SECOND EDITION

HARRISON'S

Neurology in Clinical Medicine

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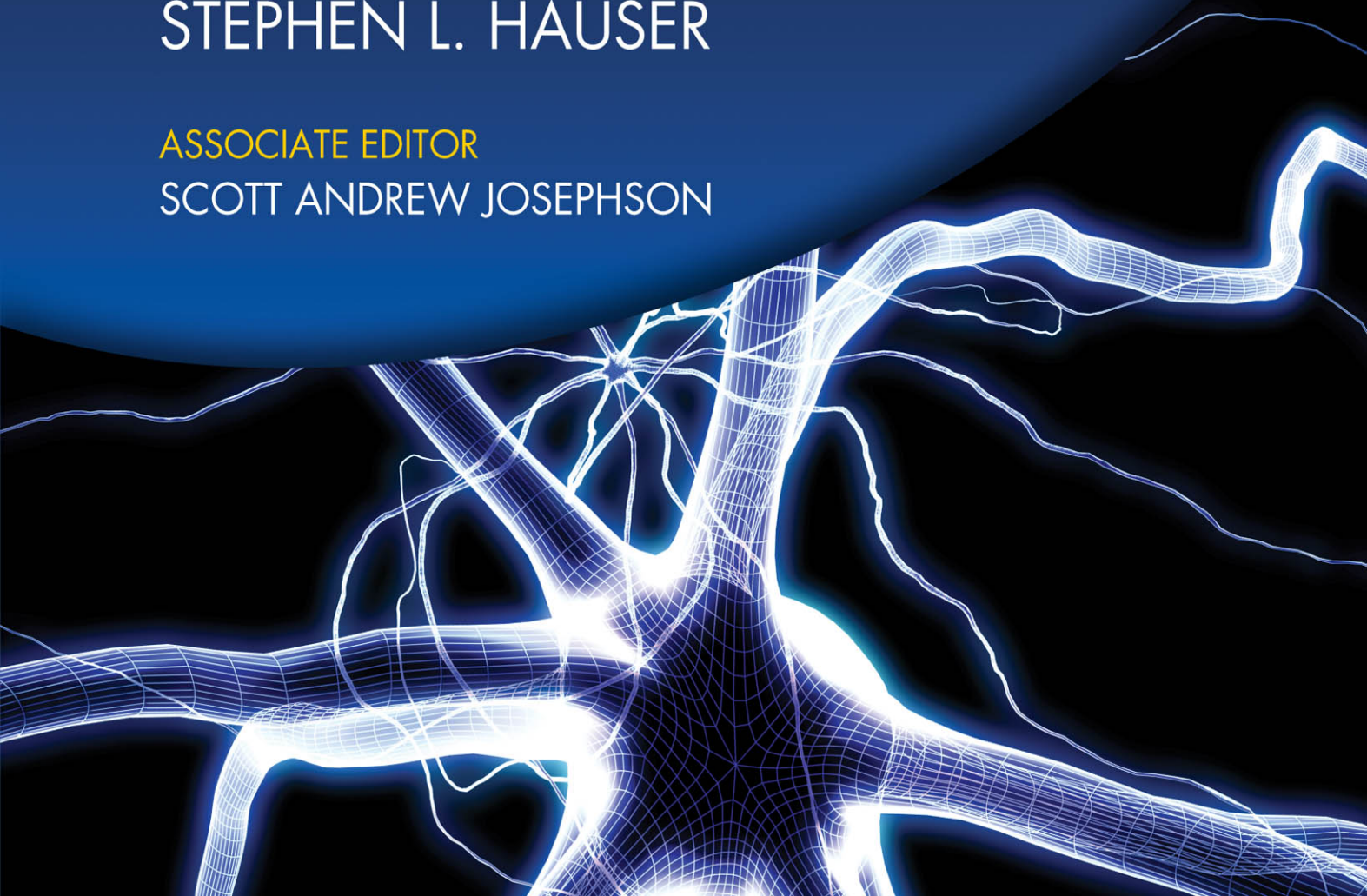

Second Edition

HARRISON'S Neurology in Clinical Medicine

Derived from Harrison's Principles of Internal Medicine, 17th Edition

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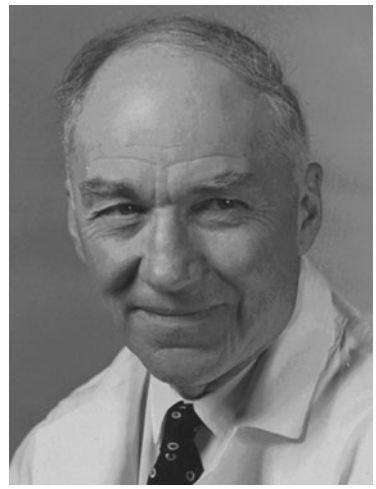

Raymond D. Adams, MD
1911–2008

For Ray Adams, editor of *Harrison's Principles of Internal Medicine* for more than three decades.

A mentor who taught by example,
a colleague who continues to inspire, and
a friend who is deeply missed.

Stephen L. Hauser, MD, for the Editors of *Harrison's*

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PREFACE

The first edition of *Harrison's Neurology in Clinical Medicine* was an unqualified success. Readers responded enthusiastically to the convenient, attractive, expanded, and updated stand-alone volume, which was based upon the neurology and psychiatry sections from *Harrison's Principles of Internal Medicine*. Our original goal was to provide, in an easy-to-use format, full coverage of the most authoritative information available anywhere of clinically important topics in neurology and psychiatry, while retaining the focus on pathophysiology and therapy that has always been characteristic of *Harrison's*.

This new edition of Harrison's *Neurology in Clinical Medicine* has been extensively rewritten to highlight recent advances in the understanding, diagnosis, treatment and prevention of neurologic and psychiatric diseases. New chapters discuss the pathogenesis and treatment of headache, the clinical approach to imbalance, and the causes of confusion and delirium. Notable also are new chapters on essential tremor and movement disorders, peripheral neuropathy, and on neurologic problems in hospitalized patients. Many illustrative neuroimaging figures appear throughout the section, and a new atlas of neuroimaging findings has been added. Extensively updated coverage of the dementias, Parkinson's disease, and related neurodegenerative disorders highlight new findings from genetics, molecular imaging, cell biology, and clinical research that have transformed understanding of these common problems. Another new chapter, authored by Steve Hyman and Eric Kandel, reviews progress in deciphering the pathogenesis of common psychiatric disorders and discusses the remaining challenges to development of more effective treatments.

For many physicians, neurologic diseases represent particularly challenging problems. Acquisition of the requisite clinical skills is often viewed as time-consuming, difficult to master, and requiring a working knowledge of obscure anatomic facts and laundry lists of diagnostic possibilities. The patients themselves may be difficult, as neurologic disorders often alter an individual's capacity to recount the history of an illness or to even recognize that something is wrong. An additional obstacle is the development of independent neurology services, departments, and training programs at many medical centers, reducing the exposure of trainees in internal medicine to neurologic problems. All of these forces, acting within the fast-paced environment of modern medical practice, can lead to an overreliance on unfocused neuroimaging tests, suboptimal patient care, and unfortunate outcomes. Because neurologists represent less than 1% of all physicians, the vast majority of neurologic care must be delivered by nonspecialists who are often generalists and usually internists.

The old adage that neurologists "know everything but do nothing" has been rendered obsolete by advances in molecular medicine, imaging, bioengineering, and clinical research. Examples of new therapies include: thrombolytic therapy for acute ischemic stroke; endovascular recanalization for cerebrovascular disorders; intensive monitoring of brain pressure and cerebral blood flow for brain injury; effective therapies for immune-mediated neurologic disorders such as multiple sclerosis, immune neuropathies, myasthenia gravis, and myositis; new designer drugs for migraine; the first generation of rational therapies for neurodegenerative diseases; neural stimulators for Parkinson's disease; drugs for narcolepsy and other sleep disorders; and control of epilepsy by surgical resection of small seizure foci precisely localized by functional imaging and electrophysiology. The pipeline continues to grow, stimulated by a quickening tempo of discoveries generating opportunities for rational design of new diagnostics, interventions, and drugs.

The founding editors of *Harrison's Principles of Internal Medicine* acknowledged the importance of neurology but were uncertain as to its proper role in a textbook of internal medicine. An initial plan to exclude neurology from the first edition (1950) was reversed at the eleventh hour, and a neurology section was hastily prepared by Houston Merritt. By the second edition, the section was considerably enlarged by Raymond D. Adams, whose influence on the textbook was profound. The third neurology editor, Joseph B. Martin, brilliantly led the book during the 1980s and 1990s as neurology was transformed from a largely descriptive discipline to one of the most dynamic and rapidly evolving areas of medicine. With these changes, the growth of neurology coverage in *Harrison's* became so pronounced that Harrison suggested the book be retitled, "The Details of Neurology and Some Principles of Internal Medicine." His humorous comment, now legendary, underscores the

depth of coverage of neurologic medicine in *Harrison's* befitting its critical role in the practice of internal medicine.

The Editors are indebted to our authors, a group of internationally recognized authorities who have magnificently distilled a daunting body of information into the essential principles required to understand and manage commonly encountered neurological problems. We are also grateful to Dr. Andrew Scott Josephson who oversaw the updating process for the second edition of *Harrison's Neurology in Clinical Medicine*. Thanks also to Dr. Elizabeth Robbins, who has served for more than a decade as managing editor of the neurology section of *Harrison's*; she has overseen the complex logistics required to produce a multiauthored textbook, and has promoted exceptional standards for clarity, language and style. Finally, we wish to acknowledge and express our great appreciation to our colleagues at McGraw-Hill. This new volume was championed by James Shanahan and impeccably managed by Kim Davis.

We live in an electronic, wireless age. Information is downloaded rather than pulled from the shelf. Some have questioned the value of traditional books in this new era. We believe that as the volume of information, and the ways to access this information, continues to grow, the need to grasp the essential concepts of medical practice becomes even more challenging. One of our young colleagues recently remarked that he uses the Internet to find facts, but that he reads *Harrison's* to learn medicine. Our aim has always been to provide the reader with an integrated, organic summary of the science and the practice of medicine rather than a mere compendium of chapters, and we are delighted and humbled by the continuing and quite remarkable growth in popularity of *Harrison's* at a time when many "classics" in medicine seem less relevant than in years past.

It is our sincere hope that you will enjoy using *Harrison's Neurology in Clinical Medicine, Second Edition* as an authoritative source for the most up-to-date information in clinical neurology.

NOTE TO READERS ON ELECTRONIC ACCESS TO THE FAMILY OF *HARRISON'S* PUBLICATIONS THE NEUROLOGIC METHOD

The *Harrison's* collection of publications has expanded as information delivery technology has evolved. *Harrison's Online (HOL)* is now one of the standard informational resources used in medical centers throughout the United States. In addition to the full content of the parent text, *HOL* offers frequent updates from and links to the emerging scientific and clinical literature; an expanded collection of reference citations; audio recordings and Podcasts of lectures by authorities in the various specialties of medicine; and other helpful supplementary materials such as a complete database of pharmacologic therapeutics, self-assessment questions for examination and board review; and an expanded collection of clinical photographs. Video clips of cardiac and endoscopic imaging are also available on *HOL*. Future iterations of *HOL* will include expanded use of such supplementary multimedia materials to illustrate further key concepts and clinical approaches discussed in the parent text.

In 2006, in recognition of the increasing time pressures placed on clinicians and the increasing use of electronic medical records systems, *Harrison's Practice of Medicine (HP)* made its debut. *HP* is a comprehensive database of specific clinical topics built from the ground up to provide authoritative guidance quickly at the point of care. *HP* is highly structured so that physicians and other health professionals can access the most salient features of any one of more than 700 diseases and clinical presentations within minutes. This innovative new application is updated regularly and includes fully integrated, detailed information on brand name and generic drugs. In addition, hyperlinks throughout *HP* enable quick access to the primary literature via PubMed. *HP* is available via the Internet and on PDA.

Stephen L. Hauser, MD

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

Review and self-assessment questions and answers were taken from Wiener C, Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J (editors) Bloomfield G, Brown CD, Schiffer J, Spivak A (contributing editors). *Harrison's Principles of Internal Medicine Self-Assessment and Board Review*, 17th ed. New York, McGraw-Hill, 2008, ISBN 978-0-07-149619-3.

The global icons call greater attention to key epidemiologic and clinical differences in the practice of medicine throughout the world.

The genetic icons identify a clinical issue with an explicit genetic relationship.

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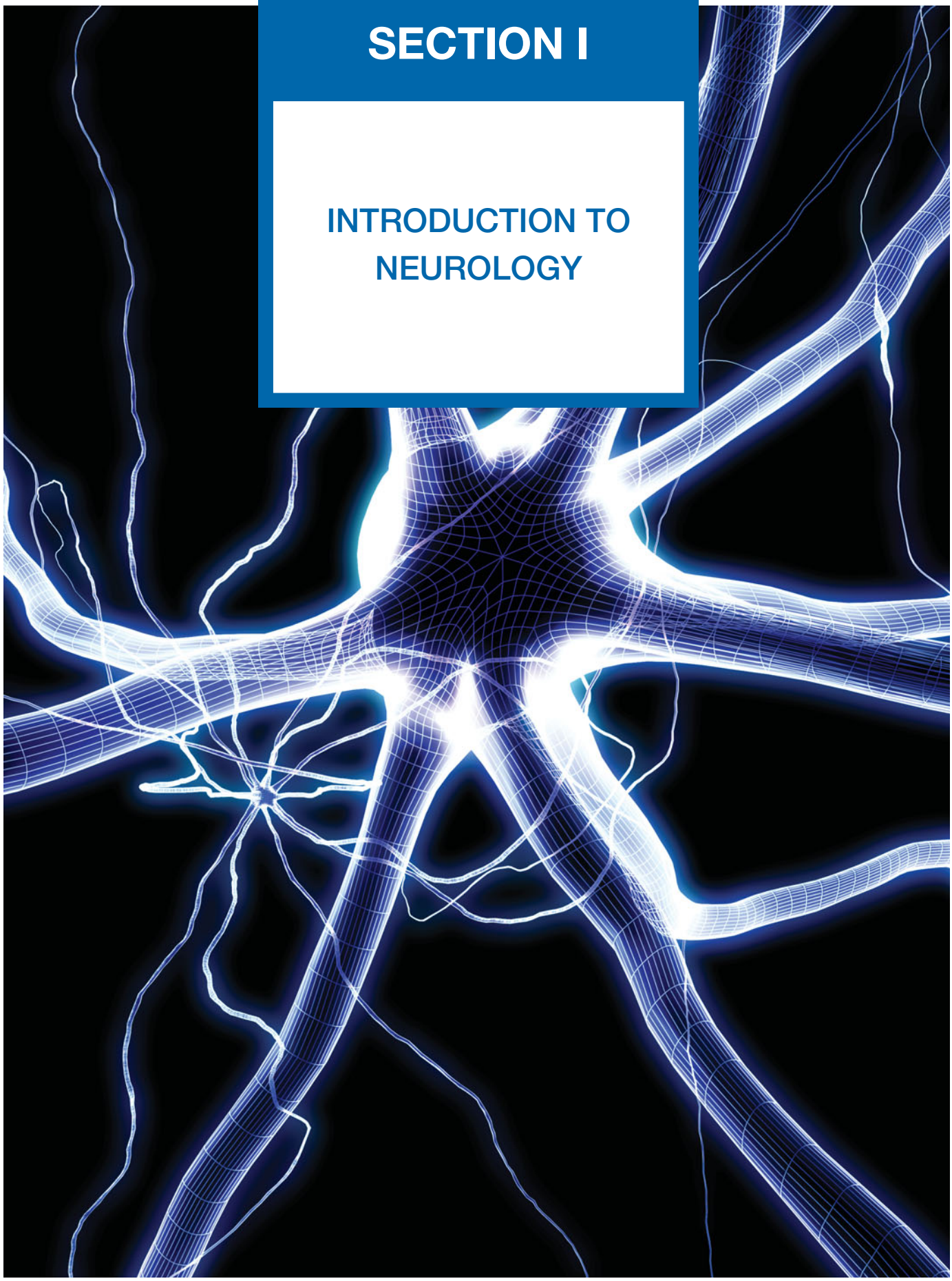
SECTION I

INTRODUCTION TO NEUROLOGY



CHAPTER 1

APPROACH TO THE PATIENT WITH NEUROLOGIC DISEASE

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- The Neurologic History 3
- The Neurologic Examination 4
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Neurologic diseases are common and costly. According to one estimate, 180 million Americans suffer from a nervous system disorder, resulting in an annual cost of over $700 billion. The aggregate cost is even greater than that for cardiovascular disease (**Table 1-1**). Globally, these disorders are responsible for 28% of all years lived with a disability. Most patients with neurologic symptoms seek care from internists and other generalists rather than from neurologists. Because therapies now exist for many neurologic disorders, a skillful approach to diagnosis is essential. Errors commonly result from an overreliance on costly neuroimaging procedures and laboratory tests, which, although useful, do not substitute for an adequate history and examination. The proper approach to the patient with a neurologic illness begins with the patient and focuses the clinical problem first in anatomic and then in pathophysiologic terms; only then should a specific diagnosis be entertained. This method ensures that technology is judiciously applied, a correct diagnosis is established in an efficient manner, and treatment is promptly initiated.

THE NEUROLOGIC METHOD

Locate the Lesion(s)

The first priority is to identify the region of the nervous system that is likely to be responsible for the symptoms. Can the disorder be mapped to one specific location, is it multifocal, or is a diffuse process present? Are the symptoms restricted to the nervous system, or do they arise in the context of a systemic illness? Is the problem in the central nervous system (CNS), the peripheral nervous system (PNS), or both? If in the CNS, is the cerebral cortex, basal ganglia, brainstem, cerebellum, or spinal cord responsible? Are the pain-sensitive meninges involved? If in the PNS, could the disorder be located in peripheral nerves and, if so, are motor or sensory nerves primarily affected, or is a lesion in the neuromuscular junction or muscle more likely?

The first clues to defining the anatomic area of involvement appear in the history, and the examination is then directed to confirm or rule out these impressions and to clarify uncertainties. A more detailed examination of a particular region of the CNS or PNS is often indicated. For example, the examination of a patient who presents with a history of ascending paresthesias and weakness should be directed toward deciding, among other things, if the location of the lesion is in the spinal cord or peripheral nerves. Focal back pain, a spinal cord sensory level, and incontinence suggest a spinal cord origin, whereas a stocking-glove pattern of sensory loss suggests peripheral nerve disease; areflexia usually indicates peripheral neuropathy but may also be present with spinal shock in acute spinal cord disorders.

Deciding "where the lesion is" accomplishes the task of limiting the possible etiologies to a manageable, finite number. In addition, this strategy safeguards against making serious errors. Symptoms of recurrent vertigo, diplopia, and nystagmus should not trigger "multiple

TABLE 1-1

PREVALENCE OF NEUROLOGIC AND PSYCHIATRIC DISEASES WORLDWIDE

DISORDER	PATIENTS, MILLIONS
Nutritional disorders and neuropathies	352
Migraine	326
Trauma	170
Depression	154
Alcoholism	91
Cerebrovascular diseases	61
Epilepsy	50
Schizophrenia	25
Dementia	24
Neurologic infections	18
Drug abuse	15

Source: World Health Organization estimates, 2002–2005.

sclerosis" as an answer (etiology) but "brainstem" or "pons" (location); then a diagnosis of brainstem arteriovenous malformation will not be missed for lack of consideration. Similarly, the combination of optic neuritis and spastic ataxic paraparesis should initially suggest optic nerve and spinal cord disease; multiple sclerosis (MS), CNS syphilis, and vitamin B_{12} deficiency are treatable disorders that can produce this syndrome. Once the question, "Where is the lesion?" is answered, then the question, "What is the lesion?" can be addressed.

Define the Pathophysiology

Clues to the pathophysiology of the disease process may also be present in the history. Primary neuronal (gray matter) disorders may present as early cognitive disturbances, movement disorders, or seizures, whereas white matter involvement produces predominantly "long tract" disorders of motor, sensory, visual, and cerebellar pathways. Progressive and symmetric symptoms often have a metabolic or degenerative origin; in such cases lesions are usually not sharply circumscribed. Thus, a patient with paraparesis and a clear spinal cord sensory level is unlikely to have vitamin B_{12} deficiency as the explanation. A Lhermitte symptom (electric shock–like sensations evoked by neck flexion) is due to ectopic impulse generation in white matter pathways and occurs with demyelination in the cervical spinal cord; among many possible causes, this symptom may indicate MS in a young adult or compressive cervical spondylosis in an older person. Symptoms that worsen after exposure to heat or exercise may indicate conduction block in demyelinated axons, as occurs in MS. A patient with recurrent episodes of diplopia and dysarthria associated with exercise or fatigue may have a disorder of neuromuscular transmission such as myasthenia gravis. Slowly advancing visual scotoma with luminous edges, termed *fortification spectra*, indicates spreading cortical depression, typically with migraine.

THE NEUROLOGIC HISTORY

Attention to the description of the symptoms experienced by the patient and substantiated by family members and others often permits an accurate localization and determination of the probable cause of the complaints, even before the neurologic examination is performed. The history also helps to bring a focus to the neurologic examination that follows. Each complaint should be pursued as far as possible to elucidate the location of the lesion, the likely underlying pathophysiology, and potential etiologies. For example, a patient complains of weakness of the right arm. What are the associated features? Does the patient have difficulty with brushing hair or reaching upward (proximal) or buttoning buttons or opening a twist-top bottle (distal)? Negative associations may also be crucial. A patient with a right hemiparesis without a language deficit likely has a lesion (internal capsule, brainstem, or spinal cord) different from that of a patient with a right hemiparesis and aphasia (left hemisphere). Other pertinent features of the history include the following:

1. *Temporal course of the illness*. It is important to determine the precise time of appearance and rate of progression of the symptoms experienced by the patient. The rapid onset of a neurologic complaint, occurring within seconds or minutes, usually indicates a vascular event, a seizure, or migraine. The onset of sensory symptoms located in one extremity that spread over a few seconds to adjacent portions of that extremity and then to the other regions of the body suggests a seizure. A more gradual onset and less well localized symptoms point to the possibility of a transient ischemic attack (TIA). A similar but slower temporal march of symptoms accompanied by headache, nausea, or visual disturbance suggests migraine. The presence of "positive" sensory symptoms (e.g., tingling or sensations that are difficult to describe) or involuntary motor movements suggests a seizure; in contrast, transient loss of function (negative symptoms) suggests a TIA. A stuttering onset where symptoms appear, stabilize, and then progress over hours or days also suggests cerebrovascular disease; an additional history of transient remission or regression indicates that the process is more likely due to ischemia rather than hemorrhage. A gradual evolution of symptoms over hours or days suggests a toxic, metabolic, infectious, or inflammatory process. Progressing symptoms associated with the systemic manifestations of fever, stiff

neck, and altered level of consciousness imply an infectious process. Relapsing and remitting symptoms involving different levels of the nervous system suggest MS or other inflammatory processes; these disorders can occasionally produce new symptoms that are rapidly progressive over hours. Slowly progressive symptoms without remissions are characteristic of neurodegenerative disorders, chronic infections, gradual intoxications, and neoplasms.

2. *Patients' descriptions of the complaint*. The same words often mean different things to different patients. "Dizziness" may imply impending syncope, a sense of disequilibrium, or true spinning vertigo. "Numbness" may mean a complete loss of feeling, a positive sensation such as tingling, or paralysis. "Blurred vision" may be used to describe unilateral visual loss, as in transient monocular blindness, or diplopia. The interpretation of the true meaning of the words used by patients to describe symptoms becomes even more complex when there are differences in primary languages and cultures.
3. *Corroboration of the history by others*. It is almost always helpful to obtain additional information from family, friends, or other observers to corroborate or expand the patient's description. Memory loss, aphasia, loss of insight, intoxication, and other factors may impair the patient's capacity to communicate normally with the examiner or prevent openness about factors that have contributed to the illness. Episodes of loss of consciousness necessitate that details be sought from observers to ascertain precisely what has happened during the event.
4. *Family history*. Many neurologic disorders have an underlying genetic component. The presence of a Mendelian disorder, such as Huntington's disease or Charcot-Marie-Tooth neuropathy, is often obvious if family data are available. More detailed questions about family history are often necessary in polygenic disorders such as MS, migraine, and many types of epilepsy. It is important to elicit family history about all illnesses, in addition to neurologic and psychiatric disorders. A familial propensity to hypertension or heart disease is relevant in a patient who presents with a stroke. There are numerous inherited neurologic diseases that are associated with multisystem manifestations that may provide clues to the correct diagnosis (e.g., neurofibromatosis, Wilson's disease, neuro-ophthalmic syndromes).
5. *Medical illnesses*. Many neurologic diseases occur in the context of systemic disorders. Diabetes mellitus, hypertension, and abnormalities of blood lipids predispose to cerebrovascular disease. A solitary mass lesion in the brain may be an abscess in a patient with valvular heart disease, a primary hemorrhage in a patient with a coagulopathy, a lymphoma or toxoplasmosis in a patient with AIDS (Chap. 37), or a metastasis in a patient with underlying cancer. Patients with malignancy may also present with a neurologic paraneoplastic syndrome (Chap. 39) or complications from chemotherapy or radiotherapy. Marfan's syndrome and related collagen disorders predispose to dissection of the cranial arteries and aneurysmal subarachnoid hemorrhage; the latter may also occur with polycystic kidney disease. Various neurologic disorders occur with dysthyroid states or other endocrinopathies. It is especially important to look for the presence of systemic diseases in patients with peripheral neuropathy. Most patients with coma in a hospital setting have a metabolic, toxic, or infectious cause.
6. *Drug use and abuse and toxin exposure*. It is essential to inquire about the history of drug use, both prescribed and illicit. Aminoglycoside antibiotics may exacerbate symptoms of weakness in patients with disorders of neuromuscular transmission, such as myasthenia gravis, and may cause dizziness secondary to ototoxicity. Vincristine and other antineoplastic drugs can cause peripheral neuropathy, and immunosuppressive agents such as cyclosporine can produce encephalopathy. Excessive vitamin ingestion can lead to disease; for example vitamin A and pseudotumor cerebri, or pyridoxine and peripheral neuropathy. Many patients are unaware that over-the-counter sleeping pills, cold preparations, and diet pills are actually drugs. Alcohol, the most prevalent neurotoxin, is often not recognized as such by patients, and other drugs of abuse such as cocaine and heroin can cause a wide range of neurologic abnormalities. A history of environmental or industrial exposure to neurotoxins may provide an essential clue; consultation with the patient's coworkers or employer may be required.
7. *Formulating an impression of the patient*. Use the opportunity while taking the history to form an impression of the patient. Is the information forthcoming, or does it take a circuitous course? Is there evidence of anxiety, depression, or hypochondriasis? Are there any clues to defects in language, memory, insight, or inappropriate behavior? The neurologic assessment begins as soon as the patient comes into the room and the first introduction is made.

THE NEUROLOGIC EXAMINATION

The neurologic examination is challenging and complex; it has many components and includes a number of skills that can be mastered only through repeated use of the same techniques on a large number of individuals with and without neurologic disease. Mastery of the complete neurologic examination is usually important only for physicians in neurology and associated specialties. However, knowledge of the basics of the examination,

especially those components that are effective in screening for neurologic dysfunction, is essential for all clinicians, especially generalists.

There is no single, universally accepted sequence of the examination that must be followed, but most clinicians begin with assessment of mental status followed by the cranial nerves, motor system, sensory system, coordination, and gait. Whether the examination is basic or comprehensive, it is essential that it be performed in an orderly and systematic fashion to avoid errors and serious omissions. Thus, the best way to learn and gain expertise in the examination is to choose one's own approach and practice it frequently and do it in exactly the same sequence each time.

The detailed description of the neurologic examination that follows describes the more commonly used parts of the examination, with a particular emphasis on the components that are considered most helpful for the assessment of common neurologic problems. Each section also includes a brief description of the minimal examination necessary for adequate screening for abnormalities in a patient who has no symptoms suggesting neurologic dysfunction. A screening examination done in this way can be completed in 3–5 min.

Several additional points about the examination are worth noting. First, in recording observations, it is important to describe what is found rather than to apply a poorly defined medical term (e.g., "patient groans to sternal rub" rather than "obtunded"). Second, subtle CNS abnormalities are best detected by carefully comparing a patient's performance on tasks that require simultaneous activation of both cerebral hemispheres (e.g., eliciting a pronator drift of an outstretched arm with the eyes closed; extinction on one side of bilaterally applied light touch, also with eyes closed; or decreased arm swing or a slight asymmetry when walking). Third, if the patient's complaint is brought on by some activity, reproduce the activity in the office. If the complaint is of dizziness when the head is turned in one direction, have the patient do this and also look for associated signs on examination (e.g., nystagmus or dysmetria). If pain occurs after walking two blocks, have the patient leave the office and walk this distance and immediately return, and repeat the relevant parts of the examination. Finally, the use of tests that are individually tailored to the patient's problem can be of value in assessing changes over time. Tests of walking a 7.5-m (25-ft) distance (normal, 5–6 s; note assistance, if any), repetitive finger or toe tapping (normal, 20–25 taps in 5 s), or handwriting are examples.

Mental Status Examination

• *The bare minimum: During the interview, look for difficulties with communication and determine whether the patient has recall and insight into recent and past events.*

The mental status examination is underway as soon as the physician begins observing and talking with the patient. If the history raises any concern for abnormalities of higher cortical function or if cognitive problems are observed during the interview, then detailed testing of the mental status is indicated. The patient's ability to understand the language used for the examination, cultural background, educational experience, sensory or motor problems, or comorbid conditions need to be factored into the applicability of the tests and interpretation of results.

The Folstein mini-mental status examination (MMSE) (Table 23-5) is a standardized screening examination of cognitive function that is extremely easy to administer and takes <10 min to complete. Using age-adjusted values for defining normal performance, the test is ~85% sensitive and 85% specific for making the diagnosis of dementia that is moderate or severe, especially in educated patients. When there is sufficient time available, the MMSE is one of the best methods for documenting the current mental status of the patient, and this is especially useful as a baseline assessment to which future scores of the MMSE can be compared.

Individual elements of the mental status examination can be subdivided into level of consciousness, orientation, speech and language, memory, fund of information, insight and judgment, abstract thought, and calculations.

Level of consciousness is the patient's relative state of awareness of the self and the environment, and ranges from fully awake to comatose. When the patient is not fully awake, the examiner should describe the responses to the minimum stimulus necessary to elicit a reaction, ranging from verbal commands to a brief, painful stimulus such as a squeeze of the trapezius muscle. Responses that are directed toward the stimulus and signify some degree of intact cerebral function (e.g., opening the eyes and looking at the examiner or reaching to push away a painful stimulus) must be distinguished from reflex responses of a spinal origin (e.g., triple flexion response—flexion at the ankle, knee, and hip in response to a painful stimulus to the foot).

Orientation is tested by asking the patient to state his or her name, location, and time (day of the week and date); time is usually the first to be affected in a variety of conditions.

Speech is assessed by observing articulation, rate, rhythm, and prosody (i.e., the changes in pitch and accentuation of syllable and words).

Language is assessed by observing the content of the patient's verbal and written output, response to spoken commands, and ability to read. A typical testing sequence is to ask the patient to name successively more detailed components of clothing, a watch or a pen; repeat the phrase "No ifs, ands, or buts"; follow a three-step, verbal command; write a sentence; and read and respond to a written command.

Memory should be analyzed according to three main time scales: (1) immediate memory can be tested by saying a list of three items and having the patient repeat the list immediately, (2) short-term memory is assessed by asking the patient to recall the same three items 5 and 15 min later, and (3) long-term memory is evaluated by determining how well the patient is able to provide a coherent chronologic history of his or her illness or personal events.

Fund of information is assessed by asking questions about major historic or current events, with special attention to educational level and life experiences.

Abnormalities of *insight and judgment* are usually detected during the patient interview; a more detailed assessment can be elicited by asking the patient to describe how he or she would respond to situations having a variety of potential outcomes (e.g., "What would you do if you found a wallet on the sidewalk?").

Abstract thought can be tested by asking the patient to describe similarities between various objects or concepts (e.g., apple and orange, desk and chair, poetry and sculpture) or to list items having the same attributes (e.g., a list of four-legged animals).

Calculation ability is assessed by having the patient carry out a computation that is appropriate to the patient's age and education (e.g., serial subtraction of 7 from 100 or 3 from 20; or word problems involving simple arithmetic).

Cranial Nerve Examination

• *The bare minimum: Check the fundi, visual fields, pupil size and reactivity, extraocular movements, and facial movements.*

The cranial nerves (CN) are best examined in numerical order, except for grouping together CN III, IV, and VI because of their similar function.

CN I (Olfactory)

Testing is usually omitted unless there is suspicion for inferior frontal lobe disease (e.g., meningioma). With eyes closed, ask the patient to sniff a mild stimulus such as toothpaste or coffee and identify the odorant.

CN II (Optic)

Check visual acuity (with eyeglasses or contact lens correction) using a Snellen chart or similar tool. Test the visual fields by confrontation, i.e., by comparing the patient's visual fields to your own. As a screening test, it is usually sufficient to examine the visual fields of both eyes simultaneously; individual eye fields should be tested if there is any reason to suspect a problem of vision by the history or other elements of the examination, or if the screening test reveals an abnormality. Face the patient at a distance of approximately 0.6–1.0 m (2–3 ft) and place your hands at the periphery of your visual fields in the plane that is equidistant between you and the patient. Instruct the patient to look directly at the center of your face and to indicate when and where he or she sees one of your fingers moving. Beginning with the two inferior quadrants and then the two superior quadrants, move your index finger of the right hand, left hand, or both hands simultaneously and observe whether the patient detects the movements. A single small-amplitude movement of the finger is sufficient for a normal response. Focal perimetry and tangent screen examinations should be used to map out visual field defects fully or to search for subtle abnormalities. Optic fundi should be examined with an ophthalmoscope, and the color, size, and degree of swelling or elevation of the optic disc noted, as well as the color and texture of the retina. The retinal vessels should be checked for size, regularity, arterial-venous nicking at crossing points, hemorrhage, exudates, etc.

CN III, IV, VI (Oculomotor, Trochlear, Abducens)

Describe the size and shape of pupils and reaction to light and accommodation (i.e., as the eyes converge while following your finger as it moves toward the bridge of the nose). To check extraocular movements, ask the patient to keep his or her head still while tracking the movement of the tip of your finger. Move the target slowly in the horizontal and vertical planes; observe any paresis, nystagmus, or abnormalities of smooth pursuit (saccades, oculomotor ataxia, etc.). If necessary, the relative position of the two eyes, both in primary and multidirectional gaze, can be assessed by comparing the reflections of a bright light off both pupils. However, in practice it is typically more useful to determine whether the patient describes diplopia in any direction of gaze; true diplopia should almost always resolve with one eye closed. Horizontal nystagmus is best assessed at 45° and not at extreme lateral gaze (which is uncomfortable for the patient); the target must often be held at the lateral position for at least a few seconds to detect an abnormality.

CN V (Trigeminal)

Examine sensation within the three territories of the branches of the trigeminal nerve (ophthalmic, maxillary, and mandibular) on each side of the face. As with other parts of the sensory examination, testing of two sensory modalities derived from different anatomic pathways (e.g., light touch and temperature) is sufficient for a screening examination. Testing of other modalities, the corneal reflex, and the motor component of CN V (jaw clench—masseter muscle) is indicated when suggested by the history.

CN VII (Facial)

Look for facial asymmetry at rest and with spontaneous movements. Test eyebrow elevation, forehead wrinkling,

eye closure, smiling, and cheek puff. Look in particular for differences in the lower versus upper facial muscles; weakness of the lower two-thirds of the face with preservation of the upper third suggests an upper motor neuron lesion, whereas weakness of an entire side suggests a lower motor neuron lesion.

CN VIII (Vestibulocochlear)

Check the patient's ability to hear a finger rub or whispered voice with each ear. Further testing for air versus mastoid bone conduction (Rinne) and lateralization of a 512-Hz tuning fork placed at the center of the forehead (Weber) should be done if an abnormality is detected by history or examination. Any suspected problem should be followed up with formal audiometry. For further discussion of assessing vestibular nerve function in the setting of dizziness or coma, see Chaps. 9 and 14, respectively.

CN IX, X (Glossopharyngeal, Vagus)

Observe the position and symmetry of the palate and uvula at rest and with phonation ("aah"). The pharyngeal ("gag") reflex is evaluated by stimulating the posterior pharyngeal wall on each side with a sterile, blunt object (e.g., tongue blade), but the reflex is often absent in normal individuals.

CN XI (Spinal Accessory)

Check shoulder shrug (trapezius muscle) and head rotation to each side (sternocleidomastoid) against resistance.

CN XII (Hypoglossal)

Inspect the tongue for atrophy or fasciculations, position with protrusion, and strength when extended against the inner surface of the cheeks on each side.

Motor Examination

• *The bare minimum: Look for muscle atrophy and check extremity tone. Assess upper extremity strength by checking for pronator drift and strength of wrist or finger extensors. Tap the biceps, patellar, and Achilles reflexes. Test for lower extremity strength by having the patient walk normally and on heels and toes.*

The motor examination includes observations of muscle appearance, tone, strength, and reflexes. Although gait is in part a test of motor function, it is usually evaluated separately at the end of the examination.

Appearance

Inspect and palpate muscle groups under good light and with the patient in a comfortable and symmetric position. Check for muscle fasciculations, tenderness, and atrophy or hypertrophy. Involuntary movements may be present at rest (e.g., tics, myoclonus, choreoathetosis), during maintained posture (pill-rolling tremor of Parkinson's disease), or with voluntary movements (intention tremor of cerebellar disease or familial tremor).

Tone

Muscle tone is tested by measuring the resistance to passive movement of a relaxed limb. Patients often have difficulty relaxing during this procedure, so it is useful to distract the patient to minimize active movements. In the upper limbs, tone is assessed by rapid pronation and supination of the forearm and flexion and extension at the wrist. In the lower limbs, while the patient is supine the examiner's hands are placed behind the knees and rapidly raised; with normal tone the ankles drag along the table surface for a variable distance before rising, whereas increased tone results in an immediate lift of the heel off the surface. Decreased tone is most commonly due to lower motor neuron or peripheral nerve disorders. Increased tone may be evident as spasticity (resistance determined by the angle and velocity of motion; corticospinal tract disease), rigidity (similar resistance in all angles of motion; extrapyramidal disease), or paratonia (fluctuating changes in resistance; frontal lobe pathways or normal difficulty in relaxing). Cogwheel rigidity, in which passive motion elicits jerky interruptions in resistance, is seen in parkinsonism.

Strength

Testing for pronator drift is an extremely useful method for screening upper limb weakness. The patient is asked to hold both arms fully extended and parallel to the ground with eyes closed. This position should be maintained for ~10 s; any flexion at the elbow or fingers or pronation of the forearm, especially if asymmetric, is a sign of potential weakness. Muscle strength is further assessed by having the patient exert maximal effort for the particular muscle or muscle group being tested. It is important to isolate the muscles as much as possible, i.e., hold the limb so that only the muscles of interest are active. It is also helpful to palpate accessible muscles as they contract. Grading muscle strength and evaluating the patient's effort is an art that takes time and practice. Muscle strength is traditionally graded using the following scale:

0 = no movement
1 = flicker or trace of contraction but no associated movement at a joint
2 = movement with gravity eliminated
3 = movement against gravity but not against resistance
4– = movement against a mild degree of resistance
4 = movement against moderate resistance
4+ = movement against strong resistance
5 = full power

However, in many cases it is more practical to use the following terms:

Paralysis = no movement
Severe weakness = movement with gravity eliminated

Moderate weakness = movement against gravity but not against mild resistance
Mild weakness = movement against moderate resistance
Full strength

Noting the pattern of weakness is as important as assessing the magnitude of weakness. Unilateral or bilateral weakness of the upper limb extensors and lower limb flexors ("pyramidal weakness") suggests a lesion of the pyramidal tract, bilateral proximal weakness suggests myopathy, and bilateral distal weakness suggests peripheral neuropathy.

Reflexes

Muscle Stretch Reflexes

Those that are typically assessed include the biceps (**C5**, C6), brachioradialis (C5, **C6**), and triceps (**C7**, C8) reflexes in the upper limbs and the patellar or quadriceps (**L3**, L4) and Achilles (**S1**, S2) reflexes in the lower limbs. The patient should be relaxed and the muscle positioned midway between full contraction and extension. Reflexes may be enhanced by asking the patient to voluntarily contract other, distant muscle groups (Jendrassik maneuver). For example, upper limb reflexes may be reinforced by voluntary teeth-clenching, and the Achilles reflex by hooking the flexed fingers of the two hands together and attempting to pull them apart. For each reflex tested, the two sides should be tested sequentially, and it is important to determine the smallest stimulus required to elicit a reflex rather than the maximum response. Reflexes are graded according to the following scale:

0 = absent
1 = present but diminished
2 = normoactive
3 = exaggerated
4 = clonus

Cutaneous Reflexes

The plantar reflex is elicited by stroking, with a noxious stimulus such as a tongue blade, the lateral surface of the sole of the foot beginning near the heel and moving across the ball of the foot to the great toe. The normal reflex consists of plantar flexion of the toes. With upper motor neuron lesions above the S1 level of the spinal cord, a paradoxical extension of the toe is observed, associated with fanning and extension of the other toes (termed an *extensor plantar response*, or *Babinski sign*). Superficial abdominal reflexes are elicited by gently stroking the abdominal surface near the umbilicus in a diagonal fashion with a sharp object (e.g., the wooden end of a cotton-tipped swab) and observing the movement of the umbilicus. Normally, the umbilicus will pull toward the stimulated quadrant. With upper motor neuron lesions, these reflexes are absent. They are most helpful when there is preservation of the upper (spinal cord level T9) but not lower (T12) abdominal reflexes, indicating a spinal lesion between T9 and T12, or when the response is asymmetric. Other useful cutaneous reflexes include the cremasteric (ipsilateral elevation of the testicle following stroking of the medial thigh; mediated by L1 and L2) and anal (contraction of the anal sphincter when the perianal skin is scratched; mediated by S2, S3, S4) reflexes. It is particularly important to test for these reflexes in any patient with suspected injury to the spinal cord or lumbosacral roots.

Primitive Reflexes

With disease of the frontal lobe pathways, several primitive reflexes not normally present in the adult may appear. The suck response is elicited by lightly touching the center of the lips, and the root response the corner of the lips, with a tongue blade; the patient will move the lips to suck or root in the direction of the stimulus. The grasp reflex is elicited by touching the palm between the thumb and index finger with the examiner's fingers; a positive response is a forced grasp of the examiner's hand. In many instances stroking the back of the hand will lead to its release. The palmomental response is contraction of the mentalis muscle (chin) ipsilateral to a scratch stimulus diagonally applied to the palm.

Sensory Examination

• *The bare minimum: Ask whether the patient can feel light touch and the temperature of a cool object in each distal extremity. Check double simultaneous stimulation using light touch on the hands.*

Evaluating sensation is usually the most unreliable part of the examination, because it is subjective and is difficult to quantify. In the compliant and discerning patient, the sensory examination can be extremely helpful for the precise localization of a lesion. With patients who are uncooperative or lack an understanding of the tests, it may be useless. The examination should be focused on the suspected lesion. For example, in spinal cord, spinal root, or peripheral nerve abnormalities, all major sensory modalities should be tested while looking for a pattern consistent with a spinal level and dermatomal or nerve distribution. In patients with lesions at or above the brainstem, screening the primary sensory modalities in the distal extremities along with tests of "cortical" sensation is usually sufficient.

The five primary sensory modalities—light touch, pain, temperature, vibration, and joint position—are tested in each limb. Light touch is assessed by stimulating the skin with single, very gentle touches of the examiner's finger or a wisp of cotton. Pain is tested

using a new pin, and temperature is assessed using a metal object (e.g., tuning fork) that has been immersed in cold and warm water. Vibration is tested using a 128-Hz tuning fork applied to the distal phalynx of the great toe or index finger just below the nailbed. By placing a finger on the opposite side of the joint being tested, the examiner compares the patient's threshold of vibration perception with his or her own. For joint position testing, the examiner grasps the digit or limb laterally and distal to the joint being assessed; small 1- to 2-mm excursions can usually be sensed. The Romberg maneuver is primarily a test of proprioception. The patient is asked to stand with the feet as close together as necessary to maintain balance while the eyes are open, and the eyes are then closed. A loss of balance with the eyes closed is an abnormal response.

"Cortical" sensation is mediated by the parietal lobes and represents an integration of the primary sensory modalities; testing cortical sensation is only meaningful when primary sensation is intact. Double simultaneous stimulation is especially useful as a screening test for cortical function; with the patient's eyes closed, the examiner lightly touches one or both hands and asks the patient to identify the stimuli. With a parietal lobe lesion, the patient may be unable to identify the stimulus on the contralateral side when both hands are touched. Other modalities relying on the parietal cortex include the discrimination of two closely placed stimuli as separate (two-point discrimination), identification of an object by touch and manipulation alone (stereognosis), and the identification of numbers or letters written on the skin surface (graphesthesia).

Coordination Examination

• *The bare minimum: Test rapid alternating movements of the hands and the finger-to-nose and heel-knee-shin maneuvers.*

Coordination refers to the orchestration and fluidity of movements. Even simple acts require cooperation of agonist and antagonist muscles, maintenance of posture, and complex servomechanisms to control the rate and range of movements. Part of this integration relies on normal function of the cerebellar and basal ganglia systems. However, coordination also requires intact muscle strength and kinesthetic and proprioceptive information. Thus, if the examination has disclosed abnormalities of the motor or sensory systems, the patient's coordination should be assessed with these limitations in mind.

Rapid alternating movements in the upper limbs are tested separately on each side by having the patient make a fist, partially extend the index finger, and then tap the index finger on the distal thumb as quickly as possible. In the lower limb, the patient rapidly taps the foot against the floor or the examiner's hand. Finger-to-nose testing is primarily a test of cerebellar function; the patient is asked to touch his or her index finger repetitively to the nose and then to the examiner's outstretched finger, which moves with each repetition. A similar test in the lower extremity is to have the patient raise the leg and touch the examiner's finger with the great toe. Another cerebellar test in the lower limbs is the heel-knee-shin maneuver; in the supine position the patient is asked to slide the heel of each foot from the knee down the shin of the other leg. For all these movements, the accuracy, speed, and rhythm are noted.

Gait Examination

• *The bare minimum: Observe the patient while walking normally, on the heels and toes, and along a straight line.*

Watching the patient walk is the most important part of the neurologic examination. Normal gait requires that multiple systems—including strength, sensation, and coordination—function in a highly integrated fashion. Unexpected abnormalities may be detected that prompt the examiner to return, in more detail, to other aspects of the examination. The patient should be observed while walking and turning normally, walking on the heels, walking on the toes, and walking heel-to-toe along a straight line. The examination may reveal decreased arm swing on one side (corticospinal tract disease), a stooped posture and short-stepped gait (parkinsonism), a broad-based unstable gait (ataxia), scissoring (spasticity), or a high-stepped, slapping gait (posterior column or peripheral nerve disease), or the patient may appear to be stuck in place (apraxia with frontal lobe disease).

NEUROLOGIC DIAGNOSIS

The clinical data obtained from the history and examination are interpreted to arrive at an anatomic localization that best explains the clinical findings (**Table 1-2**), to narrow the list of diagnostic possibilities, and to select the laboratory tests most likely to be informative. The laboratory assessment may include (1) serum electrolytes; complete blood count; and renal, hepatic, endocrine, and immune studies; (2) cerebrospinal fluid examination; (3) focused neuroimaging studies (Chap. 2); or (4) electrophysiologic studies (Chap. 3). The anatomic localization, mode of onset and course of illness, other medical data, and laboratory findings are then integrated to establish an etiologic diagnosis.

The neurologic examination may be normal even in patients with a serious neurologic disease, such as seizures, chronic meningitis, or a TIA. A comatose patient may arrive with no available history, and in such cases the approach is as described in Chap. 14. In other patients, an inadequate history may be overcome by a succession of examinations from which the course of the illness can be inferred. In perplexing cases it is useful to remember that uncommon presentations of common

TABLE 1-2

FINDINGS HELPFUL FOR LOCALIZATION WITHIN THE NERVOUS SYSTEM

	SIGNS
Cerebrum	Abnormal mental status or cognitive impairment Seizures Unilateral weakness[a] and sensory abnormalities including head and limbs Visual field abnormalities Movement abnormalities (e.g., diffuse incoordination, tremor, chorea)
Brainstem	Isolated cranial nerve abnormalities (single or multiple) "Crossed" weakness[a] and sensory abnormalities of head and limbs (e.g., weakness of right face and left arm and leg)
Spinal cord	Back pain or tenderness Weakness[a] and sensory abnormalities sparing the head Mixed upper and lower motor neuron findings Sensory level Sphincter dysfunction
Spinal roots	Radiating limb pain Weakness[b] or sensory abnormalities following root distribution (see Figs. 12-2 and 12-3) Loss of reflexes
Peripheral nerve	Mid or distal limb pain Weakness[b] or sensory abnormalities following nerve distribution (see Figs. 12-2 and 12-3) "Stocking or glove" distribution of sensory loss Loss of reflexes
Neuromuscular junction	Bilateral weakness including face (ptosis, diplopia, dysphagia) and proximal limbs Increasing weakness with exertion Sparing of sensation
Muscle	Bilateral proximal or distal weakness Sparing of sensation

[a]Weakness along with other abnormalities having an "upper motor neuron" pattern (i.e., spasticity, weakness of extensors > flexors in the upper extremity and flexors > extensors in the lower extremity, hyperreflexia).
[b]Weakness along with other abnormalities having a "lower motor neuron" pattern (i.e., flaccidity and hyporeflexia).

diseases are more likely than rare etiologies. Thus, even in tertiary care settings, multiple strokes are usually due to emboli and not vasculitis, and dementia with myoclonus is usually Alzheimer's disease and not due to a prion disorder or a paraneoplastic cause. Finally, the most important task of a primary care physician faced with a patient who has a new neurologic complaint is to assess the urgency of referral to a specialist. Here, the imperative is to rapidly identify patients likely to have nervous system infections, acute strokes, and spinal cord compression or other treatable mass lesions and arrange for immediate care.

FURTHER READINGS

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CHAPTER 2

NEUROIMAGING IN NEUROLOGIC DISORDERS

William P. Dillon

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The clinician caring for patients with neurologic symptoms is faced with an expanding number of imaging options, including computed tomography (CT), CT angiography (CTA), perfusion CT (pCT), magnetic resonance imaging (MRI), MR angiography (MRA), functional MRI (fMRI), MR spectroscopy (MRS), MR neurography, diffusion and diffusion track imaging (DTI), and perfusion MRI (pMRI). In addition, an increasing number of interventional neuroradiologic techniques are available, including angiography; embolization, coiling, and stenting of vascular structures; and spine interventions such as discography, selective nerve root injection, and epidural injections. Recent developments, such as multidetector CTA and gadolinium-enhanced MRA, have narrowed the indications for conventional angiography, which is now reserved for patients in whom small-vessel detail is essential for diagnosis or for whom interventional therapies are planned (**Table 2-1**).

In general, MRI is more sensitive than CT for the detection of lesions affecting the central nervous system (CNS), particularly those of the spinal cord, cranial nerves, and posterior fossa structures. Diffusion MR, a sequence that detects reduction of microscopic motion of water, is the most sensitive technique for detecting acute ischemic stroke and is also useful in the detection of encephalitis, abscesses, and prion diseases. CT, however, can be quickly obtained and is widely available, making it a pragmatic choice for the initial evaluation of patients with acute changes in mental status, suspected acute stroke, hemorrhage, and intracranial or spinal trauma. CT is also more sensitive than MRI for visualizing fine osseous detail and is indicated in the initial evaluation of conductive hearing loss as well as lesions affecting the skull base and calvarium.

COMPUTED TOMOGRAPHY

TECHNIQUE

The CT image is a cross-sectional representation of anatomy created by a computer-generated analysis of the attenuation of x-ray beams passed through a section of the body. As the x-ray beam, collimated to the desired slice width, rotates around the patient, it passes through selected regions in the body. X-rays that are not attenuated by the body are detected by sensitive x-ray detectors aligned 180° from the x-ray tube. A computer calculates a "back projection" image from the 360° x-ray attenuation profile. Greater x-ray attenuation, e.g., as caused by

TABLE 2-1

GUIDELINES FOR THE USE OF CT, ULTRASOUND, AND MRI

CONDITION	RECOMMENDED TECHNIQUE
Hemorrhage	
Acute parenchymal	CT, MR
Subacute/chronic	MRI
Subarachnoid hemorrhage	CT, CTA, lumbar puncture → angiography
Aneurysm	Angiography > CTA, MRA
Ischemic infarction	
Hemorrhagic infarction	CT or MRI
Bland infarction	MRI > CT, CTA, angiography
Carotid or vertebral dissection	MRI/MRA
Vertebral basilar insufficiency	CTA, MRI/MRA
Carotid stenosis	CTA > Doppler ultrasound, MRA
Suspected mass lesion	
Neoplasm, primary or metastatic	MRI + contrast
Infection/abscess	MRI + contrast
Immunosuppressed with focal findings	MRI + contrast
Vascular malformation	MRI +/– angiography
White matter disorders	MRI
Demyelinating disease	MRI +/– contrast
Dementia	MRI > CT
Trauma	
Acute trauma	CT (noncontrast)
Shear injury/chronic hemorrhage	MRI
Headache/migraine	CT (noncontrast) / MRI
Seizure	
First time, no focal neurologic deficits	CT as screen +/– contrast
Partial complex/refractory	MRI with coronal T2W imaging
Cranial neuropathy	MRI with contrast
Meningeal disease	MRI with contrast
Spine	
Low back pain	
No neurologic deficits	MRI or CT after 4 weeks
With focal deficits	MRI > CT
Spinal stenosis	MRI or CT
Cervical spondylosis	MRI or CT myelography
Infection	MRI + contrast, CT
Myelopathy	MRI + contrast > myelography
Arteriovenous malformation	MRI, myelography/angiography

Note: CT, computed tomography; MRI, magnetic resonance imaging; MRA, MR angiography; CTA, CT angiography; T2W, T2-weighted.

bone, results in areas of high "density," whereas soft tissue structures, which have poor attenuation of x-rays, are lower in density. The resolution of an image depends on the radiation dose, the detector size or collimation (slice thickness), the field of view, and the matrix size of the display. A modern CT scanner is capable of obtaining sections as thin as 0.5–1 mm with submillimeter resolution at a speed of 0.5–1 s per rotation; complete studies of the brain can be completed in 2–10 s.

Helical or multidetector CT (MDCT) is now standard in most radiology departments. Continuous CT information is obtained while the patient moves through the x-ray beam. In the helical scan mode, the table moves continuously through the rotating x-ray beam, generating a "helix" of information that can be reformatted into various slice thicknesses. Single or multiple (from 4 to 256) detectors positioned 180° to the x-ray source may result in multiple slices per revolution of the beam around the patient. Advantages of MDCT include shorter scan times, reduced patient and organ motion, and the ability to acquire images dynamically during the infusion of intravenous contrast that can be used to construct CT angiograms of vascular structures and CT perfusion images (**Figs. 2-1*B***, **2-2*B***, and **2-3*B***). CTA images are post-processed for display in three dimensions to yield angiogram-like images (**Fig. 2-1*C*** and see Fig. 21-4). CTA has proved useful in assessing the cervical and intracranial arterial and venous anatomy.

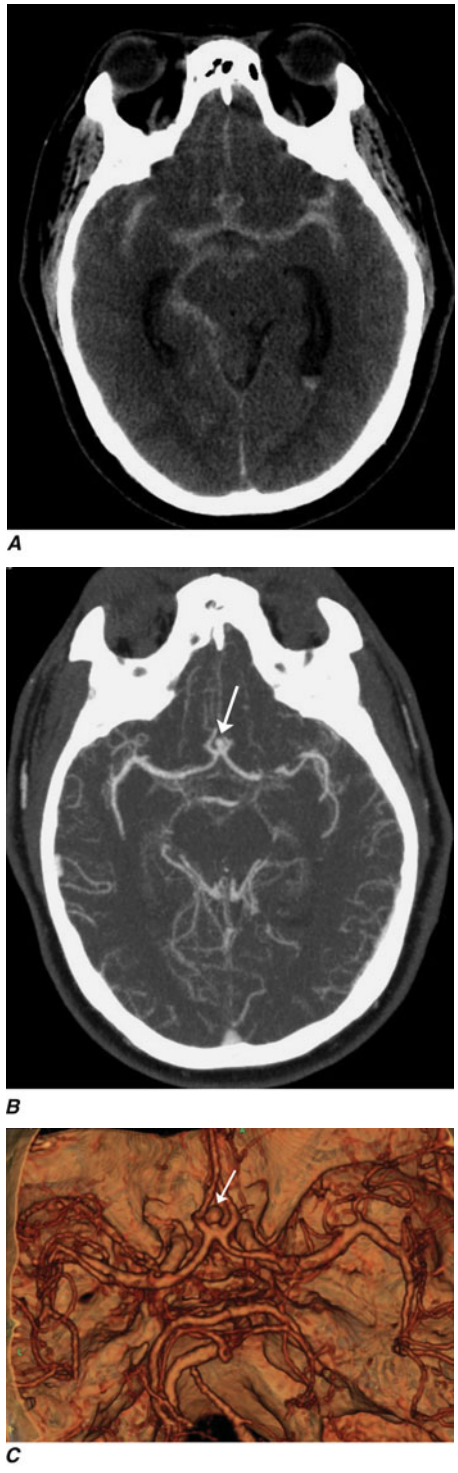


FIGURE 2-1

CT angiography (CTA) of ruptured anterior cerebral artery aneurysm in a patient presenting with acute headache. ***A.*** Noncontrast CT demonstrates subarachnoid hemorrhage and mild obstructive hydrocephalus. ***B.*** Axial maximum intensity projection from CT angiography demonstrates enlargement of the anterior cerebral artery (*arrow*). ***C.*** 3D surface reconstruction using a workstation confirms the anterior cerebral aneurysm and demonstrates its orientation and relationship to nearby vessels (*arrow*). CTA image is produced by 0.5–1 mm helical CT scans performed during a rapid bolus infusion of intravenous contrast medium.

Intravenous iodinated contrast is often administered prior to or during a CT study to identify vascular structures and to detect defects in the blood-brain barrier (BBB) that are associated with disorders such as tumors, infarcts, and infections. In the normal CNS, only vessels and structures lacking a BBB (e.g., the pituitary gland, choroid plexus, and dura) enhance after contrast administration. The use of iodinated contrast agents carries a risk of allergic reaction and adds additional expense and radiation dose. Although helpful in characterizing mass lesions as well as essential for the acquisition of CTA studies, the decision to use contrast material should always be considered carefully.

INDICATIONS

CT is the primary study of choice in the evaluation of an acute change in mental status, focal neurologic findings, acute trauma to the brain and spine, suspected subarachnoid hemorrhage, and conductive hearing loss (Table 2-1). CT is complementary to MR in the evaluation of the skull base, orbit, and osseous structures of the spine. In the spine, CT is useful in evaluating patients with osseous spinal stenosis and spondylosis, but MRI is often preferred in those with neurologic deficits. CT can also be obtained following intrathecal contrast injection to evaluate the intracranial cisterns (*CT cisternography*) for cerebrospinal fluid (CSF) fistula, as well as the spinal subarachnoid space (*CT myelography*).

COMPLICATIONS

CT is safe, fast, and reliable. Radiation exposure depends on the dose used but is normally between 3 and 5 cGy for a routine brain CT study. Care must be taken to reduce exposure when imaging children. With the advent of MDCT, CTA, and CT perfusion, care must be taken to appropriately minimize radiation dose whenever possible. The most frequent complications are associated with use of intravenous contrast agents. Two broad categories of contrast media, ionic and nonionic, are in use. Although ionic agents are relatively safe and inexpensive, they are associated with a higher incidence of reactions and side effects (**Table 2-2**). As a result, ionic agents have been largely replaced by safer nonionic compounds.

Contrast nephropathy may result from hemodynamic changes, renal tubular obstruction and cell damage, or immunologic reactions to contrast agents. A rise in serum creatinine of at least 85 μmol/L (1 mg/dL) within 48 h of contrast administration is often used as a definition of contrast nephropathy, although other causes of acute renal failure must be excluded. The prognosis is usually favorable, with serum creatinine levels returning to baseline within 1–2 weeks. Risk factors for contrast nephropathy include advanced age (>80 years),

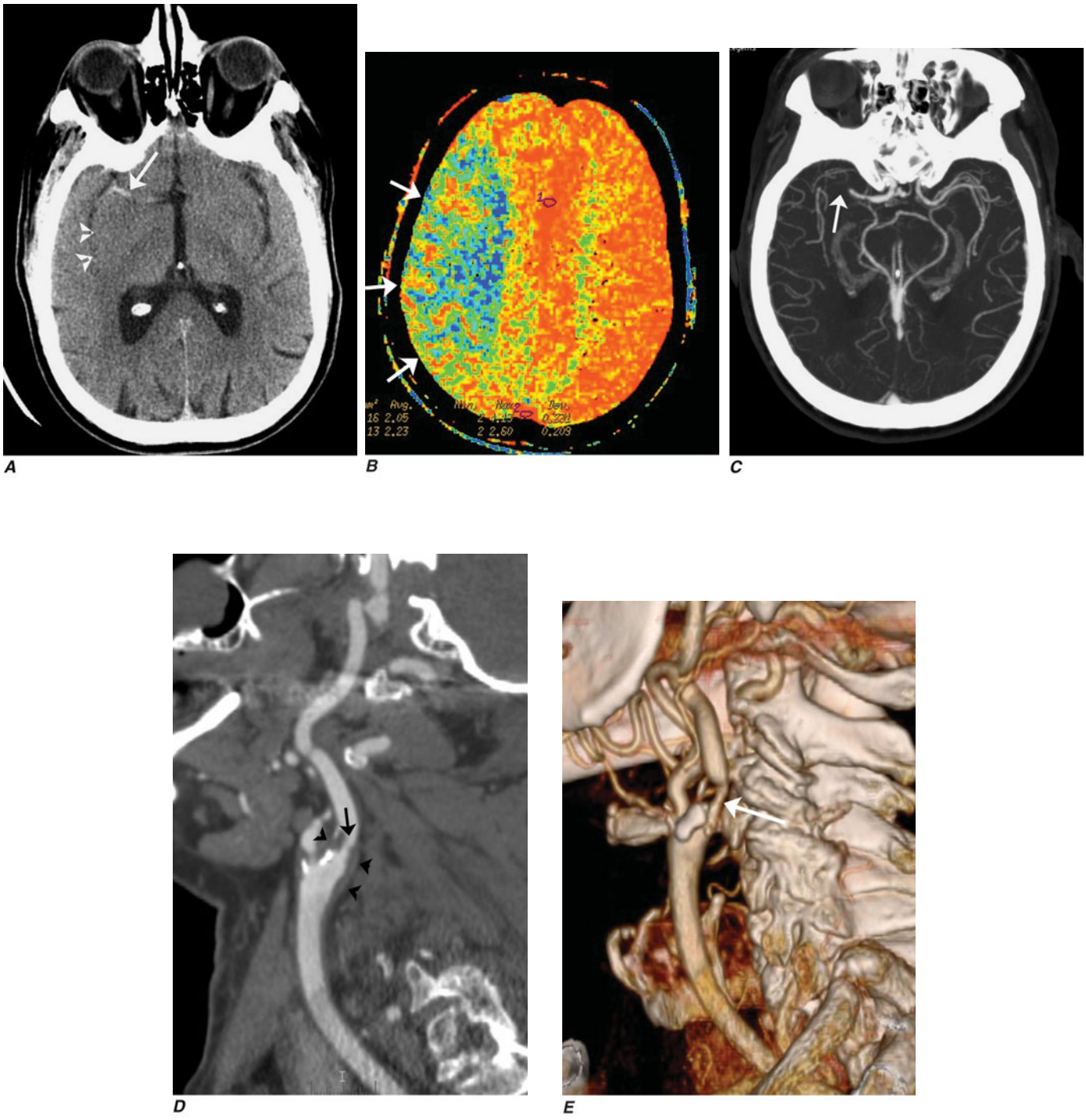


FIGURE 2-2

Acute left hemiparesis due to middle cerebral artery occlusion. ***A.*** Axial noncontrast CT scan demonstrates high density within the right middle cerebral artery (*arrow*) associated with subtle low density involving the right putamen (*arrowheads*). ***B.*** Mean transit time map calculated from a CT perfusion study; prolongation of the mean transit time is visible throughout the right hemisphere (*arrows*). ***C.*** Axial maximum intensity projection from a CTA study through the Circle of Willis demonstrates an abrupt occlusion of the proximal right middle cerebral artery (*arrow*). Reconstitution of flow via collaterals is seen distal to the occlusion; however, the patient sustained a right basal ganglia infarction. ***D.*** Sagittal reformation through the right internal carotid artery demonstrates a low-density lipid laden plaque (*arrowheads*) narrowing the lumen (*black arrow*) ***E.*** 3D surface CTA images from a different patient demonstrate calcification and narrowing of the right internal carotid artery (*arrow*), consistent with atherosclerotic disease.

TABLE 2-2

GUIDELINES FOR USE OF INTRAVENOUS CONTRAST IN PATIENTS WITH IMPAIRED RENAL FUNCTION

SERUM CREATININE, λmol/L (mg/dL)[a]	RECOMMENDATION
<133 (<1.5)	Use either ionic or nonionic at 2 mL/kg to 150 mL total
133–177 (1.5–2.0)	Nonionic; hydrate diabetics 1 mL/kg per hour × 10 h
>177 (>2.0)	Consider noncontrast CT or MRI; nonionic contrast if required
177–221 (2.0–2.5)	Nonionic only if required (as above); contraindicated in diabetics
>265 (>3.0)	Nonionic IV contrast given only to patients undergoing dialysis within 24 h

[a]Risk is greatest in patients with rising creatinine levels.
Note: CT, computed tomography; MRI, magnetic resonance imaging.

preexisting renal disease (serum creatinine exceeding 2.0 mg/dL), solitary kidney, diabetes mellitus, dehydration, paraproteinemia, concurrent use of nephrotoxic medication or chemotherapeutic agents, and high contrast dose. Patients with diabetes and those with mild renal failure should be well hydrated prior to the administration of contrast agents, although careful consideration should be given to alternative imaging techniques, such as MR imaging or noncontrast examinations. Nonionic, low-osmolar media produce fewer abnormalities in renal blood flow and less endothelial cell damage but should still be used carefully in patients at risk for allergic reaction (Table 2-3).

Other side effects are rare but include a sensation of warmth throughout the body and a metallic taste during intravenous administration of iodinated contrast media. The most serious side effects are anaphylactic reactions,

TABLE 2-3

INDICATIONS FOR USE OF NONIONIC CONTRAST MEDIA

- Prior adverse reaction to contrast media, with the exception of heat, flushing, or an episode of nausea or vomiting
- Asthma or other serious lung disease
- History of atopic allergies (pretreatment with steroid/antihistamines recommended)
- Children younger than 2 years
- Renal failure or creatinine >177 µmol/L (>2.0 mg/dL)
- Cardiac dysfunction, including recent or imminent cardiac decompensation, severe arrhythmias, unstable angina pectoris, recent myocardial infarction, and pulmonary hypertension
- Diabetes
- Severe debilitation

TABLE 2-4

GUIDELINES FOR PREMEDICATION OF PATIENTS WITH PRIOR CONTRAST ALLERGY

12 h prior to examination:
Prednisone, 50 mg PO *or* methylprednisolone, 32 mg PO
2 h prior to examination:
Prednisone, 50 mg PO *or* methylprednisolone, 32 mg PO *and*
Cimetidine, 300 mg PO *or* ranitidine, 150 mg PO
Immediately prior to examination:
Benadryl, 50 mg IV (alternatively, can be given PO 2 h prior to exam)

which range from mild hives to bronchospasm, acute anaphylaxis, and death. The pathogenesis of these allergic reactions is not fully understood but is thought to include the release of mediators such as histamine, antibody-antigen reactions, and complement activation. Severe allergic reactions occur in ~0.04% of patients receiving nonionic media, sixfold fewer than with ionic media. Risk factors include a history of prior contrast reaction, food allergies to shellfish, and atopy (asthma and hay fever). In such patients, a noncontrast CT or MRI procedure should be considered as an alternative to contrast administration. If iodinated contrast is absolutely required, a nonionic agent should be used in conjunction with pretreatment with glucocorticoids and antihistamines (Table 2-4). Patients with allergic reactions to iodinated contrast material do not usually react to gadolinium-based MR contrast material, although such reactions do occur. It would be wise to pretreat patients with a prior allergic history to MR contrast administration in a similar fashion.

MAGNETIC RESONANCE IMAGING

TECHNIQUE

Magnetic resonance is a complex interaction between hydrogen protons in biologic tissues, a static magnetic field (the magnet), and energy in the form of radiofrequency (Rf) waves of a specific frequency introduced by coils placed next to the body part of interest. Field strength of the magnet is directly related to signal-to-noise ratio. Although 1.5 Telsa magnets have become the standard high-field MRI units, 3T–8T magnets are now available and have distinct advantages in the brain and musculoskeletal systems. Spatial localization is achieved by magnetic gradients surrounding the main magnet, which impart slight changes in magnetic field throughout the imaging volume. The energy state of the hydrogen protons is transiently excited by Rf, which is administered at a frequency specific for the field strength of the magnet. The subsequent return to equilibrium energy state

(*relaxation*) of the protons results in a release of Rf energy (the *echo*), which is detected by the coils that delivered the Rf pulses. The echo is transformed by Fourier analysis into the information used to form an MR image. The MR image thus consists of a map of the distribution of hydrogen protons, with signal intensity imparted by both density of hydrogen protons and differences in the relaxation times (see below) of hydrogen protons on different molecules. Although clinical MRI currently makes use of the ubiquitous hydrogen proton, research into sodium and carbon imaging appears promising.

T1 and T2 Relaxation Times

The rate of return to equilibrium of perturbed protons is called the *relaxation rate*. The relaxation rate varies among normal and pathologic tissues. The relaxation rate of a hydrogen proton in a tissue is influenced by local interactions with surrounding molecules and atomic neighbors. Two relaxation rates, T1 and T2, influence the signal intensity of the image. The T1 relaxation time is the time, measured in milliseconds, for 63% of the hydrogen protons to return to their normal equilibrium state, while the T2 relaxation is the time for 63% of the protons to become dephased owing to interactions among nearby protons. The intensity of the signal within various tissues and image contrast can be modulated by altering acquisition parameters, such as the interval between Rf pulses (TR) and the time between the Rf pulse and the signal reception (TE). So-called T1-weighted (T1W) images are produced by keeping the TR and TE relatively short. T2-weighted (T2W) images are produced by using longer TR and TE times. Fat and subacute hemorrhage have relatively shorter T1 relaxation rates and thus higher signal intensity than brain on T1W images. Structures containing more water, such as CSF and edema, have long T1 and T2 relaxation rates, resulting in relatively lower signal intensity on T1W images and a higher signal intensity on T2W images (**Table 2-5**). Gray matter contains 10–15% more water than white matter, which accounts for much of the intrinsic contrast between the two on MRI (**Fig. 2-3**). T2W images are more sensitive than T1W images to edema, demyelination, infarction, and chronic hemorrhage, whereas T1W imaging is more sensitive to subacute hemorrhage and fat-containing structures.

Many different MR pulse sequences exist, and each can be obtained in various planes (Figs. 2-3, **2-4**, **2-5**). The selection of a proper protocol that will best answer a clinical question depends on an accurate clinical history and indication for the examination. Fluid-attenuated inversion recovery (FLAIR) is a useful pulse sequence that produces T2W images in which the normally high signal intensity of CSF is suppressed (Fig. 2-5*A*). FLAIR images are more sensitive than standard spin echo images for any water-containing lesions or edema. Gradient echo imaging is most sensitive to magnetic susceptibility generated by blood, calcium, and air and is indicated in patients with traumatic brain injury to assess for subtle contusions and shear microhemorrhages. MR images can be generated in any plane without changing the patient's position. Each sequence, however, must be obtained separately and takes 1–5 min on average to complete. Three-dimensional volumetric imaging is also possible with MRI, resulting in a volume of data that can be reformatted in any orientation on a workstation to highlight certain disease processes.

TABLE 2-5

SOME COMMON INTENSITIES ON T1- AND T2-WEIGHTED MRI SEQUENCES

			SIGNAL INTENSITY			
IMAGE	TR	TE	CSF	FAT	BRAIN	EDEMA
T1W	Short	Short	Low	High	Low	Low
T2W	Long	Long	High	Low	High	High

Note: TR, interval between radiofrequency (Rf) pulses; TE, interval between Rf pulse and signal reception; CSF, cerebrospinal fluid; T1W and T2W, T1- and T2-weighted.

MR Contrast Material

The heavy-metal element gadolinium forms the basis of all currently approved intravenous MR contrast agents. Gadolinium is a paramagnetic substance, which means that it reduces the T1 and T2 relaxation times of nearby water protons, resulting in a high signal on T1W images and a low signal on T2W images (the latter requires a sufficient local concentration, usually in the form of an intravenous bolus). Unlike iodinated contrast agents, the effect of MR contrast agents depends on the presence of local hydrogen protons on which it must act to achieve the desired effect. Gadolinium is chelated to DTPA (diethylenetriaminepentaacetic acid), which allows safe renal excretion. Approximately 0.2 mL/kg body weight is administered intravenously; the cost is ~$60 per dose. Gadolinium-DTPA does not normally cross the intact BBB immediately but will enhance lesions lacking a BBB (Fig. 2-4*A*) and areas of the brain that normally are devoid of the BBB (pituitary, choroid plexus). However, gadolinium contrast has been noted to slowly cross an intact BBB if given over time and especially in the setting of reduced renal clearance. The agents are generally well tolerated; severe allergic reactions are rare but have been reported. The adverse reaction rate in patients with a prior history of atopy or asthma is 3.7%; however, the reaction rate increases to 6.3% in those patients with a prior history of unspecified allergic reaction to iodinated contrast agents. Gadolinium contrast material can be administered

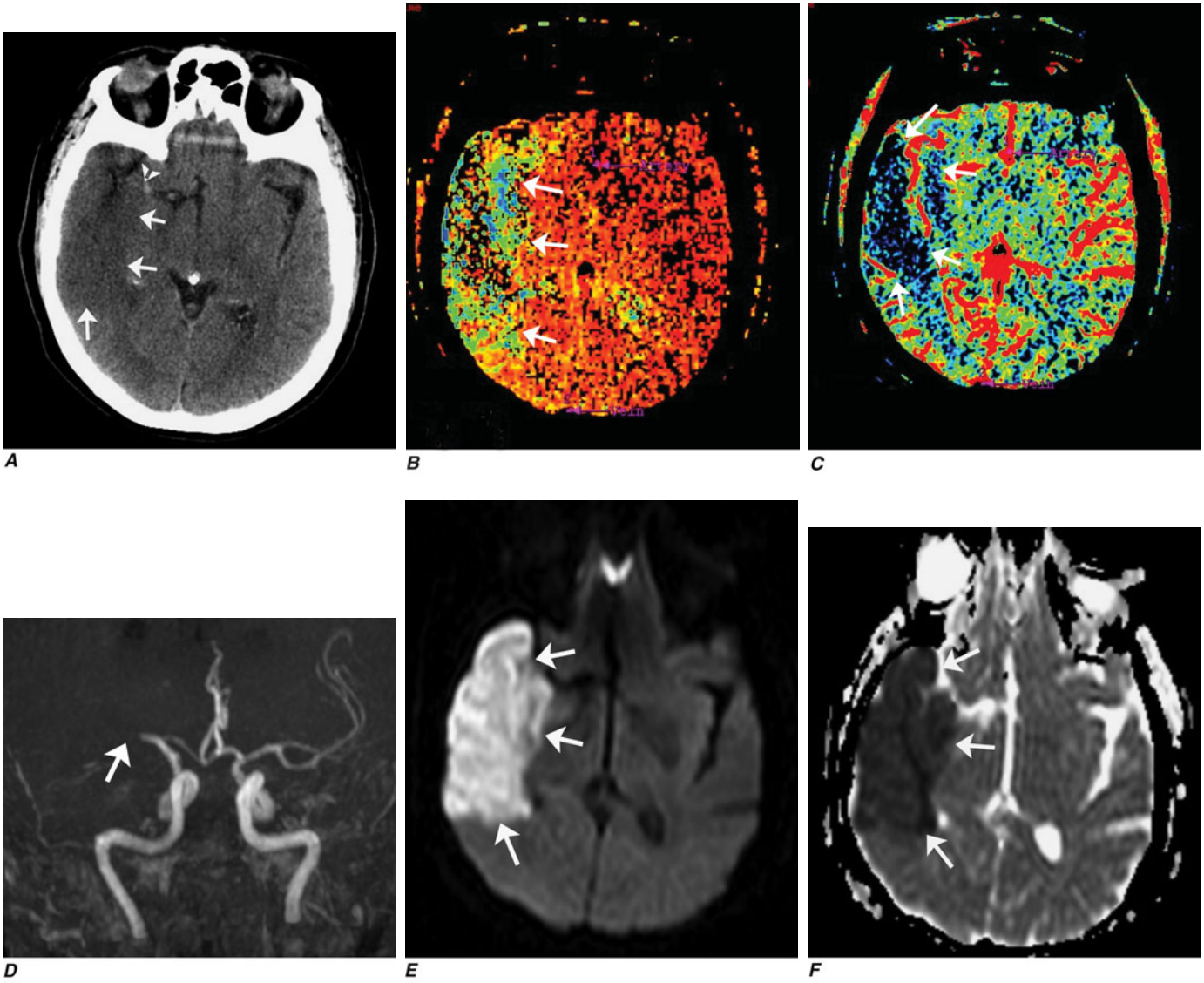


FIGURE 2-3

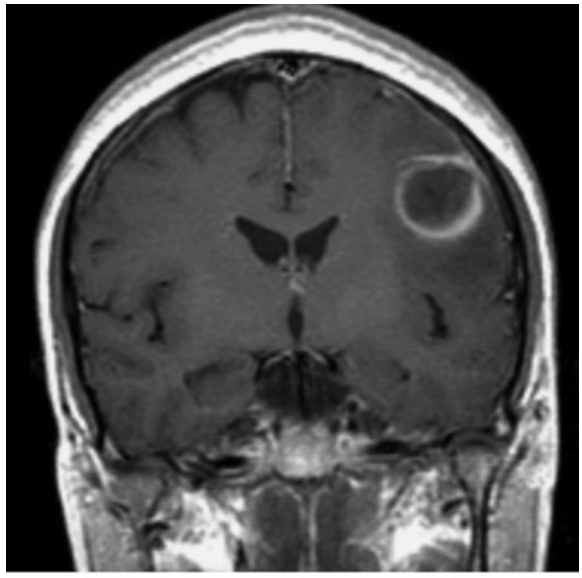
A. Axial noncontrast CT scan in a patient with left hemiparesis shows a subtle low density involving the right temporal and frontal lobes (*arrows*). The hyperdense middle cerebral artery (*arrowhead*) indicates an embolic occlusion of the middle cerebral artery. ***B.*** Mean transit time CT perfusion parametric map indicating prolonged mean transit time involving the right middle cerebral territory (*arrows*). ***C.*** Cerebral blood volume map shows reduced CBV involving an area within the defect shown in ***B***, indicating infarction (*arrows*). ***D.*** Coronal maximum intensity projection from MRA shows right middle cerebral artery (MCA) occlusion (*arrow*). ***E*** and ***F.*** Axial diffusion weighted image (***E***) and apparent diffusion coefficient image (***F***) documents the presence of a right middle cerebral artery infarction.

safely to children as well as adults, although these agents are generally avoided in those younger than 6 months. Renal failure does not occur.

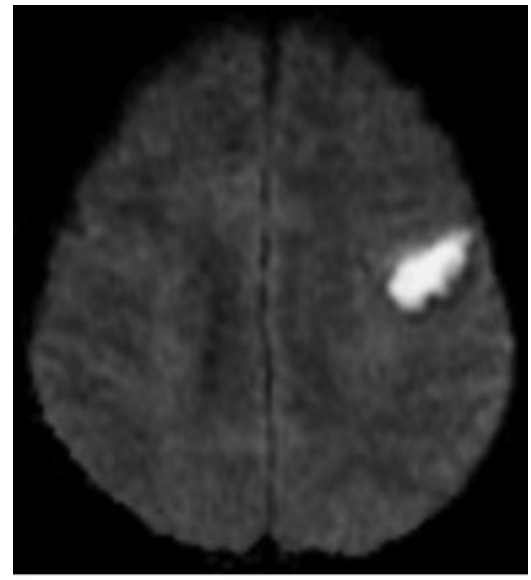
A rare complication, nephrogenic systemic fibrosis (NSF), has recently been reported in patients with renal insufficiency, who have been exposed to gadolinium contrast agents. The onset of NSF has been reported between 5 and 75 days following exposure; histologic features include thickened collagen bundles with surrounding clefts, mucin deposition, and increased numbers of fibrocytes and elastic fibers in skin. In addition to dermatologic symptoms, other manifestations include widespread fibrosis of the skeletal muscle, bone, lungs, pleura, pericardium, myocardium, kidney, muscle, bone, testes, and dura.

COMPLICATIONS AND CONTRAINDICATIONS

From the patient's perspective, an MRI examination can be intimidating, and a higher level of cooperation is required than with CT. The patient lies on a table that is moved into a long, narrow gap within the magnet. Approximately 5% of the population experiences severe



A



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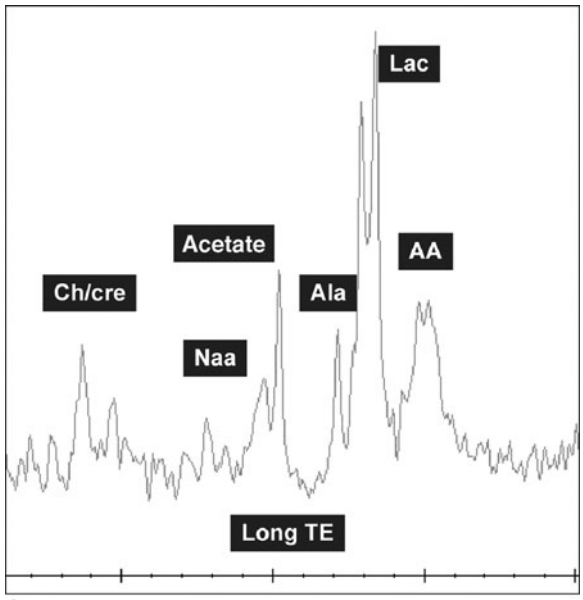

C

FIGURE 2-4
Cerebral abscess in a patient with fever and a right hemiparesis. ***A.*** Coronal postcontrast T1-weighted image demonstrates a ring enhancing mass in the left frontal lobe. ***B.*** Axial diffusion-weighted image demonstrates restricted diffusion (high signal intensity) within the lesion, which in this setting is highly suggestive of cerebral abscess. ***C.*** Single voxel proton spectroscopy (TE of 288 ms) reveals a reduced Naa peak and abnormal peaks for acetate, alanine (Ala), lactate (Lac), and amino acids (AA). These findings are highly suggestive of cerebral abscess; at biopsy a streptococcal abscess was identified.

claustrophobia in the MR environment. This can be reduced by mild sedation but remains a problem for some. Unlike CT, movement of the patient during an MR sequence distorts all the images; therefore, uncooperative patients should either be sedated for the MR study or scanned with CT. Generally, children younger than 10 years usually require conscious sedation in order to complete the MR examination without motion degradation.

MRI is considered safe for patients, even at very high field strengths (>3–4 T). Serious injuries have been caused, however, by attraction of ferromagnetic objects into the magnet, which act as missiles if brought too close to the magnet. Likewise, ferromagnetic implants, such as aneurysm clips, may torque within the magnet, causing damage to vessels and even death. Metallic foreign bodies in the eye have moved and caused intraocular hemorrhage; screening for ocular metallic fragments is indicated in those with a history of metal work or ocular metallic foreign bodies. Implanted cardiac pacemakers are generally a contraindication to MRI owing to the risk of induced arrhythmias; however, some newer pacemakers have been shown to be safe. All health care personnel and patients must be screened and educated thoroughly to prevent such disasters as the magnet is always "on." **Table 2-6** lists common contraindications for MRI.

MAGNETIC RESONANCE ANGIOGRAPHY

MR angiography (MRA) is a general term describing several MR techniques that result in vascular-weighted images. These provide a vascular flow map rather than

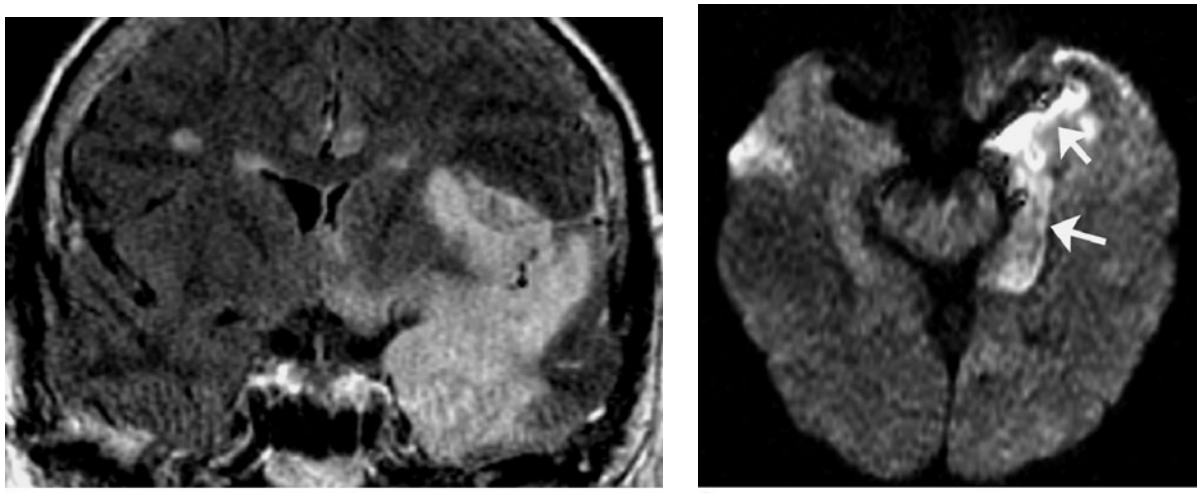

FIGURE 2-5

Herpes simplex encephalitis in a patient presenting with altered mental status and fever. *A.* Coronal T2-weighted FLAIR image demonstrates expansion and high signal intensity involving the left medial temporal lobe, insular cortex, and left cingulate gyrus. ***B.*** Diffusion-weighted image demonstrates high signal intensity indicating restricted diffusion involving the left medial temporal lobe and hippocampus (*arrows*). This is most consistent with neuronal death and can be seen in acute infarction as well as encephalitis and other inflammatory conditions. The suspected diagnosis of herpes simplex encephalitis was confirmed by CSF PCR analysis. *(Courtesy of Howard Rowley, MD, University of Wisconsin; with permission.)*

the anatomic map shown by conventional angiography. On routine spin echo MR sequences, moving protons (e.g., flowing blood, CSF) exhibit complex MR signals that range from high to low signal intensity relative to background stationary tissue. Fast-flowing blood returns no signal (flow void) on routine T1W or T2W spin echo MR images. Slower-flowing blood, as occurs in veins or distal to arterial stenosis, may appear high in signal. However, using special pulse sequences called *gradient echo sequences,* it is possible to increase the signal intensity of moving protons in contrast to the low signal background intensity of stationary tissue. This creates angiography-like images, which can be manipulated in three dimensions to highlight vascular anatomy and relationships.

TABLE 2-6

COMMON CONTRAINDICATIONS TO MR IMAGING
Cardiac pacemaker or permanent pacemaker leads
Internal defibrillatory device
Cochlear prostheses
Bone growth stimulators
Spinal cord stimulators
Electronic infusion devices
Intracranial aneurysm clips (some but not all)
Ocular implants (some) or ocular metallic foreign body
McGee stapedectomy piston prosthesis
Omniphase penile implant
Swan-Ganz catheter
Magnetic stoma plugs
Magnetic dental implants
Magnetic sphincters
Ferromagnetic IVC filters, coils, stents—safe 6 weeks after implantation
Tattooed eyeliner (contains ferromagnetic material and may irritate eyes)

Time-of-flight (TOF) imaging, currently the technique used most frequently, relies on the suppression of nonmoving tissue to provide a low-intensity background for the high signal intensity of flowing blood entering the section; arterial or venous structures may be highlighted. A typical TOF angiography sequence results in a series of contiguous, thin MR sections (0.6–0.9 mm thick), which can be viewed as a stack and manipulated to create an angiographic image data set that can be reformatted and viewed in various planes and angles, much like that seen with conventional angiography (Fig. 2-3*D*).

Phase-contrast MRA has a longer acquisition time than TOF MRA, but in addition to providing anatomic information similar to that of TOF imaging, it can be used to reveal the velocity and direction of blood flow in a given vessel. Through the selection of different imaging parameters, differing blood velocities can be highlighted; selective venous and arterial MRA images can thus be obtained. One advantage of phase-contrast MRA is the excellent suppression of high signal intensity background structures.

MRA can also be acquired during infusion of contrast material. Advantages include faster imaging times (1–2 min vs. 10 min), fewer flow-related artifacts, and higher-resolution images. Recently, contrast-enhanced

MRA has become the standard for extracranial vascular MRA. This technique entails rapid imaging using coronal three-dimensional TOF sequences during a bolus infusion of 15–20 mL of gadolinium-DTPA. Proper technique and timing of acquisition relative to bolus arrival are critical for success.

MRA has lower spatial resolution compared with conventional film-based angiography, and therefore the detection of small-vessel abnormalities, such as vasculitis and distal vasospasm, is problematic. MRA is also less sensitive to slowly flowing blood and thus may not reliably differentiate complete from near-complete occlusions. Motion, either by the patient or by anatomic structures, may distort the MRA images, creating artifacts. These limitations notwithstanding, MRA has proved useful in evaluation of the extracranial carotid and vertebral circulation as well as of larger-caliber intracranial arteries and dural sinuses. It has also proved useful in the noninvasive detection of intracranial aneurysms and vascular malformations.

ECHO-PLANAR MR IMAGING

Recent improvements in gradients, software, and high-speed computer processors now permit extremely rapid MRI of the brain. With echo-planar MRI (EPI), fast gradients are switched on and off at high speeds to create the information used to form an image. In routine spin echo imaging, images of the brain can be obtained in 5–10 min. With EPI, all of the information required for processing an image is accumulated in 50–150 ms, and the information for the entire brain is obtained in 1–2 min, depending on the degree of resolution required or desired. Fast MRI reduces patient and organ motion, permitting diffusion imaging and tractography (Figs. 2-3, 2-4, 2-5, **2-6**; and see Fig. 21-16), perfusion imaging during contrast infusion, fMRI, and kinematic motion studies.

Perfusion and diffusion imaging are EPI techniques that are useful in early detection of ischemic injury of the brain and may be useful together to demonstrate infarcted tissue as well as ischemic but potentially viable tissue at risk of infarction (e.g., the ischemic penumbra). Diffusion-weighted imaging (DWI) assesses microscopic motion of water; restriction of motion appears as relative high signal intensity on diffusion-weighted images. DWI is the most sensitive technique for detection of acute cerebral infarction of <7 days' duration and is also sensitive to encephalitis and abscess formation, all of which have reduced diffusion and result in high signal on diffusion-weighted images.

Perfusion MRI involves the acquisition of EPI images during a rapid intravenous bolus of gadolinium contrast material. Relative perfusion abnormalities can be identified on images of the relative cerebral blood volume, mean transit time, and cerebral blood flow. Delay in mean transit time and reduction in cerebral blood volume and cerebral blood flow are typical of infarction. In the setting of reduced blood flow, a prolonged mean transit time of contrast but normal or elevated cerebral blood volume may indicate tissue supplied by collateral

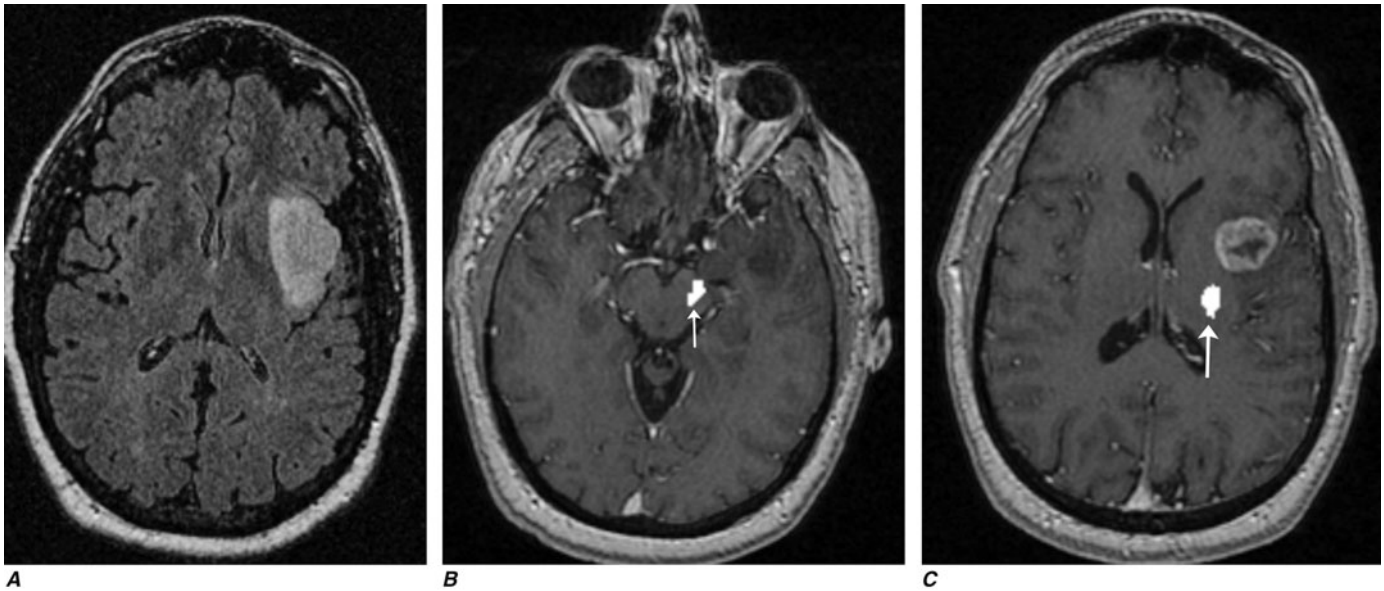

FIGURE 2-6

Diffusion tractography in cerebral glioma. *A.* An axial fast spin echo T2-weighted image shows a high signal intensity glioma of the insular cortex lateral to the fibers of the internal capsule. ***B*** and ***C.*** Axial post-gadolinium images with diffusion tractography superimposed on the image. This shows the position of the internal capsule (*arrows*) relative to the enhancing tumor.

flow that is at risk of infarction. pMRI imaging can also be used in the assessment of brain tumors to differentiate intraaxial primary tumors from extraaxial tumors or metastasis.

Diffusion tract imaging (DTI) is derived from diffusion MRI techniques. Preferential microscopic motion of water along white matter tracts is detected by diffusion MR, which can also indicate the direction of white matter fiber tracts. This new technique has great potential in the assessment of brain maturation as well as disease entities that undermine the integrity of the white matter architecture (Fig. 2-7).

fMRI of the brain is an EPI technique that localizes regions of activity in the brain following task activation. Neuronal activity elicits a slight increase in the delivery of oxygenated blood flow to a specific region of activated brain. This results in an alteration in the balance of oxyhemoglobin and deoxyhemoglobin, which yields a 2–3% increase in signal intensity within veins and local capillaries. Further studies will determine whether these techniques are cost-effective or clinically useful, but currently preoperative somatosensory and auditory cortex localization is possible. This technique has proved useful to neuroscientists interested in interrogating the localization of certain brain functions.

