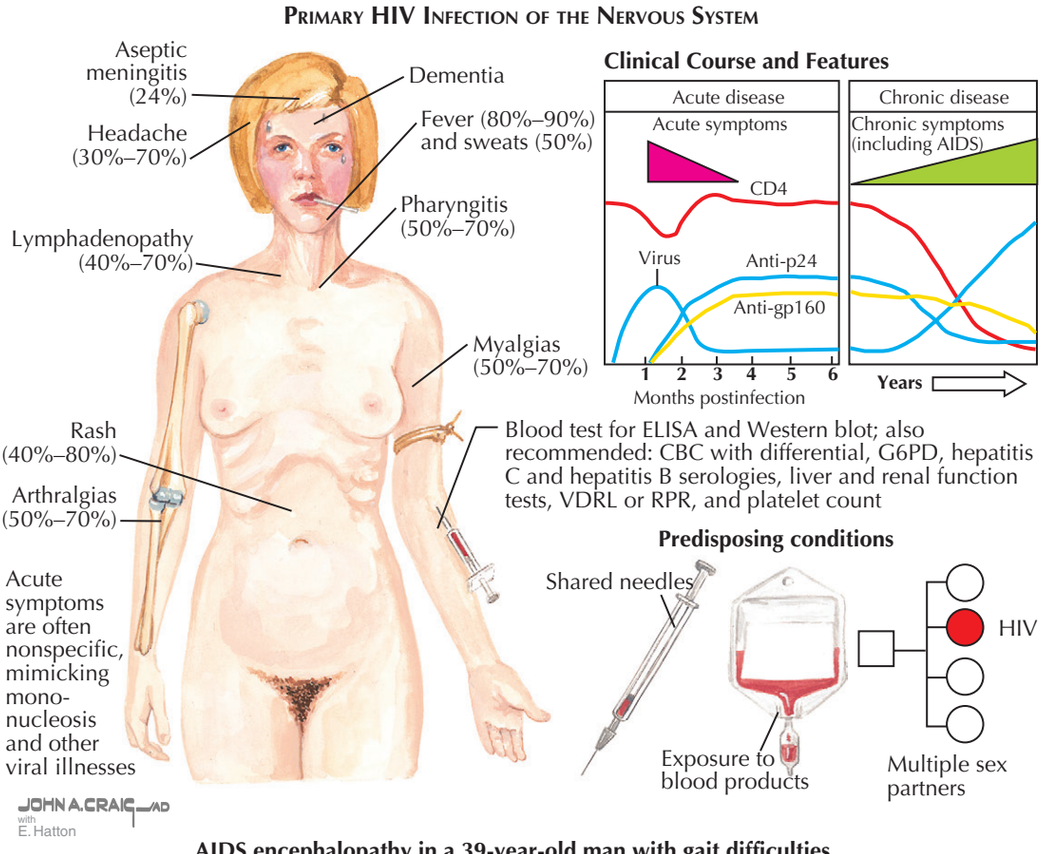
Eastern equine encephalitis virus, found in the Caribbean and eastern United States, infects humans, horses, and some bird species. Other variants of the virus occur in Central and South America, where they cause equine disease. Most infected persons are asymptomatic. When symptoms do occur, they may consists solely of a mild nonspecific flulike systemic illness, with headache, fever, malaise, aching pains, and vomiting, from which complete recovery occurs with 7 to 10 days in the absence of cerebral involvement. In uncommon instances, however, a fulminating encephalitic illness occurs after an incubation period of 3 to 10 days and is characterized by confusion, delirium, irritability, restlessness, seizures, and, eventually, loss of consciousness. The encephalitic illness is associated with a 33% mortality rate, and about Half of the survivors have residual cognitive or other neurologic deficits. There is a pleocytosis in the CSF, with an increased neutrophil count and an elevated protein concentration; glucose level is normal. Serologic diagnosis depends on IgM testing of serum and CSF, and antibody testing of acute- and convalescent-phase serum. MRI most often shows unilateral or bilateral abnormalities (increased T2 signal intensity) of the basal ganglia; the internal capsule, thalamus, brainstem, periventricular white matter, and cerebral cortex may also be involved. There is no specific therapy, and treatment is purely supportive. No vaccine is available, and prevention therefore depends on reducing exposure to mosquitoes.

The *West Nile virus*, a flavivirus usually found in Africa, West Asia, and the Middle East, was not documented in the Western Hemisphere until 1999. Reservoirs for the virus include humans, horses, certain other mammals, birds, and mosquitoes. In humans, infection may be asymptomatic or lead to mild disease (West Nile fever) with flulike symptoms (sometimes accompanied by a skin rash) that develop within 2 weeks after the bite of an infected mosquito and usually last for only a few days. However, an encephalitis, meningitis, or meningoencephalitis sometimes develops, as may a poliomyelitic illness, and sometimes leads to a fatal outcome. The CSF shows a lymphocytic pleocytosis with elevated protein and normal glucose concentrations. Polymerase chain reaction may be diagnostic, but false-negative results are common. Thus the diagnosis is usually established by serologic assays of blood and CSF. Treatment is supportive; no specific drug treatment is available. Prevention depends on avoidance of infected mosquitoes because no vaccine is available. Residual deficits, such as cognitive changes or muscle weakness, may occur in survivors.



A and **B.** Axial FLAIR images demonstrate increased signal and mild mass effect within the left hippocampus *(arrows)* and adjacent left midbrain *(arrowhead)*. An equivocal increased signal is seen within the right uncus *(open arrow)*.

C and **D.** Axial FLAIR and comparable axial T1-weighted post–gadolinium-enhanced spin echo images. The findings on FLAIR **(C)** are consistent with symmetric microvascular disease. The post–gadolinium-enhanced T1 image **(D)** shows enhancement within the right basal ganglia, suggesting acute encephalitis.



Human Immunodeficiency Virus

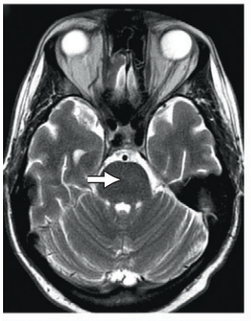
Human immunodeficiency virus (HIV) is a retrovirus that causes acquired immunodeficiency syndrome (AIDS), that is, progressive failure of the immune system with a declining $CD4^+$ cell count. Infection occurs by the transfer of blood, semen or vaginal fluid, or breast milk containing the virus. If this occurs, for example, by unprotected sex or blood transfusion, infected patients may remain asymptomatic for years. Two types of HIV are recognized, with HIV-1 being the more virulent and responsible for most infections worldwide. An acute systemic infection is followed by a variable latent period and then by the development of AIDS. A fatal outcome may follow opportunistic infection or the development of malignancies, such as non-Hodgkin lymphoma, which may involve the nervous system. Treatment is with antiretroviral drugs, which improve the prognosis but do not cure HIV infection. Preventive measures include the use of latex condoms. Depending on the $CD4^+$ count, prophylaxis against opportunistic infection is also indicated.

Acute aseptic meningitis is a common manifestation in patients with primary neurologic HIV-1 infection (PNHI) and leads to headache and meningismus. Other less common neurologic presentations are with meningoencephalitis, encephalopathy, acute disseminated encephalomyelitis, myelopathy, meningoradiculitis, and peripheral neuropathy, including a Guillain–Barré syndrome. Systemic abnormalities are commonly also present. Laboratory studies may reveal leucopenia, thrombocytopenia, and elevated transaminases. An HIV antibody study may initially be negative even if serum HIV viral load is positive. Once seroconversion occurs, patients are at risk for many neurologic complications.

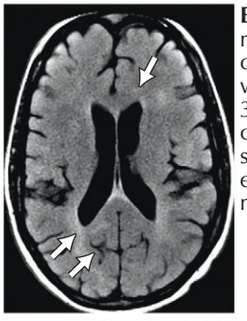
AIDS dementia complex (ADC) is an important disorder, but its prevalence has declined since highly active antiretroviral therapy (HAART) became available. Affected patients developed a dementia and behavioral disturbances, with a marked change in personality; apathy, inattention, memory disturbances, and language dysfunction are problematic. Motor deficits (slowness, clumsiness, ataxia, weakness) also occur. A primary subacute demyelinating process with a mild cellular response has been found at autopsy. A metabolic/toxic etiology related to the infection has been proposed.

Milder HIV-associated neurocognitive disorders have a high prevalence, even in HIV-positive patients with a long-standing aviremia, but usually do not limit daily activities. HAART itself seems to have little primary neurologic toxicity. Clinically asymptomatic subjects infected with HIV-1 may have abnormal brain MRIs with white matter (demyelination) and gray matter (atrophy) changes.

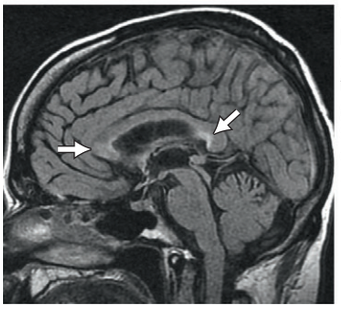
AIDS encephalopathy in a 39-year-old man with gait difficulties and cognitive decline. Brain MRI was normal 2 years ago.



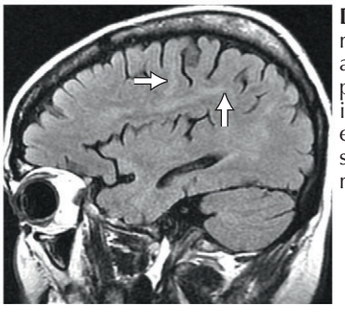
A. Axial T2 fast spin echo demonstrates ill-defined area of augmented T2 signal in upper left pons *(arrow)*.



B. Axial FLAIR shows moderate sulcal and ventricular enlargement consistent with diffuse atrophy for age 39, in addition to paraventricular augmentation of T2 signal, which in some regions extends to subcortical white matter and cortex *(arrows)*.

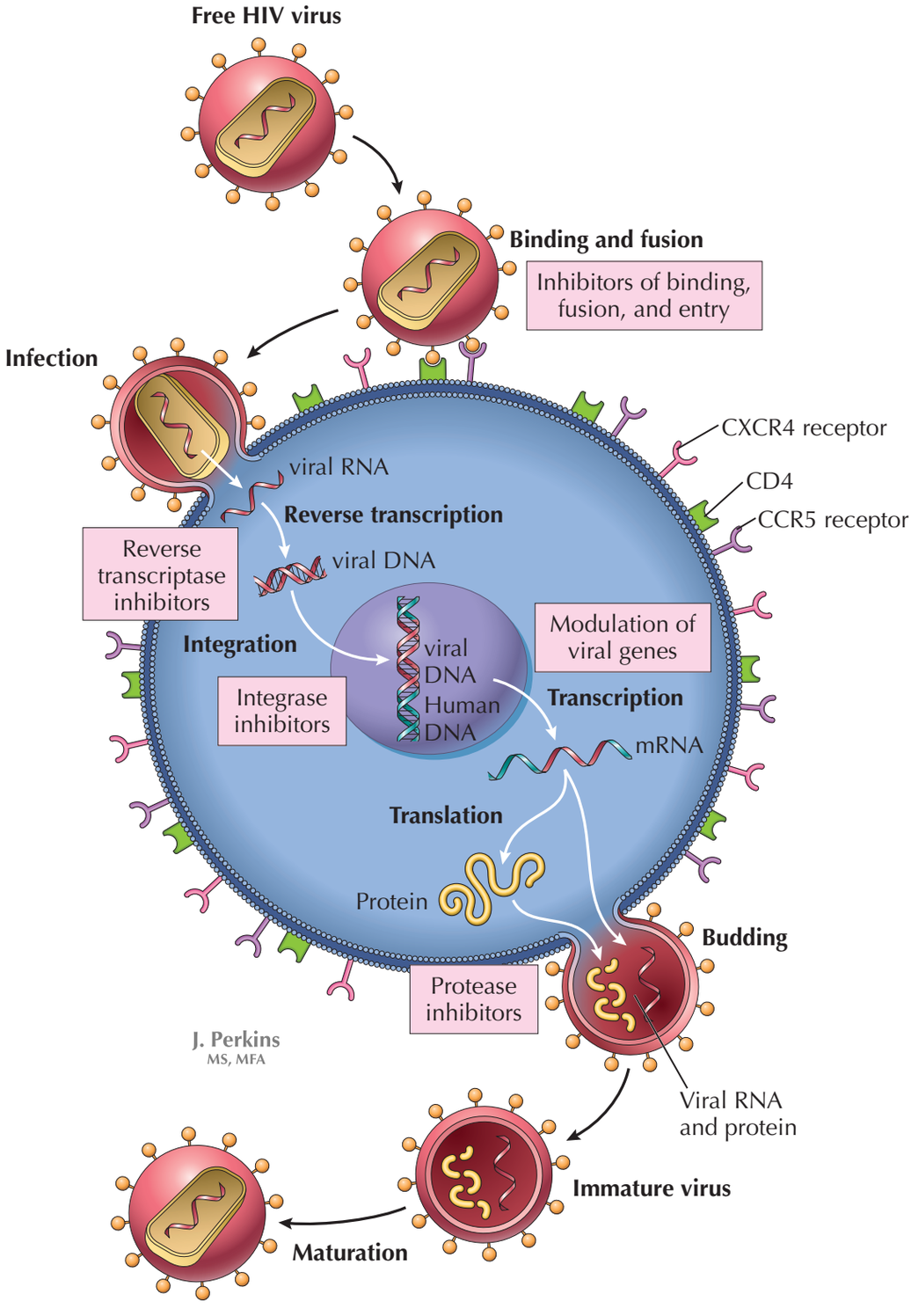


C. Midsagittal FLAIR with ill-defined augmentation in both genu and splenium of corpus callosum *(arrows)*.



D. FLAIR imaging more laterally again demonstrates paraventricular involvement extending to subcortical white matter *(arrows)*.

HIV Life Cycle and Antiretroviral Medications



Human Immunodeficiency Virus *(Continued)*

Opportunistic infection with bacteria, viruses (Epstein-Barr, cytomegalovirus, and hepatitis B), fungi (*Cryptococcus neoformans)*, or parasites (*Toxoplasma gondii*) may involve the central nervous system directly. Toxoplasmosis (see Plate 11-6) may manifest with seizures, cryptococcal meningitis with a subacute alteration of mental function. Such infections can lead also to a vasculopathy. Other, rarer causes of a CNS *vasculitis* in this context include neoplastic disease or recreational drug abuse.

A primary vacuolar and inflammatory *myelopathy* may occur in AIDS and may mimic the myelopathy of vitamin B_{12} or copper deficiency, with predominant involvement of the posterior columns. There is no effective treatment.

Symptomatic *neuropathies* are common in patients infected with HIV-1, becoming more common as the immunodeficiency worsens. Distal symmetric sensory polyneuropathy (DSPN) is the most frequent, is progressive, and presents with symmetric distal pain, paresthesias, and numbness in the feet. A similar neuropathy is associated with several of the nucleoside-analog reverse-transcriptase inhibitor drugs (NRTIs—zalcitabine [ddC], didanosine [ddI], and stavudine [d4T]), used for treating HIV infection. Acute inflammatory demyelinating polyradiculopathy sometimes occur at the time of seroconversion, but polyradiculopathy may also occur at more advanced stages of HIV-1 infection. The cerebrospinal fluid (CSF) in patients with polyradiculopathy typically contains a lymphocytosis (10-50 cells/mm^3). Mononeuritis multiplex is an infrequent complication of HIV-1 infection.

Patients co-infected with cytomegalovirus (CMV) may develop mononeuritis multiplex, polyradiculoneuropathy, or polyradiculopathy. The CSF may show a polymorphonuclear pleocytosis, and CMV polymerase chain reaction (PCR) in cerebrospinal fluid (CSF) is positive in 90% of cases.

Various *myopathies* may occur in patients infected with HIV-1, and may require biopsy for their distinction. In rare instances, rhabdomyolysis occurs. Some patients appear to have a disorder resembling polymyositis that is steroid responsive; others develop inclusion-body myositis. Various muscle-wasting syndromes have been described, as is a vasculitic myopathy. Rod-body myopathy is characterized by the presence of rod-shaped bodies and loss of thick filaments, and it may respond to corticosteroids. Opportunistic infections of muscle sometimes occur, as in muscle toxoplasmosis, and treatment is of the offending organism. Myopathies may occur as a complication of HAART. A mitochondrial myopathy sometimes occurs in patients receiving zidovudine.

POLIOMYELITIS

Poliomyelitis became an epidemic disease at the beginning of the 20th century, and the poliovirus was first isolated in 1908. By 1941 it was recognized that poliovirus infection begins as an acute gastroenteritis, and paralysis develops in less than 1 in 100 individuals infected with the poliovirus. In 1952 the epidemic reached its peak, with more than 20,000 cases of paralytic poliomyelitis reported. In 1955 an inactivated, injectable vaccine (IPV) developed by Jonas Salk became available, followed by a live, attenuated monovalent oral virus vaccine (OPV) in 1961, developed by Albert Sabin. With the widespread use of the oral poliovirus vaccine, which contains live, attenuated poliovirus strains, vaccine-associated paralytic poliomyelitis was first recognized. This eventually led to replacement of OPV with IPV in developed countries. Infants and children receive a dose of IPV at 2 months, 4 months, 6 to 18 months, and 4 to 6 years of age. Outbreaks of polio in the United States now occur mostly among unvaccinated individuals.

Poliovirus is a single-stranded ribonucleic acid (RNA) enterovirus. There are three immunologically defined serotypes of poliovirus (serotypes 1, 2, and 3), all of which cause paralytic disease. Natural polio infection occurs through ingestion of the virus, which initially replicates in the mucosa of the oropharynx and gastrointestinal tract. The virus enters the central nervous system via either the bloodstream or alternatively through afferent neural pathways into motor neurons of the anterior horn, motor nuclei of the brainstem, and Betz cells of the motor cortex.

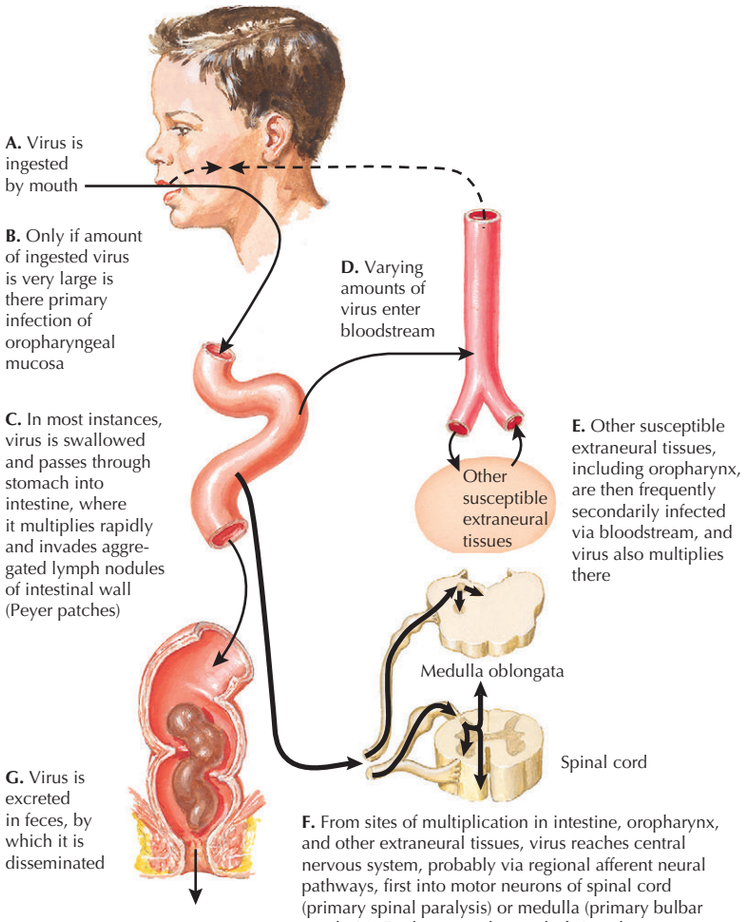
The earliest cellular change in the motor neurons is dissolution of the cytoplasmic Nissl substance (chromatolysis). Infected neurons that have only a mild degree of chromatolysis survive and continue to support motor units. In contrast, neurons that have severe chromatolysis become necrotic and cannot support motor units. As a result, permanent loss of function occurs in the muscle groups innervated by the motor unit. Historically, poliovirus infections have been divided into a minor illness and a major illness. The minor illness is characterized by fever, myalgias, nausea, and diarrhea. A major illness can be associated with the minor illness or follow the minor illness by a few afebrile days and is characterized by increasing signs of meningeal irritation, headache, and stiff neck. When the illness progresses to the paralytic form, muscle soreness is prominent, particularly in the back and neck. Patients who develop paralysis usually do so on the second to fifth day after meningeal signs and fever develop. The weakness is generally an asymmetric flaccid muscle weakness, and the legs are involved more often than the arms.

During the polio epidemic in the past century, the diagnosis was based on the clinical syndrome of fever with paralysis and lower motor neuron weakness. Today, poliovirus is the least common cause of an asymmetric flaccid lower extremity weakness. The other enteroviruses (the coxsackieviruses, the echoviruses, and the numbered enteroviruses), and the flaviviruses, most notably the West Nile virus, are the much more common etiologic agents of a flaccid paralysis.

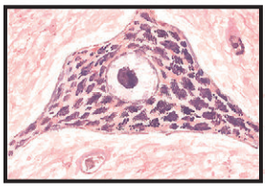
When poliovirus infection is suspected, at least two stools specimens and two throat swabs should be obtained 24 hours apart. As with all suspected enteroviral infections, acute and convalescent serology should be sent 4 weeks apart to detect a fourfold increase in immunoglobulin G (IgG). Spinal fluid analysis demonstrates a lymphocytic pleocytosis, a normal glucose concentration and enteroviral RNA by polymerase chain reaction (PCR).

The treatment of poliovirus infection is primarily supportive, and prevention with mass vaccination of all children is essential.

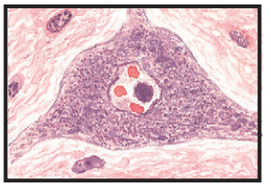
Hypothesis of pathogenesis of poliomyelitis



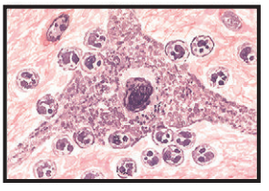
Stages in destruction of a motor neuron by poliovirus



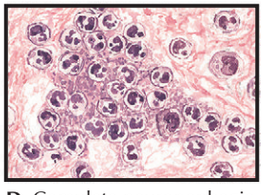
A. Normal motor neuron



B. Diffuse chromatolysis; three acidophilic nuclear inclusions around nucleolus



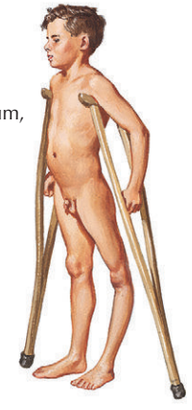
C. Polymorphonuclear cells invading necrotic neuron



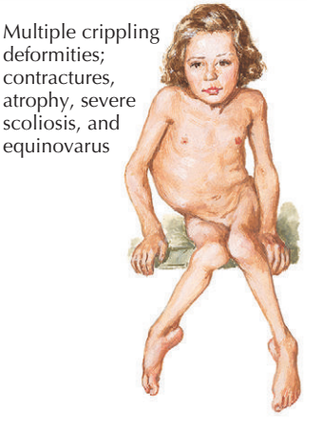
D. Complete neuronophagia

Paralytic residual of spinal poliomyelitis

Scoliosis

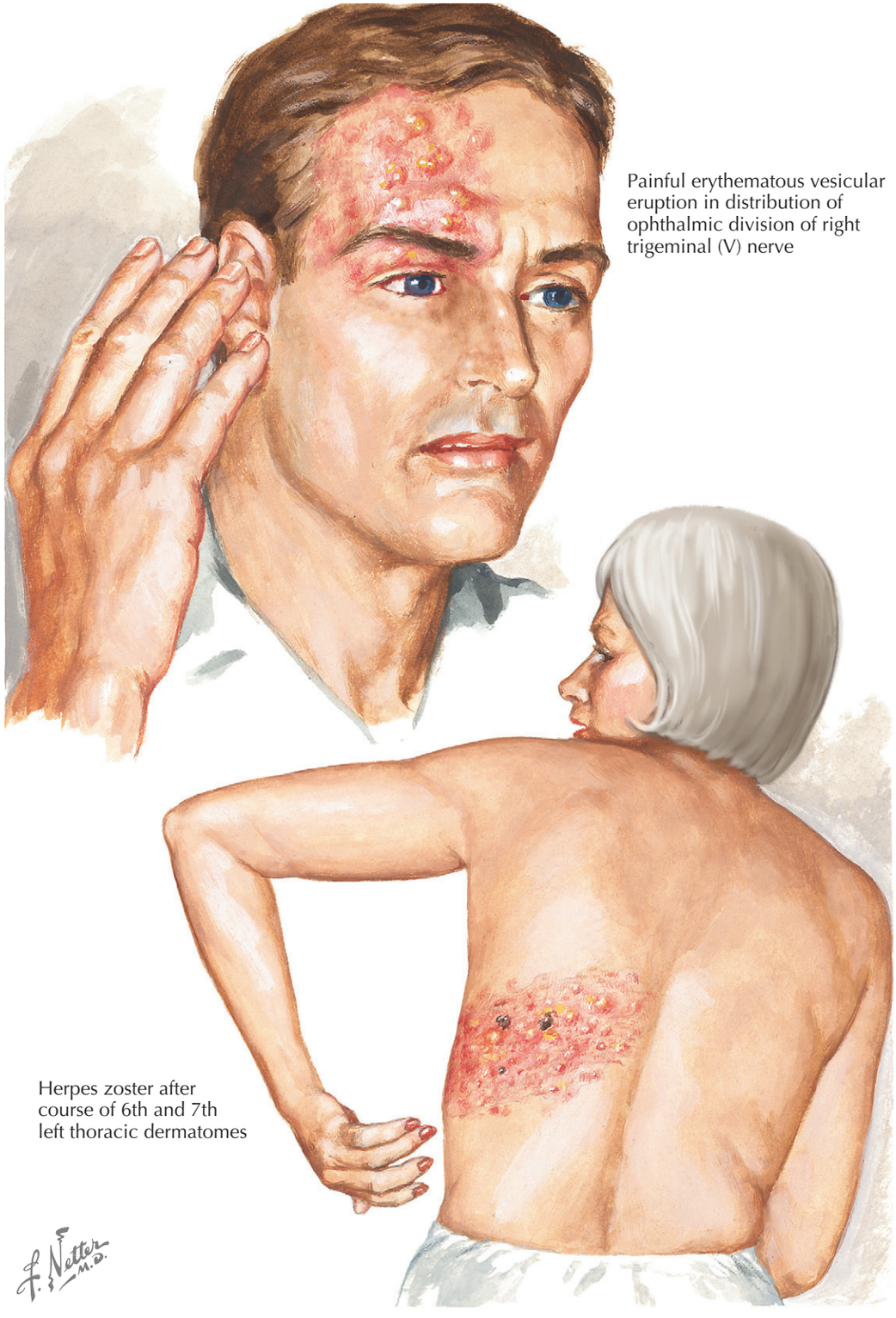


Genu recurvatum, atrophy of limb



Multiple crippling deformities; contractures, atrophy, severe scoliosis, and equinovarus

Herpes Zoster



Varicella-zoster virus (VZV) is the etiologic agent of chicken pox (varicella), and shingles (zoster). Varicella-zoster virus is a double-stranded deoxyribonucleic acid (DNA) virus. Initial infection occurs in the upper respiratory tract, followed by a viremia and the appearance of the characteristic vesicular lesions of chickenpox. Varicella-zoster virus establishes latency in the cranial nerve ganglia and dorsal root ganglia along the neuraxis. Reactivation of the virus causes shingles, which presents with severe localized pain followed within 3 to 4 days by the appearance of a vesicular rash on an erythematous base in one to three dermatomes. Zoster has a predilection for the mid to lower thoracic, upper lumbar, and ophthalmic (V1) dermatomes. The neurologic complications of varicella, or chickenpox, include encephalitis (which most often manifests as an acute cerebellar ataxia), aseptic meningitis, polyneuritis, multiple cranial neuropathies, or Reye syndrome. The neurologic complications of zoster include meningitis, encephalitis, vasculopathy, cerebellitis, Ramsay Hunt syndrome, postherpetic neuralgia, myelopathy, and chronic radicular pain without rash (zoster sine herpete).

Encephalitis. Varicella-zoster virus encephalitis can develop associated with zoster, follow zoster by days to months, or may develop without any history of a vesicular rash. The symptoms of encephalitis include fever, headache, seizures, focal neurologic deficits, and an altered level of consciousness. Varicella-zoster virus encephalitis is due to ischemic and hemorrhagic infarctions in both cortical and subcortical gray matter and white matter. Small demyelinative lesions have been attributed to a small-vessel vasculopathy. Neuroimaging in patients with varicella-zoster virus encephalitis may demonstrate ischemic and hemorrhagic infarctions and demyelinative lesions. Zoster reactivation may also cause a ventriculitis and periventriculitis with hydrocephalus, altered mental status, and gait abnormalities.

Ophthalmic Herpes Zoster. Patients with reactivation of varicella-zoster virus in the trigeminal ganglion develop vesicular lesions in the ophthalmic division of the trigeminal nerve and are at risk for infarction in the distribution of the carotid, anterior, or middle cerebral arteries due to varicella zoster virus vasculopathy. There is also a risk of corneal scarring.

Cerebellitis. An acute cerebellar ataxia can complicate childhood varicella but may also occur in adulthood.

Ramsay Hunt Syndrome. Ramsay Hunt syndrome is due to the reactivation of varicella-zoster virus in the geniculate ganglion, resulting in a peripheral facial nerve palsy. Vesicular lesions may be found on the pinna or in the mouth.

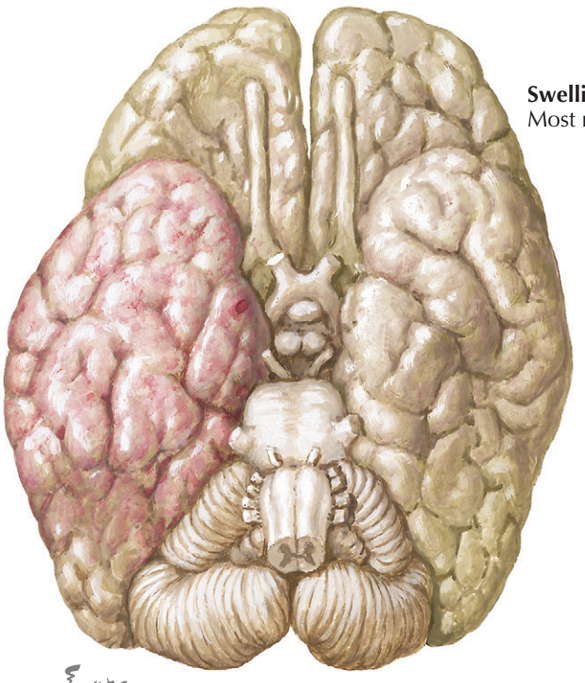
Postherpetic Neuralgia. Postherpetic neuralgia is the most common neurologic complication of varicella-zoster virus. The pain of zoster tends to resolve as the lesions heal but may be associated with or followed by postherpetic neuralgia. Postherpetic neuralgia is defined as the presence of pain in the dermatomal distribution of the vesicular rash for more than 1 month after the onset of zoster, after the lesions have healed.

Zoster Sine Herpete. Zoster sine herpete is pain in a dermatomal distribution without the appearance of a vesicular rash. It is diagnosed by either a fourfold increase in serum antibodies to varicella-zoster virus between acute and convalescent serology obtained 4 weeks later, or by the demonstration of VZV IgM in CSF and/or VZV DNA in cerebrospinal fluid (CSF) by polymerase chain reaction (PCR).

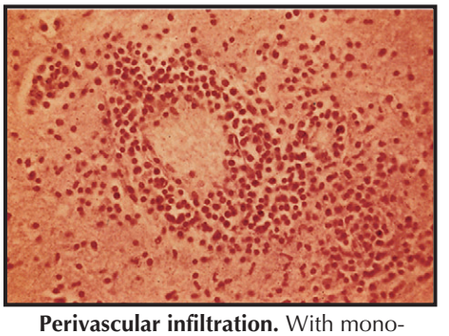
The best diagnostic test for varicella-zoster virus encephalitis is the detection of varicella-zoster virus IgM antibodies in CSF. VZV DNA can also be detected in cerebrospinal fluid by PCR, but this is less sensitive than the antibody.

Varicella-zoster virus encephalitis is treated with intravenous acyclovir. Zoster is treated with oral valacyclovir, famciclovir, or acyclovir. Postherpetic neuralgia is treated with a combination of amitriptyline and gabapentin. The routine use of the varicella vaccine in childhood has decreased the incidence of chicken pox. Effectiveness declines with time, and a booster immunization is required. There is also a zoster vaccine that decreases the risk of zoster.

Herpes simplex encephalitis



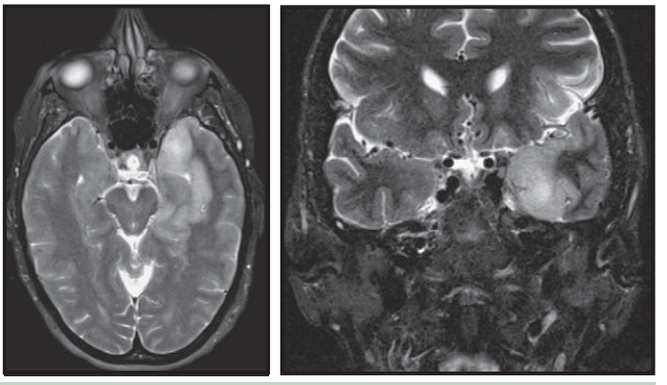
Swelling and patchy hemorrhagic areas. Most marked in right temporal lobe.



Perivascular infiltration. With mononuclear cells in disrupted brain tissue.

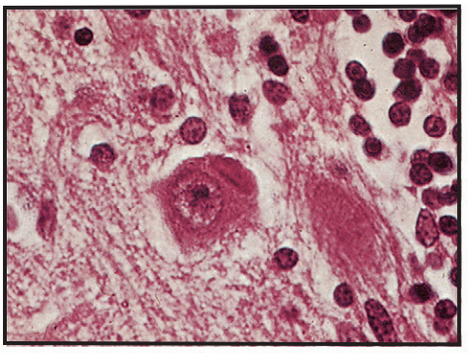
Herpes Simplex Virus Encephalitis and Rabies

Herpes simplex virus-1 is acquired in childhood by contact with oral secretions. First exposure is usually asymptomatic, but in some individuals, vesicular lesions develop in the mouth. The virus spreads by retrograde and anterograde transport to the trigeminal ganglion, where it establishes latent infection. Herpes simplex virus encephalitis is due to reactivation of latent herpes simplex virus infection and presents with a subacute progression of fever, hemicranial headache, behavioral abnormalities, focal seizure activity, and focal neurologic deficits, most often dysphasia or hemiparesis. In 90% of adult patients with herpes simplex virus encephalitis, magnetic resonance (MR) fluid attenuated inversion recovery (FLAIR), T2- and diffusion-weighted sequences demonstrate an abnormal lesion of increased signal intensity in the temporal lobe at 48 hours from symptom onset. Spinal fluid analysis demonstrates a lymphocytic pleocytosis with a normal or rarely mildly decreased glucose concentration. There may be red blood cells or xanthochromia in the cerebrospinal fluid (CSF) because this is a necrotizing encephalitis. A polymerase chain reaction (PCR) assay for HSV-1 has a sensitivity and specificity of more than 95%. The CSF HSV PCR may be negative in the first 72 hours of symptoms of HSV encephalitis. If the clinical suspicion is high, spinal fluid should be reexamined for HSV-1 deoxyribonucleic acid (DNA). Herpes simplex virus antibodies can be detected in the CSF approximately 8 to 12 days after symptom onset and for as long as 3 months. A serum to CSF ratio of less than 20:1 is considered diagnostic of HSV encephalitis. Herpes simplex virus encephalitis is treated with intravenous acyclovir for 3 weeks.

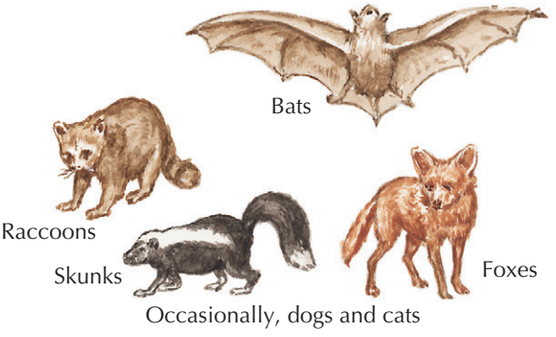


Axial T2 *(left)* and coronal T2 *(right)* MRIs showing marked asymmetric T2 hyperintense gyral cortical and juxtacortical white matter edema within the anteromedial left temporal lobe and parahippocampal gyrus

Rabies



Negri inclusion body. In Purkinje cell of brain.

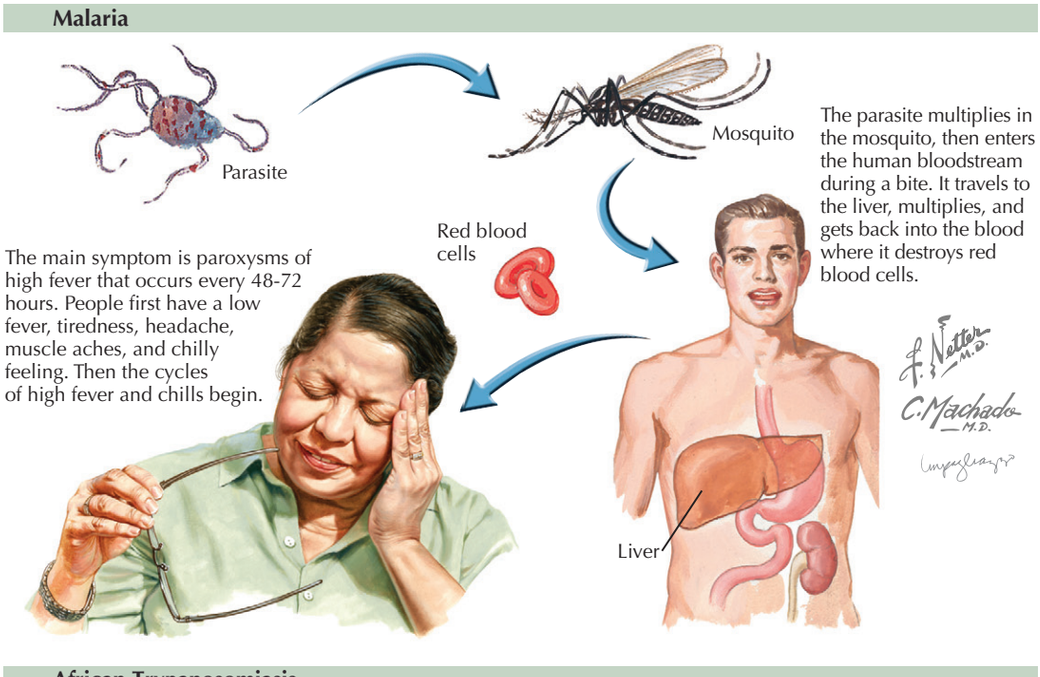


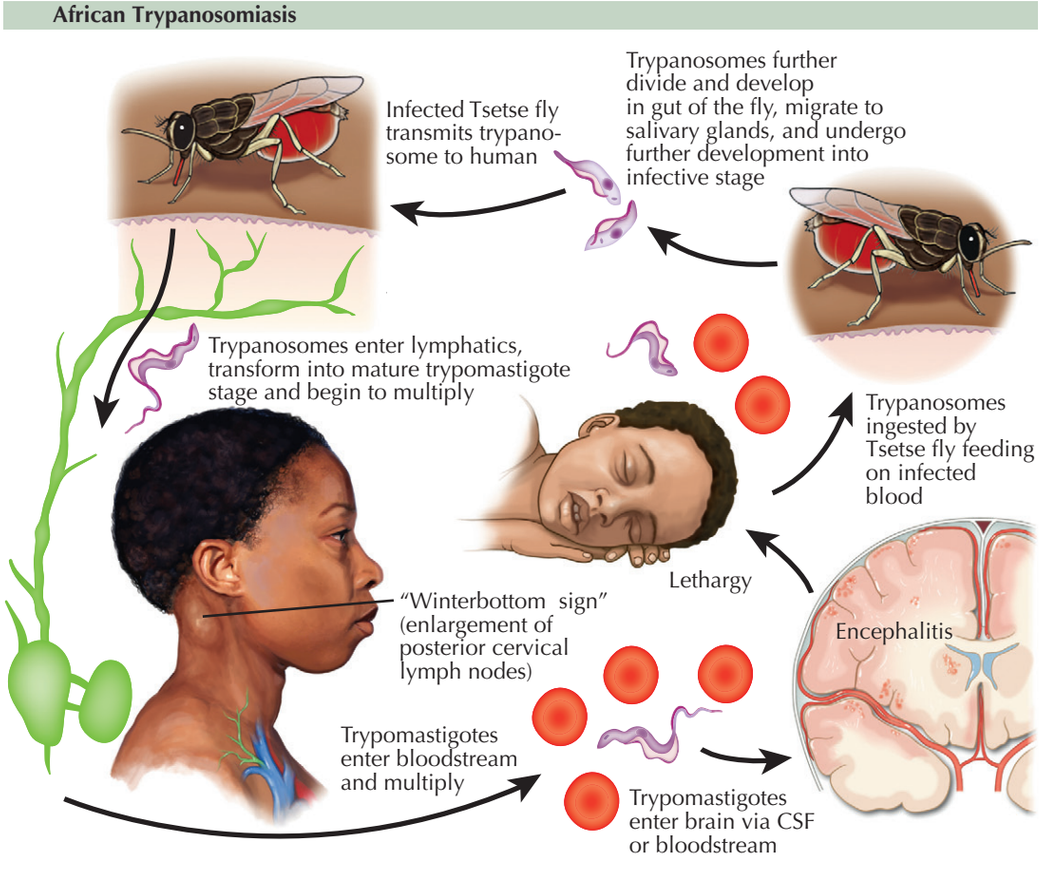
Common animal disseminators

RABIES

Humans acquire rabies from the bite of a rabid animal or from inhalation from aerosolized virus in caves inhabited by rapid bats. Two forms of classic rabies are recognized: furious rabies, which is characterized by fever, fluctuating consciousness, phobic spasms, and autonomic dysfunction, and paralytic rabies, which resembles the Guillain-Barré syndrome. Patients with bat rabies have different clinical features than those with classic rabies. Rabies acquired by the bite of a bat manifests with focal neurologic deficits, choreiform movements, myoclonus, seizures, and hallucinations. Phobic spasms are not a cardinal feature of bat rabies.

The diagnosis of rabies can be made by performing the reverse-transcriptase polymerase chain reaction (RT-PCR) on saliva, nuchal skin biopsy specimens, or CSF for rabies virus ribonucleic acid (RNA) detection. Classically, the diagnosis was made by biopsy and demonstration of cytoplasmic Negri inclusion bodies. Treatment begins with an immediate washing and flushing of the wound with soap and water and disinfecting with iodine. Rabies immunoglobulin should be infiltrated into and around the wound, and rabies vaccine is administered either intramuscularly or intradermally. Postexposure prophylaxis should not await the results of laboratory confirmation of the diagnosis.





Parasitic Infections: Cerebral Malaria and African Trypanosomiasis

Cerebral Malaria

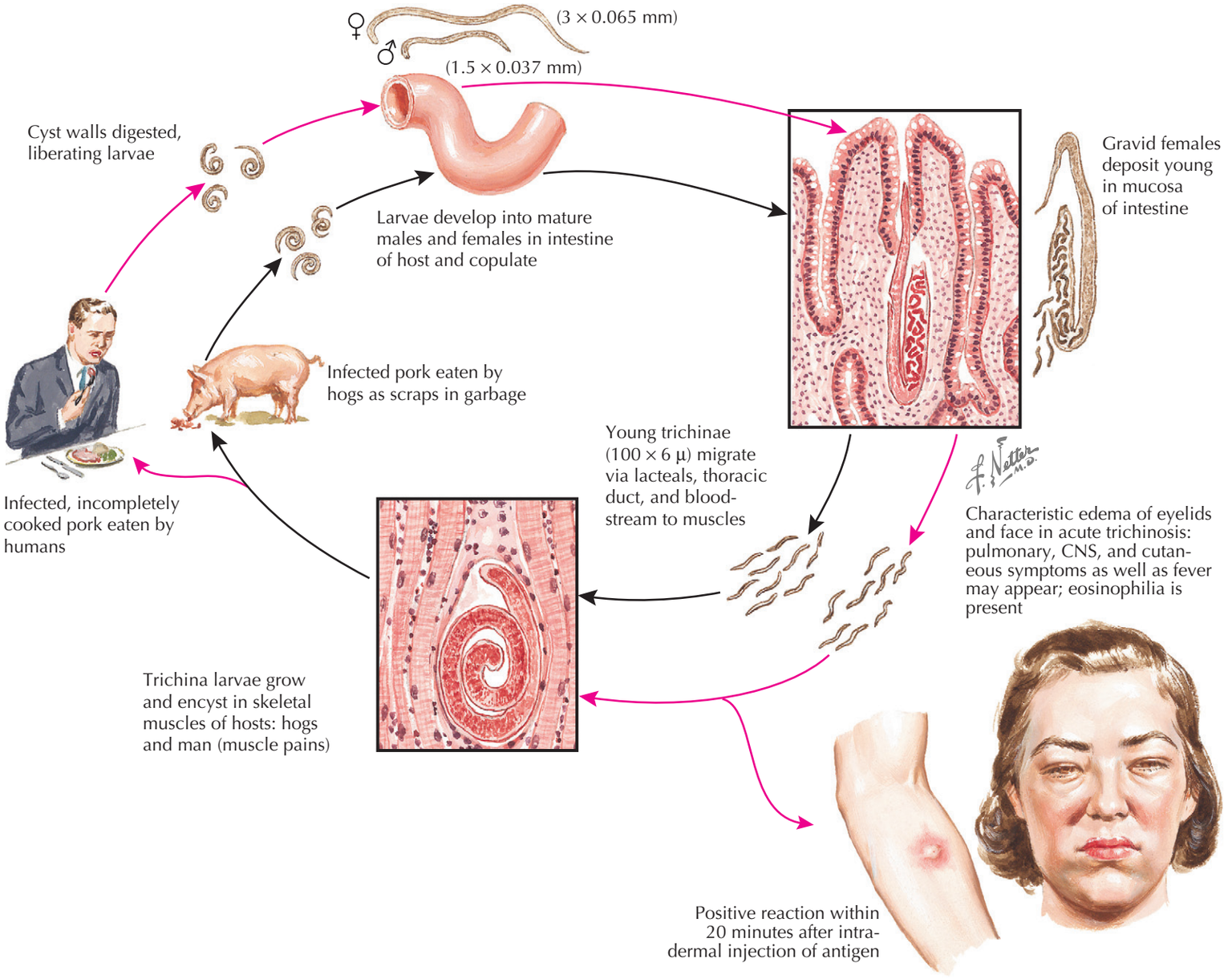
Humans bitten by *Anopheles* mosquitoes infected with *Plasmodium falciparum*, *P. vivax*, *P. ovale*, or *P. malariae* are at risk of developing malaria, a disorder that occurs mainly in Africa, Asia, and Central and South America, leading to up to a million deaths annually. Cerebral malaria—caused usually by *P. falciparum*—is the most deadly form of the disease. Fever and nonspecific symptoms give way to seizures and disorders of consciousness, ranging from irritability to obtundation and coma. Progression may be acute or more gradual. Accompanying hypoglycemia, acidosis, and anemia may exacerbate the neurologic symptoms.

Diagnosis is confirmed by examination of peripheral blood smears every 8 to 24 hours. The CSF is examined to exclude other possible causes of symptoms in patients with suspected cerebral malaria. Antimalarial chemotherapy, consisting of intravenous quinine or quinidine (in an intensive care unit [ICU] setting) or artesunate, plus doxycycline, tetracycline, or clindamycin, is started without awaiting laboratory confirmation of the clinical diagnosis. Untreated cerebral malaria is generally fatal. Neurologic sequelae are common in survivors and may include motor, sensory, cognitive, or language deficits and seizures.

African Trypanosomiasis

African trypanosomiasis in humans ("sleeping sickness") is transmitted by infected tsetse flies and takes two forms; in each, a meningoencephalitis may develop. An initial inflammatory skin lesion or chancre may occur a few days after a bite by the infected fly. Infection by *T. brucei gambiense* (in West and Central Africa) may otherwise be asymptomatic for months or years. Presentation with fever, headache, arthralgia, lymphadenopathy, and hepatosplenomegaly is followed in late stages by neurologic involvement, with lethargy, headache, personality changes, poor concentration, tremor, unsteadiness, and daytime somnolence. With further progression, the patient becomes obtunded; worsening coma leads to death. Infection by *T. brucei rhodesiense* (in East Africa) leads to a similar but more acute disorder.

Diagnosis requires identification of the trypanosome, typically in a blood smear. The CSF must be examined to confirm the diagnosis and stage the disease. A pleocytosis or increased protein concentration, or both, indicate neurologic involvement; immunoglobulin M (IgM) levels may be increased, and trypanosomes may be present. Serologic tests for the West but not East African disease are available; polymerase chain reaction (PCR) is investigational. Treatment regimens with antiprotozoal agents depend on the offending organism and whether neurologic involvement has occurred.

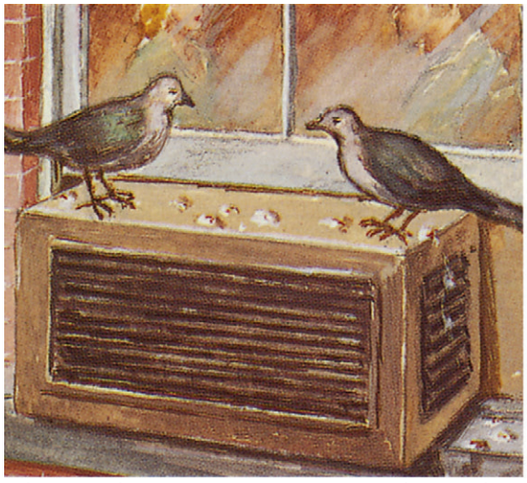


Parasitic Infections: Trichinosis (Trichinellosis)

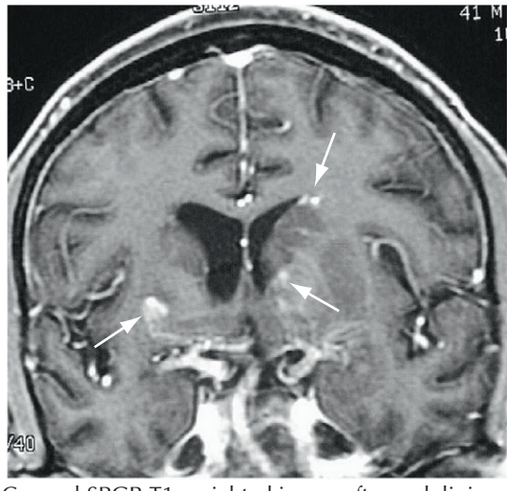
Human infection with *Trichinella spiralis* or certain other species of *Trichinella*, a nematode (roundworm), occurs most commonly by ingestion of contaminated raw or undercooked meat, especially from domestic pigs. In pigs, the larvae of *T. spiralis* are liberated from cysts in ingested meat by gastric digestion and then invade the small bowel mucosa. They develop into adult worms in the small intestine; the females are fertilized and release larvae that migrate to striated muscles, where they encyst. Thus adult worms and encysted larvae develop within the same host. Humans eating the infected pork develop trichinosis. The disorder is worldwide.

The incubation period varies with severity of infection. Abdominal pain and gastrointestinal symptoms may develop in the first week. Periorbital edema may occur for a few days. Subsequently, muscle and joint pain, muscle weakness, fever, skin rashes, headache, and other manifestations develop. Severe infections may cause meningitis or encephalitis. A myocarditis may lead to fatal cardiac arrhythmias. Pulmonary or renal involvement occurs occasionally.

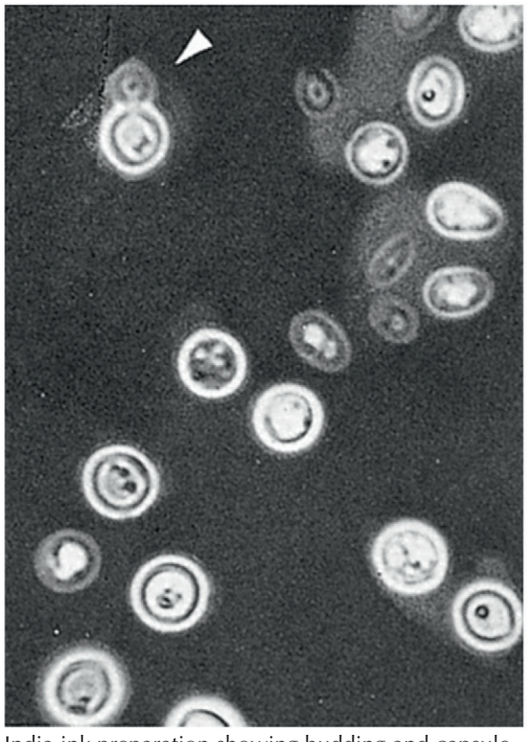
The diagnosis is suggested by the concurrence of periorbital edema, myositis, and an eosinophilia and can be confirmed serologically, but serologic tests are usually unhelpful for the first 2 or 3 weeks after infection. If necessary, skeletal muscle biopsy is performed to detect the presence of larvae. Mild infection requires only symptomatic therapy; the clinical course is self-limited. Definitive treatment is required for severe infections or neurologic involvement and consists of corticosteroids plus mebendazole or albendazole. Preventive approaches involve education about the dangers of consuming uncooked meats and control of farming techniques.



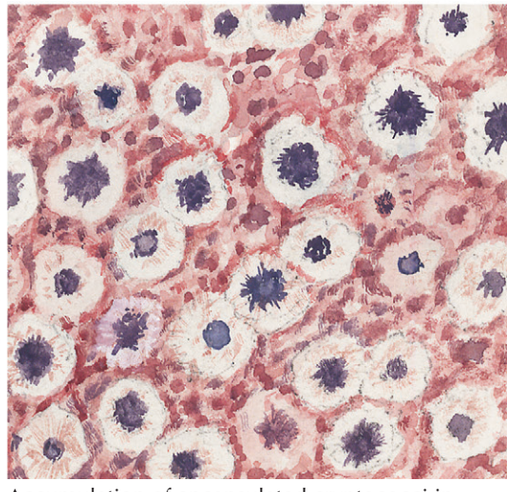
Infection is by respiratory route. Pigeon dung and air conditioners may be factors in dissemination.



Coronal SPGR T1-weighted image after gadolinium enhancement demonstrates multiple small enhancing lesions in both basal ganglia *(arrows)*



India ink preparation showing budding and capsule



Accumulation of encapsulated cryptococci in subarachnoid space (periodic acid–Schiff or methenamine-silver stain)

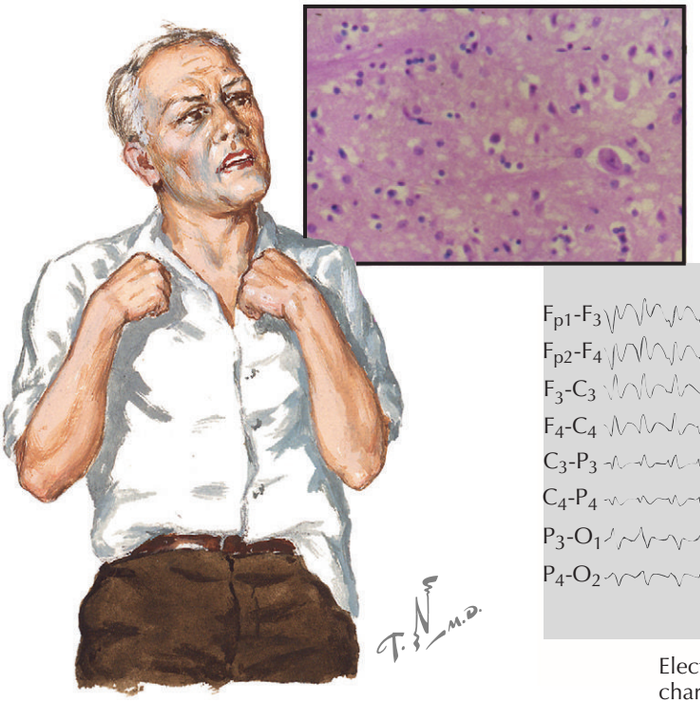
F. Netter M.D.