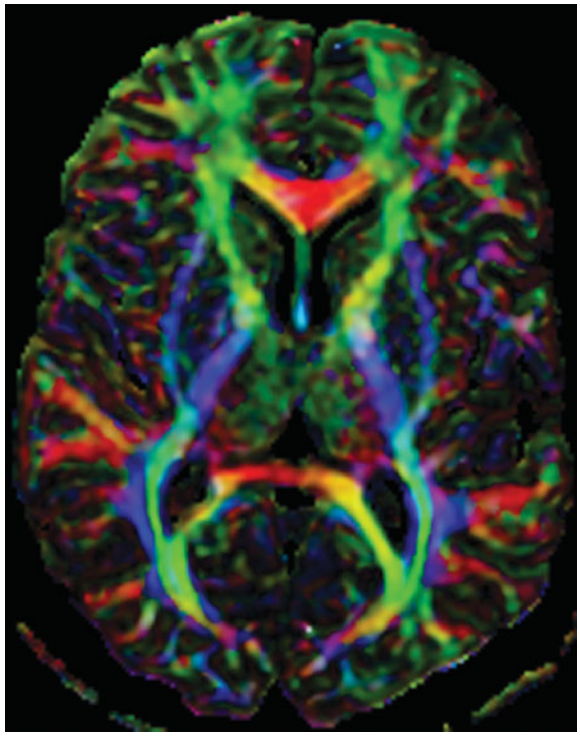

FIGURE 2-7
Diffusion tractography in a healthy individual obtained at 3T demonstrates the normal subcortical fiber pathways. The direction of the tracts have been color-coded (red, left-right; green, anterior-posterior; blue, superior-inferior). *(Courtesy of Pratik Mukherjee, MD, PhD; with permission.)*

MAGNETIC RESONANCE NEUROGRAPHY

MR neurography is an MR technique that shows promise in detecting increased signal in irritated, inflamed, or infiltrated peripheral nerves. Images are obtained with fat-suppressed fast spin echo imaging or short inversion recovery sequences. Irritated or infiltrated nerves will demonstrate high signal on T2W imaging.

POSITRON EMISSION TOMOGRAPHY (PET)

PET relies on the detection of positrons emitted during the decay of a radionuclide that has been injected into a patient. The most frequently used moiety is 2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG), which is an analogue of glucose and is taken up by cells competitively with 2-deoxyglucose. Multiple images of glucose uptake activity are formed after 45–60 min. Images reveal differences in regional glucose activity among normal and pathologic brain structures. A lower activity of FDG in the parietal lobes has been associated with Alzheimer's disease. FDG PET is used primarily for the detection of extracranial metastatic disease. Combination PET-CT scanners, in which both CT and PET are obtained at one sitting, are replacing PET scans alone for most clinical indications. Functional images superimposed on high-resolution CT scans result in more precise anatomic diagnoses.

MYELOGRAPHY

TECHNIQUE

Myelography involves the intrathecal instillation of specially formulated water-soluble iodinated contrast medium into the lumbar or cervical subarachnoid space. CT scanning is usually performed after myelography (*CT myelography*) to better demonstrate the spinal cord and roots, which appear as filling defects in the opacified subarachnoid space. *Low-dose CT myelography*, in which CT is performed after the subarachnoid injection of a small amount of relatively dilute contrast material, has replaced conventional myelography for many indications, thereby reducing exposure to radiation and contrast media. Newer multidetector scanners now obtain CT studies quickly so that reformations in sagittal and coronal planes, equivalent to traditional myelography projections, are now routine.

INDICATIONS

Myelography has been largely replaced by CT myelography and MRI for diagnosis of diseases of the spinal

canal and cord (Table 2-1). Remaining indications for conventional plain-film myelography include the evaluation of suspected meningeal or arachnoid cysts and the localization of spinal dural arteriovenous or CSF fistulas. Conventional myelography and CT myelography provide the most precise information in patients with prior spinal fusion and spinal fixation hardware.

CONTRAINDICATIONS

Myelography is relatively safe; however, it should be performed with caution in any patient with elevated intracranial pressure, evidence of a spinal block, or a history of allergic reaction to intrathecal contrast media. In patients with a suspected spinal block, MR is the preferred technique. If myelography is necessary, only a small amount of contrast medium should be instilled below the lesion in order to minimize the risk of neurologic deterioration. Lumbar puncture is to be avoided in patients with bleeding disorders, including patients receiving anticoagulant therapy, as well as in those with infections of the soft tissues.

COMPLICATIONS

Headache, nausea, and vomiting are the most frequent complications of myelography and are reported to occur in up to 38% of patients. These symptoms result from either neurotoxic effects of the contrast agent, persistent leakage of CSF at the puncture site, or psychological reactions to the procedure. Vasovagal syncope may occur during lumbar puncture; it is accentuated by the upright position used during lumbar myelography. Adequate hydration before and after myelography will reduce the incidence of this complication. Postural headache (post–lumbar puncture headache) is generally due to leakage of CSF from the puncture site, resulting in CSF hypotension. Management of post-lumbar-puncture headache is discussed in Chap. 4.

If significant headache persists for longer than 48 hours, placement of an epidural blood patch should be considered. Hearing loss is a rare complication of myelography. It may result from a direct toxic effect of the contrast medium or from an alteration of the pressure equilibrium between CSF and perilymph in the inner ear. Puncture of the spinal cord is a rare but serious complication of cervical (C1–2) and high lumbar puncture. The risk of cord puncture is greatest in patients with spinal stenosis, Chiari malformations, or conditions that reduce CSF volume. In these settings, a low-dose lumbar injection followed by thin-section CT or MRI is a safer alternative to cervical puncture. Intrathecal contrast reactions are rare, but aseptic meningitis and encephalopathy may occur. The latter is usually dose-related and associated with contrast entering the intracranial subarachnoid space. Seizures occur following myelography in 0.1–0.3% of patients. Risk factors include a preexisting seizure disorder and the use of a total iodine dose of >4500 mg. Other reported complications include hyperthermia, hallucinations, depression, and anxiety states. These side effects have been reduced by the development of nonionic, water-soluble contrast agents, as well as by head elevation and generous hydration following myelography.

SPINE INTERVENTIONS

DISCOGRAPHY

The evaluation of back pain and radiculopathy may require diagnostic procedures that attempt either to reproduce the patient's pain or relieve it, indicating its correct source prior to lumbar fusion. Discography is performed by fluoroscopic placement of a 22- to 25-gauge needle into the intervertebral disc and subsequent injection of 1–3 mL of contrast media. The intradiscal pressure is recorded, as is an assessment of the patient's response to the injection of contrast material. Typically little or no pain is felt during injection of a normal disc, which does not accept much more than 1 mL of contrast material, even at pressures as high as 415–690 kPa (60–100 lbs/in^2). CT and plain films are obtained following the procedure.

SELECTIVE NERVE ROOT AND EPIDURAL SPINAL INJECTIONS

Percutaneous selective nerve root and epidural blocks with glucocorticoid and anesthetic mixtures may be both therapeutic and diagnostic, especially if a patient's pain is relieved. Typically, 1–2 mL of an equal mixture of a long-acting glucocorticoid such as betamethasone and a long-acting anesthetic such as bupivicain 0.75% is instilled under CT or fluoroscopic guidance in the intraspinal epidural space or adjacent to an existing nerve root.

ANGIOGRAPHY

Catheter angiography is indicated for evaluating intracranial small-vessel pathology (such as vasculitis), for assessing vascular malformations and aneurysms, and in endovascular therapeutic procedures (Table 2-1). Angiography has been replaced for many indications by CT/CTA or MRI/MRA.

Angiography carries the greatest risk of morbidity of all diagnostic imaging procedures, owing to the necessity of inserting a catheter into a blood vessel, directing the catheter to the required location, injecting contrast material

to visualize the vessel, and removing the catheter while maintaining hemostasis. Therapeutic transcatheter procedures (see below) have become important options for the treatment of some cerebrovascular diseases. The decision to undertake a diagnostic or therapeutic angiographic procedure requires careful assessment of the goals of the investigation and its attendant risks.

To improve tolerance to contrast agents, patients undergoing angiography should be well hydrated before and after the procedure. Since the femoral route is used most commonly, the femoral artery must be compressed after the procedure to prevent a hematoma from developing. The puncture site and distal pulses should be evaluated carefully after the procedure; complications can include thigh hematoma or lower extremity emboli.

COMPLICATIONS

A common femoral arterial puncture provides retrograde access via the aorta to the aortic arch and great vessels. The most feared complication of cerebral angiography is stroke. Thrombus can form on or inside the tip of the catheter, and atherosclerotic thrombus or plaque can be dislodged by the catheter or guide wire or by the force of injection and can embolize distally in the cerebral circulation. Risk factors for ischemic complications include limited experience on the part of the angiographer, atherosclerosis, vasospasm, low cardiac output, decreased oxygen-carrying capacity, advanced age, and prior history of migraine. The risk of a neurologic complication varies but is ~4% for transient ischemic attack and stroke, 1% for permanent deficit, and <0.1% for death.

Ionic contrast material injected into the cerebral vasculature can be neurotoxic if the BBB is breached, either by an underlying disease or by the injection of hyperosmolar contrast agent. Ionic contrast media are less well tolerated than nonionic media, probably because they can induce changes in cell membrane electrical potentials. Patients with dolichoectasia of the basilar artery can suffer reversible brainstem dysfunction and acute short-term memory loss during angiography, owing to the slow percolation of the contrast material and the consequent prolonged exposure of the brain. Rarely, an intracranial aneurysm ruptures during an angiographic contrast injection, causing subarachnoid hemorrhage, perhaps as a result of injection under high pressure.

SPINAL ANGIOGRAPHY

Spinal angiography may be indicated to evaluate vascular malformations and tumors and to identify the artery of Adamkiewicz (Chap. 30) prior to aortic aneurysm repair. The procedure is lengthy and requires the use of relatively large volumes of contrast; the incidence of serious complications, including paraparesis, subjective visual blurring, and altered speech, is ~2%. Gadolinium-enhanced MRA has been used successfully in this setting, as has iodinated contrast CTA, which has promise for replacing diagnostic spinal angiography for some indications.

INTERVENTIONAL NEURORADIOLOGY

This rapidly developing field is providing new therapeutic options for patients with challenging neurovascular problems. Available procedures include detachable coil therapy for aneurysms, particulate or liquid adhesive embolization of arteriovenous malformations, balloon angioplasty and stenting of arterial stenosis or vasospasm, transarterial or transvenous embolization of dural arteriovenous fistulas, balloon occlusion of carotid-cavernous and vertebral fistulas, endovascular treatment of vein-of-Galen malformations, preoperative embolization of tumors, and thrombolysis of acute arterial or venous thrombosis. Many of these disorders place the patient at high risk of cerebral hemorrhage, stroke, or death.

The highest complication rates are found with the therapies designed to treat the highest-risk diseases. The advent of electrolytically detachable coils has ushered in a new era in the treatment of cerebral aneurysms. One randomized trial found a 28% reduction of morbidity and mortality at 1 year among those treated for anterior circulation aneurysm with detachable coils compared with neurosurgical clipping. It remains to be determined what the role of coils will be relative to surgical options, but in many centers, coiling has become standard therapy for many aneurysms.

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CHAPTER 3

ELECTRODIAGNOSTIC STUDIES OF NERVOUS SYSTEM DISORDERS: EEG, EVOKED POTENTIALS, AND EMG

Michael J. Aminoff

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ELECTROENCEPHALOGRAPHY

The electrical activity of the brain [the electroencephalogram (EEG)] is easily recorded from electrodes placed on the scalp. The potential difference between pairs of electrodes on the scalp (bipolar derivation) or between individual scalp electrodes and a relatively inactive common reference point (referential derivation) is amplified and displayed on a computer monitor, oscilloscope, or paper. The characteristics of the normal EEG depend on the patient's age and level of arousal. The rhythmic activity normally recorded represents the postsynaptic potentials of vertically oriented pyramidal cells of the cerebral cortex and is characterized by its frequency. In normal awake adults lying quietly with the eyes closed, an 8- to 13-Hz alpha rhythm is seen posteriorly in the EEG, intermixed with a variable amount of generalized faster (beta) activity (>13 Hz); the alpha rhythm is attenuated when the eyes are opened (**Fig. 3-1**). During drowsiness, the alpha rhythm is also attenuated; with light sleep, slower activity in the theta (4–7 Hz) and delta (<4 Hz) ranges becomes more conspicuous.

The EEG is best recorded from several different electrode arrangements (montages) in turn, and activating procedures are generally undertaken in an attempt to provoke abnormalities. Such procedures commonly include hyperventilation (for 3 or 4 min), photic stimulation, sleep, and sleep deprivation on the night prior to the recording.

Electroencephalography is relatively inexpensive and may aid clinical management in several different contexts.

THE EEG AND EPILEPSY

The EEG is most useful in evaluating patients with suspected epilepsy. The presence of electrographic seizure activity—i.e., of abnormal, repetitive, rhythmic activity having an abrupt onset and termination and a characteristic evolution—clearly establishes the diagnosis. The absence of such electrocerebral accompaniment does not exclude a seizure disorder, however, because there may be no change in the scalp-recorded EEG during simple or complex partial seizures. With generalized tonic-clonic seizures, however, the EEG is always abnormal during the episode. It is often not possible to obtain an EEG during clinical events that may represent seizures, especially when such events occur unpredictably or infrequently. Continuous monitoring for prolonged periods

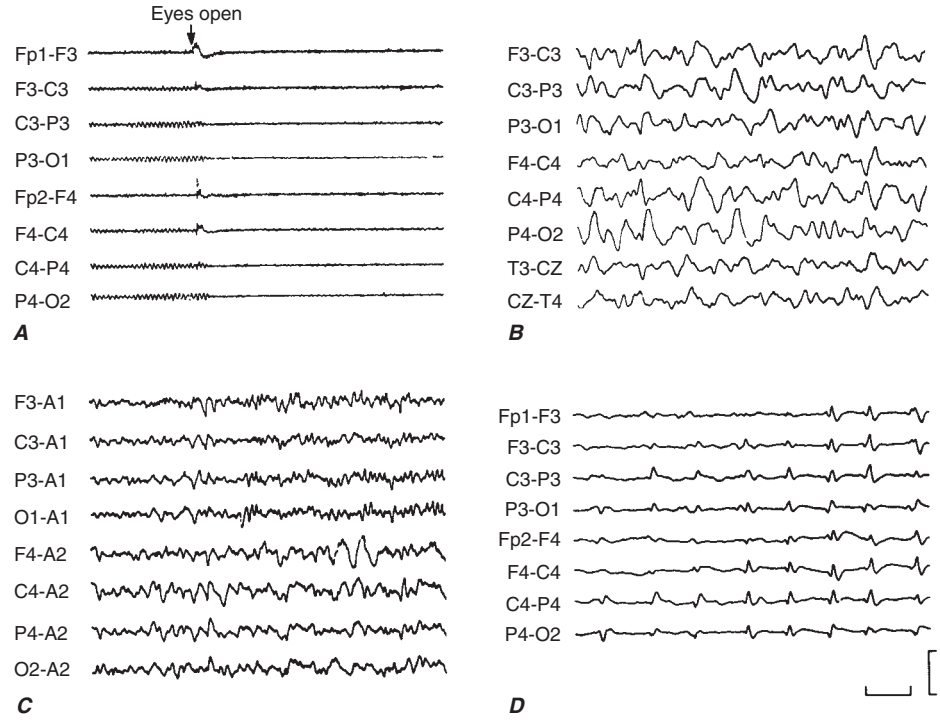

FIGURE 3-1

A. Normal EEG showing a posteriorly situated 9-Hz alpha rhythm that attenuates with eye opening. ***B.*** Abnormal EEG showing irregular diffuse slow activity in an obtunded patient with encephalitis. ***C.*** Irregular slow activity in the right central region, on a diffusely slowed background, in a patient with a right parietal glioma. ***D.*** Periodic complexes occurring once every second in a patient with Creutzfeldt-Jakob disease. Horizontal calibration: 1 s; vertical calibration: 200 μV in A, 300 μV in other panels. *(From Aminoff, 1999.)* In this and the following figure, electrode placements are indicated at the left of each panel and accord with the international 10:20 system. A, earlobe; C, central; F, frontal; Fp, frontal polar; P, parietal; T, temporal; O, occipital. Right-sided placements are indicated by even numbers, left-sided placements by odd numbers, and midline placements by Z.

in video-EEG telemetry units for hospitalized patients or the use of portable equipment to record the EEG continuously on cassettes for 24 h or longer in ambulatory patients has made it easier to capture the electrocerebral accompaniments of such clinical episodes. Monitoring by these means is sometimes helpful in confirming that seizures are occurring, characterizing the nature of clinically equivocal episodes, and determining the frequency of epileptic events.

The EEG findings may also be helpful in the interictal period by showing certain abnormalities that are strongly supportive of a diagnosis of epilepsy. Such *epileptiform activity* consists of bursts of abnormal discharges containing spikes or sharp waves. The presence of epileptiform activity is not specific for epilepsy, but it has a much greater prevalence in epileptic patients than in normal individuals. However, even in an individual who is known to have epilepsy, the initial routine interictal EEG may be normal up to 60% of the time. Thus, the EEG cannot establish the diagnosis of epilepsy in many cases.

The EEG findings have been used in classifying seizure disorders and selecting appropriate anticonvulsant medication for individual patients (**Fig. 3-2**). The episodic generalized spike-wave activity that occurs during and between seizures in patients with typical absence epilepsy contrasts with focal interictal epileptiform discharges or ictal patterns found in patients with complex partial seizures. These latter seizures may have no correlates in the scalp-recorded EEG or may be associated with abnormal rhythmic activity of variable frequency, a localized or generalized distribution, and a stereotyped pattern that varies with the patient. Focal or lateralized epileptogenic lesions are important to recognize, especially if surgical treatment is contemplated. Intensive long-term monitoring of clinical behavior and the EEG is required for operative candidates, however, and this generally also involves recording from intracranially placed electrodes (which may be subdural, extradural, or intracerebral in location).

The findings in the routine scalp-recorded EEG may indicate the prognosis of seizure disorders: in general, a normal EEG implies a better prognosis than otherwise, whereas an abnormal background or profuse epileptiform activity suggests a poor outlook. The EEG findings are not helpful in determining which patients with head injuries, stroke, or brain tumors will go on to develop

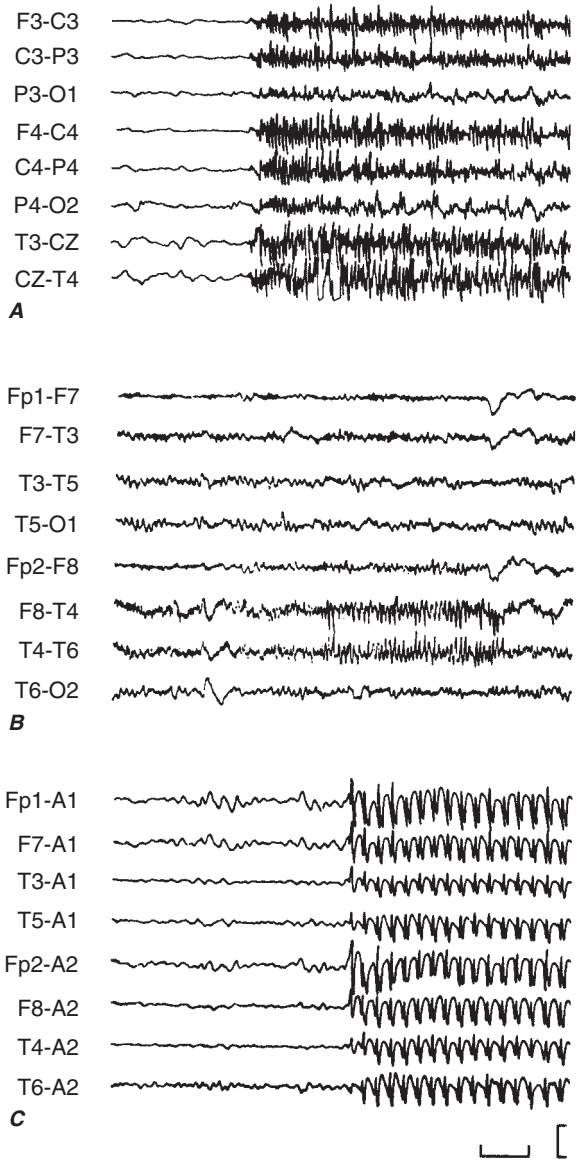

FIGURE 3-2
Electrographic seizures. ***A.*** Onset of a tonic seizure showing generalized repetitive sharp activity with synchronous onset over both hemispheres. ***B.*** Burst of repetitive spikes occurring with sudden onset in the right temporal region during a clinical spell characterized by transient impairment of external awareness. ***C.*** Generalized 3-Hz spike-wave activity occurring synchronously over both hemispheres during an absence (petit mal) attack. Horizontal calibration: 1 s; vertical calibration: 400 mV in A, 200 mV in B, and 750 mV in C. (*From Aminoff, 1999.*)

seizures, because in such circumstances epileptiform activity is commonly encountered regardless of whether seizures occur. The EEG findings are sometimes used to determine whether anticonvulsant medication can be discontinued in epileptic patients who have been seizure-free for several years, but the findings provide only a general guide to prognosis: further seizures may occur after withdrawal of anticonvulsant medication despite a normal EEG or, conversely, may not occur despite a continuing EEG abnormality. The decision to discontinue anticonvulsant medication is made on clinical grounds, and the EEG does not have a useful role in this context except for providing guidance when there is clinical ambiguity or the patient requires reassurance about a particular course of action.

The EEG has no role in the management of tonic-clonic status epilepticus except when there is clinical uncertainty whether seizures are continuing in a comatose patient. In patients treated by pentobarbital-induced coma for refractory status epilepticus, the EEG findings are useful in indicating the level of anesthesia and whether seizures are occurring. During status epilepticus, the EEG shows repeated electrographic seizures or continuous spike-wave discharges. In non-convulsive status epilepticus, a disorder that may not be recognized unless an EEG is performed, the EEG may also show continuous spike-wave activity ("spike-wave stupor") or, less commonly, repetitive electrographic seizures (complex partial status epilepticus).

THE EEG AND COMA

In patients with an altered mental state or some degree of obtundation, the EEG tends to become slower as consciousness is depressed, regardless of the underlying cause (Fig. 3-1). Other findings may also be present and may suggest diagnostic possibilities, as when electrographic seizures are found or there is a focal abnormality indicating a structural lesion. The EEG generally slows in metabolic encephalopathies, and triphasic waves may be present. The findings do not permit differentiation of the underlying metabolic disturbance but help to exclude other encephalopathic processes by indicating the diffuse extent of cerebral dysfunction. The response of the EEG to external stimulation is helpful prognostically because electrocerebral responsiveness implies a lighter level of coma than a nonreactive EEG. Serial records provide a better guide to prognosis than a single record and supplement the clinical examination in following the course of events. As the depth of coma increases, the EEG becomes nonreactive and may show a burst-suppression pattern, with bursts of mixed-frequency activity separated by intervals of relative cerebral inactivity. In other instances there is a reduction in amplitude of the EEG until eventually activity cannot be detected. Such electrocerebral silence does not necessarily reflect irreversible brain damage, because it may occur in hypothermic patients or with drug overdose. The prognosis of electrocerebral silence, when recorded using an adequate technique, depends upon the clinical context in which it is found. In patients with severe cerebral anoxia, for example, electrocerebral silence in a technically satisfactory record implies that useful cognitive recovery will not occur.

In patients with clinically suspected brain death, an EEG, when recorded using appropriate technical standards, may be confirmatory by showing electrocerebral silence. However, complicating disorders that may produce a similar but reversible EEG appearance (e.g., hypothermia or drug intoxication) must be excluded. The presence of residual EEG activity in suspected brain death fails to confirm the diagnosis but does not exclude it. The EEG is usually normal in patients with locked-in syndrome and helps in distinguishing this disorder from the comatose state with which it is sometimes confused clinically.

THE EEG IN OTHER NEUROLOGIC DISORDERS

In the developed countries, CT scanning and MRI have taken the place of EEG as a noninvasive means of screening for focal structural abnormalities of the brain, such as tumors, infarcts, or hematomas (Fig. 3-1). Nonetheless, the EEG is still used for this purpose in many parts of the world, although infratentorial or slowly expanding lesions may fail to cause any abnormalities. Focal slow-wave disturbances, a localized loss of electrocerebral activity, or more generalized electrocerebral disturbances are common findings but provide no reliable indication about the nature of the underlying pathology.

In patients with an acute encephalopathy, focal or lateralized periodic slow-wave complexes, sometimes with a sharpened outline, suggest a diagnosis of herpes simplex encephalitis, and periodic lateralized epileptiform discharges (PLEDs) are commonly found with acute hemispheric pathology such as a hematoma, abscess, or rapidly expanding tumor. The EEG findings in dementia are usually nonspecific and do not distinguish between the different causes of cognitive decline except in rare instances when, for example, the presence of complexes occurring with a regular repetition rate (so-called periodic complexes) supports a diagnosis of Creutzfeldt-Jakob disease (Fig. 3-1) or subacute sclerosing panencephalitis. In most patients with dementias, the EEG is normal or diffusely slowed, and the EEG findings alone cannot indicate whether a patient is demented or distinguish between dementia and pseudodementia.

EVOKED POTENTIALS

SENSORY EVOKED POTENTIALS

The noninvasive recording of spinal or cerebral potentials elicited by stimulation of specific afferent pathways is an important means of monitoring the functional integrity of these pathways but does not indicate the pathologic basis of lesions involving them. Such evoked potentials (EPs) are so small compared to the background EEG activity that the responses to a number of stimuli have to be recorded and averaged with a computer in order to permit their recognition and definition. The background EEG activity, which has no fixed temporal relationship to the stimulus, is averaged out by this procedure.

Visual evoked potentials (VEPs) are elicited by monocular stimulation with a reversing checkerboard pattern and are recorded from the occipital region in the midline and on either side of the scalp. The component of major clinical importance is the so-called P100 response, a positive peak having a latency of approximately 100 ms. Its presence, latency, and symmetry over the two sides of the scalp are noted. Amplitude may also be measured, but changes in size are much less helpful for the recognition of pathology. VEPs are most useful in detecting dysfunction of the visual pathways anterior to the optic chiasm. In patients with acute severe optic neuritis, the P100 is frequently lost or grossly attenuated; as clinical recovery occurs and visual acuity improves, the P100 is restored but with an increased latency that generally remains abnormally prolonged indefinitely. The VEP findings are therefore helpful in indicating previous or subclinical optic neuritis. They may also be abnormal with ocular abnormalities and with other causes of optic nerve disease, such as ischemia or compression by a tumor. Normal VEPs may be elicited by flash stimuli in patients with cortical blindness.

Brainstem auditory evoked potentials (BAEPs) are elicited by monaural stimulation with repetitive clicks and are recorded between the vertex of the scalp and the mastoid process or earlobe. A series of potentials, designated by roman numerals, occurs in the first 10 ms after the stimulus and represents in part the sequential activation of different structures in the pathway between the auditory nerve (wave I) and the inferior colliculus (wave V) in the midbrain. The presence, latency, and interpeak latency of the first five positive potentials recorded at the vertex are evaluated. The findings are helpful in screening for acoustic neuromas, detecting brainstem pathology, and evaluating comatose patients. The BAEPs are normal in coma due to metabolic/toxic disorders or bihemispheric disease but abnormal in the presence of brainstem pathology.

Somatosensory evoked potentials (SEPs) are recorded over the scalp and spine in response to electrical stimulation of a peripheral (mixed or cutaneous) nerve. The configuration, polarity, and latency of the responses depend on the nerve that is stimulated and on the recording arrangements. SEPs are used to evaluate proximal (otherwise inaccessible) portions of the peripheral nervous system and the integrity of the central somatosensory pathways.

CLINICAL UTILITY OF SEPs

EP studies may detect and localize lesions in afferent pathways in the central nervous system (CNS). They

have been used particularly to investigate patients with suspected multiple sclerosis (MS), the diagnosis of which requires the recognition of lesions involving several different regions of the central white matter. In patients with clinical evidence of only one lesion, the electrophysiologic recognition of abnormalities in other sites helps to suggest or support the diagnosis but does not establish it unequivocally. Multimodality EP abnormalities are not specific for multiple sclerosis (MS); they may occur in AIDS, Lyme disease, systemic lupus erythematosus, neurosyphilis, spinocerebellar degenerations, familial spastic paraplegia, and deficiency of vitamin E or B_{12}, among other disorders. The diagnostic utility of the electrophysiologic findings therefore depends on the circumstances in which they are found. Abnormalities may aid in the localization of lesions to broad areas of the CNS, but attempts at precise localization on electrophysiologic grounds are misleading because the generators of many components of the EP are unknown.

The EP findings are sometimes of prognostic relevance. Bilateral loss of SEP components that are generated in the cerebral cortex implies that cognition may not be regained in posttraumatic or postanoxic coma, and EP studies may also be useful in evaluating patients with suspected brain death. In patients who are comatose for uncertain reasons, preserved BAEPs suggest either a metabolic-toxic etiology or bihemispheric disease. In patients with spinal cord injuries, SEPs have been used to indicate the completeness of the lesion. The presence or early return of a cortically generated response to stimulation of a nerve below the injured segment of the cord indicates an incomplete lesion and thus a better prognosis for functional recovery than otherwise. In surgery, intraoperative EP monitoring of neural structures placed at risk by the procedure may permit the early recognition of dysfunction and thereby permit a neurologic complication to be averted or minimized.

Visual and auditory acuity may be determined using EP techniques in patients whose age or mental state precludes traditional ophthalmologic or audiologic examinations.

Cognitive Evoked Potentials

Certain EP components depend on the mental attention of the subject and the setting in which the stimulus occurs, rather than simply on the physical characteristics of the stimulus. Such "event-related" potentials (ERPs) or "endogenous" potentials are related in some manner to the cognitive aspects of distinguishing an infrequently occurring target stimulus from other stimuli occurring more frequently. For clinical purposes, attention has been directed particularly at the so-called P3 component of the ERP, which is also designated the P300 component because of its positive polarity and latency of approximately 300–400 ms after onset of an auditory target stimulus. The P3 component is prolonged in latency in many patients with dementia, whereas it is generally normal in patients with depression or other psychiatric disorders that might be mistaken for dementia. ERPs are therefore sometimes helpful in making this distinction when there is clinical uncertainty, although a response of normal latency does not exclude dementia.

Motor Evoked Potentials

The electrical potentials recorded from muscle or the spinal cord following stimulation of the motor cortex or central motor pathways are referred to as *motor evoked potentials*. For clinical purposes such responses are recorded most often as the compound muscle action potentials elicited by transcutaneous magnetic stimulation of the motor cortex. A strong but brief magnetic field is produced by passing a current through a coil, and this induces stimulating currents in the subjacent neural tissue. The procedure is painless and apparently safe. Abnormalities have been described in several neurologic disorders with clinical or subclinical involvement of central motor pathways, including MS and motor neuron disease. In addition to a possible role in the diagnosis of neurologic disorders or in evaluating the extent of pathologic involvement, the technique provides information of prognostic relevance (e.g., in suggesting the likelihood of recovery of motor function after stroke) and is useful as a means of monitoring intraoperatively the functional integrity of central motor tracts.

ELECTROPHYSIOLOGIC STUDIES OF MUSCLE AND NERVE

The motor unit is the basic element subserving motor function. It is defined as an anterior horn cell, its axon and neuromuscular junctions, and all the muscle fibers innervated by the axon. The number of motor units in a muscle ranges from approximately 10 in the extraocular muscles to several thousand in the large muscles of the legs. There is considerable variation in the average number of muscle fibers within the motor units of an individual muscle, i.e., in the innervation ratio of different muscles. Thus the innervation ratio is <25 in the human external rectus or platysma muscle and between 1600 and 1700 in the medial head of the gastrocnemius muscle. The muscle fibers of individual motor units are divided into two general types by distinctive contractile properties, histochemical stains, and characteristic responses to fatigue. Within each motor unit, all of the muscle fibers are of the same type.

ELECTROMYOGRAPHY

The pattern of electrical activity in muscle [i.e., the electromyogram (EMG)], both at rest and during activity, may be recorded from a needle electrode inserted

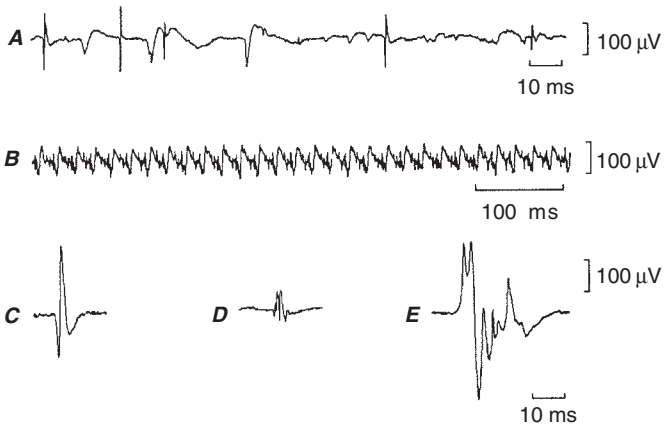

FIGURE 3-3

Activity recorded during EMG. ***A.*** Spontaneous fibrillation potentials and positive sharp waves. ***B.*** Complex repetitive discharges recorded in partially denervated muscle at rest. ***C.*** Normal triphasic motor unit action potential. ***D.*** Small, short-duration, polyphasic motor unit action potential such as is commonly encountered in myopathic disorders. ***E.*** Long-duration polyphasic motor unit action potential such as may be seen in neuropathic disorders.

into the muscle. The nature and pattern of abnormalities relate to disorders at different levels of the motor unit.

Relaxed muscle normally is electrically silent except in the end plate region, but abnormal spontaneous activity (**Fig. 3-3**) occurs in various neuromuscular disorders, especially those associated with denervation or inflammatory changes in affected muscle. Fibrillation potentials and positive sharp waves (which reflect muscle fiber irritability) and complex repetitive discharges are most often—but not always—found in denervated muscle and may also occur after muscle injury and in certain myopathic disorders, especially inflammatory disorders such as polymyositis. After an acute neuropathic lesion, they are found earlier in proximal rather than distal muscles and sometimes do not develop distally in the extremities for 4–6 weeks; once present, they may persist indefinitely unless reinnervation occurs or the muscle degenerates so completely that no viable tissue remains. Fasciculation potentials (which reflect the spontaneous activity of individual motor units) are characteristic of slowly progressive neuropathic disorders, especially those with degeneration of anterior horn cells (such as amyotrophic lateral sclerosis). Myotonic discharges—high-frequency discharges of potentials derived from single muscle fibers that wax and wane in amplitude and frequency—are the signature of myotonic disorders such as myotonic dystrophy or myotonia congenita but occur occasionally in polymyositis or other, rarer, disorders.

Slight voluntary contraction of a muscle leads to activation of a small number of motor units. The potentials generated by any muscle fibers of these units that are within the pick-up range of the needle electrode will be recorded (Fig. 3-3). The parameters of normal motor unit action potentials depend on the muscle under study and age of the patient, but their duration is normally between 5 and 15 ms, amplitude is between 200 μV and 2 mV, and most are bi- or triphasic. The number of units activated depends on the degree of voluntary activity. An increase in muscle contraction is associated with an increase in the number of motor units that are activated (recruited) and in the frequency with which they discharge. With a full contraction, so many motor units are normally activated that individual motor unit action potentials can no longer be distinguished, and a complete interference pattern is said to have been produced.

The incidence of small, short-duration, polyphasic motor unit action potentials (i.e., having more than four phases) is usually increased in myopathic muscle, and an excessive number of units is activated for a specified degree of voluntary activity. By contrast, the loss of motor units that occurs in neuropathic disorders leads to a reduction in number of units activated during a maximal contraction and an increase in their firing rate, i.e., there is an incomplete or reduced interference pattern. The configuration and dimensions of the potentials may also be abnormal, depending on the duration of the neuropathic process and on whether reinnervation has occurred. The surviving motor units are initially normal in configuration but, as reinnervation occurs, they increase in amplitude and duration and become polyphasic (Fig. 3-3).

Action potentials from the same motor unit sometimes fire with a consistent temporal relationship to each other, so that double, triple, or multiple discharges are recorded, especially in tetany, hemifacial spasm, or myokymia.

Electrical silence characterizes the involuntary, sustained muscle contraction that occurs in phosphorylase deficiency, which is designated a contracture.

EMG enables disorders of the motor units to be detected and characterized as either neurogenic or myopathic. In neurogenic disorders, the pattern of affected muscles may localize the lesion to the anterior horn cells or to a specific site as the axons traverse a nerve root, limb plexus, and peripheral nerve to their terminal arborizations. The findings do not enable a specific etiologic diagnosis to be made, however, except in conjunction with the clinical findings and results of other laboratory studies.

The findings may provide a guide to the severity of an acute disorder of a peripheral or cranial nerve (by indicating whether denervation has occurred and the completeness of the lesion) and whether the pathologic process is active or progressive in chronic or degenerative disorders such as amyotrophic lateral sclerosis. Such information is important for prognostic purposes.

Various quantitative EMG approaches have been developed. The most common is to determine the mean

duration and amplitude of 20 motor unit action potentials using a standardized technique. The technique of macro-EMG provides information about the number and size of muscle fibers in a larger volume of the motor unit territory and has also been used to estimate the number of motor units in a muscle. Scanning EMG is a computer-based technique that has been used to study the topography of motor unit action potentials and, in particular, the spatial and temporal distribution of activity in individual units. The technique of single-fiber EMG is discussed separately later.

Nerve Conduction Studies

Recording of the electrical response of a muscle to stimulation of its motor nerve at two or more points along its course (**Fig. 3-4**) permits conduction velocity to be determined in the fastest-conducting motor fibers between the points of stimulation. The latency and amplitude of the electrical response of muscle (i.e., of the compound muscle action potential) to stimulation of its motor nerve at a distal site are also compared with values defined in normal subjects. Sensory nerve conduction studies are performed by determining the conduction velocity and amplitude of action potentials in sensory fibers when these fibers are stimulated at one point and the responses are recorded at another point along the course of the nerve. In adults, conduction velocity in the arms is normally between 50 and 70 m/s, and in the legs is between 40 and 60 m/s.

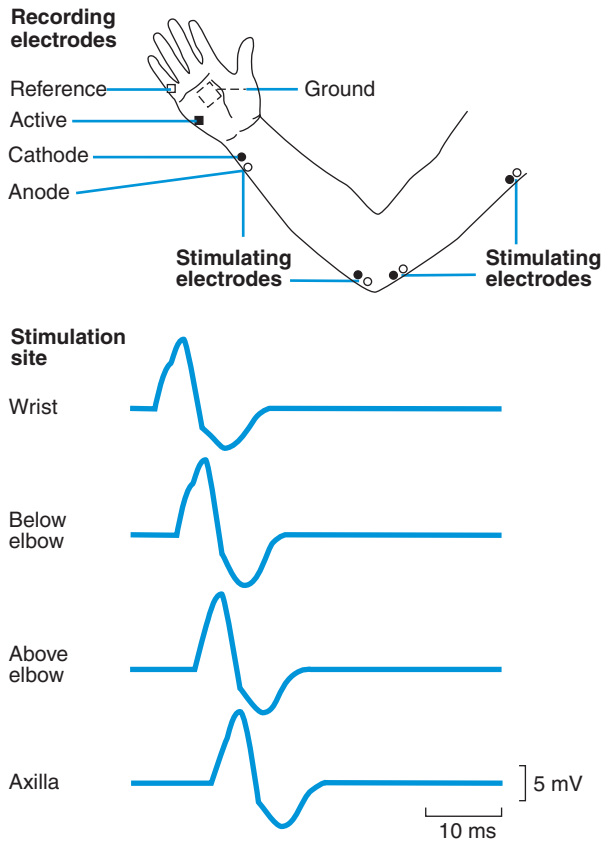

FIGURE 3-4
Arrangement for motor conduction studies of the ulnar nerve. Responses are recorded with a surface electrode from the abductor digiti minimi muscle to supramaximal stimulation of the nerve at different sites, and are shown in the lower panel. *(From Aminoff, 1998.)*

Nerve conduction studies complement the EMG examination, enabling the presence and extent of peripheral nerve pathology to be determined. They are particularly helpful in determining whether sensory symptoms are arising from pathology proximal or distal to the dorsal root ganglia (in the former instance, peripheral sensory conduction studies will be normal) and whether neuromuscular dysfunction relates to peripheral nerve disease. In patients with a mononeuropathy, they are invaluable as a means of localizing a focal lesion, determining the extent and severity of the underlying pathology, providing a guide to prognosis, and detecting subclinical involvement of other peripheral nerves. They enable a polyneuropathy to be distinguished from a mononeuropathy multiplex when this is not possible clinically, an important distinction because of the etiologic implications. Nerve conduction studies provide a means of following the progression and therapeutic response of peripheral nerve disorders and are being used increasingly for this purpose in clinical trials. They may suggest the underlying pathologic basis in individual cases. Conduction velocity is often markedly slowed, terminal motor latencies are prolonged, and compound motor and sensory nerve action potentials may be dispersed in the demyelinative neuropathies (such as in Guillain-Barré syndrome, chronic inflammatory polyneuropathy, metachromatic leukodystrophy, or certain hereditary neuropathies); conduction block is frequent in acquired varieties of these neuropathies. By contrast, conduction velocity is normal or slowed only mildly, sensory nerve action potentials are small or absent, and there is EMG evidence of denervation in axonal neuropathies such as occur in association with metabolic or toxic disorders.

The utility and complementary role of EMG and nerve conduction studies are best illustrated by reference to a common clinical problem. Numbness and paresthesia of the little finger and associated wasting of the intrinsic muscles of the hand may result from a spinal cord lesion, C8/T1 radiculopathy, brachial plexopathy (lower trunk or medial cord), or a lesion of the ulnar nerve. If sensory nerve action potentials can be recorded normally at the wrist following stimulation of the digital fibers in the affected finger, the pathology is probably proximal to the dorsal root ganglia, i.e., there is a radiculopathy or more central lesion; absence of the sensory potentials, by contrast, suggests distal pathology. EMG examination will indicate whether the pattern of affected muscles conforms to radicular or ulnar nerve

territory, or is more extensive (thereby favoring a plexopathy). Ulnar motor conduction studies will generally also distinguish between a radiculopathy (normal findings) and ulnar neuropathy (abnormal findings) and will often identify the site of an ulnar nerve lesion: the nerve is stimulated at several points along its course to determine whether the compound action potential recorded from a distal muscle that it supplies shows a marked alteration in size or area or a disproportionate change in latency, with stimulation at a particular site. The electrophysiologic findings thus permit a definitive diagnosis to be made and specific treatment instituted in circumstances where there is clinical ambiguity.

F Wave Studies

Stimulation of a motor nerve causes impulses to travel antidromically (i.e., toward the spinal cord) as well as orthodromically (to the nerve terminals). Such antidromic impulses cause a few of the anterior horn cells to discharge, producing a small motor response that occurs considerably later than the direct response elicited by nerve stimulation. The F wave so elicited is sometimes abnormal (absent or delayed) with proximal pathology of the peripheral nervous system, such as a radiculopathy, and may therefore be helpful in detecting abnormalities when conventional nerve conduction studies are normal. In general, however, the clinical utility of F wave studies has been disappointing, except perhaps in Guillain-Barré syndrome, where they are often absent or delayed.

H Reflex Studies

The H reflex is easily recorded only from the soleus muscle (S1) in normal adults. It is elicited by low-intensity stimulation of the tibial nerve and represents a monosynaptic reflex in which spindle (Ia) afferent fibers constitute the afferent arc and alpha motor axons the efferent pathway. The H reflexes are often absent bilaterally in elderly patients or with polyneuropathies and may be lost unilaterally in S1 radiculopathies.

Muscle Response to Repetitive Nerve Stimulation

The size of the electrical response of a muscle to supramaximal electrical stimulation of its motor nerve relates to the number of muscle fibers that are activated. Neuromuscular transmission can be tested by several different protocols, but the most helpful is to record with surface electrodes the electrical response of a muscle to supramaximal stimulation of its motor nerve by repetitive (2–3 Hz) shocks delivered before and at selected intervals after a maximal voluntary contraction.

There is normally little or no change in size of the compound muscle action potential following repetitive stimulation of a motor nerve at 2–3 Hz with stimuli delivered at intervals after voluntary contraction of the muscle for about 20–30 s, even though preceding activity in the junctional region influences the release of acetylcholine and thus the size of the end plate potentials elicited by a test stimulus. This is because more acetylcholine is normally released than is required to bring the motor end plate potentials to the threshold for generating muscle fiber action potentials. In disorders of neuromuscular transmission this safety factor is reduced. Thus in myasthenia gravis, repetitive stimulation, particularly at a rate of between 2 and 5 Hz, may lead to a depression of neuromuscular transmission, with a decrement in size of the response recorded from affected muscles. Similarly, immediately after a period of maximal voluntary activity, single or repetitive stimuli of the motor nerve may elicit larger muscle responses than before, indicating that more muscle fibers are responding. This postactivation facilitation of neuromuscular transmission is followed by a longer-lasting period of depression, maximal between 2 and 4 min after the conditioning period and lasting for as long as 10 min or so, during which responses are reduced in size.

Decrementing responses to repetitive stimulation at 2–5 Hz are common in myasthenia gravis but may also occur in the congenital myasthenic syndromes. In Lambert-Eaton myasthenic syndrome, in which there is defective release of acetylcholine at the neuromuscular junction, the compound muscle action potential elicited by a single stimulus is generally very small. With repetitive stimulation at rates of up to 10 Hz, the first few responses may decline in size, but subsequent responses increase. If faster rates of stimulation are used (20–50 Hz), the increment may be dramatic so that the amplitude of compound muscle action potentials eventually reaches a size that is several times larger than the initial response. In patients with botulism, the response to repetitive stimulation is similar to that in Lambert-Eaton syndrome, although the findings are somewhat more variable and not all muscles are affected.

Single-Fiber Electromyography

This technique is particularly helpful in detecting disorders of neuromuscular transmission. A special needle electrode is placed within a muscle and positioned to record action potentials from two muscle fibers belonging to the same motor unit. The time interval between the two potentials will vary in consecutive discharges; this is called the *neuromuscular jitter*. The jitter can be quantified as the mean difference between consecutive interpotential intervals and is normally between 10 and 50 μs. This value is increased when neuromuscular transmission is disturbed for any reason, and in some instances impulses in individual muscle fibers may fail to occur because of impulse blocking at the neuromuscular

junction. Single-fiber EMG is more sensitive than repetitive nerve stimulation or determination of acetylcholine receptor antibody levels in diagnosing myasthenia gravis.

Single-fiber EMG can also be used to determine the mean fiber density of motor units (i.e., mean number of muscle fibers per motor unit within the recording area) and to estimate the number of motor units in a muscle, but this is of less immediate clinical relevance.

Blink Reflexes

Electrical or mechanical stimulation of the supraorbital nerve on one side leads to two separate reflex responses of the orbicularis oculi—an ipsilateral R1 response having a latency of approximately 10 ms and a bilateral R2 response with a latency in the order of 30 ms. The trigeminal and facial nerves constitute the afferent and efferent arcs of the reflex, respectively. Abnormalities of either nerve or intrinsic lesions of the medulla or pons may lead to uni- or bilateral loss of the response, and the findings may therefore be helpful in identifying or localizing such pathology.

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CHAPTER 4

LUMBAR PUNCTURE

Elizabeth Robbins ■ Stephen L. Hauser

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In experienced hands, lumbar puncture (LP) is usually a safe procedure. Major complications are extremely uncommon but can include cerebral herniation, injury to the spinal cord or nerve roots, hemorrhage, or infection. Minor complications occur with greater frequency and can include backache, post-LP headache, and radicular pain or numbness.

IMAGING AND LABORATORY STUDIES PRIOR TO LP

Patients with an altered level of consciousness, a focal neurologic deficit, new-onset seizure, papilledema, or an immunocompromised state are at increased risk for potentially fatal cerebellar or tentorial herniation following LP. Neuroimaging should be obtained in these patients prior to LP to exclude a focal mass lesion or diffuse swelling. Imaging studies should include the spine in patients with symptoms suggesting cord compression, such as back pain, leg weakness, urinary retention, or incontinence. In patients with suspected meningitis who require neuroimaging prior to diagnostic LP, administration of antibiotics, preferably following blood culture, should precede the neuroimaging study.

Patients receiving therapeutic anticoagulation or those with coagulation defects including thrombocytopenia are at increased risk of post-LP spinal subdural or epidural hematomas, either of which can produce permanent nerve injury and/or paralysis. If a bleeding disorder is suspected, the platelet count, international normalized ratio (INR), and partial thromboplastin time should be checked prior to lumbar puncture. There are no data available to assess the safety of LP in patients with low platelet counts; a count of <20,000/μL is considered to be a contraindication to LP. Bleeding complications rarely occur in patients with platelet counts >50,000/μL and an INR ≤1.5. Patients receiving low-molecular-weight heparin are at increased risk of post-LP spinal or epidural hematoma, and doses should be held for 24 h before the procedure.

LP should not be performed through infected skin as organisms can be introduced into the subarachnoid space (SAS).

ANALGESIA

Anxiety and pain can be minimized prior to beginning the procedure. Anxiety can be allayed by the use of lorazepam, 1–2 mg given PO 30 min prior to the procedure or IV 5 min prior to the procedure. Topical anesthesia can be achieved by the application of a lidocaine-based cream. Lidocaine 4% is effective when applied 30 min prior to the procedure; lidocaine/prilocaine requires 60–120 min. The cream should be applied in a thick layer so that it completely covers the skin; an occlusive dressing is used to keep the cream in place.

POSITIONING

Proper positioning of the patient is essential. The procedure should be performed on a firm surface; if the procedure is to be performed at the bedside, the patient should be positioned at the edge of the bed and not in the middle. The patient is asked to lie on his or her side, facing away from the examiner, and to "roll up into a ball." The neck is gently ante-flexed and the thighs pulled up toward the abdomen; the shoulders and pelvis should be vertically aligned without forward or backward tilt (**Fig. 4-1**). The spinal cord terminates at approximately the L1 vertebral level in 94% of individuals. In the remaining 6%, the conus extends to the L2-L3 interspace. LP is therefore performed at or below the L3-L4 interspace. A useful anatomic guide is a line drawn between the posterior superior iliac crests, which corresponds closely to the level of the L3-L4 interspace. The interspace is chosen following gentle palpation to identify the spinous processes at each lumbar level.

An alternative to the lateral recumbent position is the seated position. The patient sits at the side of the bed, with feet supported on a chair. The patient is instructed to curl forward, trying to touch the nose to the umbilicus. It is important that the patient not simply lean forward onto a bedside table top, as this is not an optimal position for opening up the spinous processes. LP is sometimes more easily performed in obese patients if they are sitting. A disadvantage of the seated position is that measurement of opening pressure may not be accurate. In situations in which LP is difficult using palpable spinal landmarks, bedside ultrasound to guide needle placement may be employed.

TECHNIQUE

Once the desired target for needle insertion has been identified, the examiner should put on sterile gloves.

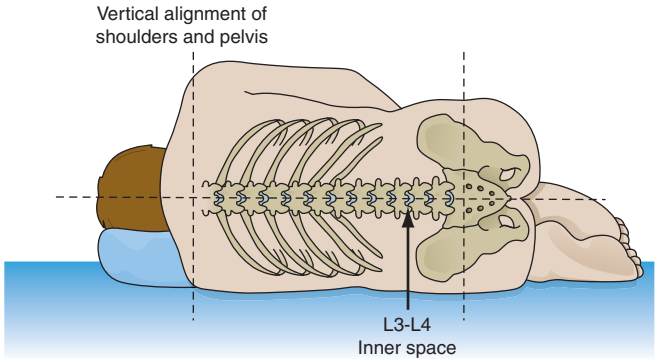

FIGURE 4-1

Proper positioning of a patient in the lateral decubitus position. Note that the shoulders and hips are in a vertical plane; the torso is perpendicular to the bed. *(From Straus et al.)*

After cleansing the skin with povidone-iodine or similar disinfectant, the area is draped with a sterile cloth; the needle insertion site is blotted dry using a sterile gauze pad. Proper local disinfection reduces the risk of introducing skin bacteria into the SAS or other sites. Local anesthetic, typically 1% lidocaine, 3–5 mL total, is injected into the subcutaneous tissue; in nonemergency situations a topical anesthetic cream can be applied (see above). When time permits, pain associated with the injection of lidocaine can be minimized by slow, serial injections, each one progressively deeper than the last, over a period of ~5 min. Approximately 0.5–1 mL of lidocaine is injected at a time; the needle is not usually withdrawn between injections. A pause of ~15 s between injections helps to minimize the pain of the subsequent injection. The goal is to inject each mini-bolus of anesthetic into an area of skin that has become numb from the preceding injection. Approximately 5–10 mini-boluses are injected, using a total of ~5 mL of lidocaine.

If possible, the LP should be delayed for 10–15 min following the completion of the injection of anesthetic; this significantly decreases and can even eliminate pain from the procedure. Even a delay of 5 min will help to reduce pain.

The LP needle (typically 20- to 22-gauge) is inserted in the midline, midway between two spinous processes, and slowly advanced. The bevel of the needle should be maintained in a horizontal position, parallel to the direction of the dural fibers and with the flat portion of the bevel pointed upward; this minimizes injury to the fibers as the dura is penetrated. When lumbar puncture is performed in patients who are sitting, the bevel should be maintained in the vertical position. In most adults, the needle is advanced 4–5 cm (1–2 in.) before the SAS is reached; the examiner usually recognizes entry as a sudden release of resistance, a "pop." If no fluid appears despite apparently correct needle placement, then the needle may be rotated 90°–180°. If there is still no fluid, the stylet is reinserted and the needle is advanced slightly. Some examiners halt needle advancement periodically to remove the stylet and check for flow of cerebrospinal fluid (CSF). If the needle cannot be advanced because it hits bone, if the patient experiences sharp radiating pain down one leg, or if no fluid appears ("dry tap"), the needle is partially withdrawn and reinserted at a different angle. If on the second attempt the needle still hits bone (indicating lack of success in introducing it between the spinous processes), then the needle should be completely withdrawn and the patient should be repositioned. The second attempt is sometimes more successful if the patient straightens the spine completely prior to repositioning. The needle can then be reinserted at the same level or at an adjacent one.

Once the SAS is reached, a manometer is attached to the needle and the opening pressure measured. The

examiner should look for normal oscillations in CSF pressure associated with pulse and respirations. The upper limit of normal opening pressure with the patient supine is 180 mm H_2O in adults but may be as high as 200–250 mm H_2O in obese adults.

CSF is allowed to drip into collection tubes; it should not be withdrawn with a syringe. Depending on the clinical indication, fluid is then obtained for studies including: (1) cell count with differential, (2) protein and glucose concentrations, (3) culture (bacterial, fungal, mycobacterial, viral), (4) smears (e.g., Gram's and acid-fast stained smears), (5) antigen tests (e.g., latex agglutination) (6) polymerase chain reaction (PCR) amplification of DNA or RNA of microorganisms (e.g., herpes simplex virus, enteroviruses), (7) antibody levels against microorganisms, (8) immunoelectrophoresis for determination of γ-globulin level and oligoclonal banding, and (9) cytology. Although 15 mL of CSF is sufficient to obtain all of the listed studies, the yield of fungal and mycobacterial cultures and cytology increases when larger volumes are sampled. In general 20–30 mL may be safely removed from adults.

A bloody tap due to penetration of a meningeal vessel (a "traumatic tap") may result in confusion with subarachnoid hemorrhage (SAH). In these situations a specimen of CSF should be centrifuged immediately after it is obtained; clear supernatant following CSF centrifugation supports the diagnosis of a bloody tap, whereas xanthochromic supernatant suggests SAH. In general, bloody CSF due to the penetration of a meningeal vessel clears gradually in successive tubes, whereas blood due to SAH does not. In addition to SAH, xanthochromic CSF may also be present in patients with liver disease and when the CSF protein concentration is markedly elevated [>1.5–2.0 g/L (150–200 mg/dL)].

Prior to removing the LP needle, the stylet is reinserted to avoid the possibility of entrapment of a nerve root in the dura as the needle is being withdrawn; entrapment could result in a dural CSF leak, causing headache. Some practitioners question the safety of this maneuver, with its potential risk of causing a needle-stick injury to the examiner. Injury is unlikely, however, given the flexibility of the small-diameter stylet, which tends to bend, rather than penetrate, on contact. Following LP, the patient is customarily positioned in a comfortable, recumbent position for 1 h before rising, although recent data suggest that assuming a recumbent position may be unnecessary as it does not appear to affect the development of headache (see below).

POST-LP HEADACHE

The principal complication of LP is headache, occurring in 10–30% of patients. Younger age and female gender are associated with an increased risk of post-LP headache. Headache usually begins within 48 h but may be delayed for up to 12 days. Head pain is dramatically positional; it begins when the patient sits or stands upright; there is relief upon reclining or with abdominal compression. The longer the patient is upright, the longer the latency before head pain subsides. The pain is usually a dull ache but may be throbbing; its location is occipitofrontal. Nausea and stiff neck often accompany headache, and occasionally, patients report blurred vision, photophobia, tinnitus, and vertigo. Symptoms usually resolve over a few days but may on occasion persist for weeks to months.

Post-LP headache is caused by a drop in CSF pressure related to persistent leakage of CSF at the site where the needle entered the subarachnoid space. Loss of CSF volume decreases the brain's supportive cushion, so that when a patient is upright there is probably dilation and tension placed on the brain's anchoring structures, the pain-sensitive dural sinuses, resulting in pain. Although intracranial hypotension is the usual explanation for severe LP headache, the syndrome can occur in patients with normal CSF pressure.

Post-LP headache usually resolves without specific treatment, and care is largely supportive with oral analgesics [acetaminophen, nonsteroidal anti-inflammatory drugs, opioids (Chap. 5)] and antiemetics. Patients may obtain relief by lying in a comfortable position. For some patients beverages with caffeine can provide temporary pain relief.

For patients with persistent pain, treatment with IV caffeine (500 mg in 500 mL saline administered over 2 h) may be effective; atrial fibrillation is an uncommon side effect. For patients who do not respond to caffeine, an epidural blood patch accomplished by injection of 15 mL of autologous whole blood is usually effective. This procedure is usually performed by a pain specialist or anesthesiologist. The mechanism for these treatment effects is not straightforward. The blood patch has an immediate effect, making it unlikely that sealing off a dural hole with blood clot is its sole mechanism of action.

Strategies to decrease the incidence of post-LP headache are listed in **Table 4-1**. Use of a smaller caliber needle is associated with a lower risk: in one study, the risk of headache following use of a 20- or 22-gauge standard (Quinke) needle was 20–40%, compared to 5–12% when a 24- to 27-gauge needle was used. The smallest gauge needles usually require the use of an introducer needle and are associated with a slower CSF flow rate. Use of an "atraumatic" (Sprotte, "pencil point," or "noncutting") needle also reduces the incidence of moderate to severe headache compared with standard LP (Quinke, or "traumatic") needles (**Fig. 4-2**). However, because atraumatic needles are more difficult to use, more attempts may be required to perform the LP, particularly

TABLE 4-1

REDUCING THE INCIDENCE OF POST-LP HEADACHE
Effective Strategies
Use of small-diameter needle (22-gauge or smaller)
Use of atraumatic needle (Sprotte and others)
Replacement of stylet prior to removal of needle
Insertion of needle with bevel oriented in a cephalad to caudad direction (when using standard needle)
Ineffective Strategies
Bed rest (up to 4 h) following LP
Supplemental fluids
Minimizing the volume of spinal fluid removed
Immediate mobilization following LP

in overweight patients. It may also be necessary to use an introducer with the atraumatic needle, which does not have the customary cutting, beveled tip. There is a low risk of needle damage, e.g., breakage, with the Sprotte atraumatic needle.

Another strategy to decrease the incidence of headache is to replace the stylet before removing the LP needle. Studies comparing mobilization immediately following LP with bed rest for up to 4 h show no significant differences in the incidence of headache, suggesting that the customary practice of remaining in a recumbent position post-LP may be unnecessary.

NORMAL VALUES

(See **Table 4-2**) In uninfected CSF, the normal white blood cell count is fewer than five mononuclear cells (lymphocytes and monocytes) per μL. Polymorphonuclear leukocytes (PMNs) are not found in normal unconcentrated CSF; however, rare PMNs can be found in centrifuged or concentrated CSF specimens such as those utilized for cytologic examination. Red blood cells (RBCs) are not normally present in CSF; if RBCs are present from a traumatic tap, their number decreases as additional CSF is collected. CSF glucose concentrations <2.2 mmol/L (<40 mg/dL) are abnormal.

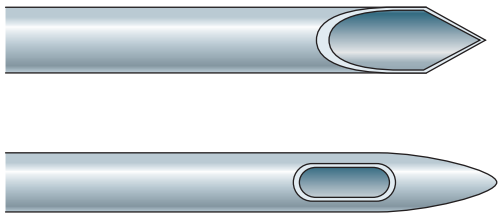

FIGURE 4-2
Comparison of the standard ("traumatic" or Quinke) LP needle with the "atraumatic" (Sprotte). The atraumatic needle has its opening on the top surface of the needle, a design intended to reduce the chance of cutting dural fibers that, by protruding through the dura, could be responsible for subsequent CSF fluid leak and post-LP headache. *(From Thomas et al.)*

TABLE 4-2

CEREBROSPINAL FLUID[a]		
CONSTITUENT	**SI UNITS**	**CONVENTIONAL UNITS**
Glucose	2.22–3.89 mmol/L	40–70 mg/dL
Lactate	1–2 mmol/L	10–20 mg/dL
Total protein		
Lumbar	0.15–0.5 g/L	15–50 mg/dL
Cisternal	0.15–0.25 g/L	15–25 mg/dL
Ventricular	0.06–0.15 g/L	6–15 mg/dL
Albumin	0.066–0.442 g/L	6.6–44.2 mg/dL
IgG	0.009–0.057 g/L	0.9–5.7 mg/dL
IgG index[b]	0.29–0.59	
Oligoclonal bands (OGB)	<2 bands not present in matched serum sample	
Ammonia	15–47 μmol/L	25–80 μg/dL
CSF pressure		50–180 mm H_2O
CSF volume (adult)	~150 mL	
Red blood cells	0	0
Leukocytes		
Total	0–5 mononuclear cells per mm^3	
Differential		
Lymphocytes	60–70%	
Monocytes	30–50%	
Neutrophils	None	

[a]Since cerebrospinal fluid concentrations are equilibrium values, measurements of the same parameters in blood plasma obtained at the same time are recommended. However, there is a time lag in attainment of equilibrium, and cerebrospinal levels of plasma constituents that can fluctuate rapidly (such as plasma glucose) may not achieve stable values until after a significant lag phase.
[b]IgG index = CSF IgG(mg/dL) × serum albumin(g/dL)/Serum IgG(g/dL) × CSF albumin(mg/dL).

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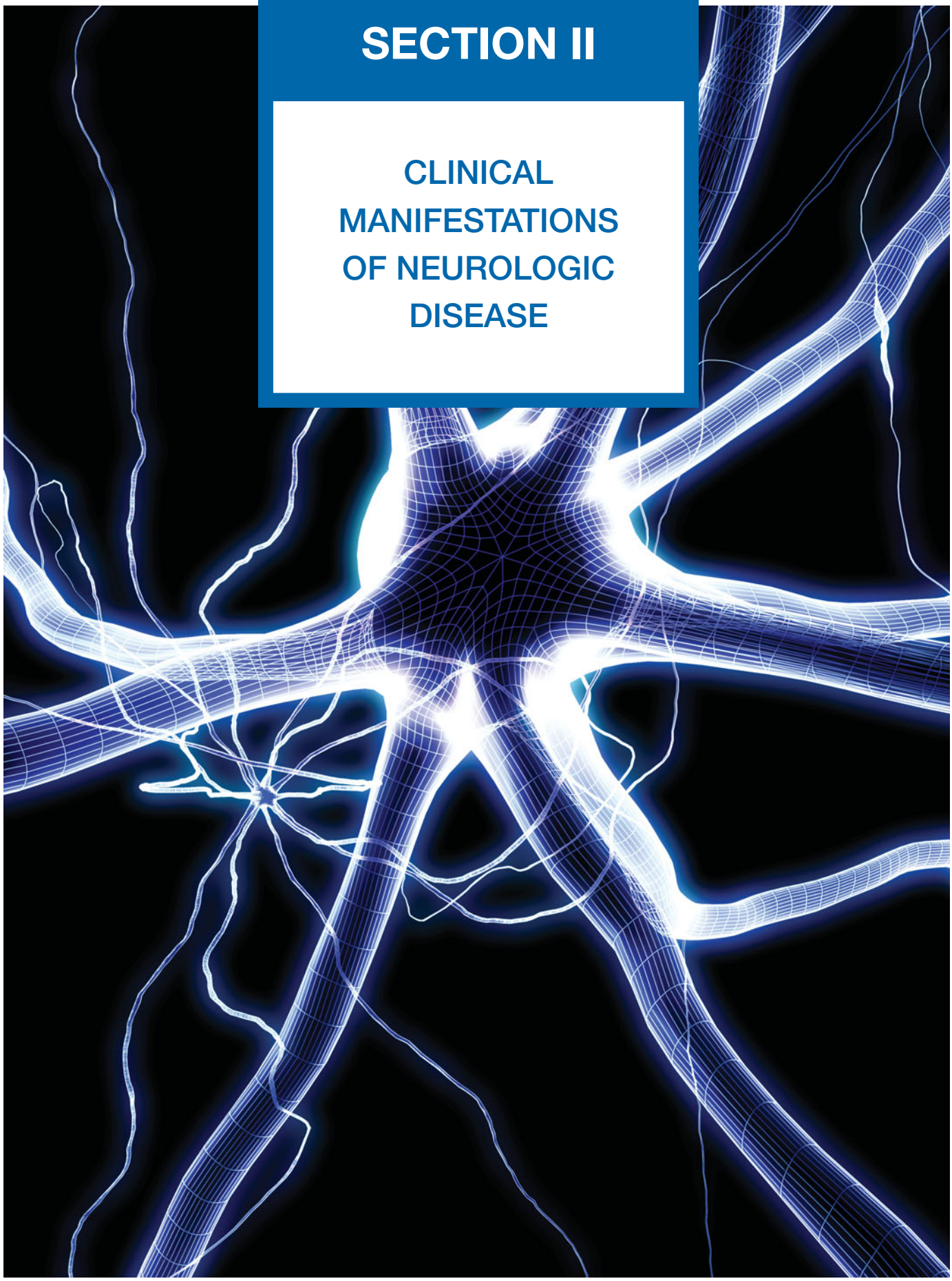
SECTION II

CLINICAL MANIFESTATIONS OF NEUROLOGIC DISEASE



CHAPTER 5

PAIN: PATHOPHYSIOLOGY AND MANAGEMENT

Howard L. Fields ■ Joseph B. Martin

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The task of medicine is to preserve and restore health and to relieve suffering. Understanding pain is essential to both these goals. Because pain is universally understood as a signal of disease, it is the most common symptom that brings a patient to a physician's attention. The function of the pain sensory system is to protect the body and maintain homeostasis. It does this by detecting, localizing, and identifying tissue-damaging processes. Since different diseases produce characteristic patterns of tissue damage, the quality, time course, and location of a patient's pain complaint and the location of tenderness provide important diagnostic clues and are used to evaluate the response to treatment. Once this information is obtained, it is the obligation of the physician to provide rapid and effective pain relief.

THE PAIN SENSORY SYSTEM

Pain is an unpleasant sensation localized to a part of the body. It is often described in terms of a penetrating or tissue-destructive process (e.g., stabbing, burning, twisting, tearing, squeezing) and/or of a bodily or emotional reaction (e.g., terrifying, nauseating, sickening). Furthermore, any pain of moderate or higher intensity is accompanied by anxiety and the urge to escape or terminate the feeling. These properties illustrate the duality of pain: it is both sensation and emotion. When acute, pain is characteristically associated with behavioral arousal and a stress response consisting of increased blood pressure, heart rate, pupil diameter, and plasma cortisol levels. In addition, local muscle contraction (e.g., limb flexion, abdominal wall rigidity) is often present.

PERIPHERAL MECHANISMS

The Primary Afferent Nociceptor

A peripheral nerve consists of the axons of three different types of neurons: primary sensory afferents, motor neurons, and sympathetic postganglionic neurons (**Fig. 5-1**). The cell bodies of primary sensory afferents are located in the dorsal root ganglia in the vertebral foramina. The primary afferent axon bifurcates to send one process into the spinal cord and the other to innervate tissues. Primary afferents are classified by their diameter, degree of myelination, and conduction velocity. The largest-diameter fibers, A-beta (Aβ), respond maximally to light touch and/or moving stimuli; they are present primarily in nerves that innervate the skin. In normal individuals, the activity of these fibers does not produce pain. There are two other classes of primary afferents: the small-diameter myelinated A-delta (Aδ) and the unmyelinated (C fiber) axons (Fig. 5-1). These fibers are present in nerves to the skin and to deep somatic and visceral structures. Some tissues, such as the cornea, are innervated only by Aδ and C afferents. Most Aδ and C afferents respond maximally only to intense (painful) stimuli and produce the subjective

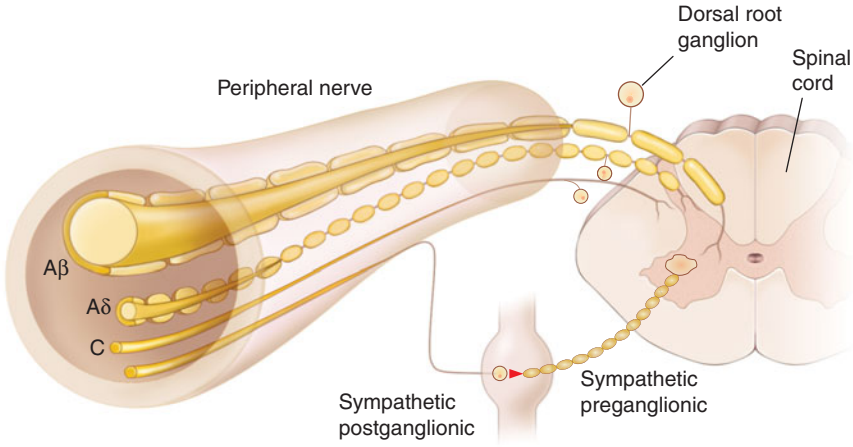

FIGURE 5-1

Components of a typical cutaneous nerve. There are two distinct functional categories of axons: primary afferents with cell bodies in the dorsal root ganglion, and sympathetic postganglionic fibers with cell bodies in the sympathetic ganglion. Primary afferents include those with large-diameter myelinated (Aβ), small-diameter myelinated (Aδ), and unmyelinated (C) axons. All sympathetic postganglionic fibers are unmyelinated.

experience of pain when they are electrically stimulated; this defines them as *primary afferent nociceptors (pain receptors*). The ability to detect painful stimuli is completely abolished when Aδ and C axons are blocked.

Individual primary afferent nociceptors can respond to several different types of noxious stimuli. For example, most nociceptors respond to heating, intense cold, intense mechanical stimuli such as a pinch, and application of irritating chemicals including ATP, serotonin, bradykinin and histamine.

Sensitization

When intense, repeated, or prolonged stimuli are applied to damaged or inflamed tissues, the threshold for activating primary afferent nociceptors is lowered and the frequency of firing is higher for all stimulus intensities. Inflammatory mediators such as bradykinin, nerve growth factor, some prostaglandins, and leukotrienes contribute to this process, which is called *sensitization*. In sensitized tissues, normally innocuous stimuli can produce pain. Sensitization is a clinically important process that contributes to tenderness, soreness, and hyperalgesia. A striking example of sensitization is sunburned skin, in which severe pain can be produced by a gentle slap on the back or a warm shower.

Sensitization is of particular importance for pain and tenderness in deep tissues. Viscera are normally relatively insensitive to noxious mechanical and thermal stimuli, although hollow viscera do generate significant discomfort when distended. In contrast, when affected by a disease process with an inflammatory component, deep structures such as joints or hollow viscera characteristically become exquisitely sensitive to mechanical stimulation.

A large proportion of Aδ and C afferents innervating viscera are completely insensitive in normal noninjured, noninflamed tissue. That is, they cannot be activated by known mechanical or thermal stimuli and are not spontaneously active. However, in the presence of inflammatory mediators, these afferents become sensitive to mechanical stimuli. Such afferents have been termed *silent nociceptors*, and their characteristic properties may explain how under pathologic conditions the relatively insensitive deep structures can become the source of severe and debilitating pain and tenderness. Low pH, prostaglandins, leukotrienes, and other inflammatory mediators such as bradykinin play a significant role in sensitization.

Nociceptor-Induced Inflammation

Primary afferent nociceptors also have a neuroeffector function. Most nociceptors contain polypeptide mediators that are released from their peripheral terminals when they are activated (Fig. 5-2). An example is substance P, an 11-amino-acid peptide. Substance P is released from primary afferent nociceptors and has multiple biologic activities. It is a potent vasodilator, degranulates mast cells, is a chemoattractant for leukocytes, and increases the production and release of inflammatory mediators. Interestingly, depletion of substance P from joints reduces the severity of experimental arthritis. Primary afferent nociceptors are not simply passive messengers of threats to tissue injury but also play an active role in tissue protection through these neuroeffector functions.

CENTRAL MECHANISMS

The Spinal Cord and Referred Pain

The axons of primary afferent nociceptors enter the spinal cord via the dorsal root. They terminate in the dorsal horn of the spinal gray matter (Fig. 5-3). The terminals of primary afferent axons contact spinal neurons that

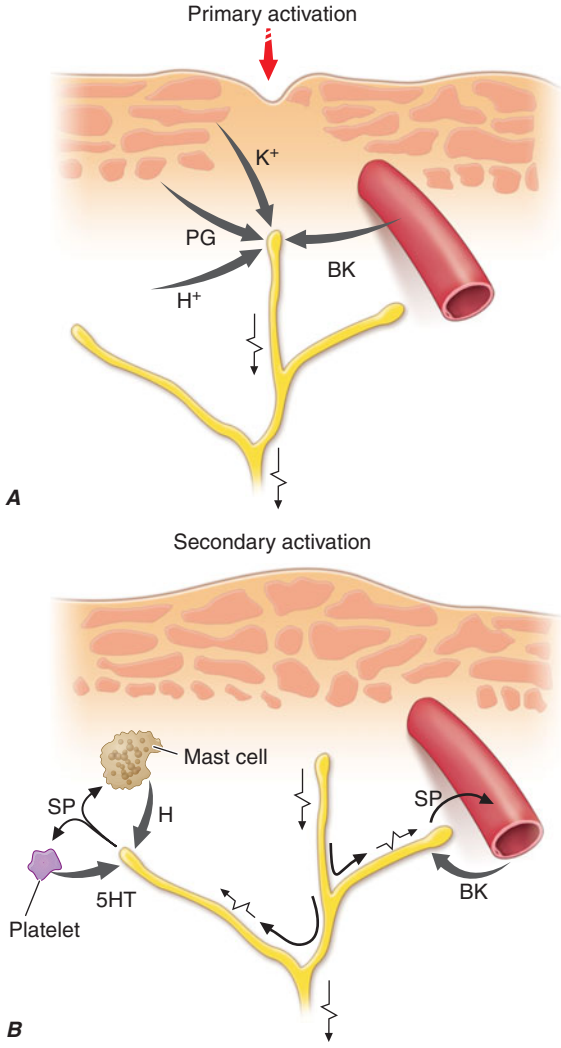

FIGURE 5-2

Events leading to activation, sensitization, and spread of sensitization of primary afferent nociceptor terminals. ***A***. Primary activation by intense pressure and consequent cell damage. Cell damage induces lower pH (H^+) and leads to release of potassium (K^+) and to synthesis of prostaglandins (PG) and bradykinin (BK). Prostaglandins increase the sensitivity of the terminal to bradykinin and other pain-producing substances. ***B***. Secondary activation. Impulses generated in the stimulated terminal propagate not only to the spinal cord but also into other terminal branches where they induce the release of peptides, including substance P (SP). Substance P causes vasodilation and neurogenic edema with further accumulation of bradykinin. Substance P also causes the release of histamine (H) from mast cells and serotonin (5HT) from platelets.

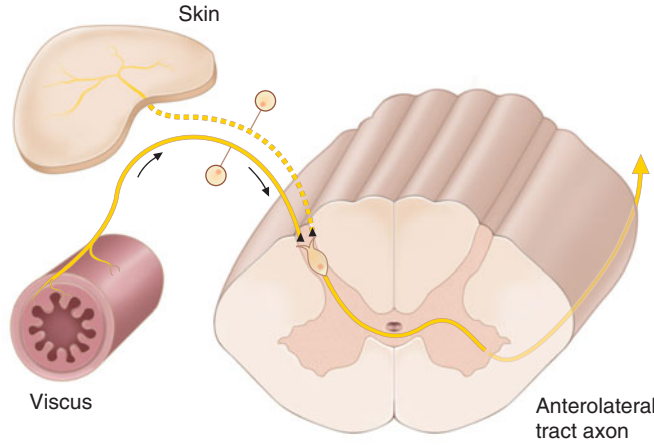

FIGURE 5-3

The convergence-projection hypothesis of referred pain. According to this hypothesis, visceral afferent nociceptors converge on the same pain-projection neurons as the afferents from the somatic structures in which the pain is perceived. The brain has no way of knowing the actual source of input and mistakenly "projects" the sensation to the somatic structure.

transmit the pain signal to brain sites involved in pain perception. When primary afferents are activated by noxious stimuli, they release neurotransmitters from their terminals that excite the spinal cord neurons. The major neurotransmitter they release is glutamate, which rapidly excites dorsal horn neurons. Primary afferent nociceptor terminals also release peptides, including substance P and calcitonin gene-related peptide, which produce a slower and longer-lasting excitation of the dorsal horn neurons. The axon of each primary afferent contacts many spinal neurons, and each spinal neuron receives convergent inputs from many primary afferents.

The convergence of sensory inputs to a single spinal pain-transmission neuron is of great importance because it underlies the phenomenon of referred pain. All spinal neurons that receive input from the viscera and deep musculoskeletal structures also receive input from the skin. The convergence patterns are determined by the spinal segment of the dorsal root ganglion that supplies the afferent innervation of a structure. For example, the afferents that supply the central diaphragm are derived from the third and fourth cervical dorsal root ganglia. Primary afferents with cell bodies in these same ganglia supply the skin of the shoulder and lower neck. Thus, sensory inputs from both the shoulder skin and the central diaphragm converge on pain-transmission neurons in the third and fourth cervical spinal segments. *Because of this convergence and the fact that the spinal neurons are most often activated by inputs from the skin, activity evoked in spinal neurons by input from deep structures is mislocalized by the patient to a place that is roughly coextensive with the region of skin innervated by the same spinal segment*. Thus, inflammation near the central diaphragm is usually reported as discomfort near the shoulder. This spatial displacement of pain sensation from the site of the injury that produces it is known as *referred pain*.

Ascending Pathways for Pain

A majority of spinal neurons contacted by primary afferent nociceptors send their axons to the contralateral

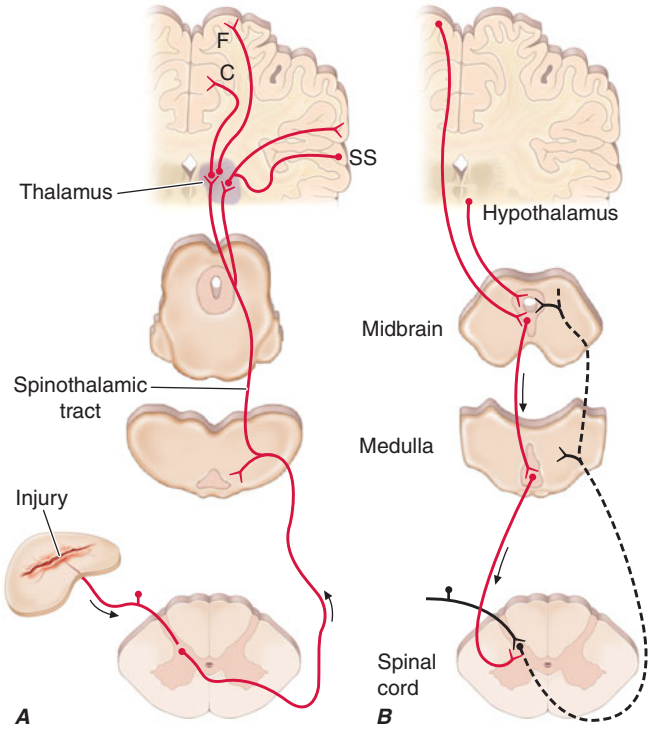

FIGURE 5-4

Pain transmission and modulatory pathways. ***A***. Transmission system for nociceptive messages. Noxious stimuli activate the sensitive peripheral ending of the primary afferent nociceptor by the process of transduction. The message is then transmitted over the peripheral nerve to the spinal cord, where it synapses with cells of origin of the major ascending pain pathway, the spinothalamic tract. The message is relayed in the thalamus to the anterior cingulate (C), frontal insular (F), and somatosensory cortex (SS). ***B***. Pain-modulation network. Inputs from frontal cortex and hypothalamus activate cells in the midbrain that control spinal pain-transmission cells via cells in the medulla.

thalamus. These axons form the contralateral spinothalamic tract, which lies in the anterolateral white matter of the spinal cord, the lateral edge of the medulla, and the lateral pons and midbrain. The spinothalamic pathway is crucial for pain sensation in humans. Interruption of this pathway produces permanent deficits in pain and temperature discrimination.

Spinothalamic tract axons ascend to several regions of the thalamus. There is tremendous divergence of the pain signal from these thalamic sites to broad areas of the cerebral cortex that subserve different aspects of the pain experience (Fig. 5-4). One of the thalamic projections is to the somatosensory cortex. This projection mediates the purely sensory aspects of pain, i.e., its location, intensity, and quality. Other thalamic neurons project to cortical regions that are linked to emotional responses, such as the cingulate gyrus and other areas of the frontal lobes, including the insular cortex. These pathways to the frontal cortex subserve the affective or unpleasant emotional dimension of pain. This affective dimension of pain produces suffering and exerts potent control of behavior. Because of this dimension, fear is a constant companion of pain.

PAIN MODULATION

The pain produced by injuries of similar magnitude is remarkably variable in different situations and in different individuals. For example, athletes have been known to sustain serious fractures with only minor pain, and Beecher's classic World War II survey revealed that many soldiers in battle were unbothered by injuries that would have produced agonizing pain in civilian patients. Furthermore, even the suggestion of relief can have a significant analgesic effect (placebo). On the other hand, many patients find even minor injuries (such as venipuncture) frightening and unbearable, and the expectation of pain has been demonstrated to induce pain without a noxious stimulus.

The powerful effect of expectation and other psychological variables on the perceived intensity of pain implies the existence of brain circuits that can modulate the activity of the pain-transmission pathways. One of these circuits has links in the hypothalamus, midbrain, and medulla, and it selectively controls spinal pain-transmission neurons through a descending pathway (Fig. 5-4).

Human brain imaging studies have implicated this pain-modulating circuit in the pain-relieving effect of attention, suggestion, and opioid analgesic medications. Furthermore, each of the component structures of the pathway contains opioid receptors and is sensitive to the direct application of opioid drugs. In animals, lesions of the system reduce the analgesic effect of systemically administered opioids such as morphine. Along with the opioid receptor, the component nuclei of this pain-modulating circuit contain endogenous opioid peptides such as the enkephalins and β-endorphin.

The most reliable way to activate this endogenous opioid-mediated modulating system is by prolonged pain and/or fear. There is evidence that pain-relieving endogenous opioids are released following surgical procedures and in patients given a placebo for pain relief.

Pain-modulating circuits can enhance as well as suppress pain. Both pain-inhibiting and pain-facilitating neurons in the medulla project to and control spinal pain-transmission neurons. Since pain-transmission neurons can be activated by modulatory neurons, it is theoretically possible to generate a pain signal with no peripheral noxious stimulus. In fact, human functional imaging studies have demonstrated increased activity in this circuit during migraine headache. A central circuit that facilitates pain could account for the finding that pain can be induced by suggestion or enhanced by expectation, and it could provide a framework for understanding how psychological factors can contribute to chronic pain.

NEUROPATHIC PAIN

Lesions of the peripheral or central nervous pathways for pain typically result in a loss or impairment of pain sensation. Paradoxically, damage to or dysfunction of these pathways can produce pain. For example, damage to peripheral nerves, as occurs in diabetic neuropathy, or to primary afferents, as in herpes zoster, can result in pain that is referred to the body region innervated by the damaged nerves. Though rare, pain may also be produced by damage to the central nervous system, particularly the spinothalamic pathway or thalamus. Such neuropathic pains are often severe and are notoriously intractable to standard treatments for pain.

Neuropathic pains typically have an unusual burning, tingling, or electric shock–like quality and may be triggered by very light touch. These features are rare in other types of pain. On examination, a sensory deficit is characteristically present in the area of the patient's pain. Hyperpathia is also characteristic of neuropathic pain; patients often complain that the very lightest moving stimuli evoke exquisite pain (allodynia). In this regard it is of clinical interest that a topical preparation of 5% lidocaine in patch form is effective for patients with postherpetic neuralgia who have prominent allodynia.

A variety of mechanisms contribute to neuropathic pain. As with sensitized primary afferent nociceptors, damaged primary afferents, including nociceptors, become highly sensitive to mechanical stimulation and begin to generate impulses in the absence of stimulation. There is evidence that this increased sensitivity and spontaneous activity is due to an increased concentration of sodium channels. Damaged primary afferents may also develop sensitivity to norepinephrine. Interestingly, spinal cord pain-transmission neurons cut off from their normal input may also become spontaneously active. Thus, both central and peripheral nervous system hyperactivity contribute to neuropathic pain.

Sympathetically Maintained Pain

Patients with peripheral nerve injury can develop a severe burning pain (causalgia) in the region innervated by the nerve. The pain typically begins after a delay of hours to days or even weeks. The pain is accompanied by swelling of the extremity, periarticular osteoporosis, and arthritic changes in the distal joints. The pain is dramatically and immediately relieved by blocking the sympathetic innervation of the affected extremity. Damaged primary afferent nociceptors acquire adrenergic sensitivity and can be activated by stimulation of the sympathetic outflow. A similar syndrome called *reflex sympathetic dystrophy* can be produced without obvious nerve damage by a variety of injuries, including fractures of bone, soft tissue trauma, myocardial infarction, and stroke. Although the pathophysiology of this condition is poorly understood, the pain and the signs of inflammation are rapidly relieved by blocking the sympathetic nervous system. This implies that sympathetic activity can activate undamaged nociceptors when inflammation is present. Signs of sympathetic hyperactivity should be sought in patients with posttraumatic pain and inflammation and no other obvious explanation.

℞ Treatment : ACUTE PAIN

The ideal treatment for any pain is to remove the cause; thus, diagnosis should always precede treatment planning. Sometimes treating the underlying condition does not immediately relieve pain. Furthermore, some conditions are so painful that rapid and effective analgesia is essential (e.g., the postoperative state, burns, trauma, cancer, sickle cell crisis). Analgesic medications are a first line of treatment in these cases, and all practitioners should be familiar with their use.

ASPIRIN, ACETAMINOPHEN, AND NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS) These drugs are considered together because they are used for similar problems and may have a similar mechanism of action (**Table 5-1**). All these compounds inhibit cyclooxygenase (COX), and, except for acetaminophen, all have anti-inflammatory actions, especially at higher dosages. They are particularly effective for mild to moderate headache and for pain of musculoskeletal origin.

Since they are effective for these common types of pain and are available without prescription, COX inhibitors are by far the most commonly used analgesics. They are absorbed well from the gastrointestinal tract and, with occasional use, have only minimal side effects. With chronic use, gastric irritation is a common side effect of aspirin and NSAIDs and is the problem that most frequently limits the dose that can be given. Gastric irritation is most severe with aspirin, which may cause erosion and ulceration of the gastric mucosa leading to bleeding or perforation. Because aspirin irreversibly acetylates platelets and thereby interferes with coagulation of the blood, gastrointestinal bleeding is a particular risk. Increased age and history of gastrointestinal disease increase the risks of aspirin and NSAIDs. In addition to NSAIDs' well-known gastrointestinal toxicity, nephrotoxicity is a significant problem for patients using them on a chronic basis, and patients at risk for renal insufficiency should be monitored closely. NSAIDs also cause an increase in blood pressure in a significant number of individuals. Long-term treatment with NSAIDs requires regular blood pressure monitoring and treatment if necessary. Although toxic to the liver when taken in a high dose, acetaminophen rarely produces gastric irritation and does not interfere with platelet function.

TABLE 5-1

DRUGS FOR RELIEF OF PAIN

GENERIC NAME	DOSE, mg	INTERVAL	COMMENTS
Nonnarcotic Analgesics: Usual Doses and Intervals			
Acetylsalicylic acid	650 PO	q 4 h	Enteric-coated preparations available
Acetaminophen	650 PO	q 4 h	Side effects uncommon
Ibuprofen	400 PO	q 4–6 h	Available without prescription
Naproxen	250–500 PO	q 12 h	Delayed effects may be due to long half-life
Fenoprofen	200 PO	q 4–6 h	Contraindicated in renal disease
Indomethacin	25–50 PO	q 8 h	Gastrointestinal side effects common
Ketorolac	15–60 IM/IV	q 4–6 h	Available for parenteral use
Celecoxib	100–200 PO	q 12–24 h	Useful for arthritis
Valdecoxib	10–20 PO	q 12–24 h	Removed from U.S. market in 2005

GENERIC NAME	PARENTERAL DOSE, mg	PO DOSE, mg	COMMENTS
Narcotic Analgesics: Usual Doses and Intervals			
Codeine	30–60 q 4 h	30–60 q 4 h	Nausea common
Oxycodone	—	5–10 q 4–6 h	Usually available with acetaminophen or aspirin
Morphine	10 q 4 h	60 q 4 h	
Morphine sustained release	—	30–200 bid to tid	Oral slow-release preparation
Hydromorphone	1–2 q 4 h	2–4 q 4 h	Shorter acting than morphine sulfate
Levorphanol	2 q 6–8 h	4 q 6–8 h	Longer acting than morphine sulfate; absorbed well PO
Methadone	10 q 6–8 h	20 q 6–8 h	Delayed sedation due to long half-life
Meperidine	75–100 q 3–4 h	300 q 4 h	Poorly absorbed PO; normeperidine a toxic metabolite
Butorphanol	—	1–2 q 4 h	Intranasal spray
Fentanyl	25–100 μg/h	—	72-h Transdermal patch
Tramadol	—	50–100 q 4–6 h	Mixed opioid/adrenergic action

GENERIC NAME	UPTAKE BLOCKADE 5-HT	UPTAKE BLOCKADE NE	SEDATIVE POTENCY	ANTICHOLINERGIC POTENCY	ORTHOSTATIC HYPOTENSION	CARDIAC ARRHYTHMIA	AVE. DOSE, mg/d	RANGE, mg/d
Antidepressants[a]								
Doxepin	++	+	High	Moderate	Moderate	Less	200	75–400
Amitriptyline	++++	++	High	Highest	Moderate	Yes	150	25–300
Imipramine	++++	++	Moderate	Moderate	High	Yes	200	75–400
Nortriptyline	+++	++	Moderate	Moderate	Low	Yes	100	40–150
Desipramine	+++	++++	Low	Low	Low	Yes	150	50–300
Venlafaxine	+++	++	Low	None	None	No	150	75–400
Duloxetine	+++	+++	Low	None	None	No	40	30–60

GENERIC NAME	PO DOSE, mg	INTERVAL	GENERIC NAME	PO DOSE, mg	INTERVAL
Anticonvulsants and Antiarrhythmics[a]					
Phenytoin	300	daily/qhs	Clonazepam	1	q 6 h
Carbamazepine	200–300	q 6 h	Gabapentin[b]	600–1200	q 8 h
Oxcarbazepine	300	bid	Pregabalin	150–600	bid

[a]Antidepressants, anticonvulsants, and antiarrhythmics have not been approved by the U.S. Food and Drug Administration (FDA) for the treatment of pain.
[b]Gabapentin in doses up to 1800 mg/d is FDA approved for postherpetic neuralgia.
Note: 5-HT, serotonin; NE, norepinephrine.

The introduction of a parenteral form of NSAID, ketorolac, extends the usefulness of this class of compounds in the management of acute severe pain. Ketorolac is sufficiently potent and rapid in onset to supplant opioids for many patients with acute severe headache and musculoskeletal pain.

There are two major classes of COX: COX-1 is constitutively expressed, and COX-2 is induced in the inflammatory state. COX-2–selective drugs have moderate analgesic potency and produce less gastric irritation than the nonselective COX inhibitors. It is not yet clear whether the use of COX-2–selective drugs is associated

with a lower risk of nephrotoxicity compared to nonselective NSAIDs. On the other hand, COX-2–selective drugs offer a significant benefit in the management of acute postoperative pain because they do not affect blood coagulation. This is a situation in which the nonselective COX inhibitors would be contraindicated because they impair platelet-mediated blood clotting and are thus associated with increased bleeding at the operative site. COX-2 inhibitors, including celecoxib (Celebrex), and valdecoxib (Bextra), are associated with increased cardiovascular risk. It is possible that this is a class effect of NSAIDs, excluding aspirin. These drugs are contraindicated in patients in the immediate period after coronary artery bypass surgery and should be used with caution in patients having a history of or significant risk factors for cardiovascular disease.

OPIOID ANALGESICS Opioids are the most potent pain-relieving drugs currently available. Furthermore, of all analgesics, they have the broadest range of efficacy, providing the most reliable and effective method for rapid pain relief. Although side effects are common, they are usually not serious except for respiratory depression and can be reversed rapidly with the narcotic antagonist naloxone. The physician should not hesitate to use opioid analgesics in patients with acute severe pain. Table 5-1 lists the most commonly used opioid analgesics.

Opioids produce analgesia by actions in the central nervous system. They activate pain-inhibitory neurons and directly inhibit pain-transmission neurons. Most of the commercially available opioid analgesics act at the same opioid receptor (μ-receptor), differing mainly in potency, speed of onset, duration of action, and optimal route of administration. Although the dose-related side effects (sedation, respiratory depression, pruritus, constipation) are similar among the different opioids, some side effects are due to accumulation of nonopioid metabolites that are unique to individual drugs. One striking example of this is normeperidine, a metabolite of meperidine. Normeperidine produces hyperexcitability and seizures that are not reversible with naloxone. Normeperidine accumulation is increased in patients with renal failure.

The most rapid relief with opioids is obtained by intravenous administration; relief with oral administration is significantly slower. Common side effects include nausea, vomiting, constipation, and sedation. The most serious side effect is respiratory depression. Patients with any form of respiratory compromise must be kept under close observation following opioid administration; an oxygen saturation monitor may be useful. The opioid antagonist naloxone should be readily available. Opioid effects are dose-related, and there is great variability among patients in the doses that relieve pain and produce side effects. Because of this, initiation of therapy requires titration to optimal dose and interval. The most important principle is to provide adequate pain relief. This requires determining whether the drug has adequately relieved the pain and the duration of the relief. *The most common error made by physicians in managing severe pain with opioids is to prescribe an inadequate dose. Since many patients are reluctant to complain, this practice leads to needless suffering.* In the absence of sedation at the expected time of peak effect, a physician should not hesitate to repeat the initial dose to achieve satisfactory pain relief.

An innovative approach to the problem of achieving adequate pain relief is the use of patient-controlled analgesia (PCA). PCA requires a device that can deliver a baseline continuous dose of an opioid drug, as well as preprogrammed additional doses whenever the patient pushes a button. The patient can then titrate the dose to the optimal level. This approach is used most extensively for the management of postoperative pain, but there is no reason why it should not be used for any hospitalized patient with persistent severe pain. PCA is also used for short-term home care of patients with intractable pain, such as that caused by metastatic cancer.

Because of patient variability in analgesia requirement, intravenous PCA is generally begun after the patient's pain has been controlled. The bolus dose of the drug (typically 1 mg morphine or 40 μg fentanyl) can then be delivered repeatedly as needed. To prevent overdosing, PCA devices are programmed with a lockout period after each demand dose is delivered (5–10 min) and a limit on the total dose delivered per hour. While some have advocated the use of a simultaneous background infusion of the PCA drug, this increases the risk of respiratory depression and has not been shown to increase the overall efficacy of the technique.

Many physicians, nurses, and patients have a certain trepidation about using opioids that is based on an exaggerated fear of addiction. In fact, there is a vanishingly small chance of patients becoming addicted to narcotics as a result of their appropriate medical use.

The availability of new routes of administration has extended the usefulness of opioid analgesics. Most important is the availability of spinal administration. Opioids can be infused through a spinal catheter placed either intrathecally or epidurally. By applying opioids directly to the spinal cord, regional analgesia can be obtained using a relatively low total dose. In this way, such side effects as sedation, nausea, and respiratory depression can be minimized. This approach has been used extensively in obstetric procedures and for lower-body postoperative pain. Opioids can also be given intranasally (butorphanol), rectally, and transdermally (fentanyl), thus avoiding the discomfort of frequent injections in patients who cannot be given oral medication.

The fentanyl transdermal patch has the advantage of providing fairly steady plasma levels, which maximizes patient comfort.

OPIOID AND COX INHIBITOR COMBINATIONS When used in combination, opioids and COX inhibitors have additive effects. Because a lower dose of each can be used to achieve the same degree of pain relief, and their side effects are nonadditive, such combinations can be used to lower the severity of dose-related side effects. Fixed-ratio combinations of an opioid with acetaminophen carry a special risk. Dose escalation as a result of increased severity of pain or decreased opioid effect as a result of tolerance may lead to levels of acetaminophen that are toxic to the liver.

CHRONIC PAIN

Managing patients with chronic pain is intellectually and emotionally challenging. The patient's problem is often difficult to diagnose; such patients are demanding of the physician's time and often appear emotionally distraught. The traditional medical approach of seeking an obscure organic pathology is usually unhelpful. On the other hand, psychological evaluation and behaviorally based treatment paradigms are frequently helpful, particularly in the setting of a multidisciplinary pain-management center.

There are several factors that can cause, perpetuate, or exacerbate chronic pain. First, of course, the patient may simply have a disease that is characteristically painful for which there is presently no cure. Arthritis, cancer, migraine headaches, fibromyalgia, and diabetic neuropathy are examples of this. Second, there may be secondary perpetuating factors that are initiated by disease and persist after that disease has resolved. Examples include damaged sensory nerves, sympathetic efferent activity, and painful reflex muscle contraction. Finally, a variety of psychological conditions can exacerbate or even cause pain.

There are certain areas to which special attention should be paid in the medical history. Because depression is the most common emotional disturbance in patients with chronic pain, patients should be questioned about their mood, appetite, sleep patterns, and daily activity. A simple standardized questionnaire, such as the Beck Depression Inventory, can be a useful screening device. It is important to remember that major depression is a common, treatable, and potentially fatal illness.

Other clues that a significant emotional disturbance is contributing to a patient's chronic pain complaint include: pain that occurs in multiple unrelated sites; a pattern of recurrent, but separate, pain problems beginning in childhood or adolescence; pain beginning at a time of emotional trauma, such as the loss of a parent or spouse; a history of physical or sexual abuse; and past or present substance abuse.

On examination, special attention should be paid to whether the patient guards the painful area and whether certain movements or postures are avoided because of pain. Discovering a mechanical component to the pain can be useful both diagnostically and therapeutically. Painful areas should be examined for deep tenderness, noting whether this is localized to muscle, ligamentous structures, or joints. Chronic myofascial pain is very common, and in these patients deep palpation may reveal highly localized trigger points that are firm bands or knots in muscle. Relief of the pain following injection of local anesthetic into these trigger points supports the diagnosis. A neuropathic component to the pain is indicated by evidence of nerve damage, such as sensory impairment, exquisitely sensitive skin, weakness and muscle atrophy, or loss of deep tendon reflexes. Evidence suggesting sympathetic nervous system involvement includes the presence of diffuse swelling, changes in skin color and temperature, and hypersensitive skin and joint tenderness compared with the normal side. Relief of the pain with a sympathetic block is diagnostic.

A guiding principle in evaluating patients with chronic pain is to assess both emotional and organic factors before initiating therapy. Addressing these issues together, rather than waiting to address emotional issues after organic causes of pain have been ruled out, improves compliance in part because it assures patients that a psychological evaluation does not mean that the physician is questioning the validity of their complaint. Even when an organic cause for a patient's pain can be found, it is still wise to look for other factors. For example, a cancer patient with painful bony metastases may have additional pain due to nerve damage and may also be depressed. Optimal therapy requires that each of these factors be looked for and treated.

Rx Treatment: CHRONIC PAIN

Once the evaluation process has been completed and the likely causative and exacerbating factors identified, an explicit treatment plan should be developed. An important part of this process is to identify specific and realistic functional goals for therapy, such as getting a good night's sleep, being able to go shopping, or returning to work. A multidisciplinary approach that utilizes medications, counseling, physical therapy, nerve blocks, and even surgery may be required to improve the patient's quality of life. There are also some newer, relatively invasive procedures that can be helpful for some patients with intractable pain. These procedures include implanting intraspinal cannulae to deliver morphine or intraspinal electrodes for spinal stimulation. There are no set criteria for predicting which patients will respond

to these procedures. They are generally reserved for patients who have not responded to conventional pharmacologic approaches. Referral to a multidisciplinary pain clinic for a full evaluation should precede any invasive procedures. Such referrals are clearly not necessary for all chronic pain patients. For some, pharmacologic management alone can provide adequate relief.

ANTIDEPRESSANT MEDICATIONS The tricyclic anti- depressants [amitriptyline, imipramine, nortriptyline, desipramine (TCAs; Table 5-1)] are extremely useful for the management of patients with chronic pain. Although developed for the treatment of depression, the tricyclics have a spectrum of dose-related biologic activities that include the production of analgesia in a variety of clinical conditions. Although the mechanism is unknown, the analgesic effect of TCAs has a more rapid onset and occurs at a lower dose than is typically required for the treatment of depression. Furthermore, patients with chronic pain who are not depressed obtain pain relief with antidepressants. There is evidence that tricyclic drugs potentiate opioid analgesia, so they may be useful adjuncts for the treatment of severe persistent pain such as occurs with malignant tumors. **Table 5-2** lists some of the painful conditions that respond to tricyclics. TCAs are of particular value in the management of neuropathic pain such as occurs in diabetic neuropathy and postherpetic neuralgia, for which there are few other therapeutic options.

The TCAs that have been shown to relieve pain have significant side effects (Table 5-1; Chap. 49). Some of these side effects, such as orthostatic hypotension, drowsiness, cardiac conduction delay, memory impairment, constipation, and urinary retention, are particularly problematic in elderly patients, and several are additive to the side effects of opioid analgesics. The serotonin-selective reuptake inhibitors such as fluoxetine (Prozac) have fewer and less serious side effects than TCAs, but they are much less effective for relieving pain. It is of interest that venlafaxine (Effexor) and duloxetine (Cymbalta), which are nontricyclic antidepressants that block both serotonin and norepinephrine reuptake, appear to retain most of the pain-relieving effect of TCAs with a side-effect profile more like that of the serotonin-selective reuptake inhibitors. These drugs may be particularly useful in patients who cannot tolerate the side effects of tricyclics.

TABLE 5-2

PAINFUL CONDITIONS THAT RESPOND TO TRICYCLIC ANTIDEPRESSANTS
Postherpetic neuralgia[a]
Diabetic neuropathy[a]
Tension headache[a]
Migraine headache[a]
Rheumatoid arthritis[a,b]
Chronic low back pain[b]
Cancer
Central post-stroke pain

[a]Controlled trials demonstrate analgesia.
[b]Controlled studies indicate benefit but not analgesia.

ANTICONVULSANTS AND ANTIARRHYTHMICS These drugs are useful primarily for patients with neuropathic pain. Phenytoin (Dilantin) and carbamazepine (Tegretol) were first shown to relieve the pain of trigeminal neuralgia. This pain has a characteristic brief, shooting, electric shock–like quality. In fact, anticonvulsants seem to be helpful largely for pains that have such a lancinating quality. Newer anticonvulsants, gabapentin (Neurontin) and pregabalin (Lyrica), are effective for a broad range of neuropathic pains.

Antiarrhythmic drugs such as low-dose lidocaine and mexiletine (Mexitil) can also be effective for neuropathic pain. These drugs block the spontaneous activity of damaged primary afferent nociceptors.

CHRONIC OPIOID MEDICATION The long-term use of opioids is accepted for patients with pain due to malignant disease. Although opioid use for chronic pain of nonmalignant origin is controversial, it is clear that for many such patients opioid analgesics are the best available option. This is understandable since opioids are the most potent and have the broadest range of efficacy of any analgesic medications. Although addiction is rare in patients who first use opioids for pain relief, some degree of tolerance and physical dependence are likely with long-term use. Therefore, before embarking on opioid therapy, other options should be explored, and the limitations and risks of opioids should be explained to the patient. It is also important to point out that some opioid analgesic medications have mixed agonist-antagonist properties (e.g., pentazocine and butorphanol). From a practical standpoint, this means that they may worsen pain by inducing an abstinence syndrome in patients who are physically dependent on other opioid analgesics.

With long-term outpatient use of orally administered opioids, it is desirable to use long-acting compounds such as levorphanol, methadone, or sustained-release morphine (Table 5-1). Transdermal fentanyl is another excellent option. The pharmacokinetic profile of these drug preparations enables prolonged pain relief, minimizes side effects such as sedation that are associated with high peak plasma levels, and reduces the likelihood of rebound pain associated with a rapid fall in plasma opioid concentration. Constipation is a virtually universal side effect of opioid use and should be treated expectantly.

TREATMENT OF NEUROPATHIC PAIN It is important to individualize treatment for patients with

neuropathic pain. Several general principles should guide therapy: the first is to move quickly to provide relief; a second is to minimize drug side effects. For example, in patients with postherpetic neuralgia and significant cutaneous hypersensitivity, topical lidocaine (Lidoderm patches) can provide immediate relief without side effects. Anticonvulsants (gabapentin or pregabalin, see earlier) or antidepressants can be used as first-line drugs for patients with neuropathic pain. Antiarrhythmic drugs such as lidocaine and mexiletene can be effective (see earlier). There is no consensus on which class of drug should be used as a first-line treatment for any chronically painful condition. However, because relatively high doses of anticonvulsants are required for pain relief, sedation is very common. Sedation is also a problem with the tricyclic antidepressants but is much less of a problem with serotonin/norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine and duloxetine). Thus, in the elderly or in those patients whose daily activities require high-level mental activity, these drugs should be considered as the first line. In contrast, opioid medications should be used as a second- or third-line drug class. While highly effective for many painful conditions, opioids are sedating, and their effect tends to lessen over time, leading to dose escalation and, occasionally, a worsening of pain due to physical dependence. Drugs of different classes can be used in combination to optimize pain control.

It is worth emphasizing that many patients, especially those with chronic pain, seek medical attention primarily because they are suffering and because only physicians can provide the medications required for pain relief. A primary responsibility of all physicians is to minimize the physical and emotional discomfort of their patients. Familiarity with pain mechanisms and analgesic medications is an important step toward accomplishing this aim.

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CHAPTER 6

HEADACHE

Peter J. Goadsby ■ Neil H. Raskin

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Headache is among the most common reasons that patients seek medical attention. Diagnosis and management is based on a careful clinical approach that is augmented by an understanding of the anatomy, physiology, and pharmacology of the nervous system pathways that mediate the various headache syndromes.

GENERAL PRINCIPLES

A classification system developed by the International Headache Society characterizes headache as primary or secondary (**Table 6–1**). *Primary headaches* are those in which headache and its associated features are the disorder in itself, whereas *secondary headaches* are those caused by exogenous disorders. Primary headache often results in considerable disability and a decrease in the patient's quality of life. Mild secondary headache, such as that seen in association with upper respiratory tract infections, is common but rarely worrisome. Life-threatening headache is relatively uncommon, but vigilance is required in order to recognize and appropriately treat patients with this category of head pain.

ANATOMY AND PHYSIOLOGY OF HEADACHE

Pain usually occurs when peripheral nociceptors are stimulated in response to tissue injury, visceral distension, or other factors (Chap. 5). In such situations, pain perception is a normal physiologic response mediated by a healthy nervous system. Pain can also result when pain-producing pathways of the peripheral or central nervous system (CNS) are damaged or activated inappropriately. Headache may originate from either or both mechanisms. Relatively few cranial structures are pain-producing; these include the scalp, middle meningeal artery, dural sinuses, falx cerebri, and proximal segments of the large pial arteries. The ventricular ependyma, choroid plexus, pial veins, and much of the brain parenchyma are not pain-producing.

The key structures involved in primary headache appear to be

- the large intracranial vessels and dura mater
- the peripheral terminals of the trigeminal nerve that innervate these structures
- the caudal portion of the trigeminal nucleus, which extends into the dorsal horns of the upper cervical spinal cord and receives input from the first and second cervical nerve roots (the trigeminocervical complex)
- the pain modulatory systems in the brain that receive input from trigeminal nociceptors

The innervation of the large intracranial vessels and dura mater by the trigeminal nerve is known as the *trigeminovascular system*. Autonomic symptoms, such as *lacrimation*

TABLE 6-1

COMMON CAUSES OF HEADACHE

PRIMARY HEADACHE		SECONDARY HEADACHE	
TYPE	**%**	**TYPE**	**%**
Migraine	16	Systemic infection	63
Tension-type	69	Head injury	4
Cluster	0.1	Vascular disorders	1
Idiopathic stabbing	2	Subarachnoid hemorrhage	<1
Exertional	1	Brain tumor	0.1

Source: After J Olesen et al: *The Headaches*. Philadelphia, Lippincott, Williams & Wilkins, 2005.

and nasal congestion, are prominent in the trigeminal autonomic cephalalgias, including cluster headache and paroxysmal hemicrania, and may also be seen in migraine. These autonomic symptoms reflect activation of cranial parasympathetic pathways, and functional imaging studies indicate that vascular changes in migraine and cluster headache, when present, are similarly driven by these cranial autonomic systems. Migraine and other primary headache types are not "vascular headaches"; these disorders do not reliably manifest vascular changes, and treatment outcomes cannot be predicted by vascular effects.

CLINICAL EVALUATION OF ACUTE, NEW-ONSET HEADACHE

The patient who presents with a new, severe headache has a differential diagnosis that is quite different from the patient with recurrent headaches over many years. In new-onset and severe headache, the probability of finding a potentially serious cause is considerably greater than in recurrent headache. Patients with recent onset of pain require prompt evaluation and often treatment. Serious causes to be considered include meningitis, subarachnoid hemorrhage, epidural or subdural hematoma, glaucoma, and purulent sinusitis. When worrisome symptoms and signs are present (Table 6-2), rapid diagnosis and management is critical.

A complete neurologic examination is an essential first step in the evaluation. In most cases, patients with an abnormal examination or a history of recent-onset headache should be evaluated by a CT or MRI study. As an initial screening procedure for intracranial pathology in this setting, CT and MRI methods appear to be equally sensitive. In some circumstances a lumbar puncture (LP) is also required, unless a benign etiology can be otherwise established. A general evaluation of acute headache might include the investigation of cardiovascular and renal status by blood pressure monitoring and urine examination; eyes by fundoscopy, intraocular pressure measurement, and refraction; cranial arteries by palpation; and cervical spine by the effect of passive movement of the head and by imaging.

TABLE 6-2

HEADACHE SYMPTOMS THAT SUGGEST A SERIOUS UNDERLYING DISORDER

"Worst" headache ever
First severe headache
Subacute worsening over days or weeks
Abnormal neurologic examination
Fever or unexplained systemic signs
Vomiting that precedes headache
Pain induced by bending, lifting, cough
Pain that disturbs sleep or presents immediately upon awakening
Known systemic illness
Onset after age 55
Pain associated with local tenderness, e.g., region of temporal artery

The psychological state of the patient should also be evaluated since a relationship exists between head pain and depression. Many patients in chronic daily pain cycles become depressed, although depression itself is rarely a cause of headache. Drugs with antidepressant actions are also effective in the prophylactic treatment of both tension-type headache and migraine.

Underlying recurrent headache disorders may be activated by pain that follows otologic or endodontic surgical procedures. Thus, pain about the head as the result of diseased tissue or trauma may reawaken an otherwise quiescent migrainous syndrome. Treatment of the headache is largely ineffective until the cause of the primary problem is addressed.

Serious underlying conditions that are associated with headache are described below. Brain tumor is a rare cause of headache and even less commonly a cause of severe pain. The vast majority of patients presenting with severe headache have a benign cause.

SECONDARY HEADACHE

The management of secondary headache focuses on diagnosis and treatment of the underlying condition.

MENINGITIS

Acute, severe headache with stiff neck and fever suggests meningitis. LP is mandatory. Often there is striking accentuation of pain with eye movement. Meningitis can be easily mistaken for migraine in that the cardinal symptoms of pounding headache, photophobia, nausea, and vomiting are present. Meningitis is discussed in Chaps. 35 and 36.

INTRACRANIAL HEMORRHAGE

Acute, severe headache with stiff neck but without fever suggests subarachnoid hemorrhage. A ruptured aneurysm,

arteriovenous malformation, or intraparenchymal hemorrhage may also present with headache alone. Rarely, if the hemorrhage is small or below the foramen magnum, the head CT scan can be normal. Therefore, LP may be required to definitively diagnose subarachnoid hemorrhage. Intraparenchymal hemorrhage is discussed in Chap. 21 and subarachnoid hemorrhage in Chap. 22.

BRAIN TUMOR

Approximately 30% of patients with brain tumors consider headache to be their chief complaint. The head pain is usually nondescript—an intermittent deep, dull aching of moderate intensity, which may worsen with exertion or change in position and may be associated with nausea and vomiting. This pattern of symptoms results from migraine far more often than from brain tumor. The headache of brain tumor disturbs sleep in about 10% of patients. Vomiting that precedes the appearance of headache by weeks is highly characteristic of posterior fossa brain tumors. A history of amenorrhea or galactorrhea should lead one to question whether a prolactin-secreting pituitary adenoma (or the polycystic ovary syndrome) is the source of headache. Headache arising de novo in a patient with known malignancy suggests either cerebral metastases or carcinomatous meningitis, or both. Head pain appearing abruptly after bending, lifting, or coughing can be due to a posterior fossa mass (or a Chiari malformation). Brain tumors are discussed in Chap. 32.

TEMPORAL ARTERITIS

Temporal (giant cell) arteritis is an inflammatory disorder of arteries that frequently involves the extracranial carotid circulation. It is a common disorder of the elderly; its annual incidence is 77 per 100,000 individuals aged 50 years and older. The average age of onset is 70 years, and women account for 65% of cases. About half of patients with untreated temporal arteritis develop blindness due to involvement of the ophthalmic artery and its branches; indeed, the ischemic optic neuropathy induced by giant cell arteritis is the major cause of rapidly developing bilateral blindness in patients >60 years. Because treatment with glucocorticoids is effective in preventing this complication, prompt recognition of the disorder is important.

Typical presenting symptoms include headache, polymyalgia rheumatica, jaw claudication, fever, and weight loss. Headache is the dominant symptom and often appears in association with malaise and muscle aches. Head pain may be unilateral or bilateral and is located temporally in 50% of patients but may involve any and all aspects of the cranium. Pain usually appears gradually over a few hours before peak intensity is reached; occasionally, it is explosive in onset. The quality of pain is only seldom throbbing; it is almost invariably described as dull and boring, with superimposed episodic stabbing pains similar to the sharp pains that appear in migraine. Most patients can recognize that the origin of their head pain is superficial, external to the skull, rather than originating deep within the cranium (the pain site for migraineurs). Scalp tenderness is present, often to a marked degree; brushing the hair or resting the head on a pillow may be impossible because of pain. Headache is usually worse at night and often aggravated by exposure to cold. Additional findings may include reddened, tender nodules or red streaking of the skin overlying the temporal arteries, and tenderness of the temporal or, less commonly, the occipital arteries.

The erythrocyte sedimentation rate (ESR) is often, though not always, elevated; a normal ESR does not exclude giant cell arteritis. A temporal artery biopsy followed by treatment with prednisone 80 mg daily for the first 4–6 weeks should be initiated when clinical suspicion is high. The prevalence of migraine among the elderly is substantial, considerably higher than that of giant cell arteritis. Migraineurs often report amelioration of their headaches with prednisone; thus, caution must be used when interpreting the therapeutic response.

GLAUCOMA

Glaucoma may present with a prostrating headache associated with nausea and vomiting. The headache often starts with severe eye pain. On physical examination, the eye is often red with a fixed, moderately dilated pupil. Glaucoma is discussed in Chap. 17.

PRIMARY HEADACHE SYNDROMES

Primary headaches are disorders in which headache and associated features occur in the absence of any exogenous cause (Table 6-1). The most common are migraine, tension-type headache, and cluster headache.

MIGRAINE HEADACHE

Migraine, the second most common cause of headache, afflicts approximately 15% of women and 6% of men. It is usually an episodic headache that is associated with certain features such as sensitivity to light, sound, or movement; nausea and vomiting often accompany the headache. A useful description of migraine is a benign and recurring syndrome of headache associated with other symptoms of neurologic dysfunction in varying admixtures (**Table 6-3**). Migraine can often be recognized by its activators, referred to as *triggers*.

The brain of the migraineur is particularly sensitive to environmental and sensory stimuli; migraine-prone patients do not habituate easily to sensory stimuli. This sensitivity is amplified in females during the menstrual cycle. Headache can be initiated or amplified by various triggers, including glare, bright lights, sounds, or other afferent stimulation; hunger; excess stress; physical

TABLE 6-3

SYMPTOMS ACCOMPANYING SEVERE MIGRAINE ATTACKS IN 500 PATIENTS

SYMPTOM	PATIENTS AFFECTED, %
Nausea	87
Photophobia	82
Lightheadedness	72
Scalp tenderness	65
Vomiting	56
Visual disturbances	36
Photopsia	26
Fortification spectra	10
Paresthesias	33
Vertigo	33
Alteration of consciousness	18
Syncope	10
Seizure	4
Confusional state	4
Diarrhea	16

Source: From NH *Raskin, Headache,* 2d ed. New York, Churchill Livingston, 1988; with permission.

exertion; stormy weather or barometric pressure changes; hormonal fluctuations during menses; lack of or excess sleep; and alcohol or other chemical stimulation. Knowledge of a patient's susceptibility to specific triggers can be useful in management strategies involving lifestyle adjustments.

Pathogenesis

The sensory sensitivity that is characteristic of migraine is probably due to dysfunction of monoaminergic sensory control systems located in the brainstem and thalamus (Fig. 6-1).

Activation of cells in the trigeminal nucleus results in the release of vasoactive neuropeptides, particularly calcitonin gene-related peptide (CGRP), at vascular terminations of the trigeminal nerve. Recently, antagonists of CGRP have shown some early promise in the therapy of migraine. Centrally, the second-order trigeminal neurons cross the midline and project to ventrobasal and posterior nuclei of the thalamus for further processing. Additionally, there are projections to the periaqueductal gray and hypothalamus, from which reciprocal descending systems have established anti-nociceptive effects. Other brainstem regions likely to be involved in descending modulation of trigeminal pain include the nucleus locus coeruleus in the pons and the rostroventromedial medulla.

Pharmacologic and other data point to the involvement of the neurotransmitter 5-hydroxytryptamine (5-HT; also known as serotonin) in migraine. Approximately 50 years ago, methysergide was found to antagonize certain peripheral

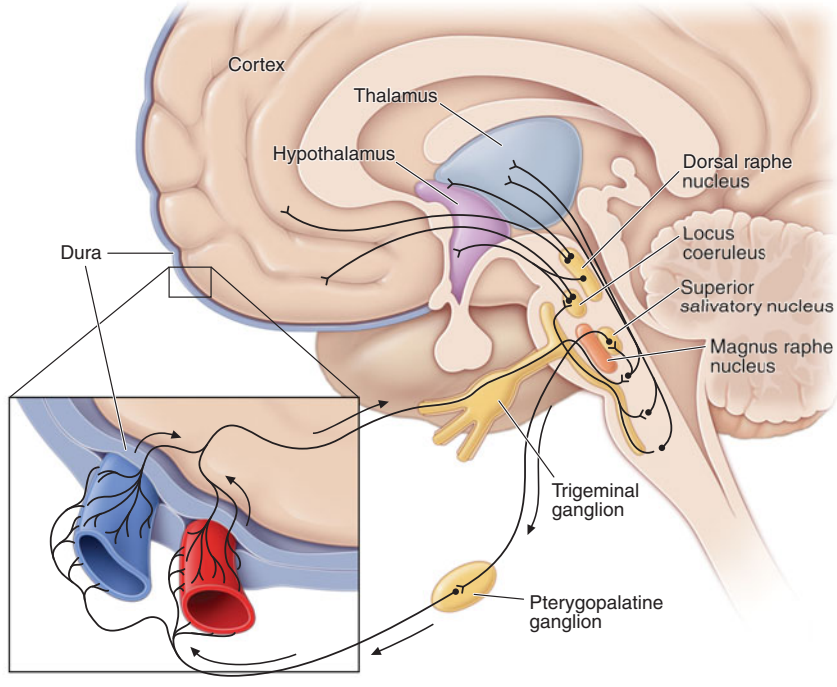

FIGURE 6-1

Brainstem pathways that modulate sensory input. The key pathway for pain in migraine is the trigeminovascular input from the meningeal vessels, which passes through the trigeminal ganglion and synapses on second-order neurons in the trigeminocervical complex. These neurons in turn project in the quintothalamic tract and, after decussating in the brainstem, synapse on neurons in the thalamus. Important modulation of the trigeminovascular nociceptive input comes from the dorsal raphe nucleus, locus coeruleus, and nucleus raphe magnus.

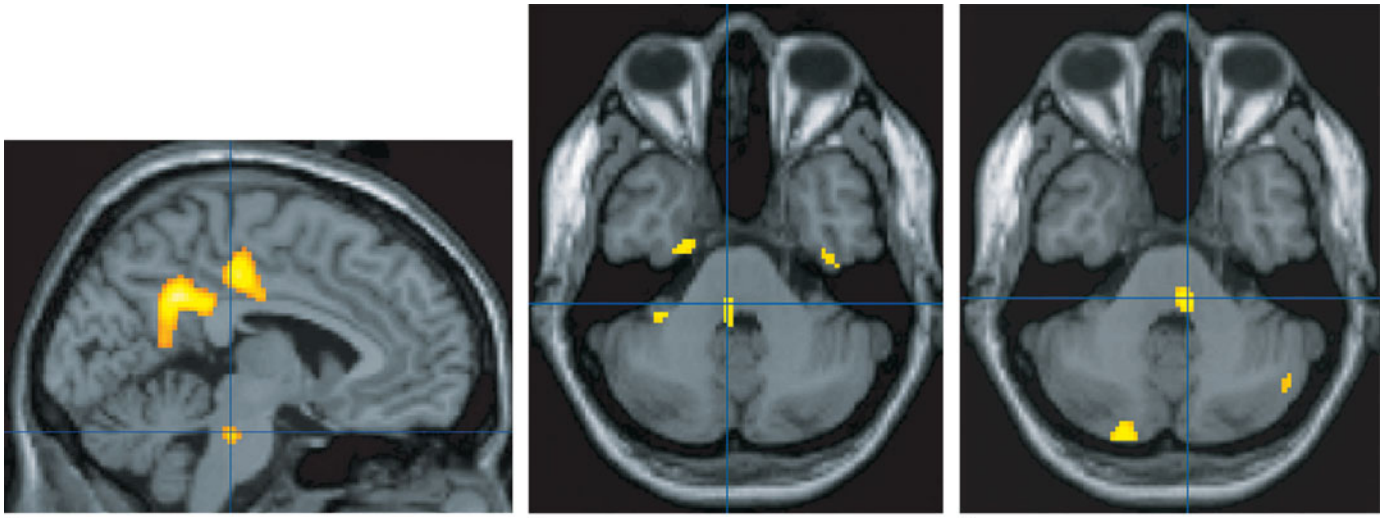

FIGURE 6-2

Positron emission tomography (PET) activation in migraine. In spontaneous attacks of episodic migraine (***A***) there is activation of the region of the dorsolateral pons (intersection of dark blue lines); an identical pattern is found in chronic migraine (not shown). This area, which includes the noradrenergic locus coeruleus, is fundamental to the expression of migraine. Moreover, lateralization of changes in this region of the brainstem correlates with lateralization of the head pain in hemicranial migraine; the scans shown in panels ***B*** and ***C*** are of patients with acute migraine headache on the right and left side, respectively. (*From S Afridi et al: Arch Neurol 62:1270, 2005; Brain 128:932, 2005.*)

actions of 5-HT and was introduced as the first drug capable of preventing migraine attacks. The triptans are designed to selectively stimulate subpopulations of 5-HT receptors; at least 14 different 5-HT receptors exist in humans. The triptans are potent agonists of 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors and are less potent at the 5-HT_{1A} receptor. A growing body of data indicates that the antimigraine efficacy of the triptans relates to their ability to stimulate 5-$HT_{1B/1D}$ receptors, which are located on both blood vessels and nerve terminals.

Data also support a role for dopamine in the pathophysiology of certain subtypes of migraine. Most migraine symptoms can be induced by dopaminergic stimulation. Moreover, there is dopamine receptor hypersensitivity in migraineurs, as demonstrated by the induction of yawning, nausea, vomiting, hypotension, and other symptoms of a migraine attack by dopaminergic agonists at doses that do not affect nonmigraineurs. Dopamine receptor antagonists are effective therapeutic agents in migraine, especially when given parenterally or concurrently with other antimigraine agents.

Migraine genes identified by studying families with familial hemiplegic migraine (FHM) reveal involvement of ion channels, suggesting that alterations in membrane excitability can predispose to migraine. Mutations involving the $Ca_v2.1$ (P/Q) type voltage-gated calcium channel *CACNA1A* gene are now known to cause FHM 1; this mutation is responsible for about 50% of FHM. Mutations in the Na^+-K^+ATPase *ATP1A2* gene, designated FHM 2, are responsible for about 20% of FHM. Mutations in the neuronal voltage-gated sodium channel *SCN1A* cause FHM 3. Functional neuroimaging has suggested that brainstem regions in migraine (**Fig. 6-2**) and the posterior hypothalamic gray matter region close to the human circadian pacemaker cells of the suprachiasmatic nucleus in cluster headache (**Fig. 6-3**) are good candidates for specific involvement in primary headache.

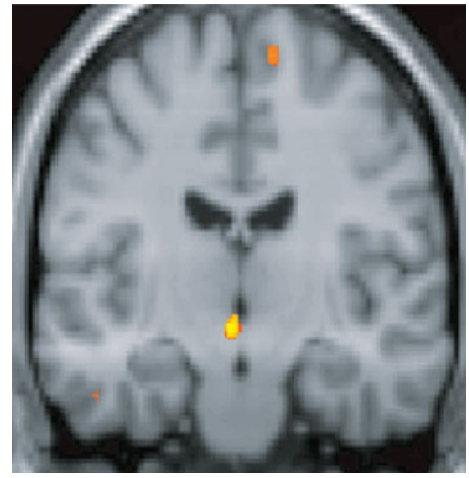

FIGURE 6-3

Posterior hypothalamic gray matter activation on positron emission tomography (PET) in a patient with acute cluster headache. (*From A May et al: Lancet 352:275, 1998.*)

TABLE 6-4

SIMPLIFIED DIAGNOSTIC CRITERIA FOR MIGRAINE

Repeated attacks of headache lasting 4–72 h in patients with a normal physical examination, no other reasonable cause for the headache, and:

At least 2 of the following features:	**Plus at least 1 of the following features:**
Unilateral pain	Nausea/vomiting
Throbbing pain	Photophobia and phonophobia
Aggravation by movement	
Moderate or severe intensity	

Source: Adapted from the International Headache Society Classification (Headache Classification Committee of the International Headache Society, 2004).

Diagnosis and Clinical Features

Diagnostic criteria for migraine headache are listed in Table 6-4. A high index of suspicion is required to diagnose migraine: the migraine aura, consisting of visual disturbances with flashing lights or zigzag lines moving across the visual field or of other neurologic symptoms, is reported in only 20–25% of patients. A headache diary can often be helpful in making the diagnosis; this is also helpful in assessing disability and the frequency of treatment for acute attacks. Patients with episodes of migraine that occur daily or near-daily are considered to have chronic migraine (see Chronic Daily Headache, below). Migraine must be differentiated from tension-type headache (discussed below), the most common primary headache syndrome seen in clinical practice. *Migraine at its most basic level is headache with associated features, and tension-type headache is headache that is featureless. Most patients with disabling headache probably have migraine.*

Patients with acephalgic migraine experience recurrent neurologic symptoms, often with nausea or vomiting, but with little or no headache. Vertigo can be prominent; it has been estimated that one-third of patients referred for vertigo or dizziness have a primary diagnosis of migraine.

℞ Treatment: MIGRAINE HEADACHES

Once a diagnosis of migraine has been established, it is important to assess the extent of a patient's disease and disability. The Migraine Disability Assessment Score (MIDAS) is a well-validated, easy-to-use tool (Fig. 6-4).

Patient education is an important aspect of migraine management. Information for patients is available at *www.achenet.org*, the website of the American Council for Headache Education (ACHE). It is helpful for patients to understand that migraine is an inherited tendency to headache; that migraine can be modified and controlled by lifestyle adjustments and medications, but it cannot be eradicated; and that, except in some occasions

***MIDAS Questionnaire**

INSTRUCTIONS: Please answer the following questions about ALL headaches you have had over the last 3 months. Write zero if you did not do the activity in the last 3 months.

1. On how many days in the last 3 months did you miss work or school because of your headaches? ..... ____ days
2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches *(do not include days you counted in question 1 where you missed work or school)*? ..... ____ days
3. On how many days in the last 3 months did you **not** do household work because of your headaches? ..... ____ days
4. How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches *(do not include days you counted in question 3 where you did not do household work)*? ..... ____ days
5. On how many days in the last 3 months did you miss family, social, or leisure activities because of your headaches? ..... ____ days

A. On how many days in the last 3 months did you have a headache? *(If a headache lasted more than one day, count each day.)* ..... ____ days

B. On a scale of 0–10, on average how painful were these headaches? *(Where 0 = no pain at all, and 10 = pain as bad as it can be.)* ..... ____

*Migraine Disability Assessment Score
(Questions 1–5 are used to calculate the MIDAS score.)
Grade I—Minimal or Infrequent Disability: 0–5
Grade II—Mild or Infrequent Disability: 6–10
Grade III—Moderate Disability: 11–20
Grade IV—Severe Disability: > 20

FIGURE 6-4

MIDAS Questionnaire. (*From Innovative Medical Research 1997.*)

in women on oral estrogens or contraceptives, migraine is not associated with serious or life-threatening illnesses. Recent studies have demonstrated an increased number of cerebellar white matter lesions of uncertain significance in those with migraine with aura.

Nonpharmacologic Management Migraine can often be managed to some degree by a variety of nonpharmacologic approaches. Most patients benefit by the identification and avoidance of specific headache triggers. A regulated lifestyle is helpful, including a healthful diet, regular exercise, regular sleep patterns, avoidance of excess caffeine and alcohol, and avoidance of acute changes in stress levels.

The measures that benefit a given individual should be used routinely since they provide a simple, cost-effective approach to migraine management. Patients with migraine do not encounter more stress than headache-free individuals; overresponsiveness to stress appears to be the issue. Since the stresses of everyday living cannot be eliminated, lessening one's response to stress by various techniques is helpful for many patients. These may include yoga, transcendental meditation, hypnosis, and conditioning techniques such as biofeedback. For most patients, this approach is, at best, an adjunct to pharmacotherapy. Nonpharmacologic measures are unlikely to prevent all migraine attacks. When these measures fail to prevent an attack, pharmacologic approaches are then needed to abort an attack.

Acute Attack Therapies for Migraine The mainstay of pharmacologic therapy is the judicious use of one or more of the many drugs that are effective in migraine (**Table 6-5**). The selection of the optimal regimen for a given patient depends on a number of factors, the most important of which is the severity of the attack. Mild migraine attacks can usually be managed by oral agents; the average efficacy rate is 50–70%. Severe migraine attacks may require parenteral therapy. Most drugs effective in the treatment of migraine are members of one of three major pharmacologic classes: anti-inflammatory agents, $5HT_{1B/1D}$ receptor agonists, and dopamine receptor antagonists.

In general, an adequate dose of whichever agent is chosen should be used as soon as possible after the onset of an attack. If additional medication is required within 60 min because symptoms return or have not abated, the initial dose should be increased for subsequent attacks. Migraine therapy must be individualized; a standard approach for all patients is not possible. A therapeutic regimen may need to be constantly refined until one is identified that provides the patient with rapid, complete, and consistent relief with minimal side effects (**Table 6-6**).

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Both the severity and duration of a migraine attack can be reduced significantly by anti-inflammatory agents (Table 6-5). Indeed, many undiagnosed migraineurs are self-treated with nonprescription NSAIDs. A general consensus is that NSAIDs are most effective when taken early in the migraine attack. However, the effectiveness of anti-inflammatory agents in migraine is usually less than optimal in moderate or severe migraine attacks. The combination of acetaminophen, aspirin, and caffeine has been approved for use by the U.S. Food and Drug Administration (FDA) for the treatment of mild to moderate migraine. The combination of aspirin and metoclopramide has been shown to be equivalent to a single dose of sumatriptan. Important side effects of NSAIDs include dyspepsia and gastrointestinal irritation.

5-HT_1 Agonists

Oral Stimulation of $5\text{-}HT_{1B/1D}$ receptors can stop an acute migraine attack. Ergotamine and dihydroergotamine are nonselective receptor agonists, while the triptans are selective $5\text{-}HT_{1B/1D}$ receptor agonists. A variety of triptans (e.g., naratriptan, rizatriptan, eletriptan, sumatriptan, zolmitriptan, almotriptan, frovatriptan) are now available for the treatment of migraine.

Each drug in the triptan class has similar pharmacologic properties but varies slightly in terms of clinical efficacy. Rizatriptan and eletriptan are the most efficacious of the triptans currently available in the United States. Sumatriptan and zolmitriptan have similar rates of efficacy as well as time to onset, whereas naratriptan and frovatriptan are the slowest-acting and least efficacious. Clinical efficacy appears to be related more to the t_{max} (time to peak plasma level) than to the potency, half-life, or bioavailability. This observation is consistent with a large body of data indicating that faster-acting analgesics are more effective than slower-acting agents.

Unfortunately, monotherapy with a selective oral $5\text{-}HT_{1B/1D}$ agonist does not result in rapid, consistent, and complete relief of migraine in all patients. Triptans are not effective in migraine with aura unless given after the aura is completed and the headache initiated. Side effects are common though often mild and transient. Moreover, $5\text{-}HT_{1B/1D}$ agonists are contraindicated in individuals with a history of cardiovascular and cerebrovascular disease. Recurrence of headache is another important limitation of triptan use and occurs at least occasionally in most patients.

Ergotamine preparations offer a nonselective means of stimulating $5\text{-}HT_1$ receptors. A nonnauseating dose of ergotamine should be sought since a dose that provokes nausea is too high and may intensify head pain. Except for a sublingual formulation of ergotamine, oral formulations of ergotamine also contain 100 mg caffeine (theoretically to enhance ergotamine absorption and possibly to add additional analgesic activity). The average oral ergotamine dose for a migraine attack is 2 mg. Since the clinical studies demonstrating the efficacy of

TABLE 6-5

TREATMENT OF ACUTE MIGRAINE

DRUG	TRADE NAME	DOSAGE
Simple Analgesics		
Acetaminophen, aspirin, caffeine	Excedrin Migraine	Two tablets or caplets q6h (max 8 per day)
NSAIDs		
Naproxen	Aleve, Anaprox, generic	220–550 mg PO bid
Ibuprofen	Advil, Motrin, Nuprin, generic	400 mg PO q3–4h
Tolfenamic acid	Clotam Rapid	200 mg PO. May repeat x 1 after 1–2 h
5-HT$_1$ Agonists		
Oral		
Ergotamine	Ergomar	One 2 mg sublingual tablet at onset and q$^1/_2$h (max 3 per day, 5 per week)
Ergotamine 1 mg, caffeine 100 mg	Ercaf, Wigraine	One or two tablets at onset, then one tablet q$^1/_2$h (max 6 per day,10 per week)
Naratriptan	Amerge	2.5 mg tablet at onset; may repeat once after 4 h
Rizatriptan	Maxalt Maxalt-MLT	5–10 mg tablet at onset; may repeat after 2 h (max 30 mg/d)
Sumatriptan	Imitrex	50–100 mg tablet at onset; may repeat after 2 h (max 200 mg/d)
Frovatriptan	Frova	2.5 mg tablet at onset, may repeat after 2 h (max 5 mg/d)
Almotriptan	Axert	12.5 mg tablet at onset, may repeat after 2 h (max 25 mg/d)
Eletriptan	Relpax	40 or 80 mg
Zolmitriptan	Zomig Zomig Rapimelt	2.5 mg tablet at onset; may repeat after 2 h (max 10 mg/d)
Nasal		
Dihydroergotamine	Migranal Nasal Spray	Prior to nasal spray, the pump must be primed 4 times; 1 spray (0.5 mg) is administered, followed in 15 min by a second spray
Sumatriptan	Imitrex Nasal Spray	5–20 mg intranasal spray as 4 sprays of 5 mg or a single 20 mg spray (may repeat once after 2 h, not to exceed a dose of 40 mg/d)
Zolmitriptan	Zomig	5 mg intranasal spray as one spray (may repeat once after 2 h, not to exceed a dose of 10 mg/d)
Parenteral		
Dihydroergotamine	DHE-45	1 mg IV, IM, or SC at onset and q1h (max 3 mg/d, 6 mg per week)
Sumatriptan	Imitrex Injection	6 mg SC at onset (may repeat once after 1 h for max of 2 doses in 24 h)
Dopamine Antagonists		
Oral		
Metoclopramide	Reglan,[a] generic[a]	5–10 mg/d
Prochlorperazine	Compazine,[a] generic[a]	1–25 mg/d
Parenteral		
Chlorpromazine	Generic[a]	0.1 mg/kg IV at 2 mg/min; max 35 mg/d
Metoclopramide	Reglan,[a] generic	10 mg IV
Prochlorperazine	Compazine,[a] generic[a]	10 mg IV
Other		
Oral		
Acetaminophen, 325 mg, *plus* dichloralphenazone, 100 mg, *plus* isometheptene, 65 mg	Midrin, Duradrin, generic	Two capsules at onset followed by 1 capsule q1h (max 5 capsules)
Nasal		
Butorphanol	Stadol[a]	1 mg (1 spray in 1 nostril), may repeat if necessary in 1–2 h
Parenteral		
Narcotics	Generic[a]	Multiple preparations and dosages; see **Table 5-1**

[a]Not all drugs are specifically indicated by the FDA for migraine. Local regulations and guidelines should be consulted.
Note: Antiemetics (e.g., domperidone 10 mg or ondansetron) or prokinetics (e.g., metoclopramide 10 mg) are sometimes useful adjuncts.
NSAIDs, nonsteroidal anti-inflammatory drugs; 5-HT, 5-hydroxytryptamine.

TABLE 6-6

CLINICAL STRATIFICATION OF ACUTE SPECIFIC MIGRAINE TREATMENTS

CLINICAL SITUATION	TREATMENT OPTIONS
Failed NSAIDS/ analgesics	**First tier** Sumatriptan 50 mg or 100 mg PO Almotriptan 12.5 mg PO Rizatriptan 10 mg PO Eletriptan 40 mg PO Zolmitriptan 2.5 mg PO **Slower effect/better tolerability** Naratriptan 2.5 mg PO Frovatriptan 2.5 mg PO **Infrequent headache** Ergotamine 1–2 mg PO Dihydroergotamine nasal spray 2 mg
Early nausea or difficulties taking tablets	Zolmitriptan 5 mg nasal spray Sumatriptan 20 mg nasal spray Rizatriptan 10 mg MLT wafer
Headache recurrence	Ergotamine 2 mg (most effective PR/usually with caffeine) Naratriptan 2.5 mg PO Almotriptan 12.5 mg PO Eletriptan 40 mg
Tolerating acute treatments poorly	Naratriptan 2.5 mg Almotriptan 12.5 mg
Early vomiting	Zolmitriptan 5 mg nasal spray Sumatriptan 25 mg PR Sumatriptan 6 mg SC
Menses-related headache	**Prevention** Ergotamine PO at night Estrogen patches **Treatment** Triptans Dihydroergotamine nasal spray
Very rapidly developing symptoms	Zolmitriptan 5 mg nasal spray Sumatriptan 6 mg SC Dihydroergotamine 1 mg IM

ergotamine in migraine predated the clinical trial methodologies used with the triptans, it is difficult to assess the clinical efficacy of ergotamine versus the triptans. In general, ergotamine appears to have a much higher incidence of nausea than triptans, but less headache recurrence.

Nasal The fastest-acting nonparenteral antimigraine therapies that can be self-administered include nasal formulations of dihydroergotamine (Migranal), zolmitriptan (Zomig nasal), or sumatriptan. The nasal sprays result in substantial blood levels within 30–60 min. Although in theory nasal sprays might provide faster and more effective relief of a migraine attack than oral formulations, their reported efficacy is only ~50–60%.

Parenteral Parenteral administration of drugs such as dihydroergotamine and sumatriptan is approved by the FDA for the rapid relief of a migraine attack. Peak plasma levels of dihydroergotamine are achieved 3 min after intravenous dosing, 30 min after intramuscular dosing, and 45 min after subcutaneous dosing. If an attack has not already peaked, subcutaneous or intramuscular administration of 1 mg dihydroergotamine suffices for about 80–90% of patients. Sumatriptan, 6 mg subcutaneously, is effective in ~70–80% of patients.

Dopamine Antagonists

Oral Oral dopamine antagonists should be considered as adjunctive therapy in migraine. Drug absorption is impaired during migraine because of reduced gastrointestinal motility. Delayed absorption occurs even in the absence of nausea and is related to the severity of the attack and not its duration. Therefore, when oral NSAIDs and/or triptan agents fail, the addition of a dopamine antagonist such as metoclopramide, 10 mg, should be considered to enhance gastric absorption. In addition, dopamine antagonists decrease nausea/vomiting and restore normal gastric motility.

Parenteral Parenteral dopamine antagonists (e.g., chlorpromazine, prochlorperazine, metoclopramide) can also provide significant acute relief of migraine; they can be used in combination with parenteral 5-$HT_{1B/1D}$ agonists. A common intravenous protocol used for the treatment of severe migraine is the administration over 2 min of a mixture of 5 mg of prochlorperazine and 0.5 mg of dihydroergotamine.

Other Medications for Acute Migraine

Oral The combination of acetaminophen, dichloralphenazone, and isometheptene, one to two capsules, has been classified by the FDA as "possibly" effective in the treatment of migraine. Since the clinical studies demonstrating the efficacy of this combination analgesic in migraine predated the clinical trial methodologies used with the triptans, it is difficult to compare the efficacy of this sympathomimetic compound to other agents.

Nasal A nasal preparation of butorphanol is available for the treatment of acute pain. As with all narcotics, the use of nasal butorphanol should be limited to a select group of migraineurs, as described below.

Parenteral Narcotics are effective in the acute treatment of migraine. For example, intravenous meperidine (50–100 mg) is given frequently in the emergency room. This regimen "works" in the sense that the pain of migraine is eliminated. However, this regimen is clearly suboptimal for patients with recurrent headache. Narcotics do not treat the underlying headache mechanism; rather, they act to alter the pain sensation. Moreover, in patients taking oral narcotics such as oxycodone or hydrocodone, narcotic addiction can greatly confuse

the treatment of migraine. Narcotic craving and/or withdrawal can aggravate and accentuate migraine. Therefore, it is recommended that narcotic use in migraine be limited to patients with severe, but infrequent, headaches that are unresponsive to other pharmacologic approaches.

Medication-Overuse Headache Acute attack medications, particularly codeine or barbiturate-containing compound analgesics, have a propensity to aggravate headache frequency and induce a state of refractory daily or near-daily headache called *medication-overuse headache*. This condition is likely not a separate headache entity but a reaction of the migraine patient to a particular medicine. Migraine patients who have two or more headache days a week should be cautioned about frequent analgesic use (see Chronic Daily Headache, below).

Preventive Treatments for Migraine Patients with an increasing frequency of migraine attacks, or with attacks that are either unresponsive or poorly responsive to abortive treatments, are good candidates for preventive agents. In general, a preventive medication should be considered in the subset of patients with five or more attacks a month. Significant side effects are associated with the use of many of these agents; furthermore, determination of dose can be difficult since the recommended doses have been derived for conditions other than migraine. The mechanism of action of these drugs is unclear; it seems likely that the brain sensitivity that underlies migraine is modified. Patients are usually started on a low dose of a chosen treatment; the dose is then gradually increased, up to a reasonable maximum to achieve clinical benefit.

Drugs that have the capacity to stabilize migraine are listed in **Table 6-7**. Drugs must be taken daily, and there is usually a lag of at least 2–12 weeks before an effect is seen. The drugs that have been approved by the FDA for the prophylactic treatment of migraine include propranolol, timolol, sodium valproate, topiramate, and methysergide (not available in the United States). In addition, a number of other drugs appear to display prophylactic efficacy. This group includes amitriptyline, nortriptyline, flunarizine, phenelzine, gabapentin, topiramate, and cyproheptadine. Phenelzine and methysergide are usually reserved for recalcitrant cases because of their serious potential side effects. Phenelzine is a monoamine oxidase inhibitor (MAOI); therefore, tyramine-containing foods, decongestants, and meperidine are contraindicated. Methysergide may cause retroperitoneal or cardiac valvular fibrosis when it is used for >6 months, and thus monitoring is required for patients using this drug; the risk of fibrosis is about 1:1500 and is likely to reverse after the drug is stopped.

The probability of success with any one of the antimigraine drugs is 50–75%. Many patients are managed adequately with low-dose amitriptyline, propranolol, topiramate, gabapentin, or valproate. If these agents fail or lead to unacceptable side effects, second-line agents such as methysergide or phenelzine can be used. Once effective stabilization is achieved, the drug is continued for 5–6 months and then slowly tapered to assess the continued need. Many patients are able to discontinue medication and experience fewer and milder attacks for long periods, suggesting that these drugs may alter the natural history of migraine.

TENSION-TYPE HEADACHE

Clinical Features

The term *tension-type headache* (TTH) is commonly used to describe a chronic head-pain syndrome characterized by bilateral tight, bandlike discomfort. The pain typically builds slowly, fluctuates in severity, and may persist more or less continuously for many days. The headache may be episodic or chronic (present >15 days per month).

A useful clinical approach is to diagnose TTH in patients whose headaches are completely without accompanying features such as nausea, vomiting, photophobia, phonophobia, osmophobia, throbbing, and aggravation with movement. Such an approach neatly separates migraine, which has one or more of these features and is the main differential diagnosis, from TTH. However, the International Headache Society's definition of TTH allows an admixture of nausea, photophobia, or phonophobia in various combinations, illustrating the difficulties in distinguishing these two clinical entities. Patients whose headaches fit the TTH phenotype and who have migraine at other times, along with a family history of migraine, migrainous illnesses of childhood, or typical migraine triggers to their migraine attacks, may be biologically different from those who have TTH headache with none of the features.

Pathophysiology

The pathophysiology of TTH is incompletely understood. It seems likely that TTH is due to a primary disorder of CNS pain modulation alone, unlike migraine, which involves a more generalized disturbance of sensory modulation. Data suggest a genetic contribution to TTH, but this may not be a valid finding: given the current diagnostic criteria, the studies undoubtedly included many migraine patients. The name *tension-type headache* implies that pain is a product of *nervous tension*, but there is no clear evidence for tension as an etiology. Muscle contraction has been considered to be a feature that distinguishes TTH from migraine, but there appear to be no differences in contraction between the two headache types.

TABLE 6-7

PREVENTIVE TREATMENTS IN MIGRAINE[a]

DRUG	DOSE	SELECTED SIDE EFFECTS
Pizotifen[b]	0.5–2 mg qd	Weight gain Drowsiness
Beta blocker		
Propranolol	40–120 mg bid	Reduced energy Tiredness Postural symptoms *Contraindicated in asthma*
Tricyclics		
Amitriptyline	10–75 mg at night	Drowsiness
Dothiepin	25–75 mg at night	
Nortriptyline	25–75 mg at night	***Note:*** Some patients may only need a total dose of 10 mg, although generally 1–1.5 mg/kg body weight is required
Anticonvulsants		
Topiramate	25–200 mg/d	Paresthesias Cognitive symptoms Weight loss Glaucoma Caution with nephrolithiasis
Valproate	400–600 mg bid	Drowsiness Weight gain Tremor Hair loss Fetal abnormalities Hematologic or liver abnormalities
Gabapentin	900–3600 mg qd	Dizziness Sedation
Serotonergic drugs		
Methysergide	1–4 mg qd	Drowsiness Leg cramps Hair loss Retroperitoneal fibrosis (1-month drug holiday is required every 6 months)
Flunarizine[b]	5–15 mg qd	Drowsiness Weight gain Depression Parkinsonism
No convincing evidence from controlled trials		
Verapamil Controlled trials demonstrate *no effect* Nimodipine Clonidine SSRIs: fluoxetine		

[a]Commonly used preventives are listed with reasonable doses and common side effects. Not all listed medicines are approved by the FDA; local regulations and guidelines should be consulted.
[b]Not available in the United States.

Rx Treatment: TENSION-TYPE HEADACHE

The pain of TTH can generally be managed with simple analgesics such as acetaminophen, aspirin, or NSAIDs. Behavioral approaches including relaxation can also be effective. Clinical studies have demonstrated that triptans in pure TTH are not helpful, although triptans are effective in TTH when the patient also has migraine. For chronic TTH, amitriptyline is the only proven treatment (Table 6-7); other tricyclics, selective serotonin reuptake inhibitors, and the benzodiazepines have not been shown to be effective. There is no evidence for the efficacy of acupuncture. Placebo controlled trials of botulinum toxin type A in chronic TTH have not shown benefit.

TRIGEMINAL AUTONOMIC CEPHALALGIAS, INCLUDING CLUSTER HEADACHE

The trigeminal autonomic cephalalgias (TACs) are a group of primary headaches that includes cluster headache, paroxysmal hemicrania, and SUNCT (*s*hort-lasting *u*nilateral *n*euralgiform headache attacks with *c*onjunctival injection and *t*earing). TACs are characterized by relatively short-lasting attacks of head pain associated with cranial autonomic symptoms, such as lacrimation, conjunctival injection, or nasal congestion (Table 6-8). Pain is usually severe and may occur more than once a day. Because of the associated nasal congestion or rhinorrhea, patients are often misdiagnosed with "sinus headache" and treated with decongestants, which are ineffective.

TACs must be differentiated from short-lasting headaches that do not have prominent cranial autonomic syndromes, notably trigeminal neuralgia, primary stabbing headache, and hypnic headache. The cycling pattern and length, frequency, and timing of attacks are useful in classifying patients. Patients with TACs should undergo pituitary imaging and pituitary function tests as there is an excess of TAC presentations in patients with pituitary tumor–related headache

Cluster Headache

Cluster headache is a rare form of primary headache with a population frequency of 0.1%. The pain is deep, usually retroorbital, often excruciating in intensity, nonfluctuating, and explosive in quality. A core feature of cluster headache is periodicity. At least one of the daily attacks of pain recurs at about the same hour each day for the duration of a cluster bout. The typical cluster headache patient has daily bouts of one to two attacks of relatively short-duration unilateral pain for 8–10 weeks a year; this is usually followed by a pain-free interval that averages 1 year. Cluster headache is characterized as chronic when there is no period of sustained remission. Patients are generally perfectly well between episodes.

TABLE 6-8

CLINICAL FEATURES OF THE TRIGEMINAL AUTONOMIC CEPHALALGIAS

	CLUSTER HEADACHE	PAROXYSMAL HEMICRANIA	SUNCT
Gender	M>F	F=M	F~M
Pain			
Type	Stabbing, boring	Throbbing, boring, stabbing	Burning, stabbing, sharp
Severity	Excruciating	Excruciating	Severe to excruciating
Site	Orbit, temple	Orbit, temple	Periorbital
Attack frequency	1/alternate day–8/d	1–40/d (>5/d for more than half the time)	3–200/d
Duration of attack	15–180 min	2–30 min	5–240 s
Autonomic features	Yes	Yes	Yes (prominent conjunctival injection and lacrimation)[a]
Migrainous features[b]	Yes	Yes	Yes
Alcohol trigger	Yes	No	No
Cutaneous triggers	No	No	Yes
Indomethacin effect	—	Yes[c]	—
Abortive treatment	Sumatriptan injection or nasal spray Oxygen	No effective treatment	Lidocaine (IV)
Prophylactic treatment	Verapamil Methysergide Lithium	Indomethacin	Lamotrigine Topiramate Gabapentin

[a]If conjunctival injection and tearing not present, consider SUNA.
[b]Nausea, photophobia, or phonophobia; photophobia and phonophobia are typically unilateral on the side of the pain.
[c]Indicates complete response to indomethacin.
Note: SUNCT, *s*hort-lasting *u*nilateral *n*euralgiform headache attacks with *c*onjunctival injection and *t*earing.

Onset is nocturnal in about 50% of patients, and men are affected three times more often than women. Patients with cluster headache tend to move about during attacks, pacing, rocking, or rubbing their head for relief; some may even become aggressive during attacks. This is in sharp contrast to patients with migraine, who prefer to remain motionless during attacks.

Cluster headache is associated with ipsilateral symptoms of cranial parasympathetic autonomic activation: conjunctival injection or lacrimation, rhinorrhea or nasal congestion, or cranial sympathetic dysfunction such as ptosis. The sympathetic deficit is peripheral and likely to be due to parasympathetic activation with injury to ascending sympathetic fibers surrounding a dilated carotid artery as it passes into the cranial cavity. When present, photophobia and phonophobia are far more likely to be unilateral and on the same side of the pain, rather than bilateral, as is seen in migraine. This phenomenon of unilateral photophobia/phonophobia is characteristic of TACs. Cluster headache is likely to be a disorder involving central pacemaker neurons in the region of the posterior hypothalamus (Fig. 6-2).

Rx Treatment: CLUSTER HEADACHE

The most satisfactory treatment is the administration of drugs to prevent cluster attacks until the bout is over. However, treatment of acute attacks is required for all cluster headache patients at some time.

ACUTE ATTACK TREATMENT Cluster headache attacks peak rapidly, and thus a treatment with quick onset is required. Many patients with acute cluster headache respond very well to oxygen inhalation. This should be given as 100% oxygen at 10–12 L/min for 15–20 min. It appears that high flow and high oxygen content are important. Sumatriptan 6 mg subcutaneously is rapid in onset and will usually shorten an attack to 10–15 min; there is no evidence of tachyphylaxis. Sumatriptan (20 mg) and zolmitriptan (5 mg) nasal sprays are both effective in acute cluster headache, offering a useful option for patients who may not wish to self-inject daily. Oral sumatriptan is not effective for prevention or for acute treatment of cluster headache.

PREVENTIVE TREATMENTS (Table 6-9) The choice of a preventive treatment in cluster headache depends in part on the length of the bout. Patients with long bouts or those with chronic cluster headache require medicines that are safe when taken for long periods. For patients with relatively short bouts, limited courses of oral glucocorticoids or methysergide (not available in the United States) can be very useful. A 10-day course of prednisone, beginning at 60 mg daily for 7 days and followed by a rapid taper, may interrupt the pain bout for many patients. When ergotamine (1–2 mg) is used, it is most effective when given 1–2 h before an expected attack. Patients who use ergotamine daily must be educated regarding the early symptoms of ergotism, which may include vomiting, numbness, tingling, pain, and cyanosis of the limbs; a weekly limit of 14 mg should be adhered to. Lithium (600–900 mg qd) appears to be particularly useful for the chronic form of the disorder.

Many experts favor verapamil as the first-line preventive treatment for patients with chronic cluster headache or prolonged bouts. While verapamil compares favorably with lithium in practice, some patients require verapamil doses far in excess of those administered for cardiac disorders. The initial dose range is 40–80 mg twice daily; effective doses may be as high as 960 mg/d. Side effects such as constipation and leg swelling can be problematic. Of paramount concern, however, is the cardiovascular safety of verapamil, particularly at high doses. Verapamil can cause heart block by slowing conduction in the atrioventricular node, a condition that can be monitored by following the PR interval on a standard ECG. Approximately 20% of patients treated with verapamil develop ECG abnormalities, which can be observed with doses as low as 240 mg/d; these abnormalities can worsen over time in patients on stable doses. A baseline ECG is recommended for all patients. The ECG is repeated 10 days after a dose change in those patients whose dose is being increased above 240 mg daily. Dose increases are usually made in 80-mg increments. For patients on long-term verapamil, ECG monitoring every 6 months is advised.

NEUROSTIMULATION THERAPY When medical therapies fail in chronic cluster headache, neurostimulation therapy strategies can be employed. Deep-brain stimulation of the region of the posterior hypothalamic gray matter has proven successful in a substantial proportion of patients. Favorable results have also been reported with the less-invasive approach of occipital nerve stimulation.

TABLE 6-9

PREVENTIVE MANAGEMENT OF CLUSTER HEADACHE

SHORT-TERM PREVENTION	LONG-TERM PREVENTION
Episodic Cluster Headache	**Episodic Cluster Headache & Prolonged Chronic Cluster Headache**
Prednisone 1 mg/kg up to 60 mg qd, tapering over 21 days	Verapamil 160–960 mg/d
Methysergide 3–12 mg/d	Lithium 400–800 mg/d
Verapamil 160–960 mg/d	Methysergide 3–12 mg/d
Greater occipital nerve injection	Topiramate[a] 100–400 mg/d
	Gabapentin[a] 1200–3600 mg/d
	Melatonin[a] 9–12 mg/d

[a]Unproven but of potential benefit.

Paroxysmal Hemicrania

Paroxysmal hemicrania (PH) is characterized by frequent unilateral, severe, short-lasting episodes of headache. Like cluster headache, the pain tends to be retroorbital but may be experienced all over the head and is associated with autonomic phenomena such as lacrimation and nasal congestion. Patients with remissions are said to have episodic PH, while those with the nonremitting form are said to have chronic PH. The essential features of PH are: unilateral, very severe pain; short-lasting attacks (2–45 min); very frequent attacks (usually more than five a day); marked autonomic features ipsilateral to the pain; rapid course (<72 h); and excellent response to indomethacin. In contrast to cluster headache, which predominantly affects males; the male:female ratio in PH is close to 1:1.

Indomethacin (25–75 mg tid), which can completely suppress attacks of PH, is the treatment of choice. Although therapy may be complicated by indomethacin-induced gastrointestinal side effects, currently there are no consistently effective alternatives. Topiramate is helpful in some cases. Piroxicam has been used, although it is not as effective as indomethacin. Verapamil, an effective treatment for cluster headache, does not appear to be useful for PH. In occasional patients, PH can coexist with trigeminal neuralgia (PH-tic syndrome); similar to cluster-tic syndrome, each component may require separate treatment.

Secondary PH has been reported with lesions in the region of the sella turcica, including arteriovenous malformation, cavernous sinus meningioma, and epidermoid tumors. Secondary PH is more likely if the patient requires high doses (>200 mg/d) of indomethacin. In patients with apparent bilateral PH, raised CSF pressure should be suspected. It is important to note that indomethacin reduces CSF pressure. When a diagnosis of PH is considered, MRI is indicated to exclude a pituitary lesion.

SUNCT/SUNA

SUNCT is a rare primary headache syndrome characterized by severe, unilateral orbital or temporal pain that is stabbing or throbbing in quality. Diagnosis requires at least 20 attacks, lasting for 5–240 s; ipsilateral conjunctival injection and lacrimation should be present. In some patients conjunctival injection or lacrimation are missing, and the diagnosis of SUNA (*s*hort-lasting *u*nilateral *n*euralgiform headache attacks with cranial *a*utonomic symptoms) has been suggested.

Diagnosis

The pain of SUNCT/SUNA is unilateral and may be located anywhere in the head. Three basic patterns can be seen: single stabs, which are usually short-lived; groups of stabs; or a longer attack comprising many stabs between which the pain does not completely resolve, thus giving a "saw-tooth" phenomenon with attacks lasting many minutes. Each pattern may be seen in the context of an underlying continuous head pain. Characteristics that lead to a suspected diagnosis of SUNCT are the cutaneous (or other) triggerability of attacks, a lack of refractory period to triggering between attacks, and the lack of a response to indomethacin. Apart from trigeminal sensory disturbance, the neurologic examination is normal in primary SUNCT.

The diagnosis of SUNCT is often confused with trigeminal neuralgia (TN) particularly in first-division TN (Chap. 29). Minimal or no cranial autonomic symptoms and a clear refractory period to triggering indicate a diagnosis of TN.

Secondary (Symptomatic) SUNCT

SUNCT can be seen with posterior fossa or pituitary lesions. All patients with SUNCT/SUNA should be evaluated with pituitary function tests and a brain MRI with pituitary views.

℞ Treatment: SUNCT/SUNA

ABORTIVE THERAPY Therapy of acute attacks is not a useful concept in SUNCT/SUNA since the attacks are of such short duration. However, intravenous lidocaine, which arrests the symptoms, can be used in hospitalized patients.

PREVENTIVE THERAPY Long-term prevention to minimize disability and hospitalization is the goal of treatment. The most effective treatment for prevention is lamotrigine, 200–400 mg/d. Topiramate and gabapentin may also be effective. Carbamazepine, 400–500 mg/d, has been reported by patients to offer modest benefit.

Surgical approaches such as microvascular decompression or destructive trigeminal procedures are seldom useful and often produce long-term complications. Greater occipital nerve injection has produced limited benefit in some patients. Mixed success with occipital nerve stimulation has been observed. Complete control with deep-brain stimulation of the posterior hypothalamic region was reported in a single patient. For intractable cases, short-term prevention with intravenous lidocaine can be effective.

CHRONIC DAILY HEADACHE

The broad diagnosis of chronic daily headache (CDH) can be applied when a patient experiences headache on 15 days or more per month. CDH is not a single entity; it encompasses a number of different headache syndromes, including chronic TTH as well as headache secondary to trauma, inflammation, infection, medication

TABLE 6-10

CLASSIFICATION OF CHRONIC DAILY HEADACHE

PRIMARY		
>4 H DAILY	<4 H DAILY	SECONDARY
Chronic migraine[a]	Chronic cluster headache[b]	Posttraumatic Head injury Iatrogenic Postinfectious
Chronic tension-type headache[a]	Chronic paroxysmal hemicrania	Inflammatory, such as Giant cell arteritis Sarcoidosis Behçet's syndrome
Hemicrania continua[a]	SUNCT/SUNA	Chronic CNS infection
New daily persistent headache[a]	Hypnic headache	Medication-overuse headache[a]

[a]May be complicated by analgesic overuse.
[b]Some patients may have headache > 4 h per day.
Note: SUNCT, short-lasting *u*nilateral *n*euralgiform *h*eadache attacks with *c*onjunctival injection and *t*earing; SUNA, short-lasting *u*nilateral *n*euralgiform headache *a*ttacks with cranial autonomic symptoms.

overuse, and other causes (Table 6-10). Population-based estimates suggest that about 4% of adults have daily or near-daily headache. Daily headache may be primary or secondary, an important consideration in guiding management of this complaint.

Approach to the Patient: CHRONIC DAILY HEADACHE

The first step in the management of patients with CDH is to diagnose any underlying condition (Table 6-10). For patients with primary headaches, diagnosis of the headache type will guide therapy. Preventive treatments such as tricyclics, either amitriptyline or doxepin at doses up to 1 mg/kg, are very useful in patients with CDH. Tricyclics are started in low doses (10–25 mg) daily and may be given 12 h before the expected time of awakening in order to avoid excess morning sleepiness. Anticonvulsants, such as topiramate, valproate, and gabapentin, are also useful in migraineurs. Flunarizine can also be very effective for some patients, as can methysergide or phenelzine.

MANAGEMENT OF MEDICALLY INTRACTABLE DISABLING CHRONIC DAILY HEADACHE The management of medically intractable headache is difficult. At this time, the only promising approach is occipital nerve stimulation, which appears to modulate thalamic processing in migraine and has shown promise in both chronic cluster headache and hemicrania continua (see below). Clinical trials using botulinum toxin in chronic migraine have failed to show any objective benefit.

MEDICATION-OVERUSE HEADACHE Overuse of analgesic medication for headache can aggravate head-ache frequency and induce a state of refractory daily or near-daily headache called *medication-overuse headache*. A proportion of patients who stop taking analgesics will experience substantial improvement in the severity and frequency of their headache. However, even after cessation of analgesic use, many patients continue to have headache, although they may feel clinically improved in some way, especially if they have been using codeine or barbiturates regularly. The residual symptoms probably represent the underlying headache disorder.

Management of Medication Overuse: Outpatients For patients who overuse medications, it is essential that analgesic use be reduced and eliminated. One approach is to reduce the medication dose by 10% every 1–2 weeks. Immediate cessation of analgesic use is possible for some patients, provided there is no contraindication. Both approaches are facilitated by the use of a medication diary maintained during the month or two before cessation; this helps to identify the scope of the problem. A small dose of an NSAID such as naproxen, 500 mg bid if tolerated, will help relieve residual pain as analgesic use is reduced. NSAID overuse is not usually a problem for patients with daily headache when the dose is taken once or twice daily; however, overuse problems may develop with more frequent dosing schedules. Once the patient has substantially reduced analgesic use, a preventive medication should be introduced. It must be emphasized that *preventives generally do not work in the presence of analgesic overuse*. The most common cause of unresponsiveness to treatment is the use of a preventive when analgesics continue to be used regularly. For some patients, discontinuing analgesics is very difficult; often the best approach is to directly inform the patient that some degree of pain is inevitable during this initial period.

Management of Medication Overuse: Inpatients Some patients will require hospitalization for detoxification. Such patients have typically failed efforts at outpatient withdrawal or have a significant medical condition, such as diabetes mellitus, which would complicate withdrawal as an outpatient. Following admission to the hospital, acute medications are withdrawn completely on the first day, in the absence of a contraindication. Antiemetics and fluids are administered as required; clonidine is used for opiate withdrawal symptoms. For acute intolerable pain during the waking hours aspirin, 1 g (not approved in United States) intravenously,

TABLE 6-11

DIFFERENTIAL DIAGNOSIS OF NEW DAILY PERSISTENT HEADACHE

PRIMARY	SECONDARY
Migrainous-type	Subarachnoid hemorrhage
Featureless (tension-type)	Low CSF volume headache
	Raised CSF pressure headache
	Posttraumatic headache[a]
	Chronic meningitis

[a]Includes postinfectious forms.

is useful. Intramuscular chlorpromazine can be helpful at night; patients must be adequately hydrated. If the patient does not improve within 3–5 days, a course of intravenous dihydroergotamine (DHE) can be employed. DHE, administered every 8 h for 3 consecutive days, can induce a significant remission that allows a preventive treatment to be established. 5-HT_3 antagonists, such as ondansetron or granisetron, are often required with DHE to prevent significant nausea.

NEW DAILY PERSISTENT HEADACHE New daily persistent headache (NDPH) is a clinically distinct syndrome; its causes are listed in Table 6-11.

Clinical Presentation The patient with NDPH presents with headache on most if not all days; the onset is recent and clearly recalled by the patient. The headache usually begins abruptly, but onset may be more gradual; evolution over 3 days has been proposed as the upper limit for this syndrome. Patients typically recall the exact day and circumstances of the onset of headache; the new, persistent head pain does not remit. The first priority is to distinguish between a primary and a secondary cause of this syndrome. Subarachnoid hemorrhage is the most serious of the secondary causes and must be excluded either by history or appropriate investigation (Chap. 22).

SECONDARY NDPH

Low CSF volume headache In these syndromes, head pain is positional: it begins when the patient sits or stands upright and resolves upon reclining. The pain, which is occipitofrontal, is usually a dull ache but may be throbbing. Patients with chronic low CSF volume headache typically present with a history of headache from one day to the next that is generally not present on waking but worsens during the day. Recumbency usually improves the headache within minutes, but it takes only minutes to an hour for the pain to return when the patient resumes an upright position.

The most common cause of headache due to persistent low CSF volume is CSF leak following lumbar puncture (LP). Post-LP headache usually begins within 48 h but may be delayed for up to 12 days. Its incidence is between 10 and 30%. Beverages with caffeine may provide temporary relief. Besides LP, index events may include epidural injection or a vigorous Valsalva maneuver, such as from lifting, straining, coughing, clearing the eustachian tubes in an airplane, or multiple orgasms. Spontaneous CSF leaks are well recognized, and the diagnosis should be considered whenever the headache history is typical, even when there is no obvious index event. As time passes from the index event, the postural nature may become less apparent; cases in which the index event occurred several years before the eventual diagnosis have been recognized. Symptoms appear to result from low volume rather than low pressure: although low CSF pressures, typically 0–50 mmH_2O, are usually identified, a pressure as high as 140 mmH_2O has been noted with a documented leak. Postural orthostatic tachycardia syndrome [POTS (Chap. 28)] can present with orthostatic headache similar to low CSF volume headache and is a diagnosis that needs consideration here.

When imaging is indicated to identify the source of a presumed leak, an MRI with gadolinium is the initial study of choice (Fig. 6-5). A striking pattern of diffuse meningeal enhancement is so typical that in the appropriate clinical context the diagnosis is established. Chiari malformations may sometimes be noted on MRI; in

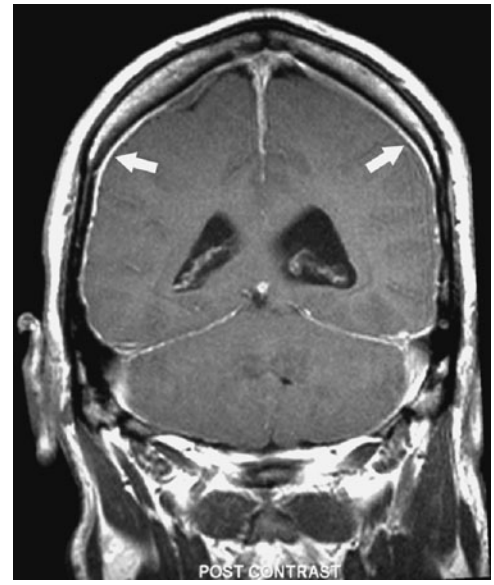

FIGURE 6-5

Magnetic resonance image showing diffuse meningeal enhancement after gadolinium administration in a patient with low CSF volume headache. High-resolution T1 weighted MRI obtained using voxel-based morphometry demonstrates increased gray matter activity, lateralized to the side of pain in a patient with cluster headache. (*From A May et al: Nat Med 5:836, 1999.*)

such cases surgery to decompress the posterior fossa usually worsens the headache. The source of CSF leakage may be identified by spinal MRI, by CT myelogram, or with ^{111}In-DTPA CSF studies; in the absence of a directly identified site of leakage, early emptying of ^{111}In-DTPA tracer into the bladder or slow progress of tracer across the brain suggests a CSF leak.

Initial treatment for low CSF volume headache is bed rest. For patients with persistent pain, intravenous caffeine (500 mg in 500 mL saline administered over 2 h) is often very effective. An EKG to screen for arrhythmia should be performed before administration. It is reasonable to administer at least two infusions of caffeine before embarking on additional tests to identify the source of the CSF leak. Since intravenous caffeine is safe and can be curative, it spares many patients the need for further investigations. If unsuccessful, an abdominal binder may be helpful. If a leak can be identified, an autologous blood patch is usually curative. A blood patch is also effective for post-LP headache; in this setting the location is empirically determined to be the site of the LP. In patients with intractable pain, oral theophylline is a useful alternative; however, its effect is less rapid than caffeine.

Raised CSF pressure headache Raised CSF pressure is well recognized as a cause of headache. Brain imaging can often reveal the cause, such as a space-occupying lesion. NDPH due to raised CSF pressure can be the presenting symptom for patients with idiopathic intracranial hypertension (pseudotumor cerebri) without visual problems, particularly when the fundi are normal. Persistently raised intracranial pressure can trigger chronic migraine. These patients typically present with a history of generalized headache that is present on waking and improves as the day goes on. It is generally worse with recumbency. Visual obscurations are frequent. The diagnosis is relatively straightforward when papilledema is present, but the possibility must be considered even in patients without fundoscopic changes. Formal visual-field testing should be performed even in the absence of overt ophthalmic involvement. Headache on rising in the morning or nocturnal headache is also characteristic of obstructive sleep apnea or poorly controlled hypertension.

Evaluation of patients suspected to have raised CSF pressure requires brain imaging. It is most efficient to obtain an MRI, including an MR venogram as the initial study. If there are no contraindications, the CSF pressure should be measured by LP; this should be done when the patient is symptomatic so that both the pressure and the response to removal of 20–30 mL of CSF can be determined. An elevated opening pressure and improvement in headache following removal of CSF is diagnostic.

Initial treatment is with acetazolamide (250–500 mg bid); the headache may improve within weeks. If ineffective, topiramate is the next treatment of choice; it has many actions that may be useful in this setting, including carbonic anhydrase inhibition, weight loss, and neuronal membrane stabilization, likely mediated via effects on phosphorylation pathways. Severely disabled patients who do not respond to medical treatment require intracranial pressure monitoring and may require shunting.

Post-traumatic headache A traumatic event can trigger a headache process that lasts for many months or years after the event. The term *trauma* is used in a very broad sense: headache can develop following an injury to the head, but it can also develop after an infectious episode, typically viral meningitis, a flulike illness, or a parasitic infection. Complaints of dizziness, vertigo, and impaired memory can accompany the headache. Symptoms may remit after several weeks or persist for months and even years after the injury. Typically the neurologic examination is normal and CT or MRI studies are unrevealing. Chronic subdural hematoma may on occasion mimic this disorder. In one series, one-third of patients with NDPH reported headache beginning after a transient flulike illness characterized by fever, neck stiffness, photophobia, and marked malaise. Evaluation reveals no apparent cause for the headache. There is no convincing evidence that persistent Epstein-Barr infection plays a role in this syndrome. A complicating factor is that many patients undergo LP during the acute illness; iatrogenic low CSF volume headache must be considered in these cases. Post-traumatic headache may also be seen after carotid dissection and subarachnoid hemorrhage, and following intracranial surgery. The underlying theme appears to be that a traumatic event involving the pain-producing meninges can trigger a headache process that lasts for many years.

Treatment is largely empirical. Tricyclic antidepressants, notably amitriptyline, and anticonvulsants such as topiramate, valproate, and gabapentin, have been used with reported benefit. The MAOI phenelzine may also be useful in carefully selected patients. The headache usually resolves within 3–5 years, but it can be quite disabling.

Primary NDPH Primary NDPH occurs in both males and females. It can be of the migrainous type, with features of migraine, or it can be featureless, appearing as new-onset TTH (Table 6-11). Migrainous features are common and include unilateral headache and throbbing pain; each feature is present in about one-third of patients. Nausea, photophobia, and/or phonophobia occur in about half of patients.

Some patients have a previous history of migraine; however, the proportion of NDPH sufferers with preexisting migraine is no greater than the frequency of migraine in the general population. At 24 months, ~86% of patients are headache-free. Treatment of migrainous-type primary NDPH consists of using the preventive therapies effective in migraine (Table 6-7). Featureless NDPH is one of the primary headache forms most refractory to treatment. Standard preventive therapies can be offered but are often ineffective.

OTHER PRIMARY HEADACHES

Hemicrania Continua

The essential features of hemicrania continua are moderate and continuous unilateral pain associated with fluctuations of severe pain; complete resolution of pain with indomethacin; and exacerbations that may be associated with autonomic features, including conjunctival injection, lacrimation, and photophobia on the affected side. The age of onset ranges from 11 to 58 years; women are affected twice as often as men. The cause is unknown.

℞ Treatment: HEMICRANIA CONTINUA

Treatment consists of indomethacin; other NSAIDs appear to be of little or no benefit. The intramuscular injection of 100 mg indomethacin has been proposed as a diagnostic tool; administration with a placebo injection has been recommended. Alternatively, a trial of oral indomethacin, starting with 25 mg tid, then 50 mg tid, and then 75 mg tid, can be given. Up to 2 weeks may be necessary to assess whether a dose has a useful effect. Topiramate can be helpful in some patients. Occipital nerve stimulation may have a role in patients with hemicrania continua who are unable to tolerate indomethacin.

Primary Stabbing Headache

The essential features of primary stabbing headache are stabbing pain confined to the head or, rarely, the face, lasting from 1 to many seconds or minutes and occurring as a single stab or a series of stabs; absence of associated cranial autonomic features; absence of cutaneous triggering of attacks; and a pattern of recurrence at irregular intervals (hours to days). The pains have been variously described as "ice-pick pains" or "jabs and jolts." They are more common in patients with other primary headaches, such as migraine, the TACs, and hemicrania continua.

℞ Treatment: PRIMARY STABBING HEADACHE

The response of primary stabbing headache to indomethacin (25–50 mg two to three times daily) is usually excellent. As a general rule the symptoms wax and wane, and after a period of control on indomethacin, it is appropriate to withdraw treatment and observe the outcome.

Primary Cough Headache

Primary cough headache is a generalized headache that begins suddenly, lasts for several minutes, and is precipitated by coughing; it is preventable by avoiding coughing or other precipitating events, which can include sneezing, straining, laughing, or stooping. In all patients with this syndrome serious etiologies must be excluded before a diagnosis of "benign" primary cough headache can be established. A Chiari malformation or any lesion causing obstruction of CSF pathways or displacing cerebral structures can be the cause of the head pain. Other conditions that can present with cough or exertional headache as the initial symptom include cerebral aneurysm, carotid stenosis, and vertebrobasilar disease. Benign cough headache can resemble benign exertional headache (below), but patients with the former condition are typically older.

℞ Treatment: PRIMARY COUGH HEADACHE

Indomethacin 25–50 mg two to three times daily is the treatment of choice. Some patients with cough headache obtain pain relief with LP; this is a simple option when compared to prolonged use of indomethacin, and it is effective in about one-third of patients. The mechanism of this response is unclear.

Primary Exertional Headache

Primary exertional headache has features resembling both cough headache and migraine. It may be precipitated by any form of exercise; it often has the pulsatile quality of migraine. The pain, which can last from 5 min to 24 h, is bilateral and throbbing at onset; migrainous features may develop in patients susceptible to migraine. Primary exertional headache can be prevented by avoiding excessive exertion, particularly in hot weather or at high altitude.

The mechanism of primary exertional headache is unclear. Acute venous distension likely explains one syndrome, the acute onset of headache with straining and breath holding, as in weightlifter's headache. As exertion

can result in headache in a number of serious underlying conditions, these must be considered in patients with exertional headache. Pain from angina may be referred to the head, probably by central connections of vagal afferents, and may present as exertional headache (cardiac cephalgia). The link to exercise is the main clinical clue that headache is of cardiac origin. Pheochromocytoma may occasionally cause exertional headache. Intracranial lesions and stenosis of the carotid arteries are other possible etiologies.

℞ Treatment: PRIMARY EXERTIONAL HEADACHE

Exercise regimens should begin modestly and progress gradually to higher levels of intensity. Indomethacin at daily doses from 25 to 150 mg is generally effective in benign exertional headache. Indomethacin (50 mg), ergotamine (1 mg orally), dihydroergotamine (2 mg by nasal spray), or methysergide (1–2 mg orally given 30–45 min before exercise) are useful prophylactic measures.

Primary Sex Headache

Sex headache is precipitated by sexual excitement. The pain usually begins as a dull bilateral headache which suddenly becomes intense at orgasm. The headache can be prevented or eased by ceasing sexual activity before orgasm. Three types of sex headache are reported: a dull ache in the head and neck that intensifies as sexual excitement increases; a sudden, severe, explosive headache occurring at orgasm; and a postural headache developing after coitus that resembles the headache of low CSF pressure. The latter arises from vigorous sexual activity and is a form of low CSF pressure headache. Headaches developing at the time of orgasm are not always benign; 5–12% of cases of subarachnoid hemorrhage are precipitated by sexual intercourse. Sex headache is reported by men more often than women and may occur at any time during the years of sexual activity. It may develop on several occasions in succession and then not trouble the patient again, even without an obvious change in sexual activity. In patients who stop sexual activity when headache is first noticed, the pain may subside within a period of 5 min to 2 h. In about half of patients, sex headache will subside within 6 months. About half of patients with sex headache have a history of exertional headaches, but there is no excess of cough headache. Migraine is probably more common in patients with sex headache.

℞ Treatment: PRIMARY SEX HEADACHE

Benign sex headaches recur irregularly and infrequently. Management can often be limited to reassurance and advice about ceasing sexual activity if a mild, warning headache develops. Propranolol can be used to prevent headache that recurs regularly or frequently, but the dosage required varies from 40 to 200 mg/d. An alternative is the calcium channel-blocking agent diltiazem, 60 mg tid. Ergotamine (1 mg) or indomethacin (25–50 mg) taken about 30–45 min prior to sexual activity can also be helpful.

Primary Thunderclap Headache

Sudden onset of severe headache may occur in the absence of any known provocation. The differential diagnosis includes the sentinel bleed of an intracranial aneurysm, cervicocephalic arterial dissection, and cerebral venous thrombosis. Headaches of explosive onset may also be caused by the ingestion of sympathomimetic drugs or of tyramine-containing foods in a patient who is taking MAOIs, or they may be a symptom of pheochromocytoma. Whether thunderclap headache can be the presentation of an unruptured cerebral aneurysm is uncertain. When neuroimaging studies and LP exclude subarachnoid hemorrhage, patients with thunderclap headache usually do very well over the long term. In one study of patients whose CT scans and CSF findings were negative, ~15% had recurrent episodes of thunderclap headache, and nearly half subsequently developed migraine or tension-type headache.

The first presentation of any sudden-onset severe headache should be vigorously investigated with neuroimaging (CT or, when possible, MRI with MR angiography) and CSF examination. Formal cerebral angiography should be reserved for those cases in which no primary diagnosis is forthcoming and for clinical situations that are particularly suggestive of intracranial aneurysm. Reversible segmental cerebral vasoconstriction may be seen in primary thunderclap headache without an intracranial aneurysm. In the presence of posterior leukoencephalopathy, the differential diagnosis includes cerebral angiitis, drug toxicity (cyclosporine, intrathecal methotrexate/cytarabine, pseudoephedrine, or cocaine), posttransfusion effects, and postpartum angiopathy. Treatment with nimodipine may be helpful, although by definition the vasoconstriction of primary thunderclap headache resolves spontaneously.

Hypnic Headache

This headache syndrome typically begins a few hours after sleep onset. The headaches last from 15 to 30 min and are typically moderately severe and generalized, although they may be unilateral and can be throbbing. Patients may report falling back to sleep only to be awakened by a further attack a few hours later; up to three repetitions of this pattern occur through the night. Daytime naps can also precipitate head pain. Most patients are women, and

the onset is usually after age 60. Headaches are bilateral in most, but may be unilateral. Photophobia or phonophobia and nausea are usually absent. The major secondary consideration in this headache type is poorly controlled hypertension; 24-h blood pressure monitoring is recommended to detect this treatable condition.

Rx Treatment: HYPNIC HEADACHE

Patients with hypnic headache generally respond to a bedtime dose of lithium carbonate (200–600 mg). For those intolerant of lithium, verapamil (160 mg) or methysergide (1–4 mg at bedtime) may be alternative strategies. One to two cups of coffee or caffeine, 60 mg orally, at bedtime may be effective in approximately one-third of patients. Case reports suggest that flunarizine, 5 mg nightly, can be effective.

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CHAPTER 7

BACK AND NECK PAIN

John W. Engstrom

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The importance of back and neck pain in our society is underscored by the following: (1) the cost of back pain in the United States is ~$100 billion annually, including direct health care expenses plus costs due to loss of productivity; (2) back symptoms are the most common cause of disability in those <45 years; (3) low back pain is the second most common reason for visiting a physician in the United States; and (4) ~1% of the U.S. population is chronically disabled because of back pain.

ANATOMY OF THE SPINE

The anterior portion of the spine consists of cylindrical vertebral bodies separated by intervertebral disks and held together by the anterior and posterior longitudinal ligaments. The intervertebral disks are composed of a central gelatinous nucleus pulposus surrounded by a tough cartilaginous ring, the annulus fibrosis; disks are responsible for 25% of spinal column length (**Figs. 7-1** and **7-2**). The disks are largest in the cervical and lumbar regions where movements of the spine are greatest. The disks are elastic in youth and allow the bony vertebrae to move easily upon each other. Elasticity is lost with age. The function of the anterior spine is to absorb the shock of body movements such as walking and running.

The posterior portion of the spine consists of the vertebral arches and seven processes. Each arch consists of paired cylindrical pedicles anteriorly and paired laminae posteriorly. The vertebral arch gives rise to two transverse processes laterally, one spinous process posteriorly, plus two superior and two inferior articular facets. The apposition of a superior and inferior facet constitutes a *facet joint*. The functions of the posterior spine are to protect the spinal cord and nerves within the spinal canal and to stabilize the spine by providing sites for the attachment of muscles and ligaments. The contraction of muscles attached to the spinous and transverse processes produces a system of pulleys and levers that results in flexion, extension, and lateral bending movements of the spine.

Nerve root injury (*radiculopathy*) is a common cause of neck, arm, low back, and leg pain (Figs. 12-2 and 12-3). The nerve roots exit at a level above their respective vertebral bodies in the cervical region (the C7 nerve root exits at the C6-C7 level) and below their respective vertebral bodies in the thoracic and lumbar regions (the T1 nerve root exits at the T1-T2 level). The cervical nerve roots follow a short intraspinal course before exiting. By contrast, because the spinal cord ends at the vertebral L1 or L2 level, the lumbar nerve roots follow a long intraspinal course and can be injured anywhere from the upper lumbar spine to their exit at the intervertebral

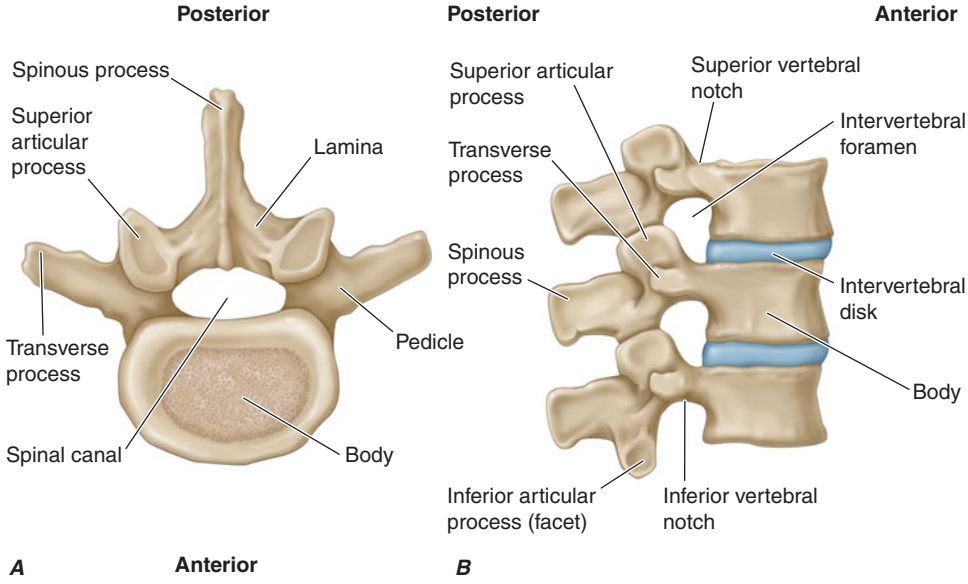


FIGURE 7-1
Vertebral anatomy. (*From A Gauthier Cornuelle, DH Gronefeld: Radiographic Anatomy Positioning. New York, McGraw-Hill, 1998; with permission.*)

foramen. For example, disk herniation at the L4-L5 level commonly produces compression of the traversing S1 nerve root (Fig. 7-3).

Pain-sensitive structures in the spine include the periosteum of the vertebrae, dura, facet joints, annulus fibrosus of the intervertebral disk, epidural veins, and the posterior longitudinal ligament. Disease of these diverse structures may explain many cases of back pain without nerve root compression. The nucleus pulposus of the intervertebral disk is not pain-sensitive under normal circumstances. Pain sensation is conveyed partially by the sinuvertebral nerve that arises from the spinal nerve at each spine segment and reenters the spinal canal through the intervertebral foramen at the same level. The lumbar and cervical spine possesses the greatest potential for movement and injury.

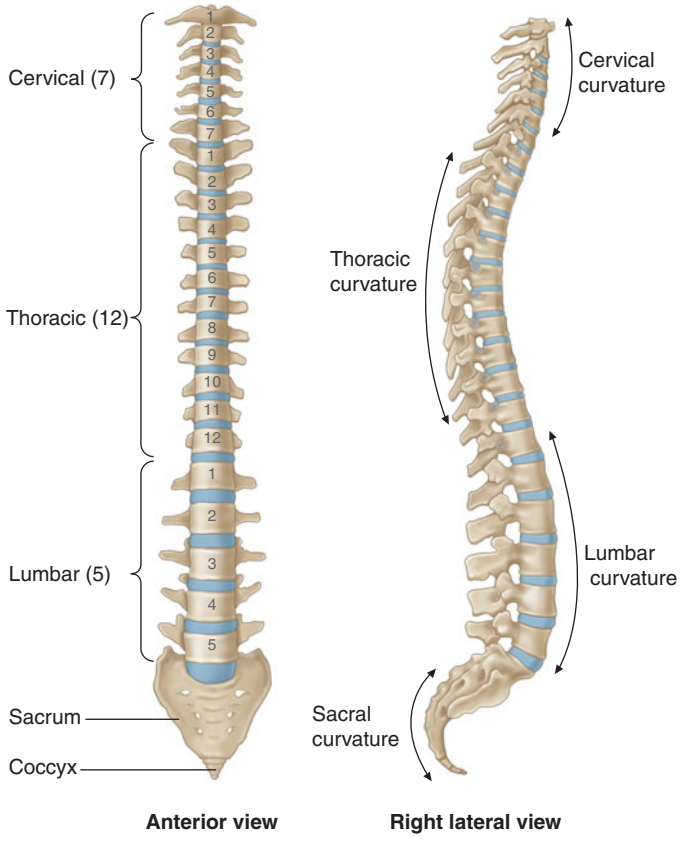


FIGURE 7-2
Spinal column. (*From A Gauthier Cornuelle, DH Gronefeld: Radiographic Anatomy Positioning. New York, McGraw-Hill, 1998; with permission.*)

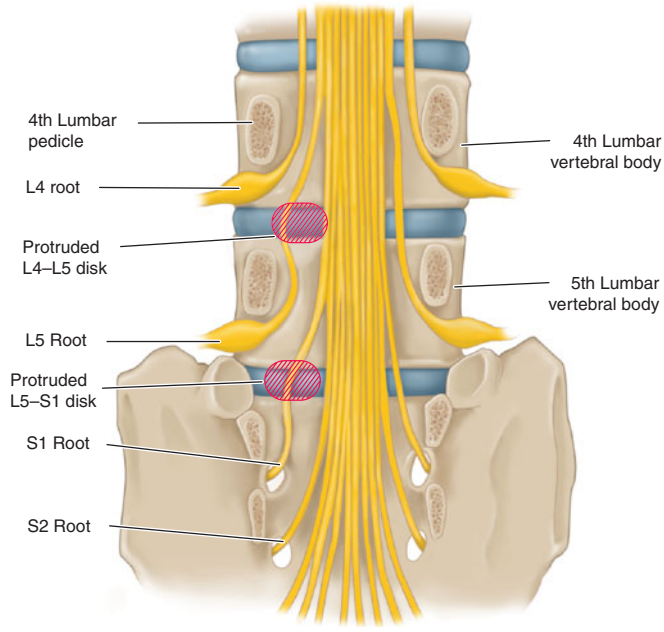


FIGURE 7-3
Compression of L5 and S1 roots by herniated disks. (*From RD Adams et al: Principles of Neurology, 8th ed. New York, McGraw-Hill, 2005; with permission.*)

Approach to the Patient: BACK PAIN

TYPES OF BACK PAIN Understanding the type of pain experienced by the patient is the essential first step. Attention is also focused on identification of risk factors for serious underlying diseases; the majority of these are due to radiculopathy, fracture, tumor, infection, or referred pain from visceral structures (Table 7-1).

Local pain is caused by stretching of pain-sensitive structures that compress or irritate sensory nerve endings. The site of the pain is near the affected part of the back.