Parasitic Infections: Cryptococcal Meningitis

Much of the human population has been infected subclinically by inhalation with *Cryptococcus neoformans*, a yeastlike fungus. The fungus is distributed in soil samples worldwide in areas inhabited especially by pigeons, but pigeons do not become infected with the fungus, transmission from pigeons to humans is not described, and the role of pigeon excreta in human infection is unclear. A focal pneumonitis develops in humans and may be evident on chest radiographs but only occasionally become symptomatic. Hematogenous spread from the lungs to the central nervous system is rare in immunocompetent persons unless there are very high cryptococcal antigen titers in the serum. In the immunocompromised, however, reactivation of latent infection or a new primary infection may cause a meningitic illness that is typically subacute or chronic. Thus cryptococcal meningitis is encountered most commonly in patients infected with human immunodeficiency virus or who are transplant recipients, have neoplastic disease, or are on long-term immunosuppressant therapy.

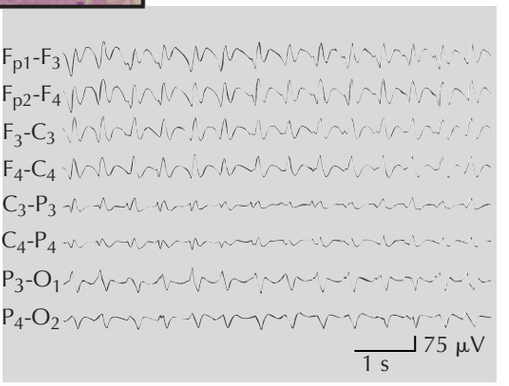
Patients present with headache, personality changes, irritability, somnolence, and cognitive changes. Intracranial pressure may be increased. There may be cranial nerve deficits. The diagnosis can only be made definitively by lumbar puncture, which typically shows an increased opening pressure, a mononuclear pleocytosis, an elevated protein concentration, and reduced glucose level in the cerebrospinal fluid (CSF). India ink preparations can define the yeast, but this is now rarely performed; cultural isolation is preferred but may take several days. Measurement of cryptococcal capsular antigen in the CSF is helpful in suggesting cryptococcal infection while the cultures are still pending. The clinical context generally requires that the brain is imaged before lumbar puncture to exclude space-occupying lesions; when present, these are typically the result of other disorders, such as lymphoma.

A fatal outcome is likely in the absence of treatment, which generally involves intravenous amphotericin B and oral flucytosine for at least 2 weeks, followed by high-dose fluconazole therapy for 2 months. Maintenance lower-dose therapy with fluconazole is then continued for at least a year, when discontinuation can be considered, depending on the response to antiretroviral therapy.

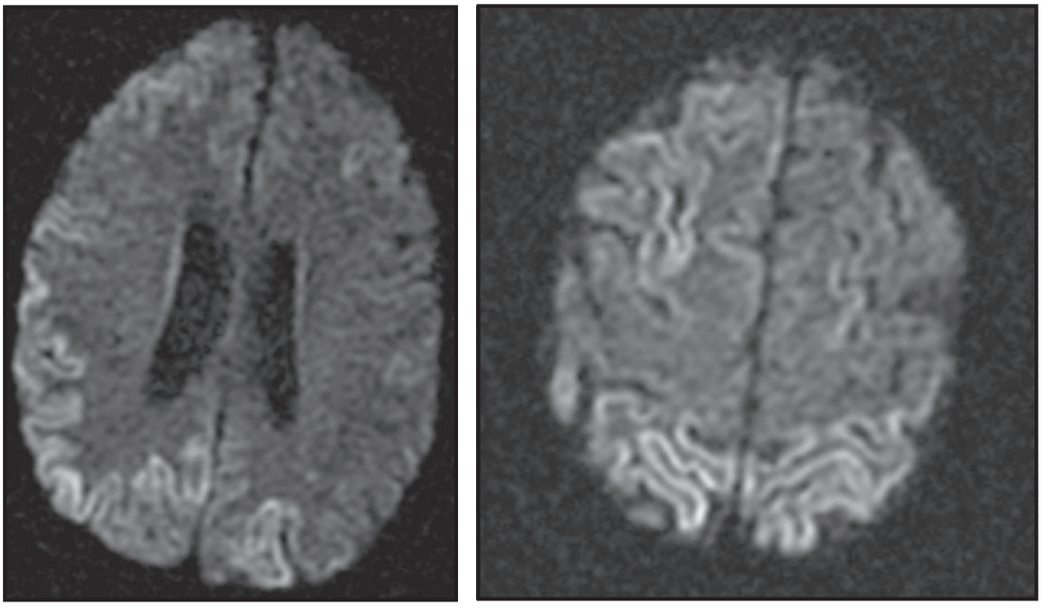


Section from putamen showing extensive loss of neurons and spongiform brain tissue. Spinal cord usually shows similar loss of motor neurons.

Myoclonus being exhibited in demented patient



Electroencephalogram showing characteristic diffuse periodic wave pattern



Axial diffusion-weighted MRIs showing marked abnormal hyperintense gyral cortical ribboning within both frontal and both (right > left) parietal lobes

Creutzfeldt-Jakob Disease

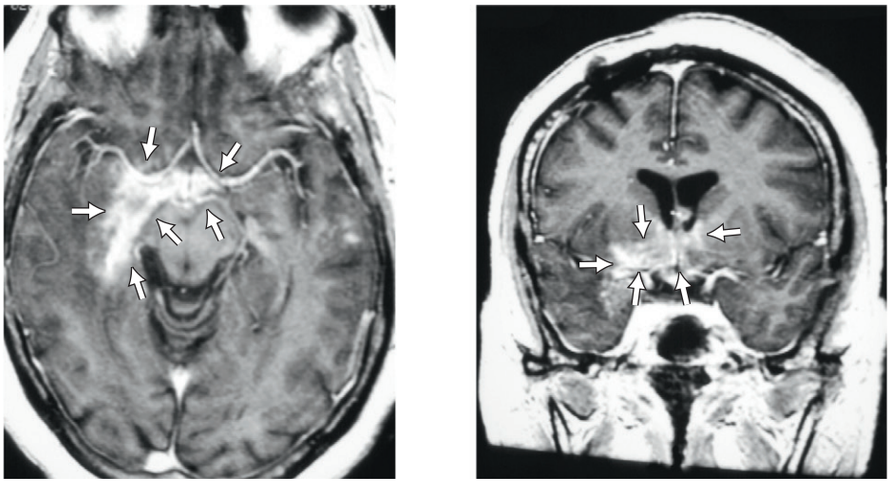
Creutzfeldt-Jakob disease (CJD) is the most common prion disease. The word prion denotes the proteinaceous "infectious" nature of the pathogenic agent. The initial event in the pathogenesis of prion diseases is the conversion of a normal cellular protein (PrP^{C}) to a pathogenic isoform (PrP^{Sc}). Creutzfeldt-Jakob disease was labeled a transmissible spongiform encephalopathy due to the pathologic evidence of extensive vacuolation (spongiform changes) and amyloid plaques in the brains of afflicted individuals.

There are a number of human prion diseases: sporadic CJD, iatrogenic CJD, variant CJD, kuru, Gerstmann-Straussler-Scheinker disease, and fatal familial insomnia.

Sporadic Creutzfeldt-Jakob Disease. The cardinal manifestations of Creutzfeldt-Jakob disease are dementia, myoclonus, and ataxia. Patients typically present with cognitive difficulty and ataxia and subsequently develop myoclonus. Diffusion-weighted magnetic resonance (MR) and fluid attenuated inversion recovery (FLAIR) show increased signal in the cortical ribbon, putamen, caudate nuclei, and thalamus. Electroencephalography (EEG) shows bisynchronous periodic sharp-wave discharges that may be time-locked to myoclonus. The presence of a CSF pleocytosis should initiate a search for another disease because an inflammatory response is characteristically absent. The CSF 14-3-3 protein has a low specificity and can be increased in a number of CNS disorders. CSF 14-3-3 protein is elevated in 95% of patients with sporadic Creutzfeldt-Jakob disease.

Iatrogenic Creutzfeldt-Jakob disease is due to prion exposure from contaminated surgical equipment, electrode implantation, dural mater grafts, cadaveric-derived human growth hormone, and corneal or organ transplantation. The clinical presentation of iatrogenic CJD depends somewhat on the route of intracerebral inoculation, with some cases resembling that described for sporadic CJD, and others, a cerebellar syndrome.

Variant CJD is acquired from ingestion of contaminated meat and typically consists of behavioral and psychiatric symptoms, peripheral sensory disturbances, and cerebellar ataxia.



Axial and coronal T1-weighted fast spin echo imaging following gadolinium demonstrate intense enhancement of hypothalamic region, adjacent basal ganglia, right temporal lobe, and dura *(arrows)*

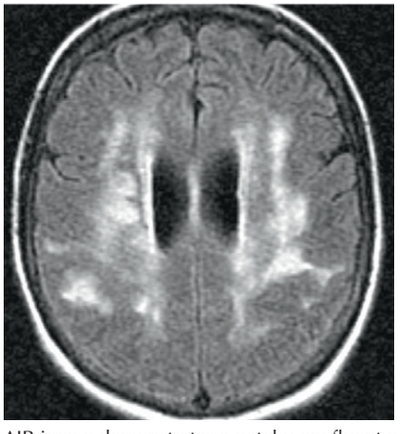
NEUROSARCOIDOSIS

Although this systemic noncaseating granulomatous disorder has not been associated with a specific infecting microorganism, it has many similarities to a chronic infective or inflammatory disease and will thus be considered in this section. Sarcoidosis is more common in African-Americans than Caucasians. It is often asymptomatic, being discovered by the presence of hilar adenopathy on a chest radiograph. Neurologic involvement is less common and may present acutely, subacutely, or more insidiously. The disease is usually monophasic but can follow a relapsing-remitting or progressive course.

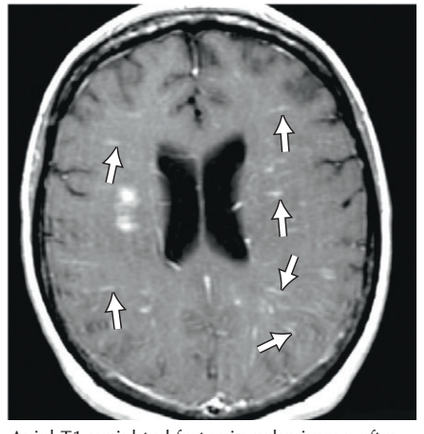
Presentation may be with cranial nerve deficits from a basal meningitis, the most common being neuropathies that affect cranial nerves (CNs) VII, V, VIII, and II. Facial nerve (CN VII) involvement may be unilateral or bilateral; when bilateral, it may occur simultaneously or sequentially on the two sides. Endocrine disturbances from hypothalamic-pituitary involvement may manifest as hypothyroidism, hypogonadism, hypoadrenalism, or hypopituitarism; diabetes insipidus sometimes occurs. An intraparenchymal lesion may lead to seizures; masquerade as a cerebral tumor, producing focal deficits and increased intracranial pressure; lead to a nonspecific encephalopathy; cause obstructive hydrocephalus; or result in a myelopathy or myeloradiculopathy if the spinal cord is affected. Neurosarcoid may affect the peripheral nervous system, causing a simple or multiple mononeuropathy or a polyneuropathy. A myopathy has also been described.

The diagnosis is established with certainty only by histopathologic examination of a biopsy specimen. All patients with suspected neurosarcoidosis require evaluation for extraneural involvement that may serve as a site for biopsy. An elevated serum angiotensin-converting enzyme (ACE) may be helpful for diagnosis but is not specific, and normal findings do not exclude the diagnosis. Cerebrospinal fluid is often abnormal and may simulate an infective process, with an increased cell count (usually a mononuclear pleocytosis) and elevated protein concentration; glucose level is normal or reduced. The immunoglobulin G (IgG) index may be increased, and oligoclonal bands may be present. The cerebrospinal fluid (CSF) ACE level is sometimes elevated, a suggestive but nonspecific finding. Chest radiographs or computed tomography (CT) scans often reveal hilar adenopathy and allow for mediastinal lymph node biopsy. Cranial CT or magnetic resonance imaging (MRI) may document the site and extent of neurologic involvement and also identify a site for biopsy, if diagnostic uncertainty persists or the response to therapy is poor.

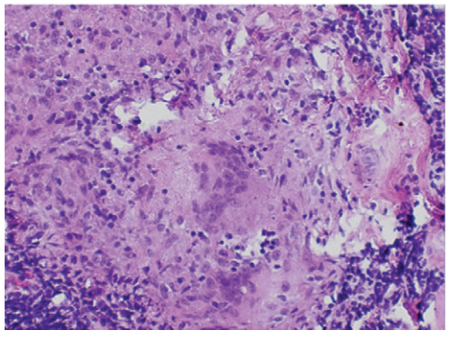
Controlled treatment trials are not available to guide therapy, but treatment with corticosteroids is the generally accepted approach. The duration of treatment is determined individually depending on disease location, severity, and response to therapy. Other immunomodulatory approaches have also been used in patients who fail or are unable to tolerate corticosteroids. In only rare instances is resection of a mass lesion necessary, although placement of a ventricular drain may be important in patients with hydrocephalus. Endocrinologic abnormalities require correction.



Axial FLAIR image demonstrates a patchy confluent pattern of involvement of paraventricular and central white matter, with extension into subcortical hemispheric white matter



Axial T1-weighted fast spin echo image after gadolinium shows some globular enhancement and a linear pattern consistent with infiltration of Virchow-Robin spaces *(arrows)*



Hilar node biopsy. Noncaseating granuloma with lymphocytes, macrophages, and epitheloid, mast, and plasma cells compatible with sarcoidosis.

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NEURO-ONCOLOGY

Clinical Presentations of Brain Tumors

Brain tumors commonly present with symptoms of elevated intracranial pressure or focal neurologic dysfunction. Elevated intracranial pressure can directly result from an enlarging mass or can be secondary to the development of hydrocephalus stemming from obstruction of the ventricular system and cerebrospinal fluid (CSF) flow by the tumor. The specific neurologic dysfunction depends on the local mass effect of the tumor.

Clinical Manifestations. Traditionally, headaches, nausea and vomiting, and papilledema constitute the clinical triad of increased intracranial pressure. Headaches resulting from elevated intracranial pressure are generalized in location and usually are worst upon awakening, occasionally even waking a patient from sleep. The vomiting is ascribed to pressure in the region of the fourth ventricle. Papilledema, or blurring of the optic disc margin due to swelling of the optic nerve (cranial nerve II) from the increased intracranial pressure, can be detected by ophthalmoscopic examination.

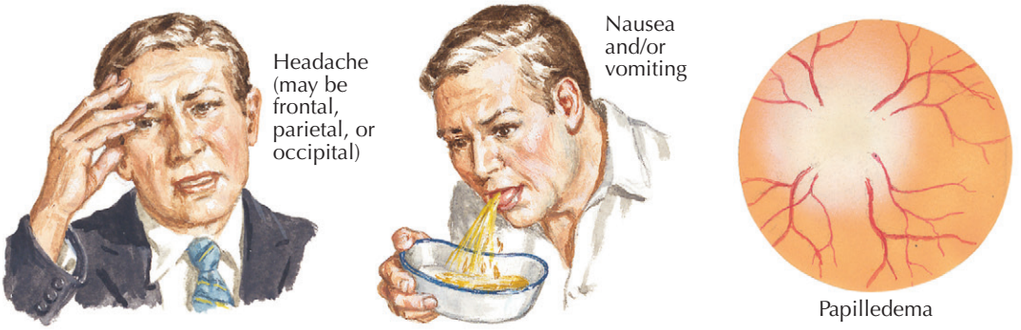
Local mass effect can result in a variety of neurologic symptoms, depending on what structures are affected. Symptoms may stem from local neural tissue invasion or compression of adjacent structures. Often, these focal signs and symptoms will manifest before the tumor enlarges to the point of causing increased intracranial pressure. Clinical presentations depend on the function of the affected tissue. In addition, *headaches* may also result from local mass effect. Typically, these headaches localize to the side of the tumor. They are usually dull and constant in character. Occasionally they may be severe. The combination of headaches associated with new neurologic abnormalities or changes in headache suggesting increased intracranial pressure should warrant consideration of an underlying neoplasm.

Seizures are another common sign that occur in association with an underlying malignancy. They can be either generalized or focal, with the focal seizures representative of the underlying location of the tumor. For example, distinct *motor or sensory symptoms*, such as weakness or numbness, relate to the functions of the cortical areas affected by the tumor. *Cognitive changes* may herald an underlying intracranial malignancy, especially if they are frontal in location. Often these changes are subtle, with patients experiencing fatigue, memory difficulties, personality changes, or apathy. *Difficulties with balance* or *disequilibrium* often occur when tumors arise in the posterior fossa. *Visual field defects*, such as a homonymous hemianopsia, may result from damage to the optic tracts, and bitemporal hemianopsia is often seen with compression of the optic chiasm by pituitary tumors. Occasionally, patients will be asymptomatic, but the physical examination may reveal subtle neurologic abnormalities, such as a drift of an upper extremity, asymmetric reflexes, or a positive Babinski sign.

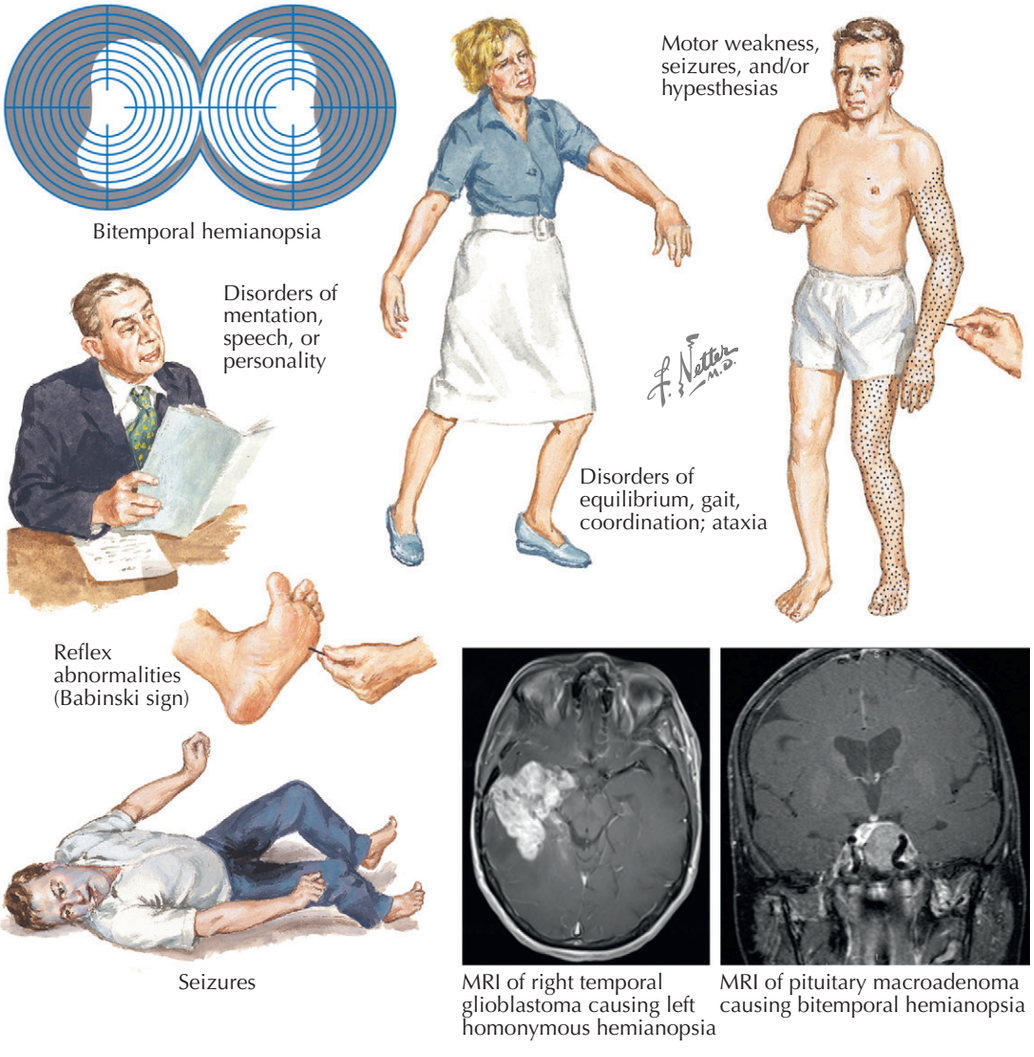
Diagnostic Studies. Once suspicion is raised of an intracranial malignancy, neuroimaging is warranted. Gadolinium-enhanced magnetic resonance imaging (MRI) is the diagnostic modality of choice because it allows visualization of the tumor in relation to the surrounding brain parenchyma, especially in the posterior fossa. Computer tomography (CT) is still used in patients for whom magnetic resonance imaging (MRI) is contraindicated or in emergent situations where time is of essence. In addition, it is superior to MRI in the detection of bony involvement, particularly in the region of the skull base. Other imaging modalities include magnetic resonance spectroscopy (MRS), which analyzes the chemical composition of the area of interest in an effort to differentiate tumor from other abnormalities, and positron emission tomography (PET) with fluorodeoxyglucose (FDG), which detects metabolically active tumors. Finally, perfusion MRI has emerged as a potentially useful technique because it identifies areas of increased vascularity, which can be useful for planning of surgical removal.

Some Common Manifestations of Brain Tumors

Intracranial pressure triad



Various focal manifestations



Gliomas

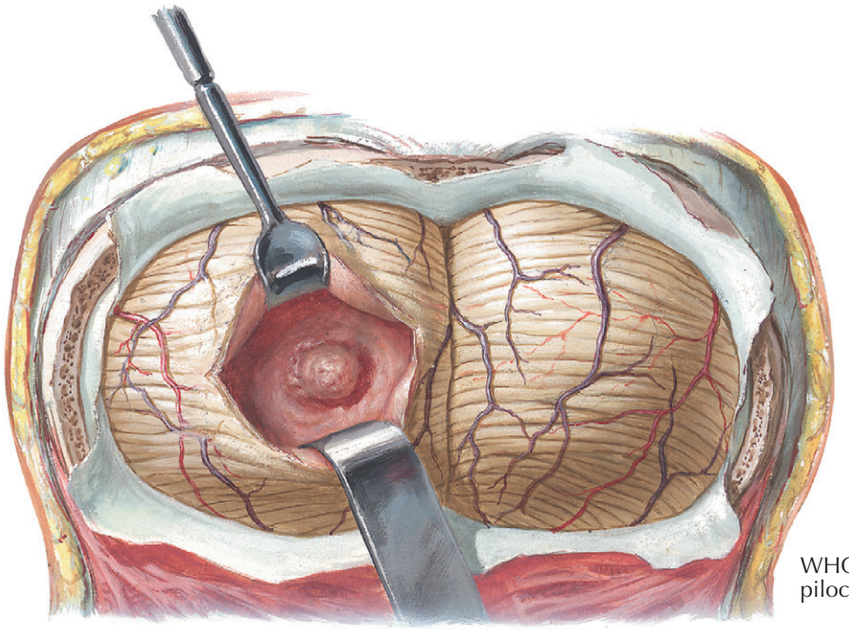
Gliomas represent tumors arising from glial cells that comprise the supporting tissue in the brain. In general, gliomas can be classified as "low grade" or "high grade" depending on the degree of aggressiveness. Low-grade gliomas (LGG) are slower-growing tumors, whereas high-grade gliomas (HGG) are more aggressive. They are further subdivided based on their histopathologic appearance. For example, astrocytomas represent tumors arising from astrocytes, whereas oligodendrogliomas have features consistent with oligodendrocytes. Other tumors falling under the category of gliomas include ependymomas, glioblastomas, and rarer tumors, such as gangliogliomas.

LGG are less common than HGG and tend to affect younger patients. LGG include those tumors designated as World Health Organization (WHO) grade I or II. The most common LGG are diffuse astrocytomas, oligodendrogliomas, and pilocytic astrocytomas, which is discussed in the pediatric section. Rarer tumors include ganglioglioma and pleomorphic xanthoastrocytoma. Although ependymomas are considered gliomas and labeled as WHO grade II, they are traditionally considered separate from the other LGG. HGG include those tumors comprising WHO grade III or higher. Anaplastic astrocytomas, anaplastic oligodendrogliomas, and anaplastic oligoastrocytomas are WHO grade III tumors, while the more common glioblastoma is WHO grade IV.

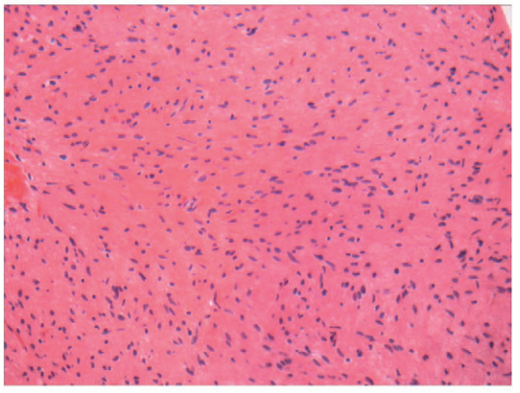
Clinical Manifestations. The neurologic presentation depends on the location and size of the tumor and its rate of growth. Very slow–growing tumors can become impressively large without causing significant symptoms. More rapidly growing small tumors located near sensitive areas, such as the cerebral cortex, may cause seizures, or difficulties with language or vision. Tumors located deep within the frontal lobe may reach significantly larger size before producing focal neurologic symptoms, even if they grow rapidly. Headache and cognitive dysfunction with memory loss and apathy may develop as early symptoms of these deep tumors, especially if the corpus callosum is involved. Tumors within the brainstem produce symptoms such as double vision, facial weakness, or difficulty swallowing related to local involvement of the brainstem nuclei. Gangliogliomas, which commonly arise in the temporal lobe, are notable for causing seizures.

Diagnostic Studies. On magnetic resonance imaging (MRI), LGG often present as an enhancing lesion. Pilocytic astrocytomas may have a large cystic component with an enhancing mural nodule (see Pediatric Brain Tumors later). Calcifications are sometimes present, most commonly seen with oligodendrogliomas of all grades. Anaplastic gliomas may resemble glioblastomas on MRI, highlighting the necessity of obtaining tissue through tumor removal or by biopsy for a definitive neuropathologic diagnosis. Ependymomas usually strongly enhance, with cystic and calcification components commonly seen. Often, the presence of calcifications in a fourth ventricle tumor is suggestive, although nondiagnostic, of an ependymoma. Because 10% of ependymomas will have disseminated upon presentation, it is necessary to image the entire brain and spine by MRI and examine the cerebrospinal fluid for the presence of malignant cells.

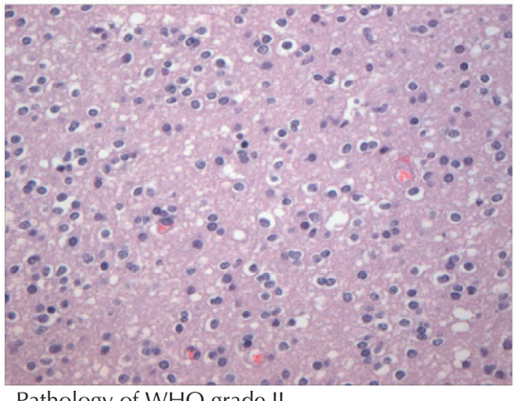
Treatment. The treatment of gliomas is highly variable and depends on the histopathologic subtype. For pilocytic astrocytomas and gangliogliomas, complete surgical resection is potentially curative. For LGG with significant residual disease after resection, the treatment consists of radiation or chemotherapy alone or in combination. In general, anaplastic gliomas are treated very similarly to glioblastomas, using a combination of radiation and chemotherapy. One exception is oligodendrogliomas with deletions of both the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q). These tumors are responsive to treatment with chemotherapy alone, and they have a favorable prognosis.



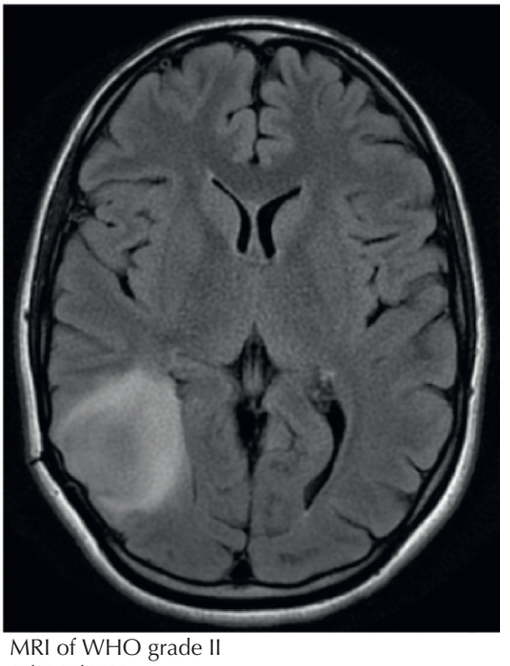
WHO grade I pilocytic astrocytoma



Pathology of WHO grade II astrocytoma

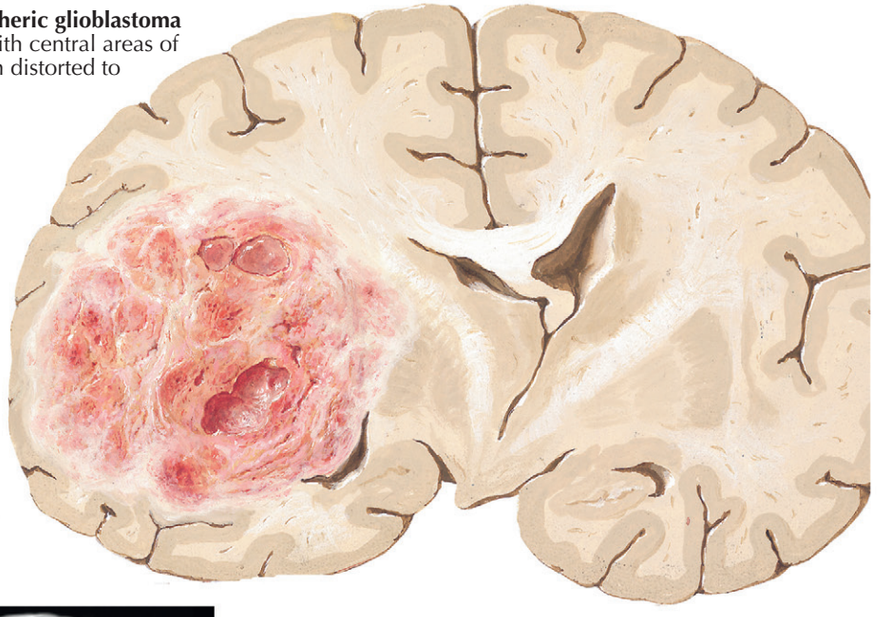


Pathology of WHO grade II oligodendroglioma



MRI of WHO grade II astrocytoma

Large, hemispheric glioblastoma multifome. With central areas of necrosis. Brain distorted to opposite side.



GLIOBLASTOMA

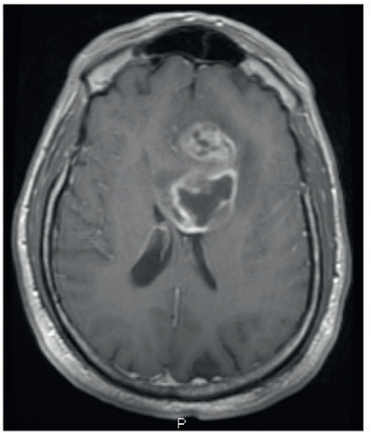
Glioblastomas are the most frequently occurring subtype of glioma and the most aggressive. As World Health Organization (WHO) grade IV tumors, their histopathologic features include nuclear atypia, hypercellularity, mitoses, microvascular proliferation, and necrosis. Middle-aged adults are most commonly affected, with a peak incidence in the fifth to eighth decade. Glioblastomas are preferentially localized to the cerebral hemispheres; very rarely, they occur in the brainstem, meninges, or the spinal cord. For "primary" or "de novo" glioblastomas that arise with no preexisting lesion, the natural history is usually short, with a median survival of 15 to 18 months. Glioblastomas that develop through progression from lower-grade gliomas are labeled "secondary." These are much less frequent, typically occur in younger patients, and are associated with longer survival than primary tumors. Comparisons of the molecular profiles of primary and secondary glioblastomas indicate that they represent distinct entities with evolution through different genetic abnormalities and through activation of different molecular signaling pathways.

Clinical Manifestations. As discussed above, signs and symptoms of underlying glioblastomas reflect the location of the tumor and its rate of growth. Because of the rapid rate of growth, symptoms tend to be of shorter duration before diagnosis. The most frequent presenting symptoms are headache and seizures.

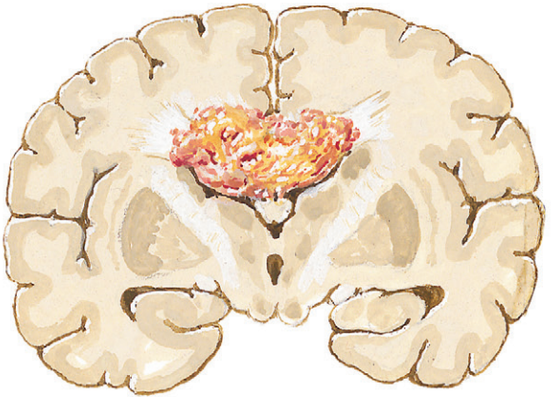
Diagnostic Studies. On MRI, glioblastomas commonly present with heterogeneous or ring-like enhancement admixed with central areas of necrosis. Fluid attenuated inversion recovery (FLAIR) and T2-weighted MRI images illustrate infiltrative tumor and surrounding edema, which is often significant. If MRI is contraindicated, CT with and without contrast is acceptable, although the anatomy is less defined.

Treatment. Treatment of glioblastomas is multimodal, involving surgery, radiation, and chemotherapy. Initial neurosurgical resection allows for definitive diagnosis, alleviation of neurologic symptoms, and debulking, which can improve outcome. After surgery, patients undergo radiation in combination with chemotherapy. External beam radiation has been shown to be the single most effective treatment for glioblastomas and other high-grade gliomas. The addition of temozolomide, a chemotherapy agent, has been shown to significantly extend survival. Despite combined therapy, the tumors almost inevitably recur and progress. Prognostic factors associated with increased survival include younger age, higher performance status, greater extent of resection, as well as some genetic factors, such as the presence of the deoxyribonucleic acid (DNA) repair enzyme O6-methylguanine–DNA-methyltransferase or isocitrate dehydrogenase (IDH1) mutation. Experimental therapies targeting angiogenesis (the formation of new blood vessels from preexisting adjacent vessels) have emerged as novel anticancer agents. For example, bevacizumab, a humanized monoclonal antibody to vascular endothelial growth factor (VEGF) was granted accelerated approval by the Food and Drug Administration (FDA); however, its effect on survival remains modest. Much current research has focused on the development and use of small molecule inhibitors to target molecular signaling pathways implicated in tumorigenesis.

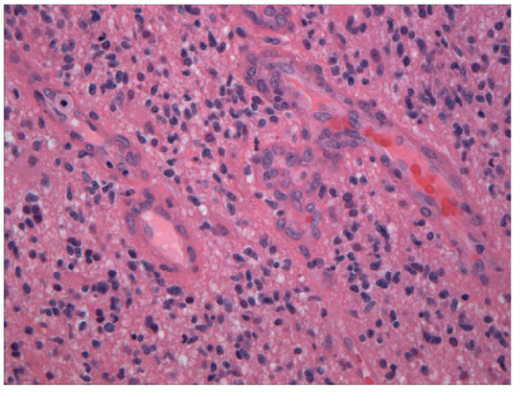
In addition to treatment of tumor growth, symptomatic treatment is equally as important. Corticosteroids are often used to relieve the surrounding edema. Antiepileptic agents are only necessary when patients suffer from seizures.



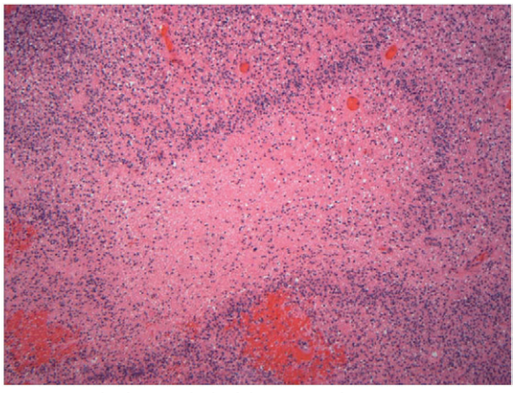
MRI of left frontal glioblastoma



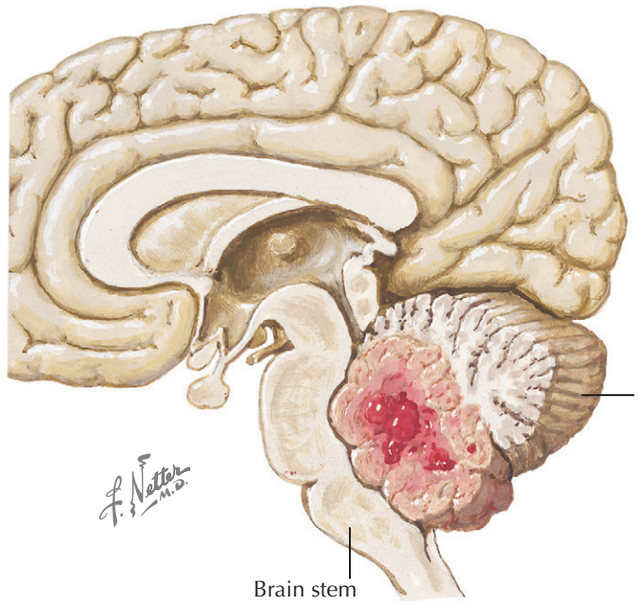
Coronal section and corpus callosum glioma



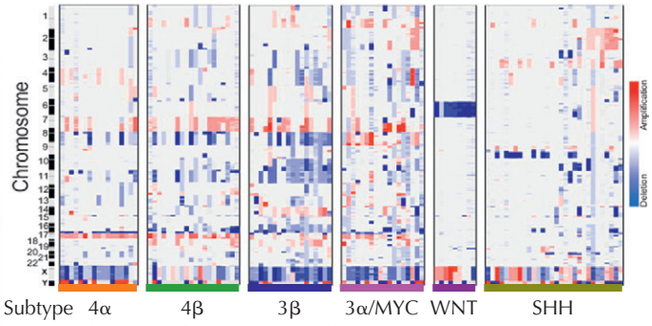
Histopathology of glioblastoma showing microvascular proliferation



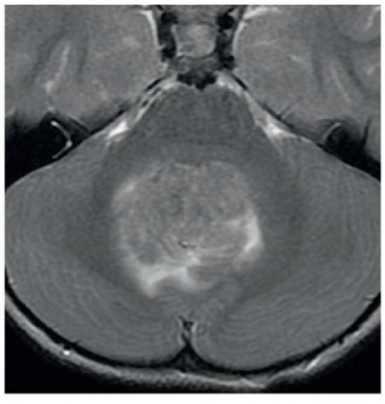
Histopathology of glioblastoma showing pseudopallisading necrosis

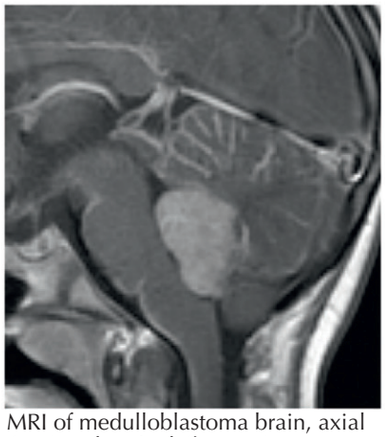


Medulloblastoma arising from vermis of cerebellum, filling 4th ventricle and protruding into cisterna magna

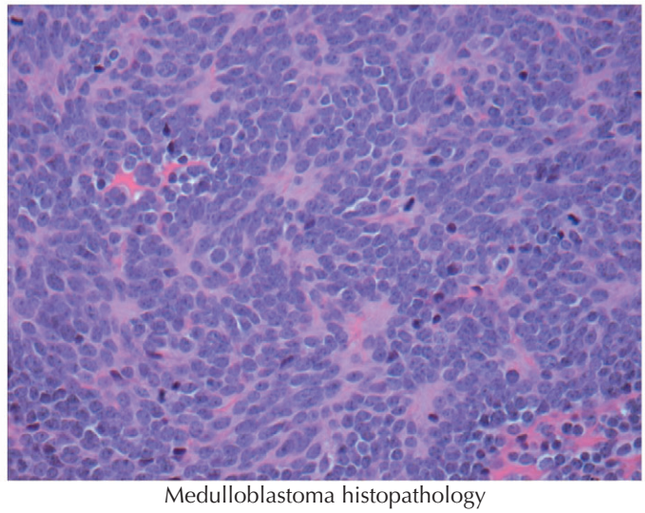


Each molecular subtype of medulloblastoma has a distinct combination of copy number alterations





MRI of medulloblastoma brain, axial *(top)* and sagittal *(bottom)*



Medulloblastoma histopathology

Pediatric Brain Tumors

Brain tumors are the second most common type of cancer in children and the most common type of solid tumor. These tumors often occur in the posterior fossa; the most common types include pilocytic astrocytomas, brainstem gliomas, and medulloblastomas.

Pilocytic astrocytomas are World Health Organization (WHO) grade I tumors. They can occur in any region of the central nervous system, but frequently arise in the cerebellum of children. The tumors often have both cystic and solid components. In some cases, the cystic component may be quite large, with the associated solid tumor mass appearing as a smaller "mural" nodule in the cyst wall.

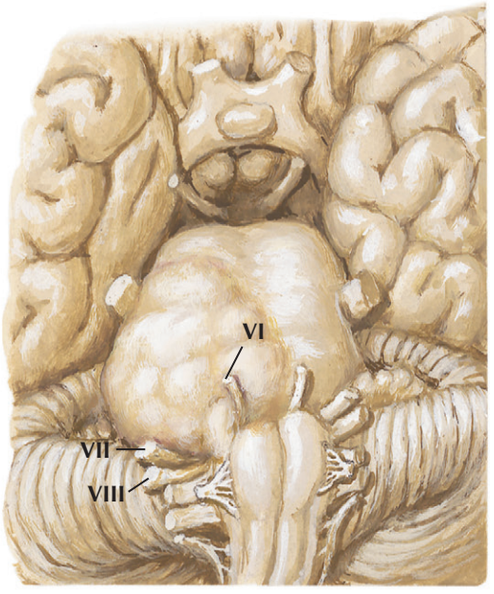
Brainstem gliomas encompass a number of tumor subtypes, each with its own pathologic and clinical characteristics. Although they can be seen in adult patients, they are far more common in children. There are four types: dorsal exophytic gliomas, tectal gliomas, cervicomedullary gliomas, and diffuse infiltrating pontine gliomas. Dorsal exophytic gliomas are slow-growing low-grade astrocytomas arising from the floor of the fourth ventricle. Intrinsic midbrain tectal gliomas tend to be low-grade astrocytomas, occurring next to the third ventricle and aqueduct of Sylvius. Cervicomedullary tumors typically are low-grade astrocytomas of the upper spinal cord and lower brainstem, although other tumor types can be seen. The most aggressive type is the diffuse infiltrating pontine glioma,. These tumors are WHO grade III or IV and have a very poor prognosis, with median survival of only 9 months despite maximal treatment with radiation and chemotherapy.

Medulloblastomas are WHO grade IV embryonal brain tumors that arise in the cerebellum and tend to disseminate through cerebrospinal fluid (CSF) pathways throughout the brain and spine. They are highly cellular tumors with highly variable prognosis that is not predicted by histologic features. Analysis of their molecular profiles has revealed that this heterogeneity arises because they consist of multiple subclasses associated with distinct demographics, genetics, clinical presentation, and outcome. The large majority of tumors are diagnosed in childhood or adolescence.

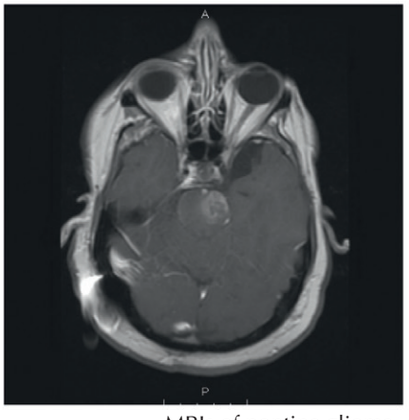
Clinical Manifestations. In general, brainstem gliomas produce symptoms reflecting the exact location of the tumor in the brainstem, rate of growth, and presence of CSF flow obstruction. Patients with tectal gliomas often display signs and symptoms of isolated hydrocephalus. Dorsal exophytic brainstem tumors may manifest with headaches due to hydrocephalus

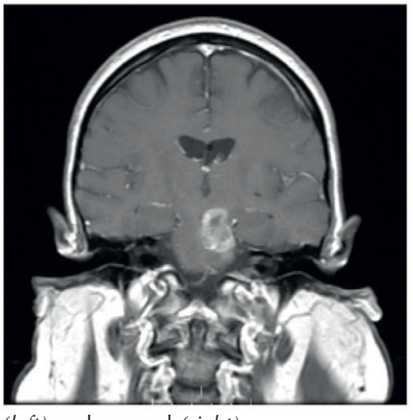
Brainstem glioma

Child with cranial nerve (VI, VIII) palsy on same side as tumor, with contralateral limb weakness

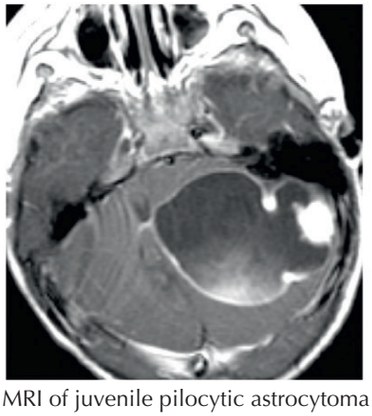


Glioma distorts brainstem and cranial nerves VI, VII, VIII





MRIs of pontine glioma, axial *(left)* and coronal *(right)*



MRI of juvenile pilocytic astrocytoma

Pediatric Brain Tumors
(Continued)

combined with ataxia from cerebellar dysfunction. Diffuse pontine gliomas often present with double vision and facial weakness due to cranial nerve VI and VII palsies, accompanied by motor and cerebellar dysfunction of the contralateral limbs. Medulloblastomas can present with ataxia from cerebellar dysfunction, cranial nerve deficits, headache and vomiting from hydrocephalus, or occasionally, signs and symptoms attributable to spinal cord or nerve root compression from extensive tumor dissemination.

Diagnostic Studies. With the advent of MRIs, the ability to diagnose brainstem tumors has improved tremendously. Tectal gliomas and diffuse intrinsic pontine gliomas frequently are diagnosed based on MRI appearance alone without biopsy. This is especially important given the high risk of neurologic injury from the biopsy procedure. Dorsal exophytic brainstem tumors tend to have sharp borders and are relatively homogeneous.

Medulloblastomas are generally well-defined midline cerebellar lesions with regions of mineralization, intratumoral cysts and blood vessels and heterogeneous enhancement. Because of the propensity for medulloblastomas to disseminate, the entire neuroaxis must be imaged. In addition, the CSF should be analyzed for the presence of tumor cells as the tumor tends to spread along the CSF pathways.

Treatment. Dorsal exophytic brainstem tumors and cervicomedullary tumors are amenable to surgical resection, followed by chemotherapy or radiation for progressive or symptomatic tumors that cannot be completely removed. Tectal gliomas are generally managed by addressing the hydrocephalus, although larger or progressive tumors may need further treatment. Diffuse infiltrating pontine lesions are treated with a combination of fractionated radiotherapy and chemotherapy.

Initial treatment of medulloblastomas consists of surgical resection, with the extent of surgical resection a significant prognostic factor. Subsequent treatment depends on whether patients fall into "average risk" (older than 3 years, with near or total resection of the tumor and no evidence of disseminated disease) or "high risk" (younger than 3 years, less than near-total resection and evidence of disseminated disease) categories. Average-risk patients are treated with lower doses of radiation and less chemotherapy.

Metastatic Tumors to Brain

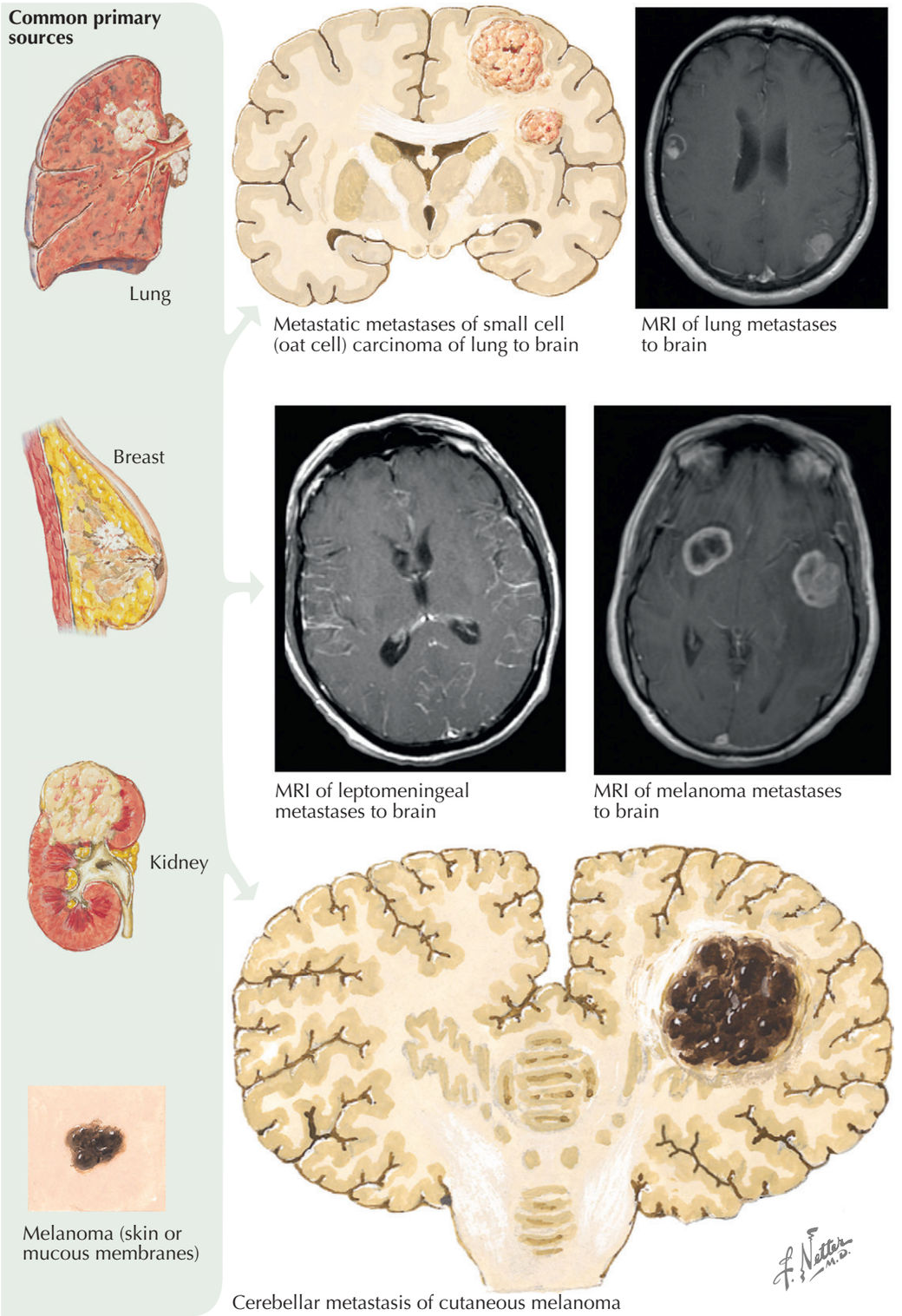
Metastasis to the brain constitutes the most common type of intracranial neoplasm in adults. The incidence appears to be increasing secondary to better control of systemic disease and to improved imaging techniques. In adults, the most common primary tumors to spread to the brain include carcinomas of the lung and breast, and melanoma. Renal carcinoma and pelvic/abdominal tumors also frequently disseminate to the brain. Metastasis to the brain occurs only rarely in children, with sarcomas and neuroblastomas the most common primary source. Typically, patients have a known diagnosis of cancer before the development of neurologic symptoms, although occasionally metastasis to the brain may be the first manifestation of the malignancy.

Three mechanisms have been described for the development of metastases. For parenchymal lesions, the most common is hematogenous spread. Metastatic lesions are usually found at the junction between gray and white matter. Metastasis can also occur via local extension from the primary tumor, such as in head and neck cancer, and via bodily fluids, such as the CSF.

Clinical Manifestations. Patients with brain metastases can present with a variety of clinical features. Thus any patient with a history of cancer who develops new neurologic symptoms warrants careful examination. About half of the patients will present with headaches with increasing frequency when multiple lesions or posterior fossa lesions are present. Other common symptoms include focal weakness and mental status changes. Up to one fifth of patients will present with seizures. Strokes can also occur in the setting of metastasis. This may be due to general hypercoagulability, disturbance of arterial flow, tumor embolization, or hemorrhage into a lesion. Melanoma, renal cell carcinoma, thyroid cancer, and choriocarcinoma have a propensity to bleed.

Diagnostic Studies. Contrast magnetic resonance imaging (MRI) is preferred for the diagnosis of brain metastasis because it is more sensitive in detecting lesions and differentiating metastatic lesions from other central nervous system abnormalities. Parenchymal brain metastasis tends to be circumscribed with large amounts of surrounding vasogenic edema relative to the size of the lesion. The presence of multiple lesions and location at the gray and white matter junction further supports a diagnosis of metastasis. Because metastatic lesions can also spread via CSF fluid, examination of CSF fluid may be necessary in some patients to evaluate for the presence of leptomeningeal involvement. Finally, if the diagnosis of metastasis is still in doubt, a biopsy should be performed for confirmation.

Treatment. The treatment plan for patients with brain metastases depends on their prognosis, which is based on their performance status, extent of extracranial disease, age, and primary diagnosis. In those patients with a favorable prognosis, treatment is aimed toward eradication or control of brain metastasis. This involves surgical resection combined with radiotherapy to eliminate residual cancer cells. Randomized trials have shown that the addition of whole brain radiation (WBRT) to surgery reduces recurrence rate but does not improve overall survival. In some cases, surgery is not a reasonable option, thus stereotactic radiosurgery (SRS) is considered. Combining WBRT with SRS seems to improve progression free survival but does not impact overall survival. In patients considered to have a poor prognosis, treatment is focused on symptom management and maintenance of neurologic function. In these cases, WBRT is preferred in order to improve neurologic deficits and prevent further deterioration. In both patient groups, corticosteroids are often used to control symptoms from mass effect and edema.



MENINGIOMAS

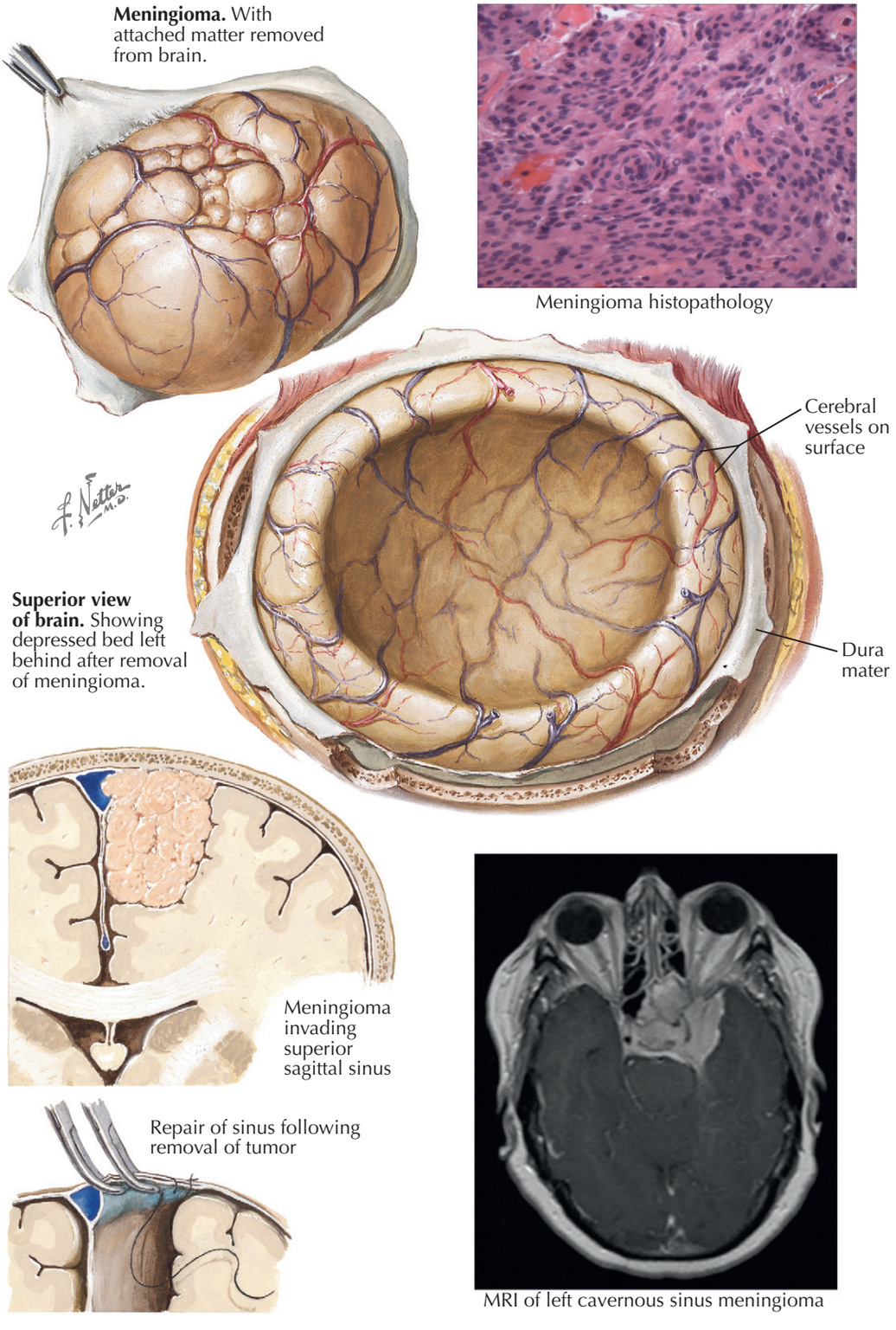
Meningiomas are the most common primary intracranial neoplasm, comprising about one third of all intracranial tumors. These tumors arise from the meningothelial cells and are World Health Organization (WHO) grade I (benign), II (atypical) or III (anaplastic). Their incidence increases with age, and they are more than twice as common in females. This gender difference is even more pronounced with spinal meningiomas, which are quite rare in males. Meningiomas are infrequently seen in children except in those with genetic syndromes, such as neurofibromatosis—(NF-2) or those with history of prior radiation exposure. Much interest has surrounded the epidemiology of meningiomas. Thus far, ionizing radiation and hormonal use have emerged as risk factors for the development of these tumors. Radiation-induced meningiomas tend to have a higher frequency of multiplicity and higher rate of malignancy than sporadic meningiomas.

The WHO classification schema is based on histopathologic morphology and correlates with prognosis. WHO grade I lesions are considered benign and by far comprise the majority of meningiomas. These are further subdivided based on their morphology into meningotheliomatous (including "psammomatous" tumors with characteristic whorl patterns of cells), fibromatous, and angioblastic types. Treatment approaches for all of these subtypes of benign meningiomas are the same. WHO grade II meningiomas are considered atypical meningiomas and constitute about 10% to 20% of cases. These are characterized by higher mitotic activity, defined as having greater than or equal to four mitoses per high-powered field, and three or more of the following features: increased cellularity, high nuclear to cytoplasmic ratio, prominent nucleoli, uninterrupted sheetlike growth, or areas of necrosis. The WHO grade III meningiomas are the least common but the most ominous. They are classified as "malignant" or "anaplastic." These tumors exhibit loss of the typical meningioma growth patterns, infiltrative growth, abundant mitosis with atypia, and multiple areas of necrosis. Grade II or III meningiomas are significantly more likely to have invasive disease, local recurrence, and shorter overall survivals.

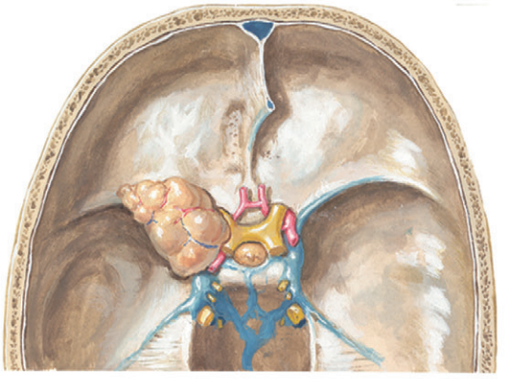
Clinical Manifestations. Presenting signs and symptoms depend on the location and growth rate of the tumor. Because most meningiomas are slow growing, patients are frequently asymptomatic, with the discovery of the tumor an incidental finding. Any signs or symptoms that do develop are usually secondary to compression of underlying structures.

Seizures are often presenting signs of meningiomas, especially those located near cerebral cortex. Focal weakness is another frequent complaint, with the pattern of weakness a potential clue as to the location of the tumor. For example, bilateral lower extremity weakness in the absence of a spinal cord lesion can often be seen with parasagittal lesions arising from the falx and compressing the adjacent motor strips of both hemispheres. A potential concern with these lesions is involvement of the sagittal sinus, which can lead to venous infarction. Spinal meningiomas can also cause bilateral leg weakness, but this is often accompanied by numbness. Foramen magnum meningiomas can present with insidious weakness of the arm and leg, which progresses to involve the contralateral limbs. This is accompanied by neck pain, worsened with neck flexion or Valsalva maneuvers. Because of the subtly progressive symptoms, this can be hard to diagnose and can be confused with multiple sclerosis.

Visual changes can be subtle but are commonly seen with meningiomas. Deficits may include visual loss, field deficits, and/ or diplopia. Olfactory groove, medial sphenoid wing, and other parasellar tumors can compress the optic nerve (CN II), resulting in blindness with optic atrophy in one eye and papilledema in the other. This is otherwise known as the Foster-Kennedy

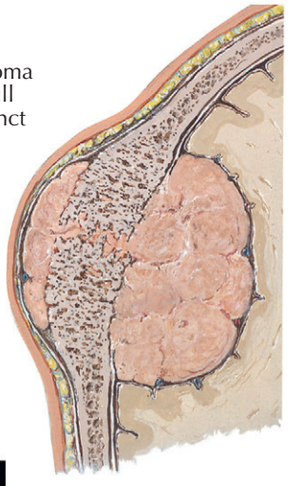


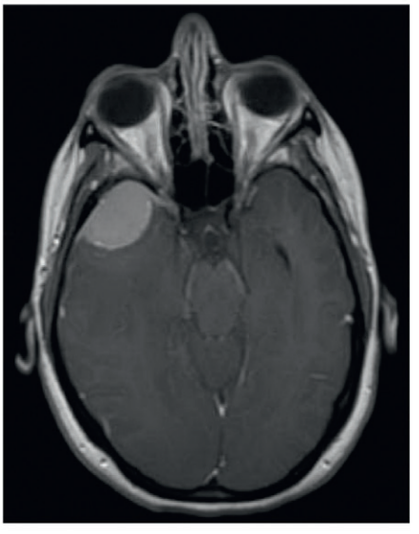
MENINGIOMAS *(Continued)*



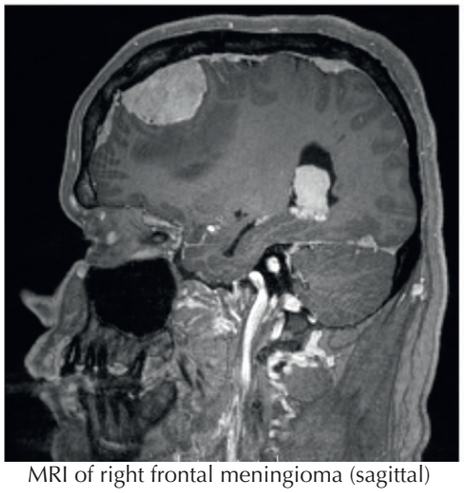
Meningioma of left medial sphenoid wing compresses optic (II) nerve and internal carotid artery

Convexity meningioma eroding through skull and producing distinct prominence

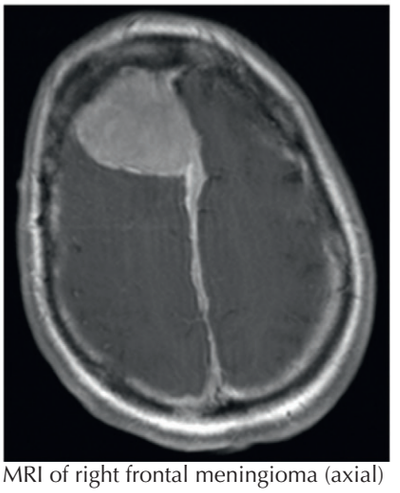




MRI of sphenoid wing meningioma



MRI of right frontal meningioma (sagittal)



MRI of right frontal meningioma (axial)

syndrome. Parasellar lesions can also cause visual field deficits. When tumors involve the cavernous sinus, ocular palsies can be seen. This is frequently accompanied by facial numbness. Finally, meningiomas can arise from the optic sheath, resulting in slowly progressive loss of vision.

Other signs and symptoms include ataxia and hemiparesis secondary to lesions in the posterior fossa, causing brainstem compression. Meningiomas arising at the cerebellopontine angle can produce sensorineural hearing loss. Occasionally, they can be quite adherent to adjacent cranial nerves and vasculature, rendering them difficult to remove. Large tumors in the posterior fossa can cause obstructive hydrocephalus.

Because the majority of meningiomas are very slowly growing, the brain has time to adapt to the enlarging mass. Thus tumors in the frontal or occipital lobe can become quite large before the tenuous pressure relationships decompensate, resulting in symptomatic presentation. Those tumors arising in the frontal lobe may present with cognitive or personality changes or other mental status changes.

Diagnostic Studies. Both magnetic resonance imaging (MRI) and computed tomography (CT) can be used to diagnose meningiomas, although MRI is the preferred imaging modality. Typically, meningiomas are isointense to hypointense on T1 and isointense to hyperintense on T2, with strong homogeneous enhancement. Often, there is a characteristic "dural tail," the marginal dural thickening that tapers at the periphery. On CT, the meningioma appears as a well-circumscribed extra-axial mass that is sometimes calcified. Similar to the MRI, homogenous enhancement is seen when intravenous contrast is administered. Occasionally, areas of necrosis, cyst formation, or hemorrhage are seen. CT is also helpful to evaluate for bony involvement. Although bony involvement from cerebral convexity tumors is rare, almost 50% of skull base tumors will have secondary involvement of the bone.

Treatment. With the availability of imaging modalities, such as MRI and CT, meningiomas are often asymptomatic incidental findings. Frequently, these tumors are unchanging or slow growing. It is reasonable to follow these patients conservatively with active surveillance, withholding treatment until the tumor becomes symptomatic or increases in size significantly. This is especially true for elderly patients (older than 70 years) or those with multiple surgical comorbidities.

The threshold for surgical intervention in younger patients is lower because morbidity is less than in older patients and because it is assumed that these lesions will eventually progress. Thus surgical intervention may be recommended for lesions in surgically accessible locations even if they are asymptomatic. In patients with symptomatic lesions or asymptomatic tumors that appear to be infiltrative or associated with vasogenic edema, surgical resection is recommended. Complete surgical resection is potentially curative, and the extent of resection correlates with prognosis. Advances in neurosurgery, such as microsurgery, intraoperative imaging, and the widespread use of MRIs have improved a surgeon's ability to successfully resect these lesions while minimizing injury to surrounding normal tissue.

In some cases, only a subtotal resection can be achieved. In these cases, adjuvant radiotherapy should be considered because retrospective studies have reported improved progression free survival, although not overall survival. Radiotherapy alone can be effective for those lesions that are surgically inaccessible with local control rates of greater than 90% in 5 years. For WHO grade II tumors, the frequency of recurrence is increased. Despite the lack of large prospective trials, adjuvant radiotherapy is recommended for incompletely resected tumors. The role of radiotherapy for after complete resection is controversial. Grade III tumors invariably require irradiation.

Pituitary Tumors and Craniopharyngiomas

Pituitary tumors account for the third most common primary intracranial tumor, with males and females equally affected. Patients often present with a variety of neurologic and endocrinologic abnormalities, depending on the tumor type and growth characteristics. Although the pituitary adenoma is the most common sellar tumor, other tumor types exist, including pituitary carcinomas, craniopharyngiomas, and Rathke cleft cysts.

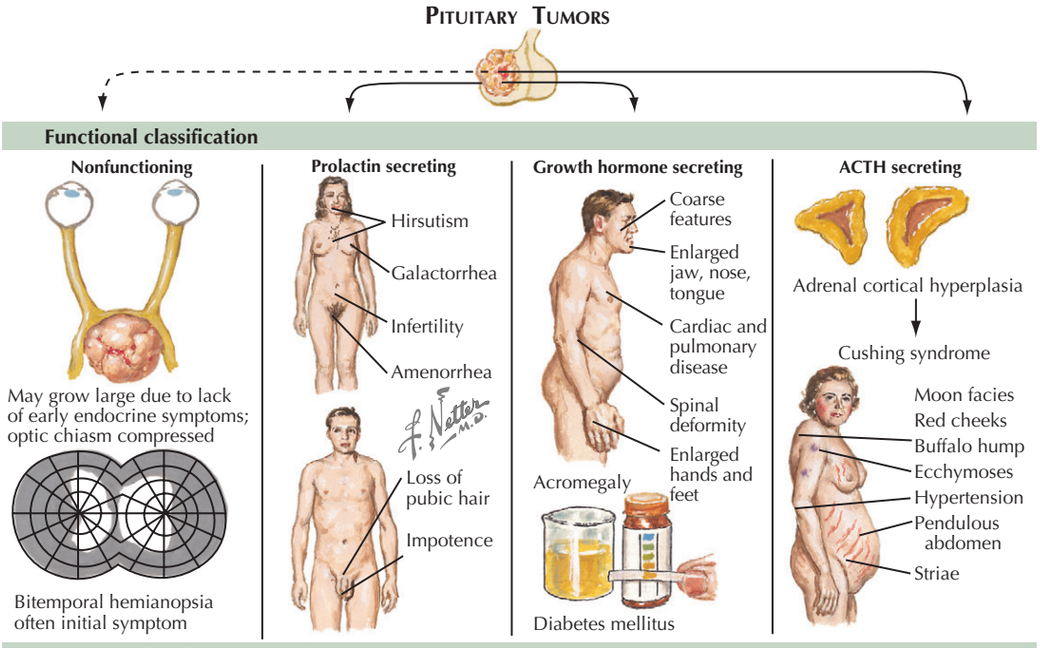
The pituitary gland is located in the sella turcica in the body of the sphenoid bone. The tuberculum sellae forms the anterior border of the sella turcica, and the dorsum sella demarcates the posterior border. The cavernous sinus is found in the lateral sellar compartment and borders each side of the pituitary. The optic apparatus lies above the sella.

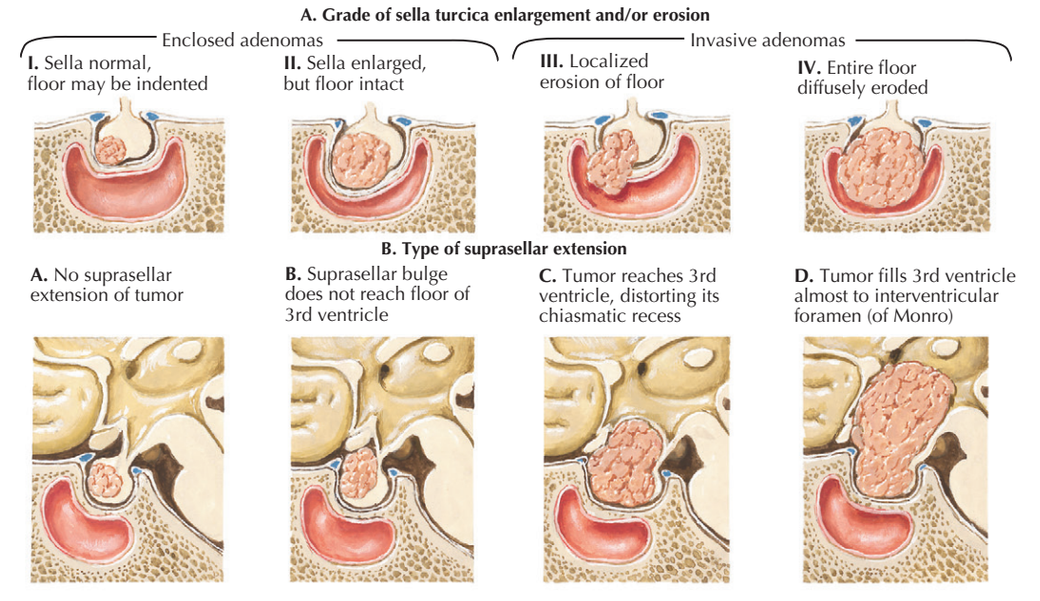
The pituitary gland is formed by two distinct lobes: anterior (adenohypophysis) and posterior (neurohypophysis). The anterior lobe contains glandular epithelial cells, which secrete endocrine hormones such as adrenocorticotropic hormone (ACTH), thyrotropin-stimulating hormone (TSH), prolactin, growth hormone (GH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). The posterior lobe represents the termination of the hypothalamohypophysial tract and stores oxytocin and vasopressin. In general, pituitary adenomas represent benign neoplasms of the anterior lobe.

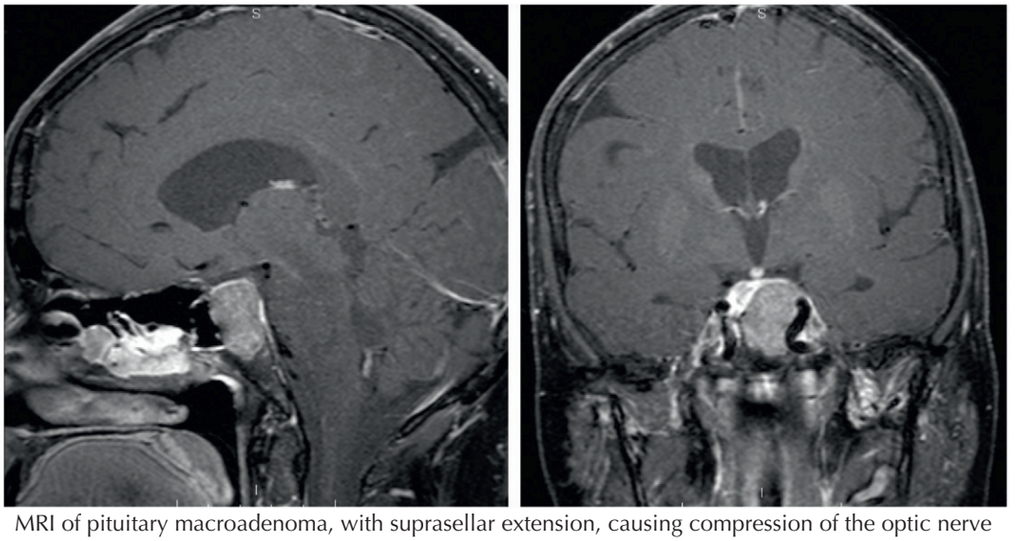
Pituitary tumors are classified according to size, with microadenomas referring to adenomas 10 mm or smaller and macroadenomas to adenomas larger than 10 mm. The tumors can also be categorized according to function with nonfunctioning adenomas, including gonadotroph adenomas, null cell adenomas, and oncocytomas. Hyperfunctioning tumors secrete growth hormone, prolactin, ACTH, and TSH.

Craniopharyngiomas are solid or mixed solid-cystic tumors which arise from the remnants of Rathke's pouch. They are relatively rare and have a bimodal age distribution, with the first peak occurring in children between 5 and 14 years of age, and the second peak developing in adults between 50 and 75 years of age. Males and females appear to be equally affected. Although these tumors are considered benign by histology, they frequently shorten life. Malignant transformation is a rare occurrence.

Clinical Manifestations. In general, the nonfunctioning adenomas cause clinical symptoms by exerting mass effects on neighboring structures. The most common symptom is progressive visual impairment secondary to compression of the optic chiasm from suprasellar growth of the adenoma. Patients may complain of diminished vision in the temporal fields (bitemporal hemianopsia) or decreased visual acuity. Other symptoms caused by a sellar lesion include headaches and diplopia from oculomotor compression. Patients may also present with hyposecretion of hormones resulting from compression of different pituitary cell types by the adenoma. Impaired secretion of LH is the most common deficiency, with females reporting amenorrhea and males complaining of decreased libido.

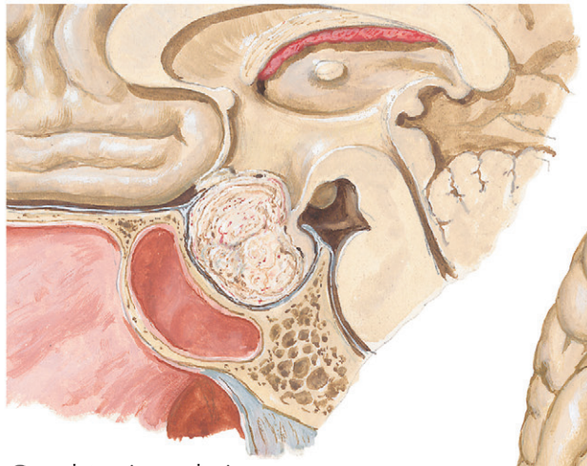




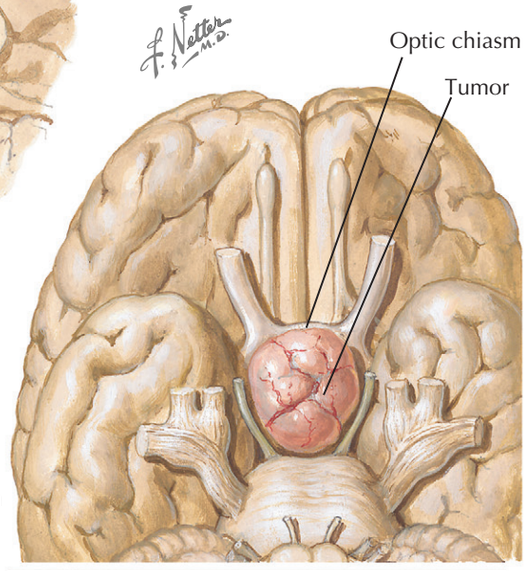


MRI of pituitary macroadenoma, with suprasellar extension, causing compression of the optic nerve

Clinically Nonfunctioning Pituitary Tumor



Gonadotropin-producing adenoma enlarging sella



Compression of optic chiasm by clinically nonfunctioning pituitary macroadenoma

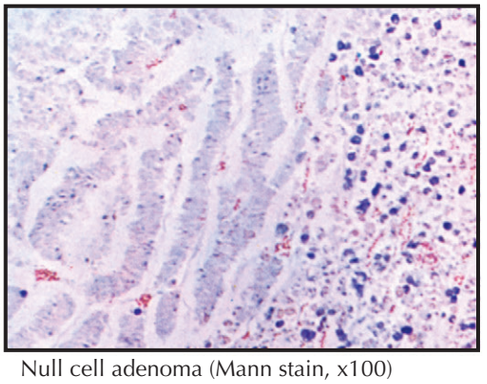
Pituitary Tumors and Craniopharyngiomas *(Continued)*

Hyperfunctioning tumors result in oversecretion of a particular hormone. The most common ones are corticotroph adenomas, lactotroph adenomas, and somatotroph adenomas. Corticotroph adenomas produce an excess of ACTH, resulting in Cushing disease. This is the most serious condition produced by any pituitary tumor and leads to typical body deformities, hyperglycemia, skin hyperpigmentation, hypertension, infertility, and electrolyte imbalances. Lactotroph adenomas cause hypersecretion of prolactin, resulting in hypogonadism in males and females. Females suffer from amenorrhea, infertility, and galactorrhea, and males complain of impotence. Somatotroph adenomas secrete excess growth hormone. In children, gigantism develops, whereas adults manifest with acromegaly, causing tissue overgrowth, metabolic disturbances, cardiovascular problems, sleep apnea, and neuropathy.

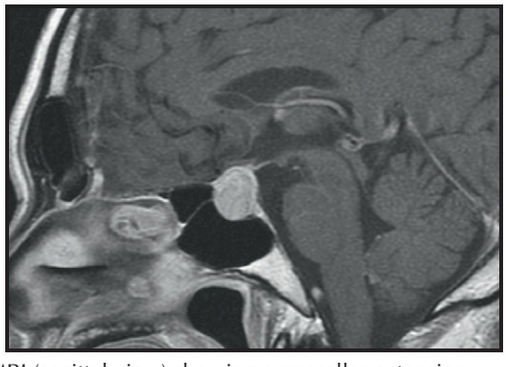
Craniopharyngiomas are typically slow growing with slow onset of symptoms. Visual deficits are a common complaint due to direct pressure of the tumor on the optic chiasm. Hormonal abnormalities can occur with compression of normal pituitary structures. In children, growth failure from hypothyroidism or growth hormone deficiency is the most common presentation, whereas sexual dysfunction is the most common presenting symptom in adults. Other symptoms include headache, depression, and lethargy.

Diagnostic Studies. Magnetic resonance imaging (MRI) has supplanted computed tomography (CT) as the imaging procedure of choice for most sellar masses. On noncontrast images, the normal pituitary gland and pituitary adenomas are isointense to the rest of the brain parenchyma. With dynamic administration of gadolinium contrast, the majority of pituitary adenomas will exhibit early enhancement before the normal gland; when this washes out, the normal pituitary gland will enhance more intensely than the adenoma. Because of the increased risk of associated hormonal dysfunction, a thorough evaluation of the hypothalamic-pituitary axis must be conducted to assess for hormonal excess or deficiency. In those patients in whom the pituitary lesion is discovered incidentally, ophthalmologic and endocrine screening should be performed.

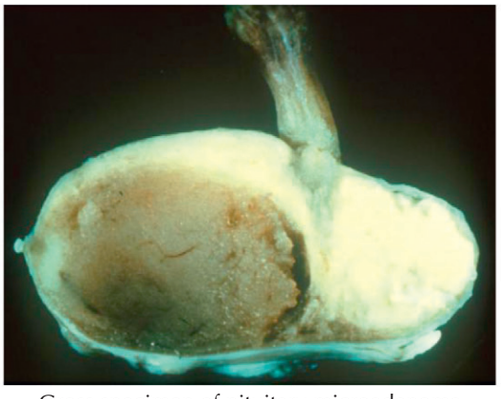
On imaging, craniopharyngiomas typically present as a parasellar mass with calcification and cystic components. In these cases, CT may be the superior diagnostic modality because it highlights calcifications and cystic lesions better than MRI. Occasionally, calcifications are not readily identified on imaging, thus a histologic diagnosis is warranted. Many patients with craniopharyngiomas will have symptoms of hypopituitarism, thus a thorough endocrine evaluation is recommended.



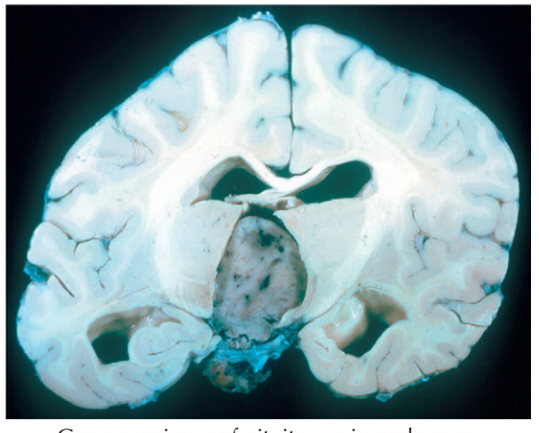
Null cell adenoma (Mann stain, x100)



MRI (sagittal view) showing suprasellar extension of a clinically nonfunctioning pituitary macroadenoma



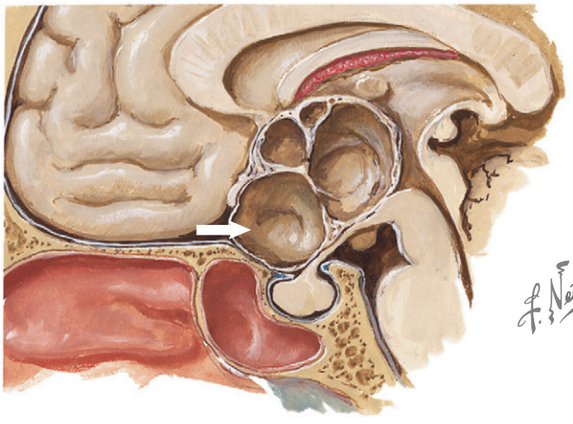
Gross specimen of pituitary microadenoma



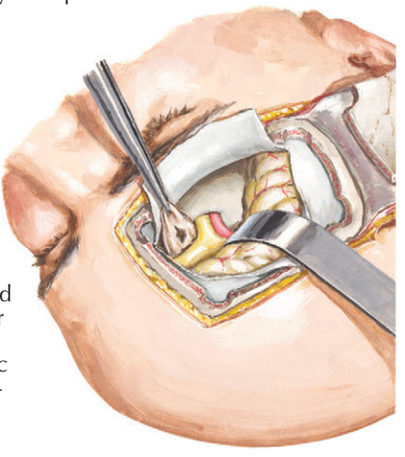
Gross specimen of pituitary microadenoma

Treatment. The primary treatment for nonfunctioning macroadenomas and most hypersecreting adenomas is trans-sphenoidal surgery. Traditionally, most surgeons enter the sphenoid sinus through a variant of the trans-septal approach, which exposes the anterior wall of the sphenoid bone. After the removal of the anterior wall, the bony floor of the sella turcica is removed, and the sella dura is then opened to allow for tumor removal. The most important aspect of the surgery is the preservation of the arachnoid membrane. Low postoperative morbidity depends on preventing blood from entering the cerebrospinal fluid (CSF) during the operation and leakage of CSF postoperatively. Afterward, the muscle is placed in the tumor cavity, occasionally with a piece of nasal cartilage. The mucosal flaps are reapproximated and the nose is packed.

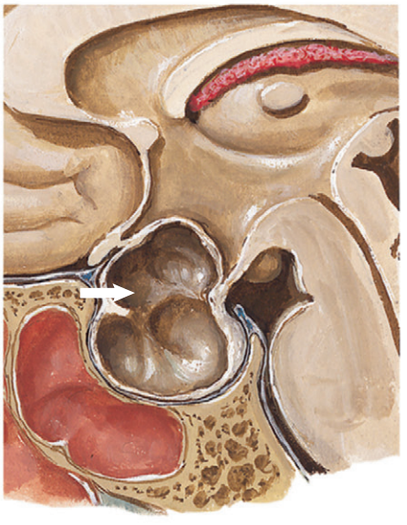
Craniopharyngioma



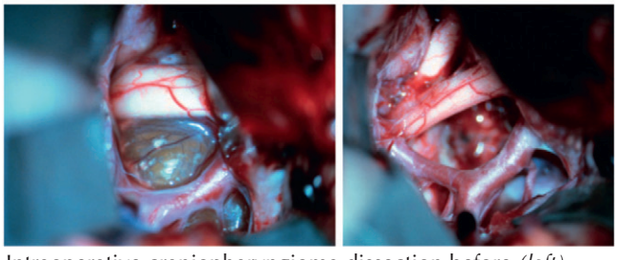
Large cystic suprasellar craniopharyngioma compressing optic chiasm and hypothalamus, filling third ventricle up to interventricular foramen (of Monro), thus causing visual impairment, diabetes insipidus, and hydrocephalus



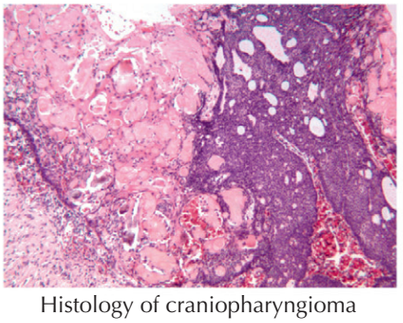
Tumor gently teased forward from under optic chiasm after evacuation of cystic contents via fronto-temporal flap



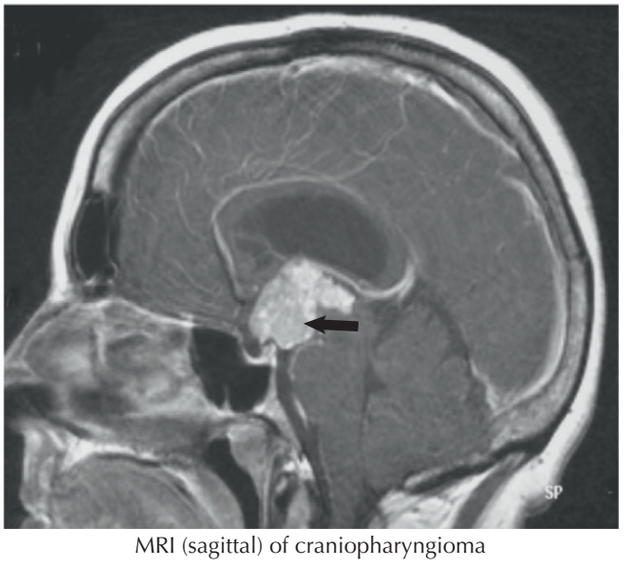
Intrasellar cystic craniopharyngioma compressing pituitary gland to cause hypopituitarism



Intraoperative craniopharyngioma dissection before *(left)* and after *(right)*



Histology of craniopharyngioma



MRI (sagittal) of craniopharyngioma

Pituitary Tumors and Craniopharyngiomas *(Continued)*

In the 1990s, the use of endoscopy to remove pituitary tumors became revitalized. Advantages with this approach include less postoperative swelling, the avoidance of nasal packing, decreased discomfort to the patient, and improvement of intrasellar and suprasellar visualization. In general, the endoscope is advanced into the choana, and the sphenoid ostium is identified. With the bilateral approach, the nasal septum is removed, revealing the sphenoid sinus. This allows visualization of the floor of the sella, which is then opened. After the dural covering is opened, the pituitary tumor is exposed, allowing removal. Before closure, careful examination for CSF leak is performed. If there is no evidence of a leak, the floor of the sella is reconstructed. Occasionally, the trans-sphenoidal approach is not ideal, such as when there is significant tumor extension into the cranial fossa or with extreme suprasellar extension. In those cases, a transcranial approach is used via craniotomy. The tumor is then carefully removed via microdissection.

With surgery, about 87% of patients have reported improvement in preoperative visual deficits, and many patients have reported improvement in preoperative endocrine deficits. Recurrence can occur but is rare in those who have undergone a complete resection. In those patients with residual disease, adjuvant radiotherapy or medical therapy can be considered, including dopamine, gonadotropin-releasing hormone, and somatostatin agonists. Radiation treatment runs the risk of affecting critical neighboring structures and does not have the advantage of significant cytoreduction. Stereotactic radiosurgery and stereotactic radiotherapy have improved the safety and effectiveness of irradiation.

Prolactinomas, on the other hand, respond well to medical therapy. Dopamine agonists can effectively normalize prolactin levels, normalize vision, and decrease tumor size in the majority of patients. Occasionally, the tumors are resistant to medical therapy, or patients are unable to tolerate them; in those cases, trans-sphenoidal surgery is advocated. Much interest has surrounded the role of medical therapy with growth hormone–secreting adenomas; however, no drug has been found to consistently reduce tumor volume by a significant amount.

Incidentally found pituitary adenomas are increasingly common. Conservative management is reasonable if the lesion is less than 10 mm and there is no evidence of neurologic and endocrinologic abnormalities.

Craniopharyngiomas can be treated either with surgery or a combination of surgery followed by radiotherapy. Surgery allows for a diagnosis, debulking of the tumor, and a chance of surgical cure. Radiation, either stereotactic radiotherapy or radiosurgery, is used to treat those incompletely resected tumors or those that have recurred after prior surgery. With modern advances in both the surgical and radiation fields, the risk of treatment-related side effects has improved, although survivors often have multiple hormonal deficiencies, pathologic obesity and disturbed sleep patterns from injury to the adjacent hypothalamus, permanent loss of peripheral vision, and disorders of memory and information processing.

Tumors of Pineal Region

Pineal tumors can be generally divided into primary intracranial germ cell tumors (GCTs) and nongerm cell tumors. GCTs typically arise in midline structures, such as the pineal and suprasellar regions. They commonly spread via the ventricular and subarachnoid space to the third ventricles and spinal cord, although extraneural spread outside the central nervous system (CNS) is quite rare. GCTs are further subdivided into germinomas and nongerminomatous germinomas. Despite their undifferentiated histopathology, germinomas are readily cured by radiation. They tend to occur in adolescence and young adulthood. Nongerminomatous germinomas, or mixed germ cell tumors, are composed of several lineages of cells, and are distinguished by their relative radioresistance and poorer prognosis. They predominate in younger children. Mature teratomas generally have a good prognosis after total surgical resection.

Non–germ cell tumors include pineal parenchymal tumors, glial tumors, and metastasis from systemic tumors. Pineal parenchymal tumors are traditionally classified as the lower-grade pineocytoma and the malignant pineoblastoma. Pineocytomas occur in middle-aged adults and are thought to be locally invasive. They are frequently managed with aggressive surgical resection and local radiotherapy for any residual tumor. Pineoblastomas resemble medulloblastomas histologically and predominate in the pediatric population. They are treated with multimodal therapy, which consists of maximal surgical resection followed by craniospinal irradiation and adjuvant chemotherapy, and they typically have a poor prognosis. Glial tumors may be low grade or high grade and are identical to glial neoplasms that occur elsewhere in the CNS. Because of their location, which is less accessible by surgery, they tend to have a poorer prognosis. Finally, cysts and meningiomas can also be found in the pineal region.

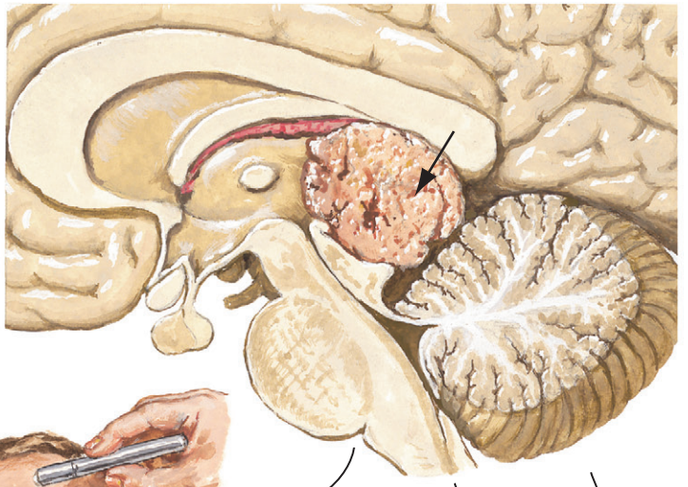
Clinical Manifestations. Clinical presentation of pineal region tumors include increased intracranial pressure from hydrocephalus, tectal dysfunction, and endocrinopathies. Obstruction of the third ventricle and cerebral aqueduct results in increased intracranial pressure, which manifests as headache, nausea, vomiting, lethargy, and papilledema. Because the lesions are located in the posterior aspect of the third ventricle, compression of the tectum often ensues. This can lead to Parinaud syndrome, which consists of vertical upward gaze paralysis, decreased or absent pupillary response to light, and convergence retraction nystagmus. Occasionally, cerebellar signs, such as ataxia and tremor, are seen with more extensive growth.

Diagnostic Studies. Neuroimaging is the first step in identifying a pineal region lesion. MRI with and without contrast is preferred because it outlines the tumor anatomy better than CT. Germinomas and pineal parenchymal tumors tend to have mixed T1 signal and increased T2 signal. Calcifications occur less frequently than in teratomas. Benign teratomas are well circumscribed and have mixed densities secondary to large cysts, areas of calcifications, and the occasional presence of teeth and hair. Although characteristic radiographic findings may be seen, they cannot substitute for histologic diagnosis.

Other studies include examination of tumor markers in the CSF. For mixed germ cell tumors, elevated alpha fetoprotein (AFP) levels confirm the presence of nongerminoma elements and high human chorionic gonadotropin (hCG) levels indicate a diagnosis of choriocarcinoma. The CSF should also be examined for the presence of malignant cells as a means to confirm the extent of disease, which can impact treatment planning.

Treatment. In general, surgery is almost always indicated for several reasons: establishment of a tissue diagnosis, symptomatic relief of hydrocephalus, and for therapeutic resection in anticipation of adjuvant treatment. For germinomas, extensive resection is not indicated; however, there is debate whether patients with nongerminomas benefit from radical surgery due to their decreased responsiveness to radiotherapy.

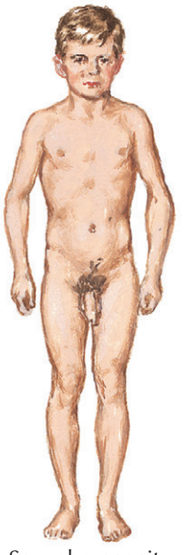
Radiation treatment is the standard treatment for pure germinomas. With radiation, long-term survival rates approximate 80% to 90%. However, this leads to genuine concerns for the potential delayed effects of therapy, such as neuroendocrine deficits, and neurocognitive deficits. Currently, there is much interest surrounding the use of chemotherapy in an effort to reduce the dose of irradiation used. Radiation is often combined with chemotherapy for treatment of nongerminomatous germinomas, which have a significantly poorer prognosis.



Tumor compressing mesencephalic tectum and corpora quadrigemina, occluding cerebral aqueduct (of Sylvius), and invading 3rd ventricle

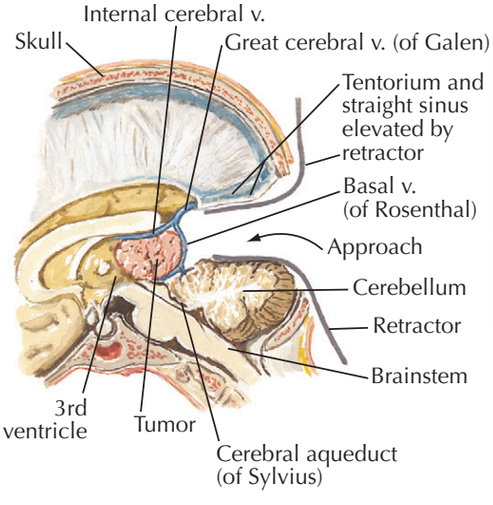
Parinaud syndrome: paresis of upward gaze, unequal pupils, loss of convergence

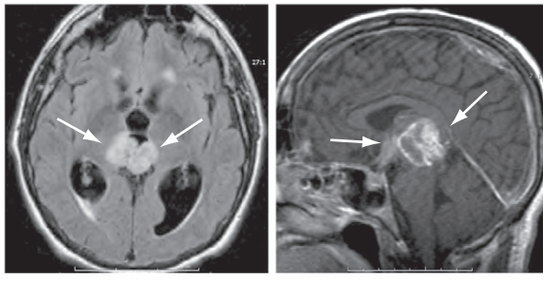
Diabetes insipidus in some patients



Sexual precocity in boys may occur

Anatomic aspects of exposure





Pineoblastoma. Axial FLAIR and sagittal T1-weighted gadolinium-enhanced images show a large mass in the pineal region, bright on FLAIR imaging, heterogeneous after gadolinium enhancement, compressing the aqueduct with enlargement of the third and lateral ventricles

Vestibular Schwannomas

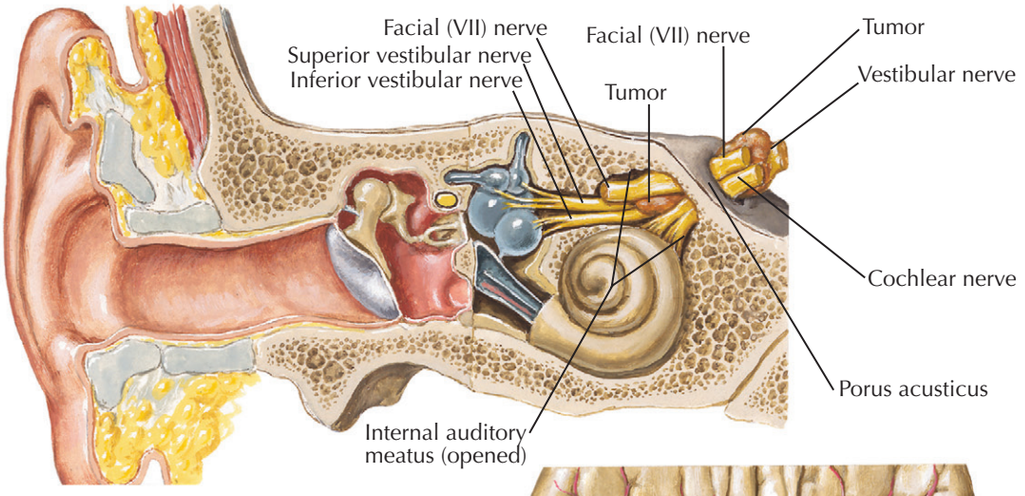
Vestibular schwannomas are tumors derived from Schwann cells surrounding the vestibular portion of the eighth cranial nerve. They are known by many different names, including acoustic neuromas, acoustic schwannomas, acoustic neurinomas, and vestibular neurilemmomas. They are more common in adults and constitute the overwhelming majority of tumors found at the cerebellopontine angle (CPA). The median age of diagnosis is about 50 years of age, and most tumors are unilateral. Bilateral vestibular schwannomas occur only in patients with an underlying diagnosis of neurofibromatosis type-2 (NF-2), a genetic disorder that predisposes to a variety of tumor types. Vestibular schwannomas are quite rare in children, usually occurring in association with NF-2.

Histologically, vestibular schwannomas appear quite similar to peripheral schwannomas. On a microscopic level, there are zones of dense and sparse cellularity, identified as Antoni A and B areas, respectively. They are typically benign, with malignant transformation a very rare occurrence.

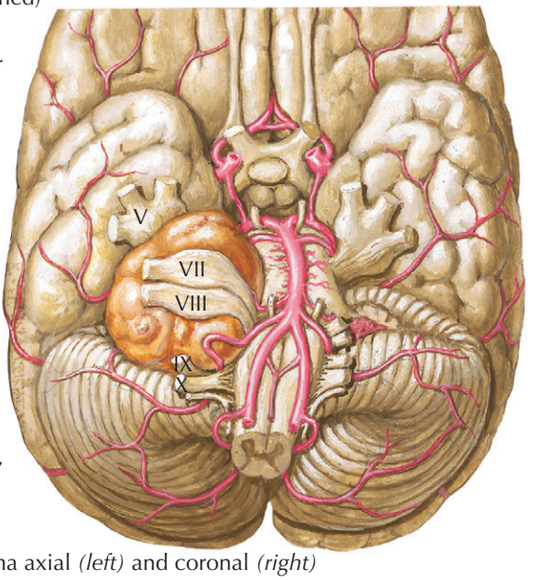
Clinical Manifestations. Clinical signs and symptoms result from cranial nerve involvement or mass effect on the cerebellum and other posterior fossa structures. Symptom onset is usually insidious, given the slow rate of growth of these tumors. Almost all patients will present with hearing loss and tinnitus secondary to cochlear nerve involvement, although patients may not necessarily be aware of their deficits. In a study of 1000 patients, 95% of patients were found to have hearing loss, but only two thirds of patients recognized their limitations. Rarely, patients will have the acute onset of hearing loss secondary to compression of the vascular supply to the auditory nerve. More than half of patients will also have involvement of the vestibular nerve with complaints of gait unsteadiness. Although true vertigo is uncommon, given the slow onset of symptoms, patients may complain of nonspecific dizziness. A minority of patients will have trigeminal involvement that can produce symptoms ranging from facial numbness to trigeminal neuralgia. Involvement of the seventh cranial nerve is rare but can occur with the onset of facial weakness, hemifacial spasm, or taste disturbance. Finally, mass effect of the tumor can cause various types of neurologic dysfunction. Compression of the cerebellum can result in ataxia, and disruption of the lower cranial nerves can cause dysarthria, dysphagia, and aspiration. Involvement of the brainstem can lead to hydrocephalus, coma, and even death.

Diagnostic Studies. When suspicion for a vestibular schwannoma is raised, pure tone and speech audiometry should be performed as an initial screening test. Typically, results will reveal asymmetric hearing loss, especially with high frequencies. Speech discrimination is reduced in the affected ear and is usually out of proportion to the measured hearing loss. Another screening measure used is brainstem-evoked response, which detects a delay on the affected side. However, it had a relatively low sensitivity and specificity compared with magnetic resonance images (MRIs), especially with smaller lesions. Thus MRI has becomes the diagnostic modality of choice when suspicion for a vestibular schwannoma is raised. Specifying fine cuts (3-mm slices or less) through the internal auditory canal (IAC) may increase the sensitivity and specificity even further. Computed tomography (CT) scans with bone windows are also useful because the extent of tumor growth in the IAC has prognostic significance. It should be noted that the diagnosis of a vestibular schwannoma is based on the clinical history (asymmetric hearing loss) in conjunction with audiometry and imaging because they constitute the majority of posterior fossa lesions that behave in this manner. These lesions are rarely biopsied. Nonetheless, other considerations include meningiomas, schwannomas of other cranial nerves, hemangiomas, gliomas, metastatic tumor, aneurysms, and arachnoid cysts.

Vestibular Schwannomas

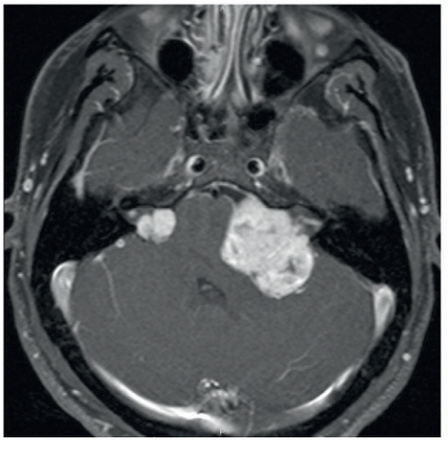


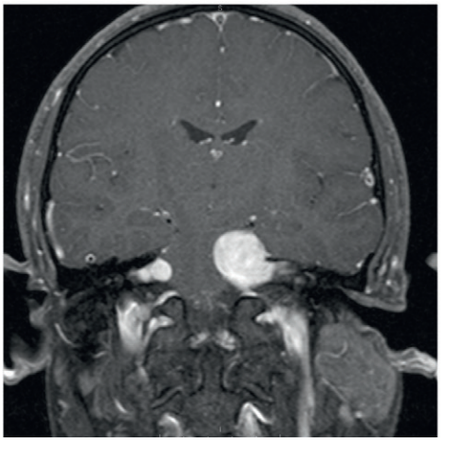
Small schwannoma arising from superior vestibular nerve in internal auditory meatus and protruding into posterior fossa



Large acoustic neurinoma filling cerebellopontine angle, distorting brainstem and cranial nerves V, VII, VIII, IX, X

MRI of vestibular schwannoma axial *(left)* and coronal *(right)*





Vestibular Schwannomas
(Continued)

Treatment. The natural history of vestibular schwannomas is highly variable, with some tumors experiencing little to no growth and others enlarging quite rapidly. The main treatment is surgery, which is potentially curative after gross total resection. Three standard approaches are generally used: retromastoidsuboccipital (retrosigmoid), translabyrinthine, and middle fossa. The choice of a particular approach depends on size of the tumor and whether hearing preservation is attempted. The translabyrinthine approach is reserved for tumors 3 mm or smaller when hearing preservation is not an issue, and the middle fossa approach attempts to preserve hearing while resecting tumors 1.5 mm or smaller. Surgical morbidity includes hearing loss, facial weakness, vestibular dysfunction, CSF leakage, and persistent headaches.

The retromastoid suboccipital approach can be used for any size tumor with or without attempts to preserve hearing. This technique allows the tumor and the important structures medial and lateral to it to be in full view in the surgical field. In general, an incision is made to the tip of the mastoid eminence. After separation of the underlying muscles, a bony opening is made, extending laterally to the sigmoid sinus. The surgeon carefully tries to preserve the planes of the arachnoid over the tumor, to protect the delicate cranial nerves and brainstem. To the right, the fifth cranial nerve and petrosal vein are seen; toward the lower portion of the field, the glossopharyngeal (IX), vagus (X), and accessory (XI) nerves are visible.

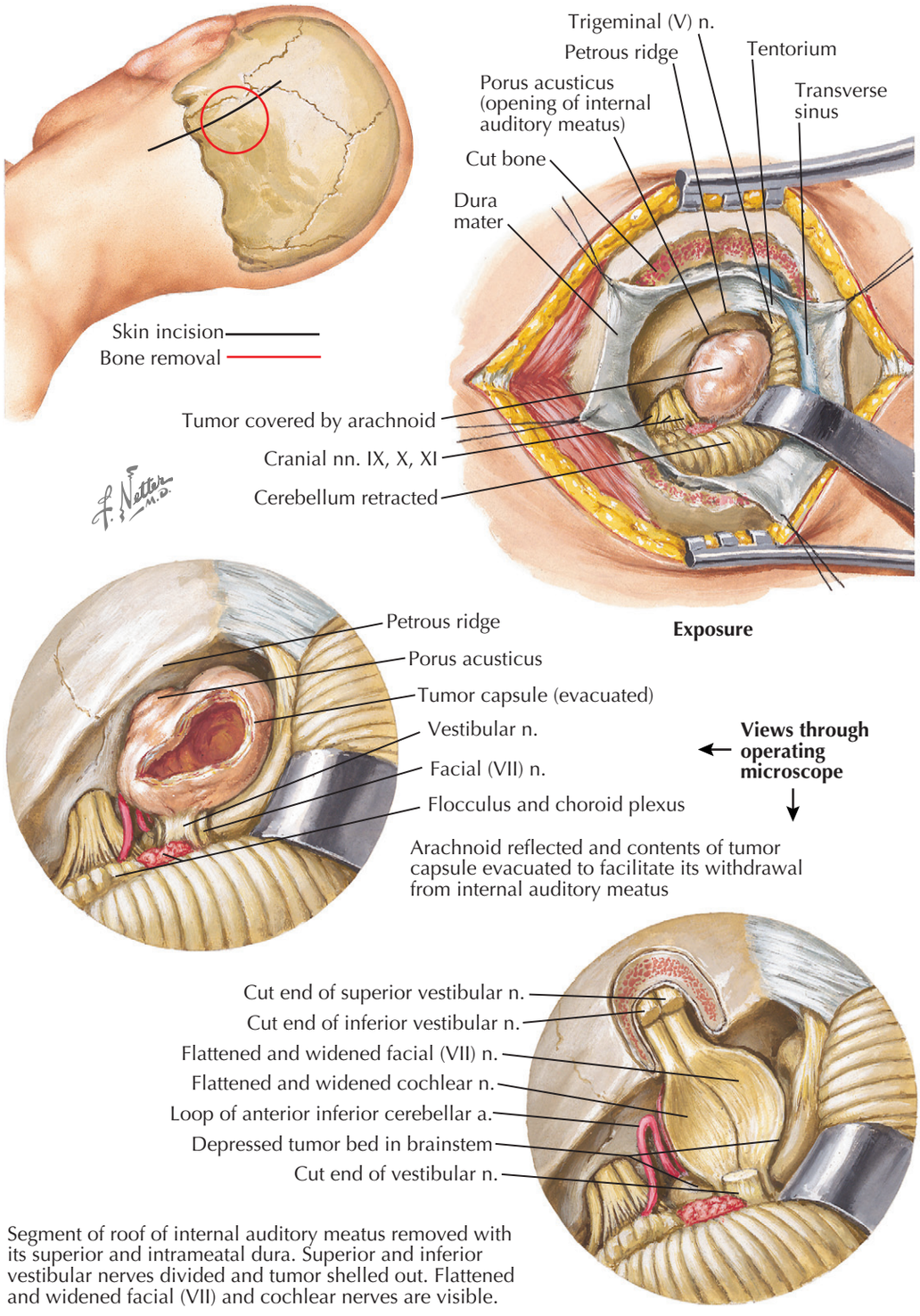
When the tumor grows in the posterior portion of the canal, the facial nerve tends to be pushed forward. Knowing this relationship is important in preserving the facial nerve, which is markedly flattened and often quite adherent just medial to the internal auditory meatus. The vestibular nerves, from which the tumor is arising, must be sectioned. If hearing has not already been irreversibly damaged, preservation of hearing may be attempted by minimizing manipulation of the cochlear nerve and protecting the labyrinthine artery, which may be a source of blood supply to the tumor. The anterior inferior cerebellar artery, which supplies the lateral portion of the brainstem and cerebellar peduncles, is another important structure to which the surgeon must be mindful.

With a larger tumor, the capsule is gutted at an early stage to facilitate atraumatic manipulation. In the second drawing above, the 9th, 10th, and 11th cranial nerve complex is visible, passing through the jugular foramen with the accompanying sigmoid sinus. The bottom drawing at right illustrates a view after the tumor has been excised. The labyrinthine artery has been preserved, and the relationship of the four main nerves in the canal is seen. Because a CSF leak through the lateral portion of the canal can develop, the lateral canal is plugged with fat and bone wax.

For patients who are not surgical candidates, stereotactic radiosurgery (SRS) and stereotactic fractionated radiotherapy have been used. Stereotactic radiosurgery focuses the beams in a single dose to a discrete tumor volume in an effort to decrease the risk of damage to neighboring structures. One large series documented a 97% tumor control rate at 10 years with SRS. Fractionated stereotactic radiation focuses the radiotherapy over a series of treatments to minimize the risk of damage to critical structures. One prospective study comparing SRS with stereotactic radiotherapy documented a 97% tumor control rate for both treatments with a higher rate of hearing preservation with the fractionated stereotactic radiotherapy. Potential concerns for radiotherapy is the risk of cranial nerve injury, secondary tumor formation, and scarring, rendering future surgeries more precarious.

Finally, conservative management is used in select patients, especially those with small symptomatic tumors or who are deemed poor candidates for immediate intervention. In these patients, close monitoring with surveillance MRIs is warranted.

Removal of Vestibular Schwannoma: Translabyrinthine Approach



Segment of roof of internal auditory meatus removed with its superior and intrameatal dura. Superior and inferior vestibular nerves divided and tumor shelled out. Flattened and widened facial (VII) and cochlear nerves are visible.