Pain referred to the back may arise from abdominal or pelvic viscera. The pain is usually described as primarily abdominal or pelvic but is accompanied by back pain and usually unaffected by posture. The patient may occasionally complain of back pain only.

Pain of spine origin may be located in the back or referred to the buttocks or legs. Diseases affecting the upper lumbar spine tend to refer pain to the lumbar region, groin, or anterior thighs. Diseases affecting the lower lumbar spine tend to produce pain referred to the buttocks, posterior thighs, or rarely the calves or feet. Provocative injections into pain-sensitive structures of the lumbar spine may produce leg pain that does not follow a dermatomal distribution. This "sclerotomal" pain may explain some cases of back and leg pain without evidence of nerve root compression.

Radicular back pain is typically sharp and radiates from the lumbar spine to the leg within the territory of a nerve root (see Lumbar Disk Disease, later in the chpater). Coughing, sneezing, or voluntary contraction of abdominal muscles (lifting heavy objects or straining at stool) may elicit the radiating pain. The pain may increase in postures that stretch the nerves and nerve roots. Sitting stretches the sciatic nerve (L5 and S1 roots) because the nerve passes posterior to the hip. The femoral nerve (L2, L3, and L4 roots) passes anterior to the hip and is not stretched by sitting. The description of the pain alone often fails to distinguish between sclerotomal pain and radiculopathy.

Pain associated with muscle spasm, although of obscure origin, is commonly associated with many spine disorders. The spasms are accompanied by abnormal posture, taut paraspinal muscles, and dull pain.

Knowledge of the circumstances associated with the onset of back pain is important when weighing possible serious underlying causes for the pain. Some patients involved in accidents or work-related injuries may exaggerate their pain for the purpose of compensation or for psychological reasons.

TABLE 7-1

ACUTE LOW BACK PAIN: RISK FACTORS FOR AN IMPORTANT STRUCTURAL CAUSE

History
Pain worse at rest or at night
Prior history of cancer
History of chronic infection (esp. lung, urinary tract, skin)
History of trauma
Incontinence
Age >50 years
Intravenous drug use
Glucocorticoid use
History of a rapidly progressive neurologic deficit
Examination
Unexplained fever
Unexplained weight loss
Percussion tenderness over the spine
Abdominal, rectal, or pelvic mass
Patrick's sign or heel percussion sign
Straight leg or reverse straight-leg raising signs
Progressive focal neurologic deficit

EXAMINATION OF THE BACK A physical examination that includes the abdomen and rectum is advisable. Back pain referred from visceral organs may be reproduced during palpation of the abdomen [pancreatitis, abdominal aortic aneurysm (AAA)] or percussion over the costovertebral angles (pyelonephritis).

The normal spine has cervical and lumbar lordosis, and a thoracic kyphosis. Exaggeration of these normal alignments may result in hyperkyphosis of the thoracic spine or hyperlordosis of the lumbar spine. Inspection may reveal a lateral curvature of the spine (scoliosis) or an asymmetry in the paraspinal muscles, suggesting muscle spasm. Back pain of bony spine origin is often reproduced by palpation or percussion over the spinous process of the affected vertebrae.

Forward bending is often limited by paraspinal muscle spasm; the latter may flatten the usual lumbar lordosis. Flexion of the hips is normal in patients with lumbar spine disease, but flexion of the lumbar spine is limited and sometimes painful. Lateral bending to the side opposite the injured spinal element may stretch the damaged tissues, worsen pain, and limit motion. Hyperextension of the spine (with the patient prone or standing) is limited when nerve root compression, facet joint pathology, or other bony spine disease is present.

Pain from hip disease may mimic pain of lumbar spine disease. Hip pain can be reproduced by internal and external rotation at the hip with the knee and hip in flexion (Patrick sign) and by tapping the heel with the examiner's palm while the leg is extended.

With the patient lying flat, passive flexion of the extended leg at the hip stretches the L5 and S1 nerve roots and the sciatic nerve. Passive dorsiflexion of the foot during the maneuver adds to the stretch.

While flexion to at least 80° is normally possible without causing pain, tight hamstring muscles are a source of pain in some patients. The *straight leg–raising (SLR)* test is positive if the maneuver reproduces the patient's usual back or limb pain. Eliciting the SLR sign in the sitting position may help determine if the finding is reproducible. The patient may describe pain in the low back, buttocks, posterior thigh, or lower leg, but the key feature is reproduction of the patient's usual pain. The *crossed SLR sign* is positive when flexion of one leg reproduces the pain in the opposite leg or buttocks. The crossed SLR sign is less sensitive but more specific for disk herniation than the SLR sign. The nerve or nerve root lesion is always on the side of the pain. The *reverse SLR sign* is elicited by standing the patient next to the examination table and passively extending each leg with the knee fully extended. This maneuver, which stretches the L2-L4 nerve roots and the femoral nerve, is considered positive if the patient's usual back or limb pain is reproduced.

The neurologic examination includes a search for focal weakness or muscle atrophy, focal reflex changes, diminished sensation in the legs, and signs of spinal cord injury. The examiner should be alert to the possibility of breakaway weakness, defined as fluctuating strength during muscle testing. Breakaway weakness may be due to pain or a combination of pain and underlying true weakness. Breakaway weakness without pain is due to lack of effort. In uncertain cases, electromyography (EMG) can determine whether or not true weakness is present. Findings with specific nerve root lesions are shown in **Table 7-2** and are discussed below.

LABORATORY, IMAGING, AND EMG STUDIES

Routine laboratory studies are rarely needed for the initial evaluation of nonspecific acute (<3 months duration) low back pain (ALBP). If risk factors for a serious underlying cause are present, then laboratory studies [complete blood count (CBC), erythrocyte sedimentation rate (ESR), urinalysis] are indicated.

CT scanning is superior to routine x-rays for the detection of fractures involving posterior spine structures, craniocervical and craniothoracic junctions, C1 and C2 vertebrae, bone fragments within the spinal canal, or malalignment; CT scans are increasingly used as a primary screening modality for moderate to severe trauma. In the absence of risk factors, these imaging studies are rarely helpful in nonspecific ALBP. MRI and CT-myelography are the radiologic tests of choice for evaluation of most serious diseases involving the spine. MRI is superior for the definition of soft tissue

TABLE 7-2

LUMBOSACRAL RADICULOPATHY—NEUROLOGIC FEATURES

LUMBOSACRAL NERVE ROOTS	EXAMINATION FINDINGS			PAIN DISTRIBUTION
	REFLEX	SENSORY	MOTOR	
L2[a]	—	Upper anterior thigh	Psoas (hip flexion)	Anterior thigh
L3[a]	—	Lower anterior thigh Anterior knee	Psoas (hip flexion) Quadriceps (knee extension) Thigh adduction	Anterior thigh, knee
L4[a]	Quadriceps (knee)	Medial calf	Quadriceps (knee extension)[b] Thigh adduction Tibialis anterior (foot dorsiflexion)	Knee, medial calf Anterolateral thigh
L5[c]	—	Dorsal surface—foot Lateral calf	Peroneii (foot eversion)[b] Tibialis anterior (foot dorsiflexion) Gluteus medius (hip abduction) Toe dorsiflexors	Lateral calf, dorsal foot, posterolateral thigh, buttocks
S1[c]	Gastrocnemius/ soleus (ankle)	Plantar surface—foot Lateral aspect—foot	Gastrocnemius/soleus (foot plantar flexion)[b] Abductor hallucis (toe flexors)[b] Gluteus maximus (hip extension)	Bottom foot, posterior calf, posterior thigh, buttocks

[a]Reverse straight leg–raising sign present—see "Examination of the Back."
[b]These muscles receive the majority of innervation from this root.
[c]Straight leg–raising sign present—see "Examination of the Back."

structures, whereas CT-myelography provides optimal imaging of the lateral recess of the spinal canal and bony lesions and is tolerated by claustrophobic patients. While the added diagnostic value of modern neuroimaging is significant, there is concern that these studies may be overutilized in patients with ALBP.

Electrodiagnostic studies can be used to assess the functional integrity of the peripheral nervous system (Chap. 3). Sensory nerve conduction studies are normal when focal sensory loss is due to nerve root damage because the nerve roots are proximal to the nerve cell bodies in the dorsal root ganglia. The diagnostic yield of needle EMG is higher than that of nerve conduction studies for radiculopathy. Denervation changes in a myotomal (segmental) distribution are detected by sampling multiple muscles supplied by different nerve roots and nerves; the pattern of muscle involvement indicates the nerve root(s) responsible for the injury. Needle EMG provides objective information about motor nerve fiber injury when the clinical evaluation of weakness is limited by pain or poor effort. EMG and nerve conduction studies will be normal when only limb pain or sensory nerve root injury or irritation is present.

CAUSES OF BACK PAIN (Table 7-3)

CONGENITAL ANOMALIES OF THE LUMBAR SPINE

Spondylolysis is a bony defect in the pars interarticularis (a segment near the junction of the pedicle with the lamina) of the vertebra; the etiology may be a stress fracture in a congenitally abnormal segment. The defect (usually bilateral) is best visualized on oblique projections in plain x-rays, CT scan, or single photon emission CT (SPECT) bone scan and occurs in the setting of a single injury, repeated minor injuries, or growth. Although frequently asymptomatic, it is the most common cause of persistent low back pain in adolescents and is often activity-related.

Spondylolisthesis is the anterior slippage of the vertebral body, pedicles, and superior articular facets, leaving the posterior elements behind. Spondylolisthesis can be associated with spondylolysis, congenital anomalies of the lumbosacral junction, infection, osteoporosis, tumor, trauma, prior surgery, or degenerative spine disease. It occurs more frequently in women. The slippage may be asymptomatic or may cause low back pain and hamstring tightness, nerve root injury (the L5 root most frequently), or symptomatic spinal stenosis. Tenderness may be elicited near the segment that has "slipped" forward (most often L4 on L5 or occasionally L5 on S1). A "step" may be present on deep palpation of the posterior elements of the segment above the spondylolisthetic joint. The trunk may be shortened and the abdomen protuberant as a result of extreme forward displacement of L4 on L5; in severe cases cauda equina syndrome (CES) may occur (see later). Surgery is considered for symptoms persisting for >1 year that do not respond to conservative measures (e.g., rest, physical therapy). Surgery is usually indicated for cases with progressive neurologic deficit, abnormal gait or postural deformity, slippage >50%, or scoliosis.

TABLE 7-3

CAUSES OF BACK AND NECK PAIN

Congenital/developmental
Spondylolysis and spondylolisthesis[a]
Kyphoscoliosis[a]
Spina bifida occulta[a]
Tethered spinal cord[a]
Minor trauma
Strain or sprain
Whiplash injury[b]
Fractures
Traumatic—falls, motor vehicle accidents
Atraumatic—osteoporosis, neoplastic infiltration, exogenous steroids
Intervertebral disk herniation
Degenerative
Disk-osteophyte complex
Internal disk disruption
Spinal stenosis with neurogenic claudication[a]
Uncovertebral joint disease[b]
Atlantoaxial joint disease (e.g., rheumatoid arthritis)[a]
Arthritis
Spondylosis
Facet or sacroiliac arthropathy
Autoimmune (e.g., anklyosing spondylitis, Reiter's syndrome)
Neoplasms—metastatic, hematologic, primary bone tumors
Infection/inflammation
Vertebral osteomyelitis
Spinal epidural abscess
Septic disk
Meningitis
Lumbar arachnoiditis[a]
Metabolic
Osteoporosis—hyperparathyroidism, immobility
Osteosclerosis (e.g., Paget's disease)
Vascular
Abdominal aortic aneurysm
Vertebral artery dissection[b]
Other
Referred pain from visceral disease
Postural
Psychiatric, malingering, chronic pain syndromes

[a]Low back pain only.
[b]Neck pain only.

Spina bifida occulta is a failure of closure of one or several vertebral arches posteriorly; the meninges and spinal cord are normal. A dimple or small lipoma may overlie the defect. Most cases are asymptomatic and discovered incidentally during evaluation for back pain.

Tethered cord syndrome usually presents as a progressive cauda equina disorder (see later), although myelopathy may also be the initial manifestation. The patient is often a young adult who complains of perineal or perianal pain, sometimes following minor trauma. Neuroimaging studies reveal a low-lying conus (below L1-L2) and a short and thickened filum terminale.

TRAUMA

A patient with a complaint of back pain and inability to move the legs may have a spinal fracture or dislocation, and, with fractures above L1, spinal cord compression. Care must be taken to avoid further damage to the spinal cord or nerve roots by immobilizing the back pending results of x-rays.

Sprains and Strains

The terms *low back sprain*, *strain*, or *mechanically induced muscle spasm* refer to minor, self-limited injuries associated with lifting a heavy object, a fall, or a sudden deceleration such as in an automobile accident. These terms are used loosely and do not clearly describe a specific anatomic lesion. The pain is usually confined to the lower back, and there is no radiation to the buttocks or legs. Patients with paraspinal muscle spasm often assume unusual postures.

Traumatic Vertebral Fractures

Most traumatic fractures of the lumbar vertebral bodies result from injuries producing anterior wedging or compression. With severe trauma, the patient may sustain a fracture-dislocation or a "burst" fracture involving the vertebral body and posterior elements. Traumatic vertebral fractures are caused by falls from a height (a pars interarticularis fracture of the L5 vertebra is common), sudden deceleration in an automobile accident, or direct injury. Neurologic impairment is common, and early surgical treatment is indicated. In victims of blunt trauma, CT scans of the chest, abdomen, or pelvis can be reformatted to detect associated vertebral fractures.

LUMBAR DISK DISEASE

This is a common cause of chronic or recurrent low back and leg pain (Figs. 7-3 and 7-4). Disk disease is most likely to occur at the L4-L5 and L5-S1 levels, but upper lumbar levels are involved occasionally. The cause is often unknown; the risk is increased in overweight individuals. Disk herniation is unusual prior to age 20 and is rare in the fibrotic disks of the elderly. Degeneration of the nucleus pulposus and the annulus fibrosus increases with age and may be asymptomatic or painful. Genetic factors may play a role in predisposing some patients to disk degeneration. The pain may be located in the low back only or referred to the leg, buttock, or hip. A sneeze, cough, or trivial movement may cause the nucleus pulposus to prolapse, pushing the frayed and weakened annulus posteriorly. With severe disk disease, the nucleus may protrude through the annulus (herniation) or become extruded to lie as a free fragment in the spinal canal.

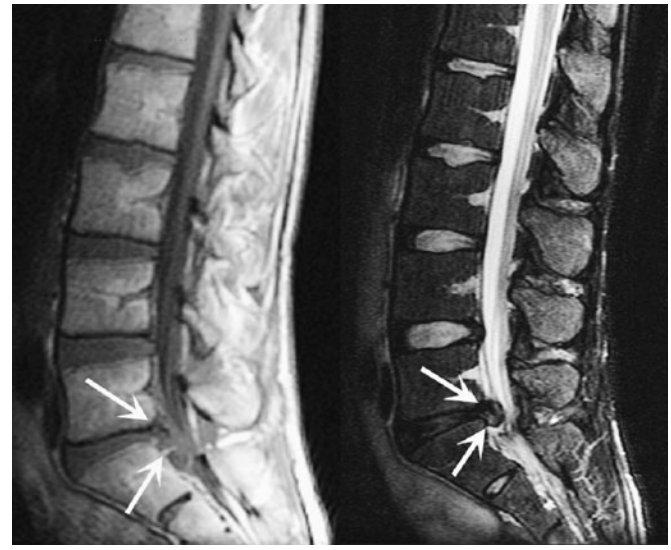


FIGURE 7-4

MRI of lumbar herniated disk; left S1 radiculopathy. Sagittal T1-weighted image on the left with arrows outlining disk margins. Sagittal T2 image on the right reveals a protruding disk at the L5–S1 level (*arrows*), which displaces the central thecal sac.

The mechanism by which intervertebral disk injury causes back pain is controversial. The inner annulus fibrosus and nucleus pulposus are normally devoid of innervation. Inflammation and production of proinflammatory cytokines within the protruding or ruptured disk may trigger or perpetuate back pain. Ingrowth of nociceptive (pain) nerve fibers into inner portions of a diseased disk may be responsible for chronic "diskogenic" pain. Nerve root injury (radiculopathy) from disk herniation may be due to compression, inflammation, or both; pathologically, demyelination and axonal loss are usually present.

Symptoms of a ruptured disk include back pain, abnormal posture, limitation of spine motion (particularly flexion), or radicular pain. A dermatomal pattern of sensory loss or a reduced or absent deep tendon reflex is more suggestive of a specific root lesion than is the pattern of pain. Motor findings (focal weakness, muscle

atrophy, or fasciculations) occur less frequently than focal sensory or reflex changes. Symptoms and signs are usually unilateral, but bilateral involvement does occur with large central disk herniations that compress multiple descending nerve roots within the spinal canal. Clinical manifestations of specific nerve root lesions are summarized in Table 7-2. There is suggestive evidence that lumbar disk herniation with a nonprogressive nerve root deficit can be managed nonsurgically. The size of the disk protrusion may naturally decrease over time.

The differential diagnosis covers a variety of serious and treatable conditions, including epidural abscess, hematoma, or tumor. Fever, constant pain uninfluenced by position, sphincter abnormalities, or signs of spinal cord disease suggests an etiology other than lumbar disk disease. Bilateral absence of ankle reflexes can be a normal finding in old age or a sign of bilateral S1 radiculopathy. An absent deep tendon reflex or focal sensory loss may indicate injury to a nerve root, but other sites of injury along the nerve must also be considered. For example, an absent knee reflex may be due to a femoral neuropathy or an L4 nerve root injury. A loss of sensation over the foot and lateral lower calf may result from a peroneal or lateral sciatic neuropathy or an L5 nerve root injury. Focal muscle atrophy may reflect a nerve root or peripheral nerve injury, an anterior horn cell disease, or disuse.

An MRI scan or CT-myelogram is necessary to establish the location and type of pathology. Spinal MRI yields exquisite views of intraspinal and adjacent soft tissue anatomy. Bony lesions of the lateral recess or intervertebral foramen are optimally visualized by CT-myelography. The correlation of neuroradiologic findings to symptoms, particularly pain, is not simple. Contrast-enhancing tears in the annulus fibrosus or disk protrusions are widely accepted as common sources of back pain; however, many studies have found that most asymptomatic adults have similar findings. Asymptomatic disk protrusions are also common and may enhance with contrast. Furthermore, in patients with known disk herniation treated either medically or surgically, persistence of the herniation 10 years later had no relationship to the clinical outcome. In summary, MRI findings of disk protrusion, tears in the annulus fibrosus, or contrast enhancement are common incidental findings that, by themselves, should not dictate management decisions for patients with back pain.

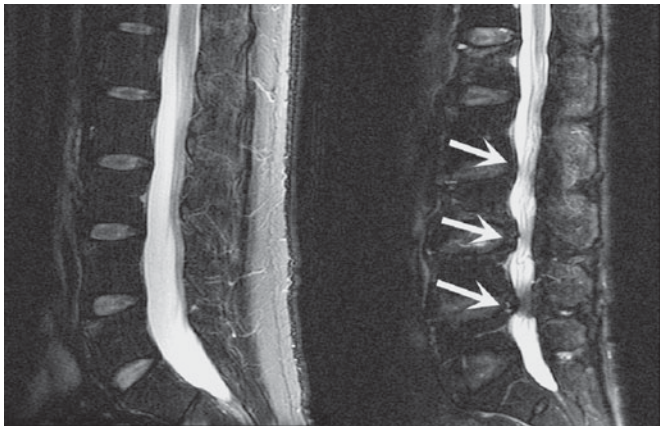
There are four indications for intervertebral disk surgery: (1) progressive motor weakness from nerve root injury demonstrated on clinical examination or EMG, (2) bowel or bladder disturbance or other signs of spinal cord compression, (3) incapacitating nerve root pain despite conservative treatment for 4 weeks at a minimum, and (4) recurrent incapacitating pain despite conservative treatment. The latter two criteria are more subjective and less well established than the others. Surgical treatment should also be considered if steady pain and/or neurologic findings do not substantially improve over 4–12 weeks.

The usual surgical procedure is a partial hemilaminectomy with excision of the prolapsed disk. Fusion of the involved lumbar segments should be considered only if significant spinal instability is present (i.e., degenerative spondylolisthesis or isthmic spondylolysis). Over a recent 5-year period, the number of lumbar fusion procedures performed in the United States more than doubled, for uncertain reasons. There are no large prospective, randomized trials comparing fusion to other types of surgical intervention. In one study, patients with persistent low back pain despite an initial diskectomy fared no better with spine fusion than with a conservative regimen of cognitive intervention and exercise.

Cauda equina syndrome (CES) signifies an injury of multiple lumbosacral nerve roots within the spinal canal. Low back pain, weakness and areflexia in the legs, saddle anesthesia, and loss of bladder function may occur. The problem must be distinguished from disorders of the lower spinal cord (conus medullaris syndrome), acute transverse myelitis (Chap. 30), and Guillain-Barré syndrome (Chap. 41). Combined involvement of the conus medullaris and cauda equina can occur. CES is commonly due to a ruptured lumbosacral intervertebral disk, lumbosacral spine fracture, hematoma within the spinal canal (e.g., following lumbar puncture in patients with coagulopathy), compressive tumor, or other mass lesion. Treatment options include surgical decompression, sometimes urgently in an attempt to restore or preserve motor or sphincter function, or radiotherapy for metastatic tumors (Chap. 32).

DEGENERATIVE CONDITIONS

Lumbar spinal stenosis describes a narrowed lumbar spinal canal. *Neurogenic claudication* is the usual symptom, consisting of back and buttock or leg pain induced by walking or standing and relieved by sitting. Symptoms in the legs are usually bilateral. Lumbar stenosis, by itself, is frequently asymptomatic, and the correlation between the severity of symptoms and degree of stenosis of the spinal canal is poor. Unlike vascular claudication, symptoms are often provoked by standing without walking. Unlike lumbar disk disease, symptoms are usually relieved by sitting. Focal weakness, sensory loss, or reflex changes may occur when spinal stenosis is associated with radiculopathy. Severe neurologic deficits, including paralysis and urinary incontinence, occur rarely. Spinal stenosis can be acquired (75%), congenital, or due to a combination of these factors. Congenital forms (achondroplasia, idiopathic) are characterized by short, thick pedicles that produce both spinal canal and lateral recess stenosis. Acquired factors that contribute to spinal stenosis include degenerative diseases (spondylosis, spondylolisthesis, scoliosis), trauma,



A B

FIGURE 7-5

Spinal stenosis. Sagittal T2 fast spin echo magnetic resonance imaging of a normal (***A***) and stenotic (***B***) lumbar spine, revealing multifocal narrowing (*arrows*) of the cerebrospinal fluid spaces surrounding the nerve roots within the thecal sac.

spine surgery, metabolic or endocrine disorders (epidural lipomatosis, osteoporosis, acromegaly, renal osteodystrophy, hypoparathyroidism), and Paget's disease. MRI provides the best definition of the abnormal anatomy (Fig. 7-5).

Conservative treatment of symptomatic spinal stenosis includes nonsteroidal anti-inflammatory drugs (NSAIDs), exercise programs, and symptomatic treatment of acute pain episodes. Surgical therapy is considered when medical therapy does not relieve symptoms sufficiently to allow for activities of daily living or when significant focal neurologic signs are present. Most patients with neurogenic claudication treated surgically experience at least 75% relief of back and leg pain. Up to 25% develop recurrent stenosis at the same spinal level or an adjacent level 5 years after the initial surgery; recurrent symptoms usually respond to a second surgical decompression.

Facet joint hypertrophy can produce unilateral radicular symptoms or signs due to bony compression; symptoms are often indistinguishable from disk-related radiculopathy. Stretch signs, focal motor weakness, hyporeflexia, or dermatomal sensory loss may be present. Hypertrophic superior or inferior facets can be visualized by x-rays, CT, or MRI. Surgical foraminotomy results in long-term relief of leg and back pain in 80–90% of these patients. The usefulness of therapeutic facet joint blocks for pain has not been rigorously studied.

ARTHRITIS

Spondylosis, or osteoarthritic spine disease, typically occurs in later life and primarily involves the cervical and lumbosacral spine. Patients often complain of back pain that is increased with movement and associated with stiffness. The relationship between clinical symptoms and radiologic findings is usually not straightforward. Pain may be prominent when x-ray, CT, or MRI findings are minimal, and large osteophytes can be seen in asymptomatic patients. Radiculopathy occurs when hypertrophied facets and osteophytes compress nerve roots in the lateral recess or intervertebral foramen. Osteophytes arising from the vertebral body may cause or contribute to central spinal canal stenosis. Disc degeneration may also play a role in reducing the cross-sectional area of the intervertebral foramen; the descending pedicle may compress the exiting nerve root. Rarely, osteoarthritic changes in the lumbar spine are sufficient to compress the cauda equina.

Ankylosing Spondylitis

This distinctive arthritic spine disease typically presents with the insidious onset of low back and buttock pain. Patients are often males below age 40. Associated features include morning back stiffness, nocturnal pain, pain unrelieved by rest, an elevated ESR, and the histocompatibility antigen HLA-B27. Onset at a young age and back pain improving with exercise are characteristic. Loss of the normal lumbar lordosis and exaggeration of thoracic kyphosis develop as the disease progresses. Inflammation and erosion of the outer fibers of the annulus fibrosus at the point of contact with the vertebral body are followed by ossification and bony growth that bridges adjacent vertebral bodies and reduces spine mobility in all planes. Radiologic hallmarks are periarticular destructive changes, sclerosis of the sacroiliac joints, and bridging of vertebral bodies to produce the fused "bamboo spine."

Stress fractures through the spontaneously ankylosed posterior bony elements of the rigid, osteoporotic spine may produce focal pain, spinal instability, spinal cord compression, or CES. Atlantoaxial subluxation with spinal cord compression occasionally occurs. Ankylosis of the ribs to the spine and a decrease in the height of the thoracic spine may compromise respiratory function. For many patients, therapy with anti-tumor necrosis factor agents is effective in reducing disease activity. Similar to ankylosing spondylitis, restricted movements may accompany Reiter's syndrome, psoriatic arthritis, and chronic inflammatory bowel disease.

NEOPLASMS

(See Chap. 32) Back pain is the most common neurologic symptom in patients with systemic cancer and may be the presenting symptom. The cause is usually vertebral metastases. Metastatic carcinoma (breast, lung, prostate, thyroid, kidney, gastrointestinal tract), multiple myeloma, and non-Hodgkin's and Hodgkin's lymphomas frequently involve the spine. Cancer-related back pain

tends to be constant, dull, unrelieved by rest, and worse at night. By contrast, mechanical low back pain usually improves with rest. Plain x-rays may or may not show destructive lesions in one or several vertebral bodies without disk space involvement. MRI, CT, and CT-myelography are the studies of choice when spinal metastasis is suspected. MRI is preferred, but the most rapidly available procedure is best because the patient's condition may worsen quickly. Less than 5% of patients who are nonambulatory at the time of diagnosis ever regain the ability to walk, thus early diagnosis is crucial.

INFECTIONS/INFLAMMATION

Vertebral osteomyelitis is usually caused by staphylococci, but other bacteria or tuberculosis (Pott's disease) may be responsible. The primary source of infection is usually the urinary tract, skin, or lungs. Intravenous drug use is a well-recognized risk factor. Whenever pyogenic osteomyelitis is found, the possibility of bacterial endocarditis should be considered. Back pain exacerbated by motion and unrelieved by rest, spine tenderness over the involved spine segment, and an elevated ESR are the most common findings in vertebral osteomyelitis. Fever or an elevated white blood cell count is found in a minority of patients. Plain radiographs may show a narrowed disk space with erosion of adjacent vertebrae; however, these diagnostic changes may take weeks or months to appear. MRI and CT are sensitive and specific for osteomyelitis; CT may be more readily available in emergency settings and better tolerated by some patients with severe back pain.

Spinal epidural abscess (Chap. 30) presents with back pain (aggravated by movement or palpation) and fever. Signs of nerve root injury or spinal cord compression may be present. The abscess may track over multiple spinal levels and is best delineated by spine MRI.

Lumbar adhesive arachnoiditis with radiculopathy is due to fibrosis following inflammation within the subarachnoid space. The fibrosis results in nerve root adhesions, and presents as back and leg pain associated with motor, sensory, or reflex changes. Causes of arachnoiditis include multiple lumbar operations, chronic spinal infections, spinal cord injury, intrathecal hemorrhage, myelography (rare), intrathecal injection of glucocorticoids or anesthetics, and foreign bodies. The MRI shows clumped nerve roots located centrally or adherent to the dura peripherally, or loculations of cerebrospinal fluid within the thecal sac. Clumped nerve roots may also occur with demyelinating polyneuropathy or neoplastic infiltration. Treatment is usually unsatisfactory. Microsurgical lysis of adhesions, dorsal rhizotomy, and dorsal root ganglionectomy have been tried, but outcomes have been poor. Dorsal column stimulation for pain relief has produced varying results. Epidural injections of glucocorticoids have been of limited value.

METABOLIC CAUSES

Osteoporosis and Osteosclerosis

Immobilization or underlying conditions such as osteomalacia, hyperparathyroidism, hyperthyroidism, multiple myeloma, metastatic carcinoma, or glucocorticoid use may accelerate osteoporosis and weaken the vertebral body, leading to compression fractures and pain. The most common causes of nontraumatic vertebral body fractures are postmenopausal (type 1) or senile (type 2) osteoporosis. Compression fractures occur in up to half of patients with severe osteoporosis, and those who sustain a fracture have a 4.5-fold increased risk for recurrence. The sole manifestation of a compression fracture may be localized back pain or radicular pain exacerbated by movement and often reproduced by palpation over the spinous process of the affected vertebra. The clinical context, neurologic signs, and x-ray appearance of the spine establish the diagnosis. Antiresorptive drugs including bisphosphonates (e.g., alendronate), transdermal estrogen, and tamoxifen have been shown to reduce the risk of osteoporotic fractures. Fewer than one-third of patients with prior compression fractures are adequately treated for osteoporosis despite the increased risk for future fractures; rates of primary prevention among individuals at risk, but without a history of fracture, are even less. Compression fractures above the midthoracic region suggest malignancy; if tumor is suspected, a bone biopsy or diagnostic search for a primary tumor is indicated.

Interventions [percutaneous vertebroplasty (PVP), kyphoplasty] exist for osteoporotic compression fractures associated with debilitating pain. Candidates for PVP have midline back pain, palpation tenderness over the spinous process of the affected vertebral body, <80% loss of vertebral body height, and onset of symptoms within the prior 4 months. The PVP technique consists of injection of polymethylmethacrylate, under fluoroscopic guidance, into the affected vertebral body. Kyphoplasty adds the inflation of a balloon in the vertebral body prior to the injection of cement. Rare complications can include extravasation of cement into the epidural space (resulting in myelopathy) or fatal pulmonary embolism from migration of cement into paraspinal veins. Approximately three-quarters of patients who meet selection criteria have reported enhanced quality of life. Relief of pain following PVP has also been reported in patients with vertebral metastases, myeloma, or hemangiomas.

Osteosclerosis, an abnormally increased bone density often due to Paget's disease, is readily identifiable on routine x-ray studies and may or may not produce back pain. Spinal cord or nerve root compression may result from bony encroachment.

REFERRED PAIN FROM VISCERAL DISEASE

Diseases of the thorax, abdomen, or pelvis may refer pain to the posterior portion of the spinal segment that innervates

the diseased organ. Occasionally, back pain may be the first and only manifestation. Upper abdominal diseases generally refer pain to the lower thoracic or upper lumbar region (eighth thoracic to the first and second lumbar vertebrae), lower abdominal diseases to the mid-lumbar region (second to fourth lumbar vertebrae), and pelvic diseases to the sacral region. Local signs (pain with spine palpation, paraspinal muscle spasm) are absent, and little or no pain accompanies routine movements of the spine.

Low Thoracic or Lumbar Pain with Abdominal Disease

Peptic ulcers or tumors of the posterior wall of the stomach or duodenum typically produce epigastric pain, but midline back or paraspinal pain may occur if retroperitoneal extension is present. Fatty foods are more likely to induce back pain associated with biliary disease. Diseases of the pancreas produce back pain to the right of the spine (head of the pancreas involved) or to the left (body or tail involved). Pathology in retroperitoneal structures (hemorrhage, tumors, pyelonephritis) produces paraspinal pain that radiates to the lower abdomen, groin, or anterior thighs. A mass in the iliopsoas region often produces unilateral lumbar pain with radiation toward the groin, labia, or testicles. The sudden appearance of lumbar pain in a patient receiving anticoagulants suggests retroperitoneal hemorrhage.

Isolated low back pain occurs in 15–20% of patients with a contained rupture of an AAA. The classic clinical triad of abdominal pain, shock, and back pain occurs in <20% of patients. Two of these three features are present in two-thirds of patients, and hypotension is present in half. The typical patient is an elderly male smoker with back pain. Frequently, the diagnosis is initially missed because the symptoms and signs can be nonspecific. Common misdiagnoses include nonspecific back pain, diverticulitis, renal colic, sepsis, and myocardial infarction. A careful abdominal examination revealing a pulsatile mass (present in 50–75% of patients) is an important physical finding. Patients with suspected AAA should be evaluated with abdominal ultrasound, CT, or MRI.

Inflammatory bowel disorders (colitis, diverticulitis) or cancers of the colon may produce lower abdominal pain, midlumbar back pain, or both. The pain may have a beltline distribution around the body. A lesion in the transverse or proximal descending colon may refer pain to the mid or left back at the L2-L3 level. Lesions of the sigmoid colon may refer pain to the upper sacral or midline suprapubic regions or left lower quadrant of the abdomen.

Sacral Pain with Gynecologic and Urologic Disease

Pelvic organs rarely cause low back pain, except for gynecologic disorders involving the uterosacral ligaments. The pain is referred to the sacral region. Endometriosis or uterine cancers may invade the uterosacral ligaments. Pain associated with endometriosis is typically premenstrual and often continues until it merges with menstrual pain. Uterine malposition may cause uterosacral ligament traction (retroversion, descensus, and prolapse) or produce sacral pain after prolonged standing.

Menstrual pain may be felt in the sacral region. The poorly localized, cramping pain can radiate down the legs. Pain due to neoplastic infiltration of nerves is typically continuous, progressive in severity, and unrelieved by rest at night. Less commonly, radiation therapy of pelvic tumors may produce sacral pain from late radiation necrosis of tissue or nerves. Low back pain that radiates into one or both thighs is common in the last weeks of pregnancy.

Urologic sources of lumbosacral back pain include chronic prostatitis, prostate cancer with spinal metastasis (Chap. 32), and diseases of the kidney and ureter. Lesions of the bladder and testes do not usually produce back pain. Infectious, inflammatory, or neoplastic renal diseases may produce ipsilateral lumbosacral pain, as can renal artery or vein thrombosis. Paraspinal lumbar pain may be a symptom of ureteral obstruction due to nephrolithiasis.

OTHER CAUSES OF BACK PAIN

Postural Back Pain

There is a group of patients with nonspecific chronic low back pain (CLBP) in whom no anatomic lesion can be found despite exhaustive investigation. These individuals complain of vague, diffuse back pain with prolonged sitting or standing that is relieved by rest. The physical examination is unrevealing except for "poor posture." Imaging studies and laboratory evaluations do not identify a specific cause. Exercises to strengthen the paraspinal and abdominal muscles are sometimes helpful.

Psychiatric Disease

CLBP may be encountered in patients who seek financial compensation; in malingerers; or in those with concurrent substance abuse, chronic anxiety states, or depression. Many patients with CLBP have a history of psychiatric illness (depression, anxiety, substance abuse) or childhood trauma (physical or sexual abuse) that antedates the onset of back pain. Preoperative psychological assessment has been used to exclude patients with marked psychological impairments that predict a poor surgical outcome.

Unidentified

The cause of low back pain occasionally remains unclear. Some patients have had multiple operations for disk

disease but have persistent pain and disability. The original indications for surgery may have been questionable, with back pain only, no definite neurologic signs, or a minor disk bulge noted on CT or MRI. Scoring systems based upon neurologic signs, psychological factors, physiologic studies, and imaging studies have been devised to minimize the likelihood of unsuccessful surgery.

Rx Treatment: BACK PAIN

ACUTE LOW BACK PAIN (ALBP) ALBP is defined as pain of <3 months' duration. Full recovery can be expected in 85% of adults with ALBP without leg pain. Most have purely "mechanical" symptoms (i.e., pain that is aggravated by motion and relieved by rest).

Observational studies have been used to justify a minimalist approach to this problem. These studies share a number of limitations: (1) a true placebo control group is often lacking; (2) patients who consult different provider groups (generalists, orthopedists, neurologists) are assumed to have similar etiologies for their back pain; (3) no information is provided about the details of treatment; and (4) no attempt to tabulate structural causes of ALBP is made.

The algorithms for the treatment of back pain (**Fig. 7-6**) draw from published clinical practice guidelines (CPGs). However, since CPGs are based on incomplete evidence, guidelines should not substitute for clinical judgment.

The initial assessment excludes serious causes of spine pathology that require urgent intervention, including infection, cancer, and trauma. Risk factors for a serious cause of ALBP are shown in Table 7-1. Laboratory studies are unnecessary if risk factors are absent. Plain spine films or CT are rarely indicated in the first month of symptoms unless a spine fracture is suspected.

Clinical trials have shown no benefit of >2 days of bed rest for uncomplicated ALBP. There is evidence that bed rest is also ineffective for patients with sciatica or for acute back pain with signs of nerve root injury. Similarly, traction is not effective for ALBP. Possible advantages of early ambulation for ALBP include maintenance of cardiovascular conditioning, improved disk and cartilage nutrition, improved bone and muscle strength, and increased endorphin levels. One trial of early vigorous exercise was negative, but the value of less vigorous exercise or other exercise programs are unknown. Early resumption of normal physical activity (without heavy manual labor) is likely to be beneficial.

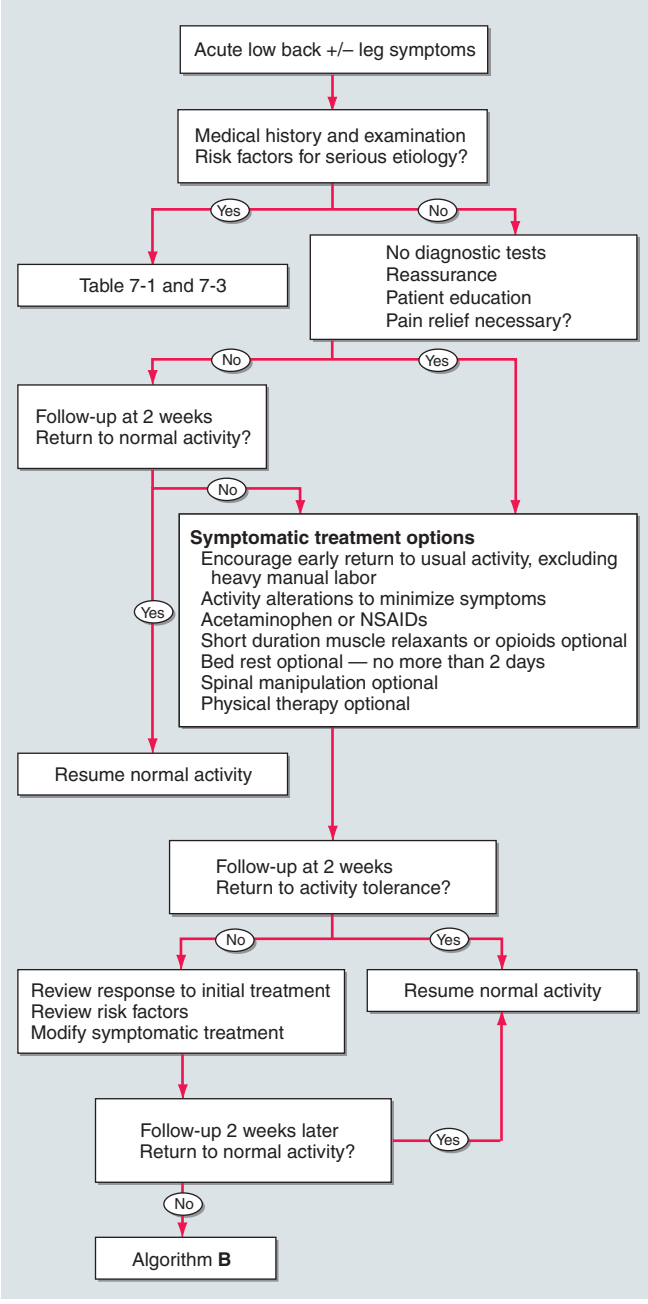
Proof is lacking to support the treatment of acute back and neck pain with acupuncture, transcutaneous electrical nerve stimulation, massage, ultrasound, diathermy, magnets, or electrical stimulation. Cervical collars can be modestly helpful by limiting spontaneous and reflex neck movements that exacerbate pain. Evidence regarding the efficacy of ice is lacking; heat may provide a short-term reduction in pain and disability. These interventions are optional given the lack of negative evidence, low cost, and low risk. Biofeedback has not been studied rigorously. Facet joint, trigger point, and ligament injections are not recommended for acute treatment.

A role for modification of posture has not been validated by rigorous clinical studies. As a practical matter, temporary suspension of activity known to increase mechanical stress on the spine (heavy lifting, prolonged sitting, bending or twisting, straining at stool) may be helpful.

Education is an important part of treatment. Satisfaction and the likelihood of follow-up increase when patients are educated about prognosis, treatment methods, activity modifications, and strategies to prevent future exacerbations. In one study, patients who felt they did not receive an adequate explanation for their symptoms wanted further diagnostic tests. Evidence for the efficacy of structured education programs ("back school") is inconclusive; there is modest evidence for a short-term benefit, but evidence for a long-term benefit is lacking. Randomized studies of back school for primary prevention of low back injury and pain have failed to demonstrate any benefit.

NSAIDs and acetaminophen (Table 5-1) are effective over-the-counter agents for ALBP. Muscle relaxants (cyclobenzaprine, 10 mg PO qhs as initial dose, up to 10 mg PO tid) provide short-term (4–7 days) benefit, particularly at night if sleep is affected, but drowsiness limits daytime use. Opioid analgesics are no more effective than NSAIDs or acetaminophen for initial treatment of ALBP, nor do they increase the likelihood of return to work. Short-term use of opioids may be necessary in patients unresponsive to or intolerant of acetaminophen or NSAIDs. There is no evidence to support the use of oral glucocorticoids or tricyclic antidepressants for ALBP.

Epidural glucocorticoids may occasionally produce short-term pain relief in ALBP with radiculopathy, but proof is lacking for pain relief beyond 1 month. Epidural glucocorticoids, anesthetics, or opioids are not indicated in the initial treatment of ALBP without radiculopathy. Diagnostic nerve root blocks have been advocated to determine if pain originates from a specific nerve root. However, improvement may result even when the nerve root is not responsible for the pain; this may occur as a placebo effect, from a pain-generating lesion located distally along the peripheral nerve, or from anesthesia of the sinuvertebral nerve. Therapeutic nerve root blocks with injection of glucocorticoids and a local anesthetic should be considered only after conservative



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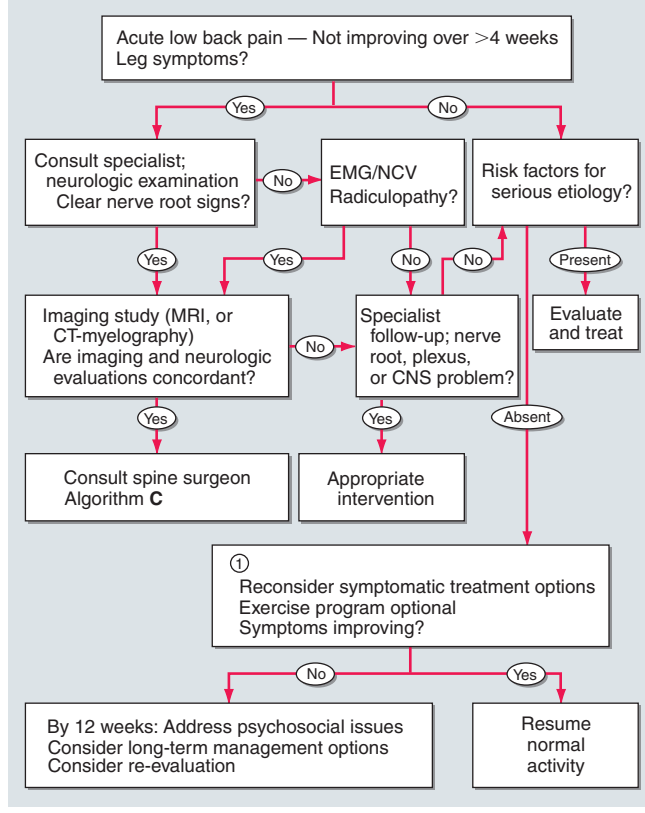

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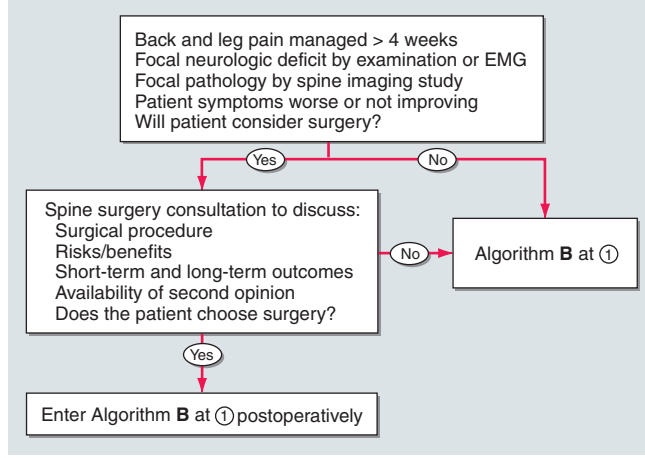

C

FIGURE 7-6

Algorithms for management of acute low back pain, age ≥18 years. ***A.*** Symptoms <3 months, first 4 weeks. ***B.*** Management weeks 4–12. ①, entry point from Algorithm C postoperatively or if patient declines surgery. ***C.*** Surgical options. (NSAIDs, nonsteroidal anti-inflammatory drugs; CBC, complete blood count; ESR, erythrocyte sedimentation rate; UA, urinalysis; EMG, electromyography; NCV, nerve conduction velocity studies; MRI, magnetic resonance imaging; CT, computed tomography; CNS, central nervous system.)

measures fail, particularly when temporary relief of pain is necessary.

A short course of lumbar spinal manipulation or physical therapy (PT) for symptomatic relief of uncomplicated ALBP is a reasonable option. Prospective, randomized studies are difficult to perform in part because there is no consensus about what constitutes an adequate placebo control. Specific PT or chiropractic protocols that may provide benefit have not been fully defined.

CHRONIC LOW BACK PAIN CLBP, defined as pain lasting >12 weeks, accounts for 50% of total back pain costs. Risk factors include obesity, female gender,

older age, prior history of back pain, restricted spinal mobility, pain radiating into a leg, high levels of psychological distress, poor self-rated health, minimal physical activity, smoking, job dissatisfaction, and widespread pain. Combinations of these premorbid factors have been used to predict which individuals with ALBP are likely to develop CLBP. The initial approach to these patients is similar to that for ALBP. Treatment of this heterogeneous group of patients is directed toward the underlying cause when known; the ultimate goal is to restore function to the maximum extent possible.

Many conditions that produce CLBP can be identified by a combination of neuroimaging and electrophysiologic studies. Spine MRI and CT-myelography are almost always the imaging techniques of choice. Imaging studies should be performed only in circumstances when the results are likely to influence management.

Injection studies can be used diagnostically to help determine the anatomic source of back pain. Reproduction of the patient's typical pain with diskography has been used as evidence that a specific disk is the pain generator. Pain relief following a foraminal nerve root block or glucocorticoid injection into a facet has been similarly used as evidence that the facet joint or nerve root is the source. However, the possibility that the injection response was a placebo effect or due to systemic absorption of the glucocorticoids is usually not considered. The value of these procedures in the treatment of CLBP or in the selection of candidates for surgery is largely unknown despite their widespread use. The value of thermography in the assessment of radiculopathy also has not been rigorously studied.

The diagnosis of nerve root injury is most secure when the history, examination, results of imaging studies, and the EMG are concordant. The correlation between CT and EMG for localization of nerve root injury is between 65 and 73%. Up to one-third of asymptomatic adults have a disk protrusion detected by CT or MRI scans. Thus, surgical intervention based solely upon radiologic findings increases the likelihood of an unsuccessful outcome.

An unblinded study in patients with chronic sciatica found that surgery could hasten relief of symptoms by ~2 months; however, at 1 year there was no advantage of surgery over conservative medical therapy, and nearly all patients (95%) in both groups made a full recovery regardless of the treatment approach. A large observational cohort study of patients with lumbar spinal stenosis showed surgery to be relatively safe, likely reducing pain at 2 years with little effect on function or disability.

CLBP can be treated with a variety of conservative measures. Acute and subacute exacerbations are managed with NSAIDs and comfort measures. There is no good evidence to suggest that one NSAID is more effective than another. Bed rest should not exceed 2 days. Activity tolerance is the primary goal, while pain relief is secondary. Exercise programs can reverse atrophy in paraspinal muscles and strengthen extensors of the trunk. Intensive physical exercise or "work hardening" regimens (under the guidance of a physical therapist) have been effective in returning some patients to work, improving walking distances, and diminishing pain. The benefit can be sustained with home exercise regimens. It is difficult to endorse one specific exercise or PT regimen given the heterogeneous nature of this patient group. The role of manipulation, back school, or epidural steroid injections in the treatment of CLBP is unproven. There is no strong evidence to support the use of acupuncture or traction. A reduction in sick leave days, long-term health care utilization, and pension expenditures may offset the initial expense of multidisciplinary treatment programs. Studies of hydrotherapy for CLBP have yielded mixed results; however, given its low risk and cost, hydrotherapy can be considered as a treatment option. Transcutaneous electrical nerve stimulation (TENS) has not been adequately studied in CLBP.

PAIN IN THE NECK AND SHOULDER (Table 7-4)

Neck pain, which usually arises from diseases of the cervical spine and soft tissues of the neck, is common (4.6% of adults in one study). Neck pain arising from the cervical spine is typically precipitated by movement and may be accompanied by focal tenderness and limitation of motion. Pain arising from the brachial plexus, shoulder, or peripheral nerves can be confused with cervical spine disease, but the history and examination usually identify a more distal origin for the pain. Cervical spine trauma, disk disease, or spondylosis may be asymptomatic or painful and can produce a myelopathy, radiculopathy, or both. The nerve roots most commonly affected are C7 and C6.

TRAUMA TO THE CERVICAL SPINE

Trauma to the cervical spine (fractures, subluxation) places the spinal cord at risk for compression. Motor vehicle accidents, violent crimes, or falls account for 87% of spinal cord injuries (Chap. 30). Immediate immobilization of the neck is essential to minimize further spinal cord injury from movement of unstable cervical spine segments. A CT scan is the diagnostic procedure of choice for detection of acute fractures. Following major

TABLE 7-4

CERVICAL RADICULOPATHY—NEUROLOGIC FEATURES

CERVICAL NERVE ROOTS	EXAMINATION FINDINGS			PAIN DISTRIBUTION
	REFLEX	SENSORY	MOTOR	
C5	Biceps	Over lateral deltoid	Supraspinatus[a] (initial arm abduction) Infraspinatus[a] (arm external rotation) Deltoid[a] (arm abduction) Biceps (arm flexion)	Lateral arm, medial scapula
C6	Biceps	Thumb, index fingers Radial hand/forearm	Biceps (arm flexion) Pronator teres (internal forearm rotation)	Lateral forearm, thumb, index finger
C7	Triceps	Middle fingers Dorsum forearm	Triceps[a] (arm extension) Wrist extensors[a] Extensor digitorum[a] (finger extension)	Posterior arm, dorsal forearm, lateral hand
C8	Finger flexors	Little finger Medial hand and forearm	Abductor pollicis brevis (abduction D1) First dorsal interosseous (abduction D2) Abductor digiti minimi (abduction D5)	4th and 5th fingers, medial forearm
T1	Finger flexors	Axilla and medial arm	Abductor pollicis brevis (abduction D1) First dorsal interosseous (abduction D2) Abductor digiti minimi (abduction D5)	Medial arm, axilla

[a]These muscles receive the majority of innervation from this root.

trauma to the cervical spine, injury to the vertebral arteries is common; most lesions are asymptomatic and can be visualized by MRI and angiography.

Whiplash injury is due to trauma (usually automobile accidents) causing cervical musculoligamental sprain or strain due to hyperflexion or hyperextension. This diagnosis should not be applied to patients with fractures, disk herniation, head injury, focal neurologic findings, or altered consciousness. Imaging of the cervical spine is not cost-effective acutely but is useful to detect disk herniations when symptoms persist for >6 weeks following the injury. Severe initial symptoms have been associated with a poor long-term outcome.

CERVICAL DISK DISEASE

Herniation of a lower cervical disk is a common cause of neck, shoulder, arm, or hand pain or tingling. Neck pain, stiffness, and a range of motion limited by pain are the usual manifestations. A herniated cervical disk is responsible for ~25% of cervical radiculopathies. Extension and lateral rotation of the neck narrows the ipsilateral intervertebral foramen and may reproduce radicular symptoms (Spurling's sign). In young persons, acute nerve root compression from a ruptured cervical disk is often due to trauma. Cervical disk herniations are usually posterolateral near the lateral recess and intervertebral foramen. Typical patterns of reflex, sensory, and motor changes that accompany specific cervical nerve root lesions are summarized in Table 7-4; however, (1) overlap in function between adjacent nerve roots is common, (2) symptoms and signs may be evident in only part of the injured nerve root territory, and (3) the location of pain is the most variable of the clinical features.

CERVICAL SPONDYLOSIS

Osteoarthritis of the cervical spine may produce neck pain that radiates into the back of the head, shoulders, or arms, or may be the source of headaches in the posterior occipital region (supplied by the C2-C4 nerve roots). Osteophytes, disk protrusions, and hypertrophic facet or uncovertebral joints may compress one or several nerve roots at the intervertebral foramina (**Fig. 7-7**); this compression accounts for 75% of cervical radiculopathies. The roots most commonly affected are C7 and C6. Narrowing of the spinal canal by osteophytes, ossification of the posterior longitudinal ligament (OPLL), or a large central disk may compress the cervical spinal cord. Combinations of radiculopathy and myelopathy may also be present. Spinal cord involvement is suggested by Lhermitt's symptom, an electrical sensation elicited by neck flexion and radiating down the spine from the neck. When little or no neck pain accompanies cord compression, the diagnosis may be confused with amyotrophic lateral sclerosis (Chap. 27), multiple sclerosis (Chap. 34), spinal cord tumors, or syringomyelia (Chap. 30). The possibility of cervical spondylosis should be considered even when the patient presents with symptoms or signs in the legs only. MRI is the study of choice to define the anatomic abnormalities, but plain CT is adequate to assess bony spurs, foraminal narrowing, or OPLL. EMG and nerve conduction studies can localize and assess the severity of the nerve root injury.

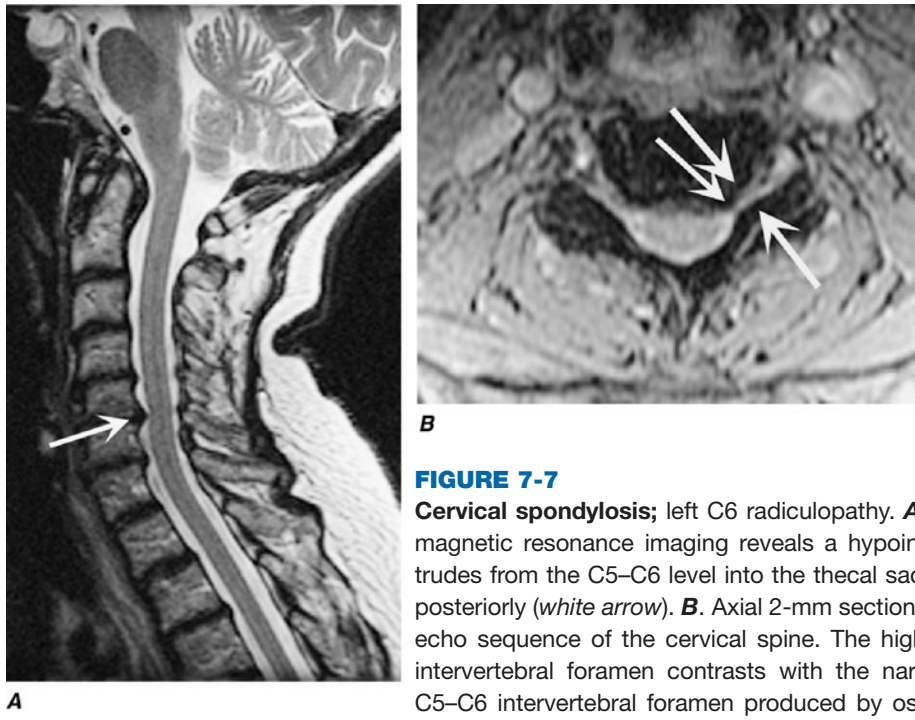

FIGURE 7-7
Cervical spondylosis; left C6 radiculopathy. ***A.*** Sagittal T2 fast spin echo magnetic resonance imaging reveals a hypointense osteophyte that protrudes from the C5–C6 level into the thecal sac, displacing the spinal cord posteriorly (*white arrow*). ***B***. Axial 2-mm section from a 3-D volume gradient echo sequence of the cervical spine. The high signal of the right C5–C6 intervertebral foramen contrasts with the narrow high signal of the left C5–C6 intervertebral foramen produced by osteophytic spurring (*arrows*).

OTHER CAUSES OF NECK PAIN

Rheumatoid arthritis (RA) of the cervical apophyseal joints produces neck pain, stiffness, and limitation of motion. In advanced RA, synovitis of the atlantoaxial joint (C1-C2; Fig. 7-2) may damage the transverse ligament of the atlas, producing forward displacement of the atlas on the axis (atlantoaxial subluxation). Radiologic evidence of atlantoaxial subluxation occurs in 30% of patients with RA. Not surprisingly, the degree of subluxation correlates with the severity of erosive disease. When subluxation is present, careful assessment is important to identify early signs of myelopathy. Occasional patients develop high spinal cord compression leading to quadriparesis, respiratory insufficiency, and death. Surgery should be considered when myelopathy or spinal instability is present.

Ankylosing spondylitis can cause neck pain and less commonly atlantoaxial subluxation; surgery may be required to prevent spinal cord compression. Acute *herpes zoster* presents as acute posterior occipital or neck pain prior to the outbreak of vesicles. *Neoplasms* metastatic to the cervical spine, *infections* (osteomyelitis and epidural abscess), and *metabolic bone diseases* may be the cause of neck pain. Neck pain may also be referred from the heart with coronary artery ischemia (cervical angina syndrome).

THORACIC OUTLET

The thoracic outlet contains the first rib, the subclavian artery and vein, the brachial plexus, the clavicle, and the lung apex. Injury to these structures may result in postural or movement-induced pain around the shoulder and supraclavicular region. *True neurogenic thoracic outlet syndrome* (TOS) results from compression of the lower trunk of the brachial plexus or ventral rami of the C8 or T1 nerve roots by an anomalous band of tissue connecting an elongate transverse process at C7 with the first rib. Signs include weakness of intrinsic muscles of the hand and diminished sensation on the palmar aspect of the fourth and fifth digits. EMG and nerve conduction studies confirm the diagnosis. Treatment consists of surgical resection of the anomalous band. The weakness and wasting of intrinsic hand muscles typically does not improve, but surgery halts the insidious progression of weakness. *Arterial TOS* results from compression of the subclavian artery by a cervical rib; the compression results in poststenotic dilatation of the artery and thrombus formation. Blood pressure is reduced in the affected limb, and signs of emboli may be present in the hand. Neurologic signs are absent. Ultrasound can confirm the diagnosis noninvasively. Treatment is with thrombolysis or anticoagulation (with or without embolectomy) and surgical excision of the cervical rib compressing the subclavian artery or vein. *Disputed TOS* includes a large number of patients with chronic arm and shoulder pain of unclear cause. The lack of sensitive and specific findings on physical examination or laboratory markers for this condition frequently results in diagnostic uncertainty. The role of surgery in disputed TOS is controversial. Multidisciplinary pain management is a conservative approach, although treatment is often unsuccessful.

BRACHIAL PLEXUS AND NERVES

Pain from injury to the brachial plexus or peripheral nerves of the arm can occasionally mimic pain of cervical spine origin. Neoplastic infiltration of the lower trunk of the brachial plexus may produce shoulder pain radiating down the arm, numbness of the fourth and fifth fingers, and weakness of intrinsic hand muscles innervated by the ulnar and median nerves. Postradiation fibrosis (most commonly from treatment of breast cancer) may produce similar findings, although pain is less often present. A Pancoast tumor of the lung is another cause and should be considered, especially when a Horner's syndrome is present. *Suprascapular neuropathy* may produce severe shoulder pain, weakness, and wasting of the supraspinatous and infraspinatous muscles. *Acute brachial neuritis* is often confused with radiculopathy; the acute onset of severe shoulder or scapular pain is followed over days to weeks by weakness of the proximal arm and shoulder girdle muscles innervated by the upper brachial plexus. The onset is often preceded by an infection. The suprascapular and long thoracic nerves are most often affected; the latter results in a winged scapula. Brachial neuritis may also present as an isolated paralysis of the diaphragm. Complete recovery occurs in 75% of patients after 2 years and in 89% after 3 years.

Occasional cases of carpal tunnel syndrome produce pain and paresthesias extending into the forearm, arm, and shoulder resembling a C5 or C6 root lesion. Lesions of the radial or ulnar nerve can mimic a radiculopathy at C7 or C8, respectively. EMG and nerve conduction studies can accurately localize lesions to the nerve roots, brachial plexus, or peripheral nerves. For further discussion of peripheral nerve disorders, see Chap. 40.

SHOULDER

Pain arising from the shoulder can on occasion mimic pain from the spine. If symptoms and signs of radiculopathy are absent, then the differential diagnosis includes mechanical shoulder pain (tendonitis, bursitis, rotator cuff tear, dislocation, adhesive capsulitis, and cuff impingement under the acromion) and referred pain (subdiaphragmatic irritation, angina, Pancoast tumor). Mechanical pain is often worse at night, associated with local shoulder tenderness and aggravated by abduction, internal rotation, or extension of the arm. Pain from shoulder disease may radiate into the arm or hand, but sensory, motor, and reflex changes are absent.

Rx Treatment: NECK PAIN

There are few well-designed clinical trials that address optimal treatment of neck pain or cervical radiculopathy. Relief of pain, prevention of recurrence, and improved neurologic function are reasonable goals. Symptomatic treatment includes the use of analgesic medications and/or a soft cervical collar. Most treatment recommendations reflect anecdotal experience, case series, or conclusions derived from studies of the lumbar spine. Controlled studies of oral prednisone or transforaminal glucocorticoid injections have not been performed. Reasonable indications for cervical disk surgery include a progressive radicular motor deficit, pain that fails to respond to conservative management and limits activities of daily living, or cervical spinal cord compression. Surgical management of herniated cervical disks usually consists of an anterior approach with diskectomy followed by anterior interbody fusion. A simple posterior partial laminectomy with diskectomy is an acceptable alternative approach. Another surgical approach involves implantation of an artificial disk; in one prospective trial, outcomes after 2 years favored the implant over a traditional anterior cervical discectomy with fusion. The artificial disk is not yet approved for general use in the United States. The risk of subsequent radiculopathy or myelopathy at cervical segments adjacent to the fusion is ~3% per year and 26% per decade. Although this risk is sometimes portrayed as a late complication of surgery, it may also reflect the natural history of degenerative cervical disk disease.

Nonprogressive cervical radiculopathy due to a herniated cervical disk may be treated conservatively, even if a focal neurologic deficit is present, with a high rate of success. However, if the cervical radiculopathy is due to bony compression from cervical spondylosis, then surgical decompression is generally indicated to forestall the progression of neurologic signs.

Cervical spondylotic myelopathy is typically managed with either anterior decompression and fusion or laminectomy in order to forestall progression of the myelopathy known to occur in 20–30% of untreated patients. However, one prospective study comparing surgery vs. conservative treatment for mild cervical spondylotic myelopathy showed no difference in outcome after 2 years of follow-up.

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CHAPTER 8

SYNCOPE

Mark D. Carlson

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Syncope, a transient loss of consciousness and postural tone due to reduced cerebral blood flow, is associated with spontaneous recovery. It may occur suddenly, without warning, or may be preceded by symptoms of faintness ("presyncope"). These symptoms include lightheadedness, dizziness, a feeling of warmth, diaphoresis, nausea, and visual blurring occasionally proceeding to transient blindness. Presyncopal symptoms vary in duration and may increase in severity until loss of consciousness occurs, or they may resolve prior to loss of consciousness if the cerebral ischemia is corrected. The differentiation of syncope from seizure is an important, sometimes difficult, diagnostic problem.

Syncope may be benign when it occurs as a result of normal cardiovascular reflex effects on heart rate and vascular tone, or serious when due to a life-threatening cardiac arrhythmia. Syncope may occur as a single event or may be recurrent. Recurrent, unexplained syncope, particularly in an individual with structural heart disease, is associated with a high risk of death (40% mortality within 2 years).

PATHOPHYSIOLOGY

Under normal circumstances systemic blood pressure is regulated by a complex process that includes the musculature, venous valves, autonomic nervous system, and renin-aldosterone-angiotensin system. Knowledge of the processes is important to understanding the pathophysiology of syncope. Approximately three-fourths of the systemic blood volume is contained in the venous bed, and any interference in venous return may lead to a reduction in cardiac output. Cerebral blood flow can be maintained if cardiac output and systemic arterial vasoconstriction compensate, but when these adjustments fail, hypotension with resultant cerebral underperfusion to less than half of normal results in syncope. Normally, the pooling of blood in the lower parts of the body is prevented by (1) pressor reflexes that induce constriction of peripheral arterioles and venules, (2) reflex acceleration of the heart by means of aortic and carotid reflexes, and (3) improvement of venous return to the heart by activity of the muscles of the limbs. Tilting a normal person upright on a tilt table causes some blood to accumulate in the lower limbs and diminishes cardiac output slightly; this may be followed by a slight transitory fall in systolic blood pressure. However, in a patient with defective vasomotor reflexes, upright tilt may produce an abrupt and sustained fall in blood pressure, precipitating a faint. A recent study suggests that susceptibility to neurally-mediated syncope is driven partly by an enhanced vascular response to hypocapnia.

CAUSES OF SYNCOPE

Transiently decreased cerebral blood flow is usually due to one of three general mechanisms: disorders of vascular tone or blood volume, cardiovascular disorders including obstructive lesions and cardiac arrhythmias, or cerebrovascular disease (Table 8-1). Not infrequently, however, the cause of syncope is multifactorial.

DISORDERS OF VASCULAR TONE OR BLOOD VOLUME

Disorders of vascular tone or blood volume that can cause syncope include the reflex syncopes and a number of conditions resulting in orthostatic intolerance. The reflex syncopes—including neurocardiogenic syncope, situational syncope, and carotid sinus hypersensitivity—share common autonomic nervous system pathophysiologic mechanisms: a cardioinhibitory component (e.g., bradycardia due to increased vagal activity), a vasodepressor component (e.g., inappropriate vasodilatation due to sympathetic withdrawal), or both.

Neurocardiogenic (Vasovagal and Vasodepressor) Syncope

The term *neurocardiogenic* is generally used to encompass both vasovagal and vasodepressor syncope. Strictly speaking, vasovagal syncope is associated with both sympathetic withdrawal (vasodilatation) and increased parasympathetic activity (bradycardia), whereas vasodepressor syncope is associated with sympathetic withdrawal alone.

These forms of syncope are the common faint that may be experienced by normal persons; they account for approximately half of all episodes of syncope. Neurocardiogenic syncope is frequently recurrent and commonly precipitated by a hot or crowded environment, alcohol, extreme fatigue, severe pain, hunger, prolonged standing, and emotional or stressful situations. Episodes are often preceded by a presyncopal prodrome lasting seconds to minutes, and rarely occur in the supine position. The individual is usually sitting or standing and experiences weakness, nausea, diaphoresis, lightheadedness, blurred vision, and often a forceful heartbeat with tachycardia followed by cardiac slowing and decreasing blood pressure prior to loss of consciousness. The individual appears pale or ashen; in dark-skinned individuals, the pallor may only be notable in the conjunctivae and lips. Patients with a gradual onset of presyncopal symptoms have time to protect themselves against injury; in others, syncope occurs suddenly, without warning.

The depth and duration of unconsciousness vary. Sometimes the patient remains partly aware of the surroundings, or there may be complete unresponsiveness. The unconscious patient usually lies motionless, with

TABLE 8-1

CAUSES OF SYNCOPE

I. Disorders of Vascular Tone or Blood Volume
  A. Reflex syncopes
    1. Neurocardiogenic
    2. Situational
      Cough
      Micturition
      Defecation
      Valsalva
      Deglutition
    3. Carotid sinus hypersensitivity
  B. Orthostatic hypotension
    1. Drug-induced (antihypertensive or vasodilator drugs)
    2. Pure autonomic failure (idiopathic orthostatic hypotension)
    3. Multisystem atrophies
    4. Peripheral neuropathy (diabetic, alcoholic, nutritional, amyloid)
    5. Physical deconditioning
    6. Sympathectomy
    7. Decreased blood volume
II. Cardiovascular Disorders
  A. Structural and obstructive causes
    1. Pulmonary embolism
    2. Pulmonary hypertension
    3. Atrial myxoma
    4. Mitral valvular stenosis
    5. Myocardial disease (massive acute myocardial infarction)
    6. Left ventricular myocardial restriction or constriction
    7. Pericardial constriction or tamponade
    8. Aortic outflow tract obstruction
    9. Aortic valvular stenosis
    10. Hypertrophic obstructive cardiomyopathy
  B. Cardiac arrhythmias
    1. Bradyarrhythmias
      a. Sinus bradycardia, sinoatrial block, sinus arrest, sick-sinus syndrome
      b. Atrioventricular block
    2. Tachyarrhythmias
      a. Supraventricular tachycardia with structural cardiovascular disease
      b. Atrial fibrillation with the Wolff-Parkinson-White syndrome
      c. Atrial flutter with 1:1 atrioventricular conduction
      d. Ventricular tachycardia
III. Cerebrovascular Disease
  A. Vertebrobasilar insufficiency
  B. Basilar artery migraine
IV. Other Disorders that May Resemble Syncope
  A. Metabolic
    1. Hypoxia
    2. Anemia
    3. Diminished carbon dioxide due to hyperventilation
    4. Hypoglycemia
  B. Psychogenic
    1. Anxiety attacks
    2. Hysterical fainting
  C. Seizures

skeletal muscles relaxed, but a few clonic jerks of the limbs and face may occur. Sphincter control is usually maintained, in contrast to a seizure. The pulse may be feeble or apparently absent, the blood pressure low or undetectable, and breathing may be almost imperceptible. The duration of unconsciousness is rarely longer than a few minutes if the conditions that provoke the episode are reversed. Once the patient is placed in a horizontal position, the strength of the pulse improves, color begins to return to the face, breathing becomes quicker and deeper, and consciousness is restored. Some patients may experience a sense of residual weakness after regaining consciousness, and rising too soon may precipitate another faint. Unconsciousness may be prolonged if an individual remains upright; thus, it is essential that individuals with vasovagal syncope assume a recumbent position as soon as possible. Although usually benign, neurocardiogenic syncope can be associated with prolonged asystole and hypotension, resulting in hypoxic-ischemic injury.

Neurocardiogenic syncope often occurs in the setting of increased peripheral sympathetic activity and venous pooling. Under these conditions, vigorous myocardial contraction of a relatively empty left ventricle is thought to activate myocardial mechanoreceptors and vagal afferent nerve fibers that inhibit sympathetic activity and increase parasympathetic activity. The resultant vasodilatation and bradycardia induce hypotension and syncope. Although the reflex involving myocardial mechanoreceptors is the mechanism usually accepted as responsible for neurocardiogenic syncope, other reflexes may also be operative. Patients with transplanted (denervated) hearts have experienced cardiovascular responses identical to those present during neurocardiogenic syncope. This should not be possible if the response depends solely on the reflex mechanisms described above, unless the transplanted heart has become reinnervated. Moreover, neurocardiogenic syncope often occurs in response to stimuli (fear, emotional stress, or pain) that may not be associated with venous pooling in the lower extremities, which suggests a cerebral component to the reflex.

As distinct from the peripheral mechanisms, the central nervous system (CNS) mechanisms responsible for neurocardiogenic syncope are uncertain, but a sudden surge in central serotonin levels may contribute to the sympathetic withdrawal. Endogenous opiates (endorphins) and adenosine are also putative participants in the pathogenesis.

Situational Syncope

A variety of activities, including cough, deglutition, micturition, and defecation, are associated with syncope in susceptible individuals. Like neurocardiogenic syncope, these syndromes may involve a cardioinhibitory response, a vasodepressor response, or both. Cough, micturition, and defecation are associated with maneuvers (such as Valsalva's, straining, and coughing) that may contribute to hypotension and syncope by decreasing venous return. Increased intracranial pressure secondary to the increased intrathoracic pressure may also contribute by decreasing cerebral blood flow.

Cough syncope typically occurs in men with chronic bronchitis or chronic obstructive lung disease during or after prolonged coughing fits. Micturition syncope occurs predominantly in middle-aged and older men, particularly those with prostatic hypertrophy and obstruction of the bladder neck; loss of consciousness usually occurs at night during or immediately after voiding. Deglutition syncope and defecation syncope occur in men and women. Deglutition syncope may be associated with esophageal disorders, particularly esophageal spasm. In some individuals, particular foods and carbonated or cold beverages initiate episodes by activating esophageal sensory receptors that trigger reflex sinus bradycardia or atrioventricular (AV) block. Defecation syncope is probably secondary to Valsalva's maneuver in older individuals with constipation.

Carotid Sinus Hypersensitivity

Syncope due to carotid sinus hypersensitivity is precipitated by pressure on the carotid sinus baroreceptors, which are located just cephalad to the bifurcation of the common carotid artery. This typically occurs in the setting of shaving, a tight collar, or turning the head to one side. Carotid sinus hypersensitivity occurs predominantly in men ≥50 years. Activation of carotid sinus baroreceptors gives rise to impulses carried via the nerve of Hering, a branch of the glossopharyngeal nerve, to the medulla in the brainstem. These afferent impulses activate efferent sympathetic nerve fibers to the heart and blood vessels, cardiac vagal efferent nerve fibers, or both. In patients with carotid sinus hypersensitivity, these responses may cause sinus arrest or AV block (a cardioinhibitory response), vasodilatation (a vasodepressor response), or both (a mixed response). The underlying mechanisms responsible for the carotid sinus hypersensitivity are not clear, and validated diagnostic criteria do not exist.

Postural (Orthostatic) Hypotension

Orthostatic intolerance can result from hypovolemia or from disturbances in vascular control. The latter may occur due to agents that affect the vasculature or due to primary or secondary abnormalities of autonomic control. Sudden rising from a recumbent position or standing quietly are precipitating circumstances. *Orthostatic hypotension may be the cause of syncope in up to 30% of the elderly; polypharmacy with antihypertensive or antidepressant drugs is often a contributor in these patients.*

Postural syncope may occur in otherwise normal persons with defective postural reflexes. Pure autonomic failure (formerly called *idiopathic postural hypotension*) is characterized by orthostatic hypotension, syncope and near syncope, neurocardiogenic bladder, constipation, heat intolerance, inability to sweat, and erectile dysfunction (Chap. 28). The disorder is more common in men than women and typically begins between 50 and 75 years of age.

Orthostatic hypotension, often accompanied by disturbances in sweating, impotence, and sphincter difficulties, is also a primary feature of a variety or other autonomic nervous system disorders (Chap. 28). Among the most common causes of neurogenic orthostatic hypotension are chronic diseases of the peripheral nervous system that involve postganglionic unmyelinated fibers (e.g., diabetic, nutritional, and amyloid polyneuropathy). Much less common are the multiple system atrophies; these are CNS disorders in which orthostatic hypotension is associated with (1) parkinsonism (Shy-Drager syndrome), (2) progressive cerebellar degeneration, or (3) a more variable parkinsonian and cerebellar syndrome (Chap. 28). A rare, acute postganglionic dysautonomia may represent a variant of Guillain-Barré syndrome (Chaps. 28 and 41); a related disorder, autoimmune autonomic neuropathy, is associated with autoantibodies to the ganglionic acetylcholine receptor.

There are several additional causes of postural syncope: (1) after physical deconditioning (such as after prolonged illness with recumbency, especially in elderly individuals with reduced muscle tone) or after prolonged weightlessness, as in space flight; (2) after sympathectomy that has abolished vasopressor reflexes; and (3) in patients receiving antihypertensive or vasodilator drugs and those who are hypovolemic because of diuretics, excessive sweating, diarrhea, vomiting, hemorrhage, or adrenal insufficiency.

Glossopharyngeal Neuralgia

Syncope due to glossopharyngeal neuralgia (Chap. 29) is preceded by pain in the oropharynx, tonsillar fossa, or tongue. Loss of consciousness is usually associated with asystole rather than vasodilatation. The mechanism is thought to involve activation of afferent impulses in the glossopharyngeal nerve that terminate in the nucleus solitarius of the medulla and, via collaterals, activate the dorsal motor nucleus of the vagus nerve.

CARDIOVASCULAR DISORDERS

Cardiac syncope results from a sudden reduction in cardiac output, caused most commonly by a cardiac arrhythmia. In normal individuals, heart rates between 30 and 180 beats/min do not reduce cerebral blood flow, especially if the person is in the supine position. As the heart rate decreases, ventricular filling time and stroke volume increase to maintain normal cardiac output. At rates <30 beats/min, stroke volume can no longer increase to compensate adequately for the decreased heart rate. At rates greater than ~180 beats/min, ventricular filling time is inadequate to maintain adequate stroke volume. In either case, cerebral hypoperfusion and syncope may occur. Upright posture; cerebrovascular disease; anemia; loss of atrioventricular synchrony; and coronary, myocardial, or valvular disease all reduce the tolerance to alterations in rate.

Bradyarrhythmias may occur as a result of an abnormality of impulse generation (e.g., sinoatrial arrest) or impulse conduction (e.g., AV block). Either may cause syncope if the escape pacemaker rate is insufficient to maintain cardiac output. Syncope due to bradyarrhythmias may occur abruptly, without presyncopal symptoms, and recur several times daily. Patients with *sick sinus syndrome* may have sinus pauses (>3 s), and those with syncope due to high-degree AV block (*Stokes-Adams-Morgagni syndrome*) may have evidence of conduction system disease (e.g., prolonged PR interval, bundle branch block). However, the arrhythmia is often transitory, and the surface electrocardiogram or continuous electrocardiographic monitor (Holter monitor) taken later may not reveal the abnormality. The *bradycardia-tachycardia syndrome* is a common form of sinus node dysfunction in which syncope generally occurs as a result of marked sinus pauses, some following termination of paroxysms of atrial tachyarrhythmias. Drugs are a common cause for bradyarrhythmias, particularly in patients with underlying structural heart disease. Digoxin, β-adrenergic receptor antagonists, calcium channel blockers, and many antiarrhythmic drugs may suppress sinoatrial node impulse generation or slow AV nodal conduction.

Syncope due to a *tachyarrhythmia* is usually preceded by palpitation or lightheadedness but may occur abruptly with no warning symptoms. *Supraventricular tachyarrhythmias* are unlikely to cause syncope in individuals with structurally normal hearts but may do so if they occur in patients with (1) heart disease that also compromises cardiac output, (2) cerebrovascular disease, (3) a disorder of vascular tone or blood volume, or (4) a rapid ventricular rate. These tachycardias result most commonly from paroxysmal atrial flutter, atrial fibrillation, or reentry involving the AV node or accessory pathways that bypass part or all of the AV conduction system. Patients with *Wolff-Parkinson-White syndrome* may experience syncope when a very rapid ventricular rate occurs due to reentry across an accessory AV connection.

In patients with structural heart disease, ventricular tachycardia is a common cause of syncope, particularly in those with a prior myocardial infarction. Patients with

aortic valvular stenosis and hypertrophic obstructive cardiomyopathy are also at risk for ventricular tachycardia. Individuals with abnormalities of ventricular repolarization (prolongation of the QT interval) are at risk to develop polymorphic ventricular tachycardia (torsades des pointes). Those with the inherited form of this syndrome often have a family history of sudden death in young individuals. Genetic markers can identify some patients with familial long-QT syndrome, but the clinical utility of these markers remains unproven. Drugs (i.e., certain antiarrhythmics and erythromycin) and electrolyte disorders (i.e., hypokalemia, hypocalcemia, hypomagnesemia) can prolong the QT interval and predispose to torsades des pointes. Antiarrhythmic medications may precipitate ventricular tachycardia, particularly in patients with structural heart disease.

In addition to arrhythmias, syncope may also occur with a variety of structural cardiovascular disorders. Episodes are usually precipitated when the cardiac output cannot increase to compensate adequately for peripheral vasodilatation. Peripheral vasodilatation may be appropriate, such as following exercise, or may occur due to inappropriate activation of left ventricular mechanoreceptor reflexes, as occurs in aortic outflow tract obstruction (aortic valvular stenosis or hypertrophic obstructive cardiomyopathy). Obstruction to forward flow is the most common reason that cardiac output cannot increase. Pericardial tamponade is a rare cause of syncope. Syncope occurs in up to 10% of patients with massive pulmonary embolism and may occur with exertion in patients with severe primary pulmonary hypertension. The cause is an inability of the right ventricle to provide appropriate cardiac output in the presence of obstruction or increased pulmonary vascular resistance. Loss of consciousness is usually accompanied by other symptoms such as chest pain and dyspnea. Atrial myxoma, a prosthetic valve thrombus, and, rarely, mitral stenosis may impair left ventricular filling, decrease cardiac output, and cause syncope.

CEREBROVASCULAR DISEASE

Cerebrovascular disease alone rarely causes syncope but may lower the threshold for syncope in patients with other causes. The vertebrobasilar arteries, which supply brainstem structures responsible for maintaining consciousness, are usually involved when cerebrovascular diseases causes or contributes to syncope. An exception is the rare patient with tight bilateral carotid stenosis and recurrent syncope, often precipitated by standing or walking. Most patients who experience lightheadedness or syncope due to cerebrovascular disease also have symptoms of focal neurologic ischemia, such as arm or leg weakness, diplopia, ataxia, dysarthria, or sensory disturbances. Basilar artery migraine is a rare disorder that causes syncope in adolescents.

DIFFERENTIAL DIAGNOSIS

ANXIETY ATTACKS AND HYPERVENTILATION SYNDROME

Anxiety, such as occurs in panic attacks, is frequently interpreted as a feeling of faintness or dizziness resembling presyncope. However, the symptoms are not accompanied by facial pallor and are not relieved by recumbency. The diagnosis is made on the basis of the associated symptoms such as a feeling of impending doom, air hunger, palpitations, and tingling of the fingers and perioral region. Attacks can often be reproduced by hyperventilation, resulting in hypocapnia, alkalosis, increased cerebrovascular resistance, and decreased cerebral blood flow. The release of epinephrine also contributes to the symptoms.

SEIZURES

A seizure may be heralded by an aura, which is caused by a focal seizure discharge and hence has localizing significance (Chap. 20). The aura is usually followed by a rapid return to normal or by a loss of consciousness. Injury from falling is frequent in a seizure and rare in syncope, since only in generalized seizures are protective reflexes abolished instantaneously. Sustained tonic-clonic movements are characteristic of convulsive seizures, but brief clonic, or tonic-clonic, seizure-like activity can accompany fainting episodes. The period of unconsciousness in seizures tends to be longer than in syncope. Urinary incontinence is frequent in seizures and rare in syncope. The return of consciousness is prompt in syncope and slow after a seizure. Mental confusion, headache, and drowsiness are common sequelae of seizures, whereas physical weakness with a clear sensorium characterizes the postsyncopal state. Repeated spells of unconsciousness in a young person at a rate of several per day or month are more suggestive of epilepsy than syncope. See Table 20-7 for a comparison of seizures and syncope.

HYPOGLYCEMIA

Severe hypoglycemia is usually due to a serious disease such as a tumor of the islets of Langerhans or advanced adrenal, pituitary, or hepatic disease; or to excessive administration of insulin.

HYSTERICAL FAINTING

The attack is usually unattended by an outward display of anxiety. Lack of change in pulse and blood pressure or color of the skin and mucous membranes distinguish it from the vasodepressor faint.

Approach to the Patient: SYNCOPE

The diagnosis of syncope is often challenging. The cause may be apparent only at the time of the event, leaving few, if any, clues when the patient is seen later by the physician. The physician should think first of those causes that constitute a therapeutic emergency, including massive internal hemorrhage or myocardial infarction, which may be painless, and cardiac arrhythmias. In elderly persons, a sudden faint, without obvious cause, should arouse the suspicion of complete heart block or a tachyarrhythmia, even though all findings are negative when the patient is seen.

Figure 8-1 depicts an algorithmic approach to syncope. A careful history is the most important diagnostic tool, both to suggest the correct cause and to exclude important potential causes (Table 8-1). The nature of the events and their time course immediately prior to, during, and after an episode of syncope often provide valuable etiologic clues. Loss of consciousness in particular situations, such as during venipuncture or micturition or with volume depletion, suggests an abnormality of vascular tone. The position of the patient at the time of the syncopal episode is important; syncope in the supine position is unlikely to be vasovagal and suggests an arrhythmia or a seizure. Syncope due to carotid sinus syndrome may occur when the individual is wearing a shirt with a tight collar, turning the head (turning to look while driving in reverse), or manipulating the neck (as in shaving). The patient's medications must be noted, including nonprescription drugs or health store supplements, with particular attention to recent changes.

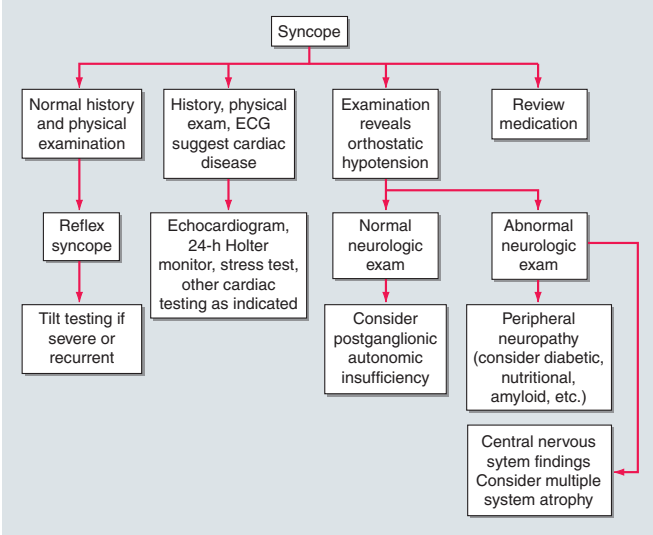

FIGURE 8-1
Approach to the patient with syncope.

The physical examination should include evaluation of heart rate and blood pressure in the supine, sitting, and standing positions. In patients with unexplained recurrent syncope, an attempt to reproduce an attack may assist in diagnosis. Anxiety attacks induced by hyperventilation can be reproduced readily by having the patient breathe rapidly and deeply for 2–3 min. Cough syncope may be reproduced by inducing the Valsalva's maneuver. Carotid sinus massage should generally be avoided, unless carotid ultrasound is negative for atheroma, because its diagnostic specificity is unknown and it may provoke a transient ischemic attack (TIA) or stroke in individuals with carotid atheromas.

DIAGNOSTIC TESTS The choice of diagnostic tests should be guided by the history and the physical examination. Measurements of serum electrolytes, glucose, and the hematocrit are usually indicated. Cardiac enzymes should be evaluated if myocardial ischemia is suspected. Blood and urine toxicology screens may reveal the presence of alcohol or other drugs. In patients with possible adrenocortical insufficiency, plasma aldosterone and mineralocorticoid levels should be obtained.

Although the surface electrocardiogram is unlikely to provide a definitive diagnosis, it may provide clues to the cause of syncope *and should be performed in almost all patients*. The presence of conduction abnormalities (PR prolongation and bundle branch block) suggests a bradyarrhythmia, whereas pathologic Q waves or prolongation of the QT interval suggests a ventricular tachyarrhythmia. Inpatients should undergo continuous electrocardiographic monitoring; outpatients should wear a Holter monitor for 24–48 h. Whenever possible, symptoms should be correlated with the occurrence of arrhythmias. Continuous electrocardiographic monitoring may establish the cause of syncope in as many as 15% of patients. Cardiac event monitors may be useful in patients with infrequent symptoms, particularly in patients with presyncope. An implantable event monitor may be necessary for patients with extremely infrequent episodes. The presence of a late potential on a signal-averaged electrocardiogram is associated with increased risk for ventricular tachyarrhythmias in patients with a prior myocardial infarction. Low-voltage (visually inapparent) T wave alternans is also associated with development of sustained ventricular arrhythmias.

Invasive cardiac electrophysiologic testing provides diagnostic and prognostic information regarding sinus node function, AV conduction, and supraventricular and ventricular arrhythmias. Prolongation of the sinus node recovery time (>1500 ms) is a specific finding

(85–100%) for diagnosis of sinus node dysfunction but has a low sensitivity; continuous electrocardiographic monitoring is usually more effective for diagnosing this abnormality. Prolongation of the HV interval and conduction block below the His bundle indicate that His-Purkinje disease may be responsible for syncope. Programmed stimulation for ventricular arrhythmias is most useful in patients who have experienced a myocardial infarction; the sensitivity and specificity of this technique is lower in patients with normal hearts or those with heart disease other than coronary artery disease.

Upright tilt table testing is indicated for recurrent syncope, a single syncopal episode that caused injury, or a single syncopal event in a "high-risk" setting (pilot, commercial vehicle driver, etc.), whether or not there is a history of preexisting heart disease or prior vasovagal episodes. In susceptible patients, upright tilt at an angle between 60° and 80° for 30–60 min induces a vasovagal episode. The protocol can be shortened if upright tilt is combined with administration of drugs that cause venous pooling or increase adrenergic stimulation (isoproterenol, nitroglycerin, edrophonium, or adenosine). The sensitivity and specificity of tilt-table testing is difficult to ascertain because of the lack of validated criteria. Moreover, the reflexes responsible for vasovagal syncope can be elicited in most, if not all, individuals given the appropriate stimulus. The specificity of tilt-table testing has been reported to be near 90%, but it is lower when pharmacologic provocation is employed. The reported sensitivity of the test ranges between 20 and 74%, the variability due to differences in populations studied, techniques used, and the absence of a true "gold standard" against which to compare test results. The reproducibility (in a time ranging from several hours to weeks) is 80–90% for an initially positive response, but may be less for an initially negative response (ranging from 30 to 90%).

A variety of other tests may be useful to determine the presence of structural heart disease that may cause syncope. The echocardiogram with Doppler examination detects valvular, myocardial, and pericardial abnormalities. The echocardiogram is the "gold standard" for the diagnosis of hypertrophic cardiomyopathy and atrial myxoma. Cardiac cine MRI provides an alternative noninvasive modality that may be useful for patients in whom diagnostic-quality echocardiographic images cannot be obtained. This test is also indicated for patients suspected of having arrhythmogenic right ventricular dysplasia or right ventricular outflow tract ventricular tachycardia. Both are associated with right ventricular structural abnormalities that are better visualized on MR imaging than by echocardiogram. Exercise testing may detect ischemia or exercise-induced arrhythmias. In some patients, cardiac catheterization may be necessary to diagnose the presence or severity of coronary artery disease or valvular abnormalities. Ultrafast CT scan, ventilation-perfusion scan, or pulmonary angiography is indicated in patients in whom syncope may be due to pulmonary embolus.

In cases of possible cerebrovascular syncope, neuroimaging tests may be indicated, including Doppler ultrasound studies of the carotid and vertebrobasilar systems, MRI, magnetic resonance angiography, and x-ray angiography of the cerebral vasculature (Chap. 2). Electroencephalography is indicated if seizures are suspected.

Rx Treatment: SYNCOPE

The treatment of syncope is directed at the underlying cause. This discussion will focus on disorders of autonomic control. Cerebrovascular disorders are discussed in Chap. 21.

Certain precautions should be taken regardless of the cause of syncope. At the first sign of symptoms, patients should make every effort to avoid injury should they lose consciousness. Patients with frequent episodes, or those who have experienced syncope without warning symptoms, should avoid situations in which sudden loss of consciousness might result in injury (e.g., climbing ladders, swimming alone, operating heavy machinery, driving). Patients should lower their head to the extent possible and preferably should lie down. Lowering the head by bending at the waist should be avoided because it may further compromise venous return to the heart. When appropriate, family members or other close contacts should be educated as to the problem. This will ensure appropriate therapy and may prevent delivery of inappropriate therapy (chest compressions associated with cardiopulmonary resuscitation) that may inflict trauma.

Patients who have lost consciousness should be placed in a position that maximizes cerebral blood flow, offers protection from trauma, and secures the airway. Whenever possible, the patient should be placed supine with the head turned to the side to prevent aspiration and the tongue from blocking the airway. Assessment of the pulse and direct cardiac auscultation may assist in determining if the episode is associated with a bradyarrhythmia or a tachyarrhythmia. Clothing that fits tightly around the neck or waist should be loosened. Peripheral stimulation, such as sprinkling cold water on the face, may be helpful. Patients should not be given

anything by mouth or be permitted to rise until the sense of physical weakness has passed.

Patients with vasovagal syncope should be instructed to avoid situations or stimuli that have caused them to lose consciousness and to assume a recumbent position when premonitory symptoms occur. These behavioral modifications alone may be sufficient for patients with infrequent and relatively benign episodes of vasovagal syncope, particularly when loss of consciousness occurs in response to a specific stimulus. Tilt training (standing and leaning against a wall for progressively longer periods each day) has been used with limited success, particularly for patients with orthostatic intolerance. Episodes associated with intravascular volume depletion may be prevented by salt and fluid loading prior to provocative events.

Drug therapy may be necessary when vasovagal syncope is resistant to the above measures, when episodes occur frequently, or when syncope is associated with a significant risk for injury. β-Adrenergic receptor antagonists (metoprolol, 25–50 mg bid; atenolol, 25–50 mg qd; or nadolol, 10–20 mg bid; all starting doses), the most widely used agents, mitigate the increase in myocardial contractility that stimulates left ventricular mechanoreceptors and also block central serotonin receptors. Serotonin reuptake inhibitors (paroxetine, 20–40 mg qd; or sertraline, 25–50 mg qd), appear to be effective for some patients. Bupropion SR (150 mg qd), another antidepressant, has also been used with success. β-Adrenergic receptor antagonists and serotonin reuptake inhibitors are well tolerated and are often used as first-line agents for younger patients. Hydrofludrocortisone (0.1–0.2 mg qd), a mineralocorticoid, promotes sodium retention, volume expansion, and peripheral vasoconstriction by increasing β-receptor sensitivity to endogenous catecholamines. Hydrofludrocortisone is useful for patients with intravascular volume depletion and for those who also have postural hypotension. Proamatine (2.5–10 mg bid or tid), an α-agonist, has been used as a first-line agent for some patients. In a randomized controlled trial, proamatine was more effective than placebo in preventing syncope during an upright tilt-test. However, in some patients, proamatine and hydrofludrocortisone may increase resting supine systemic blood pressure, which may be problematic for those with hypertension.

Disopyramide (150 mg bid), a vagolytic antiarrhythmic drug with negative inotropic properties, and transdermal scopolamine, another vagolytic, have been used to treat vasovagal syncope, as have theophylline and ephedrine. Side effects associated with these drugs have limited their use for this indication. Disopyramide is a type 1A antiarrhythmic drug and should be used with great caution, if at all, in patients who are at risk for ventricular arrhythmias.

Although several clinical trials have suggested that pharmacologic therapy for neurocardiogenic syncope is effective, the few long-term prospective randomized controlled trials have yielded mixed results. In the Prevention of Syncope Trial (POST), metoprolol was ineffective in patients <42 years but decreased the incidence of syncope in patients >42 years, raising the possibility that there may be significant age-related differences in response to pharmacologic therapy.