Intraventricular Tumors

Intraventricular tumors are composed of a histologically heterogenous group of tumors, with the most common being ependymomas. Ependymomas are frequently found within the fourth ventricle and are thought to derive from the primitive neuroepithelial cells lining the ventricles and central canal of the spinal cord. They are generally well demarcated, with low incidence of cerebrospinal fluid (CSF) dissemination. In adults, the most common intracranial location affected is the fourth ventricle. Other intraventricular tumors include gliomas, subependymomas, neurocytomas, germ cell tumors, choroid plexus tumors, meningiomas, and pineal region tumors. Most of the other histologic subtypes tend to occur in the lateral ventricles with the exception of germ cell tumors, which can be seen in the third ventricle.

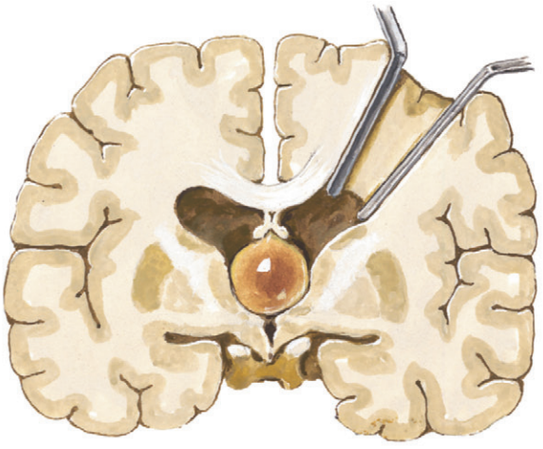
Lateral ventricle tumors, while varying in pathology, all arise from cells located within or around the ventricular walls. About half of lateral ventricular tumors consist of low-grade gliomas with choroid plexus papillomas and meningiomas, accounting for about 35%. Subependymal giant cell astrocytoma (SEGA) is a variant of astrocytomas and is found in patients with tuberous sclerosis. These are generally asymptomatic lesions, but can obstruct CSF flow. Choroid plexus tumors are most commonly seen in children, although they can occur in adults. Histology is the most important prognostic factor with choroid plexus papillomas having a much better prognosis than choroid plexus carcinomas. The remainder is made up of neurocytomas, congenital tumors, ependymomas, and metastasis. Neurocytomas are rare tumors, commonly found near the septum pellucidum near the foramen of Monro. They are very slow growing and histologically low grade.

Not all intraventricular lesions represent neoplasm. The colloid cyst is a benign remnant of the embryonic paraphysis and often seen in the intraventricular foramen of Monro, producing obstructive hydrocephalus. Some neurosurgeons approach the cyst through a cortical incision into the hydrocephalic right lateral ventricle or through the corpus callosum. Both approaches are satisfactory, although there is risk of neurologic damage.

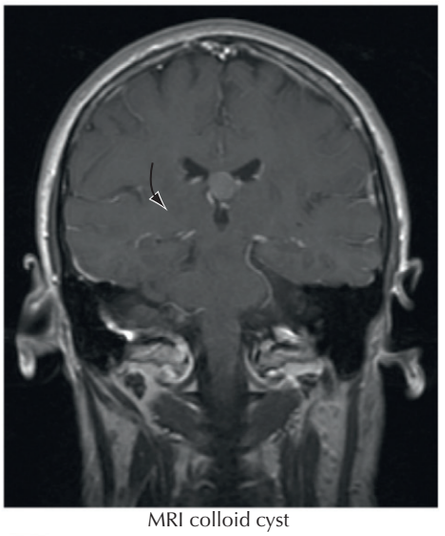
Clinical Manifestations. The most common sign and symptom with intraventricular tumors is hydrocephalus. The onset is usually insidious because the majority of the tumors are slow growing. Lesions occurring in the pineal region and third ventricle can cause Parinaud syndrome secondary to compression of the quadrigeminal plate.

Diagnostic Studies. MRI allows for easy visualization of the tumor. Subependymomas and neurocytomas often present as a heterogenous cystic lesion. SEGAs are found near the foramen of Monro and are characterized by calcifications and intense enhancement in the context of other stigmata associated with tuberous sclerosis. Choroid plexus tumors are heavily lobulated and appear as a vascular tumors centered on the choroid. As stated earlier, a complete diagnostic evaluation for ependymoma includes imaging of the entire neuroaxis and examination of the CSF.

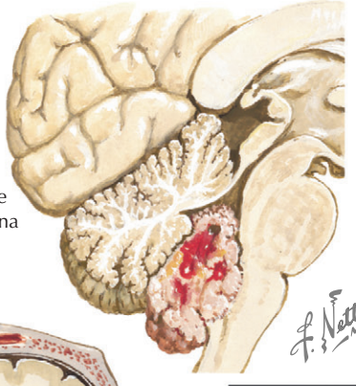
Treatment. Treatment varies, depending on the histology. Surgery is the mainstay of treatment for ependymomas, with a total or near-total resection a favorable prognostic factor. Resection of infratentorial ependymomas is technically more challenging than that of their supratentorial counterpart and associated with higher surgical morbidity. Nonetheless, attempt at gross total resection is crucial for management of ependymomas. Historically, adjuvant radiation treatment has been used based on results from retrospective studies showing that patients who received postoperative radiation had a better prognosis than those patients who only had surgery. The role of chemotherapy remains unclear, although it has been used in young children in an attempt to deter radiation. Subependymomas and neurocytomas have excellent prognosis with surgical resection without a need for adjunct therapy. Those choroid plexus tumors that can be completely excised have improved prognosis compared with those treated with subtotal resection. Radiotherapy has been associated with significantly better survival in choroid plexus carcinomas. Unfortunately, the rarity of these tumors results in limited information regarding their natural history and the optimal treatment.



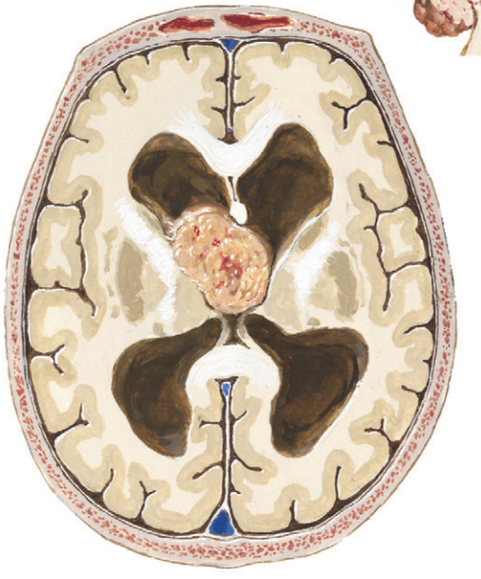
Colloid cyst of 3rd ventricle and surgical approach via right prefrontal (silent) cerebral cortex. May also be approached through corpus callosum *(arrow)*. Note enlarged lateral ventricles (posterior view).



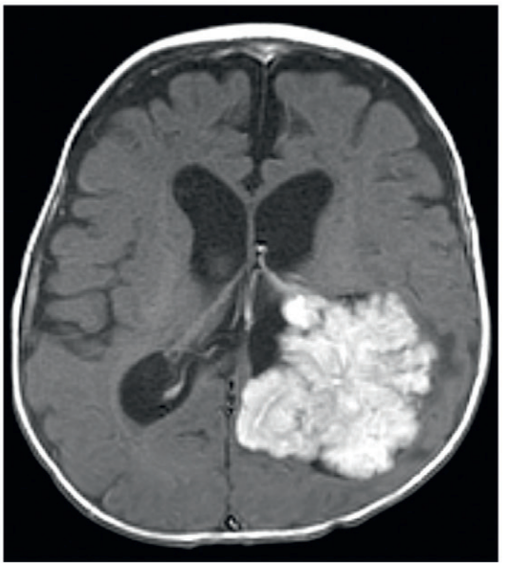
MRI colloid cyst



Ependymoma of 4th ventricle protruding into cisterna magna

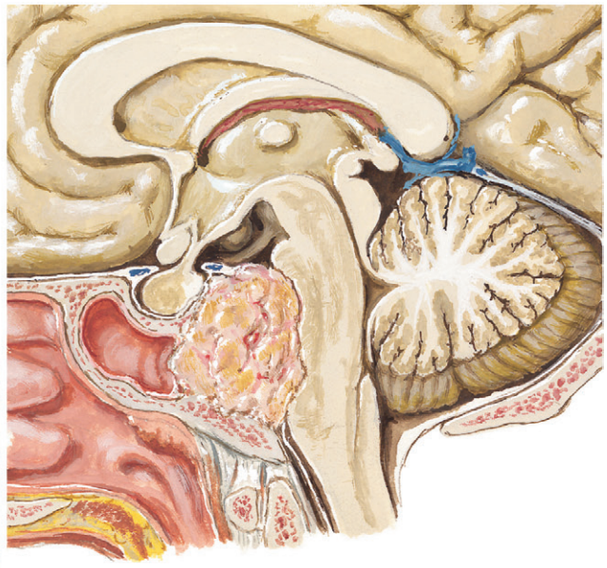


Subependymoma of anterior horn of left lateral ventricle obstructing interventricular foramen (of Monro), thus producing marked hydrocephalus



MRI of choroid plexus papilloma

Chordomas of clivus compressing pons and encroaching on sella turcica and sphenoid sinus



CHORDOMAS

Chordomas are slow growing, locally aggressive neoplasms that arise from the unabsorbed remnants of the embryonic notochord, a mesodermal structure running through the center of the vertebrae and into the clivus. These tumors may occur anywhere along the axial skeleton but are most common in the spheno-occipital region of the skull base and sacral regions of the spine. In adults, 35% arise in the skull base, 50% involve the sacrococcygeal region, and the rest occur elsewhere along the vertebral column. In general, skull base chordomas affect younger adults, whereas older patients tend to develop the tumors in the sacrococcygeal region. There appears to be a male predominance.

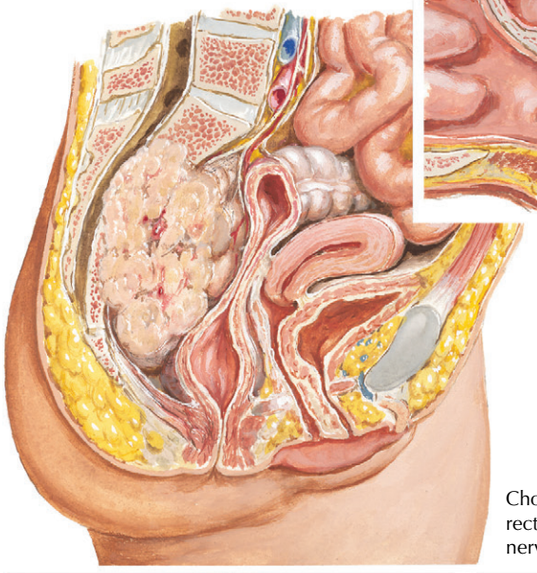
Chordomas can be classified into three subgroups. The most common are the conventional chordomas, which are distinguished by the absence of mesenchymal elements such as cartilage. On histologic examination, lobules of epithelioid cells are arranged in cords, separated by a mucinous matrix. Tumor cells have vacuolated, bubbly cytoplasm, earning the name "physaliphorous cells." Nuclear pleomorphism and mitoses are rare. Chondroid chordomas contain chondromatous and chondromatous features and often occur in the spheno-occipital region. Both the conventional chordomas and chondroid chordomas have similar prognoses. The third type includes chordomas that undergo sarcomatous transformation; these have a worse prognosis because they behave more aggressively. Histologically, the sarcomatous component is interspersed between areas of conventional chordoma. Although chordomas are slow growing, they tend to recur and occasionally metastasize.

Clinical Manifestations. Signs and symptoms depend on the location of the tumor and its effect on neighboring structures. Local pain is a common complaint. With skull base involvement, patients often complain of headache and diplopia secondary to invasion of the cavernous sinus. Involvement of the lower clivus may affect the lower cranial nerves, resulting in dysphagia or hoarseness, followed by brainstem compression. Because the onset of symptoms is quite insidious and vague, diagnosis is often delayed. Tumors of the spinal column and sacrum can cause back pain. Direct compression from spinal column tumors can lead to cord compression. Occasionally, the tumors of the sacrococcygeal region may reach enormous proportions, resulting in bladder and bowel dysfunction due to direct pressure on the rectum and involvement of sacral nerves.

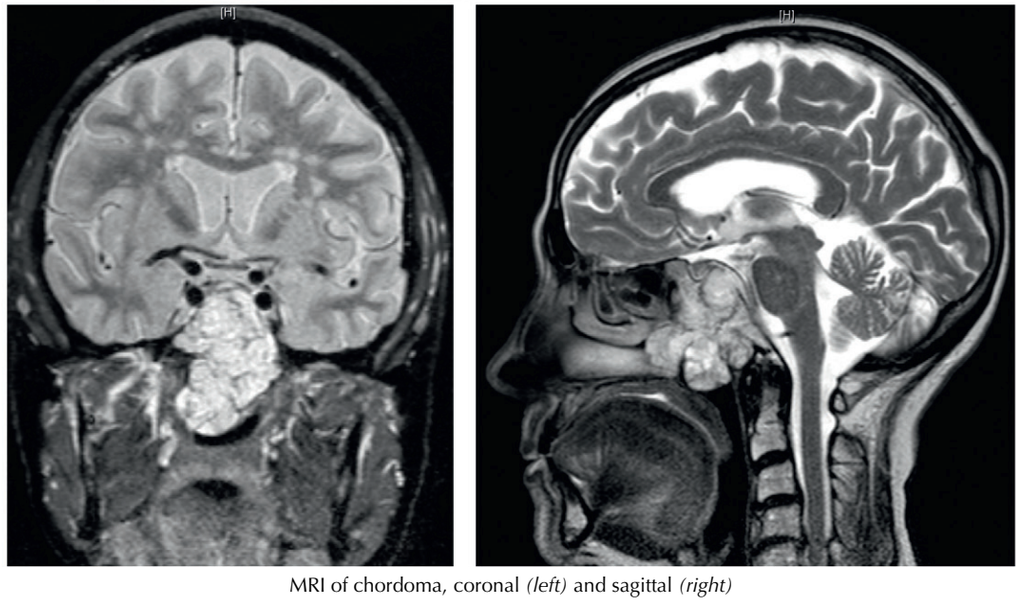
Diagnostic Studies. Both MRI and CT are used for diagnostic purposes. MRI provides detailed anatomy, providing the ability to assess the extent of soft tissue and dural involvement. CT is more effective for delineating bony lesions. There is no pathognomonic imaging findings, thus histopathologic examination from a tissue specimen is required for a definite diagnosis.

Treatment. Because of the rarity of the tumor, there are no set guidelines for treatment of chordomas. Based on small retrospective studies, a multimodal approach, combining surgery with radiotherapy, is recommended. Surgery is used for both diagnostic and therapeutic purposes; it allows for a tissue diagnosis and reduces tumor burden. Complete resection is the goal but often not feasible due to the anatomic constraints of the tumor. Their invasive nature results in a high incidence of local recurrence, and about 2% to 8% of chordomas will undergo sarcomatous transformation. Salvage therapy may include repeat surgery or radiation treatment.

Adjuvant radiotherapy has been employed with increasing frequency, especially with current advances in radiation equipment and technique. Historically, conventional radiation with photons was difficult to administer because the required doses were often associated with increased risk of damage to important structures such as the brainstem or cranial nerves. With newer techniques using proton therapy, stereotactic radiosurgery, or intensity modulated radiation therapy (IMRT), outcomes have significantly improved by allowing higher doses of radiation while minimizing injury to neighboring structures.

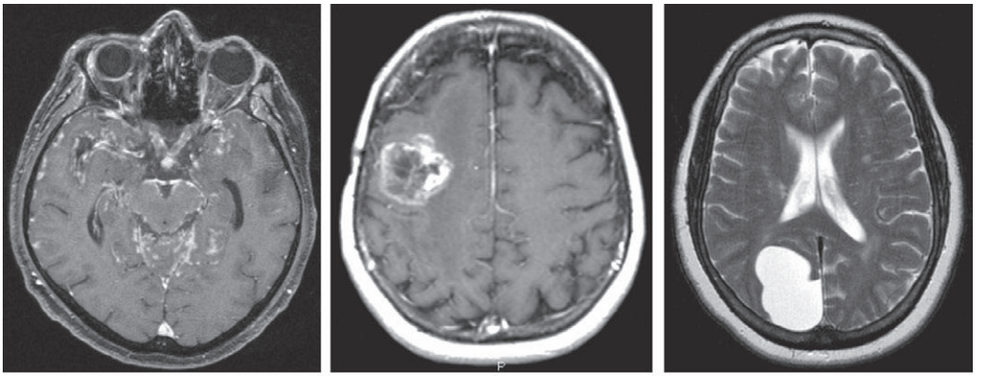


Chordoma of sacrum bulging into pelvis, compressing rectum and other pelvic organs, as well as vessels and nerves

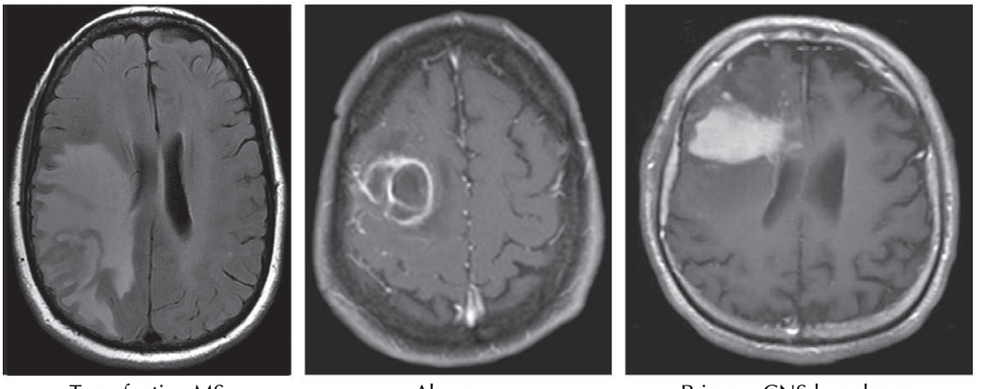


MRI of chordoma, coronal *(left)* and sagittal *(right)*

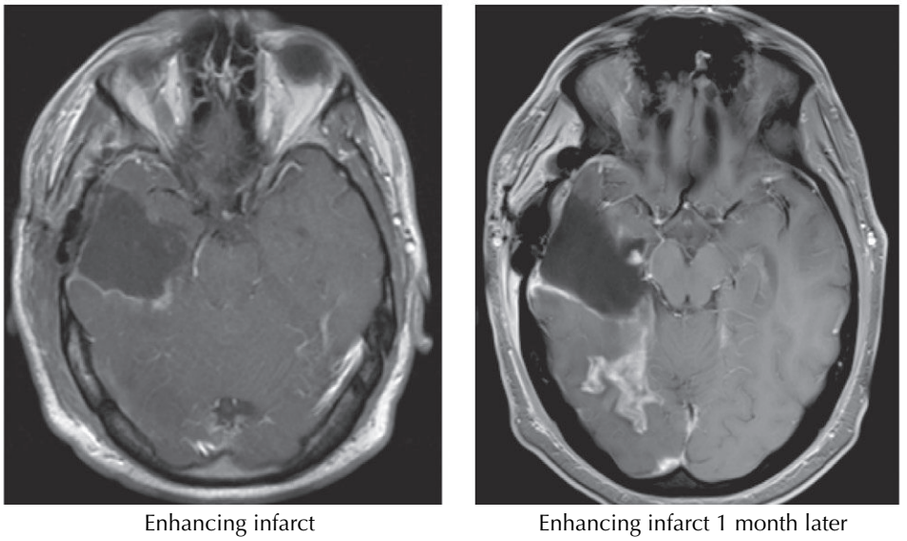
Differential Diagnosis of Central Nervous System Tumors



Neurosarcoid | Radiation necrosis | Arachnoid cyst



Tumefactive MS | Abscess | Primary CNS lymphoma



Enhancing infarct | Enhancing infarct 1 month later

Although advances in imaging have increased the incidence of CNS tumor diagnosis, other brain lesions can appear similar to neoplasms. Mimics include inflammatory lesions (secondary to demyelination), autoimmune disease, infection, and/or radiation necrosis. These lesions are often expansile masses, resulting in similar clinical manifestations, highlighting the importance of histopathologic examination. In this section, we will consider the some of the differential diagnosis of brain tumors.

Multiple Sclerosis. Multiple sclerosis (MS) is the most common demyelinating disease of the central nervous system. Imaging typically reveals multiple lesions in a characteristic pattern, such as "Dawson's fingers" (periventricular lesions oriented perpendicular to the long axis of the lateral ventricle on fluid attenuated inversion recovery [FLAIR] sequences). These plaques have very little mass effect. Active lesions are usually enhancing, representing the breakdown of the blood-brain barrier. Tumefactive MS is a special subtype that affects patients in the second or third decade. Imaging reveals large (>2 cm) tumor-like masses that demonstrate incomplete ring enhancement with the incomplete area abutting the cortical gray matter or basal ganglia. These lesions can be associated with mass effect and vasogenic edema. Unlike hypercellular brain tumors, these lesions tend to have a relatively low cerebral blood volume on perfusion imaging and an increased apparent diffusion coefficient (ADC) on diffusion sequences. Furthermore, magnetic resonance spectroscopy can help distinguish demyelinating lesions from neoplasm. Appreciation of the clinical history in conjunction with ancillary testing, such as cerebrospinal (CSF) studies or evoked potentials, may aid in the differentiation of demyelinating disease from CNS tumors.

Sarcoidosis. Sarcoidosis is a multisystem granulomatous disease that can affect the central nervous system. About 5% of known sarcoidosis patients will manifest with neurosarcoidosis, although de novo presentation is also possible. It initially develops in the leptomeninges, allowing entry of the inflammatory process into the brain parenchyma, where granulomatous masses can develop. There is a predilection for cranial nerves, hypothalamus, and the pituitary gland, but any part of the central nervous system can be affected. On imaging, neurosarcoidosis can present with meningeal or pachymeningeal enhancement in association with nonenhancing periventricular white matter lesions. With cranial nerve involvement, enhancement along the nerves can be seen, although the extracranial portion is affected more often. Less common are enhancing granulomatous nodules in the parenchyma and dural mass lesions. With the relatively high frequency of leptomeningeal involvement, neurosarcoidosis can be mistaken for carcinomatous meningitis. Again, clinical history, systemic imaging, and CSF studies must be considered in distinguishing the two.

Radiation Effects. Since the establishment of chemoradiation as the standard of care for glioblastoma, there has been an increasing awareness of a phenomenon termed "pseudoprogression," in which post-treatment imaging reveals the presence of enhancing lesions secondary to radiation injury, resulting in increased capillary permeability and breakdown of the blood-brain barrier. Eventually, these lesion decrease in size or stabilize without the need for further treatment. Evidence suggests that these treatment-related effects occur more frequently with the use of temozolomide and significantly correlate with O6-methylguanine–DNA-methyltransferase (*MGMT*) promoter methylation status. Clinically and radiographically, pseudoprogression can appear and behave identically to true tumor progression. Adjunct studies, such as dynamic susceptibility-weighted contrast-enhanced magnetic resonance imaging and positron emission tomography (PET) scans, may be useful. Pseudoprogression typically exhibits low cerebral blood volume and is "cold" on PET imaging, whereas tumor progression will have elevated cerebral blood volume and be metabolically active. Occasionally, biopsy of the lesion may be necessary to establish the correct diagnosis and appropriate management.

Cerebral Abscess. Intracranial abscesses can appear very similar to cystic or necrotic brain tumors. Both appear as ring-enhancing lesions with associated mass effect, causing associated neurologic deficits. Fever is not always present and is only found in less than half of patients. Other parameters diagnostic for infection, such as leukocytosis, elevated erythrocyte sedimentation rate (ESR), and positive blood cultures, are not reliably present in patients affected by cerebral abscess. Studies such as lumbar puncture are less useful because findings are often nonspecific and cultures are rarely positive. Proton magnetic resonance spectroscopy (MRS) and diffusion-weighted imaging have both been reported to be helpful in distinguishing abscesses from nonpyogenic lesions, with abscesses displaying a specific metabolite profile on MRS and hyperintense signal on diffusion imaging.

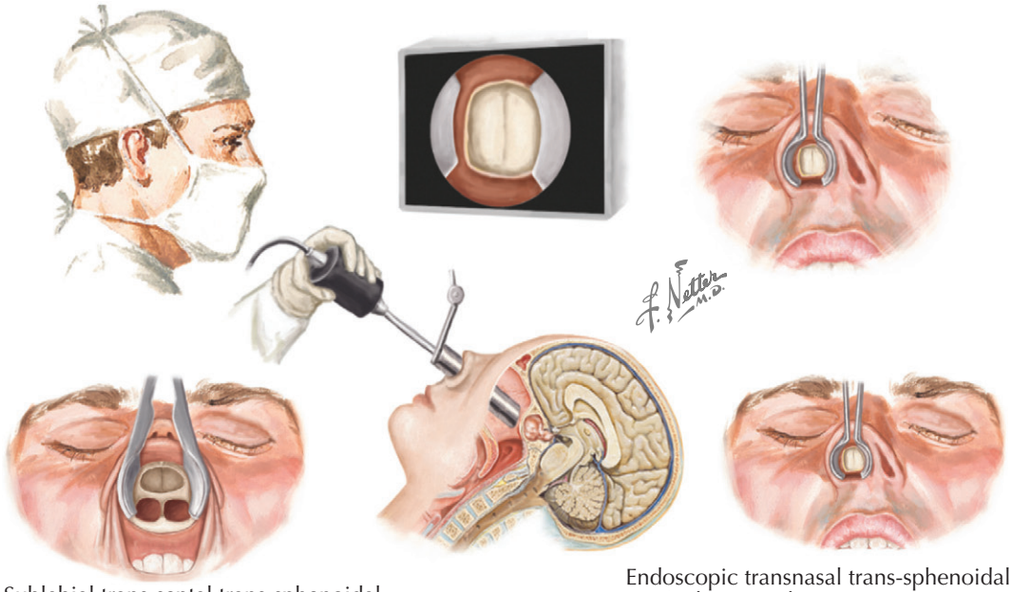
Treatment Modalities

The treatment of brain tumors requires a multidisciplinary approach that consists of neurosurgery, radiotherapy, and/or chemotherapy. In all three fields, technologic advances have improved the efficacy of each individual treatment modality. For instance, radiographic innovations have expanded neurosurgical capabilities. Functional magnetic resonance imaging (MRI), a noninvasive imaging modality that uses cortical blood flow changes as a marker for increased or decreased neuronal activity, has improved presurgical planning by delineating tumor margins from eloquent cortex. Intraoperative MRI brings the ability to update images, as needed because intraoperative deformation from secondary fluid shifts, changes in intracranial pressure, and/or the use of retractors, may render preoperative images inaccurate. The advent of endoscopy has transformed previously complex craniotomies to elegant outpatient procedures. Finally, the development of short-acting analgesic and anesthetic agents have paved the way for intraoperative mapping, allowing maximum excision of tumors in regions of eloquent cortex while minimizing neurologic damage.

Radiation therapy is frequently used as adjunctive therapy or primary therapy. Primary therapy may be for curative intent, palliation, or stabilization. Ionizing radiation is the mainstay of treatment in neuro-oncology, with the most common types of radiation being photons and protons. Radiation can be delivered either in multiple treatments as "fractions" or in a single treatment dose. Advances in radiation oncology have improved its effectiveness and decreased its complications by honing its precision in an effort to minimize surrounding neurotoxicity. This has been achieved with the advent of stereotactic treatment, which is a specialized method of targeting, and the use of three-dimensional (3D) conformal treatment in which the volumetric distribution of the desired dose mimics the shape of the target. Stereotactic intensity modulated radiotherapy (IMRT) is a type of 3D conformal therapy that delivers radiation (usually photons) in a controlled and precise fashion, limiting the toxicity to the rest of the brain. Advantages include reducing the radiation dose to at-risk dose-limiting organs, such as the optic apparatus, brainstem, and inner ear, and improving dose delivery to target organs. More recently, proton beam radiation has garnered much attention because of its ability to limit the amount of scatter to normal tissue. This has allowed radiotherapists to deliver sufficient radiation to eloquent areas. Stereotactic radiosurgery (SRS), using either the linear accelerator, gamma knife, or cyber knife, delivers a large single dose of radiation in a highly focused manner, achieving a similar biologic effect as several weeks of fractionated radiation therapy. The gamma knife uses gamma radiation derived from 201 cobalt-60 sources arranged in a circular array directed at the center of the unit, where the head is rigidly fixed. A linear accelerator targets its radiation beams by rotating the patient and treatment unit gantry simultaneously. The cyber knife utilizes an image guidance system in conjunction with a linear accelerator mounted on a robotic arm. To date, a clinically meaningful advantage has not been demonstrated comparing these different approaches.

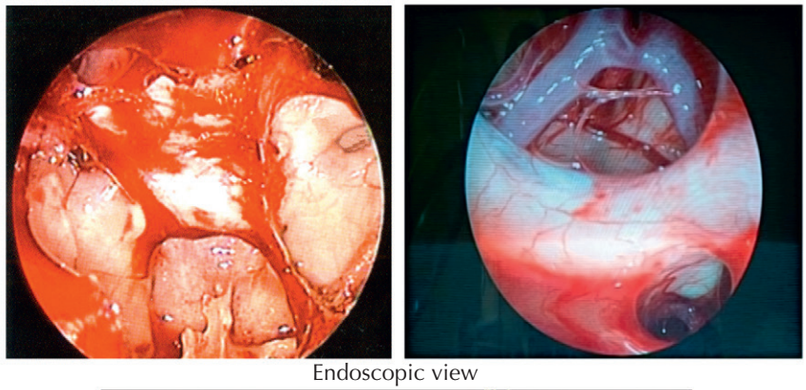
The realm of chemotherapy has also seen some advances, impacting improved overall survival and progression free survival. Temozolomide, an oral second-generation alkylating agent, received U.S. Food and Drug Administration (FDA) approval in 1999 for recurrent anaplastic astrocytoma, and approval in 2005 for use in newly diagnosed glioblastoma. Compared with previous alkylating agents, the adverse effects associated with temozolomide are generally mild to moderate and predictable. Moreover, the European Organisation for Research and Treatment of Cancer–National Cancer Institute of Canada (EORTC-NCIC) phase III trial demonstrated a significant improvement in survival with the addition of temozolomide to radiation, compared with radiation alone. Recently, the FDA granted accelerated approval to bevacizumab (Avastin, Genentech, South San Francisco, Calif.), a monoclonal antibody against human vascular endothelial growth factor as monotherapy for recurrent glioblastoma. Although its impact on overall survival remains modest, phase II trials have reported increased response rates and improved 6-month progression-free survival with this drug. Currently, small-molecule inhibitors are subject to much investigation as potential therapeutics for malignant glioma.

Surgical Approaches

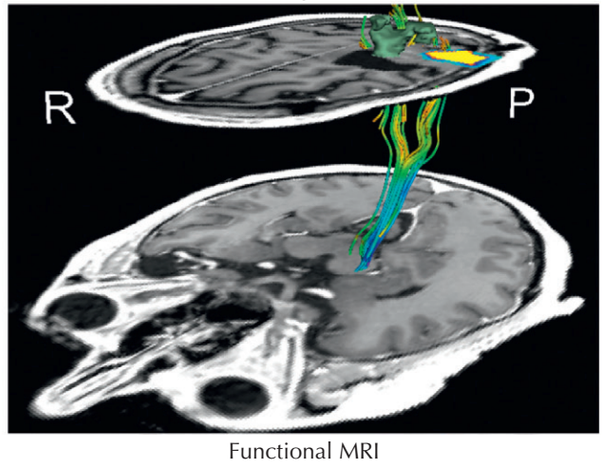


Sublabial trans-septal trans-sphenoidal surgical approach

Endoscopic transnasal trans-sphenoidal surgical approach



Endoscopic view



Functional MRI

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HEADACHE

Overview of Headaches

Headache is one of the most common reasons for consulting a physician and is one of the top three reasons for lost work days. Rather than a disease, headache is a symptom, frequently providing a valuable warning of hidden pathology.

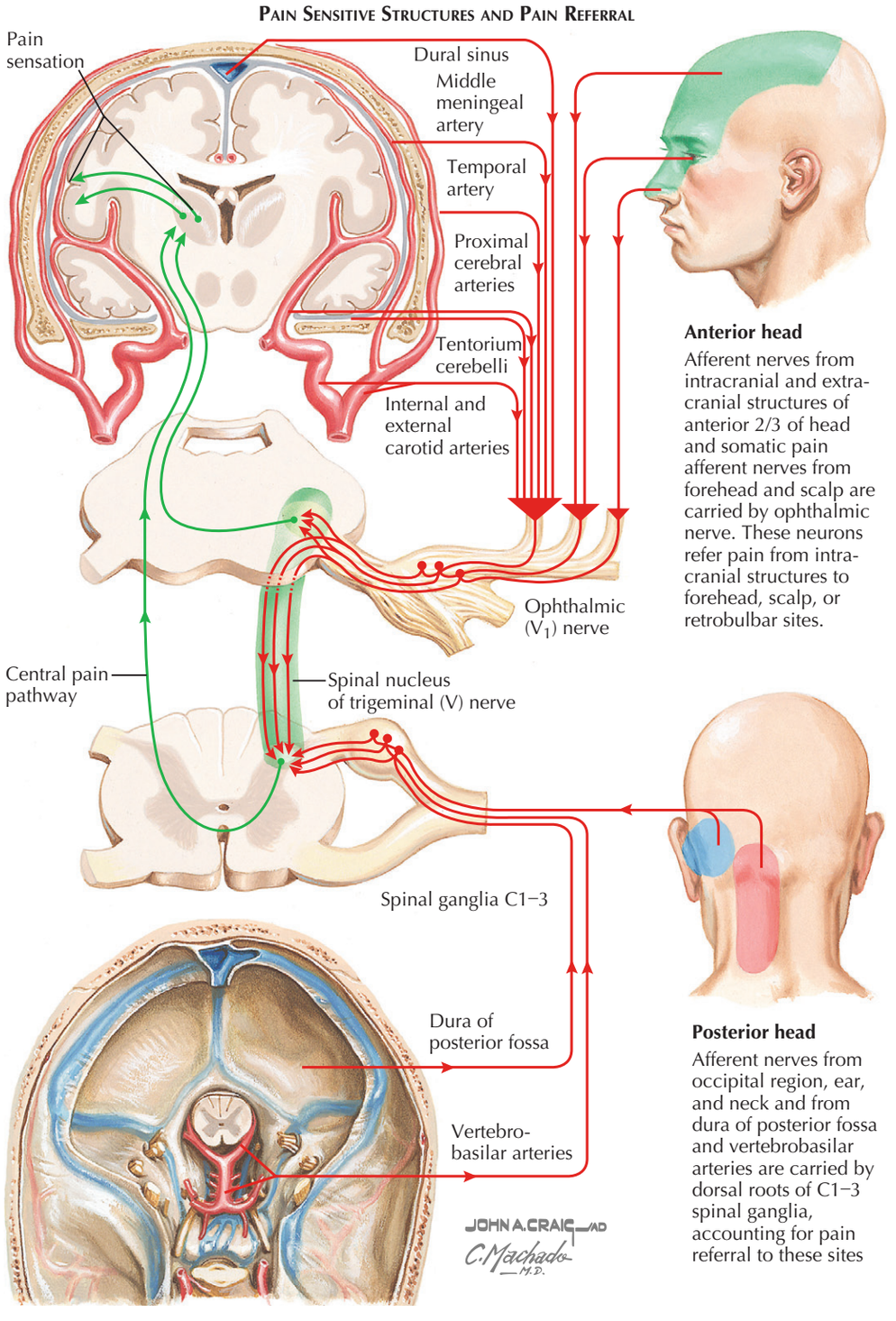
Physicians treating patients for headache must decide whether the headache represents a primary or secondary headache syndrome. *Primary headaches* are most common and include disorders such as migraine, tension-type headache, and trigeminal autonomic cephalalgias. The patient with primary headaches may have severe and incapacitating pain, but there is no identifiable cause leading to activation of nociception. In contrast, *secondary headaches* are symptomatic of a cranial or extracranial pathology, such as a brain tumor, ruptured aneurysm, meningitis, or hematoma. Headache diagnosis depends on a thorough history and neurologic and medical examinations. The history should seek information on premonitory symptoms, timing of onset (gradual vs. sudden) and duration, pain quality, and severity, location of pain, provoking factors, any associated symptoms, clinical circumstances, and details of previous investigations and treatments. A past medical history, family history, trauma history, social history, current medications, drug allergies, and review of systems are also indispensable. If a new headache is unlike any headache the patient has had in the past, it requires very expeditious evaluation, which may include ancillary laboratory and neuroradiologic imaging.

Secondary headaches, and possibly primary headaches, are thought to occur when primary afferent nociceptive neurons arising from either the trigeminal ganglion or upper cervical spinal ganglia (C1-3) are depolarized. These neurons innervate both extracranial and intracranial pain-sensitive structures. The first and second trigeminal nerve divisions provide sensory innervation for the anterior head and upper face. The trigeminal nerve innervates pain-sensitive dural structures, including the dural sinuses and tentorium cerebelli as well as many arteries, including the middle meningeal, temporal, proximal portions of the anterior and posterior cerebrals, and the internal/external carotid. The cervical spinal nerves (C1-3) provide innervation to the dural structures of the posterior fossa, the basilar and vertebral arteries, and to muscular structures in the upper neck and posterior portion of the head.

The cause of prolonged head pain is usually apparent when a secondary headache develops related to a tumor or other intracranial lesion producing ongoing traction upon a dural or vascular structure. However, patients with a primary headache disorder do not have a clearly discernible source for ongoing activation of nociceptive neurons. Therefore pathophysiologic mechanisms leading to a persistent primary headache are less clear. It is likely that the neurons within the trigeminal-cervical pain system are more than passive conduits for depolarization; however, because they also seem to play a role in pain sensitization. Sensitization is a process where, after repeated activation, neurons become increasingly responsive to painful and nonpainful stimulation. *Peripheral sensitization* (in the primary afferent neurons) and *central sensitization* (within second-order neurons in the trigeminal nucleus caudalis and higher-order neurons within the central nervous system [CNS]) may play a role in prolonging headaches and may contribute to the transformation of episodic migraine to the chronic form of migraine.

The evidence of peripheral sensitization of the primary afferents comes from both animal and human studies. In animal models, stimulation of the trigeminal system leads to increased concentrations of the vasoactive peptides, including substance P (SP), neurokinin A (NKA), and calcitonin gene–related protein (CGRP) in sagittal sinus blood. Similarly in humans, internal jugular CGRP levels reportedly rise during migraine attacks. Release of these neuropeptides is a marker for neuronal activation in primary afferents. Primary afferent neurons exposed to activating stimuli show increased spontaneous firing and lowered activation thresholds.

There is also evidence that initial activation of the primary afferent neurons leads to sensitization of second and possibly higher-order neurons. Chemical irritation of the meninges in animal models (peripheral nociceptors) causes sensitization of both trigeminovascular fibers innervating dura and central trigeminal neurons receiving convergent input from dura mater and skin. After sensitizing activation of the meninges, central trigeminal neurons respond to low-intensity mechanical and thermal stimuli from skin that previously induced minimal or no response. This change in activation threshold for central neurons receiving input from skin (which was not directly irritated) strongly implicates sensitization of second-order neurons within the central nervous system.



MIGRAINE PATHOPHYSIOLOGY

Migraine pathophysiology is not well understood. At present, migraine is viewed as a complex, often genetically based disorder that confers a susceptibility to the initiation of a cascade of events within the central nervous system (CNS), resulting in a clinical migraine attack.

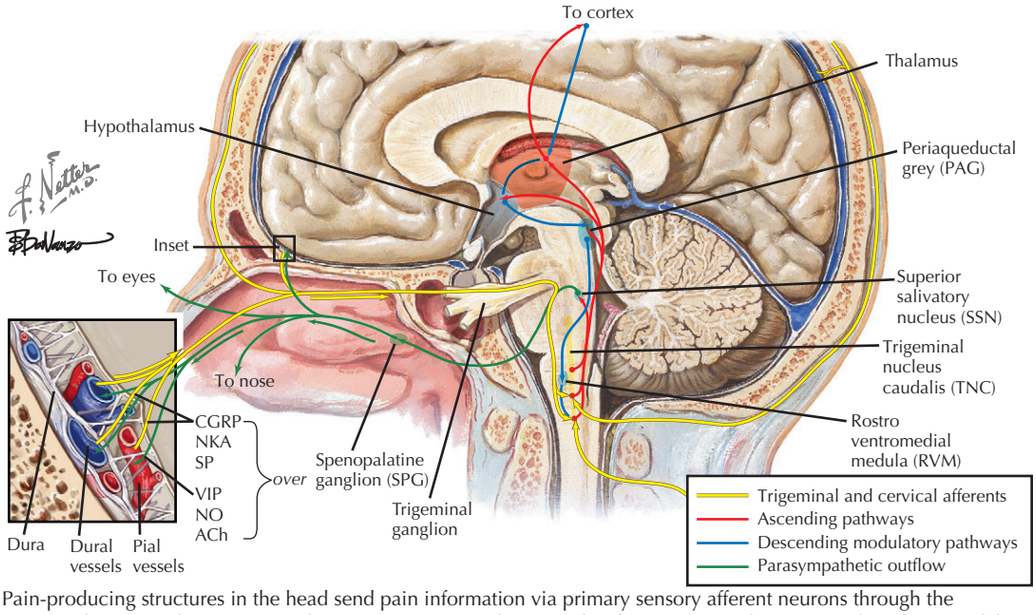
Until the 1980s, the accepted explanation for migraine attacks was the *vascular theory of migraine*, which suggested that migraine headache was caused by the dilation of cranial blood vessels, while the aura of migraine resulted from vasoconstriction. The vascular theory was based on four observations: (1) the only effective treatment of acute migraine at the time, ergotamine, was a potent vasoconstrictor; (2) nitroglycerin, a vasodilating agent, caused headaches; (3) the classic observation that branches of the external carotid arteries often became distended and pulsated during a migraine attack; and (4) finding that stimulation of intracranial vascular structures (but not the brain) in awake patients undergoing surgical procedures caused headache. However, this vascular theory did not appear to account for all of the elements of migraine pathophysiology.

A *neurogenic theory* evolved next, suggesting that the migraine aura was caused by a cortical wave of neuronal and glial depolarization, referred to as *cortical spreading depression (CSD)*. From its cerebral cortical origin, this CSD wave spreads across the cortex at a rate of 3 to 5 mm/min, a rate similar to the estimated speed of visual aura of migraine as it progresses across the primary visual cortex. In experimental CSD, there are characteristic cerebral blood flow changes, with an initial increase in blood flow (hyperemia), followed by a decrease in blood flow (oligemia) and relative tissue hypoxia. Imaging studies using functional magnetic resonance imaging (MRI) seem to corroborate these hemodynamic changes in migraineurs during visual aura. In addition to contributing to aura, CSD may also act as a trigger for the headache pain. Experimental evidence demonstrates that CSDs may result both in activation of nociceptive second-order neurons within the medullary *trigeminal nucleus caudalis* and in changes within the vessel caliber of dural vessels innervated with pain-sensitive neurons. This mechanism might certainly account for activation of the headache in patients who experience the migraine aura, but would not explain headache in migraine patients without aura. It has been suggested that migraine without aura occurs when CSD takes place in noneloquent brain areas (such as the cerebellum), where depolarization is not consciously perceived; however, there is insufficient evidence to support this possibility at this time.

The headache of migraine likely arises upon activation of nociceptive neurons in the *trigeminovascular system* (TVS). The TVS consists of small-caliber pseudounipolar sensory neurons arising from the trigeminal ganglion and upper cervical dorsal roots and project to innervate pial vessels, dura mater, large cerebral vessels, and venous sinuses. Once activated, the neurons transmit the nociceptive information to the *trigeminal nucleus caudalis* of the medulla, where they synapse on second-order neurons.

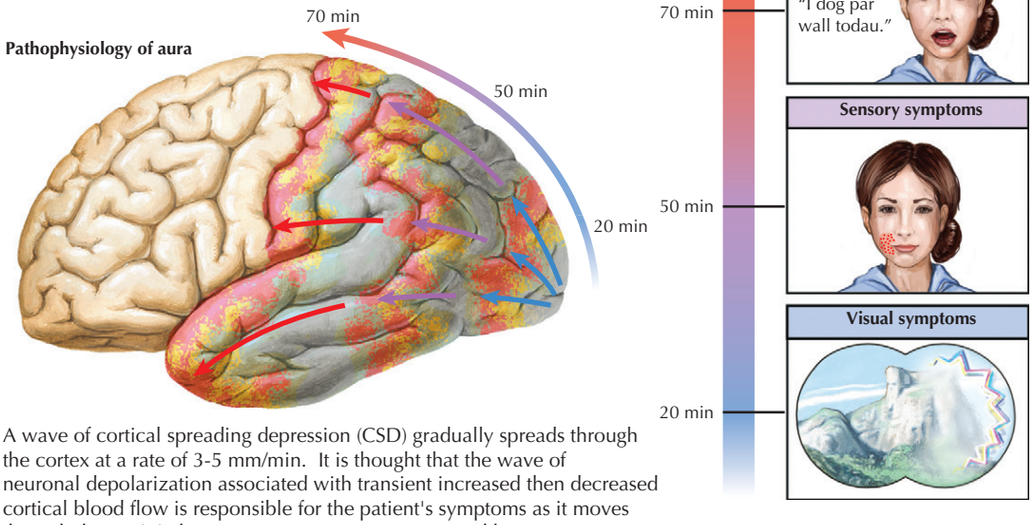
From the trigeminal nucleus caudalis, neurons that are involved in localization of pain project to the *thalamus* and then to the *sensory cortex*, where pain reaches consciousness. Central signals can be modulated by projections from several sources, including the *periaqueductal gray*, the *nucleus raphe magnus* in the *rostral ventromedial medulla*, and by *descending cortical inhibitory systems*. Other activated second-order neurons within the trigeminal nucleus caudalis project to numerous *subcortical nuclei* and to *limbic areas* of the brain involved in the emotional and vegetative responses to pain.

There is ongoing debate as to whether initial activation of primary afferent neurons is necessary for the occurrence of migraine headaches. The fact that increases in measured levels of *CGRP*, a neuropeptide known to be released by activated first-order neurons, are observed in external jugular venous blood during migraine in humans implicates activation of primary afferents neurons. However, logically, it would seem the abnormal activation or lack of regulating inhibitory tone could result in the propensity of a migraine attack in some individuals.



Pain-producing structures in the head send pain information via primary sensory afferent neurons through the trigeminal nerve and upper cervical roots to synapse on the second-order neurons in the trigeminal nucleus caudalis (TNC) as part of the trigeminocervical complex. Neurons in the TNC send projections to the thalamus (via the trigeminothalamic or quintothalamic tract, which decussates in the brainstem), which then projects to the cortex. The TNC is thought to project to other structures as well, including the periaqueductal gray (PAG), which also send signals to the thalamus and hypothalamus, with projections to the cortex. There are descending projections from the cortex back to the thalamus and hypothalamus. Descending modulation of the TNC takes place via nuclei in the hypothalamus, as well as direct projections from the PAG through the rostral ventromedial medulla (RVM).

Cranial parasympathetic outflow stems from a reflex connection from the TNC to the superior salivatory nucleus (SSN) in the pons. Efferents from the SSN (via the facial nerve) connect with neurons in the sphenopalatine ganglion (SPG; pterygopalatine). The SPG then projects to innervate intracranial vessels (vasodilation), as well as the nasal and lacrimal glands.



A wave of cortical spreading depression (CSD) gradually spreads through the cortex at a rate of 3-5 mm/min. It is thought that the wave of neuronal depolarization associated with transient increased then decreased cortical blood flow is responsible for the patient's symptoms as it moves through the occipital cortex, somatosensory cortex, and language areas.

Migraine Presentation

Migraine is a very common disorder, with a 1-year prevalence of more than 18% of women and almost 7% of men in the United States. It is most common in the third and fourth decades, although it may occur at any time of life from early childhood onward. Migraine is divided into two types based on the presence or absence of transient neurologic symptoms referred to as aura. *Migraine without aura* (formerly referred to as *common migraine*) is more common than *migraine with aura* (formerly referred to as *classic migraine*) and accounts for about three quarters of migraine patients. Both migraine with aura and migraine without aura occur in either an episodic form (<15 headache days per month) or a chronic form (≥15 headache days/mo). Over the course of a lifetime, a migraine sufferer may move back and forth between the chronic and episodic forms. The factors determining susceptibility to the development of the chronic form of migraine are poorly understood.

Although head pain is the most debilitating aspect of migraine, a migraine attack may unfold through a series of four phases: (1) *prodrome*, (2) *aura* (when present), (3) *headache*, and (4) *postdrome*. Not all individuals experience all phases. The *prodrome* occurs in up to 60% of migraine patients and consists of vague vegetative or affective symptoms that herald the onset of the attack. These symptoms may include food cravings, constipation, neck stiffness, increased yawning, irritability, euphoria, or depression. With resolution of the prodrome, the *aura* (when present) occurs generally just before or during the opening minutes of the headache.

The *migraine headache* is usually (but not always) unilateral. In fact, the term migraine is derived from the ancient Greek word, *hemikranos*, which means "half head." A migraine headache tends to have a throbbing or pulsatile quality that at times is superimposed on a constant pressure-like sensation. As the attack severity increases over the course of one to several hours, patients may experience nausea and sometimes vomiting. Most individuals report abnormal sensitivity to light (*photophobia*) and/or sound (*phonophobia*) during attacks. Individuals may also report *cutaneous allodynia* over the face or scalp on the same side as the headache. Allodynia is a tenderness or hypersensitivity in the context of which even a light touch may be perceived as painful. In adults, an untreated migraine headache will attain at least a moderate level of pain intensity that can persist from 4 hours to 3 days. Many attacks resolve with sleep that can occur as a part of the natural course of the migraine attack or as the result of treatment of the headache with sedating medications.

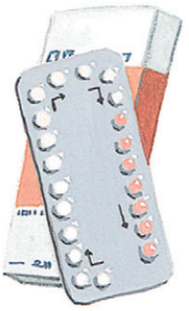
As the headache is resolving, many patients experience a *postdromal* phase in which they feel drained or exhausted, although some report a feeling of mild elation or euphoria. During the postdromal phase, sudden head movement may cause transient pain in the location of the recently resolved spontaneous throbbing of the headache.

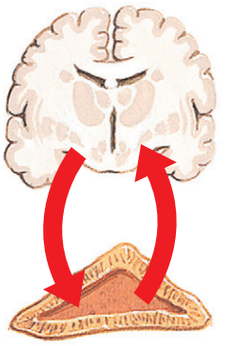
Frequently cited precipitating factors (triggers) of migraine headache include stress, fasting, sleep disturbances, weather changes, bright light or glare, ingestion of alcohol, strong odors, smoke, nitroglycerin or other vasodilating drugs, nasal congestion, withdrawal from caffeine or ergotamine-containing medicines, exercise, intercourse, and certain food substances, such as chocolates, sharp cheese, processed meats, and hot dogs. There are reports that migraine headaches frequently begin in the morning on arising and may have a predisposition to occur on a Saturday or after a prolonged or intense period of work or study. For most patients, migraine attacks occur unpredictably.

One of the most potent and frequent triggers of migraine in women is the monthly fluctuation in gonadal hormones that underlies the menstrual cycle. Typically, the headaches appear 1 to 2 days before or the first day of menstrual flow, although they may also appear during the menstrual cycle itself. Some women also experience migraine headaches at midcycle with ovulation. The headaches can be quite severe and are usually without aura, although women can also have headaches preceded by aura at other times of the month.

Triggers of Migraine

Lack of sleep


Oral contraceptives


Stress, anxiety

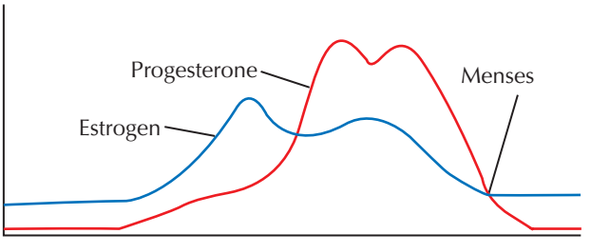

Exertion, fatigue


Head injury


Certain foods, alcohol

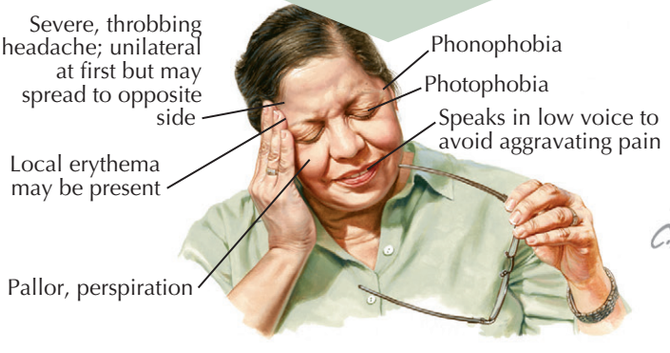

Changes in weather and temperature


Glare or dazzle



Menstruation

Common triggers



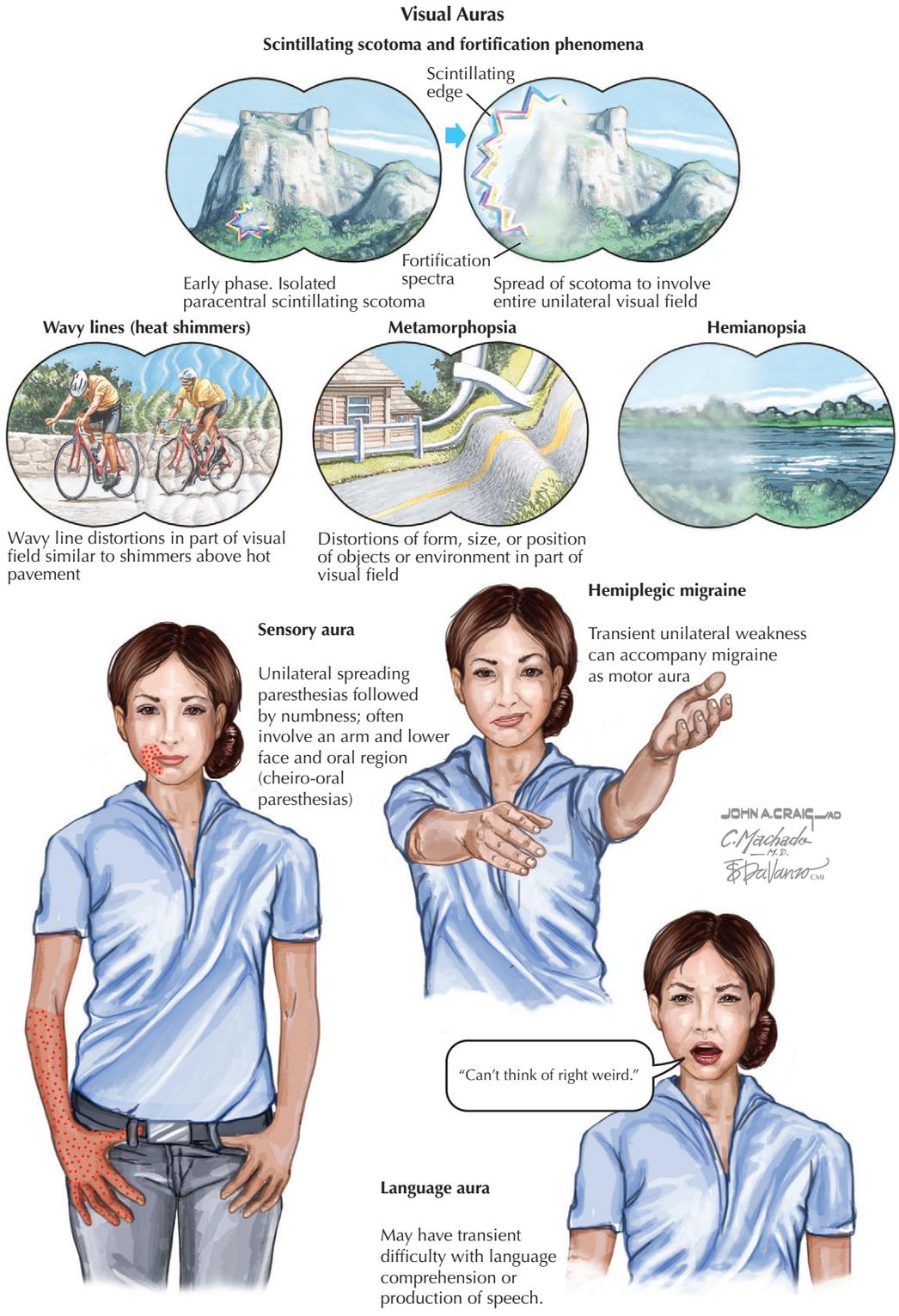
Migraine Aura

Migraine aura consists of transient focal neurologic symptoms that tend to last for 5 minutes to 1 hour and may occur before or during the headache phase. There are four types of migraine aura: visual, sensory, language, and motor. Patients may have one or more types, and auras may occur even in the absence of headache. The most common aura type, *visual aura*, may consist of positive visual symptoms (shimmering, sparkling, flashes of light) or negative symptoms (blurred vision or loss of vision) in both eyes. The most classic visual aura is a *scintillating scotoma* that starts as a small shimmering or blurred spot just lateral to the point of visual fixation. This spot expands over 5 minutes to 1 hour to involve a quadrant or half of the visual field. It often assumes a curved or sickle shape with a zigzagging or serrated border, sometimes multicolored or sparkling in appearance. This jagged edge has also been referred to as a fortification spectra based on its resemblance to the top of a medieval fortress. Over time, the positive visual phenomena tend to move toward the periphery leaving a blind spot, that is, scotoma, in their wake.

When *sensory aura* accompanies visual aura, it tends to follow visual aura within minutes. This aura typically begins as unilateral paresthesias in a limb or one side of the face. From their origin, the paresthesias may gradually march down the limb or face, often with a subsequent feeling of numbness that may last as long as an hour. The sensory aura may also expand to involve the inside of the mouth, affecting the inside of one cheek and half the tongue. The slow spread of positive symptoms (the scintillations or the tingling) followed by negative symptoms (scotoma or numbness) is very suggestive of migraine aura and contrasts significantly with an ischemic event, such as a transient ischemic attack, wherein all symptoms begin concomitantly.

A *language aura* occurs much less commonly than the visual and sensory type auras. This consists of transient language problems that may range from mild word-finding difficulties to frank dysphasia with paraphasic errors.

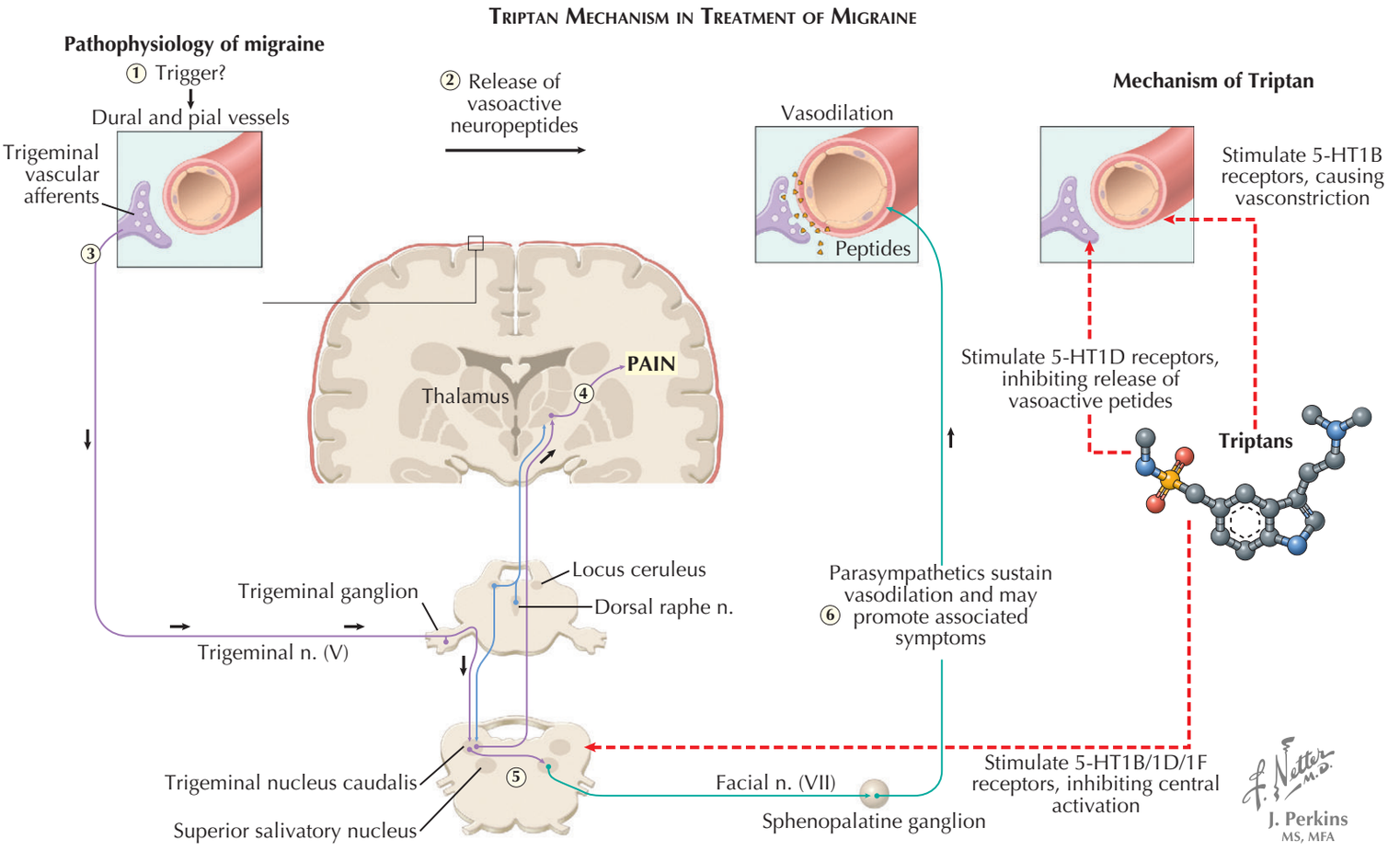
The least common aura type, *motor aura*, involves unilateral weakness in the limbs and possibly the face. Most patients with motor aura also report sensory symptoms, and many also have other attacks, including visual, sensory, or language aura. When one considers diagnosing a motor aura, it is most important to distinguish true motor weakness from clumsiness based on proprioceptive loss caused by sensory aura. To date, research studies have linked motor aura to three separate genetic mutations. As a result, motor aura is classified separately from the other forms of migraine aura, and is referred to as *hemiplegic migraine*. Hemiplegic migraine can be further classified as either familial or sporadic. *Familial hemiplegic migraine* patients have at least one first- or second-degree relative with the same disorder. *Sporadic hemiplegic migraine (SHM)* is thought to be the result of a new mutation, and a patient with SHM may or may not carry one of the three gene variants already linked to the familial form.



Other Migraine Variants

Basilar-type migraine is a variant of migraine with aura wherein the symptoms mimic occlusive disease of the posterior cerebral circulation. These include reversible vertigo, ataxia, diplopia, dysarthria, and decreased consciousness. By definition, basilar migraine must have at least one aura symptom, and this must originate from the brainstem or both hemispheres simultaneously. If, for instance, the patient has paresthesias as part of a sensory aura, these would be expected to be bilateral.

Ophthalmoplegic migraine is thought to be rare and is most often seen in children or young adults. It involves a prolonged migraine-like headache (possibly lasting a week or more) accompanied or followed by paresis of the third, fourth, and/or sixth cranial nerve that may persist for days afterward. Originally considered a migraine variant, ophthalmoplegic migraine has been reclassified as a cranial neuralgia. In patients presenting with this variant, parasellar, orbital fissure, and posterior fossa lesions must be excluded with appropriate imaging, particularly magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA). In some cases, MRI has shown gadolinium enhancement of the affected cranial nerve, suggesting the condition may represent a recurrent demyelinating neuropathy.



MIGRAINE MANAGEMENT

The medical management of migraine involves two types of therapy: acute or abortive treatments taken at the time of an attack to truncate it, and prophylactic treatments taken on a daily basis to decrease the intensity and frequency of the migraine headaches.

When migraine attacks occur infrequently (3 days or fewer per month) and are not associated with prolonged neurologic symptoms, abortive treatments are probably sufficient. However, daily prophylactic treatment should be considered if (1) headaches are usually disabling to the patient for 4 or more days per month, (2) the severity of the attacks, or even the dread of an attack, negatively impacts the patient's ability to carry out normal activities of daily living between attacks, (3) headaches are associated with neurologic deficits that persist beyond the duration of the headache phase of the attack, (4) there is a history of migraine-associated cerebral infarction, or (5) the patient obtains only incomplete relief from all tolerated abortive treatments.

Acute migraine treatment mainstays are the nonsteroidal anti-inflammatory drugs (NSAIDs), such as naproxen sodium or ketoprofen, and serotonin agonists, including the ergotamine derivative, dihydroergotamine (DHE) and the 5-hydroxtryptamine (5-HT) 1B and 5-HT 1D selective serotonin agonists, so-called "triptan" medications (sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan, and frovatriptan). DHE is available in intravenous and intranasal formulations. The "triptans" are available in subcutaneous injectable, oral, and intranasal formulations. The preferred route of delivery may vary from patient to patient or may vary based the characteristics of a given attack.

For example, attacks that awaken the patient from sleep at a fully developed stage or that very rapidly escalate may require subcutaneous injection, Attacks that start while the patient is awake and gradually increase in intensity may respond well to an oral formulation. An NSAID combined with a triptan may provide better relief than a triptan alone.

The addition of an antiemetic, such as prochlorperazine or promethazine, may further increase the effectiveness of acute treatment. Although the use of nonspecific analgesic medications containing opiates or butalbital is sometimes necessary in patients with known contraindications for the use NSAIDS or serotonin agonists, caution is advised. The use of these medications more than 2 days per week may contribute to an increasing frequency and severity of headaches over time.

When *prophylactic or preventive treatment* is necessary, as noted above, several general principles should be remembered. To minimize side effects, prophylactic medications need to be started at a low dose and gradually increased over a period of a few weeks to a therapeutic target dose. Once the therapeutic dose is attained, the patient needs to be on the medication for at least 4 to 6 additional weeks to reliably assess effectiveness. Early discontinuation may deprive the patient of a potentially effective therapy. If drugs are not completely effective but are well-tolerated as monotherapies, then a combination of two agents, each from a different class, may be tried, despite the greater risk of side effects. Unfortunately, whether there is additional benefit to be gained from the use of combination therapy has not been examined thoroughly in a prospective evidence-based fashion. To be considered successful, the prophylactic treatment should reduce the number of headache–days per month by at least 50%.

Migraine preventive treatments come from at least six classes of medications, including *beta-adrenergic blockers* (atenolol, metoprolol, nadolol, propranolol, and timolol), *tricyclic antidepressants* (amitriptyline or nortriptyline), NSAIDs (naproxen sodium), *calcium channel blockers* (verapamil), *anticonvulsants* (divalproex sodium, topiramate, and gabapentin), and *nutritional supplements* (riboflavin, feverfew, and butterbur). Recently, the injection of botulinum toxin A has been shown to be an effective migraine prophylactic strategy in patients with chronic migraine headaches more than 15 days per month. Individual patients may find that one preventative agent is more effective than another. Unfortunately, at present, there is no method for drug selection other than trial and error. For some individuals, nonpharmacologic treatments, such as cognitive-behavioral therapy and biofeedback, play an important role in migraine management as well.

Trigeminal Autonomic Cephalalgias

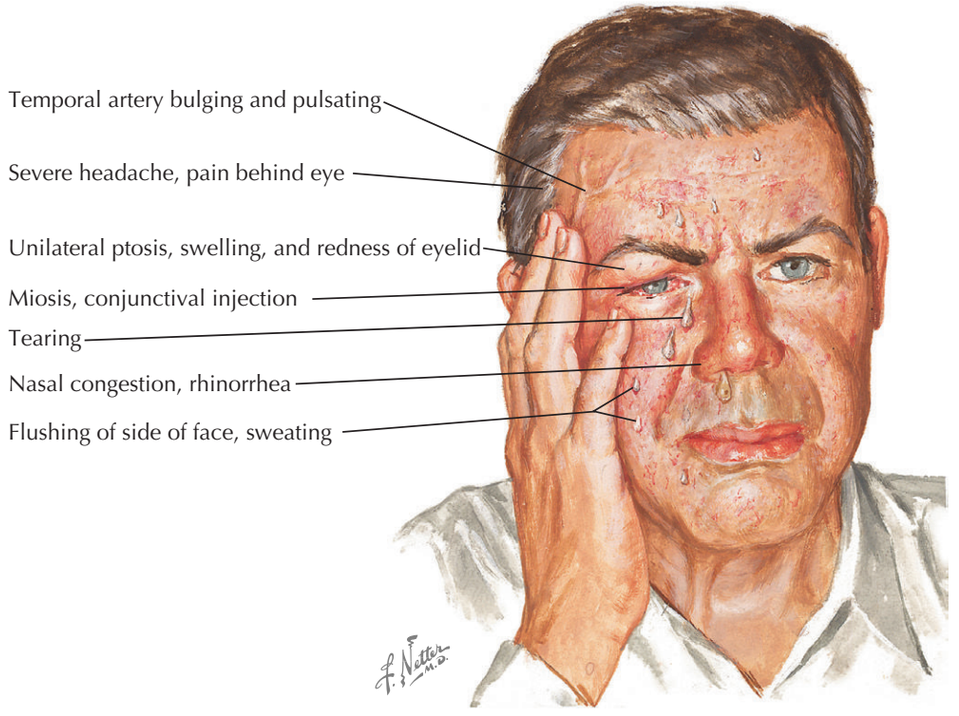
The trigeminal autonomic cephalalgias (TACs) are a category of primary headache disorders distinguished by *one-sided pain* in the trigeminal distribution that is present in combination with *ipsilateral cranial autonomic* signs and symptoms including

- Ipsilateral conjunctival injection and/or lacrimation
- Ipsilateral nasal congestion and/or rhinorrhea
- Ipsilateral forehead and facial sweating or flushing
- Ipsilateral eyelid edema
- Ptosis and/or miosis (less common)

The TAC disorders include (1) cluster headache, (2) paroxysmal hemicrania, (3) short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), and (4) short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA). Although sharing several features, the TACs differ in attack duration and frequency, as well as in their therapeutic response (see Plate 13-7). Cluster headache (CH) has the longest attack length and a relatively low-attack frequency. Paroxysmal hemicrania (PH) has an intermediate attack length and an intermediate attack frequency. SUNCT/SUNA headache attacks have the shortest attack length and the highest attack frequency. Most importantly, underlying structural brain lesions can mimic these disorders. Therefore brain magnetic resonance imaging/magnetic resonance angiography (MRI/MRA) is indicated when a TAC diagnosis is considered.

Cluster Headache

Large, strong, muscular man typical patient. Face may have peau d'orange skin, telangiectasis.



CLUSTER HEADACHE

Although rare, CH is nevertheless the most common of the TAC disorders with a prevalence of less than 1% and a male-to-female ratio of 4:1 to 5:1. In addition to the cranial autonomic symptoms, several clinical features help characterize cluster headache. The pain is usually piercing, boring, or stabbing; it usually begins precipitously without premonitory symptoms, rapidly reaching crescendo and becoming excruciatingly severe. The pain may begin in the temporal, lower facial, or occipital region, remains unilateral, and is typically maximal behind and around the eye. The headache usually lasts 60 to 90 minutes, with a range of 15 to 180 minutes, and occurs from every other day to eight times per day; often at the same time each day or night. Photophobia and phonophobia occur in up to 50% of CH individuals, typically ipsilateral to the pain. In contrast to migraine, where activity typically aggravates the pain, more than 90% of patients with cluster headache report restlessness and agitation and avoid remaining recumbent.

The term "cluster" headache was coined because, in its most prototypical form, it is episodic and usually occurs at least once every 24 hours for weeks at a time, often for 8 to 12 weeks, that is, in clusters. During an active cluster period, attacks can usually be precipitated by ingestion of alcohol. A frequent pattern, especially in the first few years, is for cluster periods to occur seasonally, often in the spring or fall. This periodicity often decreases after a few years as periods of cluster activity become less predictable, occurring any time of the year. Approximately 10% of sufferers develop chronic CH characterized by the absence of prolonged remissions.

Mechanisms of Cluster Headache. Pathophysiology of cluster headache is not well understood. The recurrence of attacks at similar times of day during cluster bouts is one of this syndrome's most striking characteristics and suggests possible hypothalamic involvement. Positron emission tomography (PET) studies support this, demonstrating activation in the posterior hypothalamus during nitroglycerin-induced cluster headaches. Once the hypothalamus is activated, it may activate the trigeminal-autonomic reflex, leading to unilateral pain mainly within the ophthalmic division of the trigeminal nerve as well as the ipsilateral autonomic features, including tearing, rhinorrhea, partial Horner syndrome, and orbital vasodilation. Oculosympathetic paresis in some patients during cluster headache attacks implicates involvement of pericarotid sympathetic fibers. The cavernous sinus is suggested as another important source for cluster headache pathogenesis because this location allows convergence of trigeminal, sympathetic, and parasympathetic fibers.

Cluster Headache Management. This is divided into treatment of acute cluster attacks as well as therapeutic options to transition out of a cluster period or prophylactic therapy preventing future attacks. Options for the acute treatment of CH include inhalation of 100% oxygen, subcutaneous sumatriptan or nasal sumatriptan, oral or nasal zolmitriptan, octreotide, nasal lidocaine, and subcutaneous dihydroergotamine.

Transitional prophylaxis may be used for a few weeks to quickly end or markedly reduce the frequency of attacks. A 2- to 3-week course of corticosteroids often leads to a substantial reduction of attacks. Greater occipital nerve blockade with a local anesthetic and a corticosteroid may significantly reduce attacks and sometimes leads to a remission. For longer-term prophylaxis, verapamil is usually the drug of choice because of its efficacy and side-effect profile. Lithium carbonate can also be efficacious but is usually reserved for chronic intractable cluster headache. The use of other agents, such as topiramate, divalproex sodium, and pizotifen, may occasionally be useful. For medically intractable chronic CH, wherein the patient's activities of daily living are totally incapacitated by the pain., occipital nerve stimulation and deep brain stimulation appear useful as rescue options.

SUNCT/SUNA

This is a very rare TAC characterized by extremely brief episodic, unilateral severe head pain in the trigeminal nerve's first division, most commonly in orbital, periorbital, or temporal regions. Some patients have pain in other cephalic locations. Pronounced cranial autonomic features accompany the pain.

TRIGEMINAL AUTONOMIC CEPHALALGIAS *(Continued)*

There are three distinct patterns of pain: (1) *Single stabs* with a mean duration of about 1 minute (range, 1-600 seconds); (2) *a series of stabs* with a mean attack duration of approximately 400 seconds, that is, 6 to 7 minutes, (range, 10-1200 seconds); (3) "*Saw-tooth*" attacks of persistent pain with multiple superimposed stabs and a mean attack length of 1200 seconds, that is 20 minutes (range, 5-12,000 seconds).

Some individuals suffer more than one of these types of attacks, and there is heterogeneity among patients in the duration of the pain and the number of episodes per day. SUNCT and SUNA attacks can be episodic with spontaneous remissions lasting weeks or longer, or these can be chronic with long symptomatic periods without spontaneous remission. Although attacks are often spontaneous, a wide array of attack triggers occur, including washing or brushing hair, shaving, touching the face or scalp, chewing or eating, brushing teeth, talking, shaving, bathing or showering, coughing, blowing the nose, exercise, and exposure to light.

Prophylactic medication is the mainstay of treatment. Lamotrigine, topiramate, and gabapentin are probably the most helpful, although a variety of other agents are useful in a few patients. Rapid treatment with lidocaine may be helpful with severe acute episodes of pain. Occipital nerve blockade with a local anesthetic and a corticosteroid are helpful in some individuals.

PAROXYSMAL HEMICRANIA

Paroxysmal hemicrania (PH) is a rare trigeminal autonomic cephalgia with an estimated prevalence of 1 in 25,000. It is distinguished by unilateral, short-lived attacks of intense pain associated with cranial autonomic features that repeat many times daily, with an average of approximately 10 to 12 per day. This is most commonly localized to the trigeminal nerve's first division and usually lasts 15 to 20 minutes. Usually the pain is described as "torturous" and is often characterized as boring, burning, sharp, stabbing, throbbing, or shooting. As with CH, there may be one or more migrainous-associated features, including photophobia, phonophobia, and nausea or vomiting. Also similar to CH, PH is frequently associated with restlessness or agitation. Approximately 20% of patients have episodic PH, diagnosed when remissions last 1 month or longer; the remaining patients have chronic paroxysmal hemicrania, in which a remission does not occur within 1 year.

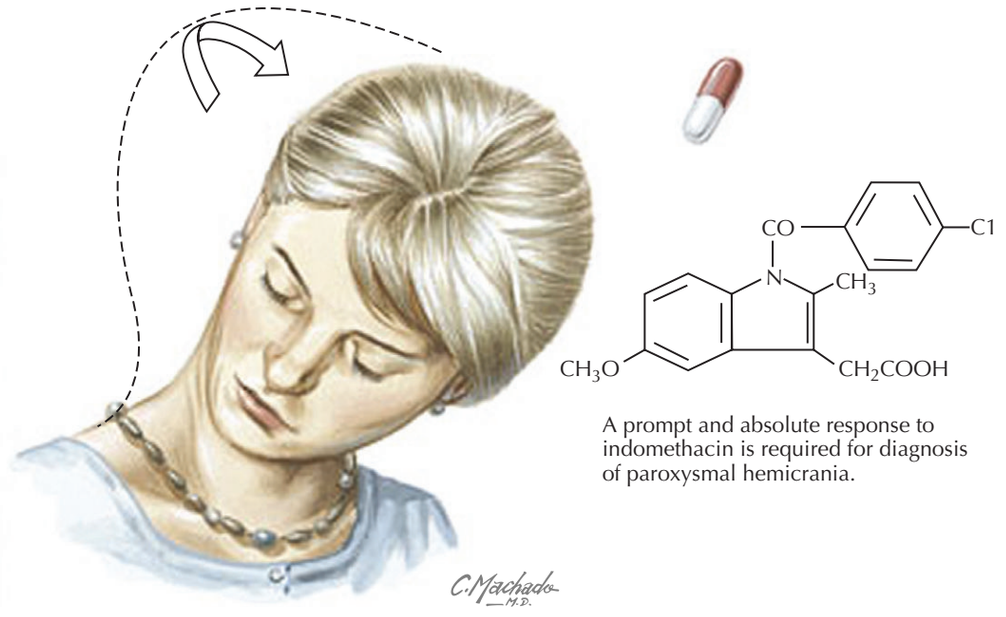
Although the preponderance of PH attacks occur spontaneously, approximately 10% may be triggered mechanically, typically by flexing or by rotating the head. Attacks are sometimes elicited by external pressure over the greater occipital nerve, C2 root, or the transverse processes of C4-5. Alcohol ingestion provokes attacks in approximately 20% of patients.

An absolute unequivocal response to a therapeutic dose of indomethacin is the primary diagnostic criterion for PH. This remains the gold standard for PH treatment. Both cyclo-oxygenase-II (COX-II) selective inhibitors, for instance, celecoxib, and topiramate are effective in some patients. Greater occipital nerve block with local anesthetic and a corticosteroid are beneficial in some patients. Finally, there may be a role for neuromodulation, such as occipital nerve stimulation in some patients.

Trigeminal autonomic cephalalgias			
	Cluster headache	**Paroxysmal hemicrania**	**SUNCT/SUNA**
Sex (M:F)	4-5:1	M≈F	1.5:1
Pain severity	++++	++++	+++/++++
Typical attack duration	15–180 minutes	2–30 minutes	5–240 seconds
Typical attack frequency/day	1–8	>5	3–200
Alcohol as trigger	++++	+	-
Cutaneous triggers	-	-	++
Agitation/restlessness in attack	++++	+++	++
Autonomic features	++++	++++	++++
Migrainous symptoms a,photo/ phononophobia, nausea	+++	+++	+
Response to indomethacin Rx	-	required for diagnosis	-

Abbreviations: M = male; F = female

Paroxysmal hemicrania (PH)



A prompt and absolute response to indomethacin is required for diagnosis of paroxysmal hemicrania.

The typical patient has symptoms that resemble cluster headache, including unilateral headache with cranial autonomic symptoms such as lacrimation, nasal stuffiness, and rhinorrhea. The attacks are shorter in duration and more frequent.

Flexion and rotation of the neck is a trigger for a headache in about 20%.

HEMICRANIA CONTINUA

Hemicrania continua (HC) is a relatively uncommon, yet likely underdiagnosed form of chronic daily headache. It is typified by a continuous, one-sided headache that changes in severity, waxing and waning, yet not resolving entirely. Episodes of worsening are typically associated with ipsilateral cranial autonomic symptoms (conjunctival injection, lacrimation, nasal rhinorrhea) but milder in severity than that seen with the trigeminal autonomic cephalalgias (TACs). The exacerbations may also be accompanied by migrainous symptoms, such as nausea, photophobia, and phonophobia. Because of the overlapping features, HC should be considered when evaluating a patient for chronic cluster headache or chronic migraine (especially if the headache is always on the same side). Similar to the TACs, it is important to rule out secondary causes of HC, such as pituitary, pineal, or posterior fossa lesions, internal carotid artery dissection, and unruptured aneurysms.

A diagnosis of this disorder also requires an absolute and marked response to indomethacin. HC sometimes responds well to other nonsteroidal anti-inflammatory drugs (NSAIDs), including COX-II inhibitors. Some patients are reported to have a favorable result with topiramate and occipital nerve blocks. There may also be a role for neuromodulation, such as occipital nerve stimulation in some patients.

Tension-Type Headache and Other Benign Episodic and Chronic Headaches

Tension-type headache (TTH), previously referred to as tension headache, muscle-contraction headache, and stress headache, is the most prevalent primary headache disorder and also frequently occurs in migraine individuals. Typically, TTH is a bilateral, mild-to-moderate severity, nonpulsatile headache not accompanied by nausea, vomiting, or photophobia. Individuals usually describe TTH pain as "pressure," "dull," "bandlike," "like a tight cap," or a "heavy weight on my head" sometimes associated with muscle tenderness of the head, neck, or shoulders. These headaches may be triggered or exacerbated by stress and mental tension.

Chronic TTH (15 or more days monthly) is the most prevalent form of chronic daily headache. *Episodic TTH* usually lasts from 30 minutes to 7 days. It is subclassified into *infrequent episodic TTH* (<1 day monthly) and *frequent episodic TTH* (1-14 days monthly).

TTH pathophysiology is poorly delineated, possibly including peripheral and central nervous system mechanisms. The previous etiologic conjecture of sustained pericranial muscle contracture has not been documented.

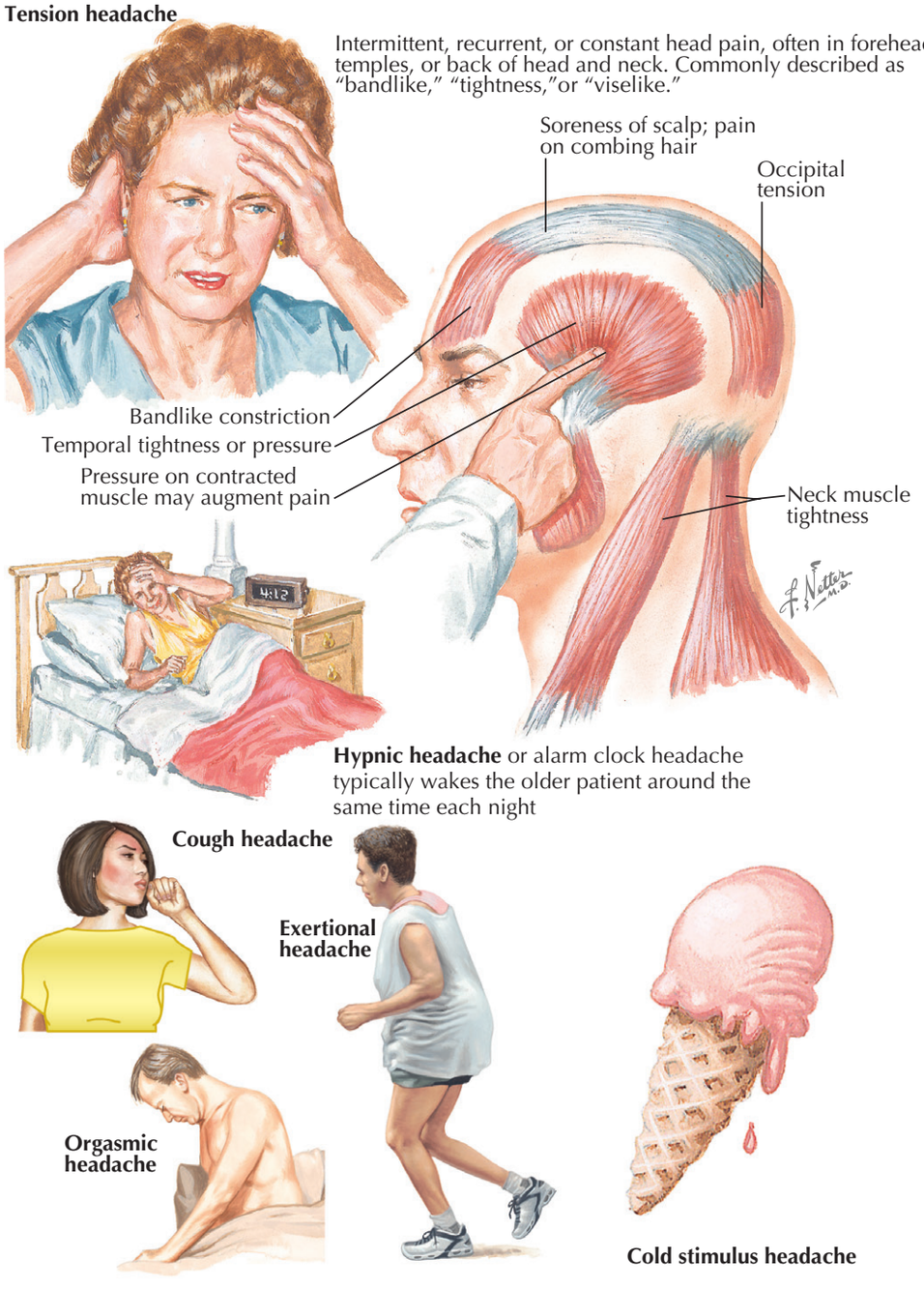
Treatment involves two primary therapies: acute or abortive during an attack, and daily prophylactic to decrease headache frequency and/or severity. Acetaminophen or NSAIDs are first-line acute treatment agents. Combination analgesics containing caffeine are sometimes more effective. Opiates and butalbital should be avoided given their propensity to lead to side-effects and overuse, particularly the development of worsening headaches.

Prophylactic therapy is appropriate for frequent, disabling, long-lasting headaches, leading to significant disability. Tricyclic antidepressants are the principal agents used for TTH. Some studies suggest that serotonin-norepinephrine reuptake inhibitors (mirtazapine and venlafaxine) are useful. Behavioral modification using cognitive-behavioral therapy, relaxation, or electromyographic (EMG) biofeedback may be helpful. Combined tricyclic antidepressant therapy with behavioral therapy may be more effective than either modality alone.

Hypnic headache, ("alarm clock headache") occurs in senior adults, typified by dull head pain stereotypically awakening them from sleep, occurring nightly at a similar time; and occasionally from daytime naps. These are unrelated to migraine or TACs. Controlled treatment trials for hypnic headache are lacking. Anecdotal successful treatments include evening caffeine, lithium carbonate, or indomethacin.

Primary stabbing headache is typified by spontaneous, transient, single or multiple, variably localized stabs of pain lasting a few seconds; occurring less than once daily to multiple times. These are more frequent in migraine headache individuals sometimes superimposed on an acute migraine. Most patients do not need treatment but individuals with frequent attacks may benefit from prophylactic indomethacin.

Primary cough headache has an abrupt onset triggered by coughing or straining, typically lasting from 1 second to 30 minutes. Although often benign, an intracranial abnormality, particularly a posterior fossa tumor or Chiari malformation, must be excluded with magnetic resonance imaging (MRI). Prophylactic treatment with indomethacin is often effective; acetazolamide, propranolol and other NSAIDs are effective in some patients.



Primary exertional headache occurs during or after physical exertion, typically building up over minutes during the physical activity. The pain is pulsatile, lasting minutes to more than a day. Exercise can sometimes precipitate migraine. Intracranial structural abnormalities, including supratentorial and posterior fossa tumors, aneurysms, and arteriovenous malformations with intracerebral hemorrhage also require consideration. Brain MRI and magnetic resonance angiography (MRA) are indicated. Exertional headache may be a manifestation of cardiac ischemia, and when suspected, an electrocardiogram (ECG) and other cardiac testing should be performed. Treatment of recurrent exertional headache includes indomethacin an hour before activity. Other medications that may be helpful include propranolol and naproxen.

Primary headaches associated with sexual activity are of two types. *Preorgasmic headache* begins with mild head and neck aching during sexual activity and builds with sexual excitement, and is often associated with neck and jaw tightness. Its average duration is 30 minutes, but it varies between minutes and a few hours. *Orgasmic headache* is sudden and severe, generalized and explosive/pulsatile, and occurs with or just before orgasm. Primary orgasmic headache must be differentiated from serious causes of thunderclap headache, including subarachnoid and intracerebral hemorrhage and cervicocephalic arterial dissections. Recurrent primary orgasmic headaches may be treated with prophylactic indomethacin an hour before anticipated sexual activity or daily propranolol. Triptan medications are effective for acute treatment of primary orgasmic headache.

Cold-stimulus headache, formerly known as "ice-cream headache," is a generalized headache attributed to ingestion or inhalation of a cold stimulus. This may also follow exposure of the unprotected head to a low environmental temperature, such as very cold weather or diving into cold water.

PEDIATRIC HEADACHE

Approximately 2% to 5% of preschool children and 10% of school-aged children will develop significant headaches, including migraine. In children, compared with adults, these headaches tend to be shorter in duration, and often have a bifrontal or bitemporal location. The typical visual aura of migraine may not be seen until after 9 years of age. Vomiting, abdominal pain, and motion sickness are frequent symptoms in children with migraine. The duration of these episodes may also be shorter in children, sometimes lasting 30 minutes or less. The typical avoidance of lights (photophobia), sounds (phonophobia), and strong odors (osmophobia) is observed.

Commonly, children have periodic syndromes that develop early as precursors to migraine. These periodic syndromes include paroxysmal torticollis of infancy, benign paroxysmal vertigo of childhood, cyclic vomiting syndrome, and abdominal migraine.

Paroxysmal torticollis of infancy is an uncommon disorder characterized by repeated episodes of head tilting associated with nausea, vomiting, and headache. Attacks usually occur in infants and may last from minutes to days. Posterior fossa abnormalities need consideration in the differential diagnosis. Recent data have linked these symptoms to mutations in the *CACNA1A* gene in some patients. Optimal treatment is unknown, but when necessary, antimigraine preventatives are used.

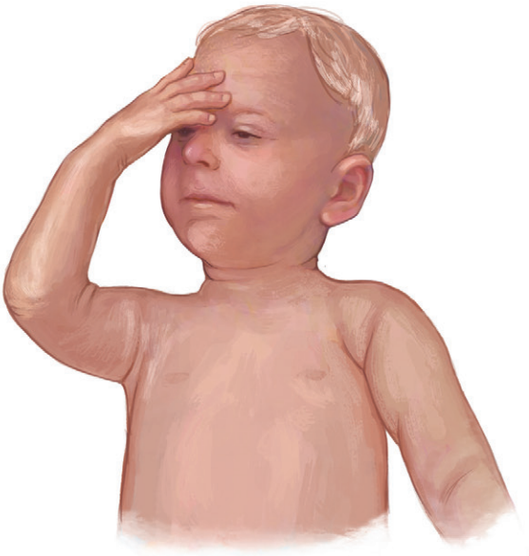
Benign paroxysmal vertigo of childhood is a condition characterized by brief episodes of vertigo, disequilibrium, and nausea, usually found in children aged 2 to 6 years. The patient may have nystagmus within but not between the attacks. The child does not have hearing loss, tinnitus, or loss of consciousness. Symptoms usually last only a few minutes. These children often develop a more common form of migraine as they mature.

Cyclic vomiting syndrome is manifested by recurrent periods of intense vomiting separated by symptom-free intervals. Many patients with cyclic vomiting have regular or cyclic patterns of illness. Symptoms usually have a rapid onset at night or in the early morning and last 6 to 48 hours. Associated symptoms include abdominal pain, nausea, retching, anorexia, pallor, lethargy, photophobia, phonophobia, and headache. The headache may not appear until the child is older. Cyclic vomiting syndrome usually begins when the patient is a toddler and resolves in adolescence or early adulthood; it rarely begins in adulthood. More females than males are affected by cyclic vomiting. Usually a family history of migraines is present. These children often experience severe fluid and electrolyte disturbances that require intravenous fluid therapy. Some children with cyclic vomiting respond to antimigraine drugs, such as amitriptyline or cyproheptadine. Migraine-associated cyclic vomiting syndrome is a diagnosis of exclusion. Other causes of cyclic vomiting include gastrointestinal disorders (malrotation), neoplasms, urinary tract disorders, metabolic, endocrine, and mitochondrial disorders.

In *abdominal migraine*, the patient may suffer from recurrent bouts of generalized abdominal pain with nausea and vomiting but often with no headache present. The episodes are often relieved by sleep, and later the child awakens feeling better. Abdominal migraine may alternate with typical migraine and can lead to typical migraine as the child matures. These children respond to migraine prophylactic medication.

The presence of fixed neurologic deficits, papilledema, or seizures should alert the physician to more concerning neurologic processes. In these instances, a neuroimaging study, such as a head MRI, should be considered.

Benign paroxymal vertigo of childhood



Cyclic vomiting syndrome has recurrent periods of intense vomiting separated by symptom-free intervals. Associated symptoms include abdominal pain, photophobia, phonophobia, and lethargy. Headache may not appear until child is older.

Benign paroxymal vertigo of childhood occurs in young children and involves brief episodes of vertigo, disequilibrium, and nausea

Paroxysmal torticollis of infancy involves recurrent episodes of head tilting associated with nausea, vomiting, and headache, lasting minutes to days

F. Netter M.D. C. Machado M.D. B. DaVanzo

Cranial Neuralgias: Trigeminal Neuralgia

Cranial neuralgias are characterized by brief but intensely severe paroxysms of pain in the distribution of a specific cranial nerve. Any cranial nerve or nerve branch may cause this type of pain, but the trigeminal nerve is the most commonly affected.

Classic trigeminal neuralgia, also known as *tic douloureux*, presents as paroxysmal attacks of severe, sharp, or stabbing pain in the cutaneous distribution of one or more divisions of the trigeminal nerve. This pain usually starts in the second or third divisions, affecting the cheek or the chin. The first division is affected alone in less than 5% of patients. These attacks may last from a fraction of a second to 2 minutes, occur multiple times per day, and tend to be stereotypic in nature.

Attacks of pain are often provoked by sensory stimuli, such as light touch, cold air or cold liquid over the face or gums (especially in small supersensitive areas known as "trigger zones"), or movements, such as talking, chewing, shaving, puckering lips, or brushing teeth. The paroxysm of pain may be followed by a refractory period where stimulation does not trigger pain. The pain is strictly unilateral. In the rare cases of bilateral trigeminal neuralgia, the episodic painful paroxysms are asynchronous and are independently triggered. Between attacks, the patient is usually pain free, although over time, some patients notice a dull or burning continuous pain in the same area.

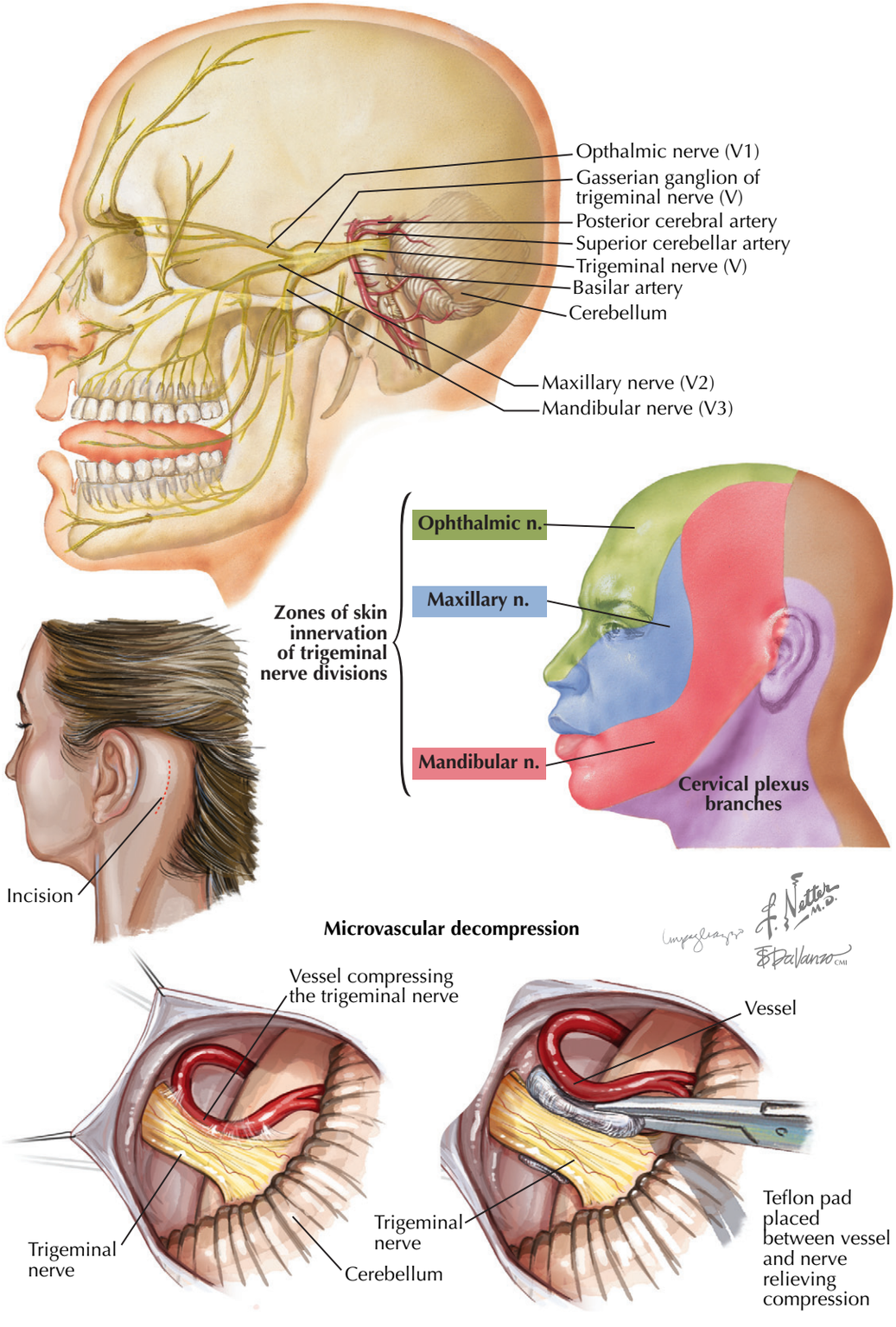
The temporal profile of trigeminal neuralgia may be fluctuating with exacerbations and spontaneous remissions lasting weeks to months, or even years. Patients with classic trigeminal neuralgia have a normal neurologic examination. The presence of a sensory deficit within the distribution of the trigeminal nerve suggests a trigeminal *neuropathy* and may indicate a secondary cause for the pain symptoms.

Although pathogenesis of trigeminal neuralgia is not completely understood, it is thought that the neuralgic pain is related to a chronic focal demyelination secondary to damage to the trigeminal nerve, usually within a few millimeters of where the nerve enters the pons, that is, the *root entry zone*. This damage is most often due to compression of the nerve by an aberrant loop of artery or vein. Rarely, this focal demyelination may also be caused by an aneurysm, arteriovenous malformation, or a neoplasm (i.e., trigeminal neuroma acoustic neuroma, epidermoid, or a meningioma). Demyelination from multiple sclerosis (MS) requires primary consideration in any young adult presenting with trigeminal neuralgia, and this is especially suspect in patients presenting with bilateral symptoms. Contrast-enhanced magnetic resonance imaging (MRI) with special sequencing of the trigeminal nerve should be performed to assess the patient for possible demyelination or a mass lesion.

There are several therapeutic options for individuals with trigeminal neuralgia. Most patients respond to carbamazepine. Other medications that may be effective include gabapentin, baclofen, or oxcarbazepine.

Patients who have failed or become intolerant to medical therapy are candidates for a variety of surgical procedures consisting of either *microvascular decompression* or *nerve ablation*. When treating the patient with open surgery, the aberrant vessel is separated from the nerve while a piece of surgical mesh is introduced between the aberrant vessel and the nerve. Surgical risks include damage to the nerve or surrounding structures, including damage to the auditory or facial nerves.

When an ablative procedure is used, the therapeutic goal is to precisely damage the trigeminal nerve so that it no longer transmits the pain signal well. These procedures include radiofrequency thermocoagulation, mechanical balloon compression, chemical (glycerol) injection, or gamma knife radiosurgery. Because the nerve is inherently damaged with these modalities, ablative procedures are accompanied by varying degrees of sensory loss. Unfortunately, trigeminal neuralgia has the potential to recur after any procedure, and may require repeat intervention.



Other Cranial Neuralgias

Glossopharyngeal neuralgia

Glossopharyngeal neuralgia is estimated to be 70 times less common than trigeminal neuralgia. This is a severe, paroxysmal, lancinating pain within the glossopharyngeal nerve distribution, usually deep in the throat, behind the tongue, and/or the ear. Characteristic triggers include swallowing, coughing, chewing, swallowing cold drinks, or touching the preauricular area. During these painful paroxysms, some patients may experience an associated bradycardia and/or asystole, which may result in syncope. Eight to 10 percent of patients will have concurrent trigeminal neuralgia.

Magnetic resonance imaging (MRI), with special attention to this nerve, is indicated to rule out secondary causes, including aberrant blood vessels, multiple sclerosis, or various mass lesions. Medical therapies are similar to those for trigeminal neuralgia. Spontaneous remissions also occur. Medically refractory individuals may require microvascular decompression or an ablative procedure, including a rhizotomy. In most cases, a rhizotomy with surgical division of the glossopharyngeal nerve and the upper rootlets of the vagus nerve provide relief.

Occipital neuralgia

This is a paroxysmal, lancinating pain within the distribution of the greater, lesser, and/or third occipital nerve, often starting at the upper neck or base of the skull and radiating to the back of the head. The stabbing, electric shocklike pain may be provoked by exposure to cold, light touch (i.e., brushing one's hair, or head and neck movement). Neurologic examination may demonstrate local nerve tenderness and percussion (Tinel sign) and may elicit painful paroxysms or paresthesias along the affected nerve's cutaneous distribution.

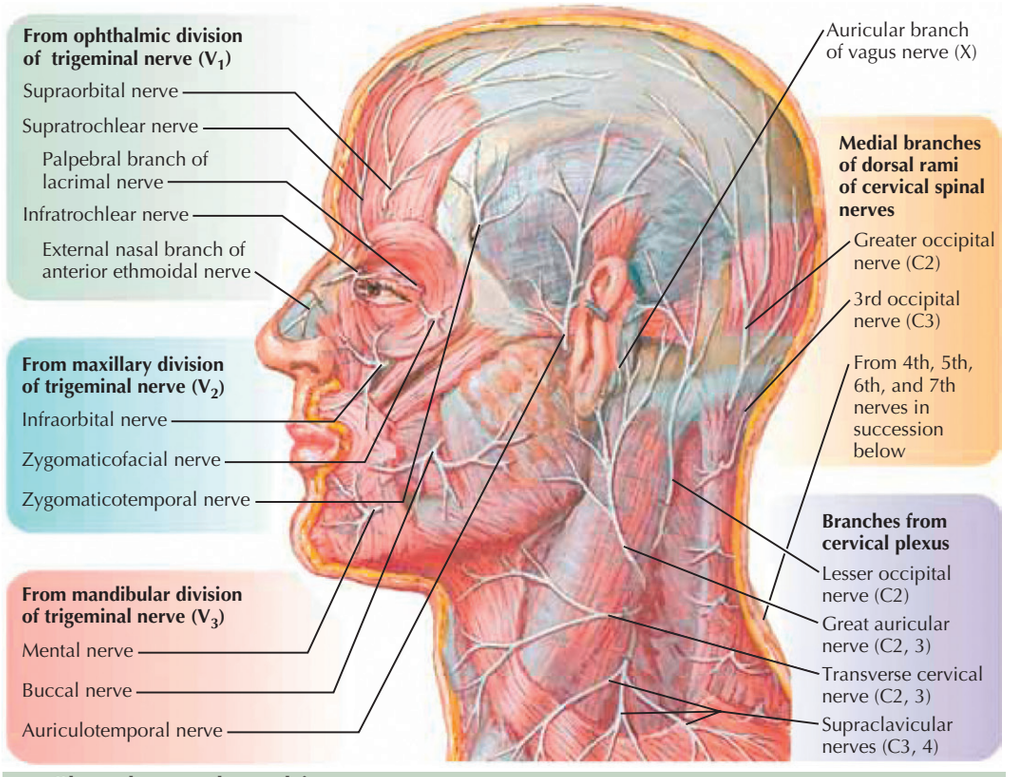
The occipital nerve is derived from the second cervical (C2) root, and therefore pain from C2 will manifest in a similar distribution. Similarly, skull base and upper cervical joint pathology may refer pain to the upper neck and posterior head. A cranial and/or cervical spine MRI focusing on the craniocervical junction is recommended.

An occipital nerve block with local anesthetic and glucocorticoids mixture is often the treatment of choice because this can be both therapeutically and diagnostically useful. After a block, the pain should ease temporarily, sometimes for weeks or months. Pain relief may be accompanied by temporary diminished sensation or dysesthesias within the occipital nerve distribution. Relief with an occipital block should be interpreted with caution because other primary headache syndromes, such as migraine and cluster, are also reported to respond to greater occipital nerve blockade.

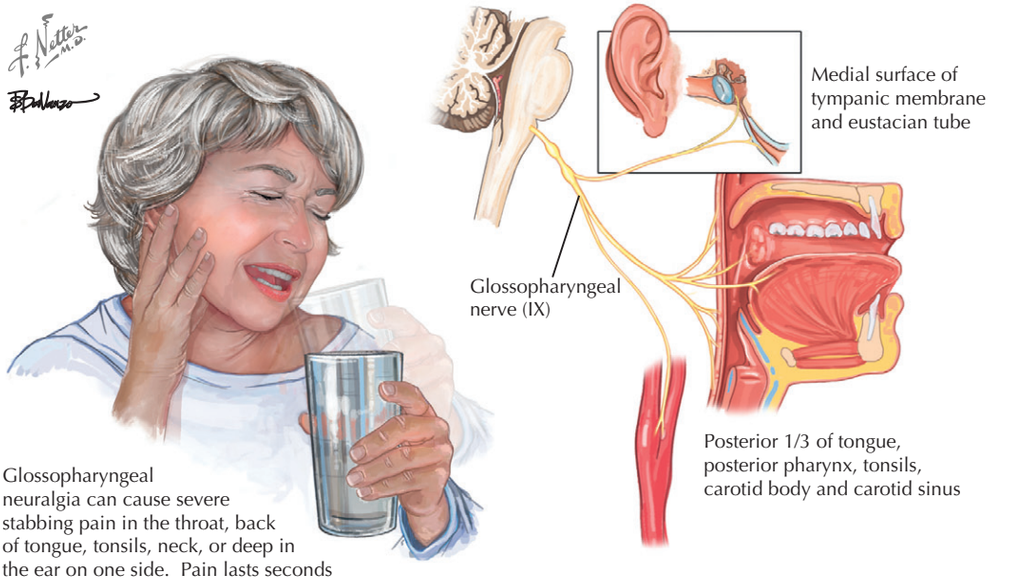
Less common cranial neuralgias

Neuralgic-type pain may arise from any nerve or nerve branch within the head or neck. This includes other nerves derived from the cervical plexus, such as the great auricular nerve, as well as terminal branches of the trigeminal nerve, for instance, supraorbital or infraorbital nerves. Neuralgia may develop spontaneously or subsequent to nerve trauma. The great auricular nerve, carrying lower-ear and jaw-line sensation, may be damaged during parotidectomy, rhytidectomy (facelift), or carotid endarterectomy.

Cutaneous head and neck nerves



Glossopharyngeal neuralgia



Glossopharyngeal neuralgia can cause severe stabbing pain in the throat, back of tongue, tonsils, neck, or deep in the ear on one side. Pain lasts seconds to minutes, and may occur spontaneously or be triggered by maneuvers such as swallowing, talking, coughing, or clearing the throat. Some patients may have severe bradycardia or asystole with episodes of pain.

It is important to inquire about *neuropathic* in contrast to *neuralgic* symptoms. Persistent pain or sensory dysfunction, that is, paresthesias, hypoesthesia, or allodynia, suggest neuropathy with underlying nerve damage. If a magnetic resonance image (MRI) is normal, evaluation for connective tissue disease and other inflammatory etiologies should be undertaken.

Two other situations deserve special mention. Persistent unilateral facial pain may rarely be the presenting symptom of lung cancer and is speculated to be due to referred pain from compression or invasion of the vagus nerve. Lung malignancy must be suspected in patients with a smoking history who report new unilateral facial pain or when weight loss or persistent cough is present. A chest x-ray or CT scan of the chest may be diagnostic.

Isolated mental or inferior alveolar nerve neuropathies occur in patients with various metastatic cancers, including hematologic malignancies as well as lung, breast, prostate, and kidney cancers. Patients present with numbness of the chin, lower lip or the gingiva of the lower teeth, with or without associated pain. This "numb chin syndrome" is usually the consequence of bone metastases or leptomeningeal seeding, but it may manifest without obvious cause.

Idiopathic Intracranial Hypertension (IIH), Pseudotumor Cerebri

Idiopathic intracranial hypertension (IIH), previously called pseudotumor cerebri, is a disorder of elevated intracranial pressure of unknown cause. It most often occurs in obese women of childbearing age. Patients commonly describe daily headaches, often severe and progressive, that may worsen with cough or strain, often accompanied by nausea. The headaches may awaken the patient from sleep. Papilledema is a diagnostic hallmark, and may be associated with blurred vision, enlarged blind spots, or visual-field defects. Additional symptoms include transient visual obscurations (blurring or loss of vision lasting seconds) or photopsia (brief sparkles or flashes of light) in one or both eyes, often provoked by positional changes and Valsalva maneuver. Horizontal diplopia due to unilateral or bilateral sixth nerve palsies may be present. Pulse-synchronous tinnitus, described as a "whooshing sound" like pulsating running water or wind, is common and is thought to represent vascular pulsations transmitted by cerebrospinal fluid under high pressure to the venous sinuses.

Diagnostic criteria include demonstrating elevated intracranial pressure by lumbar puncture, with an opening pressure greater than 200 mm H_2O in the non-obese and greater than 250 mm H_2O in the obese. Lumbar puncture needs to be performed in the lateral decubitus position with legs extended and with the patient relaxed. Falsely elevated pressures may occur in a sitting or prone position, or with anxiety. Cerebrospinal fluid (CSF) composition is normal. Neuroimaging studies tend to be unremarkable, although magnetic resonance imaging (MRI) may show findings of intracranial hypertension, including dilated optic nerve sheaths and an empty sella turcica. Diagnosis may require examination by an ophthalmologist because early or mild papilledema can be difficult to detect. Dilated funduscopic exam also helps differentiate true papilledema from pseudopapilledema secondary to optic disc drusen, tilted optic discs, or other mimickers. Photographs of the optic disc can serve as a baseline for serial monitoring. Formal visual perimetry should be performed. The most common finding is an enlarged blind spot; arcuate defects, inferonasal visual loss, or generalized visual field constriction may also be seen.

As IIH is by definition idiopathic, secondary causes of intracranial hypertension must be excluded: (1) mass lesions (i.e., intracranial tumor or abscess), (2) decreased CSF absorption via arachnoid granulations (e.g., adhesions after meningitis or subarachnoid hemorrhage), (3) increased CSF production (e.g., choroid plexus papilloma), and (4) venous outflow obstruction (e.g., cerebral venous sinus thrombosis). Because venous sinus thrombosis may mimic IIH, imaging of cerebral veins with magnetic resonance venography (MRV) is indicated with the standard MRI. Secondary intracranial hypertension also occurs with various metabolic, toxic, and hormonal disturbances, including imbalances in growth hormone, thyroid hormone, or aldosterone, and medications, including tetracycline, vitamin A, lithium, amiodarone, and corticosteroids (especially on withdrawal).

Permanent visual loss is the major morbidity associated with IIH, and management strategies depend on the degree and progression of papilledema. Serial photographs of the optic disc and serial testing of visual fields help guide treatment. The therapeutic goals are symptomatic relief by analgesia and reduction of CSF pressure. Weight reduction is very important in the management of overweight patients with IIH. If the patient has no visual loss and mild-to-moderate headache, weight loss and pain management may be all that is necessary. If the patient is taking medicines that exacerbate intracranial hypertension, these should be discontinued.

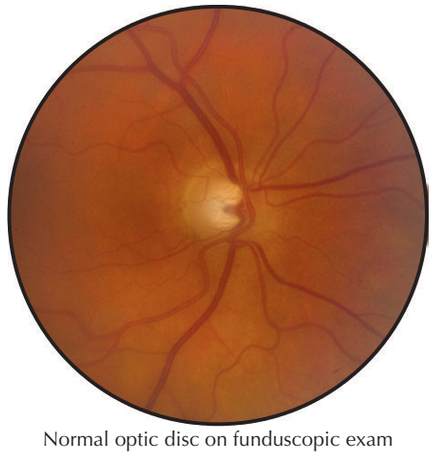
Acetazolamide is the most commonly used medical therapy for IIH. It is a carbonic anhydrase inhibitor and is thought to influence intracranial hypertension by inhibiting choroid plexus CSF secretion. It also may decrease appetite leading to weight loss.