Studies of permanent pacing for neurocardiogenic syncope have also yielded mixed results. Dual-chamber cardiac pacing may be effective for patients with frequent episodes of vasovagal syncope, particularly for those with prolonged asystole associated with vasovagal episodes. Pacemakers that can be programmed to transiently pace at a high rate (90–100 beats/min) after a profound drop in the patient's intrinsic heart rate are most effective.

Patients with orthostatic hypotension should be instructed to rise slowly and systematically (supine to seated, seated to standing) from the bed or a chair. Movement of the legs prior to rising facilitates venous return from the lower extremities. Whenever possible, medications that aggravate the problem (vasodilators, diuretics, etc.) should be discontinued. Elevation of the head of the bed [20–30 cm (8–12 in.)] and use of compression stockings may help.

Additional therapeutic modalities include salt loading and a variety of pharmacologic agents including sympathomimetic amines, monamine oxidase inhibitors, beta blockers, and levodopa. The treatment of orthostatic hypotension secondary to central or peripheral disorders of the autonomic nervous system is discussed in Chap. 28.

Glossopharyngeal neuralgia is treated with carbamazepine, which is effective for syncope as well as for pain. Patients with carotid sinus hypersensitivity should be instructed to avoid clothing and situations that stimulate carotid sinus baroreceptors. They should turn their entire body, rather than just their head, when looking to the side. Those with intractable syncope due to the cardioinhibitory response to carotid sinus stimulation should undergo permanent pacemaker implantation.

Patients with syncope should be hospitalized when there is a possibility that the episode may have resulted from a life-threatening abnormality or if recurrence with significant injury seems likely. These individuals should be admitted to a bed with continuous electrocardiographic monitoring. Patients who are known to have a normal heart and for whom the history strongly suggests vasovagal or situational syncope may be treated as outpatients if the episodes are neither frequent nor severe.

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CHAPTER 9

DIZZINESS AND VERTIGO

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Dizziness is a common and often vexing symptom. Patients use the term to encompass a variety of sensations, including those that seem semantically appropriate (e.g., lightheadedness, faintness, spinning, giddiness) and those that are misleadingly inappropriate, such as mental confusion, blurred vision, headache, or tingling. Moreover, some individuals with gait disorders caused by peripheral neuropathy, myelopathy, spasticity, parkinsonism, or cerebellar ataxia have complaint of "dizziness" despite the absence of vertigo or other abnormal cephalic sensations. In this context, the term *dizziness* is being used to describe disturbed ambulation. There may be mild associated lightheadedness, particularly with impaired sensation from the feet or poor vision; this is known as *multiple-sensory-defect dizziness* and occurs in elderly individuals who complain of dizziness only when walking. Decreased position sense (secondary to neuropathy or myelopathy) and poor vision (from cataracts or retinal degeneration) create an overreliance on the aging vestibular apparatus. A less precise but sometimes comforting designation to patients is *benign dysequilibrium of aging*. Thus, a careful history is necessary to determine exactly what a patient who states, "Doctor, I'm dizzy," is experiencing. After eliminating the misleading symptoms or gait disturbance, "dizziness" usually means either *faintness* (presyncope) or *vertigo* (an illusory or hallucinatory sense of movement of the body or environment, most often a feeling of spinning). Operationally, after obtaining the history, dizziness may be classified into three categories: (1) faintness, (2) vertigo, and (3) miscellaneous head sensations.

FAINTNESS

Prior to an actual faint (syncope), there are often prodromal presyncopal symptoms (faintness) reflecting ischemia to a degree insufficient to impair consciousness. These include lightheadedness, "dizziness" without true vertigo, a feeling of warmth, diaphoresis, nausea, and visual blurring occasionally proceeding to blindness. Presyncopal symptoms vary in duration and may increase in severity until loss of consciousness occurs or may resolve prior to loss of consciousness if the cerebral ischemia is corrected. Faintness and syncope are discussed in detail in Chap. 8.

VERTIGO

Vertigo is usually due to a disturbance in the vestibular system. The end organs of this system, situated in the bony labyrinths of the inner ears, consist of the three semicircular canals and the otolithic apparatus (utricle and saccule) on each side. The canals transduce angular acceleration, while the otoliths transduce linear acceleration and the static gravitational forces that provide a sense of head position in space. The neural output of the end organs is conveyed to the vestibular nuclei in the brainstem via the eighth cranial nerves. The principal projections from the vestibular nuclei are to the nuclei of cranial nerves III, IV, and VI; spinal cord; cerebral cortex; and cerebellum. The vestibuloocular reflex (VOR) serves to maintain visual stability during head movement and depends on direct projections from the vestibular nuclei

to the sixth cranial nerve (abducens) nuclei in the pons and, via the medial longitudinal fasciculus, to the third (oculomotor) and fourth (trochlear) cranial nerve nuclei in the midbrain. These connections account for the nystagmus (to-and-fro oscillation of the eyes) that is an almost invariable accompaniment of vestibular dysfunction. The vestibular nerves and nuclei project to areas of the cerebellum (primarily the flocculus and nodulus) that modulate the VOR. The vestibulospinal pathways assist in the maintenance of postural stability. Projections to the cerebral cortex, via the thalamus, provide conscious awareness of head position and movement.

The vestibular system is one of three sensory systems subserving spatial orientation and posture; the other two are the visual system (retina to occipital cortex) and the somatosensory system that conveys peripheral information from skin, joint, and muscle receptors. The three stabilizing systems overlap sufficiently to compensate (partially or completely) for each other's deficiencies. Vertigo may represent either physiologic stimulation or pathologic dysfunction in any of the three sensory systems.

Physiologic Vertigo

This occurs in normal individuals when (1) the brain is confronted with an intersensory mismatch among the three stabilizing sensory systems; (2) the vestibular system is subjected to unfamiliar head movements to which it is unadapted, such as in seasickness; (3) unusual head/neck positions, such as the extreme extension when painting a ceiling; or (4) following a spin. Intersensory mismatch explains carsickness, height vertigo, and the visual vertigo most commonly experienced during motion picture chase scenes; in the latter, the visual sensation of environmental movement is unaccompanied by concomitant vestibular and somatosensory movement cues. *Space sickness*, a frequent transient effect of active head movement in the weightless zero-gravity environment, is another example of physiologic vertigo.

Pathologic Vertigo

This results from lesions of the visual, somatosensory, or vestibular systems. Visual vertigo is caused by new or incorrect eyeglasses or by the sudden onset of an extraocular muscle paresis with diplopia; in either instance, central nervous system (CNS) compensation rapidly counteracts the vertigo. Somatosensory vertigo, rare in isolation, is usually due to a peripheral neuropathy or myelopathy that reduces the sensory input necessary for central compensation when there is dysfunction of the vestibular or visual systems.

The most common cause of pathologic vertigo is vestibular dysfunction involving either its end organ (labyrinth), nerve, or central connections. The vertigo is associated with jerk nystagmus and is frequently accompanied by nausea, postural unsteadiness, and gait ataxia. Since vertigo increases with rapid head movements, patients tend to hold their heads still.

Labyrinthine Dysfunction

This causes severe rotational or linear vertigo. When rotational, the hallucination of movement, whether of environment or self, is directed away from the side of the lesion. The fast phases of nystagmus beat away from the lesion side, and the tendency to fall is toward the side of the lesion, particularly in darkness or with the eyes closed.

Under normal circumstances, when the head is straight and immobile, the vestibular end organs generate a tonic resting firing frequency that is equal from the two sides. With any rotational acceleration, the anatomic positions of the semicircular canals on each side necessitate an increased firing rate from one and a commensurate decrease from the other. This change in neural activity is ultimately projected to the cerebral cortex, where it is summed with inputs from the visual and somatosensory systems to produce the appropriate conscious sense of rotational movement. After cessation of prolonged rotation, the firing frequencies of the two end organs reverse; the side with the initially increased rate decreases, and the other side increases. A sense of rotation in the opposite direction is experienced; since there is no actual head movement, this hallucinatory sensation is *physiologic postrotational vertigo*.

Any disease state that changes the firing frequency of an end organ, producing unequal neural input to the brainstem and ultimately the cerebral cortex, causes vertigo. The symptom can be conceptualized as the cortex inappropriately interpreting the abnormal neural input as indicating actual head rotation. Transient abnormalities produce short-lived symptoms. With a fixed unilateral deficit, central compensatory mechanisms ultimately diminish the vertigo. Since compensation depends on the plasticity of connections between the vestibular nuclei and the cerebellum, patients with brainstem or cerebellar disease have diminished adaptive capacity, and symptoms may persist indefinitely. Compensation is always inadequate for severe fixed bilateral lesions despite normal cerebellar connections; these patients are permanently symptomatic when they move their heads.

Acute unilateral labyrinthine dysfunction is caused by infection, trauma, and ischemia. Often, no specific etiology is uncovered, and the nonspecific terms *acute labyrinthitis*, *acute peripheral vestibulopathy*, or *vestibular neuritis* are used to describe the event. The vertiginous attacks are brief and leave the patient with mild vertigo for several days. Infection with herpes simplex virus type 1 has been implicated. It is impossible to predict whether a patient recovering from the first bout of vertigo will have recurrent episodes.

Labyrinthine ischemia, presumably due to occlusion of the labyrinthine branch of the internal auditory artery, may be the sole manifestation of vertebrobasilar insufficiency (Chap. 21); patients with this syndrome present with the abrupt onset of severe vertigo, nausea, and vomiting, but without tinnitus or hearing loss.

Acute bilateral labyrinthine dysfunction is usually the result of toxins such as drugs or alcohol. The most common offending drugs are the aminoglycoside antibiotics that damage the hair cells of the vestibular end organs and may cause a permanent disorder of equilibrium.

Recurrent unilateral labyrinthine dysfunction, in association with signs and symptoms of cochlear disease (progressive hearing loss and tinnitus), is usually due to Ménière's disease (Chap. 18). When auditory manifestations are absent, the term *vestibular neuronitis* denotes recurrent monosymptomatic vertigo. Transient ischemic attacks of the posterior cerebral circulation (vertebrobasilar insufficiency) only infrequently cause recurrent vertigo without concomitant motor, sensory, visual, cranial nerve, or cerebellar signs (Chap. 21).

Positional vertigo is precipitated by a recumbent head position, either to the right or to the left. Benign paroxysmal positional (or positioning) vertigo (BPPV) of the posterior semicircular canal is particularly common. Although the condition may be due to head trauma, usually no precipitating factors are identified. It generally abates spontaneously after weeks or months. The vertigo and accompanying nystagmus have a distinct pattern of latency, fatigability, and habituation that differs from the less common central positional vertigo (**Table 9-1**) due to lesions in and around the fourth ventricle. Moreover, the pattern of nystagmus in posterior canal BPPV is distinctive. When supine, with the head turned to the side of the offending ear (bad ear down), the lower eye displays a large-amplitude torsional nystagmus, and the upper eye has a lesser degree of torsion combined with upbeating nystagmus. If the eyes are directed to the upper ear, the vertical nystagmus in the upper eye increases in amplitude. Mild dysequilibrium when upright may also be present.

TABLE 9-1

BENIGN PAROXYSMAL POSITIONAL VERTIGO AND CENTRAL POSITIONAL VERTIGO

FEATURES	BPPV	CENTRAL
Latency[a]	3–40 s	None: immediate vertigo and nystagmus
Fatigability[b]	Yes	No
Habituation[c]	Yes	No
Intensity of vertigo	Severe	Mild
Reproducibility[d]	Variable	Good

[a]Time between attaining head position and onset of symptoms.
[b]Disappearance of symptoms with maintenance of offending position.
[c]Lessening of symptoms with repeated trials.
[d]Likelihood of symptom production during any examination session.

A *perilymphatic fistula* should be suspected when episodic vertigo is precipitated by Valsalva or exertion, particularly upon a background of a stepwise progressive sensory-neural hearing loss. The condition is usually caused by head trauma or barotrauma or occurs after middle ear surgery.

Vertigo of Vestibular Nerve Origin

This occurs with diseases that involve the nerve in the petrous bone or the cerebellopontine angle. Although less severe and less frequently paroxysmal, it has many of the characteristics of labyrinthine vertigo. The adjacent auditory division of the eighth cranial nerve is usually affected, which explains the frequent association of vertigo with unilateral tinnitus and hearing loss. The most common cause of eighth cranial nerve dysfunction is a tumor, usually a schwannoma (*acoustic neuroma*) or a meningioma. These tumors grow slowly and produce such a gradual reduction of labyrinthine output that central compensatory mechanisms can prevent or minimize the vertigo; auditory symptoms are the most common manifestations.

Central Vertigo

Lesions of the brainstem or cerebellum can cause acute vertigo, but associated signs and symptoms usually permit distinction from a labyrinthine etiology (**Table 9-2**). Occasionally, an acute lesion of the vestibulocerebellum may present with monosymptomatic vertigo indistinguishable from a labyrinthopathy.

Vertigo may be a manifestation of a migraine aura (Chap. 6), but some patients with migraine have episodes of vertigo unassociated with their headaches. Antimigrainous treatment should be considered in such patients with otherwise enigmatic vertiginous episodes.

Vestibular epilepsy, vertigo secondary to temporal lobe epileptic activity, is rare and almost always intermixed with other epileptic manifestations.

Psychogenic Vertigo

This is sometimes called phobic postural vertigo and is usually a concomitant of panic attacks (Chap. 49) or agoraphobia (fear of large open spaces, crowds, or leaving the safety of home). It should be suspected in patients so "incapacitated" by their symptoms that they adopt a prolonged housebound status. Most patients with organic vertigo attempt to function despite their discomfort. Organic vertigo is accompanied by nystagmus; a psychogenic etiology is almost certain when nystagmus is absent during a vertiginous episode. The symptoms often develop after an episode of acute labyrinthine dysfunction.

TABLE 9-2

FEATURES OF PERIPHERAL AND CENTRAL VERTIGO

SIGN OR SYMPTOM	PERIPHERAL (LABYRINTH)	CENTRAL (BRAINSTEM OR CEREBELLUM)
Direction of associated nystagmus	Unidirectional; fast phase opposite lesion[a]	Bidirectional or unidirectional
Purely horizontal nystagmus without torsional component	Uncommon	Common
Vertical or purely torsional nystagmus	Never present	May be present
Visual fixation	Inhibits nystagmus and vertigo	No inhibition
Severity of vertigo	Marked	Often mild
Direction of spin	Toward fast phase	Variable
Direction of fall	Toward slow phase	Variable
Duration of symptoms	Finite (minutes, days, weeks) but recurrent	May be chronic
Tinnitus and/or deafness	Often present	Usually absent
Associated CNS abnormalities	None	Extremely common (e.g., diplopia, hiccups, cranial neuropathies, dysarthria)
Common causes	BPPV, infection (labyrinthitis), Ménière's, neuronitis, ischemia, trauma, toxin	Vascular, demyelinating, neoplasm

[a]In Ménière's disease, the direction of the fast phase is variable.

MISCELLANEOUS HEAD SENSATIONS

This designation is used, primarily for purposes of initial classification, to describe dizziness that is neither faintness nor vertigo. Cephalic ischemia or vestibular dysfunction may be of such low intensity that the usual symptomatology is not clearly identified. For example, a small decrease in blood pressure or a slight vestibular imbalance may cause sensations different from distinct faintness or vertigo but that may be identified properly by provocative testing techniques (see below). Other causes of dizziness in this category are hyperventilation syndrome, hypoglycemia, and the somatic symptoms of a clinical depression; these patients should all have normal neurologic examinations and vestibular function tests. Depressed patients often insist that the depression is "secondary" to the dizziness.

Approach to the Patient: DIZZINESS AND VERTIGO

The most important diagnostic tool is a detailed history focused on the meaning of "dizziness" to the patient. Is it faintness (presyncope)? Is there a sensation of spinning? If either of these is affirmed and the neurologic examination is normal, appropriate investigations for the multiple causes of cephalic ischemia, presyncope (Chap. 8), or vestibular dysfunction are undertaken.

When the meaning of "dizziness" is uncertain, provocative tests may be helpful. These office procedures simulate either cephalic ischemia or vestibular dysfunction. Cephalic ischemia is obvious if the dizziness is duplicated during maneuvers that produce orthostatic hypotension. Further provocation involves the Valsalva maneuver, which decreases cerebral blood flow and should reproduce ischemic symptoms.

Hyperventilation is the cause of dizziness in many anxious individuals; tingling of the hands and face may be absent. Forced hyperventilation for 1 min is indicated for patients with enigmatic dizziness and normal neurologic examinations.

The simplest provocative test for vestibular dysfunction is rapid rotation and abrupt cessation of movement in a swivel chair. This always induces vertigo that the patients can compare with their symptomatic dizziness. The intense induced vertigo may be unlike the spontaneous symptoms, but shortly thereafter, when the vertigo has all but subsided, a lightheadedness supervenes that may be identified as "my dizziness." When this occurs, the dizzy patient, originally classified as suffering from "miscellaneous head sensations," is now properly diagnosed as having mild vertigo secondary to a vestibulopathy.

Patients with symptoms of positional vertigo should be appropriately tested (Table 9-1). A final provocative and diagnostic vestibular test, requiring the use of Frenzel eyeglasses (self-illuminated goggles with convex lenses that blur out the patient's vision, but allow the examiner to see the eyes greatly magnified), is vigorous head shaking in the horizontal plane for

about 10 s. If nystagmus develops after the shaking stops, even in the absence of vertigo, vestibular dysfunction is demonstrated. The maneuver can then be repeated in the vertical plane. If the provocative tests establish the dizziness as a vestibular symptom, an evaluation of vestibular vertigo is undertaken.

EVALUATION OF PATIENTS WITH PATHOLOGIC VESTIBULAR VERTIGO The evaluation depends on whether a central etiology is suspected (Table 9-2). If so, MRI of the head is mandatory. Such an examination is rarely helpful in cases of recurrent monosymptomatic vertigo with a normal neurologic examination. Typical BPPV requires no investigation after the diagnosis is made (Table 9-1).

Vestibular function tests serve to (1) demonstrate an abnormality when the distinction between organic and psychogenic is uncertain, (2) establish the side of the abnormality, and (3) distinguish between peripheral and central etiologies. The standard test is electronystagmography (calorics), where warm and cold water (or air) are applied, in a prescribed fashion, to the tympanic membranes, and the slow-phase velocities of the resultant nystagmus from the two are compared. A velocity decrease from one side indicates hypofunction ("canal paresis"). An inability to induce nystagmus with ice water denotes a "dead labyrinth." Some institutions have the capability of quantitatively determining various aspects of the VOR using computer-driven rotational chairs and precise oculographic recording of the eye movements.

CNS disease can produce dizzy sensations of all types. Consequently, a neurologic examination is always required even if the history or provocative tests suggest a cardiac, peripheral vestibular, or psychogenic etiology. Any abnormality on the neurologic examination should prompt appropriate neurodiagnostic studies.

TABLE 9-3

TREATMENT OF VERTIGO

AGENT[a]	DOSE[b]
Antihistamines	
Meclizine	25–50 mg 3 times/day
Dimenhydrinate	50 mg 1–2 times/day
Promethazine[c]	25–50-mg suppository or IM
Benzodiazepines	
Diazepam	2.5 mg 1–3 times/day
Clonazepam	0.25 mg 1–3 times/day
Phenothiazines	
Prochlorperazine[c]	5 mg IM or 25 mg suppository
Anticholinergic[d]	
Scopolamine transdermal	Patch
Sympathomimetics[d]	
Ephedrine	25 mg/d
Combination preparations[d]	
Ephedrine and promethazine	25 mg/d of each
Exercise therapy	
Repositioning maneuvers[e]	
Vestibular rehabilitation[f]	
Other	
Diuretics or low-salt (1 g/d) diet[g]	
Antimigrainous drugs[h]	
Inner ear surgery[i]	
Prednisone[c]	100 mg/d for 3 days, tapered by 20 mg every 3 days

[a]All listed drugs are U.S. Food and Drug Administration approved, but most are not approved for the treatment of vertigo.
[b]Usual oral (unless otherwise stated) starting dose in adults; maintenance dose can be reached by a gradual increase.
[c]For acute vertigo only.
[d]For motion sickness only.
[e]For benign paroxysmal positional vertigo.
[f]For vertigo other than Ménière's and positional.
[g]For Ménière's disease.
[h]For migraine-associated vertigo (see Chap. 6 for a listing of prophylactic antimigrainous drugs).
[i]For perilymphatic fistula and refractory cases of Ménière's disease.

Rx Treatment: VERTIGO

Treatment of acute vertigo consists of bed rest (1–2 days maximum) and vestibular suppressant drugs such as antihistaminics (meclizine, dimenhydrinate, promethazine), tranquilizers with GABA-ergic effects (diazepam, clonazepam), phenothiazines (prochlorperazine), or glucocorticoids (Table 9-3). If the vertigo persists beyond a few days, most authorities advise ambulation in an attempt to induce central compensatory mechanisms, despite the short-term discomfort to the patient. Chronic vertigo of labyrinthine origin may be treated with a systematized vestibular rehabilitation program to facilitate central compensation.

Posterior semicircular canal BPPV, the most common type, is often self-limited but, when persistent, may respond dramatically to specific repositioning exercise programs designed to empty particulate debris from the canal. One of these exercises, the Epley procedure, is graphically demonstrated, in four languages, on a website for use in both physicians' offices and self-treatment: *www.charite.de/ch/neuro/vertigo.html*

Prophylactic measures to prevent recurrent vertigo are variably effective. Antihistamines are commonly utilized but are of limited value. Ménière's disease may respond to a diuretic or, more effectively, to a very low salt diet (1 g/d). Recurrent episodes of migraine-associated vertigo should be treated with antimigrainous

therapy (Chap. 6). There are a variety of inner ear surgical procedures for refractory Ménière's disease, but these are only rarely necessary.

Psychogenic ("phobic postural") vertigo is best treated with cognitive-behavioral therapy.

Helpful websites for both physicians and vertigo patients: *www.iVertigo.net* and www.tchain.com.

GLOBAL CONSIDERATIONS

There are no epidemiologic studies indicating an increased frequency of specific types of vertigo in different geographical areas. However, whereas BPPV of the posterior semicircular canal is overwhelmingly the most common form of positional vertigo in most countries, there seems to be an unusually large number of reports of horizontal (lateral) BPPV from Italy and Korea.

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CHAPTER 10

WEAKNESS AND PARALYSIS

Michael J. Aminoff

Normal motor function involves integrated muscle activity that is modulated by the activity of the cerebral cortex, basal ganglia, cerebellum, and spinal cord. Motor system dysfunction leads to weakness or paralysis, which is discussed in this chapter, or to ataxia (Chap. 26) or abnormal movements (Chaps. 24 and 25). The mode of onset, distribution, and accompaniments of weakness help to suggest its cause.

Weakness is a reduction in the power that can be exerted by one or more muscles. Increased fatigability or limitation in function due to pain or articular stiffness is often confused with weakness by patients. *Increased fatigability* is the inability to sustain the performance of an activity that should be normal for a person of the same age, gender, and size. Increased time is sometimes required for full power to be exerted, and this *bradykinesia* may be misinterpreted as weakness. Severe proprioceptive sensory loss may also lead to complaints of weakness because adequate feedback information about the direction and power of movements is lacking. Finally, *apraxia,* a disorder of planning and initiating a skilled or learned movement unrelated to a significant motor or sensory deficit (Chap. 15), is sometimes mistaken for weakness by inexperienced medical staff.

Paralysis indicates weakness that is so severe that the muscle cannot be contracted at all, whereas *paresis* refers to weakness that is mild or moderate. The prefix "hemi-" refers to one half of the body, "para-" to both legs, and "quadri-" to all four limbs. The suffix "-plegia" signifies severe weakness or paralysis.

Weakness or paralysis is typically accompanied by other neurologic abnormalities that help to indicate the site of the responsible lesion. These include changes in tone, muscle bulk, muscle stretch reflexes, and cutaneous reflexes (**Table 10-1**).

Tone is the resistance of a muscle to passive stretch. Central nervous system (CNS) abnormalities that cause weakness generally produce *spasticity*, an increase in tone associated with disease of upper motor neurons. Spasticity is velocity-dependent, has a sudden release after reaching a maximum (the "clasp-knife" phenomenon), and predominantly affects the antigravity muscles (i.e., upper-limb flexors and lower-limb extensors). Spasticity is distinct from rigidity and paratonia, two other types of hypertonia. *Rigidity* is increased tone that is present throughout the range of motion (a "lead pipe" or "plastic" stiffness) and affects flexors and extensors equally; it sometimes has a cogwheel quality that is enhanced by voluntary movement of the contralateral limb (reinforcement). Rigidity occurs with certain extrapyramidal disorders such as Parkinson's disease. *Paratonia* (or *gegenhalten*) is increased tone that varies irregularly in a manner that may seem related to the degree of relaxation, is present throughout the range of motion, and affects flexors and extensors equally; it usually results from disease of the frontal lobes. Weakness with *decreased tone* (*flaccidity*) or normal tone occurs with disorders of *motor units.* A motor unit consists of a single lower motor neuron and all of the muscle fibers that it innervates.

Muscle bulk is generally unaffected in patients with upper motor neuron lesions, although mild disuse atrophy may eventually occur. By contrast, atrophy is often conspicuous when a lower motor neuron lesion is responsible for weakness and may also occur with advanced muscle disease.

Muscle stretch (tendon) reflexes are usually increased with upper motor neuron lesions, although they may be decreased or absent for a variable period immediately after onset of an acute lesion. This is usually—but not invariably—accompanied by abnormalities of *cutaneous reflexes* (such as superficial abdominals; Chap. 1) and, in particular, by an extensor plantar (Babinski) response. The muscle stretch reflexes are depressed in patients with lower motor neuron lesions when there is direct involvement of specific reflex arcs. The stretch reflexes

TABLE 10-1

SIGNS THAT DISTINGUISH ORIGIN OF WEAKNESS

SIGN	UPPER MOTOR NEURON	LOWER MOTOR NEURON	MYOPATHIC
Atrophy	None	Severe	Mild
Fasciculations	None	Common	None
Tone	Spastic	Decreased	Normal/decreased
Distribution of weakness	Pyramidal/regional	Distal/segmental	Proximal
Tendon reflexes	Hyperactive	Hypoactive/absent	Normal/hypoactive
Babinski's sign	Present	Absent	Absent

are generally preserved in patients with myopathic weakness except in advanced stages, when they are sometimes attenuated. In disorders of the neuromuscular junction, the intensity of the reflexes may be affected by preceding voluntary activity of affected muscles—such activity may lead to enhancement of initially depressed reflexes in Lambert-Eaton myasthenic syndrome and, conversely, to depression of initially normal reflexes in myasthenia gravis (Chap. 42).

The distinction of *neuropathic* (lower motor neuron) from *myopathic* weakness is sometimes difficult clinically, although distal weakness is likely to be neuropathic and symmetric proximal weakness myopathic. *Fasciculations* (visible or palpable twitch within a muscle due to the spontaneous discharge of a motor unit) and early atrophy indicate that weakness is neuropathic.

PATHOGENESIS

Upper Motor Neuron Weakness

This pattern of weakness results from disorders that affect the upper motor neurons or their axons in the cerebral cortex, subcortical white matter, internal capsule, brainstem, or spinal cord (**Fig. 10-1**). Such lesions produce weakness through decreased activation of the lower motor neurons. In general, distal muscle groups are affected more severely than proximal ones, and axial movements are spared unless the lesion is severe and bilateral. With corticobulbar involvement, weakness is usually observed only in the lower face and tongue; extraocular, upper facial, pharyngeal, and jaw muscles are almost always spared. With bilateral corticobulbar lesions, *pseudobulbar palsy* often develops: dysarthria, dysphagia, dysphonia, and emotional lability accompany bilateral facial weakness and a brisk jaw jerk. Spasticity accompanies upper motor neuron weakness but may not be present in the acute phase. Upper motor neuron lesions also affect the ability to perform rapid repetitive movements. Such movements are slow and coarse, but normal rhythmicity is maintained. Finger-nose-finger and heel-knee-shin maneuvers are performed slowly but adequately.

Lower Motor Neuron Weakness

This pattern results from disorders of cell bodies of lower motor neurons in the brainstem motor nuclei and the anterior horn of the spinal cord, or from dysfunction of the axons of these neurons as they pass to skeletal muscle (**Fig. 10-2**). Weakness is due to a decrease in the number of muscle fibers that can be activated, through a loss of γ motor neurons or disruption of their connections to muscle. Loss of γ motor neurons does not cause weakness but decreases tension on the muscle spindles, which decreases muscle tone and attenuates the stretch reflexes elicited on examination. An absent stretch reflex suggests involvement of spindle afferent fibers.

When a motor unit becomes diseased, especially in anterior horn cell diseases, it may spontaneously discharge, producing *fasciculations* that may be seen or felt clinically or recorded by electromyography (EMG). When α motor neurons or their axons degenerate, the denervated muscle fibers may also discharge spontaneously. These single muscle fiber discharges, or *fibrillation potentials,* cannot be seen or felt but can be recorded with EMG. If lower motor neuron weakness is present, recruitment of motor units is delayed or reduced, with fewer than normal activated at a given discharge frequency. This contrasts with weakness of upper motor neuron type, in which a normal number of motor units is activated at a given frequency but with a diminished maximal discharge frequency.

Myopathic Weakness

Myopathic weakness is produced by disorders of the muscle fibers. Disorders of the neuromuscular junctions also produce weakness, but this is variable in degree and distribution and is influenced by preceding activity of the affected muscle. At a muscle fiber, if the nerve terminal releases a normal number of acetylcholine molecules presynaptically and a sufficient number of postsynaptic acetylcholine receptors are opened, the end plate reaches threshold and thereby generates an action potential that spreads across the muscle fiber membrane

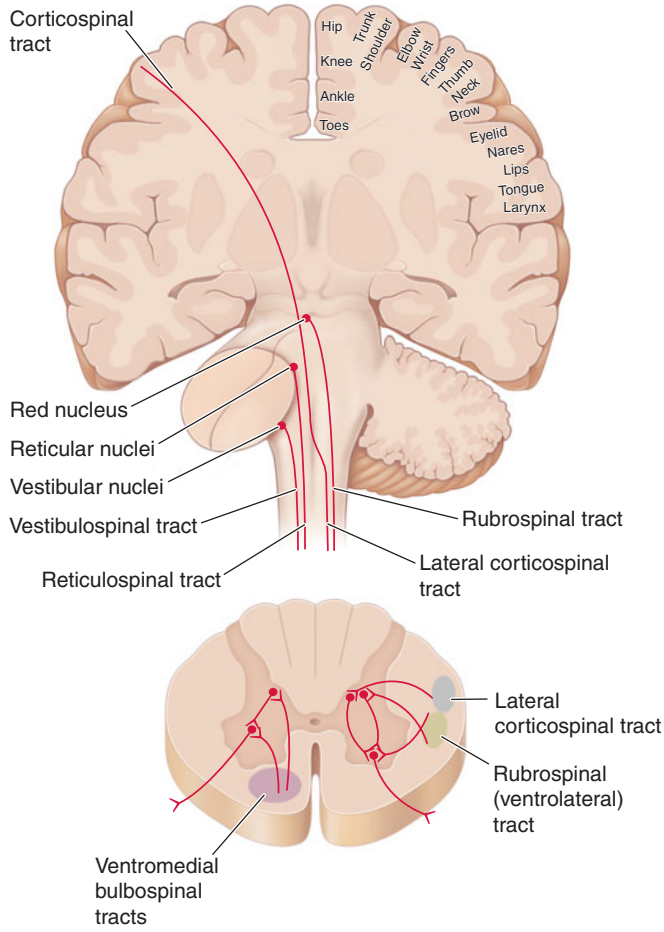

FIGURE10-1

The corticospinal and bulbospinal upper motor neuron pathways. Upper motor neurons have their cell bodies in layer V of the primary motor cortex (the precentral gyrus, or Brodmann's area 4) and in the premotor and supplemental motor cortex (area 6). The upper motor neurons in the primary motor cortex are somatotopically organized as illustrated on the right side of the figure.

Axons of the upper motor neurons descend through the subcortical white matter and the posterior limb of the internal capsule. Axons of the *pyramidal* or *corticospinal system* descend through the brainstem in the cerebral peduncle of the midbrain, the basis pontis, and the medullary pyramids. At the cervicomedullary junction, most pyramidal axons decussate into the contralateral corticospinal tract of the lateral spinal cord, but 10–30% remains ipsilateral in the anterior spinal cord. Pyramidal neurons make direct monosynaptic connections with lower motor neurons. They innervate most densely the lower motor neurons of hand muscles and are involved in the execution of learned, fine movements. Corticobulbar neurons are similar to corticospinal neurons but innervate brainstem motor nuclei.

Bulbospinal upper motor neurons influence strength and tone but are not part of the pyramidal system. The descending *ventromedial bulbospinal pathways* originate in the tectum of the midbrain (tectospinal pathway), the vestibular nuclei (vestibulospinal pathway), and the reticular formation (reticulospinal pathway). These pathways influence axial and proximal muscles and are involved in the maintenance of posture and integrated movements of the limbs and trunk. The descending *ventrolateral bulbospinal pathways*, which originate predominantly in the red nucleus (rubrospinal pathway), facilitate distal limb muscles. The bulbospinal system is sometimes referred to as the *extrapyramidal upper motor neuron system*. In all figures, nerve cell bodies and axon terminals are shown, respectively, as closed circles and forks.

and into the transverse tubular system. This electrical excitation activates intracellular events that produce an energy-dependent contraction of the muscle fiber (excitation-contraction coupling).

Myopathic weakness is produced by a decrease in the number or contractile force of muscle fibers activated within motor units. With muscular dystrophies, inflammatory myopathies, or myopathies with muscle fiber necrosis, the number of muscle fibers is reduced within many motor units. On EMG, the size of each motor unit action potential is decreased, and motor units must be recruited more rapidly than normal to produce the desired power.

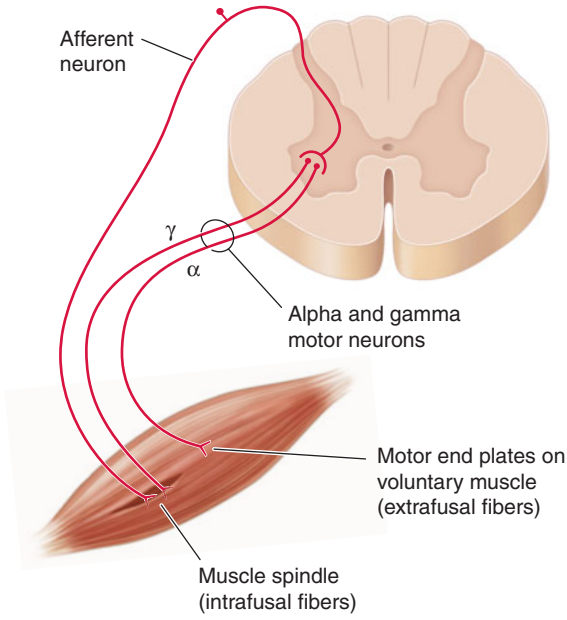

FIGURE 10-2

Lower motor neurons are divided into α and γ types. The larger α motor neurons are more numerous and innervate the extrafusal muscle fibers of the motor unit. Loss of α motor neurons or disruption of their axons produces lower motor neuron weakness. The smaller, less numerous γ motor neurons innervate the intrafusal muscle fibers of the muscle spindle and contribute to normal tone and stretch reflexes. The α motor neuron receives direct excitatory input from corticomotoneurons and primary muscle spindle afferents. The α and γ motor neurons also receive excitatory input from other descending upper motor neuron pathways, segmental sensory inputs, and interneurons. The α motor neurons receive direct inhibition from Renshaw cell interneurons, and other interneurons indirectly inhibit the α and γ motor neurons.

A tendon reflex requires the function of all illustrated structures. A tap on a tendon stretches muscle spindles (which are tonically activated by γ motor neurons) and activates the primary spindle afferent neurons. These stimulate the α motor neurons in the spinal cord, producing a brief muscle contraction, which is the familiar tendon reflex.

Some myopathies produce weakness through loss of contractile force of muscle fibers or through relatively selective involvement of the type II (fast) fibers. These may not affect the size of individual motor unit action potentials and are detected by a discrepancy between the electrical activity and force of a muscle.

Diseases of the neuromuscular junction, such as myasthenia gravis, produce weakness in a similar manner, but the loss of muscle fibers is functional (due to inability to activate them) rather than related to muscle fiber loss. The number of muscle fibers that are activated varies over time, depending on the state of rest of the neuromuscular junctions. Thus, fatigable weakness is suggestive of myasthenia gravis or other disorders of the neuromuscular junction.

Hemiparesis

Hemiparesis results from an upper motor neuron lesion above the midcervical spinal cord; most such lesions are above the foramen magnum. The presence of other neurologic deficits helps to localize the lesion. Thus, language disorders, cortical sensory disturbances, cognitive abnormalities, disorders of visual-spatial integration, apraxia, or seizures point to a cortical lesion. Homonymous visual field defects reflect either a cortical or a subcortical hemispheric lesion. A "pure motor" hemiparesis of the face, arm, or leg is often due to a small, discrete lesion in the posterior limb of the internal capsule, cerebral peduncle, or upper pons. Some brainstem lesions produce "crossed paralyses," consisting of ipsilateral cranial nerve signs and contralateral hemiparesis. The absence of cranial nerve signs or facial weakness suggests that a hemiparesis is due to a lesion in the high cervical spinal cord, especially if associated with ipsilateral loss of proprioception and contralateral loss of pain and temperature sense (the Brown-Séquard syndrome).

Acute or episodic hemiparesis usually results from ischemic or hemorrhagic stroke, but may also relate to hemorrhage occurring into brain tumors or as a result of trauma; other causes include a focal structural lesion or inflammatory process as in multiple sclerosis, abscess, or sarcoidosis. Evaluation begins immediately with a CT scan of the brain (**Fig. 10-3**) and laboratory studies. If the CT is normal and an ischemic stroke is unlikely, MRI of the brain or cervical spine is performed.

Subacute hemiparesis that evolves over days or weeks has an extensive differential diagnosis. A common cause is subdural hematoma, especially in elderly or anticoagulated patients, even when there is no history of trauma. Infectious possibilities include cerebral abscess, fungal granuloma or meningitis, and parasitic infection. Weakness from primary and metastatic neoplasms may evolve over days to weeks. AIDS may present with subacute hemiparesis due to toxoplasmosis or primary CNS lymphoma. Noninfectious inflammatory processes, such as multiple sclerosis or, less commonly, sarcoidosis, merit consideration. If the brain MRI is normal and there are no cortical and hemispheric signs, MRI of the cervical spine should be undertaken.

Chronic hemiparesis that evolves over months is usually due to a neoplasm or vascular malformation, a chronic subdural hematoma, or a degenerative disease. If an MRI of the brain is normal, the possibility of a foramen magnum or high cervical spinal cord lesion should be considered.

Paraparesis

An intraspinal lesion at or below the upper thoracic spinal cord level is most commonly responsible, but a paraparesis may also result from lesions at other locations

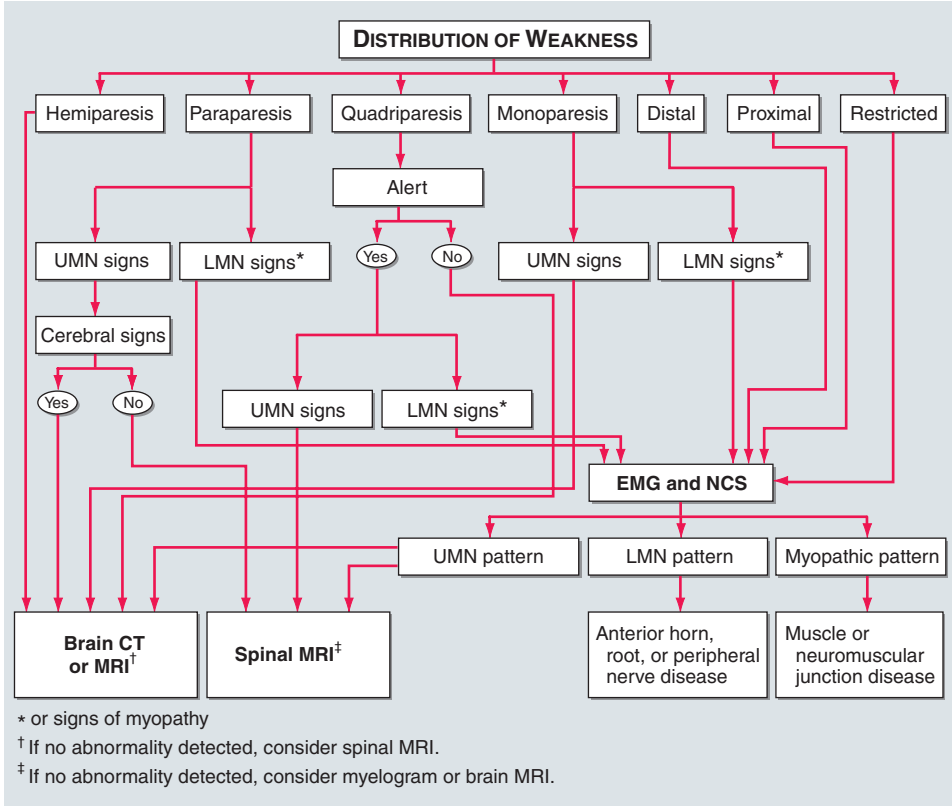

FIGURE 10-3

An algorithm for the initial workup of a patient with weakness. EMG, electromyography; LMN, lower motor neuron; NCS, nerve conduction studies; UMN, upper motor neuron.

that disturb upper motor neurons (especially parasagittal intracranial lesions) and lower motor neurons [anterior horn cell disorders, cauda equina syndromes due to involvement of nerve roots derived from the lower spinal cord (Chap. 30), and peripheral neuropathies].

Acute paraparesis may not be recognized as due to spinal cord disease at an early stage if the legs are flaccid and areflexic. Usually, however, there is sensory loss in the legs with an upper level on the trunk; a dissociated sensory loss suggestive of a central cord syndrome; or exaggerated stretch reflexes in the legs with normal reflexes in the arms. It is important to image the spinal cord (Fig. 10-3). Compressive lesions (particularly epidural tumor, abscess, or hematoma, but also a prolapsed intervertebral disk and vertebral involvement by malignancy or infection), spinal cord infarction (proprioception is usually spared), an arteriovenous fistula or other vascular anomaly, and transverse myelitis, are among the possible causes (Chap. 30).

Diseases of the cerebral hemispheres that produce acute paraparesis include anterior cerebral artery ischemia (shoulder shrug is also affected), superior sagittal sinus or cortical venous thrombosis, and acute hydrocephalus. If upper motor neuron signs are associated with drowsiness, confusion, seizures, or other hemispheric signs, MRI of the brain should be undertaken.

Paraparesis may result from a cauda equina syndrome, for example, following trauma to the low back, a midline disk herniation, or an intraspinal tumor; although sphincters are affected, hip flexion is often spared, as is sensation over the anterolateral thighs. Rarely, paraparesis is caused by a rapidly evolving anterior horn cell disease (such as poliovirus or West Nile virus infection), peripheral neuropathy (such as Guillain-Barré syndrome; Chap. 41) or myopathy (Chap. 43). In such cases, electrophysiologic studies are diagnostically helpful and refocus the subsequent evaluation.

Subacute or chronic paraparesis with spasticity is caused by upper motor neuron disease. When there is associated lower-limb sensory loss and sphincter involvement, a chronic spinal cord disorder is likely (Chap. 30). If an MRI of the spinal cord is normal, MRI of the brain may be indicated. If hemispheric signs are present, a parasagittal meningioma or chronic hydrocephalus is likely and MRI of the brain is the initial test. In the rare situation in which a longstanding paraparesis has a lower motor neuron or myopathic etiology, the localization is usually suspected on clinical grounds by the

absence of spasticity and confirmed by EMG and nerve conduction tests.

Quadriparesis or Generalized Weakness

Generalized weakness may be due to disorders of the CNS or of the motor unit. Although the terms *quadriparesis* and *generalized weakness* are often used interchangeably, quadriparesis is commonly used when an upper motor neuron cause is suspected, and generalized weakness when a disease of the motor unit is likely. Weakness from CNS disorders is usually associated with changes in consciousness or cognition, with spasticity and brisk stretch reflexes, and with alterations of sensation. Most neuromuscular causes of generalized weakness are associated with normal mental function, hypotonia, and hypoactive muscle stretch reflexes. The major causes of intermittent weakness are listed in **Table 10-2**. A patient with generalized fatigability without objective weakness may have the chronic fatigue syndrome (Chap. 47).

Acute Quadriparesis

Acute quadriparesis with onset over minutes may result from disorders of upper motor neurons (e.g., anoxia, hypotension, brainstem or cervical cord ischemia, trauma, and systemic metabolic abnormalities) or muscle (electrolyte disturbances, certain inborn errors of muscle energy metabolism, toxins, or periodic paralyses). Onset over hours to weeks may, in addition to the above, be due to lower motor neuron disorders. Guillain-Barré syndrome (Chap. 41) is the most common lower motor neuron weakness that progresses over days to 4 weeks; the finding of an elevated protein level in the cerebrospinal fluid is helpful but may be absent early in the course.

In obtunded patients, evaluation begins with a CT scan of the brain. If upper motor neuron signs are present but the patient is alert, the initial test is usually an MRI of the cervical cord. If weakness is lower motor neuron, myopathic, or uncertain in origin, the clinical approach begins with blood studies to determine the level of muscle enzymes and electrolytes and an EMG and nerve conduction study.

TABLE 10-2

CAUSES OF EPISODIC GENERALIZED WEAKNESS

1. Electrolyte disturbances, e.g., hypokalemia, hyperkalemia, hypercalcemia, hypernatremia, hyponatremia, hypophosphatemia, hypermagnesemia
2. Muscle disorders
   a. Channelopathies (periodic paralyses)
   b. Metabolic defects of muscle (impaired carbohydrate or fatty acid utilization; abnormal mitochondrial function)
3. Neuromuscular junction disorders
   a. Myasthenia gravis
   b. Lambert-Eaton myasthenic syndrome
4. Central nervous system disorders
   a. Transient ischemic attacks of the brainstem
   b. Transient global cerebral ischemia
   c. Multiple sclerosis

Subacute or Chronic Quadriparesis

When quadriparesis due to upper motor neuron disease develops over weeks, months, or years, the distinction between disorders of the cerebral hemispheres, brainstem, and cervical spinal cord is usually possible clinically. An MRI is obtained of the clinically suspected site of pathology. EMG and nerve conduction studies help to distinguish lower motor neuron disease (which usually presents with weakness that is most profound distally) from myopathic weakness, which is typically proximal.

Monoparesis

This is usually due to lower motor neuron disease, with or without associated sensory involvement. Upper motor neuron weakness occasionally presents as a monoparesis of distal and nonantigravity muscles. Myopathic weakness is rarely limited to one limb.

Acute Monoparesis

If the weakness is predominantly in distal and nonantigravity muscles and not associated with sensory impairment or pain, focal cortical ischemia is likely (Chap. 21); diagnostic possibilities are similar to those for acute hemiparesis. Sensory loss and pain usually accompany acute lower motor neuron weakness; the weakness is commonly localized to a single nerve root or peripheral nerve within the limb but occasionally reflects plexus involvement. If lower motor neuron weakness is suspected, or the pattern of weakness is uncertain, the clinical approach begins with an EMG and nerve conduction study.

Subacute or Chronic Monoparesis

Weakness and atrophy that develop over weeks or months are usually of lower motor neuron origin. If they are associated with sensory symptoms, a peripheral cause (nerve, root, or plexus) is likely; in the absence of such symptoms, anterior horn cell disease should be considered. In either case, an electrodiagnostic study is indicated. If weakness is of upper motor neuron type, a discrete cortical (precentral gyrus) or cord lesion may be responsible, and an imaging study is performed of the appropriate site.

Distal Weakness

Involvement of two or more limbs distally suggests lower motor neuron or peripheral nerve disease. Acute

distal lower limb weakness occurs occasionally from an acute toxic polyneuropathy or cauda equina syndrome. Distal symmetric weakness usually develops over weeks, months, or years and, when associated with numbness, is due to metabolic, toxic, hereditary, degenerative, or inflammatory diseases of peripheral nerves (Chap. 40). Anterior horn cell disease may begin distally but is typically asymmetric and without accompanying numbness (Chap. 27). Rarely, myopathies present with distal weakness (Chap. 43). Electrodiagnostic studies help to localize the disorder (Fig. 10-3).

Proximal Weakness

Myopathy often produces symmetric weakness of the pelvic or shoulder girdle muscles (Chap. 43). Diseases of the neuromuscular junction [such as myasthenia gravis (Chap. 42)], may present with symmetric proximal weakness often associated with ptosis, diplopia, or bulbar weakness and fluctuating in severity during the day. Extreme fatigability present in some cases of myasthenia gravis may even suggest episodic weakness, but strength rarely returns fully to normal. In anterior horn cell disease proximal weakness is usually asymmetric, but may be symmetric if familial. Numbness does not occur with any of these diseases. The evaluation usually begins with determination of the serum creatine kinase level and electrophysiologic studies.

Weakness in a Restricted Distribution

Weakness may not fit any of the above patterns, being limited, for example, to the extraocular, hemifacial, bulbar, or respiratory muscles. If unilateral, restricted weakness is usually due to lower motor neuron or peripheral nerve disease, such as in a facial palsy (Chap. 29) or an isolated superior oblique muscle paresis (Chap. 17). Weakness of part of a limb is usually due to a peripheral nerve lesion such as carpal tunnel syndrome or another entrapment neuropathy. Relatively symmetric weakness of extraocular or bulbar muscles is usually due to a myopathy (Chap. 43) or neuromuscular junction disorder (Chap. 42). Bilateral facial palsy with areflexia suggests Guillain-Barré syndrome (Chap. 41). Worsening of relatively symmetric weakness with fatigue is characteristic of neuromuscular junction disorders. Asymmetric bulbar weakness is usually due to motor neuron disease. Weakness limited to respiratory muscles is uncommon and is usually due to motor neuron disease, myasthenia gravis, or polymyositis/dermatomyositis (Chap. 44).

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CHAPTER 11

GAIT AND BALANCE DISORDERS

Lewis Sudarsky

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PREVALENCE, MORBIDITY, AND MORTALITY

Gait and balance problems are common in the elderly and contribute to the risk of falls and injury. Gait disorders have been described in 15% of individuals older than 65 years. By 80 years, one person in four will use a mechanical aid to assist ambulation. Among those 85 years and older, the prevalence of gait abnormality approaches 40%. In epidemiologic studies, gait disorders are consistently identified as a major risk factor for falls and injury.

A substantial number of older persons report insecure balance and experience falls and fear of falling. Prospective studies indicate that 20–30% of individuals >65 years fall each year, and the proportion is even higher in hospitalized elderly and nursing home patients. Each year 8% of individuals >75 years suffer a serious fall-related injury. Hip fractures often result in hospitalization and nursing home admission. For each person who is physically disabled, there are others whose functional independence is constrained by anxiety and fear of falling. Nearly one in five of elderly individuals voluntarily limit their activity because of fear of falling. With loss of ambulation, there is a diminished quality of life and increased morbidity and mortality.

ANATOMY AND PHYSIOLOGY

Upright bipedal gait depends on the successful integration of postural control and locomotion. These functions are widely distributed in the central nervous system. The biomechanics of bipedal walking are complex, and the performance is easily compromised by injury at any level. Command and control centers in the brainstem, cerebellum, and forebrain modify the action of spinal pattern generators to promote stepping. While a form of "fictive locomotion" can be elicited from quadrupedal animals after spinal transection, this capacity is limited in primates. Step generation in primates is dependent on locomotor centers in the pontine tegmentum, midbrain, and subthalamic region. Locomotor synergies are executed through the reticular formation and descending pathways in the ventromedial spinal cord. Cerebral control provides a goal and purpose for walking and is involved in avoidance of obstacles and adaptation of locomotor programs to context and terrain.

Postural control requires the maintenance of the center of mass over the base of support through the gait cycle. Unconscious postural adjustments maintain standing balance: long latency responses are measurable in the leg muscles, beginning 110 ms after a perturbation. Forward motion of the center of mass provides propulsive force for stepping, but failure to maintain the center of mass within stability limits results in falls. The anatomic substrate for dynamic balance has not been well defined, but the vestibular nucleus and midline cerebellum contribute to balance control in animals. Human patients with damage to these structures have impaired balance with standing and walking.

Standing balance depends on good quality sensory information about the position of the body center with respect to the environment, support surface, and gravitational forces. Sensory information for postural control is primarily generated by the visual system, the vestibular system, and by proprioceptive receptors in the muscle spindles and joints. A healthy redundancy of sensory afferent information is generally available, but loss of two of the three pathways is sufficient to compromise standing balance. Balance disorders in older individuals sometimes result from multiple insults in the peripheral sensory systems (e.g., visual loss, vestibular deficit, peripheral neuropathy), critically degrading the quality of afferent information needed for balance stability.

Older patients with mental status abnormalities and dementia from neurodegenerative diseases appear to be particularly prone to falls and injury. Frailty, muscle weakness, and deconditioning undoubtedly contribute to the risk. There is a growing literature on the use of attentional resources to manage locomotion. The ability to walk while attending to a cognitive task (dual tasking) may be particularly compromised in older adults with a history of falls. Walking is generally considered to be unconscious and automatic, but older patients with deficits in executive function may be unable to manage the attention needed for dynamic balance when distracted.

DISORDERS OF GAIT

The heterogeneity of gait disorders observed in clinical practice reflects the large network of neural systems involved in the task. There is the potential for abnormalities to develop, and walking is vulnerable to neurologic disease at every level. Gait disorders have been classified descriptively, based on the abnormal physiology and biomechanics. One problem with this approach is that many failing gaits look fundamentally similar. This overlap reflects common patterns of adaptation to threatened balance stability and declining performance. *The gait disorder observed clinically must be viewed as the product of a neurologic deficit and a functional adaptation.* Unique features of the failing gait are often overwhelmed by the adaptive response. Some of the common patterns of abnormal gait are summarized below. Gait disorders can also be classified by etiology, as listed in **Table 11-1.**

Cautious Gait

The term *cautious gait* is used to describe the patient who walks with an abbreviated stride and lowered center of mass, as if walking on a slippery surface. This disorder is both common and nonspecific. It is, in essence, an adaptation to a perceived postural threat. A fear of falling may be associated. In one study, this disorder was observed in more than one-third of older patients with a higher level gait disturbance. Physical therapy often improves walking to the degree that follow-up observation may reveal a more specific underlying disorder.

TABLE 11-1

ETIOLOGY OF GAIT DISORDER

	CASES	PERCENT
Sensory deficits	22	18.3
Myelopathy	20	16.7
Multiple infarcts	18	15.0
Parkinsonism	14	11.7
Cerebellar degeneration	8	6.7
Hydrocephalus	8	6.7
Toxic/metabolic	3	2.5
Psychogenic	4	3.3
Other	6	5.0
Unknown cause	17	14.2
Total	120	100%

Source: Reproduced with permission from Masdeu et al.

Stiff-Legged Gait

Spastic gait is characterized by stiffness in the legs, an imbalance of muscle tone, and a tendency to circumduct and scuff the feet. The disorder reflects compromise of corticospinal command and overactivity of spinal reflexes. The patient may walk on his or her toes. In extreme instances, the legs cross due to increased tone in the adductors. Upper motor neuron signs are present on physical examination. Shoes often reflect an uneven pattern of wear across the outside. The disorder may be cerebral or spinal in origin.

Myelopathy from cervical spondylosis is a common cause of spastic or spastic-ataxic gait. Demyelinating disease and trauma are the leading causes of myelopathy in younger patients. In a chronic progressive myelopathy of unknown cause, workup with laboratory and imaging tests may establish a diagnosis of multiple sclerosis. A family history should suggest hereditary spastic paraplegia (HSP). Genetic testing is now available for some of the common HSP mutations. Tropical spastic paraparesis related to the retrovirus HTLV-I is endemic in parts of the Caribbean and South America. A structural lesion, such as tumor or spinal vascular malformation, should be excluded with appropriate testing. Spinal cord disorders are discussed in detail in Chap. 30.

With cerebral spasticity asymmetry is common, involvement of the upper extremities is usually observed, and dysarthria is often an associated feature. Common causes include vascular disease (stroke), multiple sclerosis, and perinatal injury to the nervous system (cerebral palsy).

Other stiff-legged gaits include dystonia (Chap. 25) and stiff-person syndrome. Dystonia is a disorder characterized

by sustained muscle contractions, resulting in repetitive twisting movements and abnormal posture. It often has a genetic basis. Dystonic spasms produce plantar flexion and inversion of the feet, sometimes with torsion of the trunk. In autoimmune stiff-person syndrome, there is exaggerated lordosis of the lumbar spine and overactivation of antagonist muscles, which restricts trunk and lower limb movement and results in a wooden or fixed posture.

Parkinsonism and Freezing Gait

Parkinson's disease (Chap. 24) is common, affecting 1% of the population >55 years. The stooped posture and shuffling gait are characteristic and distinctive features. Patients sometimes accelerate (festinate) with walking or display retropulsion. There may be difficulty with gait initiation (freezing) and a tendency to turn en bloc. Imbalance and falls may develop as the disease progresses over years. Other progressive neurodegenerative disorders may also involve a freezing gait; these include progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, and primary pallidal degeneration. Such patients with atypical parkinsonian syndromes frequently present with axial stiffness, postural instability, and a shuffling gait but tend to lack the characteristic pill-rolling tremor of Parkinson's disease. Falls within the first year suggest the possibility of progressive supranuclear palsy.

Hyperkinetic movement disorders also produce characteristic and recognizable disturbances in gait. In Huntington's disease (Chap. 25), the unpredictable occurrence of choreic movements gives the gait a dancing quality. Tardive dyskinesia is the cause of many odd, stereotypic gait disorders seen in chronic psychiatric patients.

Frontal Gait Disorder

Frontal gait disorder, sometimes known as "gait apraxia," is common in the elderly and has a variety of causes. Typical features include a wide base of support, short stride, shuffling along the floor, and difficulty with starts and turns. Many patients exhibit difficulty with gait initiation, descriptively characterized as the "slipping clutch" syndrome or "gait ignition failure." The term *lower body parkinsonism* is also used to describe such patients. Strength is generally preserved, and patients are able to make stepping movements when not standing and maintaining balance at the same time. This disorder is a higher level motor control disorder, as opposed to an apraxia.

The most common cause of frontal gait disorder is vascular disease, particularly subcortical small-vessel disease. Lesions are frequently found in the deep frontal white matter and centrum ovale. Gait disorder may be the salient feature in hypertensive patients with ischemic lesions of the deep hemisphere white matter (Binswanger's disease). The clinical syndrome includes mental change (variable in degree), dysarthria, pseudobulbar affect (emotional disinhibition), increased tone, and hyperreflexia in the lower limbs.

Communicating hydrocephalus in the adult also presents with a gait disorder of this type. Other features of the diagnostic triad (mental change, incontinence) may be absent in the initial stages. MRI demonstrates ventricular enlargement, an enlarged flow void about the aqueduct, and a variable degree of periventricular white matter change. A lumbar puncture or dynamic test is necessary to confirm the presence of hydrocephalus.

Cerebellar Gait Ataxia

Disorders of the cerebellum have a dramatic impact on gait and balance. Cerebellar gait ataxia is characterized by a wide base of support, lateral instability of the trunk, erratic foot placement, and decompensation of balance when attempting to walk tandem. Difficulty maintaining balance when turning is often an early feature. Patients are unable to walk tandem heel to toe, and display truncal sway in narrow-based or tandem stance. They show considerable variation in their tendency to fall in daily life.

Causes of cerebellar ataxia in older patients include stroke, trauma, tumor, and neurodegenerative disease, including multiple system atrophy (Chaps. 24 and 26) and various forms of hereditary cerebellar degeneration (Chap. 24). MRI demonstrates the extent and topography of cerebellar atrophy. A short expansion at the site of the fragile X mutation (fragile X pre-mutation) has been associated with gait ataxia in older men. Alcoholic cerebellar degeneration can be screened by history and often confirmed by MRI.

Sensory Ataxia

As reviewed above, balance depends on high-quality afferent information from the visual and the vestibular systems and proprioception. When this information is lost or degraded, balance during locomotion is impaired and instability results. The sensory ataxia of tabetic neurosyphilis is a classic example. The contemporary equivalent is the patient with neuropathy affecting large fibers. Vitamin B_{12} deficiency is a treatable cause of large-fiber sensory loss in the spinal cord and peripheral nervous system. Joint position and vibration sense are diminished in the lower limbs. The stance in such patients is destabilized by eye closure; they often look down at their feet when walking and do poorly in the dark. Patients have been described with imbalance from bilateral vestibular loss, caused by disease or by exposure to ototoxic drugs. **Table 11-2** compares sensory ataxia with cerebellar ataxia and frontal gait disorder. Some patients exhibit a syndrome of imbalance from the combined effect of multiple sensory

TABLE 11-2

FEATURES OF CEREBELLAR ATAXIA, SENSORY ATAXIA, AND FRONTAL GAIT DISORDERS

	CEREBELLAR ATAXIA	SENSORY ATAXIA	FRONTAL GAIT
Base of support	Wide-based	Narrow base, looks down	Wide-based
Velocity	Variable	Slow	Very slow
Stride	Irregular, lurching	Regular with path deviation	Short, shuffling
Romberg	+/–	Unsteady, falls	+/–
Heel → shin	Abnormal	+/–	Normal
Initiation	Normal	Normal	Hesitant
Turns	Unsteady	+/–	Hesitant, multistep
Postural instability	+	+++	++++ Poor postural synergies getting up from a chair
Falls	Late event	Frequent	Frequent

deficits. Such patients, often elderly and diabetic, have disturbances in proprioception, vision, and vestibular sense that impair postural support.

Neuromuscular Disease

Patients with neuromuscular disease often have an abnormal gait, occasionally as a presenting feature. With distal weakness (peripheral neuropathy) the step height is increased to compensate for foot drop, and the sole of the foot may slap on the floor during weight acceptance. Neuropathy may be associated with a degree of sensory imbalance, as described earlier. Patients with myopathy or muscular dystrophy more typically exhibit proximal weakness. Weakness of the hip girdle may result in a degree of excess pelvic sway during locomotion.

Toxic and Metabolic Disorders

Alcohol intoxication is the most common cause of acute walking difficulty. Chronic toxicity from medications and metabolic disturbances can impair motor function and gait. Mental status changes may be present, and examination may reveal asterixis or myoclonus. Static equilibrium is disturbed, and such patients are easily thrown off balance. Disequilibrium is particularly evident in patients with chronic renal disease and those with hepatic failure, in whom asterixis may impair postural support. Sedative drugs, especially neuroleptics and long-acting benzodiazepines, affect postural control and increase the risk for falls. These disorders are important to recognize because they are often treatable.

Psychogenic Gait Disorder

Psychogenic disorders are common in outpatient practice, and the presentation often involves gait. Some patients with extreme anxiety or phobia walk with exaggerated caution with abduction of the arms, as if walking on ice. This inappropriately overcautious gait differs in degree from the gait of the patient who is insecure and making adjustments for imbalance. Depressed patients exhibit primarily slowness, a manifestation of psychomotor retardation, and lack of purpose in their stride. Hysterical gait disorders are among the most spectacular encountered. Odd gyrations of posture with wastage of muscular energy (astasia-abasia), extreme slow motion, and dramatic fluctuations over time may be observed in patients with somatoform disorders and conversion reaction.

Approach to the Patient:
SLOWLY PROGRESSIVE DISORDER OF GAIT

When reviewing the history it is helpful to inquire about the onset and progression of disability. Initial awareness of an unsteady gait often follows a fall. Stepwise evolution or sudden progression suggest vascular disease. Gait disorder may be associated with urinary urgency and incontinence, particularly in patients with cervical spine disease or hydrocephalus. It is always important to review the use of alcohol and medications that affect gait and balance. Information on localization derived from the neurologic examination can be helpful to narrow the list of possible diagnoses.

Gait observation provides an immediate sense of the patient's degree of disability. Characteristic patterns of abnormality are sometimes observed, though failing gaits often look fundamentally similar. Cadence

(steps/min), velocity, and stride length can be recorded by timing a patient over a fixed distance. Watching the patient get out of a chair provides a good functional assessment of balance.

Brain imaging studies may be informative in patients with an undiagnosed disorder of gait. MRI is sensitive for cerebral lesions of vascular or demyelinating disease and is a good screening test for occult hydrocephalus. Patients with recurrent falls are at risk for subdural hematoma. Many elderly patients with gait and balance difficulty have white matter abnormalities in the periventricular region and centrum semiovale. While these lesions may be an incidental finding, a substantial burden of white matter disease will ultimately impact cerebral control of locomotion.

DISORDERS OF BALANCE

Balance is the ability to maintain equilibrium: a state in which opposing physical forces cancel. In physiology, this is taken to mean the ability of the organism to control the center of mass with respect to gravity and the support surface. In reality, no one is aware of what or where the center of mass is, but everyone, including gymnasts, figure skaters, and platform divers, move so as to manage it. Imbalance implies a disturbance of equilibrium. Disorders of balance present with difficulty maintaining posture standing and walking and with a subjective sense of disequilibrium, a form of dizziness.

The cerebellum and vestibular system organize antigravity responses needed to maintain the upright posture. As reviewed earlier, these responses are physiologically complex, and the anatomic representation is not well understood. Failure, resulting in disequilibrium, can occur at several levels: cerebellar, vestibular, somatosensory, and higher level disequilibrium. Patients with hereditary ataxia or alcoholic cerebellar degeneration do not generally complain of dizziness, but balance is visibly impaired. Neurologic examination will reveal a variety of cerebellar signs. Postural compensation may prevent falls early on, but falls inevitably occur with disease progression. The progression of a neurodegenerative ataxia is often measured by the number of years to loss of stable ambulation. Vestibular disorders have symptoms and signs in three categories: vertigo, the subjective appreciation or illusion of movement; nystagmus, a vestibulo-oculomotor sign; and poor balance, an impairment of vestibulospinal function. Not every patient has all manifestations. Patients with vestibular deficits related to ototoxic drugs may lack vertigo or obvious nystagmus, but balance is impaired on standing and walking, and the patient cannot navigate in the dark. Laboratory testing is available to explore vestibulo-oculomotor and vestibulospinal deficits.

Somatosensory deficits also produce imbalance and falls. There is often a subjective sense of insecure balance and fear of falling. Postural control is compromised by eye closure (Romberg's sign); these patients also have difficulty navigating in the dark. A dramatic example is the patient with autoimmune subacute sensory neuropathy, sometimes a paraneoplastic disorder (Chap. 39). Compensatory strategies enable such patients to walk in the virtual absence of proprioception, but the task requires active visual monitoring. Patients with higher level disorders of equilibrium have difficulty maintaining balance in daily life and may present with falls. There may be reduced awareness of balance impairment. Classic examples include patients with progressive supranuclear palsy and normal pressure hydrocephalus. Patients on sedating medications are also in this category. In prospective studies, cognitive impairment and the use of sedative medications substantially increase the risk for falls.

FALLS

Falls are a common event, particularly among the elderly. Modest changes in balance function have been described in fit older subjects as a result of normal aging. Subtle deficits in sensory systems, attention, and motor reaction time contribute to the risk, and environmental hazards abound. Epidemiologic studies have identified a number of risk factors for falls, summarized in **Table 11-3.** A fall is not a neurologic problem, nor reason for referral to a specialist, but there are circumstances in which neurologic evaluation is appropriate. In a classic study, 90% of fall events occurred among 10% of individuals, a group known as *recurrent fallers*. Some of these are frail older persons with chronic diseases. Recurrent falls sometimes indicate the presence of serious balance impairment. Syncope, seizure, or falls related to loss of consciousness require appropriate evaluation and treatment (Chaps. 8 and 20).

TABLE 11-3

RISK FACTORS FOR FALLS, A META-ANALYSIS: SUMMARY OF SIXTEEN CONTROLLED STUDIES

RISK FACTOR	MEAN RR (OR)	RANGE
Weakness	4.9	1.9–10.3
Balance deficit	3.2	1.6–5.4
Gait disorder	3.0	1.7–4.8
Visual deficit	2.8	1.1–7.4
Mobility limitation	2.5	1.0–5.3
Cognitive impairment	2.4	2.0–4.7
Impaired functional status	2.0	1.0–3.1
Postural hypotension	1.9	1.0–3.4

Note: RR, relative risks from prospective studies; OR, odds ratios from retrospective studies.

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The descriptive classification of falls is as difficult as the classification of gait disorders, for many of the same reasons. Postural control systems are widely distributed, and a number of disease-related abnormalities occur. Unlike gait problems that are apparent on observation, falls are rarely observed in the office. The patient and family may have limited information about what triggered the fall. Injuries can complicate the physical examination. Although there is no standard nosology of falls, common patterns can be identified.

Slipping, Tripping, and "Mechanical Falls"

Slipping on icy pavement, tripping on obstacles, and falls related to obvious environmental factors are often termed *mechanical falls*. They occasionally occur in healthy individuals with good balance compensation. Frequent tripping falls raise suspicion about an underlying neurologic deficit. Patients with spasticity, leg weakness, or foot drop experience tripping falls.

Weakness and Frailty

Patients who lack strength in antigravity muscles have difficulty rising from a chair, fatigue easily when walking, and have difficulty maintaining their balance after a perturbation. These patients are often unable to get up after a fall and may be on the floor for an hour or more before help arrives. Deconditioning of this sort is often treatable. Resistance strength training can increase muscle mass and leg strength in people in their 80s and 90s.

Drop Attacks and Collapsing Falls

Drop attacks are sudden collapsing falls without loss of consciousness. Patients who collapse from lack of postural tone present a diagnostic challenge. The patient may report that his or her legs just gave out underneath; the family may describe the patient as "collapsing in a heap." Orthostatic hypotension may be a factor in some such falls. Asterixis or epilepsy may impair postural support. A colloid cyst of the third ventricle can present with intermittent obstruction of the foramen of Monroe, resulting in a drop attack. While collapsing falls are more common in older patients with vascular risk factors, they should not be confused with vertebrobasilar ischemic attacks.

Toppling Falls

Some patients maintain tone in antigravity muscles but fall over like a tree trunk, as if postural defenses had disengaged. There may be a consistent direction to such falls. The patient with cerebellar pathology may lean and topple over toward the side of the lesion. Patients with lesions of the vestibular system or its central pathways may experience lateral pulsion and toppling falls. Patients with progressive supranuclear palsy often fall over backwards. Falls of this nature occur in patients with advanced Parkinson's disease once postural instability has developed.

Gait Freezing

Another fall pattern in Parkinson's disease and related disorders is the fall due to freezing of gait. The feet stick to the floor and the center of mass keeps moving, resulting in a disequilibrium from which the patient cannot recover. This can result in a forward fall. Gait freezing can also occur as the patient attempts to turn and change direction. Similarly, the patient with Parkinson's disease and festinating gait may find his feet unable to keep up, resulting in a forward fall.

Falls Related to Sensory Deficit

Patients with somatosensory, visual, or vestibular deficits are prone to falls. These patients have particular difficulty dealing with poor illumination or walking on uneven ground. These patients often express subjective imbalance, apprehension, and fear of falling. Deficits in joint position and vibration sense are apparent on physical examination.

℞ Treatment: INTERVENTIONS TO REDUCE THE RISK OF FALLS AND INJURY

Efforts should be made to define the etiology of the gait disorder and mechanism of the falls. Standing blood pressure should be recorded. Specific treatment may be possible, once a diagnosis is established. Therapeutic intervention is often recommended for older patients at substantial risk for falls, even if no neurologic disease is identified. A home visit to look for environmental hazards can be helpful. A variety of modifications may be recommended to improve safety, including improved lighting and the installation of grab bars and nonslip surfaces.

Rehabilitation interventions attempt to improve muscle strength and balance stability and to make the patient more resistant to injury. High-intensity resistance strength training with weights and machines is useful to improve muscle mass, even in frail older patients. Improvements are realized in posture and gait, which should translate to reduced risk of falls and injury. The goal of sensory balance training is to improve balance stability. Measurable gains can be achieved in a few weeks of training, and benefits can be maintained over 6 months by a 10- to 20-min home exercise program. This strategy is particularly successful in patients with vestibular and somatosensory balance disorders. The Yale Health and Aging study used a strategy of targeted, multiple risk factor abatement to reduce falls in the elderly. Prescription medications were adjusted, and home-based exercise programs were

tailored to the patient's need, based on an initial geriatric assessment. The program realized a 44% reduction in falls, in comparison with a control group of patients who had periodic social visits.

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CHAPTER 12

NUMBNESS, TINGLING, AND SENSORY LOSS

Michael J. Aminoff ■ Arthur K. Asbury

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Normal somatic sensation reflects a continuous monitoring process, little of which reaches consciousness under ordinary conditions. By contrast, disordered sensation, particularly when experienced as painful, is alarming and dominates the sufferer's attention. Physicians should be able to recognize abnormal sensations by how they are described, know their type and likely site of origin, and understand their implications. Pain is considered separately in Chap. 5.

POSITIVE AND NEGATIVE SYMPTOMS

Abnormal sensory symptoms may be divided into two categories, positive and negative. The prototypical positive symptom is tingling (pins-and-needles); other positive sensory phenomena include altered sensations that are described as pricking, bandlike, lightning-like shooting feelings (lancinations), aching, knifelike, twisting, drawing, pulling, tightening, burning, searing, electrical, or raw feelings. Such symptoms are often painful.

Positive phenomena usually result from trains of impulses generated at sites of lowered threshold or heightened excitability along a peripheral or central sensory pathway. The nature and severity of the abnormal sensation depend on the number, rate, timing, and distribution of ectopic impulses and the type and function of nervous tissue in which they arise. Because positive phenomena represent excessive activity in sensory pathways, they are not necessarily associated with a sensory deficit (loss) on examination.

Negative phenomena represent loss of sensory function and are characterized by diminished or absent feeling, often experienced as numbness, and by abnormal findings on sensory examination. In disorders affecting peripheral sensation, it is estimated that at least half the afferent axons innervating a given site are lost or functionless before a sensory deficit can be demonstrated by clinical examination. This threshold varies according to how rapidly function is lost in sensory nerve fibers. If the rate of loss is slow, lack of cutaneous feeling may be unnoticed by the patient and difficult to demonstrate on examination, even though few sensory fibers are functioning; if rapid, both positive and negative phenomena are usually conspicuous. Subclinical degrees of sensory dysfunction may be revealed by sensory nerve conduction studies or somatosensory evoked potentials (Chap. 3).

Whereas sensory symptoms may be either positive or negative, sensory signs on examination are always a measure of negative phenomena.

TERMINOLOGY

Words used to characterize sensory disturbance are descriptive and based on convention. Paresthesias and dysesthesias are general terms used to denote positive sensory symptoms. The term *paresthesias* typically refers to tingling or pins-and-needles sensations but may include a wide variety of other abnormal sensations, except pain; it sometimes implies that the abnormal sensations are perceived spontaneously. The more general term *dysesthesia*s

denotes all types of abnormal sensations, including painful ones, regardless of whether a stimulus is evident.

Another set of terms refers to sensory abnormalities found on examination. *Hypesthesia* or *hypoesthesia* refers to a reduction of cutaneous sensation to a specific type of testing such as pressure, light touch, and warm or cold stimuli; *anesthesia,* to a complete absence of skin sensation to the same stimuli plus pinprick; and *hypalgesia* or *analgesia* to reduced or absent pain perception (nociception), such as perception of the pricking quality elicited by a pin. *Hyperesthesia* means pain or increased sensitivity in response to touch. Similarly, *allodynia* describes the situation in which a nonpainful stimulus, once perceived, is experienced as painful, even excruciating. An example is elicitation of a painful sensation by application of a vibrating tuning fork. *Hyperalgesia* denotes severe pain in response to a mildly noxious stimulus, and *hyperpathia*, a broad term, encompasses all the phenomena described by hyperesthesia, allodynia, and hyperalgesia. With hyperpathia, the threshold for a sensory stimulus is increased and perception is delayed, but once felt, is unduly painful.

Disorders of deep sensation, arising from muscle spindles, tendons, and joints, affect proprioception (position sense). Manifestations include imbalance (particularly with eyes closed or in the dark), clumsiness of precision movements, and unsteadiness of gait, which are referred to collectively as *sensory ataxia*. Other findings on examination usually, but not invariably, include reduced or absent joint position and vibratory sensibility and absent deep tendon reflexes in the affected limbs. Romberg's sign is positive, which means that the patient sways markedly or topples when asked to stand with feet close together and eyes closed. In severe states of deafferentation involving deep sensation, the patient cannot walk or stand unaided or even sit unsupported. Continuous involuntary movements (*pseudoathetosis*) of the outstretched hands and fingers occur, particularly with eyes closed.

ANATOMY OF SENSATION

Cutaneous afferent innervation is conveyed by a rich variety of receptors, both naked nerve endings (nociceptors and thermoreceptors) and encapsulated terminals (mechanoreceptors). Each type of receptor has its own set of sensitivities to specific stimuli, size and distinctness of receptive fields, and adaptational qualities. Much of the knowledge about these receptors has come from the development of techniques to study single intact nerve fibers intraneurally in awake, unanesthetized human subjects. It is possible not only to record from but also to stimulate single fibers in isolation. A single impulse, whether elicited by a natural stimulus or evoked by electrical microstimulation in a large myelinated afferent fiber may be both perceived and localized.

Afferent fibers of all sizes in peripheral nerve trunks traverse the dorsal roots and enter the dorsal horn of the spinal cord (Fig. 12-1). From there the smaller fibers take a different route to the parietal cortex than the larger fibers. The polysynaptic projections of the smaller fibers (unmyelinated and small myelinated), which subserve mainly nociception, temperature sensibility, and touch, cross and ascend in the opposite anterior and lateral columns of the spinal cord, through the brainstem, to the ventral posterolateral (VPL) nucleus of the thalamus, and ultimately project to the postcentral gyrus of the parietal cortex. This is the *spinothalamic pathway* or *anterolateral system*. The larger fibers, which subserve tactile and position sense and kinesthesia, project rostrally in the posterior column on the same side of the spinal cord

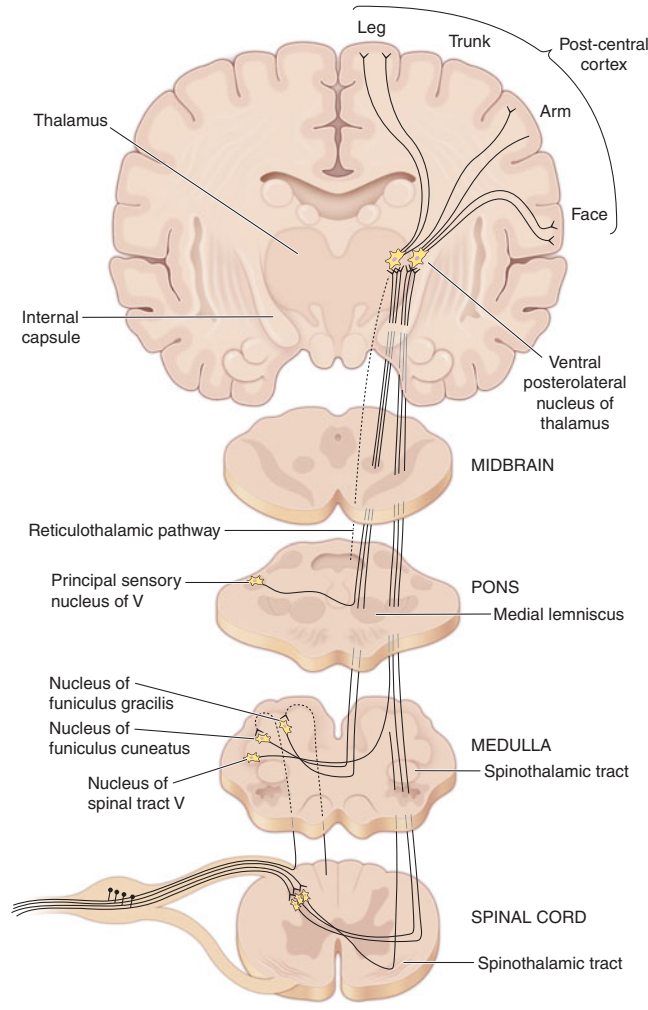

FIGURE 12-1

The main somatosensory pathways. The spinothalamic tract (pain, thermal sense) and the posterior column–lemniscal system (touch, pressure, joint position) are shown. Offshoots from the ascending anterolateral fasciculus (spinothalamic tract) to nuclei in the medulla, pons, and mesencephalon and nuclear terminations of the tract are indicated. (*From AH Ropper, RH Brown, in Adams and Victor's Principles of Neurology, 8th ed. New York, McGraw-Hill, 2007.*)

and make their first synapse in the gracile or cuneate nucleus of the lower medulla. Axons of the second-order neuron decussate and ascend in the medial lemniscus located medially in the medulla and in the tegmentum of the pons and midbrain and synapse in the VPL nucleus; the third-order neurons project to parietal cortex. This large-fiber system is referred to as the *posterior column–medial lemniscal pathway* (lemniscal, for short). Note that although the lemniscal and the anterolateral pathways both project up the spinal cord to the thalamus, it is the (crossed) anterolateral pathway that is referred to as the *spinothalamic tract*, by convention.

Although the fiber types and functions that make up the spinothalamic and lemniscal systems are relatively well known, many other fibers, particularly those associated with touch, pressure, and position sense, ascend in a diffusely distributed pattern both ipsilaterally and contralaterally in the anterolateral quadrants of the spinal cord. This explains why a complete lesion of the posterior columns of the spinal cord may be associated with little sensory deficit on examination.

EXAMINATION OF SENSATION

The main components of the sensory examination are tests of primary sensation (pain, touch, vibration, joint position, and thermal sensation; **Table 12-1**).

Some general principles pertain. The examiner must depend on patient responses, particularly when testing cutaneous sensation (pin, touch, warm, or cold), which complicates interpretation. Further, examination may be limited in some patients. In a stuporous patient, for example, sensory examination is reduced to observing the briskness of withdrawal in response to a pinch or other noxious stimulus. Comparison of response on one side of the body to the other is essential. In the alert but uncooperative patient, it may not be possible to examine cutaneous sensation, but some idea of proprioceptive function may be gained by noting the patient's best performance of movements requiring balance and precision. Frequently, patients present with sensory symptoms that do not fit an anatomic localization and that are accompanied by either no abnormalities or gross inconsistencies on examination. The examiner should then consider whether the sensory symptoms are a disguised request for help with psychological or situational problems. Discretion must be used in pursuing this possibility. Finally, sensory examination of a patient who has no neurologic complaints can be brief and consist of pinprick, touch, and vibration testing in the hands and feet plus evaluation of stance and gait, including the Romberg maneuver. Evaluation of stance and gait also tests the integrity of motor and cerebellar systems.

Primary Sensation

(See Table 12-1) The sense of pain is usually tested with a clean pin, asking the patient to focus on the pricking or unpleasant quality of the stimulus and not just the pressure or touch sensation elicited. Areas of hypalgesia should be mapped by proceeding radially from the most hypalgesic site (**Figs. 12-2** and **12-3**).

Temperature sensation, to both hot and cold, is best tested with small containers filled with water of the desired temperature. This is impractical in most settings. An alternative way to test cold sensation is to touch a metal object, such as a tuning fork at room temperature, to the skin. For testing warm temperatures, the tuning fork or other metal object may be held under warm water of the desired temperature and then used. The appreciation of both cold and warmth should be tested because different receptors respond to each.

Touch is usually tested with a wisp of cotton or a fine camelhair brush. In general, it is better to avoid testing touch on hairy skin because of the profusion of sensory endings that surround each hair follicle.

TABLE 12-1

TESTING PRIMARY SENSATION

SENSE	TEST DEVICE	ENDINGS ACTIVATED	FIBER SIZE MEDIATING	CENTRAL PATHWAY
Pain	Pinprick	Cutaneous nociceptors	Small	SpTh, also D
Temperature, heat	Warm metal object	Cutaneous thermoreceptors for hot	Small	SpTh
Temperature, cold	Cold metal object	Cutaneous thermoreceptors for cold	Small	SpTh
Touch	Cotton wisp, fine brush	Cutaneous mechanoreceptors, also naked endings	Large and small	Lem, also D and SpTh
Vibration	Tuning fork, 128 Hz	Mechanoreceptors, especially pacinian corpuscles	Large	Lem, also D
Joint position	Passive movement of specific joints	Joint capsule and tendon endings, muscle spindles	Large	Lem, also D

Note: D, diffuse ascending projections in ipsilateral and contralateral anterolateral columns; SpTh, spinothalamic projection, contralateral; Lem, posterior column and lemniscal projection, ipsilateral.

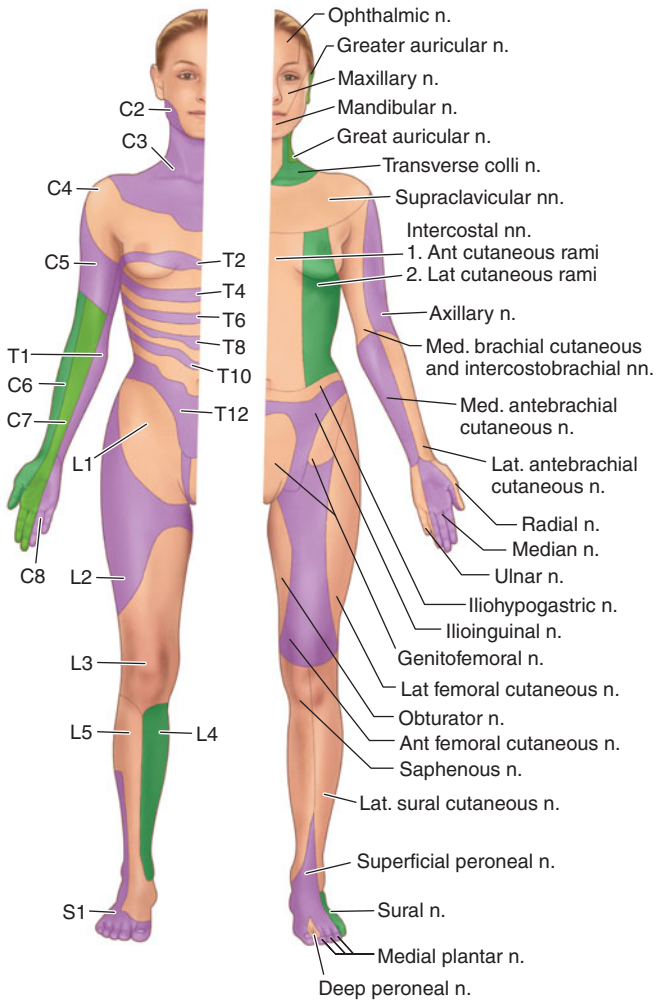

FIGURE 12-2

Anterior view of dermatomes (*left*) and cutaneous areas (*right*) supplied by individual peripheral nerves. (*Modified from MB Carpenter and J Sutin, in Human Neuroanatomy, 8th ed. Baltimore, Williams & Wilkins, 1983.*)

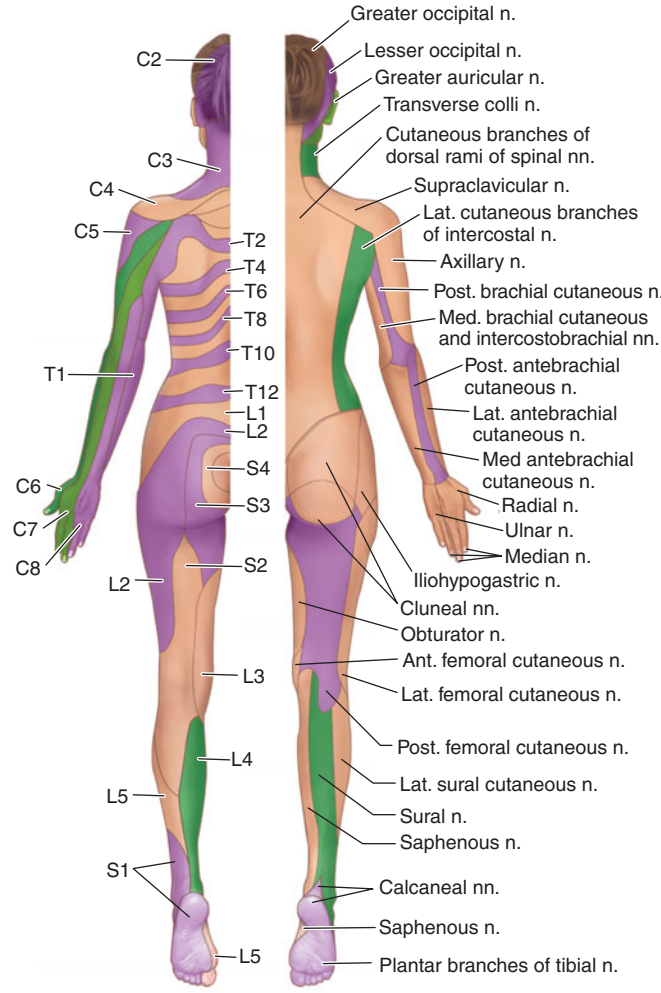

FIGURE 12-3

Posterior view of dermatomes (*left*) and cutaneous areas (*right*) supplied by individual peripheral nerves. (*Modified from MB Carpenter and J Sutin, in Human Neuroanatomy, 8th ed. Baltimore, Williams & Wilkins, 1983.*)

Joint position testing is a measure of proprioception, one of the most important functions of the sensory system. With the patient's eyes closed, joint position is tested in the distal interphalangeal joint of the great toe and fingers. If errors are made in recognizing the direction of passive movements, more proximal joints are tested. A test of proximal joint position sense, primarily at the shoulder, is performed by asking the patient to bring the two index fingers together with arms extended and eyes closed. Normal individuals can do this accurately, with errors of 1 cm or less.

The sense of vibration is tested with a tuning fork that vibrates at 128 Hz. Vibration is usually tested over bony points, beginning distally; in the feet, it is tested over the dorsal surface of the distal phalanx of the big toes and at the malleoli of the ankles, and in the hands dorsally at the distal phalanx of the fingers. If abnormalities are found, more proximal sites can be examined. Vibratory thresholds at the same site in the patient and the examiner may be compared for control purposes.

Quantitative Sensory Testing

Effective sensory testing devices are now available commercially. Quantitative sensory testing is particularly useful for serial evaluation of cutaneous sensation in clinical trials. Threshold testing for touch and vibratory and thermal sensation is the most widely used application.

Cortical Sensation

The most commonly used tests of cortical function are two-point discrimination, touch localization, and bilateral simultaneous stimulation and tests for graphesthesia and stereognosis. Abnormalities of these sensory tests, in the presence of normal primary sensation in an alert

cooperative patient, signify a lesion of the parietal cortex or thalamocortical projections to the parietal lobe. If primary sensation is altered, these cortical discriminative functions will usually be abnormal also. Comparisons should always be made between analogous sites on the two sides of the body because the deficit with a specific parietal lesion is likely to be unilateral. Interside comparisons are important for all cortical sensory testing.

Two-point discrimination is tested by special calipers, the points of which may be set from 2 mm to several centimeters apart and then applied simultaneously to the site to be tested. The pulp of the fingertips is a common site to test; a normal individual can distinguish about 3-mm separation of points there.

Touch localization is performed by light pressure for an instant with the examiner's fingertip or a wisp of cotton-wool; the patient, whose eyes are closed, is required to identify the site of touch with the fingertip. *Bilateral simultaneous stimulation* at analogous sites (e.g., the dorsum of both hands) can be carried out to determine whether the perception of touch is extinguished consistently on one side or the other. The phenomenon is referred to as *extinction*. *Graphesthesia* means the capacity to recognize with eyes closed letters or numbers drawn by the examiner's fingertip on the palm of the hand. Once again, interside comparison is of prime importance. Inability to recognize numbers or letters is termed *agraphesthesia*.

Stereognosis refers to the ability to identify common objects by palpation, recognizing their shape, texture, and size. Common standard objects, such as a key, paper clip, or coins, are best used. Patients with normal stereognosis should be able to distinguish a dime from a penny and a nickel from a quarter without looking. Patients should only be allowed to feel the object with one hand at a time. If they are unable to identify it in one hand, it should be placed in the other for comparison. Individuals unable to identify common objects and coins in one hand and who can do so in the other are said to have *astereognosis* of the abnormal hand.

LOCALIZATION OF SENSORY ABNORMALITIES

Sensory symptoms and signs can result from lesions at almost any level of the nervous system from parietal cortex to the peripheral sensory receptor. Noting the distribution and nature of sensory symptoms and signs is the most important way to localize their source. Their extent, configuration, symmetry, quality, and severity are the key observations.

Dysesthesias without sensory findings by examination may be difficult to interpret. To illustrate, tingling dysesthesias in an acral distribution (hands and feet) can be systemic in origin, e.g., secondary to hyperventilation, or induced by a medication such as acetazolamide. Distal dysesthesias can also be an early event in an evolving polyneuropathy or may herald a myelopathy, such as from vitamin B_{12} deficiency. Sometimes distal dysesthesias have no definable basis. In contrast, dysesthesias that correspond to a particular peripheral nerve territory denote a lesion of that nerve trunk. For instance, dysesthesias restricted to the fifth digit and the adjacent one-half of the fourth finger on one hand reliably point to disorder of the ulnar nerve, most commonly at the elbow.

Nerve and Root

In focal nerve trunk lesions severe enough to cause a deficit, sensory abnormalities are readily mapped and generally have discrete boundaries (Figs. 12-2 and 12-3). Root ("radicular") lesions are frequently accompanied by deep, aching pain along the course of the related nerve trunk. With compression of a fifth lumbar (L5) or first sacral (S1) root, as from a ruptured intervertebral disc, sciatica (radicular pain relating to the sciatic nerve trunk) is a frequent manifestation (Chap. 7). With a lesion affecting a single root, sensory deficits may be minimal or absent because adjacent root territories overlap extensively.

With polyneuropathies, sensory deficits are generally graded, distal, and symmetric in distribution (Chap. 40). Dysesthesias, followed by numbness, begin in the toes and ascend symmetrically. When dysesthesias reach the knees, they have usually also appeared in the fingertips. The process appears to be nerve length–dependent, and the deficit is often described as "stocking-glove" in type. Involvement of both hands and feet also occurs with lesions of the upper cervical cord or the brainstem, but an upper level of the sensory disturbance may then be found on the trunk and other evidence of a central lesion may be present, such as sphincter involvement or signs of an upper motor neuron lesion (Chap. 10). Although most polyneuropathies are pansensory and affect all modalities of sensation, selective sensory dysfunction according to nerve fiber size may occur. Small-fiber polyneuropathies are characterized by burning, painful dysesthesias with reduced pinprick and thermal sensation but sparing of proprioception, motor function, and deep tendon reflexes. Touch is involved variably; when spared, the sensory pattern is referred to as exhibiting *sensory dissociation*. Sensory dissociation may occur with spinal cord lesions as well as small-fiber neuropathies. Large-fiber polyneuropathies are characterized by vibration and position sense deficits, imbalance, absent tendon reflexes, and variable motor dysfunction but preservation of most cutaneous sensation. Dysesthesias, if present at all, tend to be tingling or bandlike in quality.

Spinal Cord

(See Chap. 30) If the spinal cord is transected, all sensation is lost below the level of transection. Bladder and bowel

function are also lost, as is motor function. Hemisection of the spinal cord produces the Brown-Séquard syndrome, with absent pain and temperature sensation contralaterally and loss of proprioceptive sensation and power ipsilaterally below the lesion (see Figs. 12-1 and 30-1).

Numbness or paresthesias in both feet may arise from a spinal cord lesion; this is especially likely when the upper level of the sensory loss extends to the trunk. When all extremities are affected, the lesion is probably in the cervical region or brainstem unless a peripheral neuropathy is responsible. The presence of upper motor neuron signs (Chap. 10) supports a central lesion; a hyperesthetic band on the trunk may suggest the level of involvement.

A dissociated sensory loss can reflect spinothalamic tract involvement in the spinal cord, especially if the deficit is unilateral and has an upper level on the torso. Bilateral spinothalamic tract involvement occurs with lesions affecting the center of the spinal cord, such as in syringomyelia. There is a dissociated sensory loss with impairment of pinprick and temperature appreciation but relative preservation of light touch, position sense, and vibration appreciation.