Patients with visual loss require urgent treatment with corticosteroids to rapidly decrease intracranial pressure. However, because of their many potential side effects (weight gain, fluid retention, and rebound increased intracranial pressure on withdrawal of use), corticosteroids are not suitable for long-term care.

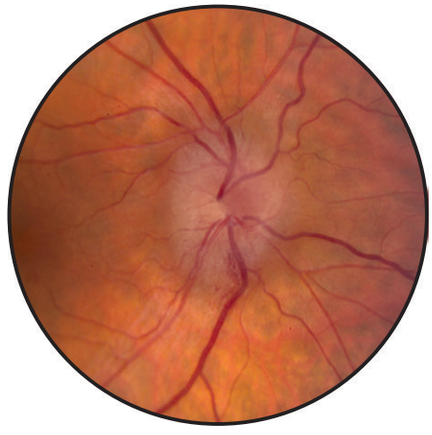
Medically intractable IIH can be treated with surgical procedures, such as optic nerve sheath fenestration or CSF shunting. Surgery is primarily indicated for visual loss or worsening vision due to papilledema.

Obese young woman: persistent headache

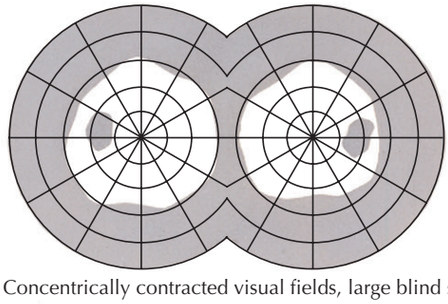
Important to exclude mimics of idiopathic intracranial hypertension (IIH), such as, sinus thrombosis, hypervitaminosis A; use of steroids, tetracycline, or nalidixic acid; chronic otitis media with dural sinus occlusion; endocrinopathy Addison or Cushing disease, hypoparathyroidism



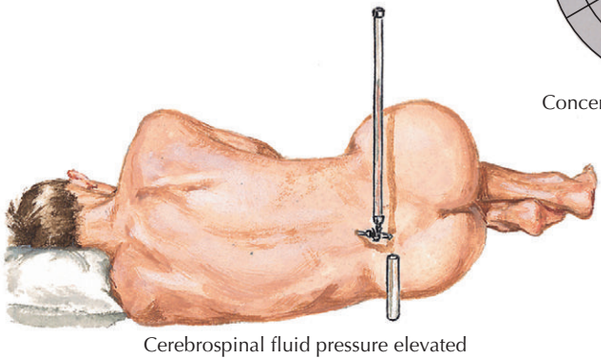
Normal optic disc on funduscopic exam



Papilledema



Concentrically contracted visual fields, large blind spots



Cerebrospinal fluid pressure elevated

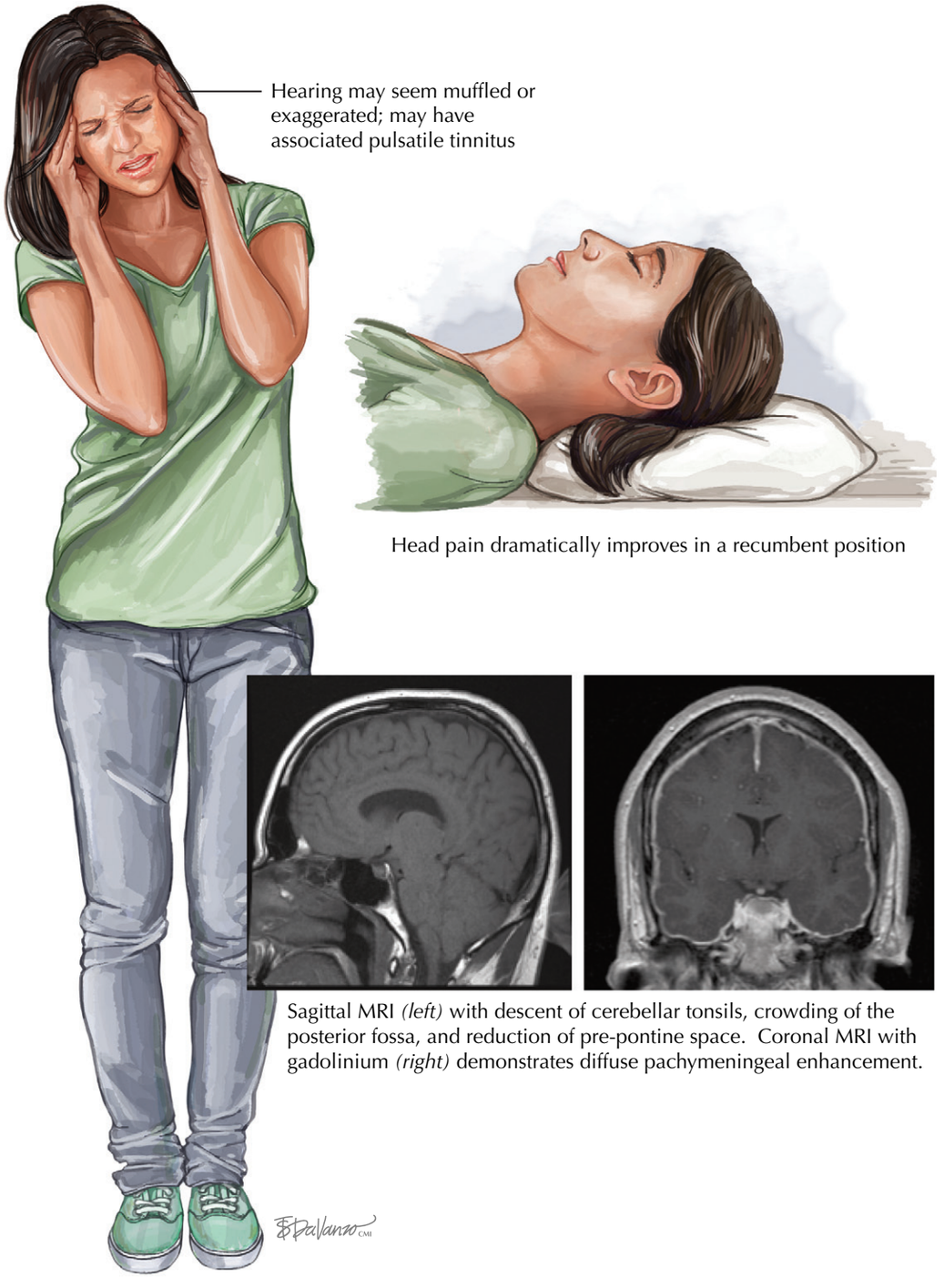
Intracranial Hypotension/ Low Cerebrospinal Fluid–pressure Headache

Orthostatic headache, a headache occurring in an upright position and relieved in a recumbent position, is the hallmark of a low cerebrospinal fluid (CSF)–pressure headache. Typically bilateral, these headaches may be throbbing or constant and are often aggravated by exertion, bending over, or Valsalva maneuvers. They may be accompanied by a variety of symptoms, including neck pain or stiffness, nausea, and photophobia. Associated hearing changes, such as "muffled hearing," tinnitus, or hyperacusis, are often present. Dizziness, visual blurring, diplopia (from sixth nerve palsy), radicular arm symptoms, and, rarely, facial numbness may also occur. The headaches may be daily (often late in the day) or intermittent. They may also present in an acute thunderclap presentation, mimicking subarachnoid hemorrhage.

The low CSF pressure or volume may relate to hypovolemia, overshunting of CSF, or a CSF leak. When the patient is upright, there is traction on the anchoring pain-sensitive structures of the brain, with brain descent or "sagging" in its cranial vault. Symptoms localizing to the cranial nerves and brainstem are thought to be due to traction or compression of these structures, although the hearing changes may relate to alteration of pressure in the perilymphatic system of the inner ear. CSF leaks may occur after any trauma to the meninges, including a lumbar puncture, an epidural injection, or spinal surgery. They may also occur spontaneously through weak meningeal diverticula or weak dura, as can be seen in connective tissue disorders. When the CSF leak is identified, it is most often at the level of the spinal cord, but rarely, intracranial leaks may occur through defects in the cribriform plate or sinuses. These patients may have clear nasal drainage, indicative of CSF rhinorrhea.

Patients with an orthostatic headache should be evaluated with a magnetic resonance image (MRI) of the brain with contrast, looking for diffuse pachymeningeal enhancement, descent of the cerebellar tonsils (mimicking a Chiari I malformation), crowding of the posterior fossa, decreased ventricle size, descent of the optic chiasm, reduction of the prepontine space, pituitary enlargement, engorgement of cerebral venous sinuses, and subdural fluid collections. A normal MRI brain does not rule out low CSF pressure headache and may be normal in up to one third of cases. If the clinical history is suggestive, other testing may be useful to identify the presence of a CSF leak. A radioisotope cisternogram involves injecting a radionuclide into the CSF and monitoring how fast it ascends and diffuses around the brain. A CSF leak can be demonstrated directly by radiotracer accumulation in the extra-arachnoid space or indirectly by a delay in radiotracer ascent to the cerebral convexities. If CSF rhinorrhea is suspected, nasal pledgets are placed with the cisternogram to determine if there is radioactivity in the nasal secretions. Beta-2 transferrin, which is present in CSF, may be detected in CSF rhinorrhea. Lumbar puncture may not be necessary for the diagnosis of low-pressure headache. When performed, this may show a normal-to-low (<60 mm H_2O) opening pressure and normal-to-high CSF protein. Mild pleocytosis (WBC 10-50) may also occur.

Most headaches due to low CSF pressure are self-limited. Conservative measures, such as bed rest, caffeine, and increased fluid intake, are advocated as first-line treatments. A persistent headache may require an epidural blood patch. If the site of the leak is known, the blood patch can be relatively targeted toward this site. In spontaneous CSF leaks, MRI of the spine might show fluid collections outside the arachnoid space, engorgement of the epidural venous plexus, or meningeal diverticula. The presence of a meningeal diverticulum does not, of course, guarantee that it is the site of CSF leak. The most reliable method for detecting the actual site of the leak is to identify extravasation of CSF into the paraspinal soft tissues, which is best seen on a computed tomography (CT) myelogram. When more conservative measures fail, surgical intervention may be considered.



Giant Cell Arteritis

Giant cell arteritis (GCA), also known as temporal arteritis, is a generalized vasculitis affecting large- and medium-sized vessels. This arteritis involves the aorta and its extracranial vessels, including the external carotid artery with its superior temporal division and, less commonly, the occipital scalp artery. Unlike other forms of vasculitis, GCA rarely involves the skin, kidneys, and lungs.

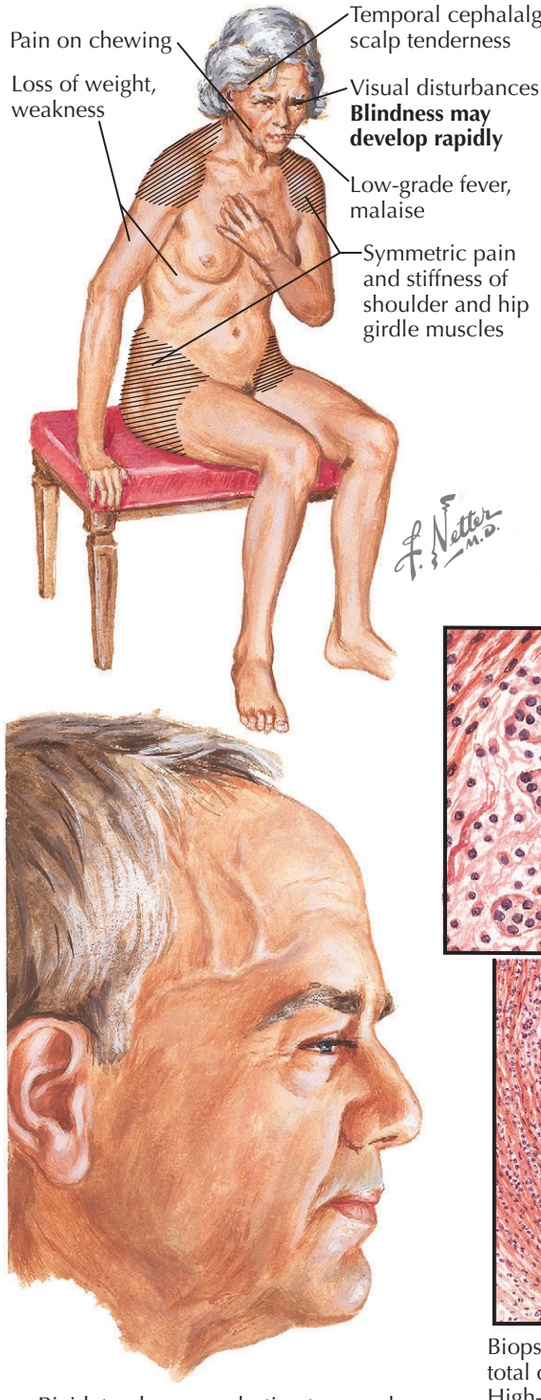
Signs and symptoms of GCA may begin quite abruptly or sometimes gradually over a number of months before becoming clinically recognizable. Its classic symptoms relate to the inflammation of, and reduced blood flow through, the involved arteries. Most patients present with bilateral headache, often complaining of scalp pain with normally non-noxious stimuli, such as brushing their hair. Transient visual loss, or even permanent visual loss, may result from involvement of the posterior ciliary, ophthalmic, and retinal arteries. Painful cramping or claudication often occurs with the use of the jaw while chewing or on movement of the tongue. Many patients have associated systemic symptoms, such as fever, malaise, sweating, and weight loss. Examination may reveal that the temporal and occipital vessels are firm, tender, and pulseless. Sausage-shaped thickenings or nodularity may be palpable along the vessel wall.

The incidence of GCA increases with advancing age and must be considered in all patients older than 50 years who develop a new headache, have a change in their previous headache characteristics, or have acute-onset transient visual loss. Polymyalgia rheumatica (PMR) is an overlapping disease, and symptoms of PMR are found in more than one third of biopsy-proven cases of GCA. These PMR symptoms include neck pain, morning stiffness, and myalgias in shoulder and pelvic muscles.

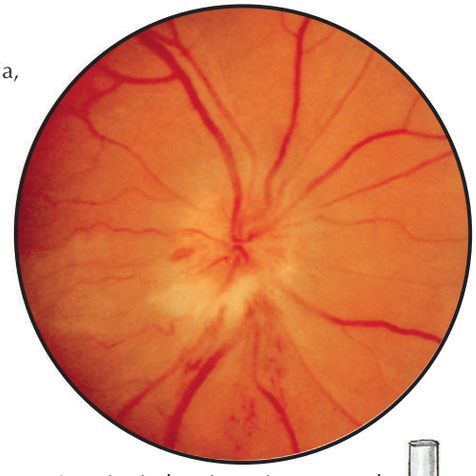
Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are nonspecific markers of inflammation that, when elevated—often to very high levels (60 to 120 mm/hr for ESR and greater than 40 for CRP)—are supportive of the diagnosis of GCA. Sedimentation rate is reported to be normal in about 5% of patients with GCA. Normochromic anemia, low albumin, and thrombocytosis are often present.

Diagnosis can only be established with certainty by biopsy of the temporal artery and demonstration of focal inflammation, giant cells, and interruption of the internal elastic lamina. Of importance, none of the testing options have a sensitivity of 100%. Because vessel involvement can be segmental, the biopsy may also be falsely negative. If the biopsy is negative but the clinical suspicion remains high, such as in an elderly patient with a new headache and jaw claudication or systemic symptoms, other tests should be performed, looking for signs of vessel inflammation. These would include another site for artery biopsy, such as the contralateral temporal artery or posterior occipital scalp artery, a magnetic resonance angiogram, duplex ultrasonography, or a positron emission tomography (PET) scan.

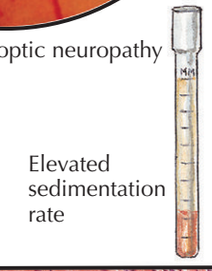
When unrecognized and untreated, GCA can lead to a variety of complications. The most devastating is sudden permanent unilateral or sequential bilateral vision loss from anterior ischemic optic neuropathy (AION) or retinal artery occlusion, cerebrovascular ischemia—more commonly in the vertebral basilar system, or even a myocardial infarction. Involvement of the aorta very rarely may lead to aortic dissection or aneurysm. Prompt treatment with corticosteroids is required to prevent permanent sequelae, especially visual loss. Headache and systemic symptoms usually improve within 48 hours of starting treatment, but visual loss and ischemic complications are often irreversible. Biopsy should be obtained within 24 hours of starting steroids.



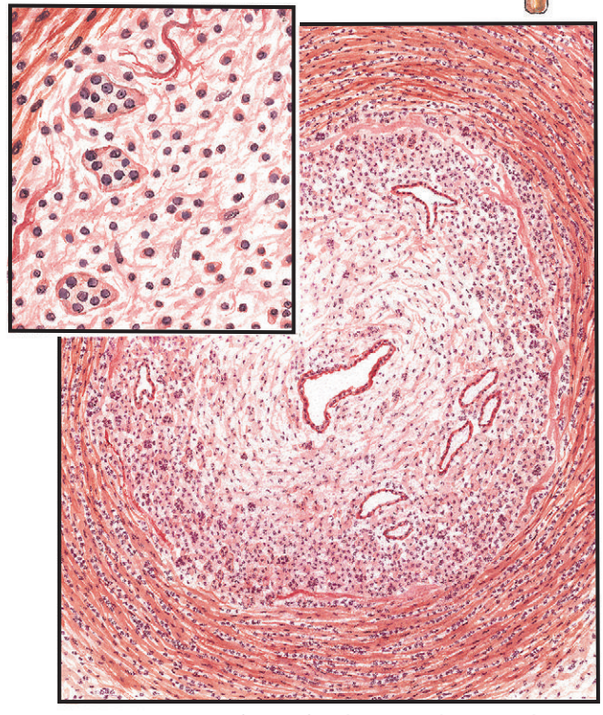
Rigid, tender, nonpulsating temporal arteries may be visible or palpable



Anterior ischemic optic neuropathy



Elevated sedimentation rate



Biopsy specimen of superficial temporal artery: almost total obliteration of lumen with some recanalization. High-power insert shows infiltration with lymphocytes, plasma cells, and giant cells; fragmentation of internal elastic lamina.

Contiguous Structure Headaches

SINUS HEADACHE

Most patients presenting with "sinus headache" actually have migraine. This misdiagnosis may arise based on the location of pain and may be even more tricky if the patient's migraine is triggered by weather changes or if it is associated with parasympathetic symptoms, such as nasal congestion, lacrimation, or rhinorrhea. When inflammation of the sinuses is the source of headache, it is almost always accompanied by facial tenderness and pain, nasal congestion, or nasal discharge. Inflammation of the sinuses is called *sinusitis*, or *rhinosinusitis* when the nasal passages are also affected.

Patients perceive *maxillary sinus* pain in the cheek, gums, and upper teeth. *Frontal sinus* pain tends to involve the forehead, while ethmoid sinusitis causes pain behind or between the eyes. *Sphenoid sinusitis* is characterized by pain in variable locations, including the frontal, occipital, temporal, or vertex locations.

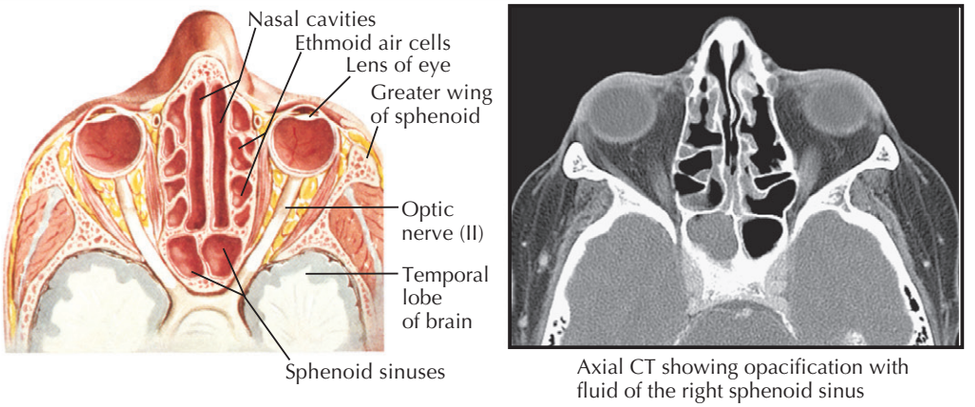
Symptoms lasting fewer than 7 days tend to be viral in origin. In contrast, acute bacterial rhinosinusitis presents with more than 7 days of purulent rhinorrhea, nasal congestion, facial or dental pain/pressure, an accompanying cough, halitosis, and, if severe, fever (50% of adults). Fungal sinusitis may be acute or chronic (lasting more than 12 weeks) and is of particular concern in patients who are immunocompromised. Rhinosinusitis can usually be diagnosed on clinical suspicion. However, diagnosing recurrent, chronic, or complicated disease depends on computed tomography (CT), magnetic resonance imaging (MRI), or direct visualization with nasal endoscopy. Treatment involves the appropriate antibacterial or antifungal medications.

Sphenoid sinusitis is an uncommon infection that may manifest as an acute or subacute headache associated with nausea and vomiting. It may accompany pan sinusitis but, when isolated, may not have associated nasal symptoms. It can mimic many other causes of headache, including aseptic meningitis, migraine, and trigeminal neuralgia. Excessive tearing, photophobia, and paresthesias in the trigeminal nerve distribution may accompany sphenoid rhinosinusitis. This should be considered in patients with a severe, intractable new-onset headache that worsens with coughing, bending, or walking; interferes with sleep; is progressive in severity; and does not respond well to analgesics.

TEMPOROMANDIBULAR DISORDER

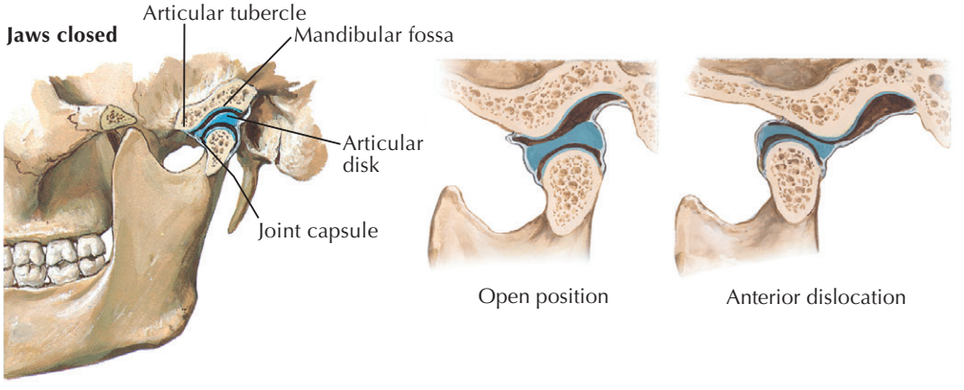
Pain from the *temporomandibular joint* (TMJ), with its associated musculature and ligaments, can be referred to the head. The manifesting symptom is usually pain in the preauricular area, TMJ, or muscles of mastication, aggravated by jaw function. Associated ear pain is common. Patients may have TMJ noise (such as clicking or crepitus) on movement, locking on jaw opening, or limited or asymmetric jaw movement. Diagnosis is confirmed by tomograms of the maxilla and mandible, including open and closed position views of bilateral TMJs, and a panoramic radiograph to look for bony pathology. Initial treatment is conservative, with an oral appliance or bite plate and possibly physical therapy. Medication such as nonsteroidal anti-inflammatory drugs, muscle relaxants, and tricyclic antidepressants can also be tried. Rarely, surgery is indicated for medically refractory patients.

Sinusitis

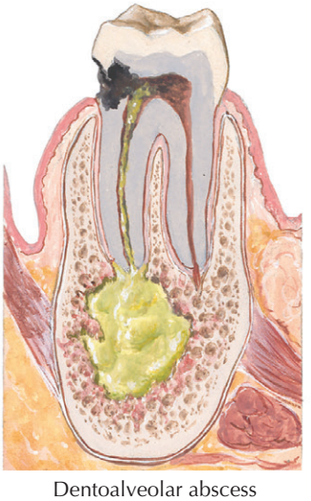


Axial CT showing opacification with fluid of the right sphenoid sinus

Temporomandibular disorder

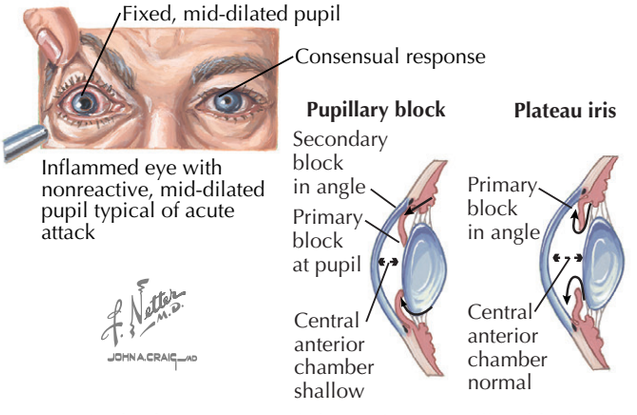


Dental disease



Dentoalveolar abscess

Glaucoma-Primary closed angle



Angle closure may result from primary pupillary block with bulging iris or from less common plateau iris (primary occlusion at periphery of iris)

DENTAL

Inflammatory dental disease may cause intense, throbbing, poorly localized pain unilaterally that is generally provoked by stimulation of the offending tooth. This is often associated with increased sensitivity to hot and cold. Occasionally, infection of the dental pulp or apical root may cause neuralgic type pain in the second and third trigeminal divisions, which is difficult to distinguish clinically from trigeminal neuralgia. For this reason, patients with trigeminal neuralgia may undergo one or more unnecessary dental procedures before the correct diagnosis is made. Conversely, it is important to exclude true dental disease before making a diagnosis of trigeminal neuralgia.

GLAUCOMA

Acute angle–closure glaucoma occurs when the normal drainage of aqueous humor is blocked, leading to sudden increased intraocular pressure. This creates severe eye pain sometimes associated with a unilateral headache, nausea/vomiting, conjunctival injection, and a mid-dilated nonreactive pupil. Patients may describe intermittent visual blurring while "seeing halos around objects." The severe unilateral headache may mimic migraine or cluster headache. Dim light and certain medications (e.g., anticholinergics, sympathomimetics) that result in pupillary dilation may precipitate the pain. Chronic open-angle glaucoma, the more common form of glaucoma, is not a cause of headaches.

Thunderclap Headache and Other Headache Presenting in the Emergency Department

Most patients who seek care in an emergency department have a primary headache disorder. Nevertheless, an emergency medicine physician must evaluate for the possibility of an underlying, secondary cause for the pain. New headaches beginning during vigorous exertion or after head/neck trauma require consideration of an intracranial hemorrhage or cervicocephalic arterial dissection. Most concerning are those patients presenting with an *explosive*, *debilitating*, *or "thunderclap"* headache often referred to as the *"worst headache of my life"* or *"I felt like I was hit with a sledge hammer."* Because of the urgency of diagnosis, every individual experiencing these symptoms must initially be investigated for a subarachnoid or intracranial hemorrhage. If either type hemorrhage is ruled out, other pathologic mechanisms for an acute severe headache require consideration (see table at right).

Equally important is the patient presenting with an acute headache and new-associated neurologic symptoms, particularly focal motor or sensory loss, language dysfunction, or encephalopathic symptomatology, such as confusion or seizures. Other historical details in the acute headache patient also cause significant concern warranting further and immediate evaluation. These include older age, immunocompromise, recent infection or fever, history of cancer, clotting or bleeding disorders (particularly including therapeutic anticoagulation), progressively worsening headache severity, or symptoms of systemic illness, that is, weight loss, fatigue, myalgia, or unexplained anemia.

Any patient whose clinical presentation with headache includes fever, alteration in consciousness or mentation, or an overall toxic appearance requires an urgent evaluation for a possible underlying infection. Nuchal rigidity usually indicates meningeal irritation, which can be seen with either subarachnoid hemorrhage or meningitis. Papilledema reflects increased intracranial pressure and warrants further investigation for disorders causing mass effect, such as tumor, infection, hemorrhage, or idiopathic intracranial hypertension.

Causes of Thunderclap Headache

	Headache	Typical Presentation	Diagnosis/Testing
Secondary	Subarachnoid hemorrhage	Sudden and severe HA +/− N/V; may have ophthalmoplegia or altered mentation	CT w/o contrast; LP for xanthochromia
	Intracranial hemorrhage	Sudden and severe HA; focal neurologic signs; seizures; altered; mentation	CT w/o contrast
	Cerebral venous sinus thrombosis	May mimic Idiopathic intracranial hypertension	Examine for papilledema; MRV; CT w/contrast for empty delta sign
	Arterial dissection	Sudden unilateral HA +/− neck pain; may be posttraumatic; may mimic migraine	Examine for Horner sign; MRI/MRA head and neck (CTA or carotid U/S if MRI not available)
	Reversible cerebral vasoconstriction syndrome	Recurrent thunderclap HA; photophobia or nausea possible	Cerebral angiogram is the gold standard: however, can start with MRA or CTA
	Ischemic stroke	New neurologic deficits, in specific vascular distribution	MRI w/DWI: Large or subacute/chronic; may show on CT
	Pituitary apoplexy	HA; visual changes +/− altered mentation	CT or MRI (MRI more sensitive)
	Third ventricular colloid cyst with hydrocephalus	Recurrent severe headaches, sometimes relieved with recumbency	CT w/ contrast or MRI
	Spontaneous intracranial hypotension	Postural HA, worse upright +/− symptoms of low CSF pressure	MRI with gadolinium; in some cases cisternogram, CT myelogram occasionally
	Posterior reversible leukoencephalopathy (PRES)	HA with vision changes, seizures or altered mentation; marked hypertension on occasion	CT or MRI (MRI more sensitive)
	Intracranial infection (e.g., bacterial meningitis)	Fever, chills, meningismus, leukocytosis	Lumbar puncture for CSF, glucose, protein, and cells; MRI may show meningeal enhancement. CT before lumbar puncture if concern for mass effect
	Glaucoma	Ipsilateral HA with slowly responsive mid-dilated pupil	Ophthalmology consult
Primary	Primary sexual or exertional HA	Sudden onset before, during, or right after orgasm or peak of exertion.	Diagnosis of exclusion especially if this is the first episode. Consider MRI/MRA to rule out aneurysm with SAH
	Primary cough HA	Sudden onset with cough or strain, 1 second to 30 minute duration	Diagnosis of exclusion
	Primary thunderclap HA	Max intensity in < 1 minute; lasts 1 hour to 10 days	Diagnosis of exclusion

DWI, Diffusion-weighted imaging, *HA,* headache, *N/V,* nausea/vomiting.

SUBARACHNOID AND INTRAPARENCHYMAL HEMORRHAGE

Although the *classic thunderclap presentation* typically heralding the rupture of an intracerebral aneurysm with subarachnoid hemorrhage (SAH) is not easily overlooked, occasional SAH patients present with more subtle symptoms. Any headache that is *unusual for the patient*, especially if there is associated neck pain or stiffness, needs to lead the clinician to question the possibility of SAH. Intraparenchymal hemorrhage is more likely to cause relatively rapid evolution of focal neurologic symptoms as well as seizures and altered mentation, depending on the size and location of the hematoma. If the blood tracks into the cerebrospinal fluid (CSF), intraparenchymal hemorrhage may also

Thunderclap Headache and Other Headache Presenting in the Emergency Department
(Continued)

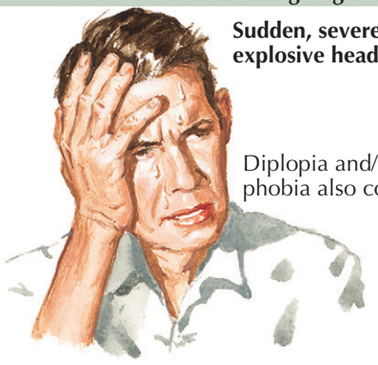
cause meningeal irritation and neck stiffness. A history of anticoagulation, especially in an older patient presenting with headache is particularly concerning for hemorrhage. A computed tomography (CT) scan is diagnostic. Information on evaluation and management of intracranial hemorrhage is detailed in Section 9.

REVERSIBLE CEREBRAL VASOCONSTRICTION SYNDROME

Reversible cerebral vasoconstriction syndrome is characterized by recurrent thunderclap headaches. Pain peaks within minutes, last minutes to hours, sometimes more than 1 day, and tends to recur over a few days to 2 weeks. Patients may have associated focal neurologic deficits, and one third of patients experience seizures. Risk factors include hypertension, preeclampsia/eclampsia (i.e., postpartum angiopathy), sympathomimetic drugs or serotonergic agents (drug-induced cerebral vasculopathy), catecholamine-secreting tumors (i.e., pheochromocytoma), and binge alcohol drinking.

Cerebrospinal fluid is normal or near normal (mild elevations in protein or white blood cells). MRI and CT may be normal, may show features similar to posterior reversible encephalopathy syndrome (PRES), or may show evidence of intracranial hemorrhage, especially cortical subarachnoid hemorrhage. The diagnostic gold standard is conventional angiography demonstrating multifocal segmental vasoconstriction subsequently reversible within 12 weeks after onset. However, magnetic resonance angiography (MRA) and computed tomography angiography (CTA) are less invasive and may provide supporting diagnostic evidence. Although there is no evidence-based study to support a specific therapy, nimodipine is the treatment most often recommended for the vasospasm.

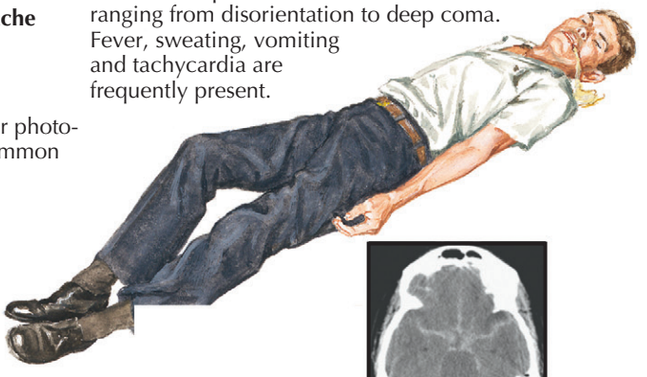
Subarachnoid hemorrhage signs and symptoms



Sudden, severe, explosive headache

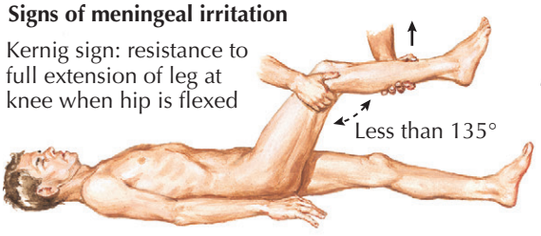
Diplopia and/or photophobia also common

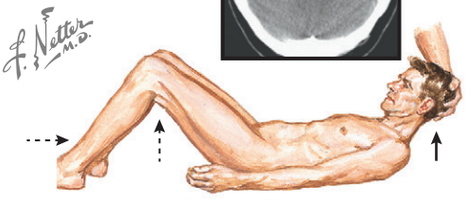
Transient or persistent alteration in consciousness ranging from disorientation to deep coma. Fever, sweating, vomiting and tachycardia are frequently present.



Signs of meningeal irritation

Kernig sign: resistance to full extension of leg at knee when hip is flexed

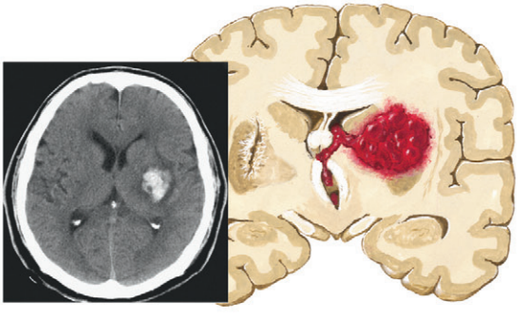




Brudzinski sign: flexion of both hips and knees when neck is passively flexed

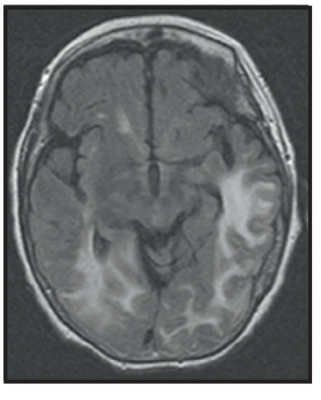
Intracerebral hemorrhage (hypertensive)

CT scan showing large putaminal hemorrhage

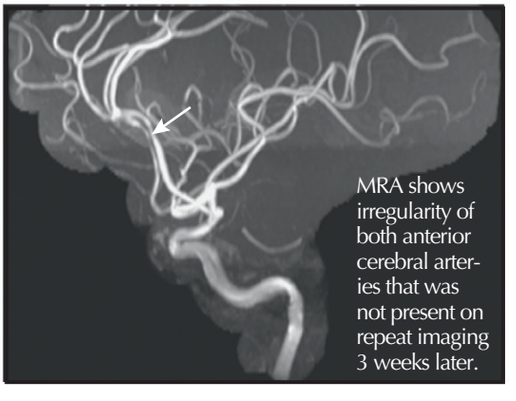


Moderate-sized intracerebral hemorrhage involving left putamen, with rupture into lateral ventricle; brain distorted to opposite side; scar of healed hemorrhage on right side

Acute hypertensive crisis/posterior reversible encephalopathy syndrome (PRES)



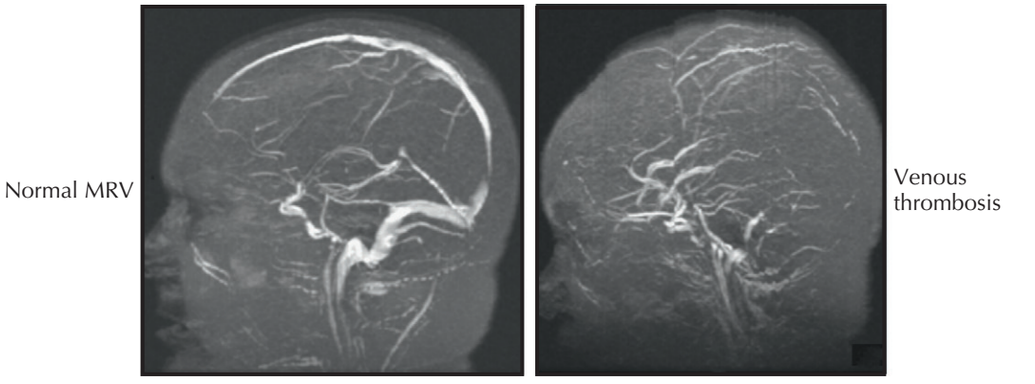
Reversible cerebral vasoconstriction syndrome

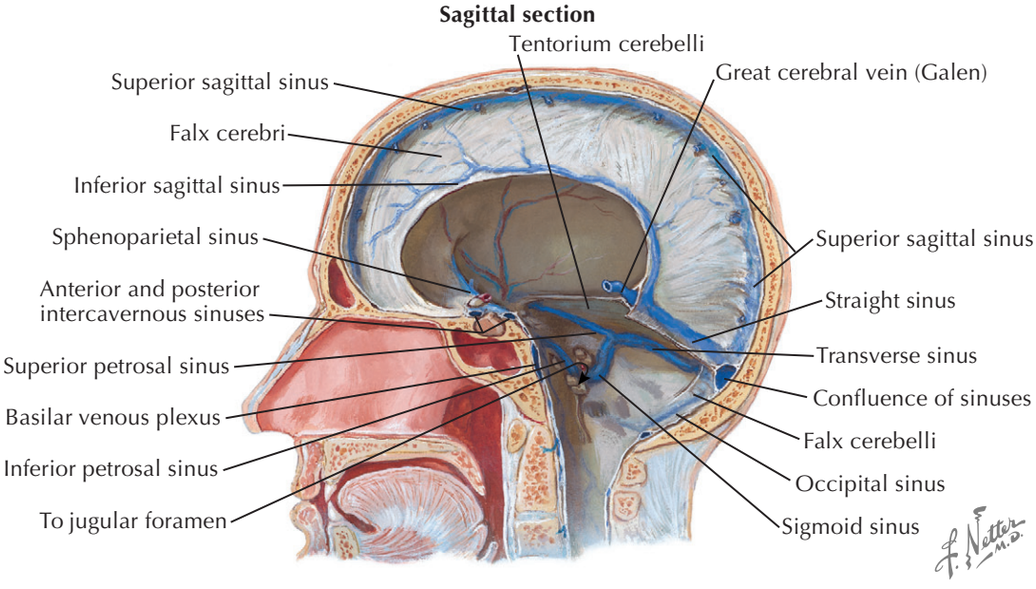


ACUTE HYPERTENSIVE CRISIS/POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (PRES)

Patients with *hypertensive crisis* may present with acute or subacute posterior headaches sometimes accompanied by dyspnea, chest pain, lightheadedness, focal neurologic deficits, and epistaxis. Markedly elevated blood pressure (generally greater than 180/120 mm Hg) may be associated with hypertensive encephalopathy or malignant hypertension with retinal hemorrhages/exudates, papilledema, intracranial hemorrhage, or other organ damage, including pulmonary edema or malignant nephrosclerosis. The cause for the hypertension needs to be identified. Immediate commencement of rapidly acting antihypertensive therapies is the primary treatment; general symptom management is also needed for the dyspnea, chest pain, and so forth.

Cerebral venous sinus thrombosis





Thunderclap Headache and Other Headache Presenting in the Emergency Department *(Continued)*

Posterior reversible leukoencephalopathy, also termed posterior reversible encephalopathy syndrome (PRES), is a syndrome involving vasogenic edema preferentially affecting the white matter of the posterior brain, including the occipital lobes and cerebellum. On MRI, the vasogenic edema appears as a relatively symmetric increased T2 signal, not conforming to a particular vascular distribution. Patients present with headache that may be accompanied by seizures, visual changes, and altered mentation. This syndrome may be associated with hypertensive encephalopathy, preeclampsia/eclampsia, and certain cytotoxic and immunosuppressant drugs.

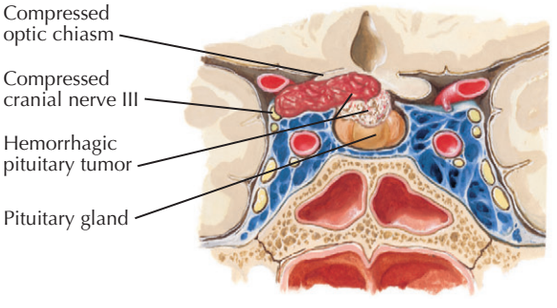
CEREBRAL VENOUS THROMBOSIS

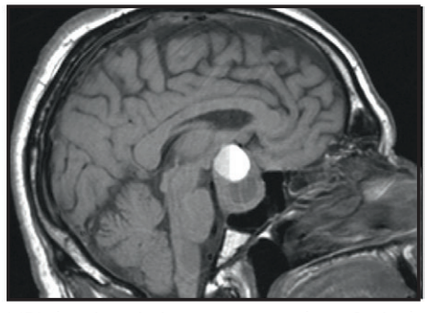
Cerebral venous thrombosis (CVT) most often has a subacute presentation; however, a minority of patients present with thunderclap headache. Headaches are persistent and tend to be worse in the morning, in a recumbent position, and with Valsalva maneuvers, such as coughing or straining. Headaches may be accompanied by other signs of increased intracranial pressure, such as papilledema, seizures, and altered mentation. If venous infarction occurs, focal neurologic deficits may be present. If the venous thrombosis is in the superior sagittal sinus, a CT scan with contrast may show a filling defect around the thrombus, called the "empty delta" sign. However, CT and MRI may be unremarkable, requiring MR venography for diagnosis. When diagnosis is established, causative or predisposing conditions need to be identified, including thrombophilic states or occult malignancy. Patients are generally treated with anticoagulation.

PITUITARY APOPLEXY

Acute pituitary apoplexy is an uncommon syndrome due to hemorrhage or infarction of the pituitary gland in the setting of a pituitary macroadenoma. Patients may present with a sudden and severe headache, ophthalmoplegia, visual disturbance, nausea/vomiting, altered mentation, meningismus, and sometimes fever. In the emergency room, this may mimic a severe migraine or aseptic meningitis, and in severe cases may cause adrenal crisis, coma, or death. Although pituitary pathology is usually noted on a noncontrast CT scan of the head, an MRI is more sensitive.

Pituitary apoplexy



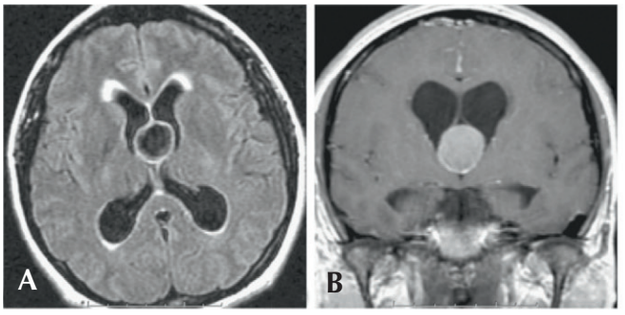


MRI showing pituitary tumor apoplexy. Sagittal image shows fluid-fluid level within the area of recent hemorrhage.

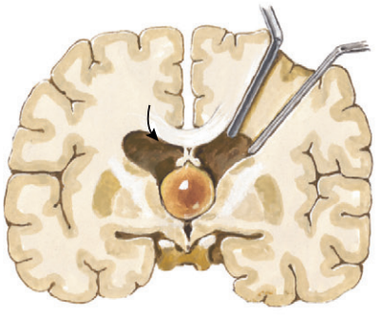
COLLOID CYST

A colloid cyst is a benign cyst that arises in the anterior third ventricle just posterior to the foramen of Monro. Because of its location, it can act as a ball-valve transiently obstructing the ventricular outflow and causing obstructive hydrocephalus. Patients may present with intermittent symptoms of increased intracranial pressure, including sudden and severe headaches with

Colloid cyst

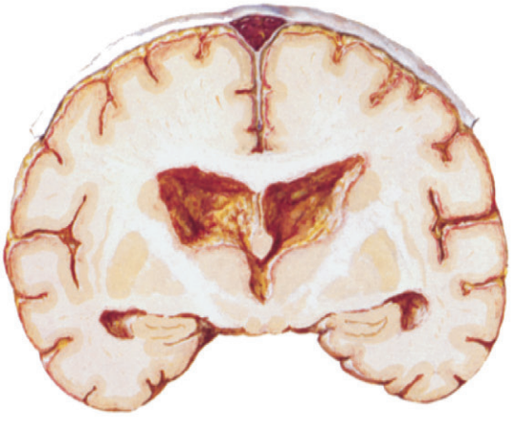


Colloid cyst. (**A**) Axial, FLAIR and (**B**) coronal, T1-weighted gadolinium enhanced images demonstrate a round cystic mass in the region of the foramina of Monro, with dilatation of the lateral ventricles. The signal characteristics are variable. This cyst is hypointense on T2-weighted images and bright on T1-weighted imaging, with minimal peripheral enhancement.

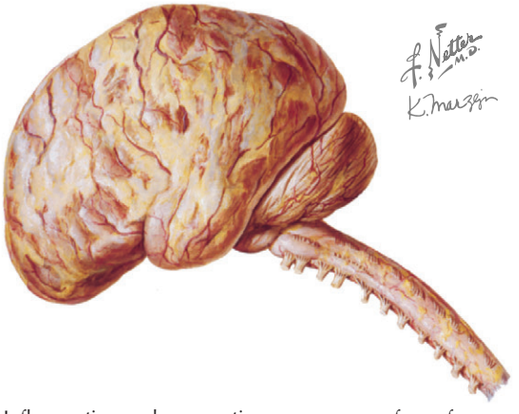


Colloid cyst of 3rd ventricle and surgical approach via right prefrontal (silent) cerebral cortex.

Bacterial meningitis

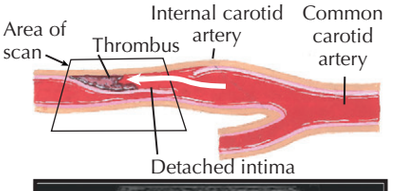


Thrombophlebitis of superior sagittal sinus and suppurative ependymitis, with beginning hydrocephalus

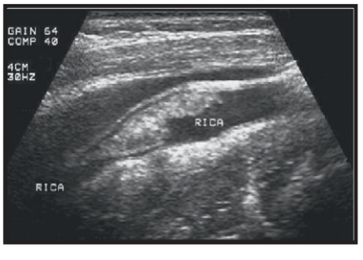


Inflammation and suppurative process on surface of leptomeninges of brain and spinal cord

Arterial dissection



Intimal tear allows blood flow to dissect beneath intimal layer, detaching it from arterial wall. Large dissection may occlude vessel lumen



Carotid dissection: Ultrasound of the carotid artery with clot formed between layers of the artery (near the upper right internal carotid artery [RICA] label)

Thunderclap Headache and Other Headache Presenting in the Emergency Department

(Continued)

nausea/vomiting; these often improve in a recumbent position. If obstructive hydrocephalus is prolonged, deterioration with altered mentation, seizures, coma, and death may occur. Diagnosis is made by CT or MRI, and early surgical intervention is necessary for symptomatic colloid cysts.

POST-TRAUMATIC HEADACHE

Most headaches after trauma are of the benign tension-type. However, a history of trauma should alert the physician to the possibility of hemorrhage, especially in the setting of anticoagulation. This includes subarachnoid and intraparenchymal hemorrhage as mentioned above, as well as subdural or epidural hematoma (see Section 14). Subdural hematomas may manifest insidiously with headache, decreased level of consciousness, balance or gait difficulty, cognitive impairment or memory loss, or focal neurologic deficits.

Carotid or vertebral arterial dissection may also occur after trauma. These often manifest as a unilateral headache, with or without neck pain, and may be associated with focal neurologic signs, such as Horner syndrome (ptosis and miosis unilaterally).

Local injury to neck structures, including cervical vertebra or disks, can create a referred headache with associated neck pain. Head trauma may be followed by the development of a postconcussive syndrome, and headaches may be accompanied by dizziness, fatigue, irritability, anxiety, insomnia, and decreased concentration.

INTRACRANIAL INFECTION

Meningitis or meningoencephalitis must be suspected in any patient with new headache accompanied by neck stiffness or fever, nausea/vomiting, and photophobia, mimicking a severe migraine. In addition to a lumbar puncture, blood cultures are drawn and antibiotics started empirically when bacterial meningitis is suspected. Patients with focal neurologic findings, papilledema, or altered mentation must have a CT or MRI before lumbar puncture, to exclude a brain abscess with associated mass effect. In a patient with a new headache associated with altered mentation or seizure, rapid initiation of acyclovir is recommended to cover for herpes simplex virus (HSV) while results of diagnostic testing are pending. The details on diagnosis and evaluation of intracranial infection are outlined in Section 11.

HEAD TRAUMA

Skull: Anterior and Lateral Aspects

The anterior, or facial, aspect of the skull is composed of the frontal part of the calvaria (skullcap) above and the facial bones below. The facial contours and proportions are largely determined by the underlying bones, and it is a commonplace observation that they show considerable variations associated with age, sex, and race. The outer surface of the frontal bone underlies the brow. The facial skeleton is irregular, a feature accentuated by the presence of the orbital openings, the piriform aperture, and the superior and inferior dental arches of the oral cavity.

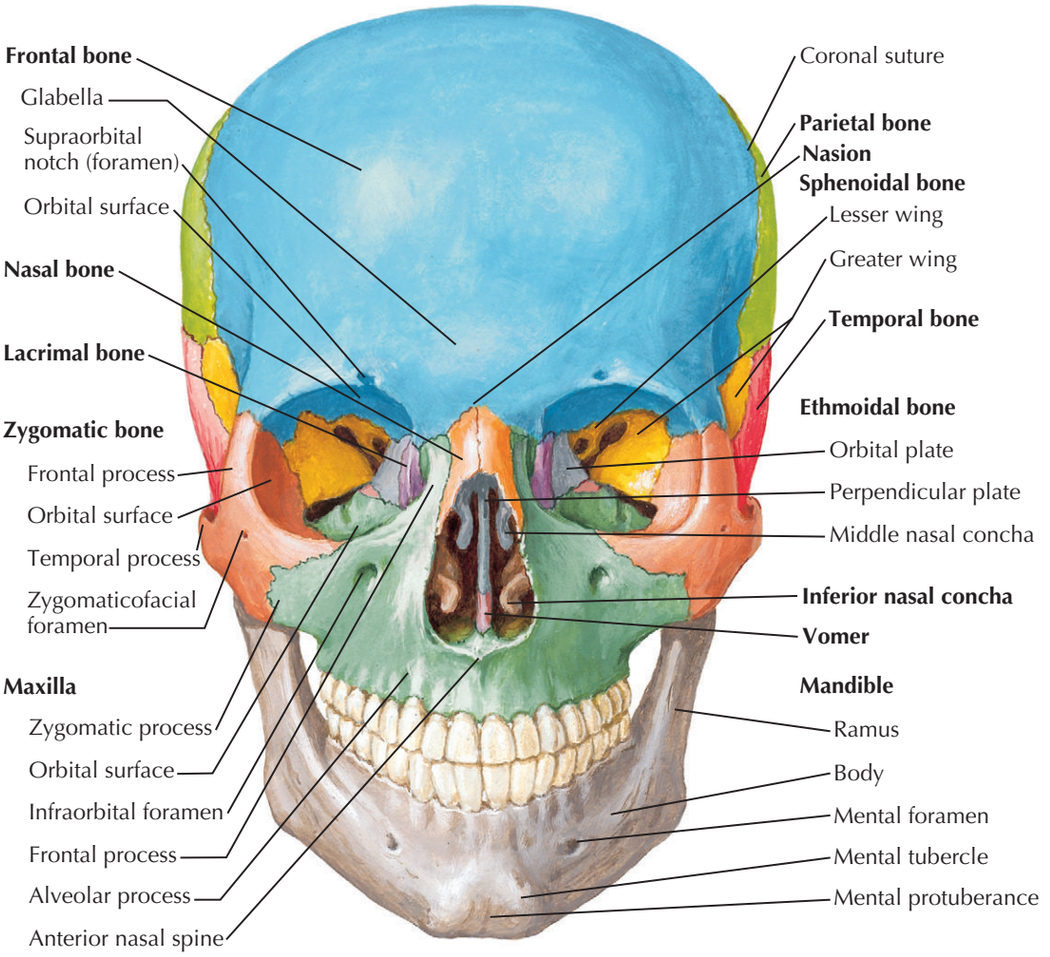
The convex anterior surface of the frontal bone is relatively smooth, but there are frontal tuberosities, or elevations, on each side. In early life, a median suture separates the two halves of the developing bone. This suture normally fuses between ages 6 and 10 years but occasionally persists as the metopic suture. *The two orbital openings* are roughly quadrangular and have supraorbital, infraorbital, medial, and lateral borders. The supraorbital notch, or fissure, carries the corresponding nerve and vessels. The infraorbital foramen, located about 1 cm below the infraorbital margin, transmits the nerve and vessels of the same name. The orbits are somewhat pyramidal in shape, with the quadrangular openings, or bases, directed forward and slightly outward, whereas the apexes correspond to the medial ends of the superior orbital fissures.

The *superior wall (roof)* separates the orbital contents from the brain and meninges in the anterior cranial fossa. Anteromedially, it is hollowed out by a variably sized frontal sinus, and anterolaterally, there is a shallow lacrimal fossa for the orbital part of the lacrimal gland. Posteriorly, the optic canal (foramen) lies between the two roots of the lesser wing of the sphenoid bone, just above the medial end of the superior orbital fissure; it transmits the optic (II) nerve and ophthalmic artery.

The *inferior wall (floor)* is formed mainly by the orbital surface of the maxilla, which separates the orbit from the maxillary sinus (antrum). A groove for the infraorbital nerve and vessels ends in the infraorbital foramen.

The thin *medial wall* separates the orbit from the ethmoidal air cells, the anterior part of the sphenoidal sinus, and the nasal cavity. At its anterior end, the lacrimal fossa is continuous below with the short nasolacrimal canal that opens into the inferior nasal meatus. The thicker *lateral wall* separates the orbit from the temporal fossa anteriorly and from the middle cranial fossa posteriorly. The orbital surface of the zygomatic bone shows a foramen for the zygomatic nerve, which bifurcates within the bone to emerge on the cheek and temporal fossa as the zygomaticofacial and zygomaticotemporal nerves, respectively.

Skull: Anterior View



Right orbit: frontal and slightly lateral view

The lateral wall and roof are continuous anteriorly but diverge posteriorly to bound the *superior orbital fissure*, which lies between the greater and lesser wings of the sphenoid bone and opens into the middle cranial fossa. The fissure transmits the oculomotor (III) and trochlear (IV) nerves, the lacrimal, frontal and nasociliary branches of the ophthalmic nerve, the abducens (VI) nerve, the ophthalmic veins, and small meningeal vessels.