Dysfunction of the posterior columns in the spinal cord or of the posterior root entry zone may lead to a bandlike sensation around the trunk or a feeling of tight pressure in one or more limbs. Flexion of the neck sometimes leads to an electric shock–like sensation that radiates down the back and into the legs (Lhermitte's sign) in patients with a cervical lesion affecting the posterior columns, such as from multiple sclerosis, cervical spondylosis, or recent irradiation to the cervical region.

Brainstem

Crossed patterns of sensory disturbance, in which one side of the face and the opposite side of the body are affected, localize to the lateral medulla. Here a small lesion may damage both the ipsilateral descending trigeminal tract and ascending spinothalamic fibers subserving the opposite arm, leg, and hemitorso (see Lateral medullary syndrome in Fig. 21-10). A lesion in the tegmentum of the pons and midbrain, where the lemniscal and spinothalamic tracts merge, causes pansensory loss contralaterally.

Thalamus

Hemisensory disturbance with tingling numbness from head to foot is often thalamic in origin but can also arise from the anterior parietal region. If abrupt in onset, the lesion is likely to be due to a small stroke (lacunar infarction), particularly if localized to the thalamus. Occasionally, with lesions affecting the VPL nucleus or adjacent white matter, a syndrome of thalamic pain, also called *Déjerine-Roussy syndrome*, may ensue. The persistent, unrelenting unilateral pain is often described in dramatic terms.

Cortex

With lesions of the parietal lobe involving either the cortex or subjacent white matter, the most prominent symptoms are contralateral hemineglect, hemi-inattention, and a tendency not to use the affected hand and arm. On cortical sensory testing (e.g., two-point discrimination, graphesthesia), abnormalities are often found but primary sensation is usually intact. Anterior parietal infarction may present as a pseudothalamic syndrome with contralateral loss of primary sensation from head to toe. Dysesthesias or a sense of numbness may also occur, and rarely, a painful state.

Focal Sensory Seizures

These are generally due to lesions in the area of the postcentral or precentral gyrus. The principal symptom of focal sensory seizures is tingling, but additional, more complex sensations may occur, such as a rushing feeling, a sense of warmth, or a sense of movement without detectable motion. Symptoms typically are unilateral; commonly begin in the arm or hand, face, or foot; and often spread in a manner that reflects the cortical representation of different bodily parts, as in a Jacksonian march. Duration of seizures is variable; they may be transient, lasting only for seconds, or persist for an hour or more. Focal motor features may supervene, often becoming generalized with loss of consciousness and tonic-clonic jerking.

CHAPTER 13

CONFUSION AND DELIRIUM

Scott Andrew Josephson ■ Bruce L. Miller

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Confusion, a mental and behavioral state of reduced comprehension, coherence, and capacity to reason, is one of the most common problems encountered in medicine, accounting for a large number of emergency department visits, hospital admissions, and inpatient consultations. *Delirium*, a term used to describe an acute confusional state, remains a major cause of morbidity and mortality, contributing billions of dollars yearly to health care costs in the United States alone. Delirium often goes unrecognized despite clear evidence that it is usually the cognitive manifestation of serious underlying medical or neurologic illness.

CLINICAL FEATURES OF DELIRIUM

A multitude of terms are used to describe delirium, including encephalopathy, acute brain failure, acute confusional state, and postoperative or intensive care unit (ICU) psychosis. Delirium has many clinical manifestations, but essentially it is defined as a relatively acute decline in cognition that fluctuates over hours or days. The hallmark of delirium is a deficit of attention, although all cognitive domains—including memory, executive function, visuospatial tasks, and language—are variably involved. Associated symptoms may include altered sleep-wake cycles, perceptual disturbances such as hallucinations or delusions, affect changes, and autonomic findings including heart rate and blood pressure instability.

Delirium is a clinical diagnosis that can only be made at the bedside. Two broad clinical categories of delirium have been described, hyperactive and hypoactive subtypes, based on differential psychomotor features. The cognitive syndrome associated with severe alcohol withdrawal remains the classic example of the hyperactive subtype, featuring prominent hallucinations, agitation, and hyperarousal, often accompanied by life-threatening autonomic instability. In striking contrast is the hypoactive subtype of delirium, exemplified by opiate intoxication, in which patients are withdrawn and quiet, with prominent apathy and psychomotor slowing.

This dichotomy between subtypes of delirium is a useful construct, but patients often fall somewhere along a spectrum between the hyperactive and hypoactive extremes, sometimes fluctuating from one to the other within minutes. Therefore, clinicians must recognize the broad range of presentations of delirium in order to identify all patients with this potentially reversible cognitive disturbance. Hyperactive patients, such as those with delirium tremens, are easily recognized by their characteristic severe agitation, tremor, hallucinations, and autonomic instability. Patients who are quietly disturbed are more often overlooked on the medical wards and in the ICU, yet multiple studies suggest that this underrecognized hypoactive subtype is associated with worse outcomes.

The reversibility of delirium is emphasized because many etiologies, such as systemic infection and medication

effects, can be easily treated. However, the long-term cognitive effects of delirium remain largely unknown and understudied. Some episodes of delirium continue for weeks, months, or even years. The persistence of delirium in some patients and its high recurrence rate may be due to inadequate treatment of the underlying etiology for the syndrome. In some instances, delirium does not disappear because there is underlying permanent neuronal damage. Even after an episode of delirium resolves, there may still be lingering effects of the disorder. A patient's recall of events after delirium varies widely, ranging from complete amnesia to repeated reexperiencing of the frightening period of confusion in a disturbing manner, similar to what is seen in patients with posttraumatic stress disorder.

RISK FACTORS

An effective primary prevention strategy for delirium begins with identification of patients at highest risk, including those preparing for elective surgery or being admitted to the hospital. Although no single validated scoring system has been widely accepted as a screen for asymptomatic patients, there are multiple well-established risk factors for delirium.

The two most consistently identified risks are older age and baseline cognitive dysfunction. Individuals who are older than 65 years or exhibit low scores on standardized tests of cognition develop delirium upon hospitalization at a rate approaching 50%. Whether age and baseline cognitive dysfunction are truly independent risk factors is uncertain. Other predisposing factors include sensory deprivation, such as preexisting hearing and visual impairment, as well as indices for poor overall health, including baseline immobility, malnutrition, and underlying medical or neurologic illness.

In-hospital risks for delirium include the use of bladder catheterization, physical restraints, sleep and sensory deprivation, and the addition of three or more new medications. Avoiding such risks remains a key component of delirium prevention as well as treatment. Surgical and anesthetic risk factors for the development of postoperative delirium include specific procedures such as those involving cardiopulmonary bypass and inadequate or excessive treatment of pain in the immediate postoperative period.

The relationship between delirium and dementia (Chap. 23) is complicated by significant overlap between these two conditions, and it is not always simple to distinguish between the two. Dementia and preexisting cognitive dysfunction serve as major risk factors for delirium, and at least two-thirds of cases of delirium occur in patients with coexisting underlying dementia. A form of dementia with parkinsonism, termed *dementia with Lewy bodies*, is characterized by a fluctuating course, prominent visual hallucinations, parkinsonism, and an attentional deficit that clinically resembles hyperactive delirium. Delirium in the elderly often reflects an insult to the brain that is vulnerable due to an underlying neurodegenerative condition. Therefore, the development of delirium sometimes heralds the onset of a previously unrecognized brain disorder.

EPIDEMIOLOGY

Delirium is a common disease, but its reported incidence has varied widely based on the criteria used to define the disorder. Estimates of delirium in hospitalized patients range from 14 to 56%, with higher rates reported for elderly patients and patients undergoing hip surgery. Older patients in the ICU have especially high rates of delirium ranging from 70 to 87%. The condition is not recognized in up to one-third of delirious inpatients, and the diagnosis is especially problematic in the ICU environment where cognitive dysfunction is often difficult to appreciate in the setting of serious systemic illness and sedation. Delirium in the ICU should be viewed as an important manifestation of organ dysfunction not unlike liver, kidney, or heart failure. Outside of the acute hospital setting, delirium occurs in nearly two-thirds of patients in nursing homes and in over 80% of those at the end of life. These estimates emphasize the remarkably high frequency of this cognitive syndrome in older patients, a population expected to grow in the upcoming decade with the aging of the "baby boom" generation.

In previous decades an episode of delirium was viewed as a transient condition that carried a benign prognosis. Delirium has now been clearly associated with substantial morbidity and increased mortality, and is increasingly recognized as a sign of serious underlying illness. Recent estimates of in-hospital mortality among delirious patients have ranged from 25–33%, a rate that is similar to patients with sepsis. Patients with an in-hospital episode of delirium have a higher mortality in the months and years following their illness compared with age-matched non-delirious hospitalized patients. Delirious hospitalized patients have a longer length of stay, are more likely to be discharged to a nursing home, and are more likely to experience subsequent episodes of delirium; as a result, this condition has enormous economic implications.

PATHOGENESIS

The pathogenesis and anatomy of delirium are incompletely understood. The attentional deficit that serves as the neuropsychological hallmark of delirium appears to have a diffuse localization with the brainstem, thalamus, prefrontal cortex, thalamus, and parietal lobes. Rarely,

focal lesions such as ischemic strokes have led to delirium in otherwise healthy persons; right parietal and medial dorsal thalamic lesions have been reported most commonly, stressing the relevance of these areas to delirium pathogenesis. In most cases, delirium results from widespread disturbances in cortical and subcortical regions, rather than a focal neuroanatomic cause. Electroencephalogram (EEG) data in persons with delirium usually show symmetric slowing, a nonspecific finding supporting diffuse cerebral dysfunction.

Deficiency of acetylcholine often plays a key role in delirium pathogenesis. Medications with anticholinergic properties can precipitate delirium in susceptible individuals, and therapies designed to boost cholinergic tone such as cholinesterase inhibitors have, in small trials, been shown to relieve symptoms of delirium. Dementia patients are susceptible to episodes of delirium, and those with Alzheimer's pathology are known to have a chronic cholinergic deficiency state due to degeneration of acetylcholine-producing neurons in the basal forebrain. Another common dementia associated with decreased acetylcholine levels, dementia with Lewy bodies, clinically mimics delirium in some patients. Other neurotransmitters are also likely involved in this diffuse cerebral disorder. For example, increases in dopamine can also lead to delirium. Patients with Parkinson's disease treated with dopaminergic medications can develop a delirious-like state that features visual hallucinations, fluctuations, and confusion. In contrast, reducing dopaminergic tone with dopamine antagonists such as typical and atypical antipsychotic medications has long been recognized as effective symptomatic treatment in patients with delirium.

Not all individuals exposed to the same insult will develop signs of delirium. A low dose of an anticholinergic medication may have no cognitive effects on a healthy young adult but may produce a florid delirium in an elderly person with known underlying dementia. However, an extremely high dose of the same anticholinergic medication may lead to delirium even in healthy young persons. This concept of delirium developing as the result of an insult in predisposed individuals is currently the most widely accepted pathogenic construct. Therefore, if a previously healthy individual with no known history of cognitive illness develops delirium in the setting of a relatively minor insult such as elective surgery or hospitalization, then an unrecognized underlying neurologic illness such as a neurodegenerative disease, multiple previous strokes, or another diffuse cerebral cause should be considered. In this context, delirium can be viewed as the symptom resulting from a "stress test for the brain" induced by the insult. Exposure to known inciting factors such as systemic infection or offending drugs can unmask a decreased cerebral reserve and herald a serious underlying and potentially treatable illness.

Approach to the Patient: DELIRIUM

As the diagnosis of delirium is clinical and made at the bedside, a careful history and physical examination is necessary when evaluating patients with possible confusional states. Screening tools can aid physicians and nurses in identifying patients with delirium, including the Confusion Assessment Method (CAM) (Table 13-1); the Organic Brain Syndrome Scale; the Delirium Rating Scale; and, in the ICU, the Delirium Detection Score and the ICU version of the CAM. These scales are based on criteria from the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM) or the World Health Organization's International Classification of Diseases (ICD). Unfortunately, these scales themselves do not identify the full spectrum of patients with delirium. All patients who are acutely confused should be presumed delirious regardless of their presentation due to the wide variety of possible clinical features. A course

TABLE 13-1

THE CONFUSION ASSESSMENT METHOD (CAM) DIAGNOSTIC ALGORITHM

The diagnosis of delirium requires the presence of features 1 and 2 and of *either* 3 or 4.[a]

- Feature 1: Acute onset and fluctuating course
  - This feature is satisfied by positive responses to these questions: Is there evidence of an acute change in mental status from the patient's baseline? Did the (abnormal) behavior fluctuate during the day—that is, tend to come and go—or did it increase and decrease in severity?
- Feature 2: Inattention
  - This feature is satisfied by a positive response to this question: Did the patient have difficulty focusing attention—for example, was easily distractible—or have difficulty keeping track of what was being said?
- Feature 3: Disorganized thinking
  - This feature is satisfied by a positive response to this question: Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?
- Feature 4: Altered level of consciousness
  - This feature is satisfied by any answer other than "alert" to this question: Overall, how would you rate this patient's level of consciousness: alert (normal), vigilant (hyperalert), lethargic (drowsy, easily aroused), stupor (difficult to arouse), or coma (unarousable)?

[a]Information is usually obtained from a reliable reporter, such as a family member, caregiver, or nurse.

Source: Modified from Inouye SK et al: Ann Intern Med 113:941, 1990.

that fluctuates over hours or days and may worsen at night (termed *sundowning*) is typical but not essential for the diagnosis. Observation of the patient will usually reveal an altered level of consciousness or a deficit of attention. Other hallmark features that may be present in the delirious patient include alteration of sleep-wake cycles, thought disturbances such as hallucinations or delusions, autonomic instability, and changes in affect.

HISTORY It may be difficult to elicit an accurate history in delirious patients who have altered levels of consciousness or impaired attention. Information from a collateral source such as a spouse or other family member is therefore invaluable. The three most important pieces of history include the patient's baseline cognitive function, the time course of the present illness, and current medications.

Premorbid cognitive function can be assessed through the collateral source or, if needed, via a review of outpatient records. Delirium by definition represents a change that is relatively acute, usually over hours to days, from a cognitive baseline. As a result, an acute confusional state is nearly impossible to diagnose without some knowledge of baseline cognitive function. Without this information, many patients with dementia or depression may be mistaken as delirious during a single initial evaluation. Patients with a more hypoactive, apathetic presentation with psychomotor slowing may only be identified as being different from baseline through conversations with family members. A number of validated instruments have been shown to accurately diagnose cognitive dysfunction using a collateral source including the modified Blessed Dementia Rating Scale and Clinical Dementia Rating (CDR). Baseline cognitive impairment is common in patients with delirium. Even when no such history of cognitive impairment is elicited, there should still be a high suspicion for previously unrecognized underlying neurologic disorder.

Establishing the time course of cognitive change is important not only to make a diagnosis of delirium but also to correlate the onset of the illness with potentially treatable etiologies such as recent medication changes or symptoms of systemic infection.

Medications remain a common cause of delirium, especially those compounds with anticholinergic or sedative properties. It is estimated that nearly one-third of all cases of delirium are secondary to medications, especially in the elderly. Medication histories should include all prescription as well as over-the-counter and herbal substances taken by the patient and any recent changes in dosing or formulation, including substitution of generics for brand-name medications.

Other important elements of the history include screening for symptoms of organ failure or systemic infection, which often contributes to delirium in the elderly. A history of illicit drug use, alcoholism, or toxin exposure is common in younger delirious patients. Finally, asking the patient and collateral source about other symptoms that may accompany delirium, such as depression or hallucinations, may help identify potential therapeutic targets.

PHYSICAL EXAMINATION The general physical examination in a delirious patient should include a careful screening for signs of infection such as fever, tachypnea, pulmonary consolidation, heart murmur, or stiff neck. The patient's fluid status should be assessed; both dehydration and fluid overload with resultant hypoxia have been associated with delirium, and each is usually easily rectified. The appearance of the skin can be helpful, showing jaundice in hepatic encephalopathy, cyanosis in hypoxia, or needle tracks in patients using intravenous drugs.

The neurologic examination requires a careful assessment of mental status. Patients with delirium often present with a fluctuating course; therefore the diagnosis can be missed when relying on a single time point of evaluation. Some but not all patients exhibit the characteristic pattern of sundowning, a worsening of their condition in the evening. In these cases, assessment only during morning rounds may be falsely reassuring.

An altered level of consciousness ranging from hyperarousal to lethargy to coma is present in most patients with delirium and can be easily assessed at the bedside. In the patient with a relatively normal level of consciousness, a screen for an attentional deficit is in order, as this deficit is the classic neuropsychological hallmark of delirium. Attention can be assessed while taking a history from the patient. Tangential speech, a fragmentary flow of ideas, or inability to follow complex commands often signifies an attentional problem. Formal neuropsychological tests to assess attention exist, but a simple bedside test of digit span forward is quick and fairly sensitive. In this task, patients are asked to repeat successively longer random strings of digits beginning with two digits in a row. Average adults can repeat a string of between five to seven digits before faltering; a digit span of four or less usually indicates an attentional deficit unless hearing or language barriers are present.

More formal neuropsychological testing can be extraordinarily helpful in assessing the delirious patient, but it is usually too cumbersome and time-consuming in the inpatient setting. A simple Mini Mental Status Examination (MMSE) (Table 23-5) can provide some information regarding orientation,

language, and visuospatial skills; however, performance of some tasks on the MMSE such as spelling "world" backwards or serial subtraction of digits will be impaired by delirious patients' attentional deficits alone and are therefore unreliable.

The remainder of the screening neurologic examination should focus on identifying new focal neurologic deficits. Focal strokes or mass lesions in isolation are rarely the cause of delirium, but patients with underlying extensive cerebrovascular disease or neurodegenerative conditions may not be able to cognitively tolerate even relatively small new insults. Patients should also be screened for additional signs of neurodegenerative conditions such as parkinsonism, which is seen not only in idiopathic Parkinson's disease but also in other dementing conditions such as Alzheimer's disease, dementia with Lewy bodies, and progressive supranuclear palsy. The presence of multifocal myoclonus or asterixis on the motor examination is nonspecific but usually indicates a metabolic or toxic etiology of the delirium.

ETIOLOGY Some etiologies can be easily discerned through a careful history and physical examination, while others require confirmation with laboratory studies, imaging, or other ancillary tests. A large, diverse group of insults can lead to delirium, and the cause in many patients is often multifactorial. Common etiologies are listed in **Table 13-2**.

Prescribed, over-the-counter, and herbal medications are common precipitants of delirium. Drugs with anticholinergic properties, narcotics, and benzodiazepines are especially frequent offenders, but nearly any compound can lead to cognitive dysfunction in a predisposed patient. While an elderly patient with baseline dementia may become delirious upon exposure to a relatively low dose of a medication, other less-susceptible individuals may only become delirious with very high doses of the same medication. This observation emphasizes the importance of correlating the timing of recent medication changes, including dose and formulation, with the onset of cognitive dysfunction.

In younger patients especially, illicit drugs and toxins are common causes of delirium. In addition to more classic drugs of abuse, the recent rise in availability of so-called club drugs, such as methylenedioxymethamphetamine (MDMA, ecstasy), γ-hydroxybutyrate (GHB), and the PCP-like agent ketamine, has led to an increase in delirious young persons presenting to acute care settings. Many common prescription drugs such as oral narcotics and benzodiazepines are now often abused and readily available on the street. Alcohol intoxication with high serum levels can cause confusion, but more commonly it is withdrawal from alcohol that leads to a classic hyperactive delirium. Alcohol and benzodiazepine withdrawal should be considered in all cases of delirium as even patients who drink only a few servings of alcohol every day can experience relatively severe withdrawal symptoms upon hospitalization.

TABLE 13-2

COMMON ETIOLOGIES OF DELIRIUM

- Toxins
  - Prescription medications: especially those with anticholinergic properties, narcotics and benzodiazepines
  - Drugs of abuse: alcohol intoxication and alcohol withdrawal, opiates, ecstasy, LSD, GHB, PCP, ketamine, cocaine
  - Poisons: inhalants, carbon monoxide, ethylene glycol, pesticides
- Metabolic conditions
  - Electrolyte disturbances: hypoglycemia, hyperglycemia, hyponatremia, hypernatremia, hypercalcemia, hypocalcemia, hypomagnesemia
  - Hypothermia and hyperthermia
  - Pulmonary failure: hypoxemia and hypercarbia
  - Liver failure/hepatic encephalopathy
  - Renal failure/uremia
  - Cardiac failure
  - Vitamin deficiencies: B_{12}, thiamine, folate, niacin
  - Dehydration and malnutrition
  - Anemia
- Infections
  - Systemic infections: urinary tract infections, pneumonia, skin and soft tissue infections, sepsis
  - CNS infections: meningitis, encephalitis, brain abscess
- Endocrinologic conditions
  - Hyperthyroidism, hypothyroidism
  - Hyperparathyroidism
  - Adrenal insufficiency
- Cerebrovascular disorders
  - Global hypoperfusion states
  - Hypertensive encephalopathy
  - Focal ischemic strokes and hemorrhages, especially nondominant parietal and thalamic lesions
- Autoimmune disorders
  - CNS vasculitis
  - Cerebral lupus
- Seizure-related disorders
  - Nonconvulsive status epilepticus
  - Intermittent seizures with prolonged post-ictal states
- Neoplastic disorders
  - Diffuse metastases to the brain
  - Gliomatosis cerebri
  - Carcinomatous meningitis
- Hospitalization
- Terminal end of life delirium

Note: LSD, lysergic acid diethylamide; GHB, γ-hydroxybutyrate; PCP, phencyclidine; CNS, central nervous system.

Metabolic abnormalities such as electrolyte disturbances of sodium, calcium, magnesium, or glucose can cause delirium, and mild derangements can lead to substantial cognitive disturbances in susceptible individuals. Other common metabolic etiologies include liver and renal failure, hypercarbia and hypoxia, vitamin deficiencies of thiamine and B_{12}, autoimmune disorders including CNS vasculitis, and endocrinopathies such as thyroid and adrenal disorders.

Systemic infections often cause delirium, especially in the elderly. A common scenario involves the development of an acute cognitive decline in the setting of a urinary tract infection in a patient with baseline dementia. Pneumonia, skin infections such as cellulitis, and frank sepsis can also lead to delirium. This so-called septic encephalopathy, often seen in the ICU, is likely due to the release of proinflammatory cytokines and their diffuse cerebral effects. CNS infections such as meningitis, encephalitis, and abscess are less-common etiologies of delirium; however, given the high mortality associated with these conditions when not treated quickly, clinicians must always maintain a high index of suspicion.

In some susceptible individuals, exposure to the unfamiliar environment of a hospital can lead to delirium. This etiology usually occurs as part of a multifactorial delirium and should be considered a diagnosis of exclusion after all other causes have been thoroughly investigated. Many primary prevention and treatment strategies for delirium involve relatively simple methods to address those aspects of the inpatient setting that are most confusing.

Cerebrovascular etiologies are usually due to global hypoperfusion in the setting of systemic hypotension from heart failure, septic shock, dehydration, or anemia. Focal strokes in the right parietal lobe and medial dorsal thalamus can rarely lead to a delirious state. A more common scenario involves a new focal stroke or hemorrhage causing confusion in a patient who has decreased cerebral reserve. In these individuals, it is sometimes difficult to distinguish between cognitive dysfunction resulting from the new neurovascular insult itself and delirium due to the infectious, metabolic, and pharmacologic complications that can accompany hospitalization after stroke.

Because a fluctuating course is often seen in delirium, intermittent seizures may be overlooked when considering potential etiologies. Both nonconvulsive status epilepticus as well as recurrent focal or generalized seizures followed by post-ictal confusion can cause delirium; EEG remains essential for this diagnosis. Seizure activity spreading from an electrical focus in a mass or infarct can explain global cognitive dysfunction caused by relatively small lesions.

It is very common for patients to experience delirium at the end of life in palliative care settings. This condition, sometimes described as *terminal restlessness*, must be identified and treated aggressively as it is an important cause of patient and family discomfort at the end of life. It should be remembered that these patients may also be suffering from more common etiologies of delirium such as systemic infection.

LABORATORY AND DIAGNOSTIC EVALUATION A cost-effective approach to the diagnostic evaluation of delirium allows the history and physical examination to guide tests. No established algorithm for workup will fit all delirious patients due to the staggering number of potential etiologies, but one step-wise approach is detailed in **Table 13-3**. If a clear precipitant is identified early, such as an offending medication, then little further workup is required. If, however, no likely etiology is uncovered with initial evaluation, an aggressive search for an underlying cause should be initiated.

Basic screening labs, including a complete blood count, electrolyte panel, and tests of liver and renal function, should be obtained in all patients with delirium. In elderly patients, screening for systemic infection, including chest radiography, urinalysis and culture, and possibly blood cultures, is important. In younger individuals, serum and urine drug and toxicology screening may be appropriate early in the workup. Additional laboratory tests addressing other autoimmune, endocrinologic, metabolic, and infectious etiologies should be reserved for patients in whom the diagnosis remains unclear after initial testing.

Multiple studies have demonstrated that brain imaging in patients with delirium is often unhelpful. However, if the initial workup is unrevealing, most clinicians quickly move toward imaging of the brain in order to exclude structural causes. A noncontrast CT scan can identify large masses and hemorrhages but is otherwise relatively insensitive for discovering an etiology of delirium. The ability of MRI to identify most acute ischemic strokes as well as to provide neuroanatomic detail that gives clues to possible infectious, inflammatory, neurodegenerative, and neoplastic conditions makes it the test of choice. Since MRI techniques are limited by availability, speed of imaging, patient cooperation, and contraindications to magnetic exposure, many clinicians begin with CT scanning and proceed to MRI if the etiology of delirium remains elusive.

Lumbar puncture (LP) must be obtained immediately, after appropriate neuroimaging, in all patients in whom CNS infection is suspected. Spinal fluid examination can also be useful in identifying inflammatory and neoplastic conditions as well as in the diagnosis

TABLE 13-3

STEP-WISE EVALUATION OF A PATIENT WITH DELIRIUM

- Initial evaluation
  - History with special attention to medications (including over-the-counter and herbals)
  - General physical examination and neurologic examination
  - Complete blood count
  - Electrolyte panel including calcium, magnesium, phosphorus
  - Liver function tests including albumin
  - Renal function tests
- First-tier further evaluation guided by initial evaluation
  - Systemic infection screen
    - Urinalysis and culture
    - Chest radiograph
    - Blood cultures
  - Electrocardiogram
  - Arterial blood gas
  - Serum and/or urine toxicology screen (perform earlier in young persons)
  - Brain imaging with MRI with diffusion and gadolinium (preferred) or CT
  - Suspected CNS infection: lumbar puncture following brain imaging
  - Suspected seizure-related etiology: electroencephalogram (EEG) (if high suspicion should be performed immediately)
- Second-tier further evaluation
  - Vitamin levels: B_{12}, folate, thiamine
  - Endocrinologic laboratories: thyroid-stimulating hormone (TSH) and free T4; cortisol
  - Serum ammonia
  - Sedimentation rate
  - Autoimmune serologies: antinuclear antibodies (ANA), complement levels; p-ANCA, c-ANCA
  - Infectious serologies: rapid plasmin reagin (RPR); fungal and viral serologies if high suspicion; HIV antibody
  - Lumbar puncture (if not already performed)
  - Brain MRI with and without gadolinium (if not already performed)

Note: p-ANCA, perinuclear antineutrophil cytoplasmic antibody; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody.

of hepatic encephalopathy through elevated CSF glutamine levels. As a result, LP should be considered in any delirious patient with a negative workup. EEG does not have a routine role in the workup of delirium, but it remains invaluable if seizure-related etiologies are considered.

Rx Treatment: DELIRIUM

Management of delirium begins with treatment of the underlying inciting factor (e.g., patients with systemic infections should be given appropriate antibiotics and underlying electrolyte disturbances judiciously corrected). These treatments often lead to prompt resolution of delirium. Blindly targeting the symptoms of delirium pharmacologically only serves to prolong the time patients remain in the confused state and may mask important diagnostic information. Recent trials of medications used to boost cholinergic tone in delirious patients have led to mixed results, and this strategy is not currently recommended.

Relatively simple methods of supportive care can be highly effective in treating patients with delirium. Reorientation by the nursing staff and family combined with visible clocks, calendars, and outside-facing windows can reduce confusion. Sensory isolation should be prevented by providing glasses and hearing aids to those patients who need them. Sundowning can be addressed to a large extent through vigilance to appropriate sleep-wake cycles. During the day, a well-lit room should be accompanied by activities or exercises to prevent napping. At night, a quiet, dark environment with limited interruptions by staff can assure proper rest. These sleep-wake cycle interventions are especially important in the ICU setting as the usual constant 24-h activity commonly provokes delirium. Attempting to mimic the home environment as much as possible has also been shown to help treat and even prevent delirium. Visits from friends and family throughout the day minimize the anxiety associated with the constant flow of new faces of staff and physicians. Allowing hospitalized patients to have access to home bedding, clothing, and nightstand objects makes the hospital environment less foreign and therefore less confusing. Simple standard nursing practices such as maintaining proper nutrition and volume status as well as managing incontinence and skin breakdown also help to alleviate discomfort and resulting confusion.

In some instances, patients pose a threat to their own safety or to the safety of staff members, and acute management is required. Bed alarms and personal sitters are more effective and much less disorienting than physical restraints. Chemical restraints should be avoided, but, when necessary, very-low-dose typical or atypical antipsychotic medications administered on an as-needed basis are effective. The recent association of atypical antipsychotic use in the elderly with increased mortality underscores the importance of using these medications judiciously and only as a last resort. Benzodiazepines are not as effective as antipsychotics and often worsen confusion via their sedative properties. Although many clinicians still use benzodiazepines to treat acute confusion, their use should be limited only to cases in which delirium is caused by alcohol or benzodiazepine withdrawal.

PREVENTION

Given the high morbidity associated with delirium and the tremendously increased health care costs that accompany it, development of an effective strategy to prevent delirium in hospitalized patients is extremely important. Successful identification of high-risk patients is the first step, followed by initiation of appropriate interventions. One trial randomized more than 850 elderly inpatients to simple standardized protocols used to manage risk factors for delirium, including cognitive impairment, immobility, visual impairment, hearing impairment, sleep deprivation, and dehydration. Significant reductions in the number and duration of episodes of delirium were observed in the treatment group, but unfortunately delirium recurrence rates were unchanged. Recent trials in the ICU have focused on identifying sedatives, such as dexmedetomidine, that are less likely to lead to delirium in critically ill patients. All hospitals and health care systems should work toward developing standardized protocols to address common risk factors with the goal of decreasing the incidence of delirium.

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In the previous edition, Allan H. Ropper contributed to a section on acute confusional states that was incorporated into this current chapter.

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CHAPTER 14

COMA

Allan H. Ropper

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Coma is among the most common and striking problems in general medicine. It accounts for a substantial portion of admissions to emergency departments and occurs on all hospital services. Because coma demands immediate attention, the physician must employ an organized approach.

There is a continuum of states of reduced alertness, the severest form being *coma*, a deep sleeplike state from which the patient cannot be aroused. *Stupor* refers to a higher degree of arousability in which the patient can be awakened only by vigorous stimuli, accompanied by motor behavior that leads to avoidance of uncomfortable or aggravating stimuli. *Drowsiness*, which is familiar to all persons, simulates light sleep and is characterized by easy arousal and the persistence of alertness for brief periods. Drowsiness and stupor are usually attended by some degree of confusion (Chap. 13). A narrative description of the level of arousal and of the type of responses evoked by various stimuli, precisely as observed at the bedside, is preferable to ambiguous terms such as lethargy, semicoma, or obtundation.

Several other neurologic conditions render patients apparently unresponsive and thereby simulate coma, and certain subsyndromes of coma must be considered separately because of their special significance. Among the latter, the *vegetative state* signifies an awake but nonresponsive state. These patients have emerged from coma after a period of days or weeks to a state in which the eyelids are open, giving the appearance of wakefulness. Yawning, coughing, swallowing, as well as limb and head movements persist, but there are few, if any, meaningful responses to the external and internal environment—in essence, an "awake coma." Respiratory and autonomic functions are retained. The term "vegetative" is unfortunate as it is subject to misinterpretation by laypersons. The possibility of incorrectly attributing meaningful behavior to these patients has created inordinate problems. There are always accompanying signs that indicate extensive damage in both cerebral hemispheres, e.g., decerebrate or decorticate limb posturing and absent responses to visual stimuli (see later). In the closely related but less severe *minimally conscious state* the patient may make intermittent rudimentary vocal or motor responses. Cardiac arrest with cerebral hypoperfusion and head injuries are the most common causes of the vegetative and minimally conscious states (Chaps. 22 and 31). The prognosis for regaining mental faculties once the vegetative state has supervened for several months is very poor, and after a year, almost nil, hence the term *persistent vegetative state*. Most reports of dramatic recovery, when investigated carefully, are found to yield to the usual rules for prognosis, but there have been rare instances in which recovery has occurred to a demented condition and, in rare childhood cases, to an even better state.

Quite apart from the above conditions, certain syndromes that affect alertness are prone to be misinterpreted as stupor or coma. *Akinetic mutism* refers to a partially or fully awake state in which the patient is able to form

impressions and think but remains virtually immobile and mute. The condition results from damage in the regions of the medial thalamic nuclei or the frontal lobes (particularly lesions situated deeply or on the orbitofrontal surfaces), or from hydrocephalus. The term *abulia* is in essence a milder form of akinetic mutism, used to describe mental and physical slowness and diminished ability to initiate activity. It is also generally the result of damage to the frontal lobe network (Chap. 15). *Catatonia* is a curious hypomobile and mute syndrome that arises as part of a major psychosis, usually schizophrenia or major depression. Catatonic patients make few voluntary or responsive movements, although they blink, swallow, and may not appear distressed. There are nonetheless signs that the patient is responsive, although it may take some ingenuity on the part of the examiner to demonstrate them. For example, eyelid elevation is actively resisted, blinking occurs in response to a visual threat, and the eyes move concomitantly with head rotation, all of which are inconsistent with the presence of a brain lesion. It is characteristic but not invariable in catatonia for the limbs to retain the postures in which they have been placed by the examiner ("waxy flexibility," or catalepsy). Upon recovery, such patients have some memory of events that occurred during their catatonic stupor. The appearance is superficially similar to akinetic mutism, but clinical evidence of cerebral damage such as Babinski signs and hypertonicity of the limbs is lacking. The singular problem of brain death is discussed later.

The *locked-in state* describes yet another type of pseudocoma in which an awake patient has no means of producing speech or volitional movement, but retains voluntary vertical eye movements and lid elevation, thus allowing the patient to signal with a clear mind. The pupils are normally reactive. Such individuals have written entire treatises using Morse code. The usual cause is an infarction or hemorrhage of the ventral pons, which transects all descending corticospinal and corticobulbar pathways. A similar awake but de-efferented state occurs as a result of total paralysis of the musculature in severe cases of Guillain-Barré syndrome (Chap. 41), critical illness neuropathy (Chap. 22), and pharmacologic neuromuscular blockade.

THE ANATOMY AND PHYSIOLOGY OF COMA

Almost all instances of diminished alertness can be traced to widespread abnormalities of the cerebral hemispheres or to reduced activity of a special thalamocortical alerting system termed the *reticular activating system*. The proper functioning of this system, its ascending projections to the cortex, and the cortex itself are required to maintain alertness and coherence of thought. It follows that the principal causes of coma are (1) lesions that damage the RAS or its projections; (2) destruction of large portions of both cerebral hemispheres; and (3) suppression of reticulo-cerebral function by drugs, toxins, or metabolic derangements such as hypoglycemia, anoxia, uremia, and hepatic failure.

The proximity of the RAS to structures that control pupillary function and eye movements permits clinical localization of the cause of coma in many cases. Pupillary enlargement with loss of light reaction and loss of vertical and adduction movements of the eyes suggests that the likely location of the lesion is in the upper brainstem. Conversely, preservation of pupillary reactivity and eye movements absolves the upper brainstem and indicates that widespread structural lesions or metabolic suppression of the cerebral hemispheres is responsible.

Coma Due to Cerebral Mass Lesions and Herniations

The cranial cavity is separated into compartments by infoldings of the dura. The two cerebral hemispheres are separated by the falx, and the anterior and posterior fossae by the tentorium. Herniation refers to displacement of brain tissue into a compartment that it normally does not occupy. Many of the signs associated with coma, and indeed coma itself, can be attributed to these tissue shifts, and certain clinical configurations are characteristic of specific herniations (**Fig. 14-1**). They are in essence "false localizing" signs since they derive from compression of brain structures at a distance from the mass.

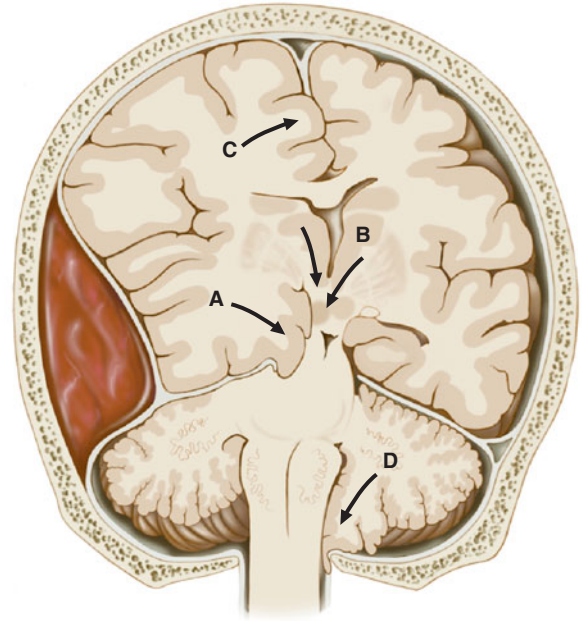
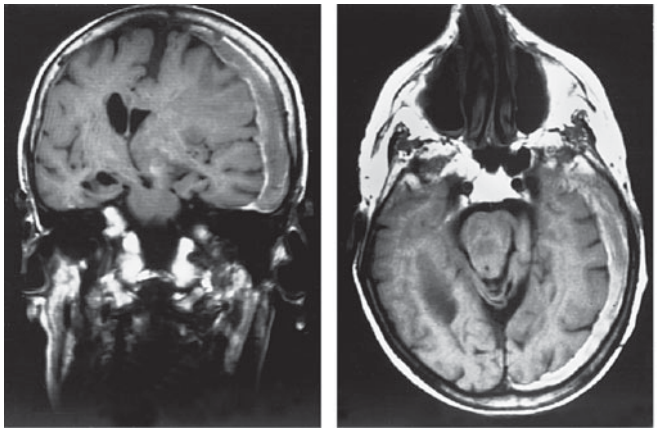


FIGURE 14-1
Types of cerebral herniation. (A) uncal; (B) central; (C) transfalcial; (D) foraminal.

The most common herniations are from the supratentorial to the infratentorial compartments through the tentorial opening, hence *transtentorial*. *Uncal transtentorial herniation* refers to impaction of the anterior medial temporal gyrus (the uncus) into the tentorial opening just anterior to and adjacent to the midbrain (Fig. 14-1, A). The displaced brain tissue compresses the third nerve as it traverses the subarachnoid space, and results in enlargement of the ipsilateral pupil (putatively because the fibers subserving parasympathetic pupillary function are located peripherally in the nerve). The coma that follows is due to compression of the midbrain against the opposite tentorial edge by the displaced parahippocampal gyrus (**Fig. 14-2**). In some cases, the lateral displacement of the midbrain causes compression of the opposite cerebral peduncle, producing a Babinski sign and hemiparesis contralateral to the original hemiparesis (the Kernohan-Woltman sign). In addition to compressing the upper brainstem, tissue shifts, including herniations, may compress major blood vessels, particularly the anterior and posterior cerebral arteries as they pass over the tentorial reflections, thus producing brain infarctions. The distortions may also entrap portions of the ventricular system, resulting in regional hydrocephalus.

Central transtentorial herniation denotes a symmetric downward movement of the thalamic medial structures through the tentorial opening with compression of the upper midbrain (Fig. 14-1, B). Miotic pupils and drowsiness are the heralding signs. Both temporal and central herniations have classically been considered to cause a progressive compression of the brainstem from above in an orderly manner: first the midbrain, then the pons, and finally the medulla. The result is a sequence of neurologic signs that corresponds to each affected level. Other forms of herniation are *transfalcial herniation* (displacement of the cingulate gyrus under the falx and across the midline, Fig. 14-1, C), and *foraminal herniation* (downward forcing of the cerebellar tonsils into the foramen magnum, Fig. 14-1, D), which causes compression of the medulla and respiratory arrest.

A direct relationship between the various configurations of transtentorial herniations and coma is not always found. Drowsiness and stupor typically occur with moderate horizontal shifts at the level of the diencephalon (thalami) well before transtentorial or other herniations are evident. Lateral shift may be quantified on axial images of CT and MRI scans (Fig. 14-2). In cases of *acutely appearing masses*, horizontal displacement of the pineal calcification of 3–5 mm is generally associated with drowsiness, 6–8 mm with stupor, and >9 mm with coma. Intrusion of the medial temporal lobe into the tentorial opening may be apparent on MRI and CT scans by an obliteration of the cisterns that surround the upper brainstem.



A B

FIGURE 14-2

Coronal (*A*) and axial (*B*) magnetic resonance images from a stuporous patient with a left third nerve palsy as a result of a large left-sided subdural hematoma (seen as a gray-white rim). The upper midbrain and lower thalamic regions are compressed and displaced horizontally away from the mass, and there is transtentorial herniation of the medial temporal lobe structures, including the uncus anteriorly. The lateral ventricle opposite to the hematoma has become enlarged as a result of compression of the third ventricle.

Coma Due to Metabolic Disorders

Many systemic metabolic abnormalities cause coma by interrupting the delivery of energy substrates (hypoxia, ischemia, hypoglycemia) or by altering neuronal excitability (drug and alcohol intoxication, anesthesia, and epilepsy). The same metabolic abnormalities that produce coma may in milder form induce widespread cortical dysfunction and an acute confusional state. Thus, in metabolic encephalopathies, clouded consciousness and coma are in a continuum.

Cerebral neurons are fully dependent on cerebral blood flow (CBF) and the related delivery of oxygen and glucose. CBF is ~75 mL per 100 g/min in gray matter and 30 mL per 100 g/min in white matter (mean = 55 mL per 100 g/min); oxygen consumption is 3.5 mL per 100 g/min, and glucose utilization is 5 mg per 100 g/min. Brain stores of glucose provide energy for ~2 min after blood flow is interrupted, and oxygen stores last 8–10 s after the cessation of blood flow. Simultaneous hypoxia and ischemia exhaust glucose more rapidly. The electroencephalogram (EEG) rhythm in these circumstances becomes diffusely slowed, typical of metabolic encephalopathies, and as conditions of substrate delivery worsen, eventually all recordable brain electrical activity ceases. In almost all instances of metabolic encephalopathy, the global metabolic activity of the brain is reduced in proportion to the degree of diminished consciousness.

Conditions such as hypoglycemia, hyponatremia, hyperosmolarity, hypercapnia, hypercalcemia, and hepatic and renal failure are associated with a variety of alterations in neurons and astrocytes. Unlike hypoxia-ischemia, which causes neuronal destruction, metabolic disorders generally cause only minor neuropathologic changes. The reversible effects of these conditions on the brain are not understood but may result from impaired energy supplies, changes in ion fluxes across neuronal membranes, and neurotransmitter abnormalities. For example, the high brain ammonia concentration of hepatic coma interferes with cerebral energy metabolism and with the Na^+, K^+-ATPase pump, increases the number and size of astrocytes, alters nerve cell function, and causes increased concentrations of potentially toxic products of ammonia metabolism; it may also result in abnormalities of neurotransmitters, including putative "false" neurotransmitters that are active at receptor sites. Apart from hyperammonemia, which of these mechanisms is of critical importance is not clear. The mechanism of the encephalopathy of renal failure is also not known. Unlike ammonia, urea itself does not produce central nervous system (CNS) toxicity. A multifactorial causation has been proposed, including increased permeability of the blood-brain barrier to toxic substances such as organic acids and an increase in brain calcium or cerebrospinal fluid (CSF) phosphate content.

Coma and seizures are a common accompaniment of any large shifts in sodium and water balance in the brain. These changes in osmolarity arise from systemic medical disorders including diabetic ketoacidosis, the nonketotic hyperosmolar state, and hyponatremia from any cause (e.g., water intoxication, excessive secretion of antidiuretic hormone or atrial natriuretic peptides). Sodium levels <125 mmol/L induce confusion, and <115 mmol/L are associated with coma and convulsions. In hyperosmolar coma the serum osmolarity is generally >350 mosmol/L. Hypercapnia depresses the level of consciousness in proportion to the rise in CO_2 tension in the blood. *In all of these metabolic encephalopathies, the degree of neurologic change depends to a large extent on the rapidity with which the serum changes occur.* The pathophysiology of other metabolic encephalopathies such as hypercalcemia, hypothyroidism, vitamin B_{12} deficiency, and hypothermia are incompletely understood but must also reflect derangements of CNS biochemistry and membrane function.

Epileptic Coma

Continuous, generalized electrical discharges of the cortex (*seizures*) are associated with coma even in the absence of epileptic motor activity (*convulsions*). The self-limited coma that follows seizures, termed the *postictal state*, may be due to exhaustion of energy reserves or effects of locally toxic molecules that are the byproduct of seizures. The postictal state produces a pattern of continuous, generalized slowing of the background EEG activity similar to that of other metabolic encephalopathies.

Toxic Drug–Induced Coma

This common class of encephalopathy is in large measure reversible and leaves no residual damage providing hypoxia does not supervene. Many drugs and toxins are capable of depressing nervous system function. Some produce coma by affecting both the brainstem nuclei, including the RAS, and the cerebral cortex. The combination of cortical and brainstem signs, which occurs in certain drug overdoses, may lead to an incorrect diagnosis of structural brainstem disease. Overdose of medications that have atropinic actions produces physical signs such as dilated pupils, tachycardia, and dry skin.

Coma Due to Widespread Damage to the Cerebral Hemispheres

This special category, comprising a number of unrelated disorders, results from widespread structural cerebral damage, thereby simulating a metabolic disorder of the cortex. The effect of prolonged hypoxia-ischemia is perhaps the best known and one in which it is not possible to distinguish the acute effects of hypoperfusion of the brain from the further effects of generalized neuronal damage. Similar bihemispheral damage is produced by disorders that occlude small blood vessels throughout the brain; examples include cerebral malaria, thrombotic thrombocytopenic purpura, and hyperviscosity. The presence of seizures and the bihemispheral damage are sometimes an indication of this class of disorder.

Approach to the Patient: COMA

Acute respiratory and cardiovascular problems should be attended to prior to neurologic assessment. In most instances, a complete medical evaluation, except for vital signs, funduscopy, and examination for nuchal rigidity, may be deferred until the neurologic evaluation has established the severity and nature of coma. The approach to the patient with cranial trauma is discussed in Chap. 31.

HISTORY In many cases, the cause of coma is immediately evident (e.g., trauma, cardiac arrest, or known drug ingestion). In the remainder, certain points are especially useful: (1) the circumstances and rapidity with which neurologic symptoms developed; (2) the antecedent symptoms (confusion, weakness, headache, fever, seizures, dizziness, double vision, or

vomiting); (3) the use of medications, illicit drugs, or alcohol; and (4) chronic liver, kidney, lung, heart, or other medical disease. Direct interrogation of family and observers on the scene, in person or by telephone, is an important part of the initial evaluation. Ambulance technicians often provide the most useful information.

GENERAL PHYSICAL EXAMINATION The temperature, pulse, respiratory rate and pattern, and blood pressure should be measured quickly. Fever suggests a systemic infection, bacterial meningitis, or encephalitis; only rarely is it attributable to a brain lesion that has disturbed hypothalamic temperature-regulating centers ("*central fever*"). A slight elevation in temperature may follow vigorous convulsions. High body temperature, 42°–44°C, associated with dry skin should arouse the suspicion of heat stroke or anticholinergic drug intoxication. Hypothermia is observed with alcoholic, barbiturate, sedative, or phenothiazine intoxication; hypoglycemia; peripheral circulatory failure; or hypothyroidism. Hypothermia itself causes coma only when the temperature is <31°C. Tachypnea may indicate systemic acidosis or pneumonia. Aberrant respiratory patterns that reflect brainstem disorders are discussed later. Marked hypertension either indicates hypertensive encephalopathy or is the result of a rapid rise in intracranial pressure (ICP; the Cushing response) most often after cerebral hemorrhage or head injury. Hypotension is characteristic of coma from alcohol or barbiturate intoxication, internal hemorrhage, myocardial infarction, sepsis, profound hypothyroidism, or Addisonian crisis.

The funduscopic examination can detect subarachnoid hemorrhage (subhyaloid hemorrhages), hypertensive encephalopathy (exudates, hemorrhages, vessel-crossing changes, papilledema), and increased ICP (papilledema). Cutaneous petechiae suggest thrombotic thrombocytopenic purpura, meningococcemia, or a bleeding diathesis from which an intracerebral hemorrhage has arisen.

NEUROLOGIC EXAMINATION First, the patient should be observed without intervention by the examiner. Tossing about in the bed, reaching up toward the face, crossing legs, yawning, swallowing, coughing, or moaning denotes a state close to normal awakeness. Lack of restless movements on one side or an outturned leg suggests a hemiplegia. Intermittent twitching movements of a foot, finger, or facial muscle may be the only sign of seizures. Multifocal myoclonus almost always indicates a metabolic disorder, particularly uremia, anoxia, or drug intoxication (lithium and haloperidol are particularly likely to cause this sign), or the rare conditions of a prion disease (Chap. 38) or "Hashimoto encephalopathy." In a drowsy and confused patient bilateral *asterixis* is a certain sign of metabolic encephalopathy or drug intoxication.

The terms *decorticate rigidity* and *decerebrate rigidity*, or "posturing," describe stereotyped arm and leg movements occurring spontaneously or elicited by sensory stimulation. Flexion of the elbows and wrists and supination of the arm (decortication) suggests bilateral damage rostral to the midbrain, whereas extension of the elbows and wrists with pronation (decerebration) indicates damage to motor tracts in the midbrain or caudal diencephalon. The less frequent combination of arm extension with leg flexion or flaccid legs is associated with lesions in the pons. These concepts have been adapted from animal work and cannot be applied with the same precision to coma in humans. In fact, acute and widespread disorders of any type, regardless of location, frequently cause limb extension, and almost all such extensor posturing becomes predominantly flexor as time passes. Posturing may also be unilateral and may coexist with purposeful limb movements, usually reflecting incomplete damage to the motor system.

LEVEL OF AROUSAL A sequence of increasingly intense stimuli is used to determine the threshold for arousal and the optimal motor response of each side of the body. The results of testing may vary from minute to minute and serial examinations are most useful. Tickling the nostrils with a cotton wisp is a moderate stimulus to arousal—all but deeply stuporous and comatose patients will move the head away and rouse to some degree. Using the hand to remove the offending stimulus represents an even greater degree of responsiveness. Stereotyped posturing in response to noxious stimuli indicates severe dysfunction of the corticospinal system. Abduction-avoidance movement of a limb is usually purposeful and denotes an intact corticospinal system. Pressure on the knuckles or bony prominences and pinprick stimulation are humane forms of noxious stimuli; pinching the skin causes unsightly ecchymoses and is generally not necessary but may be useful in eliciting abduction withdrawal movements of the limbs.

BRAINSTEM REFLEXES Assessment of brainstem function is essential to localization of the lesion in coma (**Fig. 14-3**). The brainstem reflexes that are conveniently examined are pupillary responses to light, spontaneous and elicited eye movements, corneal responses, and the respiratory pattern. As a rule, when these brainstem activities are preserved, particularly the pupil reactions and eye movements, coma must be ascribed to bilateral hemispheral disease. The converse, however, is not always true, as a mass in the hemispheres may be the underlying cause of coma but nonetheless produce brainstem signs by inducing transtentorial herniation.

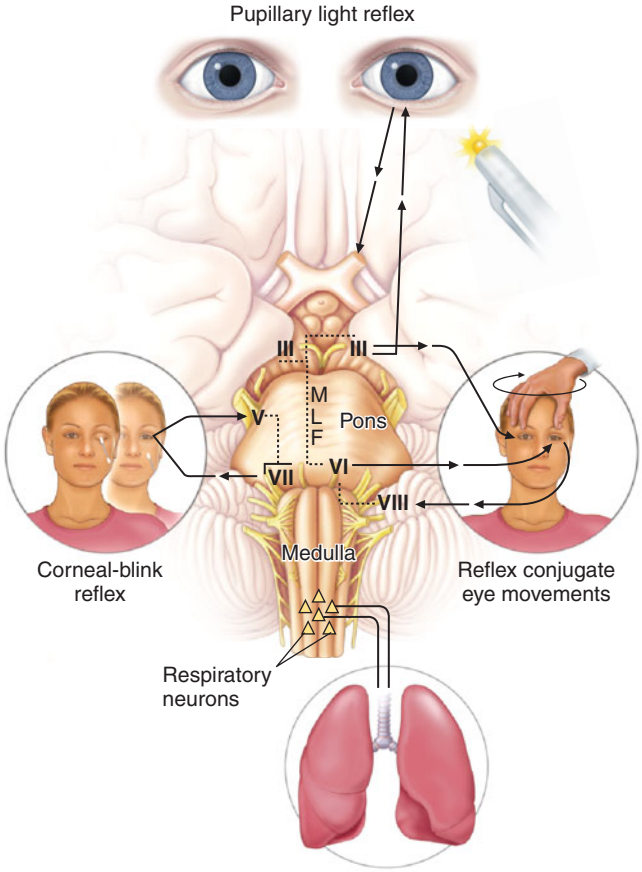


FIGURE 14-3

Examination of brainstem reflexes in coma. Midbrain and third nerve function are tested by pupillary reaction to light, pontine function by spontaneous and reflex eye movements and corneal responses, and medullary function by respiratory and pharyngeal responses. Reflex conjugate, horizontal eye movements are dependent on the medial longitudinal fasciculus (MLF) interconnecting the sixth and contralateral third nerve nuclei. Head rotation (oculocephalic reflex) or caloric stimulation of the labyrinths (oculovestibular reflex) elicits contraversive eye movements (for details see text).

Pupillary Signs Pupillary reactions are examined with a bright, diffuse light (not an ophthalmoscope); if the response is absent, this should be confirmed by observation through a magnifying lens. Normally reactive and round pupils of midsize (2.5–5 mm) essentially exclude midbrain damage, either primary or secondary to compression. Reaction to light is often difficult to appreciate in pupils <2 mm in diameter, and bright room lighting mutes pupillary reactivity. One unreactive and enlarged pupil (>6 mm) or one that is poorly reactive signifies compression of the third nerve from the effects of a mass above. Enlargement of the pupil contralateral to a mass may occur first but is infrequent. An oval and slightly eccentric pupil is a transitional sign that accompanies early midbrain–third nerve compression. The most extreme pupillary sign, bilaterally dilated and unreactive pupils, indicates severe midbrain damage, usually from compression by a supratentorial mass. Ingestion of drugs with anticholinergic activity, the use of mydriatic eye drops, and direct ocular trauma are among the causes of misleading pupillary enlargement.

Unilateral miosis in coma has been attributed to dysfunction of sympathetic efferents originating in the posterior hypothalamus and descending in the tegmentum of the brainstem to the cervical cord. It is an occasional finding with a large cerebral hemorrhage that affects the thalamus. Reactive and bilaterally small (1–2.5 mm) but not pinpoint pupils are seen in metabolic encephalopathies or in deep bilateral hemispheral lesions such as hydrocephalus or thalamic hemorrhage. Very small but reactive pupils (<1 mm) characterize narcotic or barbiturate overdoses but also occur with extensive pontine hemorrhage. The response to naloxone and the presence of reflex eye movements (see below) distinguish these.

Ocular Movements The eyes are first observed by elevating the lids and noting the resting position and spontaneous movements of the globes. Lid tone, tested by lifting the eyelids and noting their resistance to opening and the speed of closure, is reduced progressively as coma deepens. Horizontal divergence of the eyes at rest is normal in drowsiness. As coma deepens, the ocular axes may become parallel again.

Spontaneous eye movements in coma often take the form of conjugate horizontal roving. This finding alone exonerates the midbrain and pons and has the same significance as normal reflex eye movements (see below). Conjugate horizontal ocular deviation to one side indicates damage to the pons on the opposite side or alternatively, to the frontal lobe on the same side. This phenomenon is summarized by the following maxim: *The eyes look toward a hemispheral lesion and away from a brainstem lesion.* Seizures also drive the eyes to one side. On rare occasions, the eyes may turn paradoxically away from the side of a deep hemispheral lesion ("wrong-way eyes"). The eyes turn down and inward as a result of thalamic and upper midbrain lesions, typically with thalamic hemorrhage. "Ocular bobbing" describes brisk downward and slow upward movements of the eyes associated with loss of horizontal eye movements and is diagnostic of bilateral pontine damage, usually from thrombosis of the basilar artery. "Ocular dipping" is a slower, arrhythmic downward movement followed by a faster upward movement in patients with normal reflex horizontal gaze; it indicates diffuse cortical anoxic damage. Many other complex eye movements

are known but do not have the same clinical importance as those mentioned earlier.

The oculocephalic reflexes depend on the integrity of the ocular motor nuclei and their interconnecting tracts that extend from the midbrain to the pons and medulla. These reflexes are elicited by moving the head from side to side or vertically and observing evoked eye movements in the direction opposite to the head movement (Fig. 14-3). The movements, called somewhat inappropriately "doll's eyes" (which refers more accurately to the reflex elevation of the eyelids with flexion of the neck), are normally suppressed in the awake patient. The ability to elicit them therefore indicates a reduced cortical influence on the brainstem. Furthermore, preservation of evoked reflex eye movements signifies the integrity of the brainstem and implies that the origin of unconsciousness lies in the cerebral hemispheres. The opposite, an absence of reflex eye movements, usually signifies damage within the brainstem but can be produced infrequently by profound overdoses of certain drugs. Normal pupillary size and light reaction distinguishes most drug-induced comas from structural brainstem damage.

Thermal, or "caloric," stimulation of the vestibular apparatus (oculovestibular response) provides a more intense stimulus for the oculocephalic reflex but gives fundamentally the same information. The test is performed by irrigating the external auditory canal with cool water in order to induce convection currents in the labyrinths. After a brief latency, the result is tonic deviation of both eyes to the side of cool-water irrigation and nystagmus in the opposite direction. (The acronym "COWS" has been used to remind generations of medical students of the direction of nystagmus—"cold water opposite, warm water same.") The loss of conjugate ocular movements indicates brainstem damage. The absence of nystagmus despite conjugate deviation of the globes indicates that the cerebral hemispheres are damaged or metabolically suppressed.

By touching the cornea with a wisp of cotton, a response consisting of brief bilateral lid closure is normally observed. The corneal reflexes depend on the integrity of pontine pathways between the fifth (afferent) and both seventh (efferent) cranial nerves; although rarely useful alone, in conjunction with reflex eye movements they are important clinical tests of pontine function. CNS depressant drugs diminish or eliminate the corneal responses soon after reflex eye movements are paralyzed but before the pupils become unreactive to light. The corneal (and pharyngeal) response may be lost for a time on the side of an acute hemiplegia.

Respiratory Patterns These are of less localizing value in comparison to other brainstem signs. Shallow, slow, but regular breathing suggests metabolic or drug depression. Cheyne-Stokes respiration in its classic cyclic form, ending with a brief apneic period, signifies bihemispheral damage or metabolic suppression and commonly accompanies light coma. Rapid, deep (Kussmaul) breathing usually implies metabolic acidosis but may also occur with pontomesencephalic lesions. Agonal gasps are the result of lower brainstem (medullary) damage and are well known as the terminal respiratory pattern of severe brain damage. A number of other cyclic breathing variations have been described but are of lesser significance.

LABORATORY STUDIES AND IMAGING

The studies that are most useful in the diagnosis of coma are: chemical-toxicologic analysis of blood and urine, cranial CT or MRI, EEG, and CSF examination. Arterial blood-gas analysis is helpful in patients with lung disease and acid-base disorders. The metabolic aberrations commonly encountered in clinical practice require measurements of electrolytes, glucose, calcium, osmolarity, and renal (blood urea nitrogen) and hepatic (NH_3) function. Toxicologic analysis is necessary in any case of coma where the diagnosis is not immediately clear. However, the presence of exogenous drugs or toxins, especially alcohol, does not exclude the possibility that other factors, particularly head trauma, are also contributing to the clinical state. An ethanol level of 43 mmol/L (0.2 g/dL) in nonhabituated patients generally causes impaired mental activity and of >65 mmol/L (0.3 g/dL) is associated with stupor. The development of tolerance may allow the chronic alcoholic to remain awake at levels >87 mmol/L (0.4 g/dL).

The availability of CT and MRI has focused attention on causes of coma that are radiologically detectable (e.g., hemorrhages, tumors, or hydrocephalus). Resorting primarily to this approach, although at times expedient, is imprudent because most cases of coma (and confusion) are metabolic or toxic in origin. The notion that a normal CT scan excludes anatomic lesions as the cause of coma is also erroneous. Bilateral hemisphere infarction, acute brainstem infarction, encephalitis, meningitis, mechanical shearing of axons as a result of closed head trauma, sagittal sinus thrombosis, and subdural hematomas that are isodense to adjacent brain are some of the disorders that may not be detected. Nevertheless, if the source of coma remains unknown, a scan should be obtained.

The EEG is useful in metabolic or drug-induced states but is rarely diagnostic, except when coma is due to clinically unrecognized seizures, to herpesvirus encephalitis, or to prion (Creutzfeldt-Jakob) disease. The amount of background slowing of the EEG is a reflection of the severity of any diffuse encephalopathy. Predominant high-voltage

slowing (δ or triphasic waves) in the frontal regions is typical of metabolic coma, as from hepatic failure, and widespread fast (β) activity implicates sedative drugs (e.g., diazepines, barbiturates). A special pattern of "alpha coma," defined by widespread, variable 8- to 12-Hz activity, superficially resembles the normal α rhythm of waking but is unresponsive to environmental stimuli. It results from pontine or diffuse cortical damage and is associated with a poor prognosis. Most importantly, EEG recordings may reveal clinically inapparent epileptic discharges in a patient with coma. Normal α activity on the EEG, which is suppressed by stimulating the patient, also alerts the clinician to the locked-in syndrome or to hysteria or catatonia.

Lumbar puncture is performed less frequently than in the past for coma diagnosis because neuroimaging effectively excludes intracerebral and extensive subarachnoid hemorrhage. However, examination of the CSF remains indispensable in the diagnosis of meningitis and encephalitis. Lumbar puncture should therefore not be deferred if meningitis is a possibility.

DIFFERENTIAL DIAGNOSIS OF COMA

(**Table 14-1**) The causes of coma can be divided into three broad categories: those without focal neurologic signs (e.g., metabolic encephalopathies); meningitis syndromes, characterized by fever or stiff neck and an excess of cells in the spinal fluid (e.g., bacterial meningitis, subarachnoid hemorrhage); and conditions associated with prominent focal signs (e.g., stroke, cerebral hemorrhage). In most instances coma is part of an obvious medical problem such as drug ingestion, hypoxia, stroke, trauma, or liver or kidney failure. Conditions that cause sudden coma include drug ingestion, cerebral hemorrhage, trauma, cardiac arrest, epilepsy, or basilar artery embolism. Coma that appears subacutely is usually related to a preceding medical or neurologic problem, including the

TABLE 14-1

DIFFERENTIAL DIAGNOSIS OF COMA

1. Diseases that cause no focal or lateralizing neurologic signs, usually with normal brainstem functions; CT scan and cellular content of the CSF are normal
   a. Intoxications: alcohol, sedative drugs, opiates, etc.
   b. Metabolic disturbances: anoxia, hyponatremia, hypernatremia, hypercalcemia, diabetic acidosis, nonketotic hyperosmolar hyperglycemia, hypoglycemia, uremia, hepatic coma, hypercarbia, addisonian crisis, hypo- and hyperthyroid states, profound nutritional deficiency
   c. Severe systemic infections: pneumonia, septicemia, typhoid fever, malaria, Waterhouse-Friderichsen syndrome
   d. Shock from any cause
   e. Postseizure states, status epilepticus, subclinical epilepsy
   f. Hypertensive encephalopathy, eclampsia
   g. Severe hyperthermia, hypothermia
   h. Concussion
   i. Acute hydrocephalus
2. Diseases that cause meningeal irritation with or without fever, and with an excess of WBCs or RBCs in the CSF, usually without focal or lateralizing cerebral or brainstem signs; CT or MRI shows no mass lesion
   a. Subarachnoid hemorrhage from ruptured aneurysm, arteriovenous malformation, trauma
   b. Acute bacterial meningitis
   c. Viral encephalitis
   d. Miscellaneous: Fat embolism, cholesterol embolism, carcinomatous and lymphomatous meningitis, etc.
3. Diseases that cause focal brainstem or lateralizing cerebral signs, with or without changes in the CSF; CT and MRI are abnormal
   a. Hemispheral hemorrhage (basal ganglionic, thalamic) or infarction (large middle cerebral artery territory) with secondary brainstem compression
   b. Brainstem infarction due to basilar artery thrombosis or embolism
   c. Brain abscess, subdural empyema
   d. Epidural and subdural hemorrhage, brain contusion
   e. Brain tumor with surrounding edema
   f. Cerebellar and pontine hemorrhage and infarction
   g. Widespread traumatic brain injury
   h. Metabolic coma (see above) with preexisting focal damage
   i. Miscellaneous: cortical vein thrombosis, herpes simplex encephalitis, multiple cerebral emboli due to bacterial endocarditis, acute hemorrhagic leukoencephalitis, acute disseminated (postinfectious) encephalomyelitis, thrombotic thrombocytopenic purpura, cerebral vasculitis, gliomatosis cerebri, pituitary apoplexy, intravascular lymphoma, etc.

Note: CSF, cerebrospinal fluid; WBCs, white blood cells; RBCs, red blood cells.

secondary brain swelling of a mass lesion such as tumor or cerebral infarction.

Cerebrovascular diseases cause the greatest difficulty in coma diagnosis (Chap. 21). The most common categories are: (1) basal ganglia and thalamic hemorrhage (acute but not instantaneous onset, vomiting, headache, hemiplegia, and characteristic eye signs); (2) pontine hemorrhage (sudden onset, pinpoint pupils, loss of reflex eye movements and corneal responses, ocular bobbing, posturing, hyperventilation, and excessive sweating); (3) cerebellar hemorrhage (occipital headache, vomiting, gaze paresis, and inability to stand); (4) basilar artery thrombosis (neurologic prodrome or warning spells, diplopia, dysarthria, vomiting, eye movement and corneal response abnormalities, and asymmetric limb paresis); and (5) subarachnoid hemorrhage (precipitous coma after headache and vomiting). The most common stroke, infarction in the territory of the middle cerebral artery, does not generally cause coma, but edema surrounding large infarcts may expand during the first few days and act as a mass. The syndrome of acute hydrocephalus accompanies many intracranial diseases, particularly subarachnoid hemorrhage. It is characterized by headache and sometimes vomiting that may progress quickly to coma, with extensor posturing of the limbs, bilateral Babinski signs, small unreactive pupils, and impaired oculocephalic movements in the vertical direction.

If the history and examination do not indicate the cause of coma, then information obtained from CT or MRI may be needed. The majority of medical causes of coma can be established without a neuroimaging study.

BRAIN DEATH

This is a state of cessation of cerebral function while somatic function is maintained by artificial means and the heart continues to pump. It is the only type of brain damage that is recognized as equivalent to death. Several similar criteria have been advanced for the diagnosis of brain death, and it is essential to adhere to those standards endorsed by the local medical community. Ideal criteria are simple, can be assessed at the bedside, and allow no chance of diagnostic error. They contain three essential elements of clinical evidence: (1) widespread cortical destruction that is reflected by deep coma and unresponsiveness to all forms of stimulation; (2) global brainstem damage demonstrated by absent pupillary light reaction and by the loss of oculovestibular and corneal reflexes; and (3) destruction of the medulla manifested by complete apnea. The pulse rate is invariant and unresponsive to atropine. Diabetes insipidus is often present but may develop hours or days after the other clinical signs of brain death. The pupils are often enlarged but may be mid-sized; they should not, however, be constricted. The absence of deep tendon reflexes is not required because the spinal cord remains functional. There may or may not be Babinski signs.

Demonstration that apnea is due to irreversible medullary damage requires that the P_{CO2} be high enough to stimulate respiration during a test of spontaneous breathing. *Apnea testing* can be done safely by the use of diffusion oxygenation prior to removing the ventilator. This is accomplished by preoxygenation with 100% oxygen, which is then sustained during the test by oxygen administered through a tracheal cannula. CO_2 tension increases ~0.3–0.4 kPa/min (2–3 mm Hg/min) during apnea. At the end of the period of observation, typically several minutes, arterial P_{CO2} should be at least >6.6–8.0 kPa (50–60 mm Hg) for the test to be valid. Apnea is confirmed if no respiratory effort is observed in the presence of a sufficiently elevated P_{CO2}.

The possibility of profound drug-induced or hypothermic depression of the nervous system should be excluded, and some period of observation, usually 6–24 h, is desirable during which the signs of brain death are sustained. It is advisable to delay clinical testing for at least 24 h if a cardiac arrest has caused brain death or if the inciting disease is not known. An isoelectric EEG may be used as a confirmatory test for total cerebral damage. Radionuclide brain scanning, cerebral angiography, or transcranial Doppler measurements may also be used to demonstrate the absence of cerebral blood flow but they have not been extensively correlated with pathologic changes.

Although it is largely accepted in western society that the respirator can be disconnected from a brain-dead patient, problems frequently arise because of poor communication and inadequate preparation of the family by the physician. Reasonable medical practice allows the removal of support or transfer out of an intensive care unit of patients who are not brain dead but whose condition is nonetheless hopeless and are likely to live for only a brief time.

Rx Treatment: COMA

The immediate goal in a comatose patient is prevention of further nervous system damage. Hypotension, hypoglycemia, hypercalcemia, hypoxia, hypercapnia, and hyperthermia should be corrected rapidly. An oropharyngeal airway is adequate to keep the pharynx open in drowsy patients who are breathing normally. Tracheal intubation is indicated if there is apnea, upper airway obstruction, hypoventilation, or emesis, or if the patient is liable to aspirate because of coma. Mechanical ventilation is required if there is hypoventilation or a need to induce hypocapnia in order to lower ICP as described below. IV access is established, and naloxone and dextrose are administered if narcotic overdose or hypoglycemia are even remote possibilities; thiamine is given along with

glucose to avoid provoking Wernicke disease in malnourished patients. In cases of suspected basilar thrombosis with brainstem ischemia, IV heparin or a thrombolytic agent is often utilized, after cerebral hemorrhage has been excluded by a neuroimaging study. Physostigmine may awaken patients with anticholinergic-type drug overdose but should be used only by experienced physicians and with careful monitoring; many physicians believe that it should only be used to treat anticholinergic overdose-associated cardiac arrhythmias. The use of benzodiazepine antagonists offers some prospect of improvement after overdoses of soporific drugs and has transient benefit in hepatic encephalopathy. IV administration of hypotonic solutions should be monitored carefully in any serious acute brain illness because of the potential for exacerbating brain swelling. Cervical spine injuries must not be overlooked, particularly prior to attempting intubation or evaluating of oculocephalic responses. Fever and meningismus indicate an urgent need for examination of the CSF to diagnose meningitis. If the lumbar puncture in a case of suspected meningitis is delayed for any reason, an antibiotic such as a third-generation cephalosporin should be administered as soon as possible, preferably after obtaining blood cultures. The management of raised ICP is discussed in Chap. 22.

PROGNOSIS

One hopes to avoid the emotionally painful, hopeless outcome of a patient who is left severely disabled or vegetative. The uniformly poor outcome of the persistent vegetative state has already been mentioned. Children and young adults may have ominous early clinical findings such as abnormal brainstem reflexes and yet recover, so that temporization in offering a prognosis in this group of patients is wise. Metabolic comas have a far better prognosis than traumatic ones. All systems for estimating prognosis in adults should be taken as approximations, and medical judgments must be tempered by factors such as age, underlying systemic disease, and general medical condition. In an attempt to collect prognostic information from large numbers of patients with head injury, the Glasgow Coma Scale was devised; empirically it has predictive value in cases of brain trauma (Table 31-2). For anoxic and metabolic coma, clinical signs such as the pupillary and motor responses after 1 day, 3 days, and 1 week have been shown to have predictive value (Fig. 22-4). The absence of the cortical waves of the somatosensory evoked potentials has also proved a strong indicator of poor outcome in coma from any cause.

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CHAPTER 15
APHASIA, MEMORY LOSS, AND OTHER FOCAL CEREBRAL DISORDERS

M. -Marsel Mesulam

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The cerebral cortex of the human brain contains ~20 billion neurons spread over an area of 2.5 m^2. The *primary sensory* areas provide an obligatory portal for the entry of sensory information into cortical circuitry, whereas the *primary motor* areas provide final common pathways for coordinating complex motor acts. The primary sensory and motor areas constitute 10% of the cerebral cortex. The rest is subsumed by unimodal, heteromodal, paralimbic, and limbic areas, collectively known as the *association cortex* (**Fig. 15-1**). The association cortex mediates the integrative processes that subserve cognition, emotion, and behavior. A systematic testing of these mental functions is necessary for the effective clinical assessment of the association cortex and its diseases.

According to current thinking, there are no centers for "hearing words," "perceiving space," or "storing memories." Cognitive and behavioral functions (domains) are coordinated by intersecting *large-scale neural networks* that contain interconnected cortical and subcortical components. The network approach to higher cerebral function has at least four implications of clinical relevance: (1) a single domain such as language or memory can be disrupted by damage to any one of several areas, as long as these areas belong to the same network; (2) damage confined to a single area can give rise to multiple deficits, involving the functions of all networks that intersect in that region; (3) damage to a network component may give rise to minimal or transient deficits if other parts of the network undergo compensatory reorganization; and (4) individual anatomic sites within a network display a relative (but not absolute) specialization for different behavioral aspects of the relevant function. Five anatomically defined large-scale networks are most relevant to clinical practice: a perisylvian network for language; a parietofrontal network for spatial cognition; an occipitotemporal network for face and object recognition; a limbic network for retentive memory; and a prefrontal network for attention and behavior.

THE LEFT PERISYLVIAN NETWORK FOR LANGUAGE: APHASIAS AND RELATED CONDITIONS

Language allows the communication and elaboration of thoughts and experiences by linking them to arbitrary symbols known as words. The neural substrate of language is composed of a distributed network centered in the perisylvian region of the *left* hemisphere. The posterior pole of this network is located at the temporoparietal junction and includes a region known as *Wernicke's area*. An essential function of Wernicke's area is to transform sensory inputs into their lexical representations so that these can establish the distributed associations that give the word its meaning. The anterior pole of the language network is located in the inferior frontal gyrus

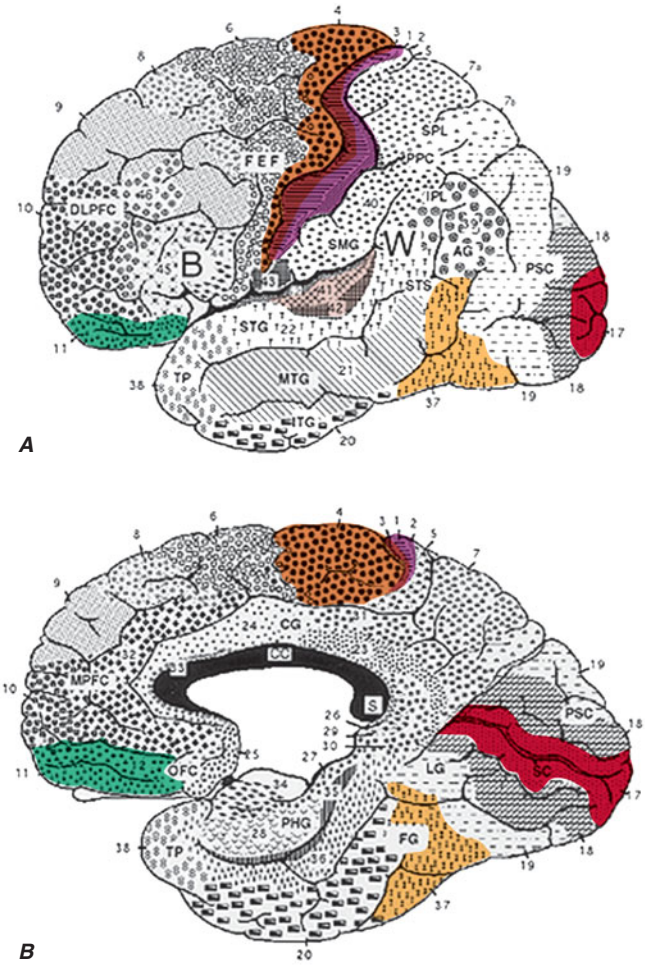


FIGURE 15-1

Lateral (*A*) and medial (*B*) views of the cerebral hemispheres. The numbers refer to the Brodmann cytoarchitectonic designations. Area 17 corresponds to the primary visual cortex, 41–42 to the primary auditory cortex, 1–3 to the primary somatosensory cortex, and 4 to the primary motor cortex. The rest of the cerebral cortex contains association areas. AG, angular gyrus; B, Broca's area; CC, corpus callosum; CG, cingulate gyrus; DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye fields (premotor cortex); FG, fusiform gyrus; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; LG, lingual gyrus; MPFC, medial prefrontal cortex; MTG, middle temporal gyrus; OFC, orbitofrontal cortex; PHG, parahippocampal gyrus; PPC, posterior parietal cortex; PSC, peristriate cortex; SC, striate cortex; SMG, supramarginal gyrus; SPL, superior parietal lobule; STG, superior temporal gyrus; STS, superior temporal sulcus; TP, temporopolar cortex; W, Wernicke's area.

and includes a region known as *Broca's area*. An essential function of this area is to transform lexical representations into their articulatory sequences so that the words can be uttered in the form of spoken language. The sequencing function of Broca's area also appears to involve the ordering of words into sentences that contain a meaning-appropriate *syntax* (grammar). Wernicke's and Broca's areas are interconnected with each other and with additional perisylvian, temporal, prefrontal, and posterior parietal regions, making up a neural network subserving the various aspects of language function. Damage to any one of these components or to their interconnections can give rise to language disturbances (*aphasia*). Aphasia should be diagnosed only when there are deficits in the formal aspects of language such as naming, word choice, comprehension, spelling, and syntax. Dysarthria and mutism do not, by themselves, lead to a diagnosis of aphasia. The language network shows a left hemisphere dominance pattern in the vast majority of the population. In ~90% of right handers and 60% of left handers, aphasia occurs only after lesions of the left hemisphere. In some individuals no hemispheric dominance for language can be discerned, and in some others (including a small minority of right handers) there is a right hemisphere dominance for language. A language disturbance occurring after a right hemisphere lesion in a right hander is called *crossed aphasia*.

CLINICAL EXAMINATION

The clinical examination of language should include the assessment of naming, spontaneous speech, comprehension, repetition, reading, and writing. A deficit of naming (*anomia*) is the single most common finding in aphasic patients. When asked to name common objects (pencil or wristwatch), the patient may fail to come up with the appropriate word, may provide a circumlocutious description of the object ("the thing for writing"), or may come up with the wrong word (*paraphasia*). If the patient offers an incorrect but legitimate word ("pen" for "pencil"), the naming error is known as a *semantic paraphasia*; if the word approximates the correct answer but is phonetically inaccurate ("plentil" for "pencil"), it is known as a *phonemic paraphasia*. Asking the patient to name body parts, geometric shapes, and component parts of objects (lapel of coat, cap of pen) can elicit mild forms of anomia in patients who can otherwise name common objects. In most anomias, the patient cannot retrieve the appropriate name when shown an object but can point to the appropriate object when the name is provided by the examiner. This is known as a one-way (or retrieval-based) naming deficit. A two-way naming deficit exists if the patient can neither provide nor recognize the correct name, indicating the presence of a language comprehension impairment. *Spontaneous speech* is described as "fluent" if it maintains appropriate output volume, phrase length, and melody or as "nonfluent" if it is sparse, halting, and average utterance length is below four words. The examiner should also note if the speech is paraphasic or circumlocutious; if it shows a relative paucity of substantive nouns and action verbs versus function words (prepositions, conjunctions); and if word

TABLE 15-1

CLINICAL FEATURES OF APHASIAS AND RELATED CONDITIONS

	COMPREHENSION	REPETITION OF SPOKEN LANGUAGE	NAMING	FLUENCY
Wernicke's	Impaired	Impaired	Impaired	Preserved or increased
Broca's	Preserved (except grammar)	Impaired	Impaired	Decreased
Global	Impaired	Impaired	Impaired	Decreased
Conduction	Preserved	Impaired	Impaired	Preserved
Nonfluent (motor) transcortical	Preserved	Preserved	Impaired	Impaired
Fluent (sensory) transcortical	Impaired	Preserved	Impaired	Preserved
Isolation	Impaired	Echolalia	Impaired	No purposeful speech
Anomic	Preserved	Preserved	Impaired	Preserved except for word-finding pauses
Pure word deafness	Impaired only for spoken language	Impaired	Preserved	Preserved
Pure alexia	Impaired only for reading	Preserved	Preserved	Preserved

order, tenses, suffixes, prefixes, plurals, and possessives are appropriate. *Comprehension* can be tested by assessing the patient's ability to follow conversation, by asking yes-no questions ("Can a dog fly?", "Does it snow in summer?") or asking the patient to point to appropriate objects ("Where is the source of illumination in this room?"). Statements with embedded clauses or passive voice construction ("If a tiger is eaten by a lion, which animal stays alive?") help to assess the ability to comprehend complex syntactic structure. Commands to close or open the eyes, stand up, sit down, or roll over should not be used to assess overall comprehension since appropriate responses aimed at such axial movements can be preserved in patients who otherwise have profound comprehension deficits.

Repetition is assessed by asking the patient to repeat single words, short sentences, or strings of words such as "No ifs, ands, or buts." The testing of repetition with tongue-twisters such as "hippopotamus" or "Irish constabulary" provides a better assessment of dysarthria and palilalia than aphasia. Aphasic patients may have little difficulty with tongue-twisters but have a particularly hard time repeating a string of function words. It is important to make sure that the number of words does not exceed the patient's attention span. Otherwise, the failure of repetition becomes a reflection of the narrowed attention span rather than an indication of an aphasic deficit. *Reading* should be assessed for deficits in reading aloud as well as comprehension. *Writing* is assessed for spelling errors, word order, and grammar. *Alexia* describes an inability to either read aloud or comprehend single words and simple sentences; *agraphia* (or dysgraphia) is used to describe an acquired deficit in the spelling or grammar of written language.

The correspondence between individual deficits of language function and lesion location does not display a rigid one-to-one relationship and should be conceptualized within the context of the distributed network model. Nonetheless, the classification of aphasias of acute onset into specific clinical syndromes helps to determine the most likely anatomic distribution of the underlying neurologic disease and has implications for etiology and prognosis (**Table 15-1**). The syndromes listed in Table 15-1 are most applicable to aphasias caused by cerebrovascular accidents (CVA). They can be divided into "central" syndromes, which result from damage to the two epicenters of the language network (Broca's and Wernicke's areas), and "disconnection" syndromes, which arise from lesions that interrupt the functional connectivity of these centers with each other and with the other components of the language network. The syndromes outlined below are idealizations; pure syndromes occur rarely.

Wernicke's Aphasia

Comprehension is impaired for spoken and written language. Language output is fluent but is highly paraphasic and circumlocutious. The tendency for paraphasic errors may be so pronounced that it leads to strings of neologisms, which form the basis of what is known as "jargon aphasia." Speech contains large numbers of function words (e.g., prepositions, conjunctions) but few substantive nouns or verbs that refer to specific actions. The output is therefore voluminous but uninformative. For example, a patient attempts to describe how his wife accidentally threw away something important, perhaps his dentures: "We don't need it anymore, she says. And with it when that was downstairs was my teeth-tick . . . a . . . den . . . dentith . . . my dentist. And they happened to be in that bag . . . see? How could this have happened? How could a thing like this happen . . . So she says we

won't need it anymore . . . I didn't think we'd use it. And now if I have any problems anybody coming a month from now, 4 months from now, or 6 months from now, I have a new dentist. Where my two . . . two little pieces of dentist that I use . . . that I . . . all gone. If she throws the whole thing away . . . visit some friends of hers and she can't throw them away."

Gestures and pantomime do not improve communication. The patient does not seem to realize that his or her language is incomprehensible and may appear angry and impatient when the examiner fails to decipher the meaning of a severely paraphasic statement. In some patients this type of aphasia can be associated with severe agitation and paranoid behaviors. One area of comprehension that may be preserved is the ability to follow commands aimed at axial musculature. The dissociation between the failure to understand simple questions ("What is your name?") in a patient who rapidly closes his or her eyes, sits up, or rolls over when asked to do so is characteristic of Wernicke's aphasia and helps to differentiate it from deafness, psychiatric disease, or malingering. Patients with Wernicke's aphasia cannot express their thoughts in meaning-appropriate words and cannot decode the meaning of words in any modality of input. This aphasia therefore has expressive as well as receptive components. Repetition, naming, reading, and writing are also impaired.

The lesion site most commonly associated with Wernicke's aphasia is the posterior portion of the language network and tends to involve at least parts of Wernicke's area. An embolus to the inferior division of the middle cerebral artery, and to the posterior temporal or angular branches in particular, is the most common etiology (Chap. 21). Intracerebral hemorrhage, severe head trauma, or neoplasm are other causes. A coexisting right hemi- or superior quadrantanopia is common, and mild right nasolabial flattening may be found, but otherwise the examination is often unrevealing. The paraphasic, neologistic speech in an agitated patient with an otherwise unremarkable neurologic examination may lead to the suspicion of a primary psychiatric disorder such as schizophrenia or mania, but the other components characteristic of acquired aphasia and the absence of prior psychiatric disease usually settle the issue. Some patients with Wernicke's aphasia due to intracerebral hemorrhage or head trauma may improve as the hemorrhage or the injury heals. In most other patients, prognosis for recovery is guarded.

Broca's Aphasia

Speech is nonfluent, labored, interrupted by many word-finding pauses, and usually dysarthric. It is impoverished in function words but enriched in meaning-appropriate nouns and verbs. Abnormal word order and the inappropriate deployment of *bound morphemes* (word endings used to denote tenses, possessives, or plurals) lead to a characteristic agrammatism. Speech is telegraphic and pithy but quite informative. In the following passage, a patient with Broca's aphasia describes his medical history: "I see . . . the dotor, dotor sent me . . . Bosson. Go to hospital. Dotor . . . kept me beside. Two, tee days, doctor send me home."

Output may be reduced to a grunt or single word ("yes" or "no"), which is emitted with different intonations in an attempt to express approval or disapproval. In addition to fluency, naming and repetition are also impaired. Comprehension of spoken language is intact, except for syntactically difficult sentences with passive voice structure or embedded clauses. Reading comprehension is also preserved, with the occasional exception of a specific inability to read small grammatical words such as conjunctions and pronouns. The last two features indicate that Broca's aphasia is not just an "expressive" or "motor" disorder and that it may also involve a comprehension deficit for function words and syntax. Patients with Broca's aphasia can be tearful, easily frustrated, and profoundly depressed. Insight into their condition is preserved, in contrast to Wernicke's aphasia. Even when spontaneous speech is severely dysarthric, the patient may be able to display a relatively normal articulation of words when singing. This dissociation has been used to develop specific therapeutic approaches (melodic intonation therapy) for Broca's aphasia. Additional neurologic deficits usually include right facial weakness, hemiparesis or hemiplegia, and a buccofacial apraxia characterized by an inability to carry out motor commands involving oropharyngeal and facial musculature (e.g., patients are unable to demonstrate how to blow out a match or suck through a straw). Visual fields are intact. The cause is most often infarction of Broca's area (the inferior frontal convolution; "B" in Fig. 15-1) and surrounding anterior perisylvian and insular cortex, due to occlusion of the superior division of the middle cerebral artery (Chap. 21). Mass lesions including tumor, intracerebral hemorrhage, or abscess may also be responsible. Small lesions confined to the posterior part of Broca's area may lead to a nonaphasic and often reversible deficit of speech articulation, usually accompanied by mild right facial weakness. When the cause of Broca's aphasia is stroke, recovery of language function generally peaks within 2–6 months, after which time further progress is limited.

Global Aphasia

Speech output is nonfluent, and comprehension of spoken language is severely impaired. Naming, repetition, reading, and writing are also impaired. This syndrome represents the combined dysfunction of Broca's and Wernicke's areas and usually results from strokes that involve the entire middle cerebral artery distribution in the left hemisphere. Most patients are initially mute or say a few words, such as "hi" or "yes." Related signs include right hemiplegia, hemisensory loss, and homonymous

hemianopia. Occasionally, a patient with a lesion in Wernicke's area will present with a global aphasia that soon resolves into Wernicke's aphasia.

Conduction Aphasia

Speech output is fluent but paraphasic, comprehension of spoken language is intact, and repetition is severely impaired. Naming and writing are also impaired. Reading aloud is impaired, but reading comprehension is preserved. The lesion sites spare Broca's and Wernicke's areas but may induce a functional disconnection between the two so that lexical representations formed in Wernicke's area and adjacent regions cannot be conveyed to Broca's area for assembly into corresponding articulatory patterns. Occasionally, a Wernicke's area lesion gives rise to a transient Wernicke's aphasia that rapidly resolves into a conduction aphasia. The paraphasic output in conduction aphasia interferes with the ability to express meaning, but this deficit is not nearly as severe as the one displayed by patients with Wernicke's aphasia. Associated neurologic signs in conduction aphasia vary according to the primary lesion site.

Nonfluent Transcortical Aphasia (Transcortical Motor Aphasia)

The features are similar to Broca's aphasia, but repetition is intact and agrammatism may be less pronounced. The neurologic examination may be otherwise intact, but a right hemiparesis can also exist. The lesion site disconnects the intact language network from prefrontal areas of the brain and usually involves the anterior watershed zone between anterior and middle cerebral artery territories or the supplementary motor cortex in the territory of the anterior cerebral artery.

Fluent Transcortical Aphasia (Transcortical Sensory Aphasia)

Clinical features are similar to those of Wernicke's aphasia, but repetition is intact. The lesion site disconnects the intact core of the language network from other temporoparietal association areas. Associated neurologic findings may include hemianopia. Cerebrovascular lesions (e.g., infarctions in the posterior watershed zone) or neoplasms that involve the temporoparietal cortex posterior to Wernicke's area are the most common causes.

Isolation Aphasia

This rare syndrome represents a combination of the two transcortical aphasias. Comprehension is severely impaired, and there is no purposeful speech output. The patient may parrot fragments of heard conversations (*echolalia*), indicating that the neural mechanisms for repetition are at least partially intact. This condition represents the pathologic function of the language network when it is isolated from other regions of the brain. Broca's and Wernicke's areas tend to be spared, but there is damage to the surrounding frontal, parietal, and temporal cortex. Lesions are patchy and can be associated with anoxia, carbon monoxide poisoning, or complete watershed zone infarctions.

Anomic Aphasia

This form of aphasia may be considered the "minimal dysfunction" syndrome of the language network. Articulation, comprehension, and repetition are intact, but confrontation naming, word finding, and spelling are impaired. Speech is enriched in function words but impoverished in substantive nouns and verbs denoting specific actions. Language output is fluent but paraphasic, circumlocutious, and uninformative. The lesion sites can be anywhere within the left hemisphere language network, including the middle and inferior temporal gyri. *Anomic aphasia is the single most common language disturbance seen in head trauma, metabolic encephalopathy, and Alzheimer's disease.*

Pure Word Deafness

The most common causes are either bilateral or left-sided middle cerebral artery strokes affecting the superior temporal gyrus. The net effect of the underlying lesion is to interrupt the flow of information from the unimodal auditory association cortex to Wernicke's area. Patients have no difficulty understanding written language and can express themselves well in spoken or written language. They have no difficulty interpreting and reacting to environmental sounds since primary auditory cortex and subcortical auditory relays are intact. Since auditory information cannot be conveyed to the language network, however, it cannot be decoded into lexical representations and the patient reacts to speech as if it were in an alien tongue that cannot be deciphered. Patients cannot repeat spoken language but have no difficulty naming objects. In time, patients with pure word deafness teach themselves lip reading and may appear to have improved. There may be no additional neurologic findings, but agitated paranoid reactions are frequent in the acute stages. Cerebrovascular lesions are the most frequent cause.

Pure Alexia without Agraphia

This is the visual equivalent of pure word deafness. The lesions (usually a combination of damage to the left occipital cortex and to a posterior sector of the corpus callosum—the splenium) interrupt the flow of visual input into the language network. There is usually a right hemianopia, but the core language network remains

unaffected. The patient can understand and produce spoken language, name objects in the left visual hemifield, repeat, and write. However, the patient acts as if illiterate when asked to read even the simplest sentence because the visual information from the written words (presented to the intact left visual hemifield) cannot reach the language network. Objects in the left hemifield may be named accurately because they activate nonvisual associations in the right hemisphere, which, in turn, can access the language network through transcallosal pathways anterior to the splenium. Patients with this syndrome may also lose the ability to name colors, although they can match colors. This is known as a *color anomia*. The most common etiology of pure alexia is a vascular lesion in the territory of the posterior cerebral artery or an infiltrating neoplasm in the left occipital cortex that involves the optic radiations as well as the crossing fibers of the splenium. Since the posterior cerebral artery also supplies medial temporal components of the limbic system, the patient with pure alexia may also experience an amnesia, but this is usually transient because the limbic lesion is unilateral.

Aphemia

There is an acute onset of severely impaired fluency (often mutism), which cannot be accounted for by corticobulbar, cerebellar, or extrapyramidal dysfunction. Recovery is the rule and involves an intermediate stage of hoarse whispering. Writing, reading, and comprehension are intact, so this is not a true aphasic syndrome. Partial lesions of Broca's area or subcortical lesions that undercut its connections with other parts of the brain may be present. Occasionally, the lesion site is on the medial aspects of the frontal lobes and may involve the supplementary motor cortex of the left hemisphere.

Apraxia

This generic term designates a complex motor deficit that cannot be attributed to pyramidal, extrapyramidal, cerebellar, or sensory dysfunction and that does not arise from the patient's failure to understand the nature of the task. The form that is most frequently encountered in clinical practice is known as *ideomotor apraxia*. Commands to perform a specific motor act ("cough," "blow out a match") or to pantomime the use of a common tool (a comb, hammer, straw, or toothbrush) in the absence of the real object cannot be followed. The patient's ability to comprehend the command is ascertained by demonstrating multiple movements and establishing that the correct one can be recognized. Some patients with this type of apraxia can imitate the appropriate movement (when it is demonstrated by the examiner) and show no impairment when handed the real object, indicating that the sensorimotor mechanisms necessary for the movement are intact. Some forms of ideomotor apraxia represent a disconnection of the language network from pyramidal motor systems: commands to execute complex movements are understood but cannot be conveyed to the appropriate motor areas, even though the relevant motor mechanisms are intact. *Buccofacial apraxia* involves apraxic deficits in movements of the face and mouth. *Limb apraxia* encompasses apraxic deficits in movements of the arms and legs. Ideomotor apraxia is almost always caused by lesions in the left hemisphere and is commonly associated with aphasic syndromes, especially Broca's aphasia and conduction aphasia. Its presence cannot be ascertained in patients with language comprehension deficits. The ability to follow commands aimed at axial musculature ("close the eyes," "stand up") is subserved by different pathways and may be intact in otherwise severely aphasic and apraxic patients. Patients with lesions of the anterior corpus callosum can display a special type of ideomotor apraxia confined to the left side of the body. Since the handling of real objects is not impaired, ideomotor apraxia, by itself, causes no major limitation of daily living activities.

Ideational apraxia refers to a deficit in the execution of a goal-directed sequence of movements in patients who have no difficulty executing the individual components of the sequence. For example, when asked to pick up a pen and write, the sequence of uncapping the pen, placing the cap at the opposite end, turning the point toward the writing surface, and writing may be disrupted, and the patient may be seen trying to write with the wrong end of the pen or even with the removed cap. These motor sequencing problems are usually seen in the context of confusional states and dementias rather than focal lesions associated with aphasic conditions. *Limb-kinetic apraxia* involves a clumsiness in the actual use of tools that cannot be attributed to sensory, pyramidal, extrapyramidal, or cerebellar dysfunction. This condition can emerge in the context of focal premotor cortex lesions or *corticobasal ganglionic degeneration*.

Gerstmann's Syndrome

The combination of *acalculia* (impairment of simple arithmetic), *dysgraphia* (impaired writing), *finger anomia* (an inability to name individual fingers such as the index or thumb), and *right-left confusion* (an inability to tell whether a hand, foot, or arm of the patient or examiner is on the right or left side of the body) is known as Gerstmann's syndrome. In making this diagnosis it is important to establish that the finger and left-right naming deficits are not part of a more generalized anomia and that the patient is not otherwise aphasic. When Gerstmann's syndrome is seen in isolation, it is commonly associated with damage to the inferior parietal lobule (especially the angular gyrus) in the left hemisphere.

Aprosodia

Variations of melodic stress and intonation influence the meaning and impact of spoken language. For example, the two statements "He *is* clever." and "He is *clever*?" contain an identical word choice and syntax but convey vastly different messages because of differences in the intonation and stress with which the statements are uttered. This aspect of language is known as *prosody*. Damage to perisylvian areas in the right hemisphere can interfere with speech prosody and can lead to syndromes of aprosodia. Damage to right hemisphere regions corresponding to Wernicke's area can selectively impair decoding of speech prosody, whereas damage to right hemisphere regions corresponding to Broca's area yields a greater impairment in the ability to introduce meaning-appropriate prosody into spoken language. The latter deficit is the most common type of aprosodia identified in clinical practice—the patient produces grammatically correct language with accurate word choice but the statements are uttered in a monotone that interferes with the ability to convey the intended stress and affect. Patients with this type of aprosodia give the mistaken impression of being depressed or indifferent.

Subcortical Aphasia

Damage to subcortical components of the language network (e.g., the striatum and thalamus of the left hemisphere) can also lead to aphasia. The resulting syndromes contain combinations of deficits in the various aspects of language but rarely fit the specific patterns described in Table 15-1. In a patient with a CVA, an anomic aphasia accompanied by dysarthria or a fluent aphasia with hemiparesis should raise the suspicion of a subcortical lesion site.

Progressive Aphasias

In clinical practice, acquired aphasias are most commonly encountered in one of two contexts: CVAs and degenerative diseases. Aphasias caused by CVAs start suddenly and display maximal deficits at the onset. The underlying lesion is relatively circumscribed and associated with a total loss of neural function at the lesion site. These are the "classic" aphasias described earlier where relatively reproducible relationships between lesion site and aphasia pattern can be discerned. Aphasias caused by neurodegenerative diseases have an insidious onset and relentless progression so that the symptomatology changes over time. Since the neuronal loss within the areas encompassed by the neurodegeneration is partial and since it tends to include multiple components of the language network, distinctive clinical patterns and clinicoanatomic correlations are less obvious.

Dementia is a generic term used to designate a neurodegenerative disease that impairs intellect and behavior to the point where customary daily living activities become compromised (Chap. 23). Alzheimer's disease is the single most common cause of dementia. The neuropathology of Alzheimer's disease causes the earliest and most profound neuronal loss in memory-related parts of the brain such as the entorhinal cortex and the hippocampus. This is why progressive forgetfulness for recent events and experiences is the cardinal feature of Alzheimer's disease. In time, the neuronal pathology in Alzheimer's disease spreads to the language network and a progressive aphasia, usually of the anomic type, becomes added to the progressive amnesia. There are other patterns of dementia, however, where neurodegeneration initially targets the language rather than memory network of the brain, leading to the emergence of a progressive aphasia that becomes the most prominent aspect of the clinical picture during the initial phases of the disease. Primary progressive aphasia (PPA) is the most widely recognized syndrome with this pattern of selective language impairment.

Clinical Presentation and Diagnosis of PPA

The patient with PPA comes to medical attention because of word-finding difficulties, abnormal speech patterns, and spelling errors of recent onset. PPA is diagnosed when other mental faculties such as memory for daily events, visuospatial skills (assessed by tests of drawing and face recognition), and comportment (assessed by history obtained from a third party) remain relatively intact; when language is the major area of dysfunction for the first few years of the disease; and when structural brain imaging does not reveal a specific lesion, other than atrophy, to account for the language deficit. Impairments in other cognitive functions may also emerge, but the language dysfunction remains the most salient feature and deteriorates most rapidly throughout the illness.

Language in PPA

The language impairment in PPA varies from patient to patient. Some patients cannot find the right words to express thoughts; others cannot understand the meaning of heard or seen words; still others cannot name objects in the environment. The language impairment can be fluent (that is, with normal articulation, flow, and number of words per utterance) or nonfluent. The single most common sign of primary progressive aphasia is anomia, manifested by an inability to come up with the right word during conversation and/or an inability to name objects shown by the examiner. Many patients remain in an anomic phase through most of the disease and experience a gradual intensification of word-finding deficits to the point of near-mutism. Others, however, proceed to develop distinct forms of agrammatism and/or word comprehension deficits. The agrammatism consists of inappropriate word order and misuse of small

grammatical words. One patient, for example, sent the following e-mail to her daughter: "I will come my house in your car and drive my car into chicago. . . .You will back get your car and my car park in my driveway. Love, Mom." Comprehension deficits, if present, start with an occasional inability to understand single low-frequency words and gradually progress to encompass the comprehension of conversational speech.

The impairments of syntax, comprehension, naming, or writing in PPA are no different from those seen in aphasias of cerebrovascular causes. However, they form slightly different patterns. According to a classification proposed by Gorno-Tempini and colleagues, three variants of PPA can be recognized: an agrammatical variant characterized by poor fluency and impaired syntax, a semantic variant characterized by preserved fluency and syntax but poor single word comprehension, and a logopenic variant characterized by preserved syntax and comprehension but frequent word-finding pauses during spontaneous speech. The agrammatical variant is also known as *progressive nonfluent aphasia* and displays similarities to Broca's aphasia. However, dysarthria is usually absent. The semantic variant of PPA is also known as *semantic dementia* and displays similarities to Wernicke's aphasia, but the comprehension difficulty tends to be milder. The most obvious difference between aphasias caused by CVA and those caused by neurodegenerative disease is the post-stroke improvement in CVA-related aphasias, leading to a progressive crystallization of the subtypes listed in Table 15-1, versus the gradual deterioration that leads to a loss of syndromic specificity as the disease progresses.

Pathophysiology

Patients with PPA display progressive atrophy (indicative of neuronal loss), electroencephalographic slowing, decreased blood flow (measured by single photon emission CT) and decreased glucose utilization (measured by positron emission tomography) that are most pronounced within the language network of the brain. The abnormalities may remain confined to left hemisphere perisylvian and anterior temporal cortices for many years. The clinical focality of primary progressive aphasia is thus matched by the anatomic selectivity of the underlying pathologic process.

The three variants display overlapping distributions of neuronal loss but the agrammatical variant is most closely associated with atrophy in the anterior parts of the language network (where Broca's area is located), the semantic variant with atrophy in the temporal components of the language network, and the logopenic variant with atrophy in the temporoparietal component of the language network. The relationship between poor language comprehension and damage to Wernicke's area, which is a feature of CVA-related aphasias, is not present in PPA. Instead, poor comprehension is most closely associated with neuronal loss in the lateral and anterior temporal cortex.

Neuropathology

Approximately 30% of patients have shown the microscopic pathology of Alzheimer's disease, presumably with an atypical distribution of lesions. In the majority of cases, the neuropathology falls within the family of frontotemporal lobar degenerations (FTLD) and displays various combinations of focal neuronal loss, gliosis, tau-positive inclusions, Pick bodies, and tau-negative ubiquitin inclusions (Chap. 23). Familial forms of PPA with tau-negative ubiquinated inclusions have recently been linked to mutations of the progranulin gene on chromosome 17. Apolipoprotein E and prion protein genotyping has shown differences between patients with typical clinical patterns of Alzheimer's disease and those with a diagnosis of PPA. The intriguing possibility has been raised that a personal or family history of dyslexia may be a risk factor for primary progressive aphasia, at least in some patients, suggesting that this disease may arise on a background of genetic or developmental vulnerability affecting language-related areas of the brain.

THE PARIETOFRONTAL NETWORK FOR SPATIAL ORIENTATION: NEGLECT AND RELATED CONDITIONS

HEMISPATIAL NEGLECT

Adaptive orientation to significant events within the extrapersonal space is subserved by a large-scale network containing three major cortical components. The *cingulate cortex* provides access to a limbic-motivational mapping of the extrapersonal space, the *posterior parietal cortex* to a sensorimotor representation of salient extrapersonal events, and the *frontal eye fields* to motor strategies for attentional behaviors (**Fig. 15-2**). Subcortical components of this network include the striatum and the thalamus. Contralesional hemispatial neglect represents one outcome of damage to any of the cortical or subcortical components of this network. *The traditional view that hemispatial neglect always denotes a parietal lobe lesion is inaccurate*. In keeping with this anatomic organization, the clinical manifestations of neglect display three behavioral components: sensory events (or their mental representations) within the neglected hemispace have a lesser impact on overall awareness; there is a paucity of exploratory and orienting acts directed toward the neglected hemispace; and the patient behaves as if the neglected hemispace was motivationally devalued.

According to one model of spatial cognition, the right hemisphere directs attention within the *entire* extrapersonal space, whereas the left hemisphere directs attention mostly within the contralateral right hemispace.

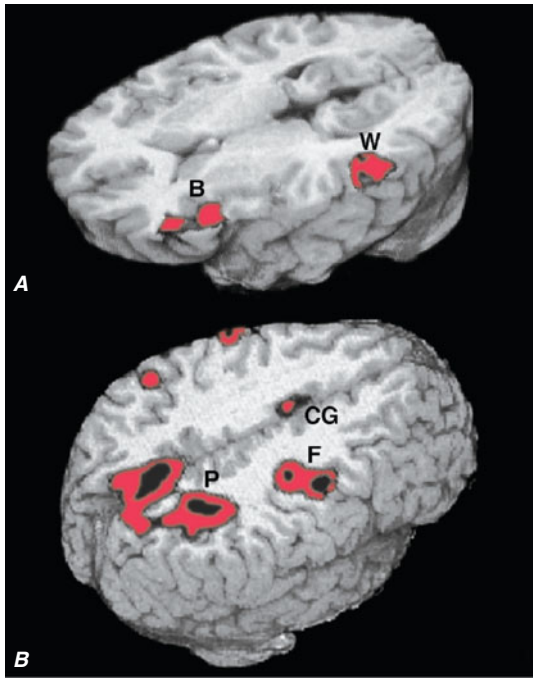


FIGURE 15-2

Functional magnetic resonance imaging of language and spatial attention in neurologically intact subjects. The dark areas show regions of task-related significant activation. (***A***) The subjects were asked to determine if two words were synonymous. This language task led to the simultaneous activation of the two epicenters of the language network, Broca's area (B) and Wernicke's area (W). The activations are exclusively in the left hemisphere. (***B***) The subjects were asked to shift spatial attention to a peripheral target. This task led to the simultaneous activation of the three epicenters of the attentional network, the posterior parietal cortex (P), the frontal eye fields (F), and the cingulate gyrus (CG). The activations are predominantly in the right hemisphere. (*Courtesy of Darren Gitelman, MD; with permission.*)

Consequently, unilateral left hemisphere lesions do not give rise to much contralesional neglect since the global attentional mechanisms of the right hemisphere can compensate for the loss of the *contralaterally* directed attentional functions of the left hemisphere. Unilateral right hemisphere lesions, however, give rise to severe contralesional left hemispatial neglect because the unaffected left hemisphere does not contain ipsilateral attentional mechanisms. This model is consistent with clinical experience, which shows that contralesional neglect is more common, severe, and lasting after damage to the right hemisphere than after damage to the left hemisphere. Severe neglect for the right hemispace is rare, even in left handers with left hemisphere lesions.

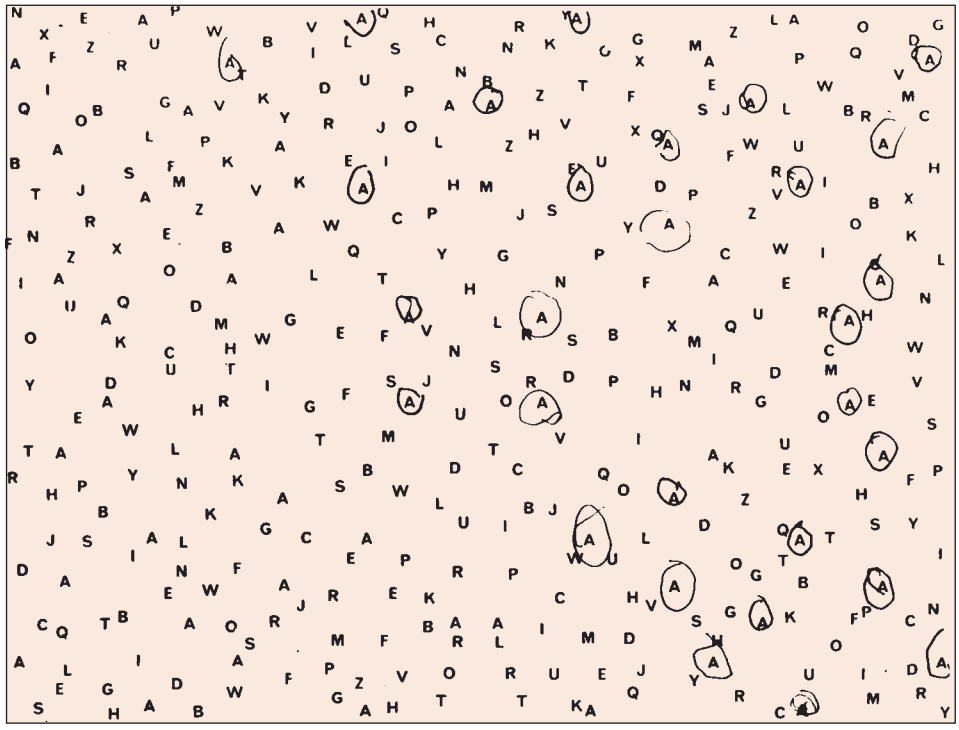
Patients with severe neglect may fail to dress, shave, or groom the left side of the body; may fail to eat food placed on the left side of the tray; and may fail to read the left half of sentences. When the examiner draws a large circle [12–15 cm (5–6 in.) in diameter] and asks the patient to place the numbers 1–12 as if the circle represented the face of a clock, there is a tendency to crowd the numbers on the right side and leave the left side empty. When asked to copy a simple line drawing, the patient fails to copy detail on the left; and when asked to write, there is a tendency to leave an unusually wide margin on the left.

Two bedside tests that are useful in assessing neglect are *simultaneous bilateral stimulation* and *visual target cancellation*. In the former, the examiner provides either unilateral or simultaneous bilateral stimulation in the visual, auditory, and tactile modalities. Following right hemisphere injury, patients who have no difficulty detecting unilateral stimuli on either side experience the bilaterally presented stimulus as coming only from the right. This phenomenon is known as *extinction* and is a manifestation of the sensory-representational aspect of hemispatial neglect. In the target detection task, targets (e.g., As) are interspersed with foils (e.g., other letters of the alphabet) on a 21.5 × 28.0 cm (8.5 × 11 in.) sheet of paper and the patient is asked to circle all the targets. A failure to detect targets on the left is a manifestation of the exploratory deficit in hemispatial neglect (**Fig. 15-3*A***). Hemianopia, by itself, does not interfere with performance in this task since the patient is free to turn the head and eyes to the left. The normal tendency in target detection tasks is to start from the left upper quadrant and move systematically in horizontal or vertical sweeps. Some patients show a tendency to start the process from the right and proceed in a haphazard fashion. This represents a subtle manifestation of left neglect, even if the patient eventually manages to detect all the appropriate targets. Some patients with neglect may also deny the existence of hemiparesis and may even deny ownership of the paralyzed limb, a condition known as *anosognosia*.

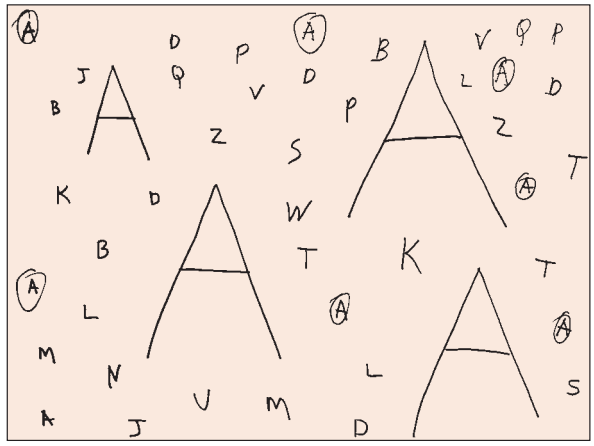
Cerebrovascular lesions and neoplasms in the right hemisphere are the most common causes of hemispatial neglect. Depending on the site of the lesion, the patient with neglect may also have hemiparesis, hemihypesthesia, and hemianopia on the left, but these are not invariant findings. The majority of patients display considerable improvement of hemispatial neglect, usually within the first several weeks.

BÁLINT'S SYNDROME, SIMULTANAGNOSIA, DRESSING APRAXIA, AND CONSTRUCTION APRAXIA

Bilateral involvement of the network for spatial attention, especially its parietal components, leads to a state of severe spatial disorientation known as *Bálint's syndrome*. Bálint's syndrome involves deficits in the orderly visuomotor



A



B

FIGURE 15-3
Evidence of left hemispatial neglect and simultanagnosia. ***A.*** A 47-year-old man with a large frontoparietal lesion in the right hemisphere was asked to circle all the As. Only targets on the right are circled. This is a manifestation of left hemispatial neglect. ***B.*** A 70-year-old woman with a 2-year history of degenerative dementia was able to circle most of the small targets but ignored the larger ones. This is a manifestation of simultanagnosia.

scanning of the environment (*oculomotor apraxia*) and in accurate manual reaching toward visual targets (*optic ataxia*). The third and most dramatic component of Bálint's syndrome is known as *simultanagnosia* and reflects an inability to integrate visual information in the center of gaze with more peripheral information. The patient gets stuck on the detail that falls in the center of gaze without attempting to scan the visual environment for additional information. The patient with simultanagnosia "misses the forest for the trees." Complex visual scenes cannot be grasped in their entirety, leading to severe limitations in the visual identification of objects and scenes. For example, a patient who is shown a table lamp and asked to name the object may look at its circular base and call it an ash tray. Some patients with simultanagnosia report that objects they look at may suddenly vanish, probably indicating an inability to look back at the original point of gaze after brief saccadic displacements. Movement and distracting stimuli greatly exacerbate the difficulties of visual perception. Simultanagnosia can sometimes occur without the other two components of Bálint's syndrome.

A modification of the letter cancellation task described above can be used for the bedside diagnosis of simultanagnosia. In this modification, some of the targets (e.g., As) are made to be much larger than the others [7.5–10 cm vs 2.5 cm (3–4 in. vs 1 in.) in height], and all targets are embedded among foils. Patients with simultanagnosia display a counterintuitive but characteristic tendency to miss the larger targets (**Fig. 15-3*B***). This

occurs because the information needed for the identification of the larger targets cannot be confined to the immediate line of gaze and requires the integration of visual information across a more extensive field of view. The greater difficulty in the detection of the larger targets also indicates that poor acuity is not responsible for the impairment of visual function and that the problem is central rather than peripheral. Bálint's syndrome results from bilateral dorsal parietal lesions; common settings include watershed infarction between the middle and posterior cerebral artery territories, hypoglycemia, sagittal sinus thrombosis, or atypical forms of Alzheimer's disease. In patients with Bálint's syndrome due to stroke, bilateral visual field defects (usually inferior quadrantanopias) are common.

Another manifestation of bilateral (or right-sided) dorsal parietal lobe lesions is *dressing apraxia*. The patient with this condition is unable to align the body axis with the axis of the garment and can be seen struggling as he or she holds a coat from its bottom or extends his or her arm into a fold of the garment rather than into its sleeve. Lesions that involve the posterior parietal cortex also lead to severe difficulties in copying simple line drawings. This is known as a *construction apraxia* and is much more severe if the lesion is in the right hemisphere. In some patients with right hemisphere lesions, the drawing difficulties are confined to the left side of the figure and represent a manifestation of hemispatial neglect; in others, there is a more universal deficit in reproducing contours and three-dimensional perspective. Dressing apraxia and construction apraxia represent special instances of a more general disturbance in spatial orientation.

THE OCCIPITOTEMPORAL NETWORK FOR FACE AND OBJECT RECOGNITION: PROSOPAGNOSIA AND OBJECT AGNOSIA

Perceptual information about faces and objects is initially encoded in primary (striate) visual cortex and adjacent (upstream) peristriate visual association areas. This information is subsequently relayed first to the downstream visual association areas of occipitotemporal cortex and then to other heteromodal and paralimbic areas of the cerebral cortex. Bilateral lesions in the fusiform and lingual gyri of the occipitotemporal cortex disrupt this process and interfere with the ability of otherwise intact perceptual information to activate the distributed multimodal associations that lead to the recognition of faces and objects. The resultant face and object recognition deficits are known as *prosopagnosia* and *visual object agnosia*.

The patient with prosopagnosia cannot recognize familiar faces, including, sometimes, the reflection of his or her own face in the mirror. This is not a perceptual deficit since prosopagnosic patients can easily tell if two faces are identical or not. Furthermore, a prosopagnosic patient who cannot recognize a familiar face by visual inspection alone can use auditory cues to reach appropriate recognition if allowed to listen to the person's voice. The deficit in prosopagnosia is therefore modality-specific and reflects the existence of a lesion that prevents the activation of otherwise intact multimodal templates by relevant visual input. Damasio has pointed out that the deficit in prosopagnosia is not limited to the recognition of faces but that it can also extend to the recognition of individual members of larger generic object groups. For example, prosopagnosic patients characteristically have no difficulty with the generic identification of a face as a face or of a car as a car, but they cannot recognize the identity of an individual face or the make of an individual car. This reflects a visual recognition deficit for proprietary features that characterize individual members of an object class. When recognition problems become more generalized and extend to the generic identification of common objects, the condition is known as visual object agnosia. In contrast to prosopagnosic patients, those with object agnosia cannot recognize a face as a face or a car as a car.

It is important to distinguish visual object agnosia from anomia. The patient with anomia cannot name the object but can describe its use. In contrast, the patient with visual agnosia is unable either to name a visually presented object or to describe its use. The characteristic lesions in prosopagnosia and visual object agnosia consist of bilateral infarctions in the territory of the posterior cerebral arteries. Associated deficits can include visual field defects (especially superior quadrantanopias) or a centrally based color blindness known as *achromatopsia*. Rarely, the responsible lesion is unilateral. In such cases, prosopagnosia is associated with lesions in the right hemisphere and object agnosia with lesions in the left.

THE LIMBIC NETWORK FOR MEMORY: AMNESIAS

Limbic and paralimbic areas (such as the hippocampus, amygdala, and entorhinal cortex), the anterior and medial nuclei of the thalamus, the medial and basal parts of the striatum, and the hypothalamus collectively constitute a distributed network known as the *limbic system*. The behavioral affiliations of this network include the coordination of emotion, motivation, autonomic tone, and endocrine function. An additional area of specialization for the limbic network, and the one which is of most relevance to clinical practice, is that of declarative (conscious) memory for recent episodes and experiences. A disturbance in this function is known as an *amnestic state*. In the absence of deficits in motivation,

attention, language, or visuospatial function, the clinical diagnosis of a persistent global amnestic state is always associated with bilateral damage to the limbic network, usually within the hippocampo-entorhinal complex or the thalamus.

Although the limbic network is the site of damage for amnestic states, it is almost certainly not the storage site for memories. Memories are stored in widely distributed form throughout the cerebral cortex. The role attributed to the limbic network is to bind these distributed fragments into coherent events and experiences that can sustain conscious recall. Damage to the limbic network does not necessarily destroy memories but interferes with their conscious (declarative) recall in coherent form. The individual fragments of information remain preserved despite the limbic lesions and can sustain what is known as *implicit memory*. For example, patients with amnestic states can acquire new motor or perceptual skills, even though they may have no conscious knowledge of the experiences that led to the acquisition of these skills.

The memory disturbance in the amnestic state is multimodal and includes retrograde and anterograde components. The *retrograde amnesia* involves an inability to recall experiences that occurred before the onset of the amnestic state. Relatively recent events are more vulnerable to retrograde amnesia than more remote and more extensively consolidated events. A patient who comes to the emergency department complaining that he cannot remember his identity but who can remember the events of the previous day is almost certainly not suffering from a neurologic cause of memory disturbance. The second and most important component of the amnestic state is the *anterograde amnesia*, which indicates an inability to store, retain, and recall new knowledge. Patients with amnestic states cannot remember what they ate a few minutes ago or the details of an important event they may have experienced a few hours ago. In the acute stages, there may also be a tendency to fill in memory gaps with inaccurate, fabricated, and often implausible information. This is known as *confabulation*. Patients with the amnestic syndrome forget that they forget and tend to deny the existence of a memory problem when questioned.

The patient with an amnestic state is almost always disoriented, especially to time. Accurate temporal orientation and accurate knowledge of current news rule out a major amnestic state. The anterograde component of an amnestic state can be tested with a list of four to five words read aloud by the examiner up to five times or until the patient can immediately repeat the entire list without intervening delay. In the next phase of testing, the patient is allowed to concentrate on the words and to rehearse them internally for 1 min before being asked to recall them. Accurate performance in this phase indicates that the patient is motivated and sufficiently attentive to hold the words online for at least 1 min. The final phase of the testing involves a retention period of 5–10 min, during which the patient is engaged in other tasks. Adequate recall at the end of this interval requires offline storage, retention, and retrieval. Amnestic patients fail this phase of the task and may even forget that they were given a list of words to remember. Accurate recognition of the words by multiple choice in a patient who cannot recall them indicates a less severe memory disturbance that affects mostly the retrieval stage of memory. The retrograde component of an amnesia can be assessed with questions related to autobiographical or historic events. The anterograde component of amnestic states is usually much more prominent than the retrograde component. In rare instances, usually associated with temporal lobe epilepsy or benzodiazepine intake, the retrograde component may dominate.

The assessment of memory can be quite challenging. Bedside evaluations may only detect the most severe impairments. Less severe memory impairments, as in the case of patients with temporal lobe epilepsy, mild head injury, or early dementia, require quantitative evaluations by neuropsychologists. Confusional states caused by toxic-metabolic encephalopathies and some types of frontal lobe damage interfere with attentional capacity and lead to secondary memory impairments, even in the absence of any limbic lesions. This sort of memory impairment can be differentiated from the amnestic state by the presence of additional impairments in the attention-related tasks described later in the section on the frontal lobes.

Many neurologic diseases can give rise to an amnestic state. These include tumors (of the sphenoid wing, posterior corpus callosum, thalamus, or medial temporal lobe), infarctions (in the territories of the anterior or posterior cerebral arteries), head trauma, herpes simplex encephalitis, Wernicke-Korsakoff encephalopathy, paraneoplastic limbic encephalitis, and degenerative dementias such as Alzheimer's or Pick's disease. The one common denominator of all these diseases is that they lead to the bilateral lesions within one or more components in the limbic network, most commonly the hippocampus, entorhinal cortex, the mammillary bodies of the hypothalamus, and the limbic thalamus. Occasionally, unilateral left-sided lesions can give rise to an amnestic state, but the memory disorder tends to be transient. Depending on the nature and distribution of the underlying neurologic disease, the patient may also have visual field deficits, eye movement limitations, or cerebellar findings.

Transient global amnesia is a distinctive syndrome usually seen in late middle age. Patients become acutely disoriented and repeatedly ask who they are, where they are, what they are doing. The spell is characterized by anterograde amnesia (inability to retain new information) and a retrograde amnesia for relatively recent events that

occurred before the onset. The syndrome usually resolves within 24–48 h and is followed by the filling-in of the period affected by the retrograde amnesia, although there is persistent loss of memory for the events that occurred during the ictus. Recurrences are noted in ~20% of patients. Migraine, temporal lobe seizures, and transient ischemic events in the posterior cerebral territory have been postulated as causes of transient global amnesia. The absence of associated neurologic findings may occasionally lead to the incorrect diagnosis of a psychiatric disorder.

THE PREFRONTAL NETWORK FOR ATTENTION AND BEHAVIOR

Approximately one-third of all the cerebral cortex in the human brain is located in the frontal lobes. The frontal lobes can be subdivided into motor-premotor, dorsolateral prefrontal, medial prefrontal, and orbitofrontal components. The terms *frontal lobe syndrome* and *prefrontal cortex* refer only to the last three of these four components. These are the parts of the cerebral cortex that show the greatest phylogenetic expansion in primates and especially in humans. The dorsolateral prefrontal, medial prefrontal, and orbitofrontal areas, and the subcortical structures with which they are interconnected (i.e., the head of the caudate and the dorsomedial nucleus of the thalamus), collectively make up a large-scale network that coordinates exceedingly complex aspects of human cognition and behavior.

The prefrontal network plays an important role in behaviors that require an integration of thought with emotion and motivation. There is no simple formula for summarizing the diverse functional affiliations of the prefrontal network. Its integrity appears important for the simultaneous awareness of context, options, consequences, relevance, and emotional impact so as to allow the formulation of adaptive inferences, decisions, and actions. Damage to this part of the brain impairs mental flexibility, reasoning, hypothesis formation, abstract thinking, foresight, judgment, the online (attentive) holding of information, and the ability to inhibit inappropriate responses. Behaviors impaired by prefrontal cortex lesions, especially those related to the manipulation of mental content, are often referred to as "executive functions."

Even very large bilateral prefrontal lesions may leave all sensory, motor, and basic cognitive functions intact while leading to isolated but dramatic alterations of personality and behavior. The most common clinical manifestations of damage to the prefrontal network take the form of two relatively distinct syndromes. In the *frontal abulic syndrome*, the patient shows a loss of initiative, creativity, and curiosity and displays a pervasive emotional blandness and apathy. In the *frontal disinhibition syndrome*, the patient becomes socially disinhibited and shows severe impairments of judgment, insight, and foresight. The dissociation between intact cognitive function and a total lack of even rudimentary common sense is striking. Despite the preservation of all essential memory functions, the patient cannot learn from experience and continues to display inappropriate behaviors without appearing to feel emotional pain, guilt, or regret when such behaviors repeatedly lead to disastrous consequences. The impairments may emerge only in real-life situations when behavior is under minimal external control and may not be apparent within the structured environment of the medical office. Testing judgment by asking patients what they would do if they detected a fire in a theater or found a stamped and addressed envelope on the road is not very informative since patients who answer these questions wisely in the office may still act very foolishly in the more complex real-life setting. The physician must therefore be prepared to make a diagnosis of frontal lobe disease on the basis of historic information alone even when the office examination of mental state may be quite intact.

The abulic syndrome tends to be associated with damage to the dorsolateral prefrontal cortex, and the disinhibition syndrome with the medial prefrontal or orbitofrontal cortex. These syndromes tend to arise almost exclusively after bilateral lesions, most frequently in the setting of head trauma, stroke, ruptured aneurysms, hydrocephalus, tumors (including metastases, glioblastoma, and falx or olfactory groove meningiomas), or focal degenerative diseases. Unilateral lesions confined to the prefrontal cortex may remain silent until the pathology spreads to the other side. The emergence of developmentally primitive reflexes, also known as frontal release signs, such as grasping (elicited by stroking the palm) and sucking (elicited by stroking the lips) are seen primarily in patients with large structural lesions that extend into the premotor components of the frontal lobes or in the context of metabolic encephalopathies. The vast majority of patients with prefrontal lesions and frontal lobe behavioral syndromes do not display these reflexes.

Damage to the frontal lobe disrupts a variety of attention-related functions including working memory (the transient online holding of information), concentration span, the scanning and retrieval of stored information, the inhibition of immediate but inappropriate responses, and mental flexibility. The capacity for focusing on a trend of thought and the ability to voluntarily shift the focus of attention from one thought or stimulus to another can become impaired. Digit span (which should be seven forward and five reverse) is decreased; the recitation of the months of the year in reverse order (which should take less than 15 s) is slowed; and the fluency in producing words starting with *a*, *f*, or *s* that can be generated in 1 min (normally $\geq$12 per letter) is diminished even in nonaphasic patients. Characteristically,

there is a progressive slowing of performance as the task proceeds; e.g., the patient asked to count backwards by 3s may say "100, 97, 94, . . . 91, . . . 88," etc., and may not complete the task. In "go–no-go" tasks (where the instruction is to raise the finger upon hearing one tap but to keep it still upon hearing two taps), the patient shows a characteristic inability to keep still in response to the "no-go" stimulus; mental flexibility (tested by the ability to shift from one criterion to another in sorting or matching tasks) is impoverished; distractibility by irrelevant stimuli is increased; and there is a pronounced tendency for impersistence and perseveration.

These attentional deficits disrupt the orderly registration and retrieval of new information and lead to *secondary* memory deficits. Such memory deficits can be differentiated from the *primary* memory impairments of the amnestic state by showing that they improve when the attentional load of the task is decreased. Working memory (also known as immediate memory) is an attentional function based on the temporary online holding of information. It is closely associated with the integrity of the prefrontal network and the ascending reticular activating system. Retentive memory, on the other hand, depends on the stable (offline) storage of information and is associated with the integrity of the limbic network. The distinction of the underlying neural mechanisms is illustrated by the observation that severely amnestic patients who cannot remember events that occurred a few minutes ago may have intact if not superior working memory capacity as shown in tests of digit span.

Lesions in the caudate nucleus or in the dorsomedial nucleus of the thalamus (subcortical components of the prefrontal network) can also produce a frontal lobe syndrome. This is one reason why the mental state changes associated with degenerative basal ganglia diseases, such as Parkinson's or Huntington's disease, may take the form of a frontal lobe syndrome. Because of its widespread connections with other regions of association cortex, one essential computational role of the prefrontal network is to function as an integrator, or "orchestrator," for other networks. Bilateral multifocal lesions of the cerebral hemispheres, none of which are individually large enough to cause specific cognitive deficits such as aphasia or neglect, can collectively interfere with the connectivity and integrating function of the prefrontal cortex. A frontal lobe syndrome is the single most common behavioral profile associated with a variety of bilateral multifocal brain diseases including metabolic encephalopathy, multiple sclerosis, vitamin B_{12} deficiency, and others. In fact, the vast majority of patients with the clinical diagnosis of a frontal lobe syndrome tend to have lesions that do not involve prefrontal cortex but involve either the subcortical components of the prefrontal network or its connections with other parts of the brain. In order to avoid making a diagnosis of "frontal lobe syndrome" in a patient with no evidence of frontal cortex disease, it is advisable to use the diagnostic term *frontal network syndrome*, with the understanding that the responsible lesions can lie anywhere within this distributed network.

The patient with frontal lobe disease raises potential dilemmas in differential diagnosis: the abulia and blandness may be misinterpreted as depression, and the disinhibition as idiopathic mania or acting-out. Appropriate intervention may be delayed while a treatable tumor keeps expanding. An informed approach to frontal lobe disease and its behavioral manifestations may help to avoid such errors.

CARING FOR THE PATIENT WITH DEFICITS OF HIGHER CEREBRAL FUNCTION

Some of the deficits described in this chapter are so complex that they may bewilder not only the patient and family but also the physician. It is imperative to carry out a systematic clinical evaluation in order to characterize the nature of the deficits and explain them in lay terms to the patient and family. Such an explanation can allay at least some of the anxieties, address the mistaken impression that the deficit (e.g., social disinhibition or inability to recognize family members) is psychologically motivated, and lead to practical suggestions for daily living activities. The consultation of a skilled neuropsychologist may aid in the formulation of diagnosis and management. Patients with simultanagnosia, for example, may benefit from the counterintuitive instruction to stand back when they cannot find an item so that a greater search area falls within the immediate field of gaze. Some patients with frontal lobe disease can be extremely irritable and abusive to spouses and yet display all the appropriate social graces during the visit to the medical office. In such cases, the history may be more important than the bedside examination in charting a course of treatment.

Reactive depression is common in patients with higher cerebral dysfunction and should be treated. These patients may be sensitive to the usual doses of antidepressants or anxiolytics and deserve a careful titration of dosage. Brain damage may cause a dissociation between feeling states and their expression, so that a patient who may superficially appear jocular could still be suffering from an underlying depression that deserves to be treated. In many cases, agitation may be controlled with reassurance. In other cases, treatment with sedating antidepressants may become necessary. The use of neuroleptics for the control of agitation should be reserved for refractory cases since extrapyramidal side effects are frequent in patients with coexisting brain damage.

Spontaneous improvement of cognitive deficits due to acute neurologic lesions is common. It is most rapid

in the first few weeks but may continue for up to 2 years, especially in young individuals with single brain lesions. The mechanisms for this recovery are incompletely understood. Some of the initial deficits appear to arise from remote dysfunction (diaschisis) in parts of the brain that are interconnected with the site of initial injury. Improvement in these patients may reflect, at least in part, a normalization of the remote dysfunction. Other mechanisms may involve functional reorganization in surviving neurons adjacent to the injury or the compensatory use of homologous structures, e.g., the right superior temporal gyrus with recovery from Wernicke's aphasia. In some patients with large lesions involving Broca's and Wernicke's areas, only Wernicke's area may show contralateral compensatory reorganization (or bilateral functionality), giving rise to a situation where a lesion that should have caused a global aphasia becomes associated with a residual Broca's aphasia. Prognosis for recovery from aphasia is best when Wernicke's area is spared. Cognitive rehabilitation procedures have been used in the treatment of higher cortical deficits. There are few controlled studies, but some do show a benefit of rehabilitation in the recovery from hemispatial neglect and aphasia. Some types of deficits may be more prone to recovery than others. For example, patients with nonfluent aphasias are more likely to benefit from speech therapy than patients with fluent aphasias and comprehension deficits. In general, lesions that lead to a denial of illness (e.g., anosognosia) are associated with cognitive deficits that are more resistant to rehabilitation. The recovery from higher cortical dysfunction is rarely complete. Periodic neuropsychological assessment is necessary for quantifying the pace of the improvement and for generating specific recommendations for cognitive rehabilitation, modifications in the home environment, and the timetable for returning to school or work.

In general medical practice, most patients with deficits in higher cognitive functions will be suffering from dementia. There is a mistaken belief that dementias are anatomically diffuse and that they cause global cognitive impairments. This is only true at the terminal stages. During most of the clinical course, dementias are exquisitely selective with respect to anatomy and cognitive pattern. Alzheimer's disease, for example, causes the greatest destruction in medial temporal areas belonging to the memory network and is clinically characterized by a correspondingly severe amnesia. There are other dementias where memory is intact. Frontal lobe dementia results from a selective degeneration of the frontal lobe and leads to a gradual dissolution of behavior and complex attention. Primary progressive aphasia is characterized by a gradual atrophy of the left perisylvian language network and leads to a progressive dissolution of language that can remain isolated for up to 10 years. An enlightened approach to the differential diagnosis and treatment of these patients requires an understanding of the principles that link neural networks to higher cerebral functions.

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CHAPTER 16

SLEEP DISORDERS

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Disturbed sleep is among the most frequent health complaints physicians encounter. More than one-half of adults in the United States experience at least intermittent sleep disturbances. For most, it is an occasional night of poor sleep or daytime sleepiness. However, the Institute of Medicine estimates that 50–70 million Americans suffer from a chronic disorder of sleep and wakefulness, which can lead to serious impairment of daytime functioning. In addition, such problems may contribute to or exacerbate medical or psychiatric conditions. Thirty years ago, many such complaints were treated with hypnotic medications without further diagnostic evaluation. Since then, a distinct class of sleep and arousal disorders has been identified.

PHYSIOLOGY OF SLEEP AND WAKEFULNESS

Most adults sleep 7–8 h per night, although the timing, duration, and internal structure of sleep vary among healthy individuals and as a function of age. At the extremes, infants and the elderly have frequent interruptions of sleep. In the United States, adults of intermediate age tend to have one consolidated sleep episode per day, although in some cultures sleep may be divided into a mid-afternoon nap and a shortened night sleep. Two principal systems govern the sleep-wake cycle: one actively generates sleep and sleep-related processes and another times sleep within the 24-h day. Either intrinsic abnormalities in these systems or extrinsic disturbances (environmental, drug- or illness-related) can lead to sleep or circadian rhythm disorders.

STATES AND STAGES OF SLEEP

States and stages of human sleep are defined on the basis of characteristic patterns in the electroencephalogram (EEG), the electrooculogram (EOG—a measure of eye-movement activity), and the surface electromyogram (EMG) measured on the chin and neck. The continuous recording of this array of electrophysiologic parameters to define sleep and wakefulness is termed *polysomnography*.

Polysomnographic profiles define two states of sleep: (1) rapid-eye-movement (REM) sleep, and (2) non-rapid-eye-movement (NREM) sleep. NREM sleep is further subdivided into four stages, characterized by increasing arousal threshold and slowing of the cortical EEG. REM sleep is characterized by a low-amplitude, mixed-frequency EEG similar to that of NREM stage 1 sleep. The EOG shows bursts of REM similar to those seen during eyes-open wakefulness. Chin EMG activity

is absent, reflecting the brainstem-mediated muscle atonia that is characteristic of that state.

ORGANIZATION OF HUMAN SLEEP

Normal nocturnal sleep in adults displays a consistent organization from night to night (Fig. 16-1). After sleep onset, sleep usually progresses through NREM stages 1–4 within 45–60 min. Slow-wave sleep (NREM stages 3 and 4) predominates in the first third of the night and comprises 15–25% of total nocturnal sleep time in young adults. The percentage of slow-wave sleep is influenced by several factors, most notably age (see below). Prior sleep deprivation increases the rapidity of sleep onset and both the intensity and amount of slow-wave sleep.

The first REM sleep episode usually occurs in the second hour of sleep. More rapid onset of REM sleep in a young adult (particularly if <30 min) may suggest pathology such as endogenous depression, narcolepsy, circadian rhythm disorders, or drug withdrawal. NREM and REM alternate through the night with an average period of 90–110 min (the "ultradian" sleep cycle). Overall, REM sleep constitutes 20–25% of total sleep, and NREM stages 1 and 2 are 50–60%.

Age has a profound impact on sleep state organization (Fig. 16-1). Slow-wave sleep is most intense and prominent during childhood, decreasing sharply at puberty and across the second and third decades of life. After age 30, there is a progressive decline in the amount of slow-wave sleep, and the amplitude of delta EEG activity comprising slow-wave sleep is profoundly reduced. The depth of slow-wave sleep, as measured by the arousal threshold to auditory stimulation, also decreases with age. In the otherwise healthy older person, slow-wave sleep may be completely absent, particularly in males.

A different age profile exists for REM sleep than for slow-wave sleep. In infancy, REM sleep may comprise 50% of total sleep time, and the percentage is inversely proportional to developmental age. The amount of REM sleep falls off sharply over the first postnatal year as a mature REM-NREM cycle develops; thereafter, REM sleep occupies a relatively constant percentage of total sleep time.

NEUROANATOMY OF SLEEP

Experimental studies in animals have variously implicated the medullary reticular formation, the thalamus, and the basal forebrain in the generation of sleep, while the brainstem reticular formation, the midbrain, the subthalamus, the thalamus, and the basal forebrain have all been suggested to play a role in the generation of wakefulness or EEG arousal.

Current models suggest that the capacity for sleep and wakefulness generation is distributed along an axial "core" of neurons extending from the brainstem rostrally to the basal forebrain. A cluster of γ-aminobutyric acid (GABA) and galaninergic neurons in the ventrolateral preoptic (VLPO) hypothalamus is selectively activated coincident with sleep onset. These neurons project to and inhibit multiple distinct wakefulness centers including the tuberomammilary (histaminergic) nucleus that are important to the ascending arousal system, indicating that the hypothalamic VLPO neurons play a key executive role in sleep regulation.

Specific regions in the pons are associated with the neurophysiologic correlates of REM sleep. Small lesions in the dorsal pons result in the loss of the descending muscle inhibition normally associated with REM sleep; microinjections of the cholinergic agonist carbachol into the pontine reticular formation appear to produce a state with all

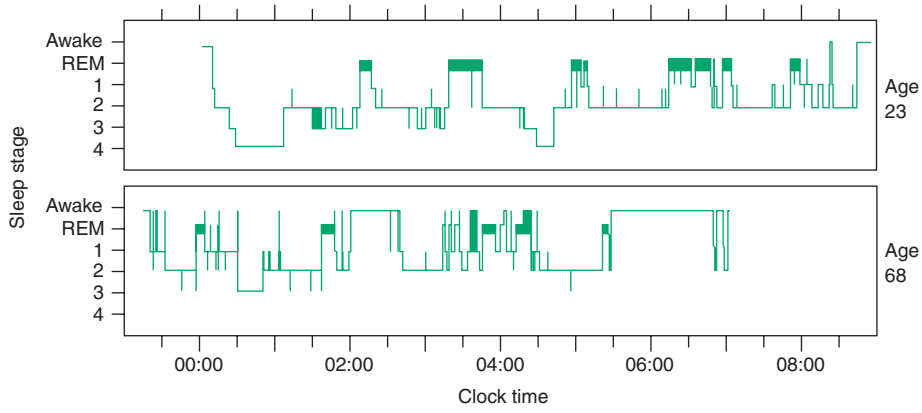

FIGURE 16-1

Stages of REM sleep (solid bars), the four stages of NREM sleep, and wakefulness over the course of the entire night for representative young and older adult men. Characteristic features of sleep in older people include reduction of slow-wave sleep, frequent spontaneous awakenings, early sleep onset, and early morning awakening. *(From the Division of Sleep Medicine, Brigham and Women's Hospital.)*

of the features of REM sleep. These experimental manipulations are mimicked by pathologic conditions in humans and animals. In narcolepsy, for example, abrupt, complete, or partial paralysis (cataplexy) occurs in response to a variety of stimuli. In dogs with this condition, physostigmine, a central cholinesterase inhibitor, increases the frequency of cataplectic attacks, while atropine decreases their frequency. Conversely, in REM sleep behavior disorder (see later), patients suffer from incomplete motor inhibition during REM sleep, resulting in involuntary, occasionally violent movement during REM sleep.

NEUROCHEMISTRY OF SLEEP

Early experimental studies that focused on the raphe nuclei of the brainstem appeared to implicate serotonin as the primary sleep-promoting neurotransmitter, while catecholamines were considered to be responsible for wakefulness. Simple neurochemical models have given way to more complex formulations involving multiple parallel waking systems. Pharmacologic studies suggest that histamine, acetylcholine, dopamine, serotonin, and noradrenaline are all involved in wake promotion. In addition, pontine cholinergic neurotransmission is known to play a role in REM sleep generation. The alerting influence of caffeine implicates adenosine, whereas the hypnotic effect of benzodiazepines and barbiturates suggests a role for endogenous ligands of the $GABA_A$ receptor complex. A newly characterized neuropeptide, hypocretin (orexin), has recently been implicated in the pathophysiology of narcolepsy (see later), but its role in normal sleep regulation remains to be defined.

A variety of sleep-promoting substances have been identified, although it is not known whether they are involved in the endogenous sleep-wake regulatory process. These include prostaglandin D_2, delta sleep–inducing peptide, muramyl dipeptide, interleukin 1, fatty acid primary amides, and melatonin. The hypnotic effect of these substances is commonly limited to NREM or slow-wave sleep, although peptides that increase REM sleep have also been reported. Many putative "sleep factors," including interleukin 1 and prostaglandin D_2, are immunologically active as well, suggesting a link between immune function and sleep-wake states.

PHYSIOLOGY OF CIRCADIAN RHYTHMICITY

The sleep-wake cycle is the most evident of the many 24-h rhythms in humans. Prominent daily variations also occur in endocrine, thermoregulatory, cardiac, pulmonary, renal, gastrointestinal, and neurobehavioral functions. At the molecular level, endogenous circadian rhythmicity is driven by self-sustaining transcriptional/translational feedback loops (Fig. 16-2). In evaluating a daily variation in humans, it is important to distinguish between those rhythmic components passively evoked by periodic environmental or behavioral changes (e.g., the increase in blood pressure and heart rate upon assumption of the upright posture) and those actively driven by an endogenous oscillatory process (e.g., the circadian variation in plasma cortisol that persists under a variety of environmental and behavioral conditions).

While it is now recognized that many peripheral tissues in mammals have circadian clocks that regulate diverse physiologic processes, these independent tissue-specific oscillations are coordinated by a central neural pacemaker located in the suprachiasmatic nuclei (SCN) of the hypothalamus. Bilateral destruction of these nuclei results in a loss of the endogenous circadian rhythm of

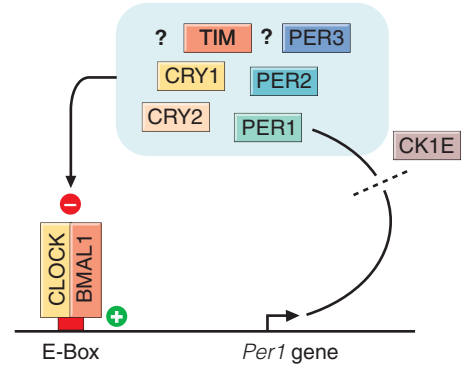

FIGURE 16-2

Model of the molecular feedback loop at the core of the mammalian circadian clock. The positive element of the feedback loop (+) is the transcriptional activation of the *Per1* gene (and probably other clock genes) by a heterodimer of the transcription factors CLOCK and BMAL1 (also called MOP3) bound to an E-box DNA regulatory element. The *Per1* transcript and its product, the clock component PER1 protein, accumulate in the cell cytoplasm. As it accumulates, the PER1 protein is recruited into a multiprotein complex thought to contain other circadian clock component proteins such as cryptochromes (CRYs), Period proteins (PERs), and others. This complex is then transported into the cell nucleus (across the dotted line), where it functions as the negative element in the feedback loop (–) by inhibiting the activity of the CLOCK-BMAL1 transcription factor heterodimer. As a consequence of this action, the concentration of PER1 and other clock proteins in the inhibitory complex falls, allowing CLOCK-BMAL1 to activate transcription of *Per1* and other genes and begin another cycle. The dynamics of the 24-h molecular cycle are controlled at several levels, including regulation of the rate of PER protein degradation by casein kinase-1 epsilon (CK1E). Additional limbs of this genetic regulatory network, omitted for the sake of clarity, are thought to contribute stability. Question marks denote putative clock proteins, such as Timeless (TIM), as yet lacking genetic proof of a role in the mammalian clock mechanism. *(Copyright Charles J. Weitz, Ph.D., Department of Neurobiology, Harvard Medical School.)*

locomotor activity, which can be restored only by transplantation of the same structure from a donor animal. The genetically determined period of this endogenous neural oscillator, which averages ~24.2 h in humans, is normally synchronized to the 24-h period of the environmental light-dark cycle. Small differences in circadian period underlie variations in diurnal preference, with the circadian period shorter in individuals who typically rise early compared to those who typically go to bed late. Entrainment of mammalian circadian rhythms by the light-dark cycle is mediated via the retinohypothalamic tract, a monosynaptic pathway that links specialized, photoreceptive retinal ganglion cells directly to the SCN. Humans are exquisitely sensitive to the resetting effects of light, particularly at the blue end (~460–480 nm) of the visible spectrum.

The timing and internal architecture of sleep are directly coupled to the output of the endogenous circadian pacemaker. Paradoxically, the endogenous circadian rhythms of sleep tendency, sleepiness, and REM sleep propensity all peak near the habitual wake time, just after the nadir of the endogenous circadian temperature cycle, whereas the circadian wake propensity rhythm peaks 1–3 h before the habitual bedtime. These rhythms are thus timed to oppose the homeostatic decline of sleep tendency during the habitual sleep episode and the rise of sleep tendency throughout the usual waking day, respectively. Misalignment of the output of the endogenous circadian pacemaker with the desired sleep-wake cycle can, therefore, induce insomnia, decreased alertness, and impaired performance evident in night-shift workers and airline travelers.

BEHAVIORAL CORRELATES OF SLEEP STATES AND STAGES

Polysomnographic staging of sleep correlates with behavioral changes during specific states and stages. During the transitional state between wakefulness and sleep (stage 1 sleep), subjects may respond to faint auditory or visual signals without "awakening." Memory incorporation is inhibited at the onset of NREM stage 1 sleep, which may explain why individuals aroused from that transitional sleep stage frequently deny having been asleep. Such transitions may intrude upon behavioral wakefulness after sleep deprivation, notwithstanding attempts to remain continuously awake (see Shift-Work Disorder, later in the chapter).

Awakenings from REM sleep are associated with recall of vivid dream imagery >80% of the time. The reliability of dream recall increases with REM sleep episodes occurring later in the night. Imagery may also be reported after NREM sleep interruptions, though these typically lack the detail and vividness of REM sleep dreams. The incidence of NREM sleep dream recall can be increased by selective REM sleep deprivation, suggesting that REM sleep and dreaming per se are not inexorably linked.

PHYSIOLOGIC CORRELATES OF SLEEP STATES AND STAGES

All major physiologic systems are influenced by sleep. Changes in cardiovascular function include a decrease in blood pressure and heart rate during NREM and particularly during slow-wave sleep. During REM sleep, phasic activity (bursts of eye movements) is associated with variability in both blood pressure and heart rate mediated principally by the vagus. Cardiac dysrhythmias may occur selectively during REM sleep. Respiratory function also changes. In comparison to relaxed wakefulness, respiratory rate becomes more regular during NREM sleep (especially slow-wave sleep) and tonic REM sleep and becomes very irregular during phasic REM sleep. Minute ventilation decreases in NREM sleep out of proportion to the decrease in metabolic rate at sleep onset, resulting in a higher P_{CO_2}.

Endocrine function also varies with sleep. Slow-wave sleep is associated with secretion of growth hormone, while sleep in general is associated with augmented secretion of prolactin. Sleep has a complex effect on the secretion of luteinizing hormone (LH): during puberty, sleep is associated with increased LH secretion, whereas sleep in the postpubertal female inhibits LH secretion in the early follicular phase of the menstrual cycle. Sleep onset (and probably slow-wave sleep) is associated with inhibition of thyroid-stimulating hormone and of the adrenocorticotropic hormone–cortisol axis, an effect that is superimposed on the prominent circadian rhythms in the two systems.

The pineal hormone melatonin is secreted predominantly at night in both day- and night-active species, reflecting the direct modulation of pineal activity by the circadian pacemaker through a circuitous neural pathway from the SCN to the pineal gland. Melatonin secretion is not dependent upon the occurrence of sleep, persisting in individuals kept awake at night. In addition, exogenous melatonin increases sleepiness and increases sleep duration when administered to healthy adults attempting to sleep during daylight hours, at a time when endogenous melatonin levels are low. The efficacy of melatonin as a sleep-promoting therapy for patients with insomnia is currently not known.

Sleep is also accompanied by alterations of thermoregulatory function. NREM sleep is associated with an attenuation of thermoregulatory responses to either heat or cold stress, and animal studies of thermosensitive neurons in the hypothalamus document an NREM-sleep-dependent reduction of the thermoregulatory set-point. REM sleep is associated with complete absence of thermoregulatory responsiveness, effectively resulting in functional poikilothermy. However, the potential adverse impact of this failure of thermoregulation is blunted by inhibition of REM sleep by extreme ambient temperatures.

DISORDERS OF SLEEP AND WAKEFULNESS

Approach to the Patient: SLEEP DISORDERS

Patients may seek help from a physician because of one of several symptoms: (1) an acute or chronic inability to initiate or maintain sleep adequately at night (insomnia); (2) chronic fatigue, sleepiness, or tiredness during the day; or (3) a behavioral manifestation associated with sleep itself. Complaints of insomnia or excessive daytime sleepiness should be approached as symptoms (much like fever or pain) of underlying disorders. Knowledge of the differential diagnosis of these presenting complaints is essential to identify any underlying medical disorder. Only then can appropriate treatment, rather than nonspecific approaches (e.g., over-the-counter sleeping aids), be applied. Diagnoses of exclusion, such as primary insomnia, should be made only after other diagnoses have been ruled out. Table 16-1 outlines the diagnostic and therapeutic approach to the patient with a complaint of excessive daytime sleepiness.

A careful history is essential. In particular, the duration, severity, and consistency of the symptoms are important, along with the patient's estimate of the consequences of the sleep disorder on waking function. Information from a friend or family member can be invaluable; some patients may be unaware of, or will underreport, such potentially embarrassing symptoms as heavy snoring or falling asleep while driving.

Patients with excessive sleepiness should be advised to avoid all driving until effective therapy has been achieved.

Completion by the patient of a day-by-day sleep-work-drug log for at least 2 weeks can help the physician understand the nature of the complaint better. Work times and sleep times (including daytime naps and nocturnal awakenings) as well as drug and alcohol use, including caffeine and hypnotics, should be noted each day.

Polysomnography is necessary for the diagnosis of specific disorders such as narcolepsy and sleep apnea and may be of utility in other settings as well. In addition to the three electrophysiologic variables used to define sleep states and stages, the standard clinical polysomnogram includes measures of respiration (respiratory effort, air flow, and oxygen saturation), anterior tibialis EMG, and electrocardiogram.

EVALUATION OF INSOMNIA

Insomnia is the complaint of inadequate sleep; it can be classified according to the nature of sleep disruption and the duration of the complaint. Insomnia is subdivided into difficulty falling asleep (*sleep onset insomnia*), frequent or sustained awakenings (*sleep maintenance insomnia*), early

TABLE 16-1

EVALUATION OF THE PATIENT WITH THE COMPLAINT OF EXCESSIVE DAYTIME SOMNOLENCE

FINDINGS ON HISTORY AND PHYSICAL EXAMINATION	DIAGNOSTIC EVALUATION	DIAGNOSIS	THERAPY
Obesity, snoring, hypertension	Polysomnography with respiratory monitoring	Obstructive sleep apnea	Continuous positive airway pressure; ENT surgery (e.g., uvulopalatopharyngoplasty); dental appliance; pharmacologic therapy (e.g., protriptyline); weight loss
Cataplexy, hypnogogic hallucinations, sleep paralysis, family history	Polysomnography with multiple sleep latency testing	Narcolepsy-cataplexy syndrome	Stimulants (e.g., modafinil, methylphenidate); REM-suppressant antidepressants (e.g., protriptyline); genetic counseling
Restless legs, disturbed sleep, predisposing medical condition (e.g., iron deficiency or renal failure)	Assesment for predisposing medical conditions	Restless legs syndrome	Treatment of predisposing condition, if possible; dopamine agonists (e.g., pramipexole, ropinirole)
Disturbed sleep, predisposing medical conditions (e.g., asthma) and/or predisposing medical therapies (e.g., theophylline)	Sleep-wake diary recording	Insomnias (see text)	Treatment of predisposing condition and/or change in therapy, if possible; behavioral therapy; short-acting benzodiazepine receptor agonist (e.g., zolpidem)

Note: ENT, ears, nose, throat; REM, rapid eye movement; EMG, electromyogram.

morning awakenings (*sleep offset insomnia*), or persistent sleepiness/fatigue despite sleep of adequate duration (*nonrestorative sleep*). Similarly, the duration of the symptom influences diagnostic and therapeutic considerations. An insomnia complaint lasting one to several nights (within a single episode) is termed *transient insomnia* and is typically the result of situational stress or a change in sleep schedule or environment (e.g., jet lag disorder). *Short-term insomnia* lasts from a few days to 3 weeks. Disruption of this duration is usually associated with more protracted stress, such as recovery from surgery or short-term illness. *Long-term insomnia*, or *chronic insomnia*, lasts for months or years and, in contrast with short-term insomnia, requires a thorough evaluation of underlying causes (see below). Chronic insomnia is often a waxing and waning disorder, with spontaneous or stressor-induced exacerbations.

An occasional night of poor sleep, typically in the setting of stress or excitement about external events, is both common and without lasting consequences. However, persistent insomnia can lead to impaired daytime function, injury due to accidents, and the development of major depression. In addition, there is emerging evidence that individuals with chronic insomnia have increased utilization of health care resources, even after controlling for co-morbid medical and psychiatric disorders.

All insomnias can be exacerbated and perpetuated by behaviors that are not conducive to initiating or maintaining sleep. *Inadequate sleep hygiene* is characterized by a behavior pattern prior to sleep or a bedroom environment that is not conducive to sleep. Noise or light in the bedroom can interfere with sleep, as can a bed partner with periodic limb movements during sleep or one who snores loudly. Clocks can heighten the anxiety about the time it has taken to fall asleep. Drugs that act on the central nervous system, large meals, vigorous exercise, or hot showers just before sleep may all interfere with sleep onset. Many individuals participate in stressful work-related activities in the evening, producing a state incompatible with sleep onset. In preference to hypnotic medications, patients should be counseled to avoid stressful activities before bed, develop a soporific bedtime ritual, and to prepare and reserve the bedroom environment for sleeping. Consistent, regular rising times should be maintained daily, including weekends.

PRIMARY INSOMNIA

Many patients with chronic insomnia have no clear, single identifiable underlying cause for their difficulties with sleep. Rather, such patients often have multiple etiologies for their insomnia, which may evolve over the years. In addition, the chief sleep complaint may change over time, with initial insomnia predominating at one point, and multiple awakenings or nonrestorative sleep occurring at other times. Subsyndromal psychiatric disorders (e.g., anxiety and mood complaints), negative conditioning to the sleep environment (psychophysiologic insomnia, see later in the chapter), amplification of the time spent awake (paradoxical insomnia), physiologic hyperarousal, and poor sleep hygiene (see earlier) may all be present. As these processes may be both causes and consequences of chronic insomnia, many individuals will have a progressive course to their symptoms in which the severity is proportional to the chronicity, and much of the complaint may persist even after effective treatment of the initial inciting etiology. Treatment of insomnia is often directed to each of the putative contributing factors: behavior therapies for anxiety and negative conditioning (see later), pharmacotherapy and/or psychotherapy for mood/anxiety disorders, and an emphasis on maintenance of good sleep hygiene.

If insomnia persists after treatment of these contributing factors, empirical pharmacotherapy is often used on a nightly or intermittent basis. A variety of sedative compounds are used for this purpose. Alcohol and antihistamines are the most commonly used nonprescription sleep aids. The former may help with sleep onset but is associated with sleep disruption during the night and can escalate into abuse, dependence, and withdrawal in the predisposed individual. Antihistamines may be of benefit when used intermittently but often produce rapid tolerance and may have multiple side effects (especially anticholinergic), which limit their use, particularly in the elderly. Benzodiazepine-receptor agonists are the most effective and well-tolerated class of medications for insomnia. The broad range of half-lives allows flexibility in the duration of sedative action. The most commonly prescribed agents in this family are zaleplon (5–20 mg), with a half-life of 1–2 h; zolpidem (5–10 mg) and triazolam (0.125–0.25 mg), with half-lives of 2–3 h; eszopiclone (1–3 mg), with a half-life of 5.5–8 h; and temazepam (15–30 mg) and lorazepam (0.5–2 mg), with half-lives of 6–12 h. Generally, side effects are minimal when the dose is kept low and the serum concentration is minimized during the waking hours (by using the shortest-acting, effective agent). Recent data suggest that at least one benzodiazepine receptor agonist (eszopiclone) continues to be effective for 6 months of nightly use. However, longer durations of use have not been evaluated, and it is unclear whether this is true of other agents in this class. Moreover, with even brief continuous use of benzodiazepine-receptor agonists, rebound insomnia can occur upon discontinuation. The likelihood of rebound insomnia and tolerance can be minimized by short durations of treatment, intermittent use, or gradual tapering of the dose. For acute insomnia, nightly use of a benzodiazepine receptor agonist for a maximum of 2–4 weeks is advisable. For chronic insomnia, intermittent use is recommended, unless the consequences

of untreated insomnia outweigh concerns regarding chronic use. Benzodiazepine receptor agonists should be avoided, or used very judiciously, in patients with a history of substance or alcohol abuse. The heterocyclic antidepressants (trazodone, amitriptyline, and doxepin) are the most commonly prescribed alternatives to benzodiazepine receptor agonists due to their lack of abuse potential and lower cost. Trazodone (25–100 mg) is used more commonly than the tricyclic antidepressants as it has a much shorter half-life (5–9 h), has much less anticholinergic activity (sparing patients, particularly the elderly, constipation, urinary retention, and tachycardia), is associated with less weight gain, and is much safer in overdose. The risk of priapism is small (~1 in 10,000).

Psychophysiologic Insomnia

Persistent *psychophysiologic insomnia* is a behavioral disorder in which patients are preoccupied with a perceived inability to sleep adequately at night. This sleep disorder begins like any other acute insomnia; however, the poor sleep habits and sleep-related anxiety ("insomnia phobia") persist long after the initial incident. Such patients become hyperaroused by their own efforts to sleep or by the sleep environment, and the insomnia becomes a conditioned or learned response. Patients may be able to fall asleep more easily at unscheduled times (when not trying) or outside the home environment. Polysomnographic recording in patients with psychophysiologic insomnia reveals an objective sleep disturbance, often with an abnormally long sleep latency; frequent nocturnal awakenings; and an increased amount of stage 1 transitional sleep. Rigorous attention should be paid to improving sleep hygiene, correction of counterproductive, arousing behaviors before bedtime, and minimizing exaggerated beliefs regarding the negative consequences of insomnia. Behavioral therapies are the treatment modality of choice, with intermittent use of medications. When patients are awake for >20 min, they should read or perform other relaxing activities to distract themselves from insomnia-related anxiety. In addition, bedtime and wake time should be scheduled to restrict time in bed to be equal to their perceived total sleep time. This will generally produce sleep deprivation, greater sleep drive, and, eventually, better sleep. Time in bed can then be gradually expanded. In addition, methods directed toward producing relaxation in the sleep setting (e.g., meditation, muscle relaxation) are encouraged.

Adjustment Insomnia (Acute Insomnia)

This typically develops after a change in the sleeping environment (e.g., in an unfamiliar hotel or hospital bed) or before or after a significant life event, such as a change of occupation, loss of a loved one, illness, or anxiety over a deadline or examination. Increased sleep latency, frequent awakenings from sleep, and early morning awakening can all occur. Recovery is generally rapid, usually within a few weeks. Treatment is symptomatic, with intermittent use of hypnotics and resolution of the underlying stress. *Altitude insomnia* describes a sleep disturbance that is a common consequence of exposure to high altitude. Periodic breathing of the Cheyne-Stokes type occurs during NREM sleep about half the time at high altitude, with restoration of a regular breathing pattern during REM sleep. Both hypoxia and hypocapnia are thought to be involved in the development of periodic breathing. Frequent awakenings and poor quality sleep characterize altitude insomnia, which is generally worse on the first few nights at high altitude but may persist. Treatment with acetazolamide can decrease time spent in periodic breathing and substantially reduce hypoxia during sleep.

COMORBID INSOMNIA

Insomnia Associated with Mental Disorders

Approximately 80% of patients with psychiatric disorders describe sleep complaints. There is considerable heterogeneity, however, in the nature of the sleep disturbance both between conditions and among patients with the same condition. *Depression* can be associated with sleep onset insomnia, sleep maintenance insomnia, or early morning wakefulness. However, hypersomnia occurs in some depressed patients, especially adolescents and those with either bipolar or seasonal (fall/winter) depression (Chap. 49). Indeed, sleep disturbance is an important vegetative sign of depression and may commence before any mood changes are perceived by the patient. Consistent polysomnographic findings in depression include decreased REM sleep latency, lengthened first REM sleep episode, and shortened first NREM sleep episode; however, these findings are not specific for depression, and the extent of these changes varies with age and symptomatology. Depressed patients also show decreased slow-wave sleep and reduced sleep continuity.

In *mania* and *hypomania*, sleep latency is increased and total sleep time can be reduced. Patients with *anxiety disorders* tend not to show the changes in REM sleep and slow-wave sleep seen in endogenously depressed patients. *Chronic alcoholics* lack slow-wave sleep, have decreased amounts of REM sleep (as an acute response to alcohol), and have frequent arousals throughout the night. This is associated with impaired daytime alertness. The sleep of chronic alcoholics may remain disturbed for years after discontinuance of alcohol usage. Sleep architecture and physiology are disturbed in *schizophrenia* (with a decreased amount of stage 4 sleep and a lack of augmentation of REM sleep following REM sleep deprivation); chronic schizophrenics often show day-night reversal, sleep fragmentation, and insomnia.

Insomnia Associated with Neurologic Disorders

A variety of neurologic diseases result in sleep disruption through both indirect, nonspecific mechanisms (e.g., pain in cervical spondylosis or low back pain) or by impairment of central neural structures involved in the generation and control of sleep itself. For example, *dementia* from any cause has long been associated with disturbances in the timing of the sleep-wake cycle, often characterized by nocturnal wandering and an exacerbation of symptomatology at night (so-called sundowning).

Epilepsy may rarely present as a sleep complaint (Chap. 20). Often the history is of abnormal behavior, at times with convulsive movements during sleep. The differential diagnosis includes REM sleep behavior disorder, sleep apnea syndrome, and periodic movements of sleep (see earlier). Diagnosis requires nocturnal polysomnography with a full EEG montage. Other neurologic diseases associated with abnormal movements, such as *Parkinson's disease*, *hemiballismus*, *Huntington's chorea*, and *Tourette syndrome* (Chaps. 24 and 25), are also associated with disrupted sleep, presumably through secondary mechanisms. However, the abnormal movements themselves are greatly reduced during sleep. Headache syndromes (*migraine* or *cluster headache*) may show sleep-associated exacerbations (Chap. 6) by unknown mechanisms.

Fatal familial insomnia is a rare hereditary disorder caused by degeneration of anterior and dorsomedial nuclei of the thalamus. Insomnia is a prominent early symptom. Patients develop progressive autonomic dysfunction, followed by dysarthria, myoclonus, coma, and death. The pathogenesis is a mutation in the prion gene (Chap. 38).

Insomnia Associated with Other Medical Disorders

A number of medical conditions are associated with disruptions of sleep. The association is frequently nonspecific, e.g., sleep disruption due to chronic pain from rheumatologic disorders. Attention to this association is important in that sleep-associated symptoms are often the presenting or most bothersome complaint. Treatment of the underlying medical problem is the most useful approach. Sleep disruption can also result from the use of medications such as glucocorticoids (see later).

One prominent association is between sleep disruption and *asthma*. In many asthmatics there is a prominent daily variation in airway resistance that results in marked increases in asthmatic symptoms at night, especially during sleep. In addition, treatment of asthma with theophylline-based compounds, adrenergic agonists, or glucocorticoids can independently disrupt sleep. When sleep disruption is a side effect of asthma treatment, inhaled glucocorticoids (e.g., beclomethasone) that do not disrupt sleep may provide a useful alternative.

Cardiac ischemia may also be associated with sleep disruption. The ischemia itself may result from increases in sympathetic tone as a result of sleep apnea. Patients may present with complaints of nightmares or vivid, disturbing dreams, with or without awareness of the more classic symptoms of angina or of the sleep disordered breathing. Treatment of the sleep apnea may substantially improve the angina and the nocturnal sleep quality. *Paroxysmal nocturnal dyspnea* can also occur as a consequence of sleep-associated cardiac ischemia that causes pulmonary congestion exacerbated by the recumbent posture.

Chronic obstructive pulmonary disease is also associated with sleep disruption, as is *cystic fibrosis*, *menopause*, *hyperthyroidism*, *gastroesophageal reflux*, *chronic renal failure*, and *liver failure*.

Medication-, Drug-, or Alcohol-Dependent Insomnia

Disturbed sleep can result from ingestion of a wide variety of agents. Caffeine is perhaps the most common pharmacologic cause of insomnia. It produces increased latency to sleep onset, more frequent arousals during sleep, and a reduction in total sleep time for up to 8–14 h after ingestion. Even small amounts of coffee can significantly disturb sleep in some patients; therefore, a 1- to 2-month trial without caffeine should be attempted in patients with these symptoms. Similarly, alcohol and nicotine can interfere with sleep, despite the fact that many patients use them to relax and promote sleep. Although alcohol can increase drowsiness and shorten sleep latency, even moderate amounts of alcohol increase awakenings in the second half of the night. In addition, alcohol ingestion prior to sleep is contraindicated in patients with sleep apnea because of the inhibitory effects of alcohol on upper airway muscle tone. Acutely, amphetamines and cocaine suppress both REM sleep and total sleep time, which return to normal with chronic use. Withdrawal leads to a REM sleep rebound. A number of prescribed medications can produce insomnia. Antidepressants, sympathomimetics, and glucocorticoids are common causes. In addition, severe rebound insomnia can result from the acute withdrawal of hypnotics, especially following the use of high doses of benzodiazepines with a short half-life. For this reason, hypnotic doses should be low to moderate and prolonged drug tapering is encouraged.

RESTLESS LEGS SYNDROME (RLS)

Patients with this sensory-motor disorder report an irresistible urge to move the legs, or sometimes the upper extremities that is often associated with a creepy-crawling or aching dysesthesias deep within the affected limbs. For most patients with RLS, the dysesthesias and restlessness are much worse in the evening or night compared to the daytime and frequently interferes with the ability to fall

asleep. The symptoms appear with inactivity and are temporarily relieved by movement. In contrast, paresthesias secondary to peripheral neuropathy persist with activity. The severity of this chronic disorder may wax and wane over time and can be exacerbated by sleep deprivation, caffeine, alcohol, serotonergic antidepressants, and pregnancy. The prevalence is 1–5% of young to middle-aged adults and 10–20% of those >60 years. There appear to be important differences in RLS prevalence among racial groups, with higher prevalence in those of Northern European ancestry. Roughly one-third of patients (particularly those with an early age of onset) will have multiple affected family members. At least three separate chromosomal loci have been identified in familial RLS, though no gene has been identified to date. Iron deficiency and renal failure may cause RLS, which is then considered secondary RLS. The symptoms of RLS are exquisitely sensitive to dopaminergic drugs (e.g., pramipexole 0.25–0.5 mg q8PM or ropinirole 0.5–4.0 mg q8PM), which are the treatments of choice. Opiods, benzodiazepines, and gabapentin may also be of therapeutic value. Most patients with restless legs also experience periodic limb movements of sleep, although the reverse is not the case.

PERIODIC LIMB MOVEMENT DISORDER (PLMD)

Periodic limb movements of sleep (PLMS), previously known as *nocturnal myoclonus*, consists of stereotyped, 0.5- to 5.0-s extensions of the great toe and dorsiflexion of the foot, which recur every 20–40 s during NREM sleep, in episodes lasting from minutes to hours, as documented by bilateral surface EMG recordings of the anterior tibialis on polysomnography. PLMS is the principal objective polysomnographic finding in 17% of patients with insomnia and 11% of those with excessive daytime somnolence (**Fig. 16-3**). It is often unclear whether it is an incidental finding or the cause of disturbed sleep. When deemed to be the latter, PLMS is called PLMD. PLMS occurs in a wide variety of sleep disorders (including narcolepsy, sleep apnea, REM sleep behavior disorder, and various forms of insomnia) and may be associated with frequent arousals and an increased number of sleep-stage transitions. The pathophysiology is not well understood, though individuals with high spinal transections can exhibit periodic leg movements during sleep, suggesting the existence of a spinal generator. Treatment options include dopaminergic medications or benzodiazepines.

EVALUATION OF DAYTIME SLEEPINESS

Daytime impairment due to sleep loss may be difficult to quantify for several reasons. First, sleepiness is not necessarily proportional to subjectively assessed sleep deprivation. In obstructive sleep apnea, for example, the repeated brief interruptions of sleep associated with resumption of respiration at the end of apneic episodes

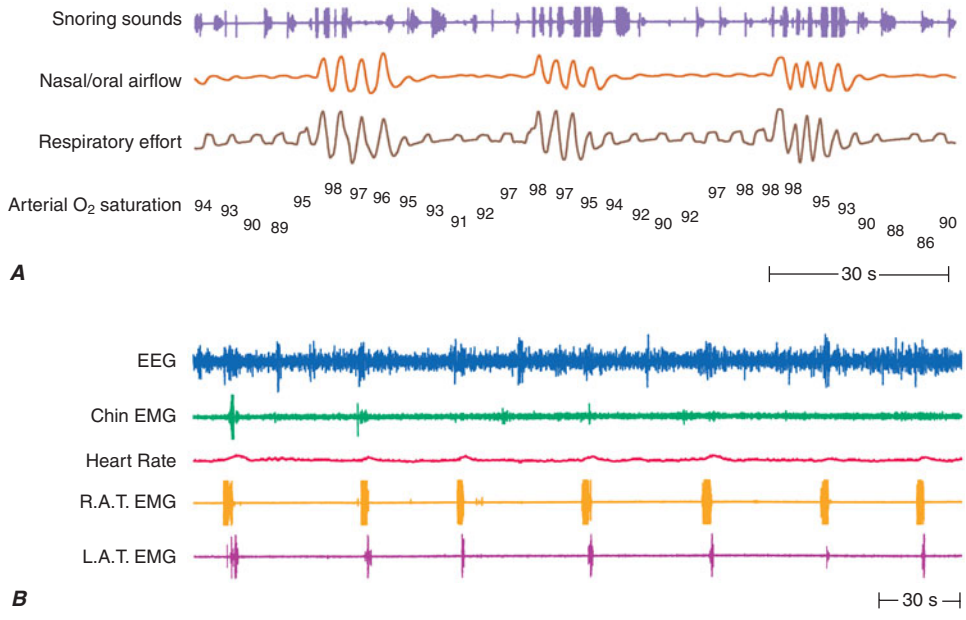

FIGURE 16-3

Polysomnographic recordings of (*A*) obstructive sleep apnea and (*B*) periodic limb movement of sleep. Note the snoring and reduction in air flow in the presence of continued respiratory effort, associated with the subsequent oxygen desaturation (upper panel). Periodic limb movements occur with a relatively constant intermovement interval and are associated with changes in the EEG and heart rate acceleration (lower panel). R.A.T., right anterior tibialis; L.A.T., left anterior tibialis. *(From the Division of Sleep Medicine, Brigham and Women's Hospital.)*

result in daytime sleepiness, despite the fact that the patient may be unaware of the sleep fragmentation. Second, subjective descriptions of waking impairment vary from patient to patient. Patients may describe themselves as "sleepy," "fatigued," or "tired" and may have a clear sense of the meaning of those terms, while others may use the same terms to describe a completely different condition. Third, sleepiness, particularly when profound, may affect judgment in a manner analogous to ethanol, such that subjective awareness of the condition and the consequent cognitive and motor impairment is reduced. Finally, patients may be reluctant to admit that sleepiness is a problem, both because they are generally unaware of what constitutes normal alertness and because sleepiness is generally viewed pejoratively, ascribed more often to a deficit in motivation than to an inadequately addressed physiologic sleep need.

Specific questioning about the occurrence of sleep episodes during normal waking hours, both intentional and unintentional, is necessary to determine the extent of the adverse effects of sleepiness on a patient's daytime function. Specific areas to be addressed include the occurrence of inadvertent sleep episodes while driving or in other safety-related settings, sleepiness while at work or school (and the relationship of sleepiness to work and school performance), and the effect of sleepiness on social and family life. Driving is particularly hazardous for patients with increased sleepiness. Reaction time is equally impaired by 24 h of sleep loss as by a blood alcohol level of 0.10 g/dL. More than half of Americans admit to driving when drowsy. An estimated 250,000 motor vehicle crashes per year are due to drowsy drivers, thus causing 20% of all serious crash injuries. Drowsy driving legislation, aimed at improving education of all drivers about the hazards of driving drowsy and establishing sanctions comparable to those for drunk driving, is pending in several states. Screening for sleep disorders, provision of an adequate number of safe highway rest areas, maintenance of unobstructed shoulder rumble strips, and strict enforcement and compliance monitoring of hours-of-service policies are needed to reduce the risk of sleep-related transportation crashes. Evidence for significant daytime impairment [in association either with the diagnosis of a primary sleep disorder, such as narcolepsy or sleep apnea, or with imposed or self-selected sleep-wake schedules (see Shift-Work Disorder, later)] raises the issue of the physician's responsibility to notify motor vehicle licensing authorities of the increased risk of sleepiness-related vehicle accidents. As with epilepsy, legal requirements vary from state to state, and existing legal precedents do not provide a consistent interpretation of the balance between the physician's responsibility and the patient's right to privacy. At a minimum, physicians should document discussions with the patient regarding the increased risk of operating a vehicle, as well as a recommendation that driving be suspended until successful treatment or a schedule modification can be instituted.

The distinction between fatigue and sleepiness can be useful in the differentiation of patients with complaints of fatigue or tiredness in the setting of disorders such as fibromyalgia, chronic fatigue syndrome (Chap. 47), or endocrine deficiencies such as hypothyroidism or Addison's disease. Although patients with these disorders can typically distinguish their daytime symptoms from the sleepiness that occurs with sleep deprivation, substantial overlap can occur. This is particularly true when the primary disorder also results in chronic sleep disruption (e.g., sleep apnea in hypothyroidism) or in abnormal sleep (e.g., fibromyalgia).

Although clinical evaluation of the complaint of excessive sleepiness is usually adequate, objective quantification is sometimes necessary. Assessment of daytime functioning as an index of the adequacy of sleep can be made with the multiple sleep latency test (MSLT), which involves repeated measurement of sleep latency (time to onset of sleep) under standardized conditions during a day following quantified nocturnal sleep. The average latency across four to six tests (administered every 2 h across the waking day) provides an objective measure of daytime sleep tendency. Disorders of sleep that result in pathologic daytime somnolence can be reliably distinguished with the MSLT. In addition, the multiple measurements of sleep onset may identify direct transitions from wakefulness to REM sleep that are suggestive of specific pathologic conditions (e.g., narcolepsy).

NARCOLEPSY

Narcolepsy is both a disorder of the ability to sustain wakefulness voluntarily and a disorder of REM sleep regulation (Table 16-2). The classic "narcolepsy tetrad" consists of excessive daytime somnolence plus three specific symptoms related to an intrusion of REM sleep characteristics (e.g., muscle atonia, vivid dream imagery) into the transition between wakefulness and sleep:

TABLE 16-2

PREVALENCE OF SYMPTOMS IN NARCOLEPSY

SYMPTOM	PREVALENCE, %
Excessive daytime somnolence	100
Disturbed sleep	87
Cataplexy	76
Hypnagogic hallucinations	68
Sleep paralysis	64
Memory problems	50

Source: *Modified from TA Roth, L Merlotti in SA Burton et al (eds), Narcolepsy 3rd International Symposium: Selected Symposium Proceedings, Chicago, Matrix Communications, 1989.*

(1) sudden weakness or loss of muscle tone without loss of consciousness, often elicited by emotion (cataplexy); (2) hallucinations at sleep onset (hypnogogic hallucinations) or upon awakening (hypnopompic hallucinations); and (3) muscle paralysis upon awakening (sleep paralysis). The severity of cataplexy varies, as patients may have two to three attacks per day or per decade. Some patients with objectively confirmed narcolepsy (see later) may show no evidence of cataplexy. In those with cataplexy, the extent and duration of an attack may also vary, from a transient sagging of the jaw lasting a few seconds to rare cases of flaccid paralysis of the entire voluntary musculature for up to 20–30 min. Symptoms of narcolepsy typically begin in the second decade, although the onset ranges from ages 5–50. Once established, the disease is chronic without remissions. Secondary forms of narcolepsy have been described (e.g., after head trauma).

Narcolepsy affects about 1 in 4000 people in the United States and appears to have a genetic basis. Recently, several convergent lines of evidence suggest that the hypothalamic neuropeptide hypocretin (orexin) is involved in the pathogenesis of narcolepsy: (1) a mutation in the hypocretin receptor 2 gene has been associated with canine narcolepsy; (2) hypocretin "knockout" mice that are genetically unable to produce this neuropeptide exhibit behavioral and electrophysiologic features resembling human narcolepsy; and (3) cerebrospinal fluid levels of hypocretin are reduced in most patients who have narcolepsy with cataplexy. The inheritance pattern of narcolepsy in humans is more complex than in the canine model. However, almost all narcoleptics with cataplexy are positive for HLA DQB1*0602, suggesting that an autoimmune process may be responsible.

Diagnosis

The diagnostic criteria continue to be a matter of debate. Certainly, objective verification of excessive daytime somnolence, typically with MSLT mean sleep latencies <8 min, is an essential if nonspecific diagnostic feature. Other conditions that cause excessive sleepiness, such as sleep apnea or chronic sleep deprivation, must be rigorously excluded. The other objective diagnostic feature of narcolepsy is the presence of REM sleep in at least two of the naps during the MSLT. Abnormal regulation of REM sleep is also manifested by the appearance of REM sleep immediately or within minutes after sleep onset in 50% of narcoleptic patients, a rarity in unaffected individuals maintaining a conventional sleep-wake schedule. The REM-related symptoms of the classic narcolepsy tetrad are variably present. There is increasing evidence that narcoleptics with cataplexy (one-half to two-thirds of patients) may represent a more homogeneous group than those without this symptom. However, a history of cataplexy can be difficult to establish reliably. Hypnogogic and hypnopompic hallucinations and sleep paralysis are often found in nonnarcoleptic individuals and may be present in only one-half of narcoleptics. Nocturnal sleep disruption is commonly observed in narcolepsy but is also a nonspecific symptom. Similarly, a history of "automatic behavior" during wakefulness (a trancelike state during which simple motor behaviors persist) is not specific for narcolepsy and serves principally to corroborate the presence of daytime somnolence.

℞ Treatment: NARCOLEPSY

The treatment of narcolepsy is symptomatic. Somnolence is treated with wake-promoting therapeutics. Modafinil is now the drug of choice, principally because it is associated with fewer side effects than older stimulants and has a long half-life; 200–400 mg is given as a single daily dose. Older drugs such as methylphenidate (10 mg bid to 20 mg qid) or dextroamphetamine (10 mg bid) are still used as alternatives, particularly in refractory patients. These latter medications are now available in slow-release formulations, extending their duration of action and allowing once daily dosing.

Treatment of the REM-related phenomena cataplexy, hypnogogic hallucinations, and sleep paralysis requires the potent REM sleep suppression produced by antidepressant medications. The tricyclic antidepressants [e.g., protriptyline (10–40 mg/d) and clomipramine (25–50 mg/d)] and the selective serotonin reuptake inhibitors (SSRIs) [e.g., fluoxetine (10–20 mg/d)] are commonly used for this purpose. Efficacy of the antidepressants is limited largely by anticholinergic side effects (tricyclics) and by sleep disturbance and sexual dysfunction (SSRIs). Alternately, gamma hydroxybutyrate (GHB), given at bed time, and 4 h later, is effective in reducing daytime cataplectic episodes. Adequate nocturnal sleep time and planned daytime naps (when possible) are important preventative measures.

SLEEP APNEA SYNDROMES

Respiratory dysfunction during sleep is a common, serious cause of excessive daytime somnolence as well as of disturbed nocturnal sleep. An estimated 2–5 million individuals in the United States have a reduction or cessation of breathing for 10–150 s, from thirty to several hundred times every night during sleep. These episodes may be due to either an occlusion of the airway (*obstructive sleep apnea*), absence of respiratory effort (*central sleep apnea*), or a combination of these factors (*mixed sleep apnea*) (Fig. 16-3). Failure to recognize and treat these conditions

appropriately may lead to impairment of daytime alertness, increased risk of sleep-related motor vehicle accidents, hypertension and other serious cardiovascular complications, and increased mortality. Sleep apnea is particularly prevalent in overweight men and in the elderly, yet it is estimated to remain undiagnosed in 80–90% of affected individuals. This is unfortunate since effective treatments are available.

PARASOMNIAS

The term *parasomnia* refers to abnormal behaviors or experiences that arise from or occur during sleep. A continuum of parasomnias arises from NREM sleep, from brief confusional arousals to sleepwalking and night terrors. The presenting complaint is usually related to the behavior itself, but the parasomnias can disturb sleep continuity or lead to mild impairments in daytime alertness. Two main parasomnias occur in REM sleep: REM sleep behavior disorder (RBD), which will be described later, and nightmare disorder.

Sleepwalking (Somnambulism)

Patients affected by this disorder carry out automatic motor activities that range from simple to complex. Individuals may walk, urinate inappropriately, eat, or exit from the house while remaining only partially aware. Full arousal may be difficult, and individuals may rarely respond to attempted awakening with agitation or even violence. Sleepwalking arises from stage 3 or 4 NREM sleep, usually in the first 2 hours of the night, and is most common in children and adolescents, when these sleep stages are most robust. Episodes are usually isolated but may be recurrent in 1–6% of patients. The cause is unknown, though it has a familial basis in roughly one-third of cases.

Sleep Terrors

This disorder, also called *pavor nocturnus*, occurs primarily in young children during the first several hours after sleep onset, in stages 3 and 4 of NREM sleep. The child suddenly screams, exhibiting autonomic arousal with sweating, tachycardia, and hyperventilation. The individual may be difficult to arouse and rarely recalls the episode on awakening in the morning. Parents are usually reassured to learn that the condition is self-limited and benign and that no specific therapy is indicated. Both sleep terrors and sleepwalking represent abnormalities of arousal. In contrast, *nightmares* occur during REM sleep and cause full arousal, with intact memory for the unpleasant episode.

Sleep Bruxism

Bruxism is an involuntary, forceful grinding of teeth during sleep that affects 10–20% of the population. The patient is usually unaware of the problem. The typical age of onset is 17–20 years, and spontaneous remission usually occurs by 40 years. Sex distribution appears to be equal. In many cases, the diagnosis is made during dental examination, damage is minor, and no treatment is indicated. In more severe cases, treatment with a rubber tooth guard is necessary to prevent disfiguring tooth injury. Stress management or, in some cases, biofeedback can be useful when bruxism is a manifestation of psychological stress. There are anecdotal reports of benefit using benzodiazepines.

Sleep Enuresis

Bedwetting, like sleepwalking and night terrors, is another parasomnia that occurs during sleep in the young. Before age 5 or 6, nocturnal enuresis should probably be considered a normal feature of development. The condition usually improves spontaneously by puberty, has a prevalence in late adolescence of 1–3%, and is rare in adulthood. In older patients with enuresis a distinction must be made between primary and secondary enuresis, the latter being defined as bedwetting in patients who have previously been fully continent for 6–12 months. Treatment of primary enuresis is reserved for patients of appropriate age (>5 or 6 years) and consists of bladder training exercises and behavioral therapy. Urologic abnormalities are more common in primary enuresis and must be assessed by urologic examination. Important causes of secondary enuresis include emotional disturbances, urinary tract infections or malformations, cauda equina lesions, epilepsy, sleep apnea, and certain medications. Symptomatic pharmacotherapy is usually accomplished with desmopressin (0.2 mg qhs), oxybutynin chloride (5–10 mg qhs) or imipramine (10–50 mg qhs).

Miscellaneous Parasomnias

Other clinical entities may be characterized as a parasomnia or a sleep-related movement disorder in that they occur selectively during sleep and are associated with some degree of sleep disruption. Examples include *jactatio capitis nocturna* (nocturnal headbanging, rhythmic movement disorder), confusional arousals, sleep-related eating disorder, and nocturnal leg cramps.

REM Sleep Behavior Disorder (RBD)

RBD is a rare condition that is distinct from other parasomnias in that it occurs during REM sleep. It primarily afflicts men of middle age or older, many of whom have an existing, or developing, neurologic disease. Approximately one-half of patients with RBD will develop Parkinson's disease (Chap. 24) within 10–20 years. Presenting symptoms consist of agitated or violent behavior

during sleep, as reported by a bed partner. In contrast to typical somnambulism, injury to the patient or bed partner is not uncommon, and, upon awakening, the patient reports vivid, often unpleasant, dream imagery. The principal differential diagnosis is nocturnal seizures, which can be excluded with polysomnography. In RBD, seizure activity is absent on the EEG, and disinhibition of the usual motor atonia is observed in the EMG during REM sleep, at times associated with complex motor behaviors. The pathogenesis is unclear, but damage to brainstem areas mediating descending motor inhibition during REM sleep may be responsible. In support of this hypothesis are the remarkable similarities between RBD and the sleep of animals with bilateral lesions of the pontine tegmentum in areas controlling REM sleep motor inhibition. Treatment with clonazepam (0.5–1.0 mg qhs) provides sustained improvement in almost all reported cases.

CIRCADIAN RHYTHM SLEEP DISORDERS

A subset of patients presenting with either insomnia or hypersomnia may have a disorder of sleep *timing* rather than sleep *generation*. Disorders of sleep timing can be either organic (i.e., due to an intrinsic defect in the circadian pacemaker or its input from entraining stimuli) or environmental (i.e., due to a disruption of exposure to entraining stimuli from the environment). Regardless of etiology, the symptoms reflect the influence of the underlying circadian pacemaker on sleep-wake function. Thus, effective therapeutic approaches should aim to entrain the oscillator at an appropriate phase.

Jet Lag Disorder

More than 60 million persons experience transmeridian air travel annually, which is often associated with excessive daytime sleepiness, sleep onset insomnia, and frequent arousals from sleep, particularly in the latter half of the night. Gastrointestinal discomfort is common. The syndrome is transient, typically lasting 2–14 d depending on the number of time zones crossed, the direction of travel, and the traveler's age and phase-shifting capacity. Travelers who spend more time outdoors reportedly adapt more quickly than those who remain in hotel rooms, presumably due to bright (outdoor) light exposure. Avoidance of antecedent sleep loss and obtaining nap sleep on the afternoon prior to overnight travel greatly reduces the difficulty of extended wakefulness. Laboratory studies suggest that sub-milligram doses of the pineal hormone melatonin can enhance sleep efficiency, but only if taken when endogenous melatonin concentrations are low (i.e., during biologic daytime), and that melatonin may induce phase shifts in human rhythms. A large-scale clinical trial evaluating the safety and efficacy of melatonin as a treatment for jet lag disorder and other circadian sleep disorders is needed.

Shift-Work Disorder

More than 7 million workers in the United States regularly work at night, either on a permanent or rotating schedule. In addition, each week millions more elect to remain awake at night to meet deadlines, drive long distances, or participate in recreational activities. This results in both sleep loss and misalignment of the circadian rhythm with respect to the sleep-wake cycle.

Studies of regular night-shift workers indicate that the circadian timing system usually fails to adapt successfully to such inverted schedules. This leads to a misalignment between the desired work-rest schedule and the output of the pacemaker and in disturbed daytime sleep in most individuals. Sleep deprivation, increased length of time awake prior to work, and misalignment of circadian phase produce decreased alertness and performance, increased reaction time, and increased risk of performance lapses, thereby resulting in greater safety hazards among night workers and other sleep-deprived individuals. Sleep disturbance nearly doubles the risk of a fatal work accident. Additional problems include higher rates of cancer and of cardiac, gastrointestinal, and reproductive disorders in chronic night-shift workers.

Sleep onset is associated with marked attenuation in perception of both auditory and visual stimuli and lapses of consciousness. The sleepy individual may thus attempt to perform routine and familiar motor tasks during the transition state between wakefulness and sleep (stage 1 sleep) in the absence of adequate processing of sensory input from the environment. Motor vehicle operators are especially vulnerable to sleep-related accidents since the sleep-deprived driver or operator often fails to heed the warning signs of fatigue. Such attempts to override the powerful biologic drive for sleep by the sheer force of will can yield a catastrophic outcome when sleep processes intrude involuntarily upon the waking brain. Such sleep-related attentional failures typically last only seconds but are known on occasion to persist for longer durations. These frequent brief intrusions of stage 1 sleep into behavioral wakefulness are a major component of the impaired psychomotor performance seen with sleepiness. There is a significant increase in the risk of sleep-related, fatal-to-the-driver highway crashes in the early morning and late afternoon hours, coincident with bimodal peaks in the daily rhythm of sleep tendency.

Medical housestaff constitute another group of workers at risk for accidents and other adverse consequences of lack of sleep and misalignment of the circadian rhythm. Recent research has demonstrated that the practice of scheduling interns and residents to work shifts of 30 consecutive hours both doubles the risk of

attentional failures among intensive care unit interns working at night and significantly increases the risk of serious medical errors in intensive care units. Moreover, working for >24 h consecutively increases the risk of needlestick injuries and more than doubles the risk of motor vehicle crashes on the commute home. Some 20% of hospital interns report making a fatigue-related mistake that injured a patient, and 5% admit making a mistake that results in the death of a patient.