The lateral wall and floor of the orbit are also continuous anteriorly but are separated posteriorly by the *inferior orbital fissure*, most of which is located between the greater wing of the sphenoid bone and the orbital surface of the maxilla. The inferior orbital fissure connects the orbit with the pterygopalatine and infratemporal fossae. The maxillary nerve passes from the pterygopalatine fossa into the orbit through the inferior orbital fissure and continues forward as the infraorbital

SKULL: ANTERIOR AND LATERAL ASPECTS *(Continued)*

nerve. Anastomotic channels between the orbital and pterygoid venous plexuses, and orbital fascicles from the pterygopalatine ganglion, also traverse this fissure.

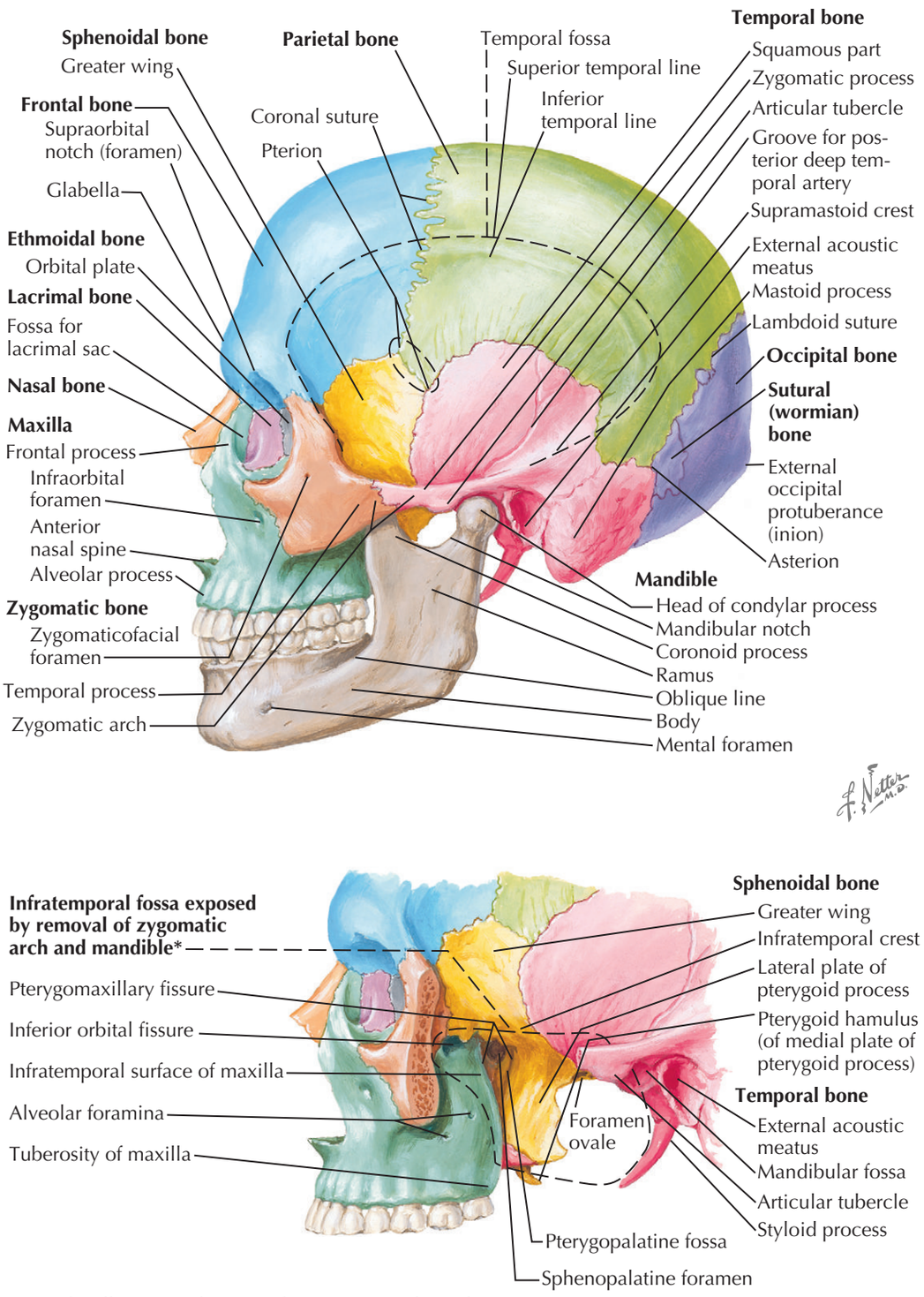
The anterior nasal (piriform) aperture is bounded by the nasal and maxillary bones. The nasal bones articulate with each other in the midline, with the frontal bone above and with the frontal processes of the maxillae behind. The irregular lower borders of the nasal bones give attachment to the lateral nasal cartilages.

The lower face is supported by both the maxillary alveolar processes and the mandible. The inferior margin of each *maxilla* projects downward as the curved alveolar process, which unites in front with its fellow to form the U-shaped alveolar arch containing the sockets for the upper teeth. The roots of the teeth produce slight surface elevations, the most obvious of which are produced by the canine teeth. The upper border of the body of the *mandible* is called the alveolar part and contains sockets for the lower teeth, whose roots also produce slight surface elevations.

Viewed from the side, the skull is divided into the larger ovoid braincase and the smaller facial skeleton. The two are connected by the zygomatic bone, which acts as a yoke (zygon) between the temporal, sphenoid (greater wing) and frontal bones, and the maxilla. Other features on the lateral aspect of the skull include parts of the sutures between the frontal, parietal, sphenoid, and temporal bones (which form most of the braincase), and the sutures between such facial bones as the nasal, lacrimal, ethmoid, and maxilla. Clearly seen are the parts of the mandible and the temporomandibular joint, the external acoustic meatus and the various foramina that transmit nerves and vessels of the same name. Not readily visible are the foramen ovale and the foramen spinosum.

Certain features deserve particular mention. The curved *superior* and *inferior temporal lines* arch upward and backward over the frontal bone from the vicinity of the frontozygomatic suture, pass over the coronal suture and the parietal bone, and then turn downward and forward across the temporal squama to end above the mastoid process. The superior and inferior temporal lines provide attachments, respectively, for the temporal fascia and the upper margin of the temporal muscle, which occupies most of the *temporal fossa*. This fossa is bounded above by the superior temporal line, and below it is bounded by the infratemporal crest, separating the greater wing of the sphenoid bone from the pterygoid processes. The anteroinferior corner of the parietal bone usually fills the angle between the greater wing of the sphenoid and the frontal bone, although sometimes the squamous part of the temporal bone may extend forward to articulate directly with the frontal bone, thus excluding the sphenoid. This area is the *pterion*, and its internal surface is deeply grooved by the anterior branches of the middle meningeal vessels. It is situated about 3.5 cm behind the frontozygomatic suture (usually palpable as a slight ridge) and 4 cm above the zygomatic arch. As the most common site of damage to these vessels from a skull fracture, it is a surgical landmark.

The *infratemporal fossa* is an irregular space lying below the infratemporal crest. It is continuous above with the temporal fossa through the gap between the crest and the zygomatic arch. It is bounded medially by the lateral plate of the pterygoid process and the infratemporal surface of the maxilla, and laterally, by the ramus of the mandible. It communicates through the pterygomaxillary fissure with the pterygopalatine fossa.



*Superficially, mastoid process forms posterior boundary.

SKULL: MIDSAGITTAL SECTION

The rigid braincase is formed by the bones of the calvaria (see Plate 14-4) and the base of the skull (see Plate 14-5), which is divided into anterior, middle, and posterior cranial fossae (see Plates 14-6 and 14-7). These divisions are less visible on a sagittal section of the skull.

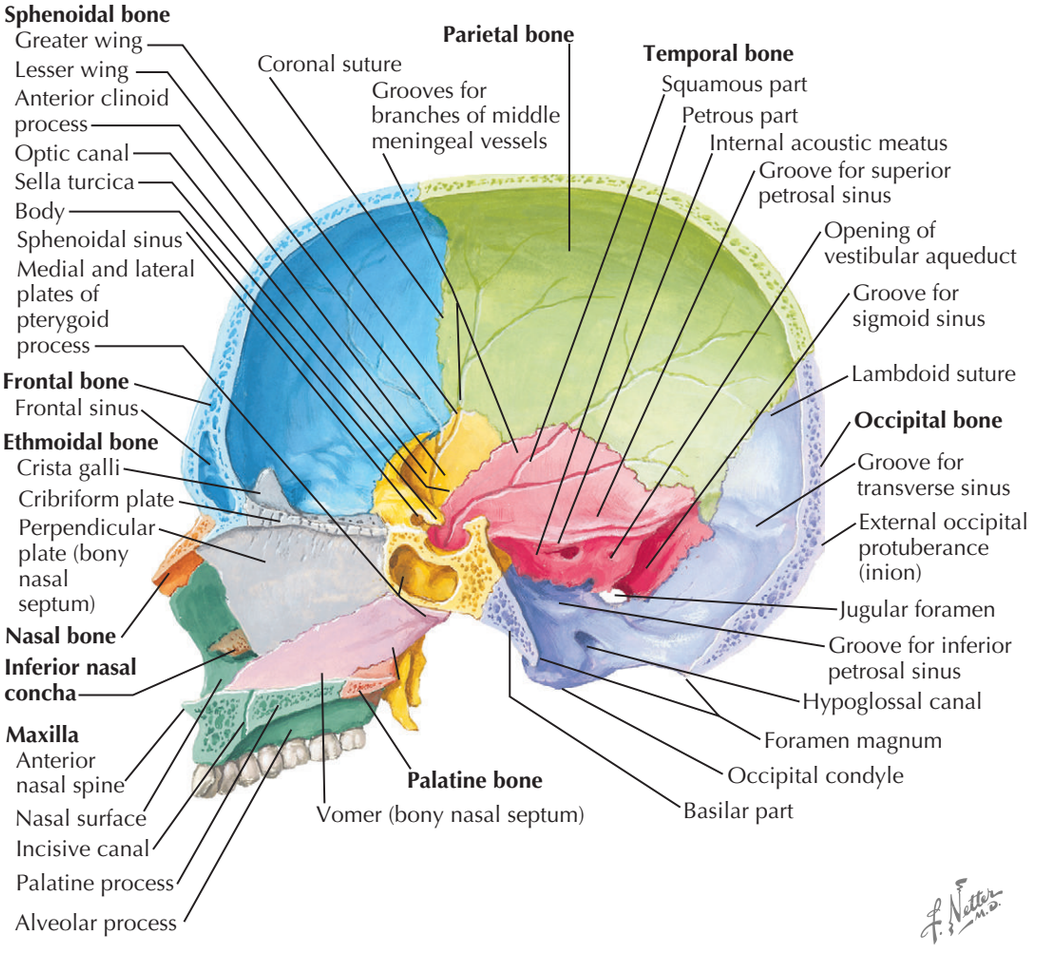
The *occipital bone* bounds most of the posterior cranial fossa. It is pierced by the foramen magnum, through which the medulla oblongata and spinal cord, surrounded by their meninges, become continuous; it also transmits the vertebral arteries, a few small veins, the spinal roots of the accessory (XI) nerves, and the recurrent meningeal branches from the upper spinal nerves. The occipital condyle articulates with the homolateral superior atlantoarticular process. The hypoglossal (XII) nerve passes through the corresponding canal. The jugular foramen lodges the superior bulb of the internal jugular vein (in which the sigmoid and inferior petrosal sinuses end); the glossopharyngeal (IX), vagus (X), and accessory nerves pass through it anteromedial to the bulb, and it provides an entry for the recurrent meningeal branches of the vagus and small meningeal branches of the ascending pharyngeal and occipital arteries. The basilar part of the occipital bone unites with the body of the sphenoid to form a sloping platform anterior to the pons and medulla oblongata.

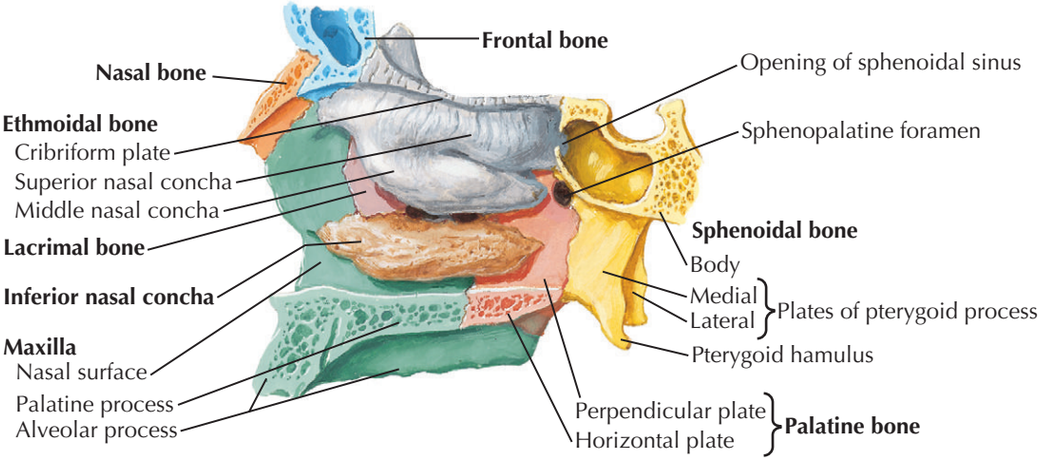
The squamous part of the *temporal bone* is grooved by the posterior branches of the middle meningeal vessels and the sulcus along the superior border of its petrous part is for the superior petrosal sinus. The inferior petrosal sinus lies in the sulcus between the petrous temporal and occipital bones. The internal acoustic meatus is a canal about 1 cm long, ending in a cribriform septum that separates it from the internal ear. It transmits the facial (VII) nerve and its nervus intermedius, the vestibulocochlear (VIII) nerve, and the internal auditory (labyrinthine) artery.

The *sphenoid bone* has a central body from which two greater and two lesser wings and two pterygoid processes arise. The body contains two air sinuses separated by a septum that is often incomplete. Its concave upper surface, the sella turcica, houses the pituitary gland. The optic canal transmits the optic (II) nerve and the ophthalmic artery.

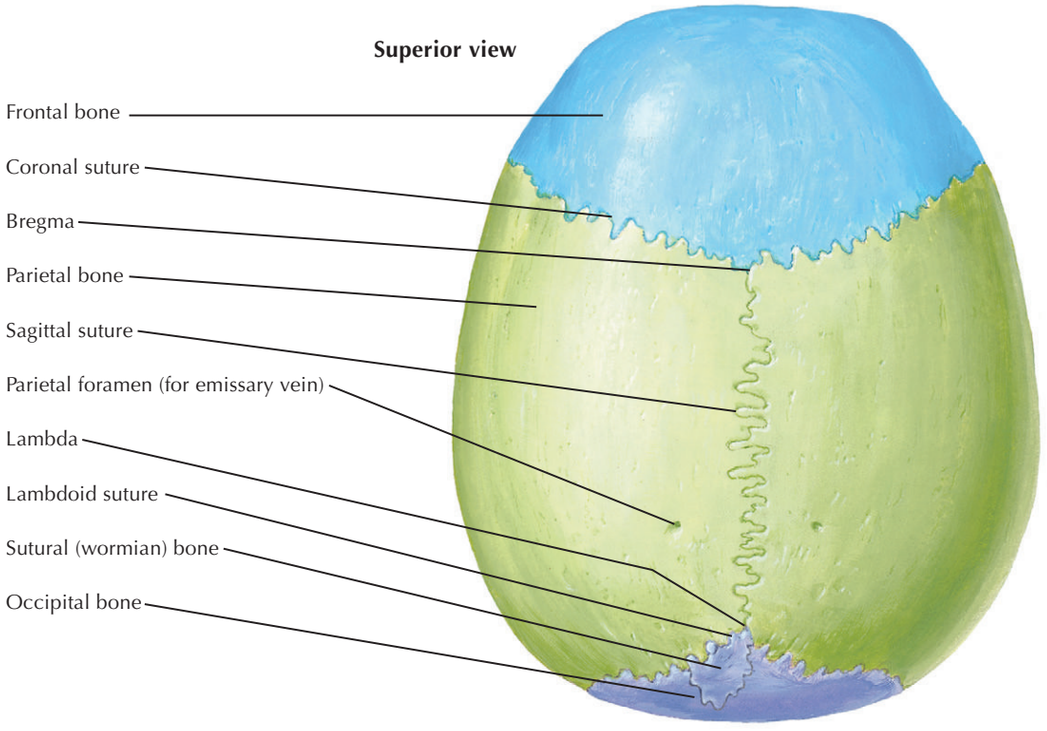
The nasal cavity is roofed over mainly by the cribriform plate of the ethmoid bone, augmented anteriorly by small parts of the frontal and nasal bones, and posteriorly, by the anteroinferior surface of the sphenoidal body. Its floor is formed by the palatine processes of the maxillae and by the horizontal plates of the palatine bones. The *incisive canal* transmits the nasopalatine nerves and branches of the greater palatine arteries. Each lateral wall is formed above by the nasal surface of the ethmoid bone that covers the ethmoidal labyrinth and supports thin, shell-like projections, the *superior* and *middle nasal conchae*. These overhang the corresponding nasal meatuses. Below, each lateral wall is formed by the nasal surface of the maxilla, the perpendicular plate of the palatine bone and the medial pterygoid plate. The maxillary and palatine bones articulate with a separate bone, the *inferior nasal concha*, overhanging the inferior nasal meatus. The sphenoidal air sinuses open into the nose through the *sphenoidal aperture* in the sphenoethmoidal recess posterosuperior to the superior concha. The frontal and maxillary air sinuses open into the middle meatus through a *semilunar hiatus*, and the multiple air cells forming the ethmoidal labyrinth open into the superior and middle meatuses. The lower opening of the *nasolacrimal duct* is near the anterior end of the inferior meatus. The *sphenopalatine foramen* behind the middle concha transmits the nasopalatine nerve.

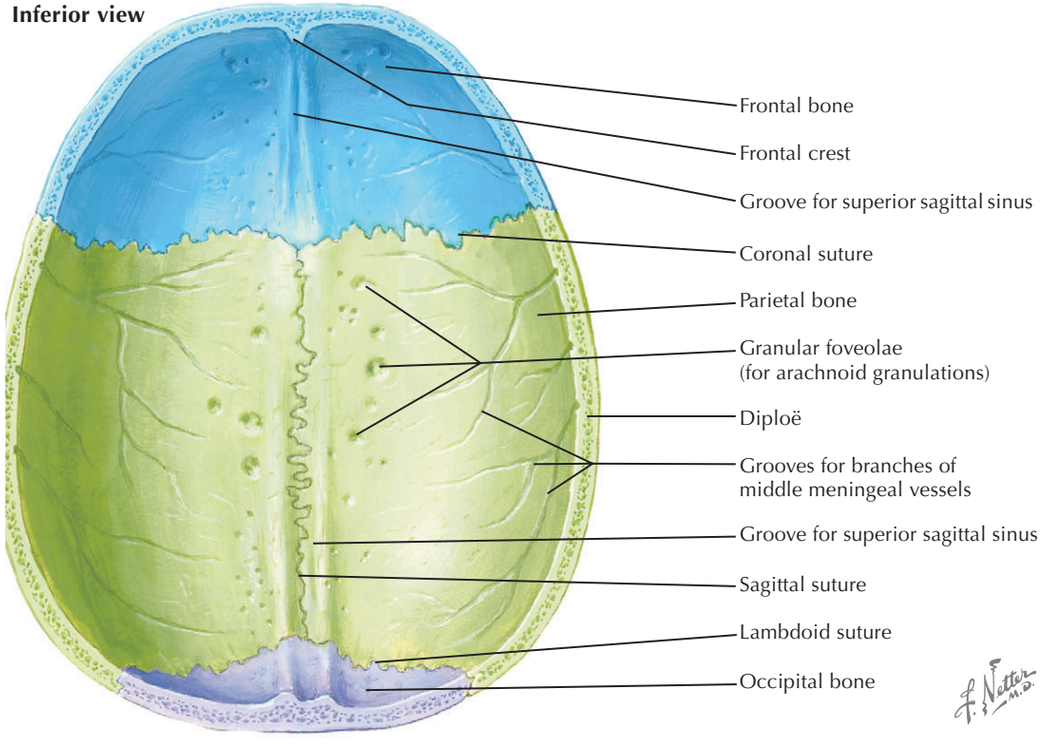
The nasal cavity is subdivided by a more-or-less vertical *septum* formed by the perpendicular ethmoidal plate and the vomer. The triangular gap between them anteriorly is filled in by the nasal *septal cartilage* (not shown in the illustration).





View of lateral nasal wall with nasal septum removed





CALVARIA

The *calvaria*, or skullcap, is the roof of the cranium and is formed by the frontal, parietal, and occipital bones. It is ovoid in shape and widest toward the posterior parts of the parietal bones, but there are individual variations in size and shape associated with age, race, and sex; thus minor degrees of asymmetry are common.

The anterior part, or brow, is formed by the frontal bone, which extends backward to the *coronal suture* between the frontal bone and the parietal bones. The latter bones curve upward and inward to meet at the midline *sagittal suture*. Posteriorly, the parietal bones articulate with the triangular upper part of the occipital squama along the *lambdoid suture*. The meeting points of the sagittal suture with the coronal and lambdoid sutures are termed, respectively, *bregma* and *lambda*. In the fetal skull, they are the sites of the anterior and posterior fontanelles. The *vertex*, or highest point, of the skull lies near the middle of the sagittal suture. Parietal foramina are usually present; they transmit emissary veins passing between the superior sagittal sinus and the veins of the scalp.

The deeply concave internal, or endocranial, surface of the calvaria is made up of the inner aspects of the bones, sutures, and foramina mentioned above. The bones show indistinct impressions produced by related cerebral gyri, more evident grooves for dural venous sinuses and meningeal vessels, and small pits, or *foveolae*, for arachnoid granulations. Thus there is a median groove in the frontal, parietal, and occipital bones extending backward from the frontal crest to the internal occipital protuberance; it increases in width posteriorly and lodges the *superior sagittal sinus*. The frontal crest seen in the midline is produced by the coalescence of the anterior ends of the lips of the groove for the superior sagittal sinus. There are other, narrower grooves for meningeal vessels. The largest of these, the *middle meningeal arteries and veins*, leave their imprints in particular on the parietal bones, and the channels containing them may become tunnels where the anteroinferior angles of the parietal bones meet the greater wings of the sphenoid bone. The skull varies in thickness, and the area around the pterion is thin. It is relatively easily fractured by a blow to the side of the head, with possible tearing of the middle meningeal vessels. The resulting hemorrhage can be serious if it is not recognized and treated promptly.

The cut edge of the skullcap reveals that the constituent bones possess outer and inner laminae of compact bone separated by the *diploë*, a layer of cancellous bone. The outer lamina is thicker and tougher than the more brittle inner lamina.

External Aspect of Skull Base

The inferior surface of the base of the skull, the *norma basilaris*, is formed anteriorly by the arched hard palate, fringed by the maxillary alveolar processes and teeth; posteriorly by the wider occipital squama, pierced by the foramen magnum; and, in between, by an irregular area comprising several bony processes for muscular and tendinous attachments, articular and other fossae, and many foramina. The bones and fissures shown in the illustration need no added description, but the nerves and vessels traversing the foramina will be listed.

The *incisive foramen* transmits the terminal branches of the nasopalatine nerves and greater palatine vessels. The *major* and *minor palatine foramina* are traversed by the corresponding arteries and nerves. The *choanae* are the posterior nasal apertures.

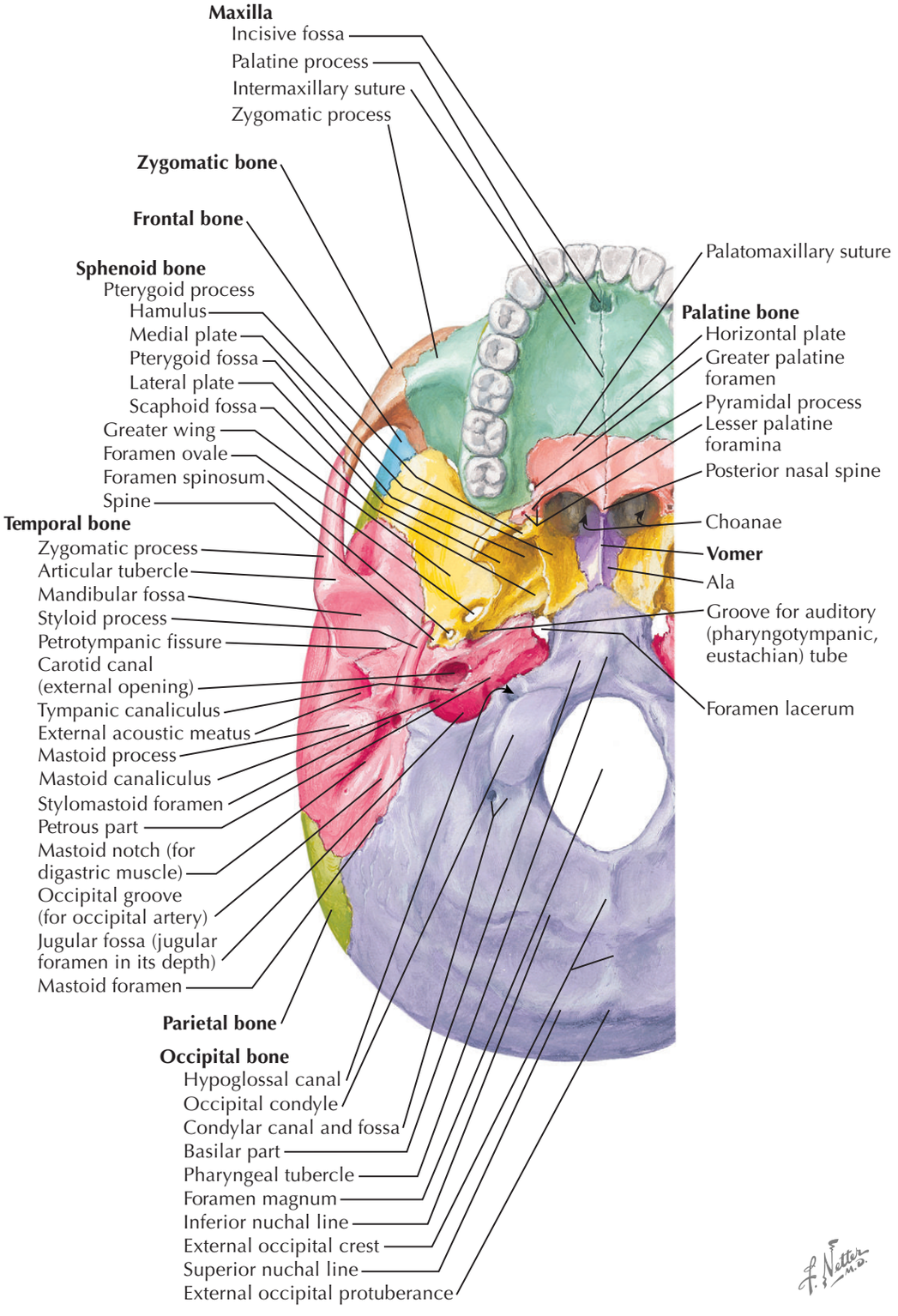
The *foramen ovale* pierces the greater sphenoidal wing near the lateral pterygoid plate and the sulcus for the auditory tube; the mandibular nerve, the accessory meningeal artery, and communications between the cavernous sinuses and pterygoid venous plexus pass through it. The *foramen spinosum*, anteromedial to the sphenoidal spine, transmits the middle meningeal artery and the meningeal branch of the mandibular nerve.

The *foramen lacerum* is an irregular canal between the sphenoidal body, the apex of the petrous part of the temporal bone and the basilar part of the occipital bone. The upper end of the carotid canal opens into it, and the internal carotid artery with its nerves and veins, on emerging from the canal, turn upward to enter the cavernous sinus. Meningeal branches of the ascending pharyngeal artery and emissary veins from the cavernous sinus pass through the foramen lacerum, and the deep and greater petrosal nerves unite within it to form the nerve of the pterygoid canal.

The anterior part of the *mandibular fossa* articulates with the mandibular head and belongs to the temporal squama, but the posterior nonarticular part is derived from the tympanic plate. The *tympanosquamous fissure* between them is continued medially as the *petrotympanic fissure*, through which the chorda tympani nerve emerges. The *stylomastoid foramen* behind the root of the styloid process transmits the facial (VII) nerve and the stylomastoid branch of the posterior auricular artery.

The lower opening of the *carotid canal* is anterior to the *jugular fossa*, which lodges the superior bulb of the internal jugular vein. The canal bends at right angles within the petrous part of the temporal bone, and its upper end opens into the foramen lacerum. The *tympanic canaliculus* pierces the ridge between the carotid canal and the jugular fossa and conveys the tympanic branch of the glossopharyngeal (IX) nerve to the tympanic plexus. The *mastoid canaliculus* opens on the lateral wall of the fossa and transmits the auricular branch of the vagus (X) nerve. The *jugular foramen* in the depth of the fossa may be partly or completely divided into three parts by bony spicules. The anteromedial compartment transmits the inferior petrosal sinus and a meningeal branch of the ascending pharyngeal artery; the intermediate part transmits the glossopharyngeal, vagus, and accessory (XI) nerves; and the posterolateral part conveys the sigmoid sinus to the superior bulb of the internal jugular vein. Often seen near the posterior border of the mastoid process is a *mastoid foramen*, which is traversed by an emissary vein from the sigmoid sinus and a meningeal twig from the occipital artery. The anterior end of the *hypoglossal canal* (for the hypoglossal [XII] nerve and some small meningeal vessels) is above the anterior end of the occipital condyle. Behind the condyle is a shallow condylar fossa, usually pierced by a *condylar foramen* conveying an emissary vein between the sigmoid sinus and cervical veins.

The posterior part of the base of the skull is formed predominantly by the occipital squama; these are marked by nuchal lines, occipital crest, and so forth, which serve mainly for muscular and ligamentous attachments. However, the most notable feature is the *foramen magnum*, through which the medulla oblongata and spinal cord become continuous. The vertebral arteries, spinal roots of the accessory nerves, and recurrent meningeal branches from the upper cervical nerves ascend through the foramen magnum, while down through it pass the anterior and posterior spinal arteries.



Bones, Markings, and Orifices of Skull Base

The internal surface of the base of the skull has adapted its shape to the configuration of the adjacent parts of the brain. It consists of three cranial fossae, the anterior, middle, and posterior, which are separated by conspicuous ridges and increase in size and depth from front to back.

The anterior cranial fossa is the shallowest of the three fossae and lodges the lower parts of the frontal lobes of the brain. The sulci and gyri of the lobes are mirrored in the irregularities of the bony surfaces. It is limited anteriorly and laterally by the frontal bone. On each side, the floor is formed by the slightly domed and ridged *orbital plate of the frontal bone*, which supports the orbital surface of the homolateral frontal lobe of the brain and its meninges and separates them from the orbit. Posterior extensions from the frontal air sinuses may expand the orbital plates for varying distances, and the medial parts of these plates overlie the ethmoidal labyrinths.

On each side of the midline *crista galli* are the grooved *ethmoidal cribriform plates* that help to form the roof of the nasal cavity, lodge the olfactory bulbs, and provide numerous orifices for the delicate olfactory nerves. A small pit exists between the frontal crest and the crista galli, the *foramen cecum*, which occasionally transmits a tiny vein from the nose to the superior sagittal sinus. The crista galli and frontal crest give attachment to the anterior end of the falx cerebri.

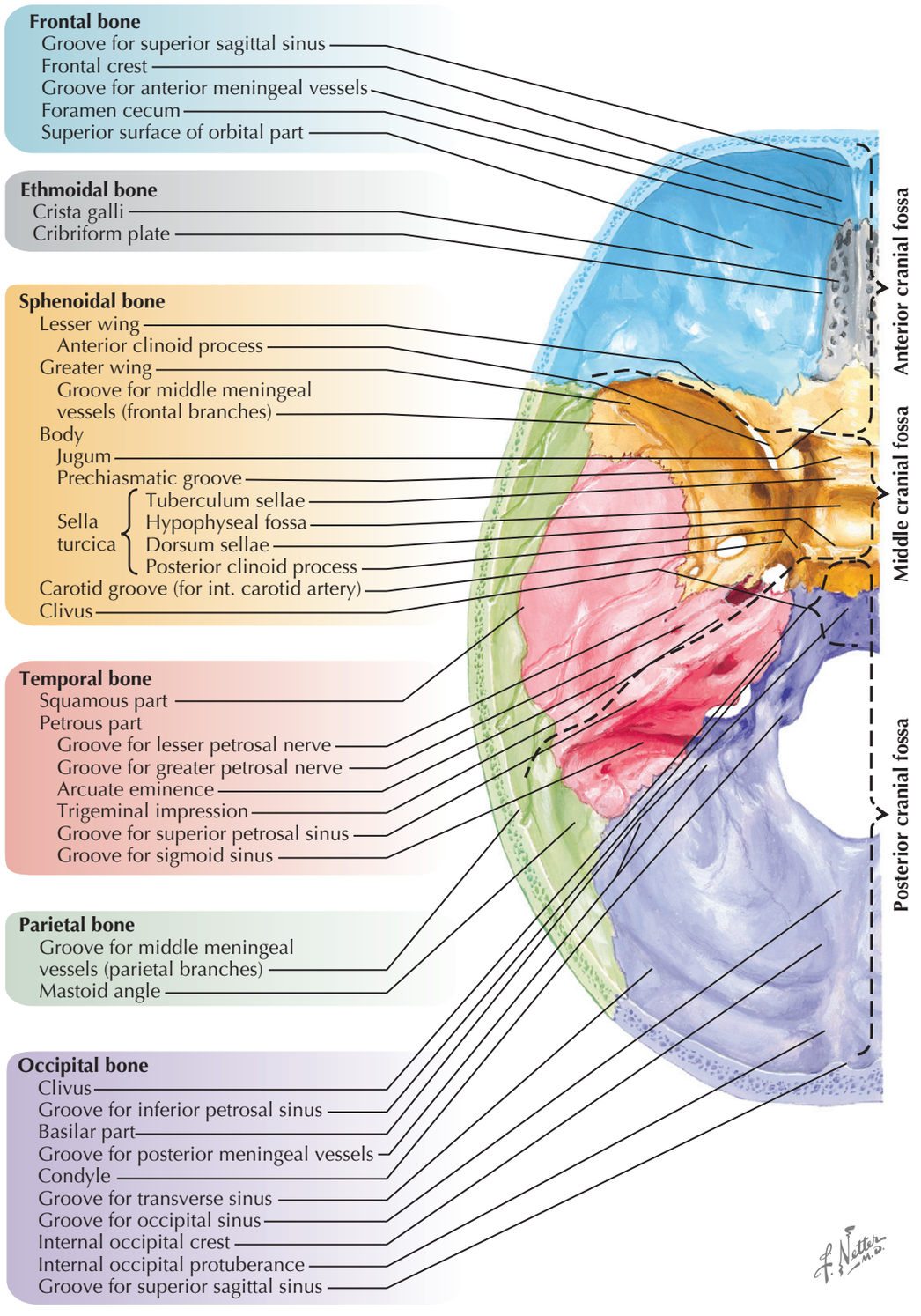
Posterior to the ethmoid and frontal bones, the floor of the anterior cranial fossa is formed by the anterior part of the body of the sphenoid bone, the *jugum sphenoidale*, and on each side, by the *lesser wings* of this bone. These lesser wings slightly overlap the anterior part of the middle cranial fossa and project into the stems of the lateral cerebral sulci, thus forming the upper boundaries of the superior orbital fissures.

The medial ends of the posterior borders of the lesser wings end in small, rounded projections, the *anterior clinoid processes*, which provide attachments for the anterior ends of the free border of the tentorium cerebelli. Each anterior process is grooved on its medial side by the internal carotid artery, and each may be joined to the inconstant middle clinoid process by a thin osseous bar, thus forming a narrow bony ring around the artery as it emerges from the cavernous sinus.

The middle cranial fossa is intermediate in depth between the anterior and posterior fossae. It is narrow and elevated medially but expands and becomes deeper at each side to lodge and protect the temporal lobes of the brain. It is bounded anteriorly by the posterior borders of the lesser wings of the sphenoid bone and the anterior margin of the prechiasmatic sulcus; posteriorly by the superior borders of the petrous parts of the temporal bones, which are grooved by the superior petrosal sinuses and by the dorsum sellae of the sphenoid; and laterally by the greater wings of the sphenoid, the frontal angles of the parietal bones, and the temporal squamae.

The floor in the median area is formed by the *body of the sphenoid bone*, containing the sphenoidal air sinuses.

Internal Aspects of Base of Skull: Bones



The lesser wings of the sphenoid are attached to its body by two roots, separated from each other by the *optic canals* that transmit the optic (II) nerves and ophthalmic arteries. Behind the prechiasmatic sulcus is a median elevation, the *tuberculum sellae*, and the *hypophyseal fossa* housing the pituitary gland. The fossa is limited behind by the *dorsum sellae*, an upward-projecting bony plate with a concave upper border expanding laterally into the *posterior clinoid processes*.

Lateral to the sellae is a shallow, sinuous *groove for the internal carotid artery*; at its anterior end on the medial side may be a small tubercle, the *middle clinoid process*.

The lateral parts of the middle fossa are related in front to the orbits, on each side to the temporal fossae, and below to the infratemporal fossae. The middle fossa communicates with the orbits through the *superior orbital fissures*.

Bones, Markings, and Orifices of Skull Base
(Continued)

Various other, more-or-less symmetric openings exist on each side. The *foramen rotundum* pierces the greater wing of the sphenoid bone just below and behind the inner end of the superior orbital fissure, and then it opens anteriorly into the pterygopalatine fossa. The *foramen ovale* also penetrates the greater sphenoidal wing posterolateral to the foramen rotundum and leads downward into the infratemporal fossa. The smaller *foramen spinosum* lies posterolateral to the foramen ovale and opens below into the infratemporal fossa close to the sphenoidal spine; the sulcus for the middle meningeal vessels starts at this foramen. The *foramen lacerum* is an irregular aperture between the body and greater wing of the sphenoid bone and the apex of the petrous part of the temporal bone; it marks the point of entry of the internal carotid artery into the cavernous sinus. Behind the foramen lacerum is the shallow *depression for the trigeminal (semilunar) ganglion* on the anterior surface of the petrous temporal bone, and lateral to this are two narrow grooves leading to the hiatuses for the lesser (minor) and greater (major) petrosal nerves.

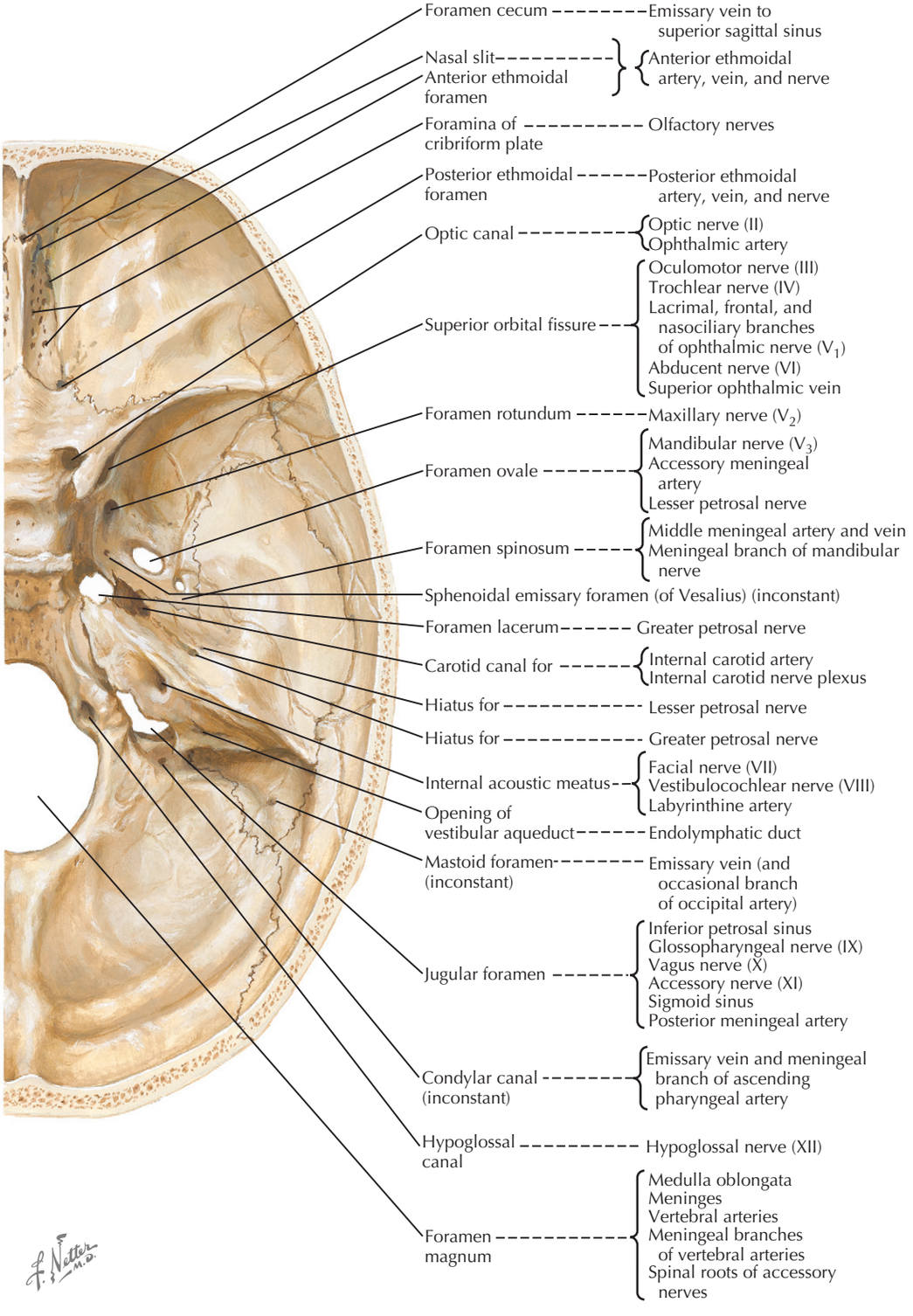
The *arcuate eminence* is produced by the superior semicircular canal of the internal ear. Anterolateral to this eminence is a thin plate of bone, the *tegmen tympani*, forming the roof of the tympanic cavity and mastoid antrum and extending forward and medially to cover the bony part of the auditory (pharyngotympanic) tube.

The posterior cranial fossa is the largest and deepest of the cranial fossae and lodges the cerebellum, pons, and medulla oblongata. It is bounded anteriorly by the dorsum sellae, the back of the body of the sphenoid bone, and the basilar part of the occipital bones; posteriorly by the squama of the occipital bone below the sulci for the transverse sinuses and the internal occipital protuberance; and laterally by the petrous and mastoid parts of the temporal bones, the mastoid angles of the parietal bones, and the lateral parts of the occipital bone.

The posterior fossa is pierced by a number of foramina and is grooved by various dural venous sinuses. A large median opening in the floor of the fossa, the *foramen magnum*, penetrates the occipital bone. The medulla oblongata and spinal cord and their surrounding meninges become directly continuous immediately below the foramen. The petrous part of the temporal bone and the occipital bone are separated by the *petro-occipital fissure* and the *sulcus for the inferior petrosal sinus*; the fissure ends behind, in the *jugular foramen*. The inferior petrosal and sigmoid sinuses pass through the anterior and posterior parts of this foramen, respectively, while the glossopharyngeal (IX), vagus (X), and accessory (XI) nerves occupy an intermediate position as they leave the skull.

Two canals are associated with the occipital condyles: the *hypoglossal canal*, for the twelfth cranial nerve, and the *condylar canal*.

Internal Aspects of Base of Skull: Orifices



Above the jugular foramen, the *internal acoustic meatus* tunnels into the petrous part of the temporal bone. It is about 1 cm long and is separated laterally from the internal ear by a thin bony plate pierced by many apertures for fascicles of the facial (VII) and vestibulocochlear (VIII) nerves. Behind the orifice of this meatus is the slitlike opening of the *vestibular aqueduct*, which lodges the blind end of the endolymphatic duct.

The internal opening of the inconstant *mastoid foramen* is close to the *sulcus for the sigmoid sinus*, which winds downward from the transverse sinus to the jugular foramen, where it ends in the superior bulb of the internal jugular vein. The *internal occipital protuberance* is related to the confluence of the superior sagittal, straight, occipital, and transverse sinuses. The margins of the sulci for the transverse sinuses give attachment to the tentorium cerebelli.

Skull Injuries

The mechanical forces resulting in traumatic brain injuries may produce a variety of different structural injuries, each of which requires different surgical or medical treatment.

Before the introduction of computed tomography (CT) scans, plain skull radiographs were of vital importance in evaluating patients with head injuries. The presence of a skull fracture strongly suggested the possibility of a significant, underlying intracranial injury. Fracture is present in 66% to 100% of patients with epidural hematoma; 18% to 60% with acute subdural hematoma; and 40% to 80% with contusions or intracerebral hematoma. Such intracranial injuries are now immediately identified by CT, and an associated skull fracture is often noticed only in passing.

There are, however, several types of skull fracture that are of clinical significance. The most classic is the basilar skull fracture, which may be associated with cerebrospinal fluid (CSF) leak and cranial nerve injuries. Basilar skull fracture has been reported in up to 25% of patients sustaining a head injury. Even with CT, basilar skull fractures may not be identified because of their orientation to the plane of the scan. Special thin cuts or coronal views may be required. The majority of basilar skull fractures occur through the petrous bone or the anterior cranial fossa. Clival fractures are less common. Petrous bone fractures occur either transversely or longitudinally, and their orientation predisposes to various complications.

The classic clinical presentation of a petrous bone fracture is with the Battle sign—a retromastoid hematoma. Raccoon eyes—periorbital hematomas—may be seen with anterior skull base fractures. CSF leaks, otorrhea or rhinorrhea, have been reported in approximately 10% of patients with basal skull fractures. Otorrhea is typically associated with petrous fractures, whereas rhinorrhea may emanate from either frontal fossa fractures through the cribriform plate or the petrous bone through the eustachian canal. In either case, with bed rest and head elevation, the CSF leak ceases spontaneously in more than 85% of patients. The administration of antibiotics is not advised because this may predispose to antibiotic-resistant infection. Persisting leaks may be treated with a lumbar drain; only a small number require direct or endoscopic surgical repair.

If there is any question as to whether drainage from the nose or ear represents CSF, the fluid can be checked for glucose, which typically is greater than 30 mg/mL in CSF, or β-2-transferrin, which is found only in the CSF.

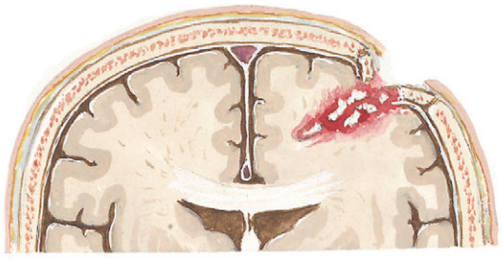
Cranial nerve injuries may complicate up to 5% of basal skull fractures, the most common of which is facial nerve injury in association with petrous fractures. Such an injury may occur in up to 50% of patients with transverse and 20% with longitudinal fractures. The facial nerve is especially prone to injury in the narrow fallopian canal as swelling occurs or by compression from fracture fragments. If facial paralysis is immediate and complete, the chances of recovery are small. More minor injuries tend to recover well, and steroids are often used for treatment. Some advocate early surgical exploration and decompression of the nerve.

Two other types of skull fractures require specific clinical management: open depressed and frontal sinus fractures.

Open, or compound, depressed skull fractures have been said to be associated with infection and post-traumatic epilepsy. They definitely are associated with potentially significant underlying brain injury. Common practice until recently was to operate on all such fractures. Contemporary literature, however, has shown that the risk of post-traumatic epilepsy is not significantly increased, and the risk of infection may be greater in those patients treated operatively than nonoperatively. It thus appears possible to manage conservatively all but the most contaminated and comminuted fractures with reasonable safety.

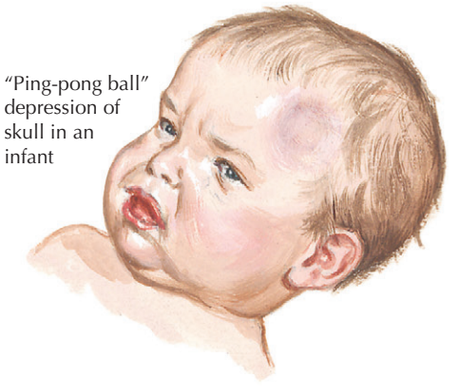
The primary concern over frontal sinus fractures is the status of the posterior wall of the sinus, with the possibility of dural violation and the risk of CSF leak, pneumocephalus, and infection. As a general rule, unless there is overt evidence of CSF leak or pneumocephalus with posterior wall fragments in-driven more than 3 to 4 mm, nonoperative management is usually successful. Some, however, advocate surgery on the majority of frontal sinus fractures to prevent the development of a mucocele.

Open fracture

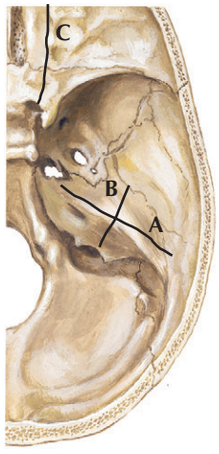


Indriven fragments of bone

Depressed fracture

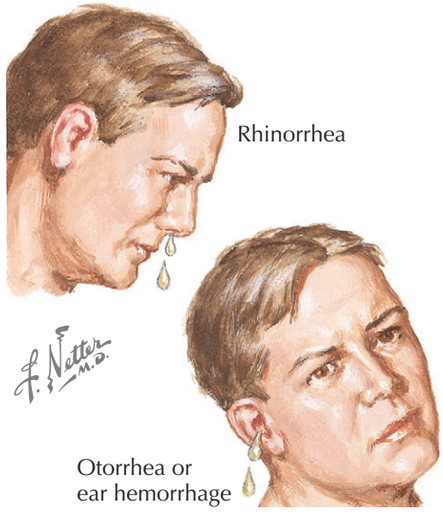


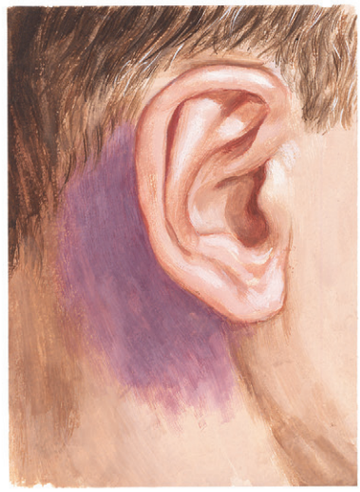
Basilar skull fractures



Longitudinal (**A**) and transverse (**B**) fractures of petrous pyramid of temporal bone, and anterior basal skull fracture (**C**)

"Panda bear" or "raccoon" sign due to leakage of blood from anterior fossa into periorbital tissues. Absence of conjunctival injection differentiates fracture from direct eye trauma.





Battle sign: postauricular hematoma

CONCUSSION

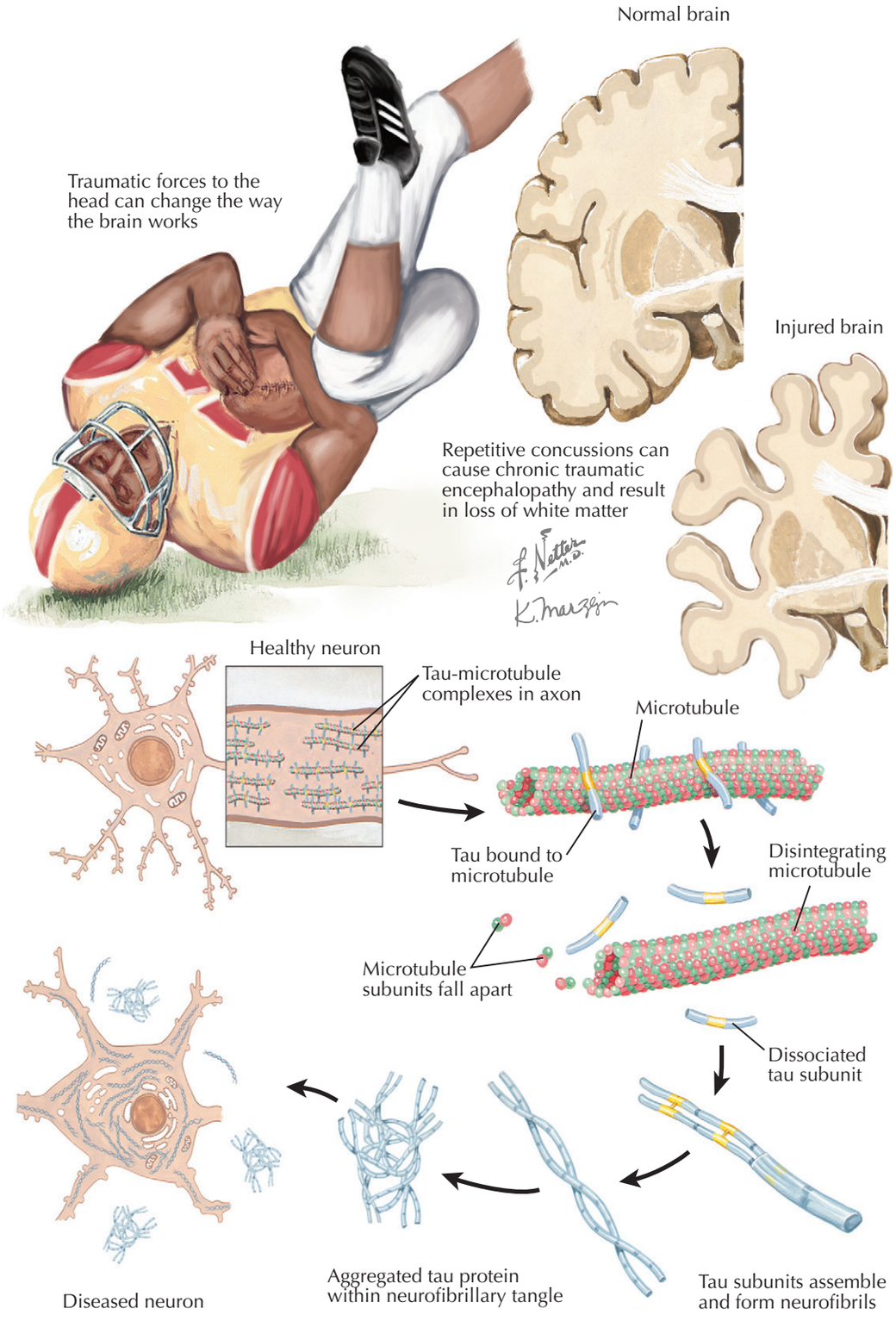
A concussion is a type of traumatic brain injury that changes the way the brain normally works and is caused by traumatic forces to the head or body. Most concussions occur without loss of consciousness. The Centers for Disease Control and Prevention estimates that between 1.6 and 3.8 million concussions occur in sports and recreational activities each year. Concussions or mild traumatic brain injuries can result in short- and long-term health risks. In athletes, there is a correlation between repetitive concussions and a neurodegenerative disease called *chronic traumatic encephalopathy*. There is also an entity called "second impact syndrome." The potential public health problem of concussion is such that more than 40 states in the United States have either laws or pending bills addressing the problem of concussions in youth sports.

At the level of the neuron, linear and rotational forces can lead to structural and metabolic changes that transiently impair function and contribute to physical, cognitive, and emotional symptoms. The molecular substrate for these acute clinical changes is the subject of much current research on cellular ionic transients in sodium and calcium, axonal integrity, bioenergetics, neurovascular coupling, and genetics. What is apparent in sufferers of a concussion is that symptoms may persist for days, weeks, or months after a concussive event.

Clinical Symptomatology. The signs and symptoms of concussions are diverse. Typically, individuals have difficulty with thinking and memory skills, and their emotions may be affected. The physical problems include headache, nausea, and visual disturbances. The Centers for Disease Control and Prevention advocates that any athlete suspected of having a concussion should be immediately removed from play, evaluated by a health-care professional, and only allowed to return when cleared by a health-care professional. At present, there are no "neuroprotective" drugs that can be used for this condition, and it is recommended that for safety, physical and mental activities that excessively stimulate the injured brain should be discontinued. Furthermore, a graded return-to-play system is recommended as the safest way to bring an athlete back to full contact activities.

Second Impact Syndrome. Second impact syndrome is the most devastating, yet rare, consequence of repeat concussion in the postinjury phase. This condition occurs when an individual experiences a second traumatic episode to the brain before the brain has fully recovered from the initial traumatic injury. These subjects rapidly develop global cerebral edema, coma, severe neurologic impairment, and the potential for death. This rare condition has been observed mainly in youths younger than 21 years. At present, there are no methods for determining the recovery period after a concussion or even the duration of a "window of vulnerability" after a concussion. Hence much of the current emphasis in the management of concussion and return-to-playing of sports in young athletes is on reducing any potential for second impact syndrome.

Repeat Concussions and Chronic Traumatic Encephalopathy. Individuals who suffer an isolated concussive event should recover completely if they allow an appropriate time for recovery, with rest and cessation of sports. In contrast, brain autopsy studies of former professional athletes in contact sports, such as boxing, football, and hockey, have revealed a chronic, neurodegenerative disease termed chronic traumatic encephalopathy. This disease was first described in 1928 as *dementia pugilistica* in deceased boxers. The clinical syndrome associated with this pathology, so-called "punch drunk" condition, was believed to be limited to boxers who displayed progressive cognitive, emotional, and behavioral symptoms, such as depression, agitation, and dementia, years after repeated traumatic brain injuries. Recently, however, many other cases of chronic traumatic encephalopathy have been described in deceased players from other sports, for example, football, hockey, and wrestling. Although the cases vary in severity of neuropathology, they share the common feature of increased deposition of aggregated tau protein within neurofibrillary tangles, which is similar to neurodegenerative diseases such as Alzheimer disease. In addition, earlier stages of chronic traumatic encephalopathy are being reported in athletes as young as 18 years old, where there is evidence of white matter loss in brain imaging.



Acute Epidural Hematoma

The overall incidence of acute epidural hematoma (EDH) after head injury is approximately 5%, but it approaches 10% in patients presenting in coma. EDHs are almost always traumatic in nature. There are rare reports of spontaneous occurrence in association with anticoagulation or thrombocytopenia. The classic clinical presentation is with a loss of consciousness that is followed by a lucid interval and then by progressively severe headache and decreasing level of consciousness. However, most EDHs result from motor vehicle collisions, and greater than 60% of patients are unconscious at the scene or on hospital arrival.

Computed tomography scan shows a variably sized oval or "lens-shaped" hyperdensity between the bone and the dura.

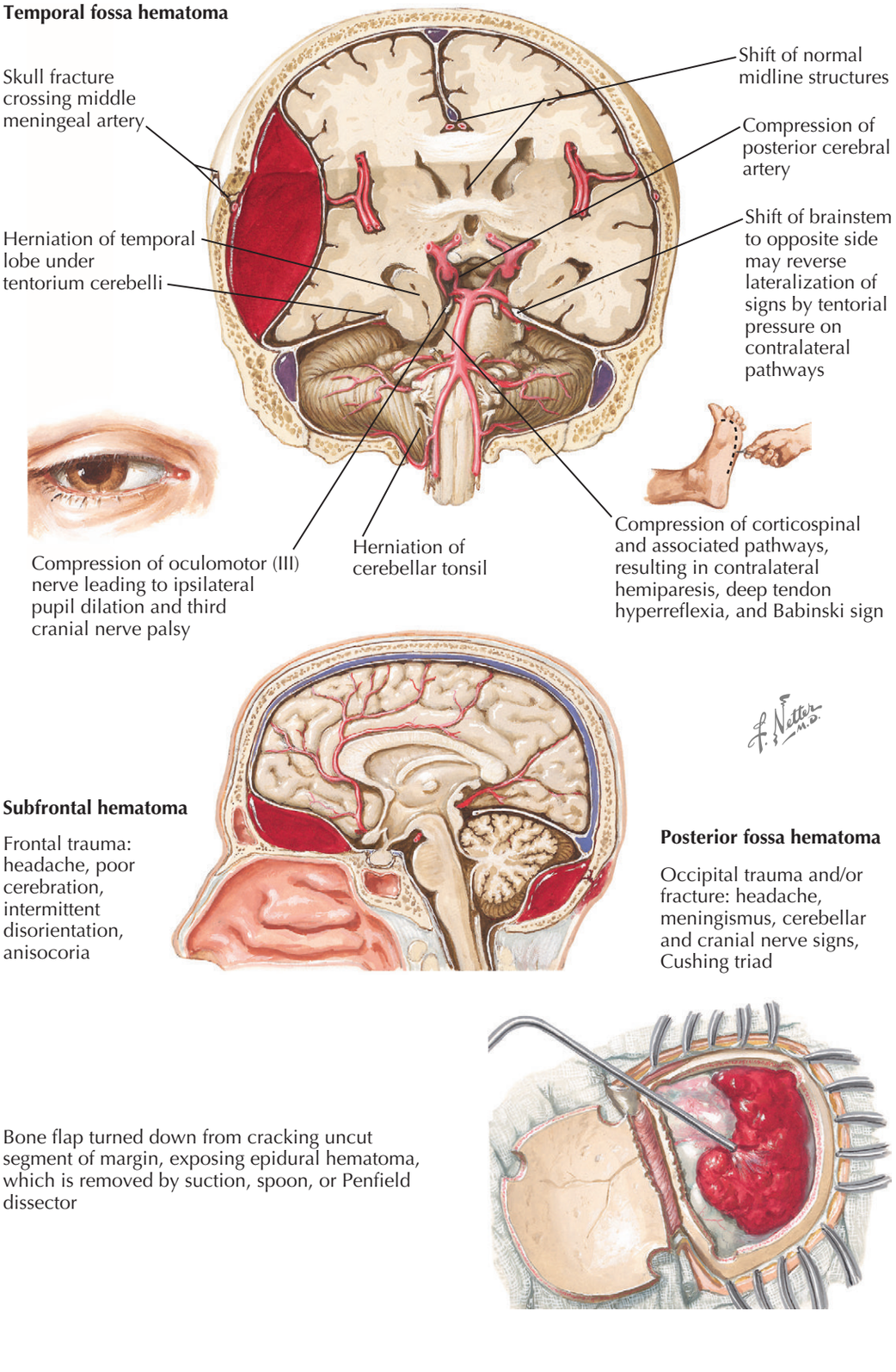
The most common clinical location for an EDH is the temporal fossa, typically associated with a temporal bone fracture that lacerates the middle meningeal artery and leads to arterial bleeding. This can result in the well-known transtentorial herniation syndrome. As the ipsilateral temporal lobe is forced medially, the third nerve is trapped against the brainstem, resulting in ipsilateral pupillary dilation. As more pressure develops, the ipsilateral posterior cerebral artery may be so severely compressed as to result in an occipital lobe stroke that is typically seen on CT scan a day or two after the event. With increasing shift of the brain to the opposite side, the brainstem is compressed, and the cerebral peduncle is forced into the edge of the tentorium, creating a so-called Kernohan notch and resulting in hemiparesis ipsilateral to the dilated pupil. If the compression remains severe for too long, Duret hemorrhages occur in the brainstem from compression or tearing of the small perforating arteries coming off the basilar artery. Such hemorrhages can be seen on magnetic resonance imaging (MRI) and portend a poor prognosis.

Venous epidural hematomas may also occur and are most common in the posterior fossa in children.

The following are recently published guidelines by the Brain Trauma Foundation (New York) for the treatment of EDH:

- An EDH greater than 30 cm^3 should be surgically evacuated regardless of the patient's score on the Glasgow Coma Scale (GCS).
- An EDH less than 30 cm^3 and with less than 15-mm thickness and with less than a 5-mm midline shift in patients with a GCS greater than 8 without focal neurologic deficit can be managed conservatively with serial CT scanning and close neurologic observation in a neurosurgical center.
- It is strongly recommended that patients with an acute EDH in coma (GCS < 9) with anisocoria undergo surgical evacuation as soon as possible.

In a truly urgent situation when, for example, weather or distance precludes getting the patient to a center with neurosurgical capabilities, a burr hole may release sufficient blood to be lifesaving. Definitive treatment is evacuation through a large "trauma" bone flap. An active bleeding point is virtually always found on the dura. Occasionally, bleeding may be seen to be coming from underneath the temporal lobe, and the middle meningeal artery will be found lacerated at or within the foramen spinosus. With rapid, aggressive treatment, mortality across all age groups and all GCS scores is less than 10%.



Bone flap turned down from cracking uncut segment of margin, exposing epidural hematoma, which is removed by suction, spoon, or Penfield dissector

Acute Subdural Hematoma

Acute subdural hematoma (ASDH) is the primary structural abnormality in up to 30% of patients after severe traumatic brain injury (TBI) and, in most instances, is associated with other significant structural injuries such as contusions.

The injury occurs typically after a high-speed motor vehicle collision. ASDH, however, is being increasingly seen in elderly patients after same-height falls, and especially in patients on anticoagulant or antiplatelet medication. Bleeding is typically venous in nature, resulting from shearing of cortical veins, bridging veins, or veins from one of the cerebral venous sinuses.

A computed tomography (CT) scan typically shows a hyperdense crescent of blood between the dura and the brain. Despite a relatively small amount of blood, there is typically significant underlying hemispheric cerebral edema with associated midline shift. An entity known as a hyperacute ASDH has been described on CT: the presence of mixed hyperdensity indicates ongoing active bleeding. Contusions are also frequent and typically will worsen after surgical evacuation of the ASDH.

The decision to operate is based on a number of factors, but increasing, age is an extremely strong independent factor indicating a poor prognosis.

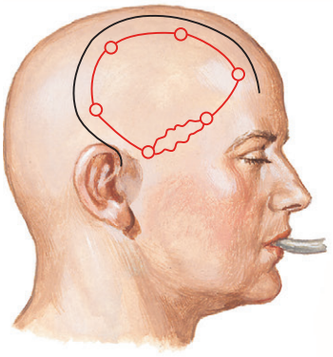
The following recommendations by the Brain Trauma Foundation (New York) have been proposed for surgical management:

- An ASDH with a thickness greater than 10 mm or a midline shift greater than 5 mm should be surgically evacuated regardless of the patient's GCS.
- All patients with ASDH with GCS less than 9 should undergo intracranial pressure monitoring.
- A patient with a GCS less than 9 and with an ASDH less than 10 mm thick and a midline shift less than 5 mm should undergo surgical evacuation of the lesion if the GCS decreases by 2 or more points between injury and hospital admission and/or the patient presents with asymmetric or fixed and dilated pupils and/or the intracranial pressure (ICP) exceeds 20 mm Hg.
- Patients with ASDH and indications for surgery should have evacuation performed as soon as possible.

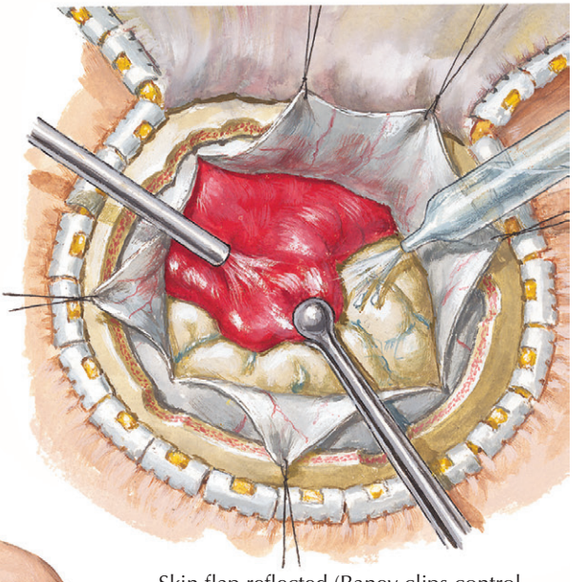
The issue of "as soon as possible" for surgical intervention has been widely studied. In a landmark paper in 1981, it was found that patients undergoing surgery within 4 hours of injury had a lower (30%) mortality rate than those undergoing surgery at later than 4 hours (90%). A subsequent paper in 1991 did not find any significant difference in mortality for patients undergoing surgery within or after 4 hours. It has been suggested that the degree and extent of underlying brain injury is probably the more important determinant of recovery than is the absolute timing of surgery.

The goal of surgery is the most complete evacuation of the ASDH as is possible through a large "trauma craniotomy" flap. Attention should be directed to coagulating any bleeding cortical veins or bridging veins. If there appears to have been avulsion of a vein from one of the venous sinuses, unless there has been adequate exposure of the area, such is best controlled by packing with hemostatic agents. If there is significant brain swelling, it is often best not to replace the craniotomy flap.

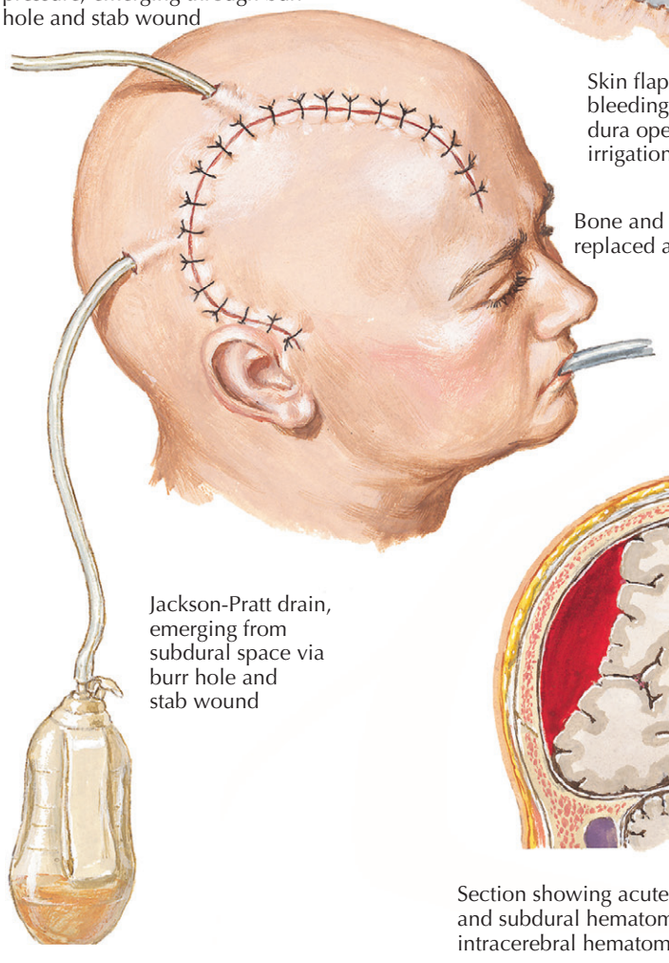
Unfortunately, despite the most aggressive neurocritical care, the mortality rate from ASDH remains high, ranging from 40% to 60% across all GCS categories and greater than 70% in patients presenting in coma.



"Question mark" skin incision (black); outline of free bone flap and burr holes (red)



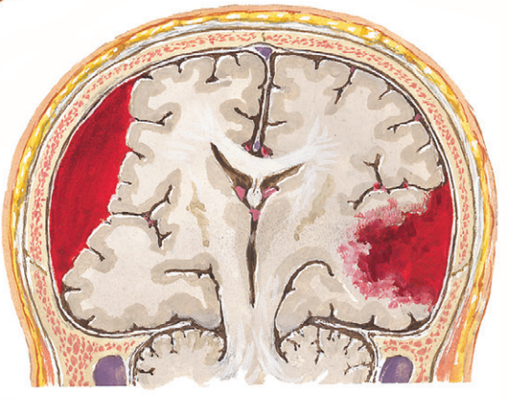
Skin flap reflected (Raney clips control bleeding); free bone flap removed and dura opened; clot evacuated by irrigation, suction, and forceps



Catheter to monitor intracranial pressure, emerging through burr hole and stab wound

Bone and skin flaps replaced and sutured

Jackson-Pratt drain, emerging from subdural space via burr hole and stab wound



Section showing acute subdural hematoma on right side and subdural hematoma associated with temporal lobe intracerebral hematoma ("burst" temporal lobe) on left

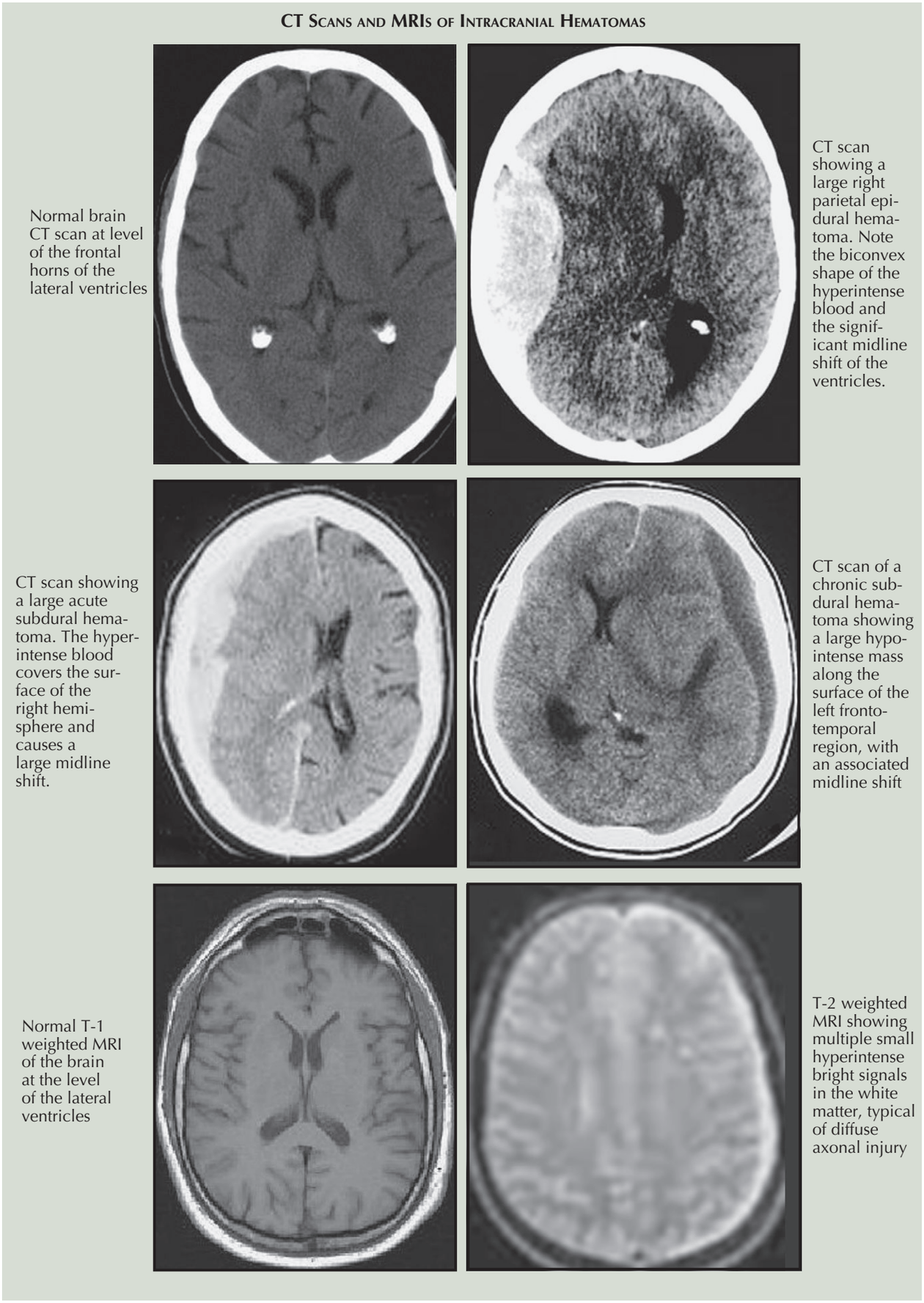
CONTUSIONS

Contusions are parenchymal mass lesions that occur in up to 35% of patients with severe TBI. Approximately 30% will enlarge progressively or become associated with significant surrounding edema. Although most can be managed medically, it has been recommended that surgery be considered in the following setting: patients with GCS scores of 6 to 8 with frontal or temporal contusions greater than 20 cm^3 in volume, with midline shift of at least 5 mm and/or cisternal compression on CT scan, and any patients with any lesion greater than 50 cm^3 in volume should be treated operatively.

DIFFUSE AXONAL INJURY

Diffuse axonal injury (DAI) or shear injury, as the name implies, results from stretching and tearing of axons throughout the brain. Although the injury is diffuse, two of the most common areas of involvement are the corpus callosum and the posterolateral quadrants of the upper brainstem. CT scans may show discrete punctuate hemorrhages in these and other white matter tracts. Magnetic resonance imaging (MRI) is very sensitive to DAI lesions, which appear hyperintense on T2-weighted images. Severe DAI is unfortunately associated with a poor outcome.

CT Scans and MR Images of Intracranial Hematomas



VASCULAR INJURY

CAROTID-CAVERNOUS FISTULA

Carotid-cavernous fistula (CCF), occurring in less than 3% of head-injured patients, is the most well-characterized sequela of intracranial vascular injury, having first been described in 1757. Although CCF may arise from other causes such as ruptured intracavernous aneurysm or infection, trauma is the most common cause. CCF occurs when there has been an injury to the cavernous sinus segment of the carotid artery, resulting in redirection, overfilling, and pressurization of the venous inflow and outflow of the cavernous sinus. The resulting clinical syndrome is characterized by pulsating exophthalmos and a bruit.

The carotid artery enters the cavernous sinus as it exits the foramen lacerum at the base of the skull. It then rises toward the posterior clinoid process before acutely turning anteriorly for approximately 2 cm (the horizontal segment), leaving the cavernous sinus just below the anterior clinoid. There are several small branches of the carotid inside the cavernous sinus, including the meningohypophyseal trunk and the artery of the inferior cavernous sinus. The cavernous sinus itself is an intricate plexus of venous channels surrounding the carotid artery. It lies lateral to the pituitary gland and sphenoid sinus, extending from the superior orbital fissure to the apex of the petrous bone. Among many other venous and sinus connections, the superior and inferior ophthalmic veins and the central retinal artery drain into the cavernous sinus, the former accounting for the exophthalmos and the latter for the possibility of intracranial hemorrhage. The third, fourth, and all three branches of the fifth cranial nerve run within the lateral wall of the cavernous sinus; the sixth nerve passes directly through the sinus alongside the carotid, whereas ocular sympathetic fibers form a plexus on the wall of the carotid.

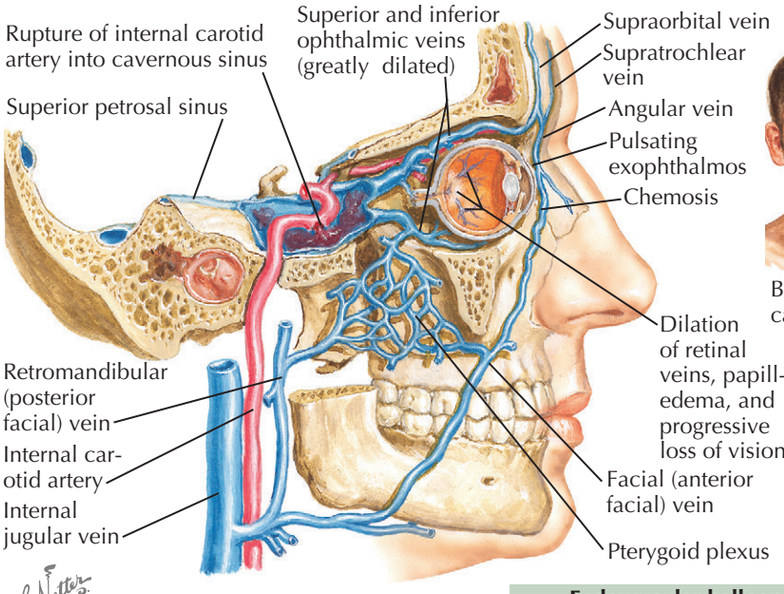
The classic signs and symptoms of the complete syndrome resulting from CCF include pulsating exophthalmos, a bruit that patients often appreciate, chemosis (conjunctival injection), diplopia, visual loss, and headache. These may evolve over the course of several weeks or months. Their pathophysiologic basis can be deduced readily from the previously described anatomy.

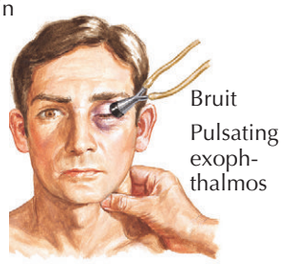
Although a CCF can typically be seen on computed tomography (CT) or magnetic resonance imaging (MRI), angiography is necessary to define the anatomy of the fistula and to identify the associated abnormal venous drainage so as to allow for planning of optimal treatment. Because traumatic CCFs rarely resolve spontaneously, surgical intervention is usually indicated. The timing of intervention depends on the degree and extent of visual loss. Visual deterioration is due to ischemia secondary to increased intraocular pressure and subsequent hypoxia as a result of reduced arterial flow and venous hypertension.

Before the development of endovascular surgical techniques, the most common treatment approach involved occluding the internal carotid artery in the neck as well as intracranially just distal to its exit from the cavernous sinus. Unfortunately, this usually meant sacrificing the ophthalmic artery as well, given its origin just below the anterior clinoid process, with the associated risk of further visual loss.

The current treatment of choice is selective endovascular balloon occlusion of the fistulous connection itself, preserving the carotid artery and its branches. The fistula may be accessed by a variety of routes, including the superior ophthalmic vein, the carotid artery, and the superior petrosal sinus.

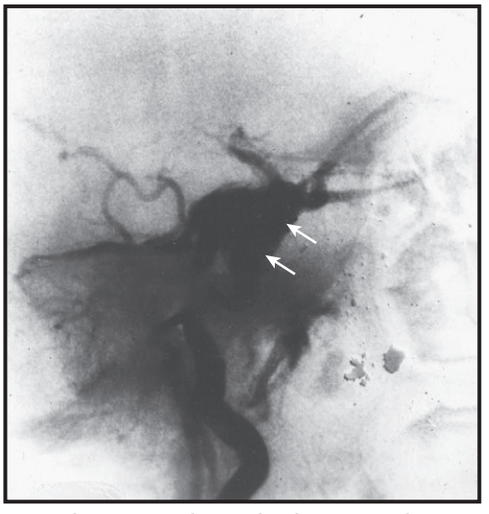
Large series of patients with CCFs treated endovascularly have demonstrated a 99% occlusion rate with less than 5% complications.





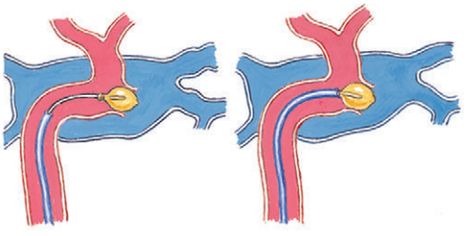
Bruit obliterated by carotid compression

Tachycardia, cardiac hypertrophy, dyspnea, and increased blood volume may occur



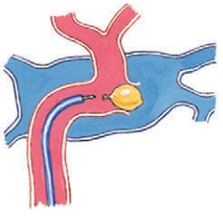
Carotid arteriography, early phase, reveals prominent opacificaton of cavernous sinus *(arrows)* via carotid-cavernous fistula

Endovascular balloon occlusion of fistula



Balloon inflated with radiopaque fluid occluding fistula

Outer catheter advanced over inner catheter to engage balloon cuff



Balloon liberated by slight pull on inner catheter. Balloon neck spontaneously constricted by tense latex tie. All catheters then withdrawn.

SECONDARY COMPLICATIONS OF TRAUMATIC BRAIN INJURY

A significant number of patients die or are left severely disabled after TBI, not by the primary injury itself but by the secondary insults that follow. The most common of these are hypotension and hypoxia.

Hypoxia (oxygen saturation less than 90%) and/or hypotension (systolic blood pressure less than 90 mm Hg) was found to occur in greater than one third of patients with severe TBI in the National Coma Data Bank. A single episode of hypotension at any point is associated with a doubling of mortality; of hypoxia with a 33% increase; and the combination with a 75% increase. Thus every effort should be made to prevent or minimize the occurrence of these events.

Another serious secondary insult is intracranial hypertension. It is reasonably well established that maintaining intracranial pressure (ICP) below 20 mm Hg at all times is associated with greater than 90% survival; controlling ICP below this level for greater than 50% of the time is associated with greater than 50% survival; and an inability to ever bring ICP below 20 mm Hg, is accompanied by a greater than 90% mortality.

An important, but still uncontrolled problem is the damaging biochemical cascade that is initiated shortly after injury. The final common pathway to energy failure, and ultimately to cell death, relates to loss of calcium homeostasis and to mitochondrial damage. Opening the cellular membranes to calcium influx is triggered by a variety of mechanisms, including oxygen free-radical production, excitatory neurotoxicity, caspases, and cytokines. The resulting damage may exceed that created by the primary injury. Randomized controlled clinical trials of pharmacologic agents to block this biochemical cascade have not yielded benefit.

Initial Assessment and Management of Head Injury

As with any potentially life-threatening injury, the airway, breathing, and circulation (ABC) protocol takes precedence. In a comatose patient in whom the airway has not been secured in the prehospital phase, intubation takes priority. Even brief episodes of hypoxia are associated with significantly worse outcomes. Rapid-sequence intubation utilizing agents such as thiopental or propofol with a muscle relaxant is optimal in minimizing the risk of aspiration, but it also renders uninterpretable the findings on neurologic examination. Thus it is preferable that a reliable Glasgow Coma Score is established before intubation. Initial ventilation should aim to normalize Pao_2 and Pco_2, at greater than 90% and 35 to 40 mm Hg, respectively. Hyperventilation is not advised unless attempting to treat suspected increased intracranial pressure (ICP), and then for only short periods.

Hypotension (systolic blood pressure < 90 mm Hg) may increase mortality markedly after head injury. Lactated Ringer solution or normal saline are the resuscitation fluids of choice. Glucose solutions should be avoided because hyperglycemia may worsen the outcome. Hypertonic saline (HS) is being used increasingly. Effective resuscitation can be accomplished with as little as 1 to 2 mL/kg, and HS may have a variety of neuroprotective effects. If an adequate systolic blood pressure cannot be restored with 2 to 3 liters of crystalloid, packed RBCs should be given.

It is important to rigorously follow the Advanced Trauma Life Support guidelines. Up to 70% of severely head-injured patients will have thoracic, abdominal, or major orthopaedic injuries, which may require more immediate attention than the head injury. On occasion, a patient may be so hemodynamically unstable as to require urgent thoracotomy, laparotomy, or endovascular intervention before the head injury can be fully evaluated. Simultaneous ICP monitoring during the ongoing intervention should be considered.

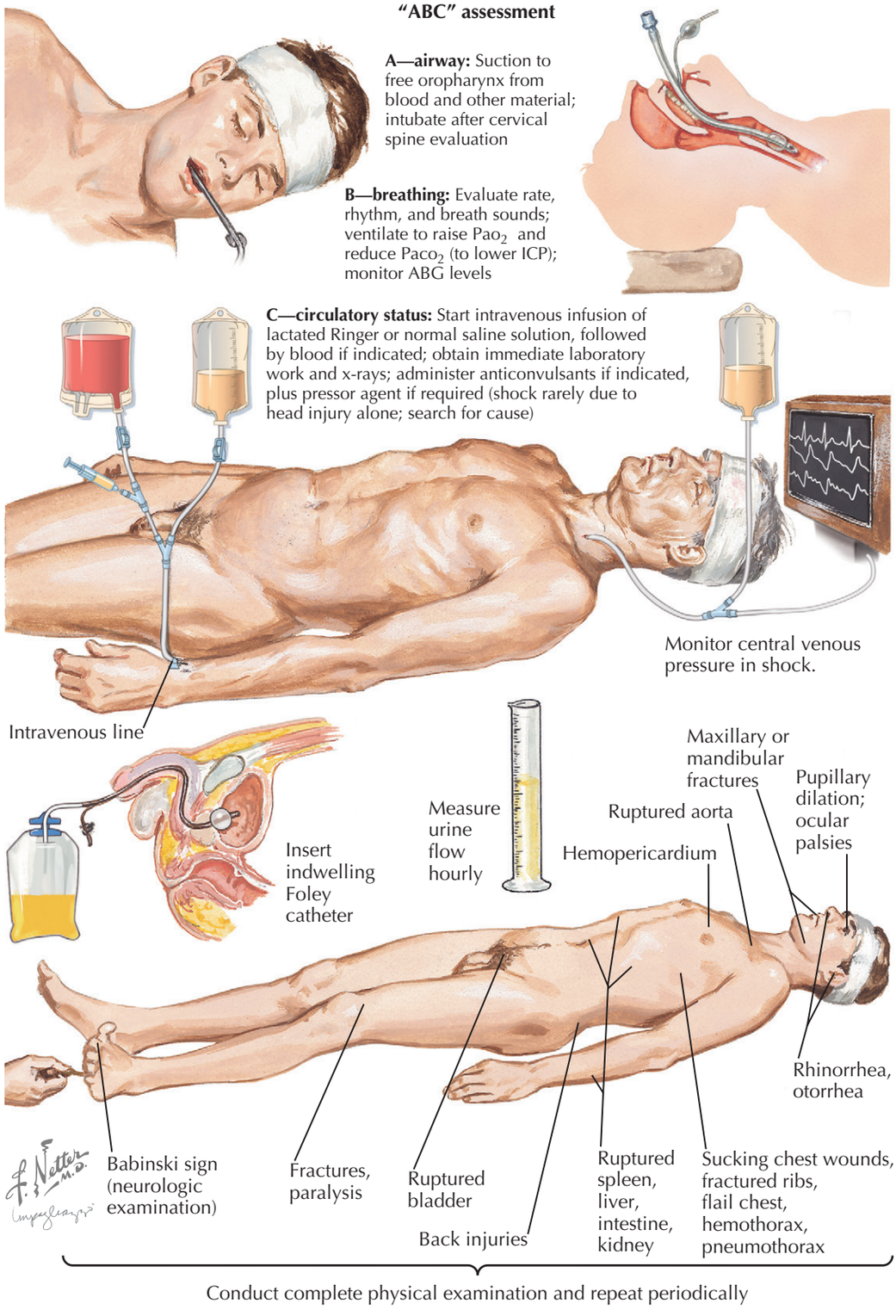
It is important to obtain a computed tomography (CT) scan of the head as soon as possible during initial management so as to determine the degree and extent of structural damage to the brain and prepare for immediate operative intervention, if appropriate. When a large mass lesion or early evidence of significantly increased ICP (such as obliteration of the basal cisterns) is present, mannitol 0.5 to 1.0 mg/kg may be given to reduce ICP. However, mannitol may initiate a diuresis that causes or exacerbates hypotension.

Additional problems are posed by patients on anticoagulants or antiplatelet medications. If such a history cannot be elicited, an important component to the initial laboratory studies is determination of the international normalized ratio (INR) and clotting time. In patients with any evidence of traumatic intracranial bleeding, the INR must be corrected with vitamin K and fresh frozen plasma. Many are using recombinant factor VIIa for this purpose. Dealing with current antiplatelet agents is particularly problematic because platelet function may be impaired for up to 7 days. Platelet transfusions may be helpful. Desamino-D-arginine vasopressin (DDAVP) can be administered as well.

Unless a patient is on chronic steroid therapy, steroids are contraindicated as a treatment for head injury. Anticonvulsant prophylaxis should be initiated as soon as possible after severe head injury and maintained for 7 days unless the patient seizes. Dilantin and Keppra are the most frequently used drugs for this purpose.

At some early point, the spine must be evaluated because spinal injury occurs in more than 5% of severely head-injured patients. Cervical immobilization must be maintained with a collar until structural injury to the cervical spine is definitively excluded. It is important to remove a hard backboard as soon as possible, while maintaining the patient flat, to immobilize the thoracolumbar spine. Skin ischemia, potentially leading to decubiti, can begin after 30 minutes on a backboard, especially in hypotensive patients.

A plain radiograph of the spine, supplemented with CT scan, will rule out the majority of bony injuries, but the possibility remains of a significant ligamentous injury. Magnetic resonance imaging (MRI) within the first 24 to 48 hours of injury has been advocated as a reliable method of assessing for ligamentous damage, but many physicians prefer to leave a cervical collar in place until clinical assessment is complete.



Glasgow Coma Score

Teasdale and Jeanette introduced the Glasgow Coma Score (GCS) in 1974 as an objective measure of level of consciousness after traumatic brain injury (TBI). The GCS quickly became universally accepted as the best clinical measure of the severity of TBI, allowing for a reliable, standardized method of assessing and reporting sequential evaluation across all health-care providers. The GCS measures level of consciousness, not neurologic deficits. An appropriate neurologic examination should accompany the GCS.

The GCS evaluates three independent neurologic responses: eye opening, motor response, and verbal response All parameters may be significantly affected by systemic factors such as severe hypotension or significant drug/alcohol intoxication or by local factors, including ocular trauma, intubation, extremity fractures, and spinal cord injury. Iatrogenic paralysis/sedation affects the score and may render the GCS inapplicable.

The eye opening and verbal responses are simple to record. The motor response has traditionally been recorded as the best reaction in response to deep pressure or pain. Thus a patient who is hemiplegic may still receive a motor score of 6. In their original paper, Teasdale and Jennett specifically proscribed the manner in which the evaluation of all three parameters was to be undertaken. Noxious stimuli to the nailbed were to be applied to elicit decorticate or decerebrate responses, while painful stimuli to the head neck or trunk were used to test for localization. Eye opening in response to pain was to be tested distant to the face to prevent a grimacing reflex from keeping the eye shut.

It is generally accepted that a GCS of 13 to 15 is associated with minor TBI, a GCS of 9 to 12 reflects moderately severe TBI, and a GCS of 3 to 8 indicates severe TBI. It is common practice to attach a modifier ("t") after the score if a verbal response cannot be recorded due to intubation.

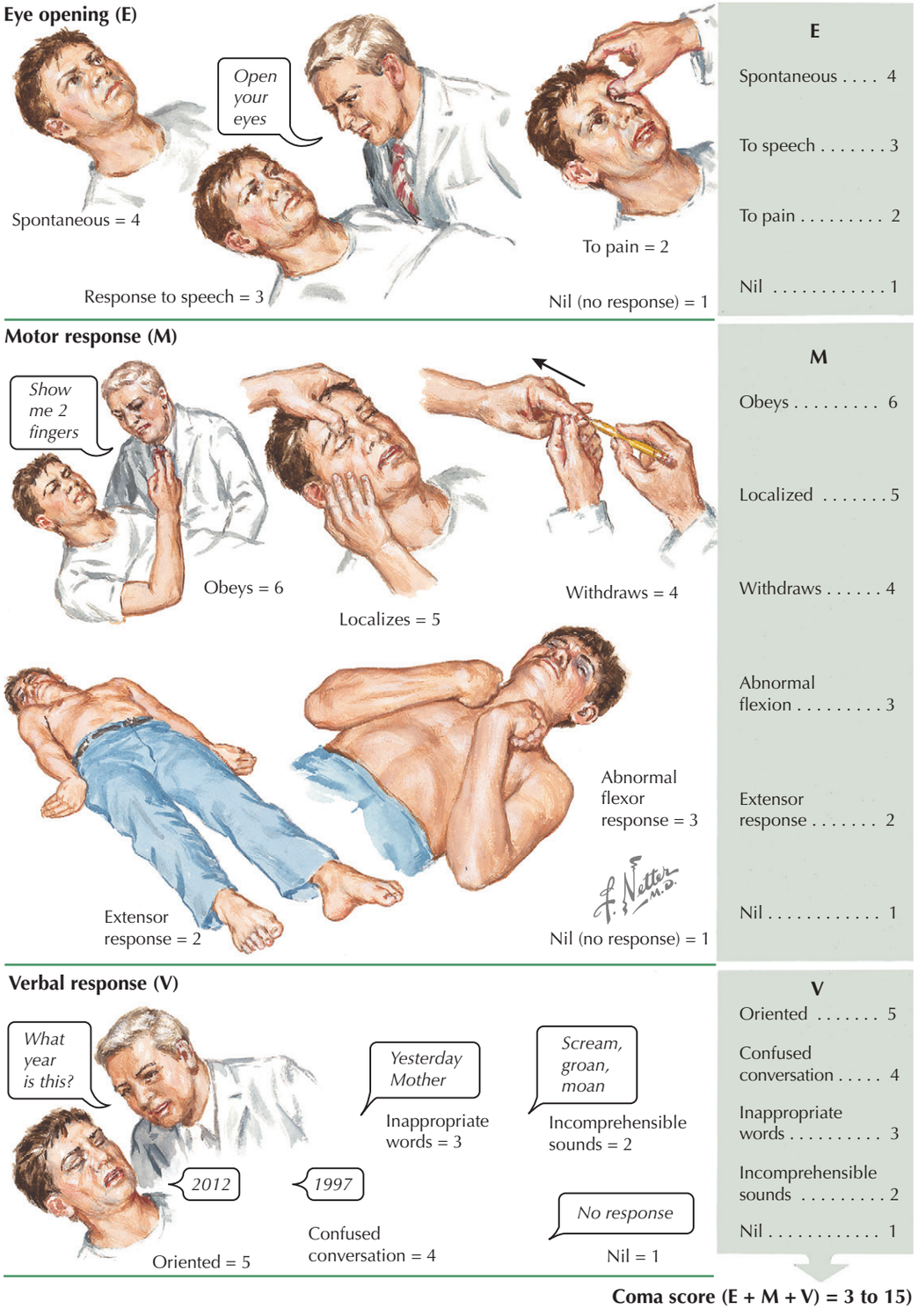
The GCS cannot be used in preverbal children, and a children's coma scale has been developed. The eye and motor responses mirror those of the GCS. For the verbal response, a score of 5 is given if the child smiles, orients to sounds, follows objects, and interacts. Scores of 4 to 1 include both a component related to crying and one to interaction. Thus a score of 4 indicates that the child cries consolably and interacts inappropriately; 3, that crying is inconsistently consolable and there is moaning; 2, that the child cries inconsolably and is restless; and 1, that there is an absence of crying or interaction.

Several studies have shown an association between both a prehospital and in-hospital GCS and outcome. As an example, patients having a GCS of 6 to 15 in the field were 30 times more likely to have a good outcome than with a GCS less than 6. A prospective study of emergency medical service (EMS) and in-hospital GCS determination found a positive predictive value of 77% for a poor outcome (dead, vegetative, or severely disabled) in patients with a GCS of 3 to 5 and 26% with a GCS of 6 to 8.

From a clinical perspective, the GCS is routinely recorded at regular intervals during the neurocritical care phase of TBI management. Various clinical decisions have come to be based on GCS thresholds, such as the need for intubation and consideration of ICP monitoring when the GCS is less than 8. Similarly, during ongoing evaluation, a decline of two or more points is generally considered clinically significant.

Efforts in developing the GCS have been extended to outcome assessment. The Glasgow Outcome Scale (GOS) was introduced in 1975 and is the cornerstone in outcome assessment, with high intrarater reliability. There are five potential outcomes, that is, death, persistent vegetative state, severe disability, moderate disability, and a good outcome.

A good recovery is defined as a resumption of a normal life despite minor ongoing disability. With moderate disability, a patient is disabled but independent, able to perform all activities of daily living, and work in a sheltered setting. Severely disabled patients are conscious but totally dependent on others for care. In the persistent vegetative state, the patient is unresponsive and speechless but may open the eyes and appear to be able to track.



Neurocritical Care and Management after Traumatic Brain Injury

Care of the severely injured patient is challenging and often requires a team approach. Systemic and intracranial physiology may vary at different times. In 1996, the Brain Trauma Foundation in conjunction with the American Association of Neurologic Surgeons published the first evidence-based guidelines for the medical management of severe TBI.

The first priority in severe TBI is to establish complete and rapid physiologic resuscitation, which includes a secure airway and maintenance of O_2 saturation of greater than 90% and arterial systolic pressure greater than 90 mm Hg. If not already performed, endotrachial intubation should be undertaken in any patient with a GCS less than 9 or one who remains hypoxic despite supplemental oxygen. It is routine to place an arterial line for continuous blood pressure (BP) recording. Central or Swan Ganz lines may be helpful in guiding fluid resuscitation.

The optimal resuscitation and maintenance intravenous fluids have been discussed earlier.

Once the patient is medically and surgically stabilized, the next priority is to establish intracranial pressure (ICP) monitoring in patients with a GCS less than 9 who have abnormal computed tomography (CT) scans. ICP monitoring is also important in comatose patients with normal CT scans if two of the following are present: age greater than 40 years, systolic BP less than 90 mm Hg, or there is unilateral or bilateral motor posturing.

There are various devices for ICP monitoring. The intraventricular catheter is considered the gold standard and also allows for the drainage of cerebrospinal fluid (CSF) when ICP is elevated. However, placement of a ventricular catheter may be difficult in the swollen and/or shifted brain, and a variety of parenchymal monitors may serve as reasonable substitutes.

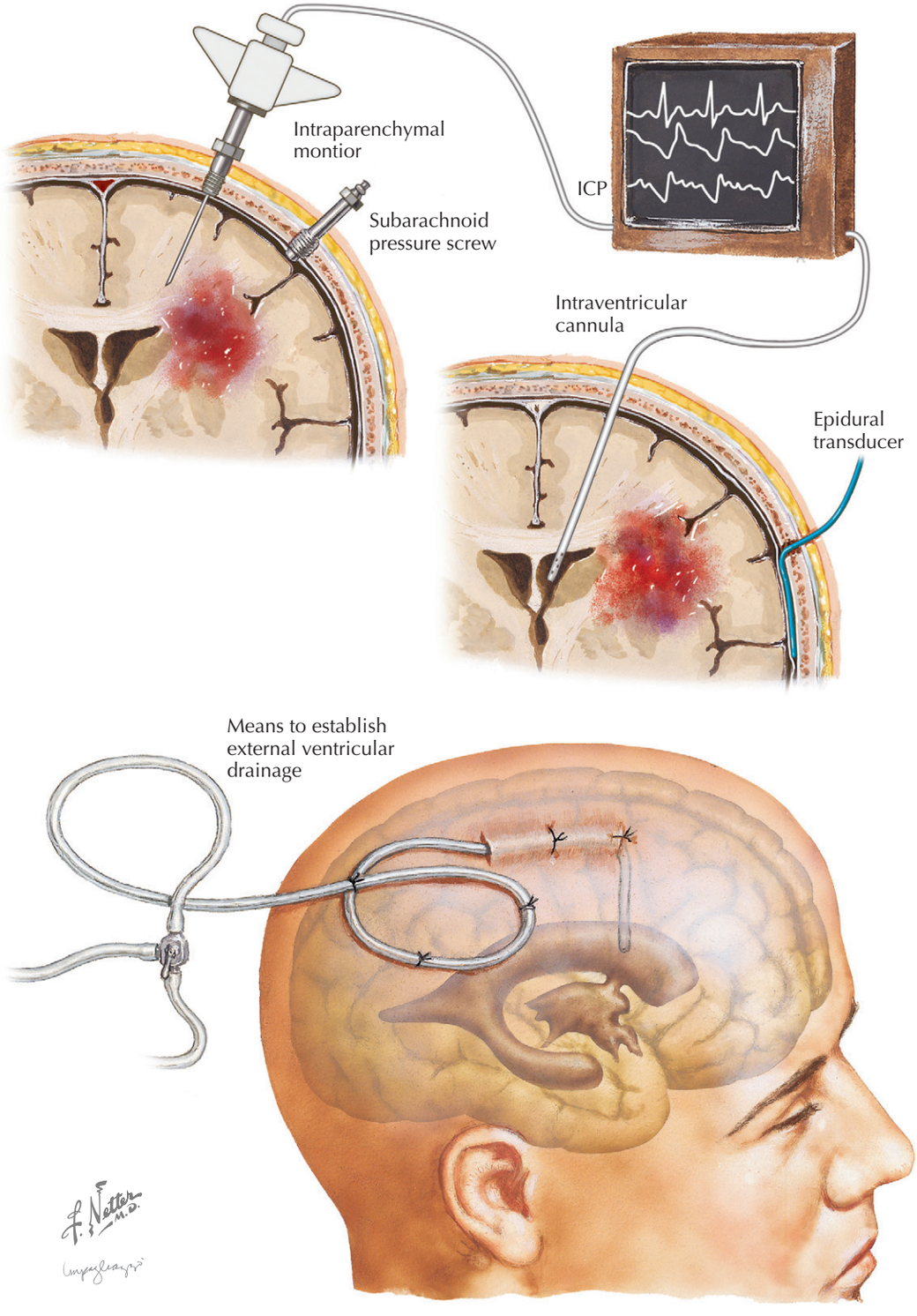
Brain oxygen saturations (PBo_2) are being increasingly monitored in severe TBI; however, their true usefulness is unclear. Early information suggests that PBo_2 less than 20 mm Hg may be associated with worse outcomes, but it is unclear whether this represents the severity of the underlying brain injury or a potentially treatable "secondary injury."

Less commonly used is cerebral microdialysis, which can measure a variety of neurotransmitters and metabolites, such as glutamate, aspartate, and lactate. It is likewise unclear how information obtained in this way will play a role in the institution of a specific therapy.

The central tenant of severe TBI management is control of ICP and, by extension, cerebral perfusion pressure (CPP). CPP is the mean arterial pressure minus the ICP and is the driver of cerebral blood flow. As has been noted, persistently elevated ICP (>20 mm Hg) is associated with significant mortality. An optimal CPP is generally in the range of 60 to 70 mm Hg.

First-line therapies for ICP control include sedation, paralysis, head-of-bed elevation to 20 to 30 degrees, and avoidance of hyperthermia (>38.5° C).

Devices for Monitoring Intracranial Pressure



Mannitol is the most commonly used pharmacologic agent to lower ICP. The primary action of mannitol is in inducing an osmotic gradient between plasma and cells, thus drawing edema fluid from the brain into the circulation. This causes an expansion of blood volume and a potential elevation in blood pressure but ultimately results in a diuresis that may lower blood pressure. Secondary effects of mannitol include a reduction in blood viscosity, which increases cerebral blood and cerebral oxygen delivery. Effective doses of mannitol range from 0.25 g/kg to 1 g/kg and lead to ICP reduction within 15 to 30 minutes.

Because mannitol is an osmotic diuretic, it is excreted entirely by the kidneys and thus should be used with caution in patients with renal failure. It is important to follow serum sodium and osmolality and limit use if serum sodium is elevated to greater than 155 mEq/L or osmolality is greater than 320 mOsm/L.

Neurocritical Care and Management after Traumatic Brain Injury *(Continued)*

Hypertonic saline (3%) is being increasingly used to treat intracranial hypertension. Its mechanism of action is clearance of edema fluid through bulk flow. Additional potential benefits include immunomodulation—prevention of leukocyte adherence and release of prostaglandins—and inhibition of excitotoxity. Typically, administered doses are intermittent boluses of 250 mL or a continuous infusion of 1 mL/kg/hr. As with mannitol, use should be limited if serum sodium exceeds 155 mEq/L or osmolality 320 mOsm/L.

Hyperventilation can rapidly decrease ICP by causing vasoconstriction and reducing intracranial blood volume. Prolonged prophylactic hyperventilation was previously a mainstay of ICP management but has been found to worsen outcome, probably by inducing ischemia. Currently, it is recommended that hyperventilation should only be used for short periods and that Pco_2 be kept above 30 mm Hg.

If the ICP is uncontrollable despite these measures, high-dose barbiturate therapy may be necessary. This suppresses metabolism and lessens cerebral blood-flow requirements. The patient must, however, be hemodynamically stable because barbiturates can have a direct cardiac depressant effect. Pentobarbital is the barbiturate most commonly used. A typical loading dose is 10 mg/kg over 30 minutes, followed by 5 mg/kg hourly for three doses, with a maintenance dose of 1 mg/kg/hr. Continuous electroencephalographic monitoring is necessary as the goal of therapy is to induce burst suppression.

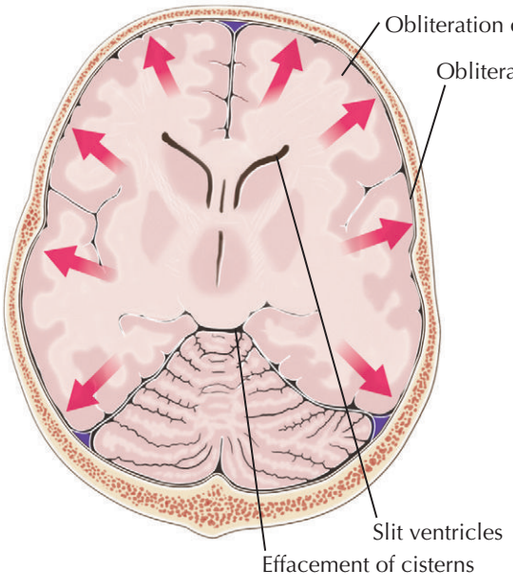
Decompressive craniectomy (DC) has come to supplant barbiturates as the "final" treatment for intractable ICP elevations. Originally introduced in the 1960s, the procedure fell out of favor because, although mortality was lowered after severe TBI, the quality of survival was unchanged. The procedure involves removal of large portions of the skull in an attempt to control ICP. Over the past decade, numerous published articles on DC have used different ICP-based criteria for undergoing the procedure, such as ICP greater than 20 mm Hg for more than 30 minutes or ICP greater than 30 mm Hg for more than 20 minutes. Regardless of the criteria used, there is a direct correlation between the amount of bone removed and the ability to control ICP. There is a less than 40% reduction in ICP if bone removal is less than 8000 mm^3 and greater than 80% reduction with removal of more than 12,000 mm^3.

The DC may be unilateral or bilateral. When unilateral, bone is removed from the supraorbital ridge anteriorly to the inion posteriorly, superiorly to within 1 cm of the superior sagittal sinus and inferiorly to the floor of the temporal fossa. Bilateral DC is typically bifrontal from the supraorbital ridge to behind the coronal suture (including a generous subtemporal decompression), leaving a 1-cm strip of bone over the superior sagittal sinus. The bone is saved for later replacement either by implantation into an abdominal subcutaneous pocket or by freezing. It is typically replaced within 1 to 3 months. Some advocate replacement of the bone before hospital discharge to minimize the risk of infection, especially if the bone has been implanted, and other complications associated with DC. Greater than 20% of patients will develop symptomatic hydrocephalus or subdural hygromas after DC. This is related in part to the brain being exposed to atmospheric pressure once the ICP has normalized.

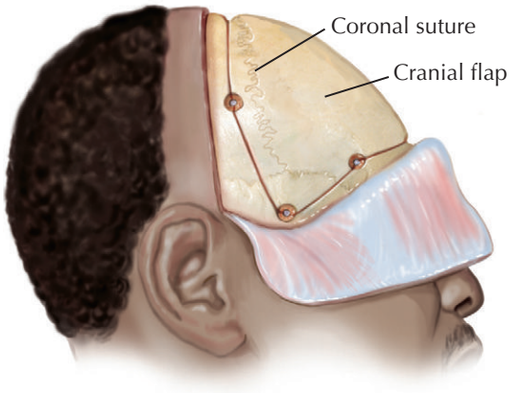
Although DC can be highly effective in controlling elevated ICP, it remains unclear whether it improves the quality of survival. A Cochrane meta-analysis of what little prospective, randomized data currently exist yielded 50% odds of unfavorable outcome after DC. The Decompressive Craniotomy (DECRA) Trial of DC was recently published, and in adults with diffuse TBI and uncontrollable intracranial hypertension, it found early bifrontal DC decreased intracranial pressure and intensive care unit (ICU) length of stay but was associated with more unfavorable outcomes.

Decompressive Craniectomy

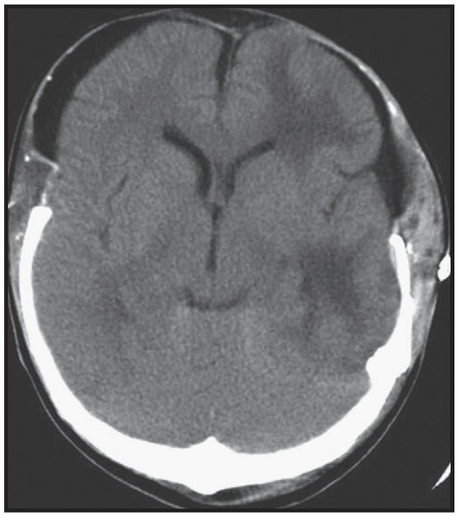
Increased intracranial pressure refactory to medical management



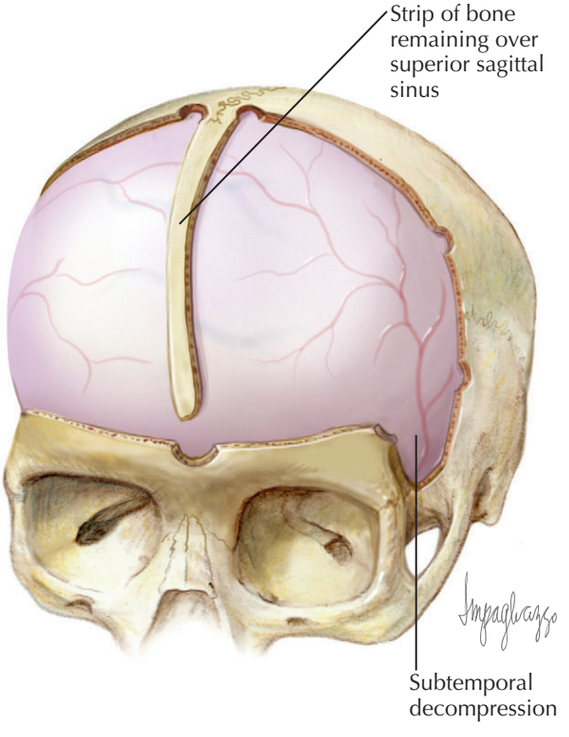
Decompressive craniectomy



After bifrontal craniectomy



CT appearance after extensive bifrontal craniectomy for ICP control. Note that all of the cranial bone from the coronal suture forward has been removed.



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