From 5–10% of individuals scheduled to work at night or in the early morning hours have much greater than average difficulties remaining awake during night work and sleeping during the day; these individuals are diagnosed with chronic and severe shift-work disorder (SWD). Patients with this disorder have a level of excessive sleepiness during night work and insomnia during day sleep that the physician judges to be clinically significant; the condition is associated with an increased risk of sleep-related accidents and with some of the illnesses associated with night-shift work. Patients with chronic and severe SWD are profoundly sleepy at night. In fact, their sleep latencies during night work average just 2 min, comparable to mean sleep latency durations of patients with narcolepsy or severe daytime sleep apnea.

℞ Treatment: SHIFT-WORK DISORDER

Caffeine is frequently used to promote wakefulness. However, it cannot forestall sleep indefinitely, and it does not shield users from sleep-related performance lapses. Postural changes, exercise, and strategic placement of nap opportunities can sometimes temporarily reduce the risk of fatigue-related performance lapses. Properly timed exposure to bright light can facilitate rapid adaptation to night-shift work.

While many techniques (e.g., light treatment) used to facilitate adaptation to night shift work may help patients with this disorder, modafinil is the only therapeutic intervention that has ever been evaluated as a treatment for this specific patient population. Modafinil (200 mg, taken 30–60 min before the start of each night shift) is approved by the U.S. Food and Drug Administration as a treatment for the excessive sleepiness during night work in patients with SWD. Although treatment with modafinil significantly increases sleep latency and reduces the risk of lapses of attention during night work, SWD patients remain excessively sleepy at night, even while being treated with modafinil.

Safety programs should promote education about sleep and increase awareness of the hazards associated with night work. The goal should be to minimize both sleep deprivation and circadian disruption. Work schedules should be designed to minimize: (1) exposure to night work, (2) the frequency of shift rotation so that shifts do not rotate more than once every 2–3 weeks, (3) the number of consecutive night shifts, and (4) the duration of night shifts. Shift durations of >16 h should be universally recognized as increasing the risk of sleep-related errors and performance lapses to a level that is unacceptable in nonemergency circumstances.

Delayed Sleep Phase Disorder

Delayed sleep phase disorder is characterized by: (1) reported sleep onset and wake times intractably later than desired, (2) actual sleep times at nearly the same clock hours daily, and (3) essentially normal all-night polysomnography except for delayed sleep onset. Patients exhibit an abnormally delayed endogenous circadian phase, with the temperature minimum during the constant routine occurring later than normal. This delayed phase could be due to: (1) an abnormally long, genetically determined intrinsic period of the endogenous circadian pacemaker; (2) an abnormally reduced phase-advancing capacity of the pacemaker; or (3) an irregular prior sleep-wake schedule, characterized by frequent nights when the patient chooses to remain awake well past midnight (for social, school, or work reasons). In most cases, it is difficult to distinguish among these factors, since patients with an abnormally long intrinsic period are more likely to "choose" such late-night activities because they are unable to sleep at that time. Patients tend to be young adults. This self-perpetuating condition can persist for years and does not usually respond to attempts to reestablish normal bedtime hours. Treatment methods involving bright-light phototherapy during the morning hours or melatonin administration in the evening hours show promise in these patients, although the relapse rate is high.

Advanced Sleep Phase Disorder

Advanced sleep phase disorder (ASPD) is the converse of the delayed sleep phase syndrome. Most commonly, this syndrome occurs in older people, 15% of whom report that they cannot sleep past 5 A.M., with twice that number complaining that they wake up too early at least several times per week. Patients with ASPD experience excessive daytime sleepiness during the evening hours, when they have great difficulty remaining awake, even in social settings. Typically, patients awaken from 3–5 A.M. each day, often several hours before their desired wake times. In addition to age-related ASPD, an early-onset familial variant of this condition has also been reported. In one such family, autosomal dominant ASPD was due to a missense mutation in a circadian clock component (PER2, as shown in Fig. 16-2) that altered the circadian

period. Patients with ASPD may benefit from bright-light phototherapy during the evening hours, designed to reset the circadian pacemaker to a later hour.

Non-24-Hour Sleep-Wake Disorder

This condition can occur when the maximal phase-advancing capacity of the circadian pacemaker is not adequate to accommodate the difference between the 24-h geophysical day and the intrinsic period of the pacemaker in the patient. Alternatively, patients' self-selected exposure to artificial light may drive the circadian pacemaker to a >24-h schedule. Affected patients are not able to maintain a stable phase relationship between the output of the pacemaker and the 24-h day. Such patients typically present with an incremental pattern of successive delays in sleep onsets and wake times, progressing in and out of phase with local time. When the patient's endogenous rhythms are out of phase with the local environment, insomnia coexists with excessive daytime sleepiness. Conversely, when the endogenous rhythms are in phase with the local environment, symptoms remit. The intervals between symptomatic periods may last several weeks to several months. Blind individuals unable to perceive light are particularly susceptible to this disorder. Nightly low-dose (0.5 mg) melatonin administration has been reported to improve sleep and, in some cases, to induce synchronization of the circadian pacemaker.

MEDICAL IMPLICATIONS OF CIRCADIAN RHYTHMICITY

Prominent circadian variations have been reported in the incidence of acute myocardial infarction, sudden cardiac death, and stroke, the leading causes of death in the United States. Platelet aggregability is increased after arising in the early morning hours, coincident with the peak incidence of these cardiovascular events. A better understanding of the possible role of circadian rhythmicity in the acute destabilization of a chronic condition such as atherosclerotic disease could improve the understanding of the pathophysiology.

Diagnostic and therapeutic procedures may also be affected by the time of day at which data are collected. Examples include blood pressure, body temperature, the dexamethasone suppression test, and plasma cortisol levels. The timing of chemotherapy administration has been reported to have an effect on the outcome of treatment. Few physicians realize the extent to which routine measures are affected by the time (or sleep/wake state) when the measurement is made.

In addition, both the toxicity and effectiveness of drugs can vary during the day. For example, more than a fivefold difference has been observed in mortality rates following administration of toxic agents to experimental animals at different times of day. Anesthetic agents are particularly sensitive to time-of-day effects. Finally, the physician must be increasingly aware of the public health risks associated with the ever-increasing demands made by the duty-rest-recreation schedules in our round-the-clock society.

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CHAPTER 17

DISORDERS OF VISION

Jonathan C. Horton

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THE HUMAN VISUAL SYSTEM

The visual system provides a supremely efficient means for the rapid assimilation of information from the environment to aid in the guidance of behavior. The act of seeing begins with the capture of images focused by the cornea and lens upon a light-sensitive membrane in the back of the eye, called the *retina*. The retina is actually part of the brain, banished to the periphery to serve as a transducer for the conversion of patterns of light energy into neuronal signals. Light is absorbed by photopigment in two types of receptors: rods and cones. In the human retina there are 100 million rods and 5 million cones. The rods operate in dim (scotopic) illumination. The cones function under daylight (photopic) conditions. The cone system is specialized for color perception and high spatial resolution. The majority of cones are located within the macula, the portion of the retina serving the central 10° of vision. In the middle of the macula a small pit termed the *fovea*, packed exclusively with cones, provides best visual acuity.

Photoreceptors hyperpolarize in response to light, activating bipolar, amacrine, and horizontal cells in the inner nuclear layer. After processing of photoreceptor responses by this complex retinal circuit, the flow of sensory information ultimately converges upon a final common pathway: the ganglion cells. These cells translate the visual image impinging upon the retina into a continuously varying barrage of action potentials that propagates along the primary optic pathway to visual centers within the brain. There are a million ganglion cells in each retina, and hence a million fibers in each optic nerve.

Ganglion cell axons sweep along the inner surface of the retina in the nerve fiber layer, exit the eye at the optic disc, and travel through the optic nerve, optic chiasm, and optic tract to reach targets in the brain. The majority of fibers synapse upon cells in the lateral geniculate body, a thalamic relay station. Cells in the lateral geniculate body project in turn to the primary visual cortex. This massive afferent retinogeniculocortical sensory pathway provides the neural substrate for visual perception. Although the lateral geniculate body is the main target of the retina, separate classes of ganglion cells project to other subcortical visual nuclei involved in different functions. Ganglion cells that mediate pupillary constriction and circadian rhythms are light sensitive, owing to a novel visual pigment, melanopsin. Pupil responses are mediated by input to the pretectal olivary nuclei in the midbrain. The pretectal nuclei send their output to the Edinger-Westphal nuclei, which in turn provide parasympathetic innervation to the iris sphincter via an interneuron in the ciliary ganglion. Circadian rhythms are timed by a retinal projection to the suprachiasmatic nucleus. Visual orientation and eye movements are served by retinal input to the superior

colliculus. Gaze stabilization and optokinetic reflexes are governed by a group of small retinal targets known collectively as the *brainstem accessory optic system*.

The eyes must be rotated constantly within their orbits to place and maintain targets of visual interest upon the fovea. This activity, called *foveation*, or looking, is governed by an elaborate efferent motor system. Each eye is moved by six extraocular muscles, supplied by cranial nerves from the oculomotor (III), trochlear (IV), and abducens (VI) nuclei. Activity in these ocular motor nuclei is coordinated by pontine and midbrain mechanisms for smooth pursuit, saccades, and gaze stabilization during head and body movements. Large regions of the frontal and parietooccipital cortex control these brainstem eye movement centers by providing descending supranuclear input.

CLINICAL ASSESSMENT OF VISUAL FUNCTION

REFRACTIVE STATE

In approaching the patient with reduced vision, the first step is to decide whether refractive error is responsible. In *emmetropia*, parallel rays from infinity are focused perfectly upon the retina. Sadly, this condition is enjoyed by only a minority of the population. In *myopia*, the globe is too long, and light rays come to a focal point in front of the retina. Near objects can be seen clearly, but distant objects require a diverging lens in front of the eye. In *hyperopia*, the globe is too short, and hence a converging lens is used to supplement the refractive power of the eye. In *astigmatism*, the corneal surface is not perfectly spherical, necessitating a cylindrical corrective lens. In recent years it has become possible to correct refractive error with the excimer laser by performing LASIK (laser in situ keratomileusis) to alter the curvature of the cornea.

With the onset of middle age, *presbyopia* develops as the lens within the eye becomes unable to increase its refractive power to accommodate upon near objects. To compensate for presbyopia, the emmetropic patient must use reading glasses. The patient already wearing glasses for distance correction usually switches to bifocals. The only exception is the myopic patient, who may achieve clear vision at near simply by removing glasses containing the distance prescription.

Refractive errors usually develop slowly and remain stable after adolescence, except in unusual circumstances. For example, the acute onset of diabetes mellitus can produce sudden myopia because of lens edema induced by hyperglycemia. Testing vision through a pinhole aperture is a useful way to screen quickly for refractive error. If the visual acuity is better through a pinhole than with the unaided eye, the patient needs a refraction to obtain best corrected visual acuity.

VISUAL ACUITY

The Snellen chart is used to test acuity at a distance of 6 m (20 ft). For convenience, a scale version of the Snellen chart, called the Rosenbaum card, is held at 36 cm (14 in) from the patient (Fig. 17-1). All subjects should be able to read the 6/6 m (20/20 ft) line with each eye using their refractive correction, if any. Patients who need reading glasses because of presbyopia must wear them for accurate testing with the Rosenbaum card. If 6/6 (20/20)

FIGURE 17-1

The Rosenbaum card is a miniature, scale version of the Snellen chart for testing visual acuity at near. When the visual acuity is recorded, the Snellen distance equivalent should bear a notation indicating that vision was tested at near, not at 6 m (20 ft), or else the Jaeger number system should be used to report the acuity.

acuity is not present in each eye, the deficiency in vision must be explained. If worse than 6/240 (20/800), acuity should be recorded in terms of counting fingers, hand motions, light perception, or no light perception. Legal blindness is defined by the Internal Revenue Service as a best corrected acuity of 6/60 (20/200) or less in the better eye, or a binocular visual field subtending 20° or less. For driving the laws vary by state, but most require a corrected acuity of 6/12 (20/40) in at least one eye for unrestricted privileges. Patients with a homonymous hemianopia should not drive.

PUPILS

The pupils should be tested individually in dim light with the patient fixating on a distant target. If they respond briskly to light, there is no need to check the near response, because isolated loss of constriction (miosis) to accommodation does not occur. For this reason, the ubiquitous abbreviation PERRLA (pupils equal, round, and reactive to light and accommodation) implies a wasted effort with the last step. However, it is important to test the near response if the light response is poor or absent. Light-near dissociation occurs with neurosyphilis (Argyll Robertson pupil), lesions of the dorsal midbrain (obstructive hydrocephalus, pineal region tumors), and after aberrant regeneration (oculomotor nerve palsy, Adie's tonic pupil).

An eye with no light perception has no pupillary response to direct light stimulation. If the retina or optic nerve is only partially injured, the direct pupillary response will be weaker than the consensual pupillary response evoked by shining a light into the other eye. This *relative afferent pupillary defect* (Marcus Gunn pupil) can be elicited with the swinging flashlight test (**Fig. 17-2**). It is an extremely useful sign in retrobulbar optic neuritis and other optic nerve diseases, where it may be the sole objective evidence for disease.

Subtle inequality in pupil size, up to 0.5 mm, is a fairly common finding in normal persons. The diagnosis of essential or physiologic anisocoria is secure as long as the relative pupil asymmetry remains constant as ambient lighting varies. Anisocoria that increases in dim light indicates a sympathetic paresis of the iris dilator muscle. The triad of miosis with ipsilateral ptosis and anhidrosis constitutes *Horner's syndrome*, although anhidrosis is an inconstant feature. Brainstem stroke, carotid dissection, or neoplasm impinging upon the sympathetic chain are occasionally identified as the cause of Horner's syndrome, but most cases are idiopathic.

Anisocoria that increases in bright light suggests a parasympathetic palsy. The first concern is an oculomotor nerve paresis. This possibility is excluded if the eye movements are full and the patient has no ptosis or diplopia. Acute pupillary dilation (mydriasis) can occur from damage to the ciliary ganglion in the orbit. Common mechanisms are infection (herpes zoster, influenza), trauma (blunt, penetrating, surgical), or ischemia (diabetes, temporal arteritis). After denervation of the iris sphincter the pupil does not respond well to light, but the response to near is often relatively intact. When the near stimulus is removed, the pupil redilates very slowly compared with the normal pupil, hence the term *tonic pupil*. In *Adie's syndrome*, a tonic pupil occurs in conjunction with weak or absent tendon reflexes in the lower extremities. This benign disorder, which occurs

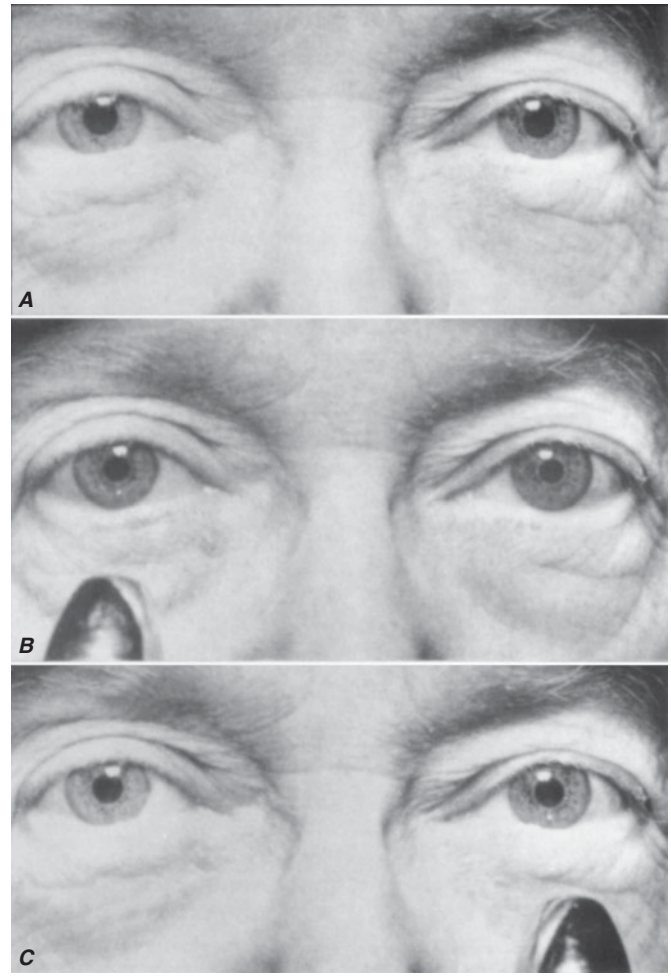

FIGURE 17-2

Demonstration of a relative afferent pupil defect (Marcus Gunn pupil) in the left eye, done with the patient fixating upon a distant target. ***A.*** With dim background lighting, the pupils are equal and relatively large. ***B.*** Shining a flashlight into the right eye evokes equal, strong constriction of both pupils. ***C.*** Swinging the flashlight over to the damaged left eye causes dilation of both pupils, although they remain smaller than in ***A***. Swinging the flashlight back over to the healthy right eye would result in symmetric constriction back to the appearance shown in ***B***. Note that the pupils always remain equal; the damage to the left retina/optic nerve is revealed by weaker bilateral pupil constriction to a flashlight in the left eye compared with the right eye. (*From P Levatin, Arch Ophthalmol 62:768, 1959.*)

predominantly in healthy young women, is assumed to represent a mild dysautonomia. Tonic pupils are also associated with Shy-Drager syndrome, segmental hypohidrosis, diabetes, and amyloidosis. Occasionally, a tonic pupil is discovered incidentally in an otherwise completely normal, asymptomatic individual. The diagnosis is confirmed by placing a drop of dilute (0.125%) pilocarpine into each eye. Denervation hypersensitivity produces pupillary constriction in a tonic pupil, whereas the normal pupil shows no response. Pharmacologic dilation from accidental or deliberate instillation of anticholinergic agents (atropine, scopolamine drops) into the eye can also produce pupillary mydriasis. In this situation, normal strength (1%) pilocarpine causes no constriction.

Both pupils are affected equally by systemic medications. They are small with narcotic use (morphine, heroin) and large with anticholinergics (scopolamine). Parasympathetic agents (pilocarpine, demecarium bromide) used to treat glaucoma produce miosis. In any patient with an unexplained pupillary abnormality, a slit-lamp examination is helpful to exclude surgical trauma to the iris, an occult foreign body, perforating injury, intraocular inflammation, adhesions (synechia), angle-closure glaucoma, and iris sphincter rupture from blunt trauma.

EYE MOVEMENTS AND ALIGNMENT

Eye movements are tested by asking the patient with both eyes open to pursue a small target such as a penlight into the cardinal fields of gaze. Normal ocular versions are smooth, symmetric, full, and maintained in all directions without nystagmus. Saccades, or quick refixation eye movements, are assessed by having the patient look back and forth between two stationary targets. The eyes should move rapidly and accurately in a single jump to their target. Ocular alignment can be judged by holding a penlight directly in front of the patient at about 1 m. If the eyes are straight, the corneal light reflex will be centered in the middle of each pupil. To test eye alignment more precisely, the cover test is useful. The patient is instructed to gaze upon a small fixation target in the distance. One eye is covered suddenly while observing the second eye. If the second eye shifts to fixate upon the target, it was misaligned. If it does not move, the first eye is uncovered and the test is repeated on the second eye. If neither eye moves, the eyes are aligned orthotropically. If the eyes are orthotropic in primary gaze but the patient complains of diplopia, the cover test should be performed with the head tilted or turned in whatever direction elicits diplopia. With practice the examiner can detect an ocular deviation (heterotropia) as small as 1–2° with the cover test. Deviations can be measured by placing prisms in front of the misaligned eye to determine the power required to neutralize the fixation shift evoked by covering the other eye.

STEREOPSIS

Stereoacuity is determined by presenting targets with retinal disparity separately to each eye using polarized images. The most popular office tests measure a range of thresholds from 800–40 seconds of arc. Normal stereoacuity is 40 seconds of arc. If a patient achieves this level of stereoacuity, one is assured that the eyes are aligned orthotropically and that vision is intact in each eye. Random dot stereograms have no monocular depth cues and provide an excellent screening test for strabismus and amblyopia in children.

COLOR VISION

The retina contains three classes of cones, with visual pigments of differing peak spectral sensitivity: red (560 nm), green (530 nm), and blue (430 nm). The red and green cone pigments are encoded on the X chromosome; the blue cone pigment on chromosome 7. Mutations of the blue cone pigment are exceedingly rare. Mutations of the red and green pigments cause congenital X-linked color blindness in 8% of men. Affected individuals are not truly color blind; rather, they differ from normal subjects in how they perceive color and how they combine primary monochromatic lights to match a given color. Anomalous trichromats have three cone types, but a mutation in one cone pigment (usually red or green) causes a shift in peak spectral sensitivity, altering the proportion of primary colors required to achieve a color match. Dichromats have only two cone types and will therefore accept a color match based upon only two primary colors. Anomalous trichromats and dichromats have 6/6 (20/20) visual acuity, but their hue discrimination is impaired. Ishihara color plates can be used to detect red-green color blindness. The test plates contain a hidden number, visible only to subjects with color confusion from red-green color blindness. Because color blindness is almost exclusively X-linked, it is worth screening only male children.

The Ishihara plates are often used to detect acquired defects in color vision, although they are intended as a screening test for congenital color blindness. Acquired defects in color vision frequently result from disease of the macula or optic nerve. For example, patients with a history of optic neuritis often complain of color desaturation long after their visual acuity has returned to normal. Color blindness can also occur from bilateral strokes involving the ventral portion of the occipital lobe (cerebral achromatopsia). Such patients can perceive only shades of gray and may also have difficulty recognizing faces (prosopagnosia). Infarcts of the dominant occipital lobe sometimes give rise to color anomia. Affected patients can discriminate colors, but they cannot name them.

VISUAL FIELDS

Vision can be impaired by damage to the visual system anywhere from the eyes to the occipital lobes. One can localize the site of the lesion with considerable accuracy by mapping the visual field deficit by finger confrontation and then correlating it with the topographic anatomy of the visual pathway (Fig. 17-3). Quantitative visual field mapping is performed by computer-driven perimeters (Humphrey, Octopus) that present a target of variable intensity at fixed positions in the visual field (Fig. 17-3*A*). By generating an automated printout of light thresholds, these static perimeters provide a sensitive means of detecting scotomas in the visual field. They are exceedingly useful for serial assessment of visual function in chronic diseases such as glaucoma or pseudotumor cerebri.

The crux of visual field analysis is to decide whether a lesion is before, at, or behind the optic chiasm. If a scotoma is confined to one eye, it must be due to a lesion anterior to the chiasm, involving either the optic

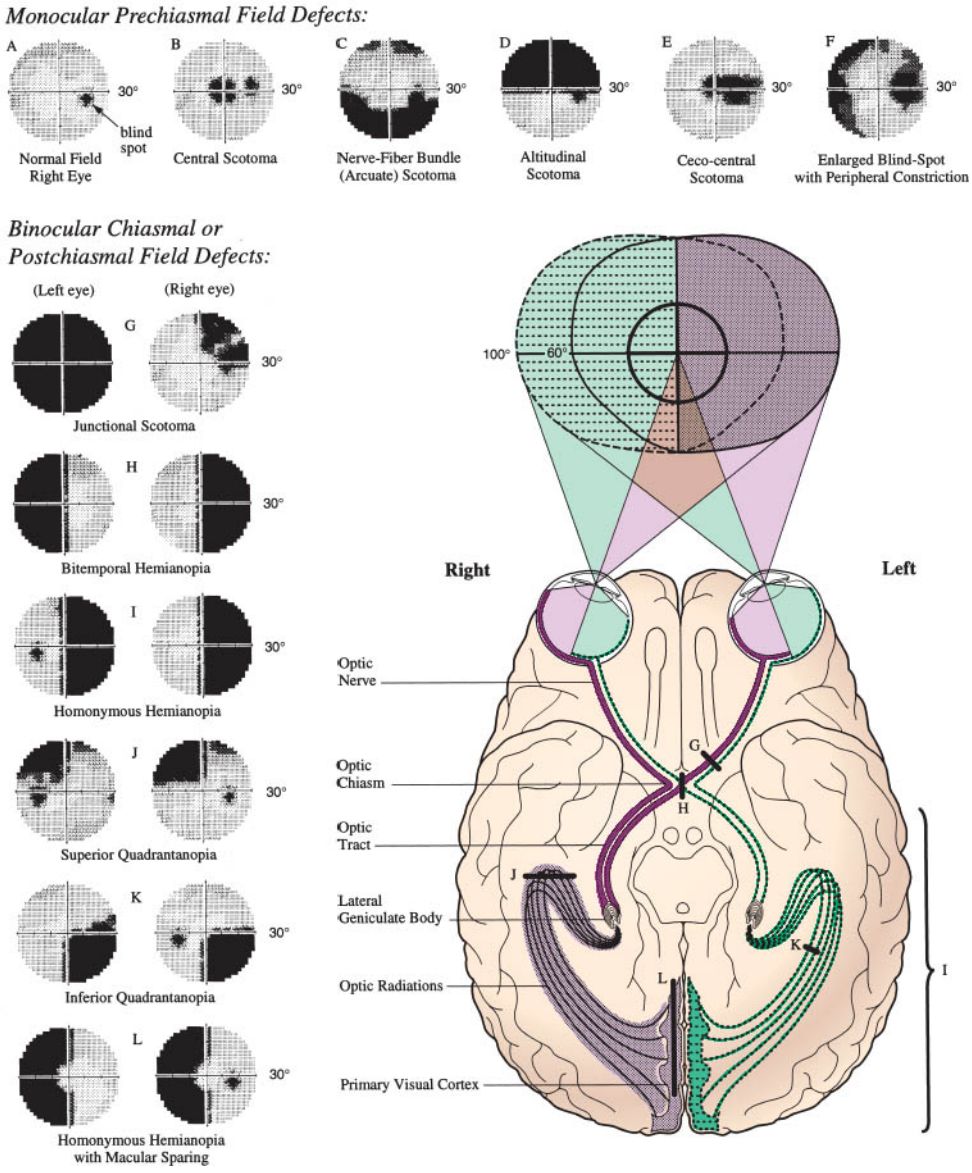

FIGURE 17-3

Ventral view of the brain, correlating patterns of visual field loss with the sites of lesions in the visual pathway. The visual fields overlap partially, creating 120° of central binocular field flanked by a 40° monocular crescent on either side. The visual field maps in this figure were done with a computer-driven perimeter (Humphrey Instruments, Carl Zeiss, Inc.). It plots the retinal sensitivity to light in the central 30° using a gray scale format. Areas of visual field loss are shown in black. The examples of common monocular, prechiasmal field defects are all shown for the right eye. By convention, the visual fields are always recorded with the left eye's field on the left, and the right eye's field on the right, just as the patient sees the world.

nerve or retina. Retinal lesions produce scotomas that correspond optically to their location in the fundus. For example, a superior-nasal retinal detachment results in an inferior-temporal field cut. Damage to the macula causes a central scotoma (Fig. 17-3*B*).

Optic nerve disease produces characteristic patterns of visual field loss. Glaucoma selectively destroys axons that enter the superotemporal or inferotemporal poles of the optic disc, resulting in arcuate scotomas shaped like a Turkish scimitar, which emanate from the blind spot and curve around fixation to end flat against the horizontal meridian (Fig. 17-3*C*). This type of field defect mirrors the arrangement of the nerve fiber layer in the temporal retina. Arcuate or nerve fiber layer scotomas also occur from optic neuritis, ischemic optic neuropathy, optic disc drusen, and branch retinal artery or vein occlusion.

Damage to the entire upper or lower pole of the optic disc causes an altitudinal field cut that follows the horizontal meridian (Fig. 17-3*D*). This pattern of visual field loss is typical of ischemic optic neuropathy but also occurs from retinal vascular occlusion, advanced glaucoma, and optic neuritis.

About half the fibers in the optic nerve originate from ganglion cells serving the macula. Damage to papillomacular fibers causes a cecocentral scotoma encompassing the blind spot and macula (Fig. 17-3*E*). If the damage is irreversible, pallor eventually appears in the temporal portion of the optic disc. Temporal pallor from a cecocentral scotoma may develop in optic neuritis, nutritional optic neuropathy, toxic optic neuropathy, Leber's hereditary optic neuropathy, and compressive optic neuropathy. It is worth mentioning that the temporal side of the optic disc is slightly more pale than the nasal side in most normal individuals. Therefore, it can sometimes be difficult to decide whether the temporal pallor visible on fundus examination represents a pathologic change. Pallor of the nasal rim of the optic disc is a less equivocal sign of optic atrophy.

At the optic chiasm, fibers from nasal ganglion cells decussate into the contralateral optic tract. Crossed fibers are damaged more by compression than uncrossed fibers. As a result, mass lesions of the sellar region cause a temporal hemianopia in each eye. Tumors anterior to the optic chiasm, such as meningiomas of the tuberculum sella, produce a junctional scotoma characterized by an optic neuropathy in one eye and a superior-temporal field cut in the other eye (Fig. 17-3*G*). More symmetric compression of the optic chiasm by a pituitary adenoma, meningioma, craniopharyngioma, glioma, or aneurysm results in a bitemporal hemianopia (Fig. 17-3*H*). The insidious development of a bitemporal hemianopia often goes unnoticed by the patient and will escape detection by the physician unless each eye is tested separately.

It is difficult to localize a postchiasmal lesion accurately, because injury anywhere in the optic tract, lateral geniculate body, optic radiations, or visual cortex can produce a homonymous hemianopia, i.e., a temporal hemifield defect in the contralateral eye and a matching nasal hemifield defect in the ipsilateral eye (Fig. 17-3*I*). A unilateral postchiasmal lesion leaves the visual acuity in each eye unaffected, although the patient may read the letters on only the left or right half of the eye chart. Lesions of the optic radiations tend to cause poorly matched or incongruous field defects in each eye. Damage to the optic radiations in the temporal lobe (Meyer's loop) produces a superior quadrantic homonymous hemianopia (Fig. 17-3*J*), whereas injury to the optic radiations in the parietal lobe results in an inferior quadrantic homonymous hemianopia (Fig. 17-3*K*). Lesions of the primary visual cortex give rise to dense, congruous hemianopic field defects. Occlusion of the posterior cerebral artery supplying the occipital lobe is a frequent cause of total homonymous hemianopia. Some patients with hemianopia after occipital stroke have macular sparing, because the macular representation at the tip of the occipital lobe is supplied by collaterals from the middle cerebral artery (Fig. 17-3*L*). Destruction of both occipital lobes produces cortical blindness. This condition can be distinguished from bilateral prechiasmal visual loss by noting that the pupil responses and optic fundi remain normal.

DISORDERS

RED OR PAINFUL EYE

Corneal Abrasions

These are seen best by placing a drop of fluorescein in the eye and looking with the slit lamp using a cobalt-blue light. A penlight with a blue filter will suffice if no slit lamp is available. Damage to the corneal epithelium is revealed by yellow fluorescence of the exposed basement membrane underlying the epithelium. It is important to check for foreign bodies. To search the conjunctival fornices, the lower lid should be pulled down and the upper lid everted. A foreign body can be removed with a moistened cotton-tipped applicator after placing a drop of topical anesthetic, such as proparacaine, in the eye. Alternatively, it may be possible to flush the foreign body from the eye by irrigating copiously with saline or artificial tears. If the corneal epithelium has been abraded, antibiotic ointment and a patch should be applied to the eye. A drop of an intermediate-acting cycloplegic, such as cyclopentolate hydrochloride 1%, helps to reduce pain by relaxing the ciliary body. The eye should be reexamined the next day. Minor abrasions may not require patching and cycloplegia.

Subconjunctival Hemorrhage

This results from rupture of small vessels bridging the potential space between the episclera and conjunctiva.

Blood dissecting into this space can produce a spectacular red eye, but vision is not affected and the hemorrhage resolves without treatment. Subconjunctival hemorrhage is usually spontaneous but can occur from blunt trauma, eye rubbing, or vigorous coughing. Occasionally it is a clue to an underlying bleeding disorder.

Pinguecula

This is a small, raised conjunctival nodule at the temporal or nasal limbus. In adults such lesions are extremely common and have little significance, unless they become inflamed (pingueculitis). A *pterygium* resembles a pinguecula but has crossed the limbus to encroach upon the corneal surface. Removal is justified when symptoms of irritation or blurring develop, but recurrence is a common problem.

Blepharitis

This refers to inflammation of the eyelids. The most common form occurs in association with acne rosacea or seborrheic dermatitis. The eyelid margins are usually colonized heavily by staphylococci. Upon close inspection, they appear greasy, ulcerated, and crusted with scaling debris that clings to the lashes. Treatment consists of warm compresses, strict eyelid hygiene, and topical antibiotics such as *erythromycin*. An external *hordeolum* (sty) is caused by staphylococcal infection of the superficial accessory glands of Zeis or Moll located in the eyelid margins. An internal hordeolum occurs after suppurative infection of the oil-secreting meibomian glands within the tarsal plate of the eyelid. Systemic antibiotics, usually tetracyclines, are sometimes necessary for treatment of meibomian gland inflammation (meibomitis) or chronic, severe blepharitis. A *chalazion* is a painless, granulomatous inflammation of a meibomian gland that produces a pealike nodule within the eyelid. It can be incised and drained, or injected with glucocorticoids. Basal cell, squamous cell, or meibomian gland carcinoma should be suspected for any nonhealing, ulcerative lesion of the eyelids.

Dacrocystitis

An inflammation of the lacrimal drainage system, this can produce epiphora (tearing) and ocular injection. Gentle pressure over the lacrimal sac evokes pain and reflux of mucus or pus from the tear puncta. Dacrocystitis usually occurs after obstruction of the lacrimal system. It is treated with topical and systemic antibiotics, followed by probing or surgery to reestablish patency. *Entropion* (inversion of the eyelid) or *ectropion* (sagging or eversion of the eyelid) can also lead to epiphora and ocular irritation.

Conjunctivitis

This is the most common cause of a red, irritated eye. Pain is minimal, and the visual acuity is reduced only slightly. The most common viral etiology is adenovirus infection. It causes a watery discharge, mild foreign-body sensation, and photophobia. Bacterial infection tends to produce a more mucopurulent exudate. Mild cases of infectious conjunctivitis are usually treated empirically with broad-spectrum topical ocular antibiotics, such as sulfacetamide 10%, polymixin-bacitracin-neomycin, or trimethoprim-polymixin combination. Smears and cultures are usually reserved for severe, resistant, or recurrent cases of conjunctivitis. To prevent contagion, patients should be admonished to wash their hands frequently, not to touch their eyes, and to avoid direct contact with others.

Allergic Conjunctivitis

This condition is extremely common and often mistaken for infectious conjunctivitis. Itching, redness, and epiphora are typical. The palpebral conjunctiva may become hypertropic with giant excrescences called cobblestone papillae. Irritation from contact lenses or any chronic foreign body can also induce formation of cobblestone papillae. *Atopic conjunctivitis* occurs in subjects with atopic dermatitis or asthma. Symptoms caused by allergic conjunctivitis can be alleviated with cold compresses, topical vasoconstrictors, antihistamines, and mast cell stabilizers such as cromolyn sodium. Topical glucocorticoid solutions provide dramatic relief of immune-mediated forms of conjunctivitis, but their long-term use is ill-advised because of the complications of glaucoma, cataract, and secondary infection. Topical nonsteroidal anti-inflammatory agents (NSAIDs) such as ketorolac tromethamine are a better alternative.

Keratoconjunctivitis Sicca

Also known as dry eye, it produces a burning, foreign-body sensation, injection, and photophobia. In mild cases the eye appears surprisingly normal, but tear production measured by wetting of a filter paper (Schirmer strip) is deficient. A variety of systemic drugs, including antihistaminic, anticholinergic, and psychotropic medications, result in dry eye by reducing lacrimal secretion. Disorders that involve the lacrimal gland directly, such as sarcoidosis or Sjögren's syndrome, also cause dry eye. Patients may develop dry eye after radiation therapy if the treatment field includes the orbits. Problems with ocular drying are also common after lesions affecting cranial nerves V or VII. Corneal anesthesia is particularly dangerous, because the absence of a normal blink reflex exposes the cornea to injury without pain to warn the patient. Dry eye is managed by frequent and liberal application of artificial tears and ocular lubricants. In severe cases the tear puncta can be plugged or cauterized to reduce lacrimal outflow.

Keratitis

This is a threat to vision because of the risk of corneal clouding, scarring, and perforation. Worldwide, the two leading causes of blindness from keratitis are trachoma from chlamydial infection and vitamin A deficiency related to malnutrition. In the United States, contact lenses play a major role in corneal infection and ulceration. They should not be worn by anyone with an active eye infection. In evaluating the cornea, it is important to differentiate between a superficial infection (*keratoconjunctivitis*) and a deeper, more serious ulcerative process. The latter is accompanied by greater visual loss, pain, photophobia, redness, and discharge. Slit-lamp examination shows disruption of the corneal epithelium, a cloudy infiltrate or abscess in the stroma, and an inflammatory cellular reaction in the anterior chamber. In severe cases, pus settles at the bottom of the anterior chamber, giving rise to a hypopyon. Immediate empirical antibiotic therapy should be initiated after corneal scrapings are obtained for Gram's stain, Giemsa stain, and cultures. Fortified topical antibiotics are most effective, supplemented with subconjunctival antibiotics as required. A fungal etiology should always be considered in the patient with keratitis. Fungal infection is common in warm humid climates, especially after penetration of the cornea by plant or vegetable material.

Herpes Simplex

The *herpes viruses* are a major cause of blindness from keratitis. Most adults in the United States have serum antibodies to herpes simplex, indicating prior viral infection. Primary ocular infection is generally caused by herpes simplex type 1, rather than type 2. It manifests as a unilateral follicular blepharoconjunctivitis, easily confused with adenoviral conjunctivitis unless telltale vesicles appear on the periocular skin or conjunctiva. A dendritic pattern of corneal epithelial ulceration revealed by fluorescein staining is pathognomonic for herpes infection but is seen in only a minority of primary infections. Recurrent ocular infection arises from reactivation of the latent herpes virus. Viral eruption in the corneal epithelium may result in the characteristic herpes dendrite. Involvement of the corneal stroma produces edema, vascularization, and iridocyclitis. Herpes keratitis is treated with topical antiviral agents, cycloplegics, and oral acyclovir. Topical glucocorticoids are effective in mitigating corneal scarring but must be used with extreme caution because of the danger of corneal melting and perforation. Topical glucocorticoids also carry the risk of prolonging infection and inducing glaucoma.

Herpes Zoster

Herpes zoster from reactivation of latent varicella (chickenpox) virus causes a dermatomal pattern of painful vesicular dermatitis. Ocular symptoms can occur after zoster eruption in any branch of the trigeminal nerve but are particularly common when vesicles form on the nose, reflecting nasociliary (V1) nerve involvement (Hutchinson's sign). Herpes zoster ophthalmicus produces corneal dendrites, which can be difficult to distinguish from those seen in herpes simplex. Stromal keratitis, anterior uveitis, raised intraocular pressure, ocular motor nerve palsies, acute retinal necrosis, and postherpetic scarring and neuralgia are other common sequelae. Herpes zoster ophthalmicus is treated with antiviral agents and cycloplegics. In severe cases, glucocorticoids may be added to prevent permanent visual loss from corneal scarring.

Episcleritis

This is an inflammation of the episclera, a thin layer of connective tissue between the conjunctiva and sclera. Episcleritis resembles conjunctivitis but is a more localized process and discharge is absent. Most cases of episcleritis are idiopathic, but some occur in the setting of an autoimmune disease. *Scleritis* refers to a deeper, more severe inflammatory process, frequently associated with a connective tissue disease such as rheumatoid arthritis, lupus erythematosus, polyarteritis nodosa, Wegener's granulomatosis, or relapsing polychondritis. The inflammation and thickening of the sclera can be diffuse or nodular. In anterior forms of scleritis, the globe assumes a violet hue and the patient complains of severe ocular tenderness and pain. With posterior scleritis the pain and redness may be less marked, but there is often proptosis, choroidal effusion, reduced motility, and visual loss. Episcleritis and scleritis should be treated with NSAIDs. If these agents fail, topical or even systemic glucocorticoid therapy may be necessary, especially if an underlying autoimmune process is active.

Uveitis

Involving the anterior structures of the eye, this is also called *iritis* or *iridocyclitis*. The diagnosis requires slit-lamp examination to identify inflammatory cells floating in the aqueous humor or deposited upon the corneal endothelium (keratic precipitates). Anterior uveitis develops in sarcoidosis, ankylosing spondylitis, juvenile rheumatoid arthritis, inflammatory bowel disease, psoriasis, Reiter's syndrome, and Behçet's disease. It is also associated with herpes infections, syphilis, Lyme disease, onchocerciasis, tuberculosis, and leprosy. Although anterior uveitis can occur in conjunction with many diseases, no cause is found to explain the majority of cases. For this reason, laboratory evaluation is usually reserved for patients with recurrent or severe anterior uveitis. Treatment is aimed at reducing inflammation and scarring by judicious use of topical glucocorticoids. Dilation of the pupil reduces pain and prevents the formation of synechiae.

Posterior Uveitis

This is diagnosed by observing inflammation of the vitreous, retina, or choroid on fundus examination. It is more likely than anterior uveitis to be associated with an identifiable systemic disease. Some patients have panuveitis, or inflammation of both the anterior and posterior segments of the eye. Posterior uveitis is a manifestation of autoimmune diseases such as sarcoidosis, Behçet's disease, Vogt-Koyanagi-Harada syndrome, and inflammatory bowel disease (Fig. 17-4). It also accompanies diseases such as toxoplasmosis, onchocerciasis, cysticercosis, coccidioidomycosis, toxocariasis, and histoplasmosis; infections caused by organisms such as *Candida*, *Pneumocystis carinii*, *Cryptococcus*, *Aspergillus*, herpes, and cytomegalovirus; and other diseases such as syphilis, Lyme disease, tuberculosis, cat-scratch disease, Whipple's disease, and brucellosis. In multiple sclerosis, chronic inflammatory changes can develop in the extreme periphery of the retina (pars planitis or intermediate uveitis).

Acute Angle-Closure Glaucoma

This is a rare and frequently misdiagnosed cause of a red, painful eye. Susceptible eyes have a shallow anterior chamber, either because the eye has a short axial length (hyperopia) or a lens enlarged by the gradual development of cataract. When the pupil becomes mid-dilated, the peripheral iris blocks aqueous outflow via the anterior chamber angle and the intraocular pressure rises abruptly, producing pain, injection, corneal edema, obscurations, and blurred vision. In some patients, ocular symptoms are overshadowed by nausea, vomiting, or headache, prompting a fruitless workup for abdominal or neurologic disease. The diagnosis is made by measuring the intraocular pressure during an acute attack or by observing a narrow chamber angle by means of a specially mirrored contact lens. Acute angle closure is treated with acetazolamide (PO or IV), topical beta blockers, prostaglandin analogues, α_2-adrenergic agonists, and pilocarpine to induce miosis. If these measures fail, a laser can be used to create a hole in the peripheral iris to relieve pupillary block. Many physicians are reluctant to dilate patients routinely for fundus examination because they fear precipitating an angle-closure glaucoma. The risk is actually remote and more than outweighed by the potential benefit to patients of discovering a hidden fundus lesion visible only through a fully dilated pupil. Moreover, a single attack of angle closure after pharmacologic dilation rarely causes any permanent damage to the eye and serves as an inadvertent provocative test to identify patients with narrow angles who would benefit from prophylactic laser iridectomy.

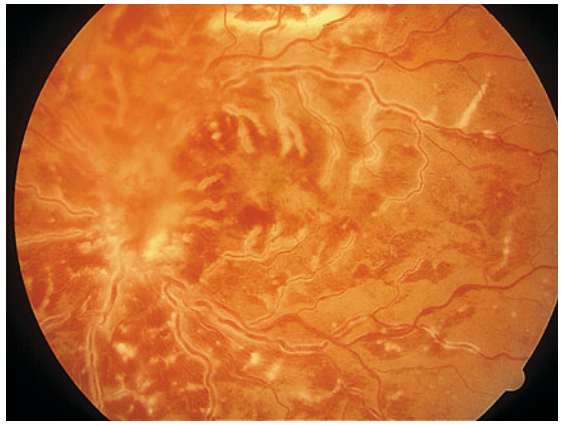

FIGURE 17-4
Retinal vasculitis, uveitis, and hemorrhage in a 32-year-old woman with Crohn's disease. Note that the veins are frosted with a white exudate. Visual acuity improved from 20/400 to 20/20 following treatment with intravenous methylprednisolone.

Endophthalmitis

This occurs from bacterial, viral, fungal, or parasitic infection of the internal structures of the eye. It is usually acquired by hematogenous seeding from a remote site. Chronically ill, diabetic, or immunosuppressed patients, especially those with a history of indwelling IV catheters or positive blood cultures, are at greatest risk for endogenous endophthalmitis. Although most patients have ocular pain and injection, visual loss is sometimes the only symptom. Septic emboli, from a diseased heart valve or a dental abscess, that lodge in the retinal circulation can give rise to endophthalmitis. White-centered retinal hemorrhages (Roth's spots) are considered pathognomonic for subacute bacterial endocarditis, but they also appear in leukemia, diabetes, and many other conditions. Endophthalmitis also occurs as a complication of ocular surgery, occasionally months or even years after the operation. An occult penetrating foreign body or unrecognized trauma to the globe should be considered in any patient with unexplained intraocular infection or inflammation.

TRANSIENT OR SUDDEN VISUAL LOSS

Amaurosis Fugax

This term refers to a transient ischemic attack of the retina (Chap. 21). Because neural tissue has a high rate of metabolism, interruption of blood flow to the retina for more than a few seconds results in *transient monocular blindness*, a term used interchangeably with amaurosis fugax. Patients describe a rapid fading of vision like a curtain descending, sometimes affecting only a portion

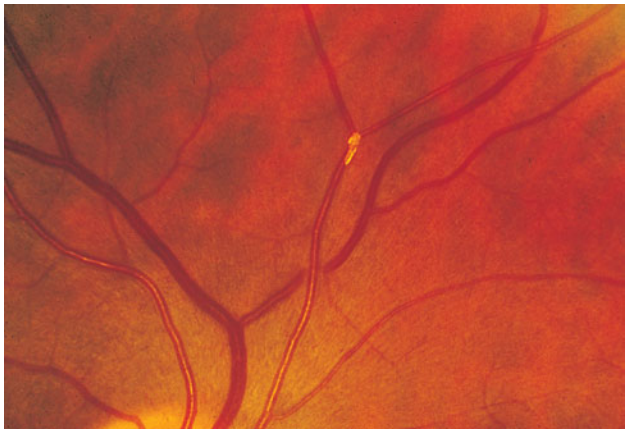

FIGURE 17-5

Hollenhorst plaque lodged at the bifurcation of a retinal arteriole proves that a patient is shedding emboli from either the carotid artery, great vessels, or heart.

of the visual field. Amaurosis fugax usually occurs from an embolus that becomes stuck within a retinal arteriole (Fig. 17-5). If the embolus breaks up or passes, flow is restored and vision returns quickly to normal without permanent damage. With prolonged interruption of blood flow, the inner retina suffers infarction. Ophthalmoscopy reveals zones of whitened, edematous retina following the distribution of branch retinal arterioles. Complete occlusion of the central retinal artery produces arrest of blood flow and a milky retina with a cherry-red fovea (Fig. 17-6). Emboli are composed of either cholesterol (Hollenhorst plaque), calcium, or platelet-fibrin debris. The most common source is an atherosclerotic plaque in the carotid artery or aorta, although emboli can also arise from the heart, especially in patients with diseased valves, atrial fibrillation, or wall motion abnormalities.

In rare instances, amaurosis fugax occurs from low central retinal artery perfusion pressure in a patient with a critical stenosis of the ipsilateral carotid artery and poor collateral flow via the circle of Willis. In this situation, amaurosis fugax develops when there is a dip in systemic blood pressure or a slight worsening of the carotid stenosis. Sometimes there is contralateral motor or sensory loss, indicating concomitant hemispheric cerebral ischemia.

Retinal arterial occlusion also occurs rarely in association with retinal migraine, lupus erythematosus, anticardiolipin antibodies (Fig. 17-6), anticoagulant deficiency states (protein S, protein C, and antithrombin III deficiency), pregnancy, IV drug abuse, blood dyscrasias, dysproteinemias, and temporal arteritis.

Marked *systemic hypertension* causes sclerosis of retinal arterioles, splinter hemorrhages, focal infarcts of the nerve fiber layer (cotton-wool spots), and leakage of lipid and fluid (hard exudate) into the macula (Fig. 17-7). In hypertensive crisis, sudden visual loss can result from vasospasm of retinal arterioles and retinal ischemia. In addition, acute hypertension may produce visual loss from ischemic swelling of the optic disc. Patients with acute hypertensive retinopathy should be treated by lowering the blood pressure. However, the blood pressure should not be reduced precipitously, because there is a danger of optic disc infarction from sudden hypoperfusion.

Impending *branch* or *central retinal vein occlusion* can produce prolonged visual obscurations that resemble those described by patients with amaurosis fugax. The veins appear engorged and phlebitic, with numerous retinal hemorrhages (Fig. 17-8). In some patients, venous blood

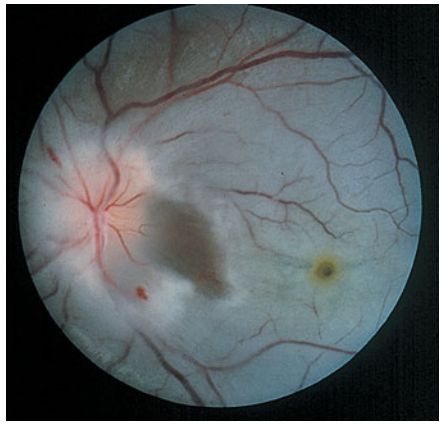

FIGURE 17-6

Central retinal artery occlusion combined with ischemic optic neuropathy in a 19-year-old woman with an elevated titer of anticardiolipin antibodies. Note the orange dot (rather than cherry red) corresponding to the fovea and the spared patch of retina just temporal to the optic disc.

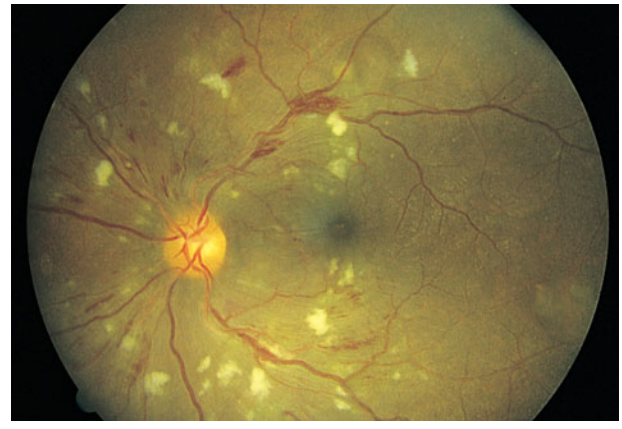

FIGURE 17-7

Hypertensive retinopathy with scattered flame (splinter) hemorrhages and cotton-wool spots (nerve fiber layer infarcts) in a patient with headache and a blood pressure of 234/120.

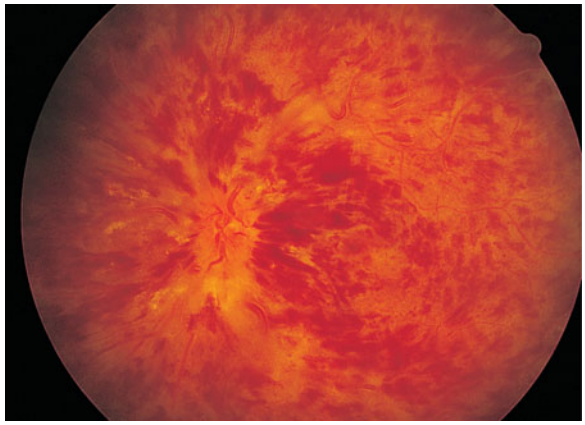

FIGURE 17-8
Central retinal vein occlusion can produce massive retinal hemorrhage ("blood and thunder"), ischemia, and vision loss.

flow recovers spontaneously, while others evolve a frank obstruction with extensive retinal bleeding ("blood and thunder" appearance), infarction, and visual loss. Venous occlusion of the retina is often idiopathic, but hypertension, diabetes, and glaucoma are prominent risk factors. Polycythemia, thrombocythemia, or other factors leading to an underlying hypercoagulable state should be corrected; aspirin treatment may be beneficial.

Anterior Ischemic Optic Neuropathy (AION)

This is caused by insufficient blood flow through the posterior ciliary arteries supplying the optic disc. It produces painless, monocular visual loss that is usually sudden, although some patients have progressive worsening. The optic disc appears swollen and surrounded by nerve fiber layer splinter hemorrhages (Fig. 17-9). AION is divided into two forms: arteritic and nonarteritic. The nonarteritic form of AION is most common. No specific cause can be identified, although diabetes and hypertension are frequent risk factors. No treatment is available. About 5% of patients, especially those older than 60 years, develop the arteritic form of AION in conjunction with giant cell (temporal) arteritis. It is urgent to recognize arteritic AION so that high doses of glucocorticoids can be instituted immediately to prevent blindness in the second eye. Symptoms of polymyalgia rheumatica may be present; the sedimentation rate and C-reactive protein level are usually elevated. In a patient with visual loss from suspected arteritic AION, temporal artery biopsy is mandatory to confirm the diagnosis. Glucocorticoids should be started immediately, without waiting for the biopsy to be completed. The diagnosis of arteritic AION is difficult to sustain in the face of a negative temporal artery biopsy, but such cases do occur rarely.

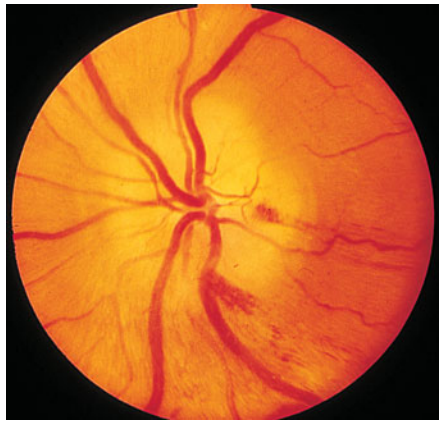

FIGURE 17-9
Anterior ischemic optic neuropathy from temporal arteritis in a 78-year-old woman with pallid disc swelling, hemorrhage, visual loss, myalgia, and an erythrocyte sedimentation rate of 86 mm/h.

Posterior Ischemic Optic Neuropathy

This is an infrequent cause of acute visual loss, induced by the combination of severe anemia and hypotension. Cases have been reported after major blood loss during surgery, exsanguinating trauma, gastrointestinal bleeding, and renal dialysis. The fundus usually appears normal, although optic disc swelling develops if the process extends far enough anteriorly. Vision can be salvaged in some patients by prompt blood transfusion and reversal of hypotension.

Optic Neuritis

This is a common inflammatory disease of the optic nerve. In the Optic Neuritis Treatment Trial (ONTT), the mean age of patients was 32 years, 77% were women, 92% had ocular pain (especially with eye movements), and 35% had optic disc swelling. In most patients, the demyelinating event was retrobulbar and the ocular fundus appeared normal on initial examination (Fig. 17-10), although optic disc pallor slowly developed over subsequent months.

Virtually all patients experience a gradual recovery of vision after a single episode of optic neuritis, even without treatment. This rule is so reliable that failure of vision to improve after a first attack of optic neuritis casts doubt upon the original diagnosis. Treatment with high-dose IV methylprednisolone (250 mg every 6 h for 3 days) followed by oral prednisone (1 mg/kg per day for 11 days) makes no difference in final acuity (measured 6 months after the attack), but the recovery of visual function occurs more rapidly.

For some patients, optic neuritis remains an isolated event. However, the ONTT showed that the 10-year cumulative probability of developing clinically definite multiple sclerosis following optic neuritis is 38%. In

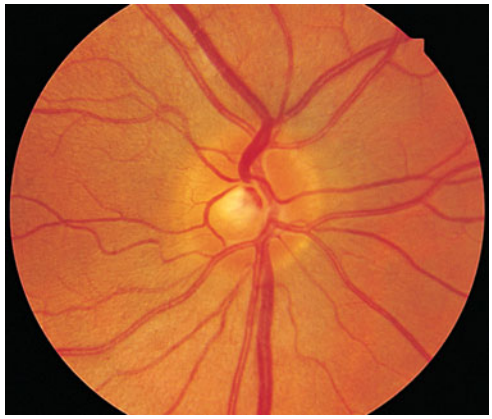

FIGURE 17-10
Retrobulbar optic neuritis is characterized by a normal fundus examination initially, hence the rubric, "the doctor sees nothing, and the patient sees nothing." Optic atrophy develops after severe or repeated attacks.

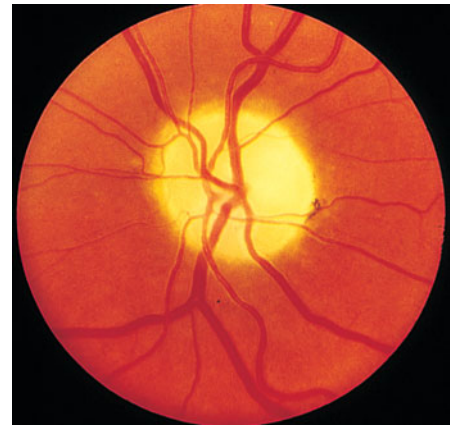

FIGURE 17-11
Optic atrophy is not a specific diagnosis, but refers to the combination of optic disc pallor, arteriolar narrowing, and nerve fiber layer destruction produced by a host of eye diseases, especially optic neuropathies.

patients with two or more demyelinating plaques on brain magnetic resonance (MR) imaging, treatment with interferon beta-1a can retard the development of more lesions. In summary, an MR scan is recommended in every patient with a first attack of optic neuritis. When visual loss is severe (worse than 20/100), treatment with intravenous followed by oral glucocorticoids hastens recovery. If multiple lesions are present on the MR scan, treatment with interferon beta-1a should be considered.

Leber's Hereditary Optic Neuropathy

This disease usually affects young men, causing gradual, painless, severe, central visual loss in one eye, followed weeks or months later by the same process in the other eye. Acutely, the optic disc appears mildly plethoric with surface capillary telangiectases, but no vascular leakage on fluorescein angiography. Eventually optic atrophy ensues. Leber's optic neuropathy is caused by a point mutation at codon 11778 in the mitochondrial gene encoding nicotinamide adenine dinucleotide dehydrogenase (NADH) subunit 4. Additional mutations responsible for the disease have been identified, most in mitochondrial genes encoding proteins involved in electron transport. Mitochondrial mutations causing Leber's neuropathy are inherited from the mother by all her children, but usually only sons develop symptoms. There is no treatment.

Toxic Optic Neuropathy

This can result in acute visual loss with bilateral optic disc swelling and central or cecocentral scotomas. Such cases have been reported to result from exposure to ethambutol, methyl alcohol (moonshine), ethylene glycol (antifreeze), or carbon monoxide. In toxic optic neuropathy, visual loss can also develop gradually and produce optic atrophy (Fig. 17-11) without a phase of acute optic disc edema. Many agents have been implicated as a cause of toxic optic neuropathy, but the evidence supporting the association for many is weak. The following is a partial list of potential offending drugs or toxins: disulfiram, ethchlorvynol, chloramphenicol, amiodarone, monoclonal anti-CD3 antibody, ciprofloxacin, digitalis, streptomycin, lead, arsenic, thallium, D-penicillamine, isoniazid, emetine, and sulfonamides. Deficiency states, induced either by starvation, malabsorption, or alcoholism, can lead to insidious visual loss. Thiamine, vitamin B_{12}, and folate levels should be checked in any patient with unexplained, bilateral central scotomas and optic pallor.

Papilledema

This connotes bilateral optic disc swelling from raised intracranial pressure (Fig. 17-12). Headache is a frequent, but not invariable, accompaniment. All other forms of optic disc swelling, e.g., from optic neuritis or ischemic optic neuropathy, should be called "optic disc edema." This convention is arbitrary but serves to avoid confusion. Often it is difficult to differentiate papilledema from other forms of optic disc edema by fundus examination alone. Transient visual obscurations are a classic symptom of papilledema. They can occur in only one eye or simultaneously in both eyes. They usually last seconds but can persist longer. Obscurations follow abrupt shifts in posture or happen spontaneously. When obscurations are prolonged or spontaneous, the papilledema is more threatening. Visual acuity is not affected by papilledema unless the papilledema is severe, long-standing, or accompanied by macular edema and hemorrhage. Visual field testing

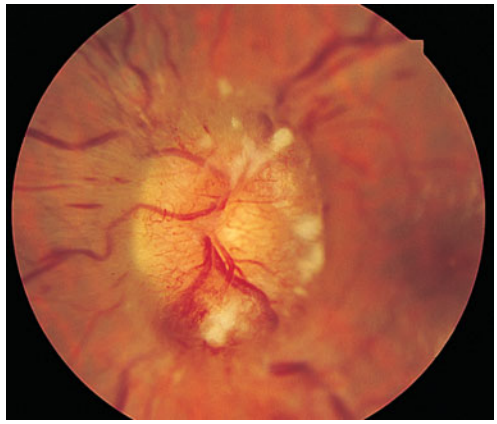

FIGURE 17-12

Papilledema means optic disc edema from raised intracranial pressure. This obese young woman with pseudotumor cerebri was misdiagnosed as a migraineur until fundus examination was performed, showing optic disc elevation, hemorrhages, and cotton-wool spots.

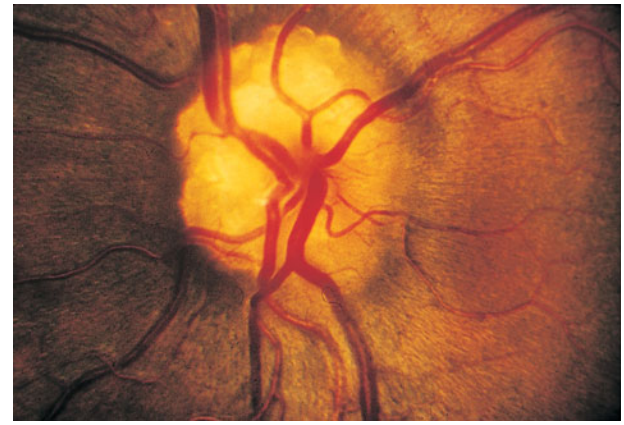

FIGURE 17-13

Optic disc drusen are calcified deposits of unknown etiology within the optic disc. They are sometimes confused with papilledema.

shows enlarged blind spots and peripheral constriction (Fig. 17-3*F*). With unremitting papilledema, peripheral visual field loss progresses in an insidious fashion while the optic nerve develops atrophy. In this setting, reduction of optic disc swelling is an ominous sign of a dying nerve rather than an encouraging indication of resolving papilledema.

Evaluation of papilledema requires neuroimaging to exclude an intracranial lesion. MR angiography is appropriate in selected cases to search for a dural venous sinus occlusion or an arteriovenous shunt. If neuroradiologic studies are negative, the subarachnoid opening pressure should be measured by lumbar puncture. An elevated pressure, with normal cerebrospinal fluid, points by exclusion to the diagnosis of *pseudotumor cerebri* (idiopathic intracranial hypertension). The majority of patients are young, female, and obese. Treatment with a carbonic anhydrase inhibitor such as acetazolamide lowers intracranial pressure by reducing the production of cerebrospinal fluid. Weight reduction is vital but often unsuccessful. If acetazolamide and weight loss fail, and visual field loss is progressive, a shunt should be performed without delay to prevent blindness. Occasionally, emergency surgery is required for sudden blindness caused by fulminant papilledema.

Optic Disc Drusen

These are refractile deposits within the substance of the optic nerve head (**Fig. 17-13**). They are unrelated to drusen of the retina, which occur in age-related macular degeneration. Optic disc drusen are most common in people of northern European descent. Their diagnosis is obvious when they are visible as glittering particles upon the surface of the optic disc. However, in many patients they are hidden beneath the surface, producing pseudopapilledema. It is important to recognize optic disc drusen to avoid an unnecessary evaluation for papilledema. Ultrasound or CT scanning is sensitive for detection of buried optic disc drusen because they contain calcium. In most patients, optic disc drusen are an incidental, innocuous finding, but they can produce visual obscurations. On perimetry they give rise to enlarged blind spots and arcuate scotomas from damage to the optic disc. With increasing age, drusen tend to become more exposed on the disc surface as optic atrophy develops. Hemorrhage, choroidal neovascular membrane, and AION are more likely to occur in patients with optic disc drusen. No treatment is available.

Vitreous Degeneration

This occurs in all individuals with advancing age, leading to visual symptoms. Opacities develop in the vitreous, casting annoying shadows upon the retina. As the eye moves, these distracting "floaters" move synchronously, with a slight lag caused by inertia of the vitreous gel. Vitreous traction upon the retina causes mechanical stimulation, resulting in perception of flashing lights. This photopsia is brief and confined to one eye, in contrast to the bilateral, prolonged scintillations of cortical migraine. Contraction of the vitreous can result in sudden separation from the retina, heralded by an alarming shower of floaters and photopsia. This process, known as *vitreous detachment*, is a frequent involutional event in the elderly. It is not harmful unless it damages the retina. A careful examination of the dilated fundus is important in any patient complaining of floaters or photopsia to

search for peripheral tears or holes. If such a lesion is found, laser application can forestall a retinal detachment. Occasionally a tear ruptures a retinal blood vessel, causing vitreous hemorrhage and sudden loss of vision. On attempted ophthalmoscopy the fundus is hidden by a dark red haze of blood. Ultrasound is required to examine the interior of the eye for a retinal tear or detachment. If the hemorrhage does not resolve spontaneously, the vitreous can be removed surgically. Vitreous hemorrhage also occurs from the fragile neovascular vessels that proliferate on the surface of the retina in diabetes, sickle cell anemia, and other ischemic ocular diseases.

Retinal Detachment

This produces symptoms of floaters, flashing lights, and a scotoma in the peripheral visual field corresponding to the detachment (**Fig. 17-14**). If the detachment includes the fovea, there is an afferent pupil defect and the visual acuity is reduced. In most eyes, retinal detachment starts with a hole, flap, or tear in the peripheral retina (rhegmatogenous retinal detachment). Patients with peripheral retinal thinning (lattice degeneration) are particularly vulnerable to this process. Once a break has developed in the retina, liquified vitreous is free to enter the subretinal space, separating the retina from the pigment epithelium. The combination of vitreous traction upon the retinal surface and passage of fluid behind the retina leads inexorably to detachment. Patients with a history of myopia, trauma, or prior cataract extraction are at greatest risk for retinal detachment. The diagnosis is confirmed by ophthalmoscopic examination of the dilated eye.

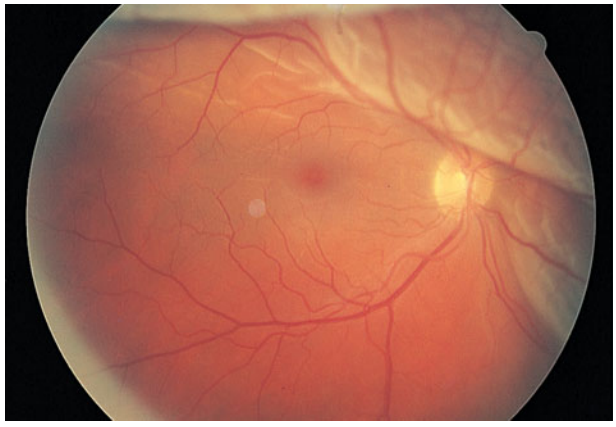

FIGURE 17-14
Retinal detachment appears as an elevated sheet of retinal tissue with folds. In this patient the fovea was spared, so acuity was normal, but a superior detachment produced an inferior scotoma.

Classic Migraine

(See also Chap. 6) This usually occurs with a visual aura lasting about 20 min. In a typical attack, a small central disturbance in the field of vision marches toward the periphery, leaving a transient scotoma in its wake. The expanding border of migraine scotoma has a scintillating, dancing, or zig-zag edge, resembling the bastions of a fortified city, hence the term *fortification spectra*. Patients' descriptions of fortification spectra vary widely and can be confused with amaurosis fugax. Migraine patterns usually last longer and are perceived in both eyes, whereas amaurosis fugax is briefer and occurs in only one eye. Migraine phenomena also remain visible in the dark or with the eyes closed. Generally they are confined to either the right or left visual hemifield, but sometimes both fields are involved simultaneously. Patients often have a long history of stereotypic attacks. After the visual symptoms recede, headache develops in most patients.

Transient Ischemic Attacks

Vertebrobasilar insufficiency may result in acute homonymous visual symptoms. Many patients mistakenly describe symptoms in their left or right eye, when in fact they are occurring in the left or right hemifield of both eyes. Interruption of blood supply to the visual cortex causes a sudden fogging or graying of vision, occasionally with flashing lights or other positive phenomena that mimic migraine. Cortical ischemic attacks are briefer in duration than migraine, occur in older patients, and are not followed by headache. There may be associated signs of brainstem ischemia, such as diplopia, vertigo, numbness, weakness, or dysarthria.

Stroke

This occurs when interruption of blood supply from the posterior cerebral artery to the visual cortex is prolonged. The only finding on examination is a homonymous visual field defect that stops abruptly at the vertical meridian. Occipital lobe stroke is usually due to thrombotic occlusion of the vertebrobasilar system, embolus, or dissection. Lobar hemorrhage, tumor, abscess, and arteriovenous malformation are other common causes of hemianopic cortical visual loss.

Factitious (Functional, Nonorganic) Visual Loss

This is claimed by hysterics or malingerers. The latter comprise the vast majority, seeking sympathy, special treatment, or financial gain by feigning loss of sight. The diagnosis is suspected when the history is atypical, physical findings are lacking or contradictory, inconsistencies emerge on testing, and a secondary motive can be identified. In our litigious society, the fraudulent pursuit of recompense has spawned an epidemic of factitious visual loss.

Cataract

This is a clouding of the lens sufficient to reduce vision. Most cataracts develop slowly as a result of aging, leading to gradual impairment of vision. The formation of cataract occurs more rapidly in patients with a history of ocular trauma, uveitis, or diabetes mellitus. Cataracts are acquired in a variety of genetic diseases, such as myotonic dystrophy, neurofibromatosis type 2, and galactosemia. Radiation therapy and glucocorticoid treatment can induce cataract as a side effect. The cataracts associated with radiation or glucocorticoids have a typical posterior subcapsular location. Cataract can be detected by noting an impaired red reflex when viewing light reflected from the fundus with an ophthalmoscope or by examining the dilated eye using the slit lamp.

The only treatment for cataract is surgical extraction of the opacified lens. Over a million cataract operations are performed each year in the United States. The operation is generally done under local anesthesia on an outpatient basis. A plastic or silicone intraocular lens is placed within the empty lens capsule in the posterior chamber, substituting for the natural lens and leading to rapid recovery of sight. More than 95% of patients who undergo cataract extraction can expect an improvement in vision. In some patients, the lens capsule remaining in the eye after cataract extraction eventually turns cloudy, causing secondary loss of vision. A small opening is made in the lens capsule with a laser to restore clarity.

Glaucoma

This is a slowly progressive, insidious optic neuropathy, usually associated with chronic elevation of intraocular pressure. In Americans of African descent it is the leading cause of blindness. The mechanism whereby raised intraocular pressure injures the optic nerve is not understood. Axons entering the inferotemporal and superotemporal aspects of the optic disc are damaged first, producing typical nerve fiber bundle or arcuate scotomas on perimetric testing. As fibers are destroyed, the neural rim of the optic disc shrinks and the physiologic cup within the optic disc enlarges (Fig. 17-15). This process is referred to as pathologic "cupping." The cup-to-disc diameter is expressed as a ratio (e.g., 0.2/1). The cup-to-disc ratio ranges widely in normal individuals, making it difficult to diagnose glaucoma reliably simply by observing an unusually large or deep optic cup. Careful documentation of serial examinations is helpful. In the patient with physiologic cupping, the large cup remains stable, whereas in the patient with glaucoma it expands relentlessly over the years. Detection of visual field loss by computerized perimetry also contributes to the diagnosis. Finally, most patients with glaucoma have raised intraocular pressure. However, many patients with typical glaucomatous cupping and visual field loss have intraocular pressures that apparently never exceed the normal limit of 20 mm Hg (so-called low-tension glaucoma).

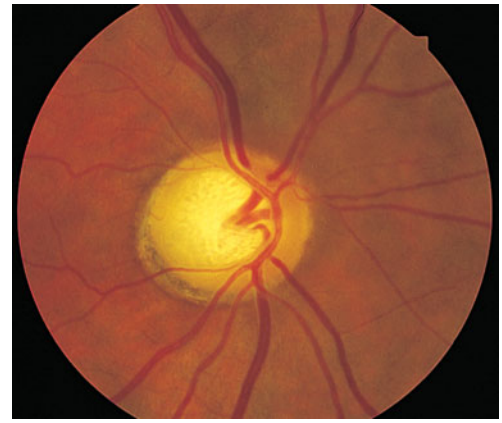

FIGURE 17-15
Glaucoma results in "cupping" as the neural rim is destroyed and the central cup becomes enlarged and excavated. The cup-to-disc ratio is about 0.7/1.0 in this patient.

In acute angle-closure glaucoma, the eye is red and painful due to abrupt, severe elevation of intraocular pressure. Such cases account for only a minority of glaucoma cases: most patients have open, anterior chamber angles. The cause of raised intraocular pressure in open angle glaucoma is unknown, but it is associated with gene mutations in the heritable forms.

Glaucoma is usually painless (except in angle-closure glaucoma). Foveal acuity is spared until end-stage disease is reached. For these reasons, severe and irreversible damage can occur before either the patient or physician recognizes the diagnosis. Screening of patients for glaucoma by noting the cup-to-disc ratio on ophthalmoscopy and by measuring intraocular pressure is vital. Glaucoma is treated with topical adrenergic agonists, cholinergic agonists, beta blockers, and prostaglandin analogues. Occasionally, systemic absorption of beta blocker from eye drops can be sufficient to cause side effects of bradycardia, hypotension, heart block, bronchospasm, or depression. Topical or oral carbonic anhydrase inhibitors are used to lower intraocular pressure by reducing aqueous production. Laser treatment of the trabecular meshwork in the anterior chamber angle improves aqueous outflow from the eye. If medical or laser treatments fail to halt optic nerve damage from glaucoma, a filter must be constructed surgically (trabeculectomy) or a valve placed to release aqueous from the eye in a controlled fashion.

Macular Degeneration

This is a major cause of gradual, painless, bilateral central visual loss in the elderly. The old term, "senile macular

degeneration," misinterpreted by many patients as an unflattering reference, has been replaced with "age-related macular degeneration." It occurs in a nonexudative (dry) form and an exudative (wet) form. Inflammation may be important in both forms of macular degeneration; recent genetic data indicates that susceptibility is associated with variants in the gene for complement factor H, an inhibitor of the alternative complement pathway. The nonexudative process begins with the accumulation of extracellular deposits, called drusen, underneath the retinal pigment epithelium. On ophthalmoscopy, they are pleomorphic but generally appear as small discrete yellow lesions clustered in the macula (Fig. 17-16). With time they become larger, more numerous, and confluent. The retinal pigment epithelium becomes focally detached and atrophic, causing visual loss by interfering with photoreceptor function. Treatment with vitamins C and E, beta carotene, and zinc may retard dry macular degeneration.

Exudative macular degeneration, which develops in only a minority of patients, occurs when neovascular vessels from the choroid grow through defects in Bruch's membrane into the potential space beneath the retinal pigment epithelium. Leakage from these vessels produces elevation of the retina and pigment epithelium, with distortion (metamorphopsia) and blurring of vision. Although onset of these symptoms is usually gradual, bleeding from subretinal choroidal neovascular membranes sometimes causes acute visual loss. The neovascular membranes can be difficult to see on fundus examination because they are beneath the retina. Fluorescein or indocyanine green angiography is extremely useful for their detection. Neovascular membranes are treated with either photodynamic therapy or intraocular injection of vascular endothelial growth factor antagonists. Surgical attempts to remove subretinal membranes in age-related macular degeneration have not improved vision in most patients. However, outcomes have been more encouraging for patients with choroidal neovascular membranes from ocular histoplasmosis syndrome.

Major or repeated hemorrhage under the retina from neovascular membranes results in fibrosis, development of a round (disciform) macular scar, and permanent loss of central vision.

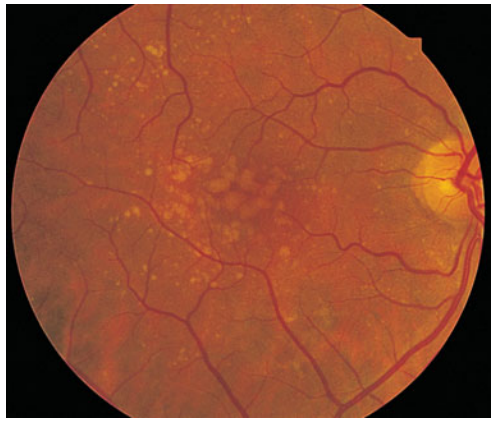

FIGURE 17-16
Age-related macular degeneration begins with the accumulation of drusen within the macula. They appear as scattered yellow subretinal deposits.

Central Serous Chorioretinopathy

This primarily affects men between 20 and 50 years of age. Leakage of serous fluid from the choroid causes small, localized detachment of the retinal pigment epithelium and the neurosensory retina. These detachments produce acute or chronic symptoms of metamorphopsia and blurred vision when the macula is involved. They are difficult to visualize with a direct ophthalmoscope because the detached retina is transparent and only slightly elevated. Diagnosis of central serous chorioretinopathy is made easily by fluorescein angiography, which shows dye streaming into the subretinal space. The cause of central serous chorioretinopathy is unknown. Symptoms may resolve spontaneously if the retina reattaches, but recurrent detachment is common. Laser photocoagulation has benefited some patients with this condition.

Diabetic Retinopathy

A rare disease until 1921, when the discovery of insulin resulted in a dramatic improvement in life expectancy for patients with diabetes mellitus, it is now a leading cause of blindness in the United States. The retinopathy of diabetes takes years to develop but eventually appears in nearly all cases. Regular surveillance of the dilated fundus is crucial for any patient with diabetes. In advanced diabetic retinopathy, the proliferation of neovascular vessels leads to blindness from vitreous hemorrhage, retinal detachment, and glaucoma. These complications can be avoided in most patients by administration of panretinal laser photocoagulation at the appropriate point in the evolution of the disease.

Retinitis Pigmentosa

This is a general term for a disparate group of rod and cone dystrophies characterized by progressive night blindness, visual field constriction with a ring scotoma, loss of acuity, and an abnormal electroretinogram (ERG). It occurs sporadically or in an autosomal recessive, dominant, or X-linked pattern. Irregular black deposits of clumped pigment in the peripheral retina, called *bone spicules* because of their vague resemblance to the spicules of cancellous bone, give the disease its name (Fig. 17-17). The name is actually a misnomer because retinitis pigmentosa is not an inflammatory process. Most cases are

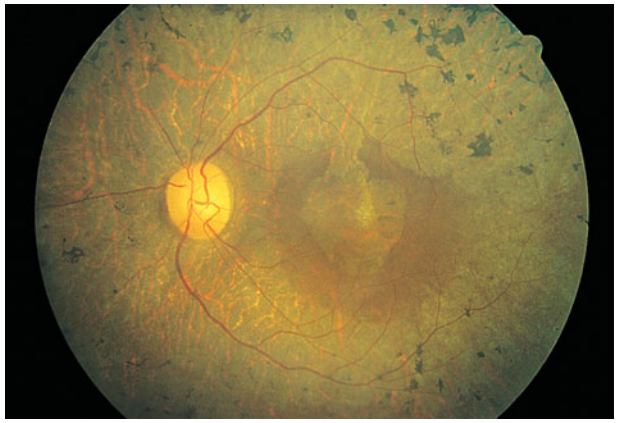

FIGURE 17-17
Retinitis pigmentosa with black clumps of pigment in the retinal periphery known as "bone spicules." There is also atrophy of the retinal pigment epithelium, making the vasculature of the choroid easily visible.

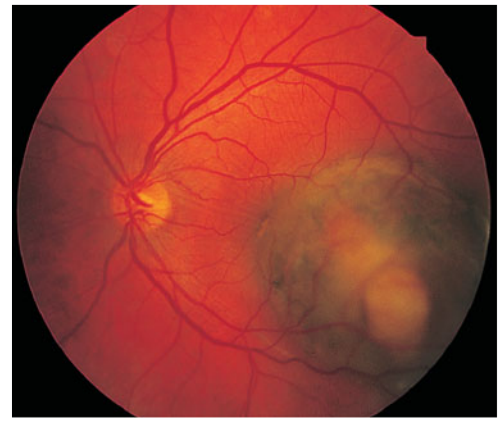

FIGURE 17-18
Melanoma of the choroid, appearing as an elevated dark mass in the inferior temporal fundus, just encroaching upon the fovea.

due to a mutation in the gene for rhodopsin, the rod photopigment, or in the gene for peripherin, a glycoprotein located in photoreceptor outer segments. Vitamin A (15,000 IU/day) slightly retards the deterioration of the ERG in patients with retinitis pigmentosa but has no beneficial effect on visual acuity or fields. Some forms of retinitis pigmentosa occur in association with rare, hereditary systemic diseases (olivopontocerebellar degeneration, Bassen-Kornzweig disease, Kearns-Sayre syndrome, Refsum's disease). Chronic treatment with chloroquine, hydroxychloroquine, and phenothiazines (especially thioridazine) can produce visual loss from a toxic retinopathy that resembles retinitis pigmentosa.

Epiretinal Membrane

This is a fibrocellular tissue that grows across the inner surface of the retina, causing metamorphopsia and reduced visual acuity from distortion of the macula. A crinkled, cellophane-like membrane is visible on the retinal examination. Epiretinal membrane is most common in patients older than 50 years and is usually unilateral. Most cases are idiopathic, but some occur as a result of hypertensive retinopathy, diabetes, retinal detachment, or trauma. When visual acuity is reduced to the level of about 6/24 (20/80), vitrectomy and surgical peeling of the membrane to relieve macular puckering are recommended. Contraction of an epiretinal membrane sometimes gives rise to a *macular hole*. Most macular holes, however, are caused by local vitreous traction within the fovea. Vitrectomy can improve acuity in selected cases.

Melanoma and Other Tumors

Melanoma is the most common primary tumor of the eye (Fig. 17-18). It causes photopsia, an enlarging scotoma, and loss of vision. A small melanoma is often difficult to differentiate from a benign choroidal nevus. Serial examinations are required to document a malignant pattern of growth. Treatment of melanoma is controversial. Options include enucleation, local resection, and irradiation. *Metastatic tumors* to the eye outnumber primary tumors. Breast and lung carcinoma have a special propensity to spread to the choroid or iris. Leukemia and lymphoma also commonly invade ocular tissues. Sometimes their only sign on eye examination is cellular debris in the vitreous, which can masquerade as a chronic posterior uveitis. *Retrobulbar tumor* of the optic nerve (meningioma, glioma) or *chiasmal tumor* (pituitary adenoma, meningioma) produces gradual visual loss with few objective findings, except for optic disc pallor. Rarely, sudden expansion of a pituitary adenoma from infarction and bleeding (*pituitary apoplexy*) causes acute retrobulbar visual loss, with headache, nausea, and ocular motor nerve palsies. In any patient with visual field loss or optic atrophy, CT or MR scanning should be considered if the cause remains unknown after careful review of the history and thorough examination of the eye.

PROPTOSIS

When the globes appear asymmetric, the clinician must first decide which eye is abnormal. Is one eye recessed within the orbit (*enophthalmos*) or is the other eye protuberant (*exophthalmos*, or *proptosis*)? A small globe or a Horner's syndrome can give the appearance of enophthalmos. True enophthalmos occurs commonly after trauma, from atrophy of retrobulbar fat, or fracture of the orbital floor. The position of the eyes within the orbits is measured using a Hertel exophthalmometer, a hand-held instrument that records the position of the

anterior corneal surface relative to the lateral orbital rim. If this instrument is not available, relative eye position can be judged by bending the patient's head forward and looking down upon the orbits. A proptosis of only 2 mm in one eye is detectable from this perspective. The development of proptosis implies a space-occupying lesion in the orbit, and usually warrants CT or MR imaging.

Graves' Ophthalmopathy

This is the leading cause of proptosis in adults. The proptosis is often asymmetric and can even appear to be unilateral. Orbital inflammation and engorgement of the extraocular muscles, particularly the medial rectus and the inferior rectus, account for the protrusion of the globe. Corneal exposure, lid retraction, conjunctival injection, restriction of gaze, diplopia, and visual loss from optic nerve compression are cardinal symptoms. Graves' ophthalmopathy is treated with oral prednisone (60 mg/d) for 1 month, followed by a taper over several months, topical lubricants, eyelid surgery, eye muscle surgery, or orbital decompression. Radiation therapy is not effective.

Orbital Pseudotumor

This is an idiopathic, inflammatory orbital syndrome, frequently confused with Graves' ophthalmopathy. Symptoms are pain, limited eye movements, proptosis, and congestion. Evaluation for sarcoidosis, Wegener's granulomatosis, and other types of orbital vasculitis or collagen-vascular disease is negative. Imaging often shows swollen eye muscles (orbital myositis) with enlarged tendons. By contrast, in Graves' ophthalmopathy the tendons of the eye muscles are usually spared. The Tolosa-Hunt syndrome may be regarded as an extension of orbital pseudotumor through the superior orbital fissure into the cavernous sinus. The diagnosis of orbital pseudotumor is difficult. Biopsy of the orbit frequently yields nonspecific evidence of fat infiltration by lymphocytes, plasma cells, and eosinophils. A dramatic response to a therapeutic trial of systemic glucocorticoids indirectly provides the best confirmation of the diagnosis.

Orbital Cellulitis

This causes pain, lid erythema, proptosis, conjunctival chemosis, restricted motility, decreased acuity, afferent pupillary defect, fever, and leukocytosis. It often arises from the paranasal sinuses, especially by contiguous spread of infection from the ethmoid sinus through the lamina papyracea of the medial orbit. A history of recent upper respiratory tract infection, chronic sinusitis, thick mucous secretions, or dental disease is significant in any patient with suspected orbital cellulitis. Blood cultures should be obtained, but they are usually negative. Most patients respond to empirical therapy with broad-spectrum IV antibiotics. Occasionally, orbital cellulitis follows an overwhelming course, with massive proptosis, blindness, septic cavernous sinus thrombosis, and meningitis. To avert this disaster, orbital cellulitis should be managed aggressively in the early stages, with immediate imaging of the orbits and antibiotic therapy that includes coverage of methicillin-resistant *Staphylococcus aureus*. Prompt surgical drainage of an orbital abscess or paranasal sinusitis is indicated if optic nerve function deteriorates despite antibiotics.

Tumors

Tumors of the orbit cause painless, progressive proptosis. The most common primary tumors are hemangioma, lymphangioma, neurofibroma, dermoid cyst, adenoid cystic carcinoma, optic nerve glioma, optic nerve meningioma, and benign mixed tumor of the lacrimal gland. Metastatic tumor to the orbit occurs frequently in breast carcinoma, lung carcinoma, and lymphoma. Diagnosis by fine-needle aspiration followed by urgent radiation therapy can sometimes preserve vision.

Carotid Cavernous Fistulas

With anterior drainage through the orbit these produce proptosis, diplopia, glaucoma, and corkscrew, arterialized conjunctival vessels. Direct fistulas usually result from trauma. They are easily diagnosed because of the prominent signs produced by high-flow, high-pressure shunting. Indirect fistulas, or dural arteriovenous malformations, are more likely to occur spontaneously, especially in older women. The signs are more subtle and the diagnosis is frequently missed. The combination of slight proptosis, diplopia, enlarged muscles, and an injected eye is often mistaken for thyroid ophthalmopathy. A bruit heard upon auscultation of the head, or reported by the patient, is a valuable diagnostic clue. Imaging shows an enlarged superior ophthalmic vein in the orbits. Carotid cavernous shunts can be eliminated by intravascular embolization.

PTOSIS

Blepharoptosis

This is an abnormal drooping of the eyelid. Unilateral or bilateral ptosis can be congenital, from dysgenesis of the levator palpebrae superioris, or from abnormal insertion of its aponeurosis into the eyelid. Acquired ptosis can develop so gradually that the patient is unaware of the problem. Inspection of old photographs is helpful in dating the onset. A history of prior trauma, eye surgery, contact lens use, diplopia, systemic symptoms (e.g., dysphagia or peripheral muscle weakness), or a family history of ptosis should be sought. Fluctuating ptosis that worsens late in the day is typical of myasthenia gravis. Examination should focus upon evidence for proptosis, eyelid masses or deformities, inflammation, pupil inequality, or limitation of motility. The width of the

palpebral fissures is measured in primary gaze to quantitate the degree of ptosis. The ptosis will be underestimated if the patient compensates by lifting the brow with the frontalis muscle.

Mechanical Ptosis

This occurs in many elderly patients from stretching and redundancy of eyelid skin and subcutaneous fat (dermatochalasis). The extra weight of these sagging tissues causes the lid to droop. Enlargement or deformation of the eyelid from infection, tumor, trauma, or inflammation also results in ptosis on a purely mechanical basis.

Aponeurotic Ptosis

This is an acquired dehiscence or stretching of the aponeurotic tendon, which connects the levator muscle to the tarsal plate of the eyelid. It occurs commonly in older patients, presumably from loss of connective tissue elasticity. Aponeurotic ptosis is also a frequent sequela of eyelid swelling from infection or blunt trauma to the orbit, cataract surgery, or hard contact lens usage.

Myogenic Ptosis

The causes of *myogenic ptosis* include myasthenia gravis (Chap. 42) and a number of rare myopathies that manifest with ptosis. The term *chronic progressive external ophthalmoplegia* refers to a spectrum of systemic diseases caused by mutations of mitochondrial DNA. As the name implies, the most prominent findings are symmetric, slowly progressive ptosis and limitation of eye movements. In general, diplopia is a late symptom because all eye movements are reduced equally. In the *Kearns-Sayre* variant, retinal pigmentary changes and abnormalities of cardiac conduction develop. Peripheral muscle biopsy shows characteristic "ragged-red fibers." *Oculopharyngeal dystrophy* is a distinct autosomal dominant disease with onset in middle age, characterized by ptosis, limited eye movements, and trouble swallowing. *Myotonic dystrophy*, another autosomal dominant disorder, causes ptosis, ophthalmoparesis, cataract, and pigmentary retinopathy. Patients have muscle wasting, myotonia, frontal balding, and cardiac abnormalities.

Neurogenic Ptosis

This results from a lesion affecting the innervation to either of the two muscles that open the eyelid: Müller's muscle or the levator palpebrae superioris. Examination of the pupil helps to distinguish between these two possibilities. In Horner's syndrome, the eye with ptosis has a smaller pupil and the eye movements are full. In an oculomotor nerve palsy, the eye with the ptosis has a larger, or a normal, pupil. If the pupil is normal but there is limitation of adduction, elevation, and depression, a pupil-sparing oculomotor nerve palsy is likely (see next section). Rarely, a lesion affecting the small, central subnucleus of the oculomotor complex will cause bilateral ptosis with normal eye movements and pupils.

DOUBLE VISION (DIPLOPIA)

The first point to clarify is whether diplopia persists in either eye after covering the opposite eye. If it does, the diagnosis is monocular diplopia. The cause is usually intrinsic to the eye and therefore has no dire implications for the patient. Corneal aberrations (e.g., keratoconus, pterygium), uncorrected refractive error, cataract, or foveal traction may give rise to monocular diplopia. Occasionally it is a symptom of malingering or psychiatric disease. Diplopia alleviated by covering one eye is binocular diplopia and is caused by disruption of ocular alignment. Inquiry should be made into the nature of the double vision (purely side-by-side versus partial vertical displacement of images), mode of onset, duration, intermittency, diurnal variation, and associated neurologic or systemic symptoms. If the patient has diplopia while being examined, motility testing should reveal a deficiency corresponding to the patient's symptoms. However, subtle limitation of ocular excursions is often difficult to detect. For example, a patient with a slight left abducens nerve paresis may appear to have full eye movements, despite a complaint of horizontal diplopia upon looking to the left. In this situation, the cover test provides a more sensitive method for demonstrating the ocular misalignment. It should be conducted in primary gaze, and then with the head turned and tilted in each direction. In the above example, a cover test with the head turned to the right will maximize the fixation shift evoked by the cover test.

Occasionally, a cover test performed in an asymptomatic patient during a routine examination will reveal an ocular deviation. If the eye movements are full and the ocular misalignment is equal in all directions of gaze (concomitant deviation), the diagnosis is strabismus. In this condition, which affects about 1% of the population, fusion is disrupted in infancy or early childhood. To avoid diplopia, vision is suppressed from the nonfixating eye. In some children, this leads to impaired vision (amblyopia, or "lazy" eye) in the deviated eye.

Binocular diplopia occurs from a wide range of processes: infectious, neoplastic, metabolic, degenerative, inflammatory, and vascular. One must decide if the diplopia is neurogenic in origin or due to restriction of globe rotation by local disease in the orbit. Orbital pseudotumor, myositis, infection, tumor, thyroid disease, and muscle entrapment (e.g., from a blowout fracture) cause restrictive diplopia. The diagnosis of restriction is usually made by recognizing other associated signs and symptoms of local orbital disease in conjunction with imaging.

Myasthenia Gravis

(See Chap. 42) This is a major cause of diplopia. The diplopia is often intermittent, variable, and not confined to any single ocular motor nerve distribution. The pupils are always normal. Fluctuating ptosis may be present. Many patients have a purely ocular form of the disease, with no evidence of systemic muscular weakness. The diagnosis can be confirmed by an IV edrophonium injection or by an assay for antiacetylcholine receptor antibodies. Negative results from these tests do not exclude the diagnosis. *Botulism* from food or wound poisoning can mimic ocular myasthenia.

After restrictive orbital disease and myasthenia gravis are excluded, a lesion of a cranial nerve supplying innervation to the extraocular muscles is the most likely cause of binocular diplopia.

Oculomotor Nerve

The third cranial nerve innervates the medial, inferior, and superior recti; inferior oblique; levator palpebrae superioris; and the iris sphincter. Total palsy of the oculomotor nerve causes ptosis, a dilated pupil, and leaves the eye "down and out" because of the unopposed action of the lateral rectus and superior oblique. This combination of findings is obvious. More challenging is the diagnosis of early or partial oculomotor nerve palsy. In this setting, any combination of ptosis, pupil dilation, and weakness of the eye muscles supplied by the oculomotor nerve may be encountered. Frequent serial examinations during the evolving phase of the palsy help ensure that the diagnosis is not missed. The advent of an oculomotor nerve palsy with a pupil involvement, especially when accompanied by pain, suggests a compressive lesion, such as a tumor or circle of Willis aneurysm. Neuroimaging should be obtained, along with a CT or MR angiogram. Occasionally, a catheter arteriogram must be done to exclude an aneurysm.

A lesion of the oculomotor nucleus in the rostral midbrain produces signs that differ from those caused by a lesion of the nerve itself. There is bilateral ptosis because the levator muscle is innervated by a single central subnucleus. There is also weakness of the contralateral superior rectus, because it is supplied by the oculomotor nucleus on the other side. Occasionally both superior recti are weak. Isolated nuclear oculomotor palsy is rare. Usually neurologic examination reveals additional signs to suggest brainstem damage from infarction, hemorrhage, tumor, or infection.

Injury to structures surrounding fascicles of the oculomotor nerve descending through the midbrain has given rise to a number of classic eponymic designations. In *Nothnagel's syndrome*, injury to the superior cerebellar peduncle causes ipsilateral oculomotor palsy and contralateral cerebellar ataxia. In *Benedikt's syndrome*, injury to the red nucleus results in ipsilateral oculomotor palsy and contralateral tremor, chorea, and athetosis. *Claude's syndrome* incorporates features of both the aforementioned syndromes, by injury to both the red nucleus and the superior cerebellar peduncle. Finally, in *Weber's syndrome*, injury to the cerebral peduncle causes ipsilateral oculomotor palsy with contralateral hemiparesis.

In the subarachnoid space the oculomotor nerve is vulnerable to aneurysm, meningitis, tumor, infarction, and compression. In cerebral herniation the nerve becomes trapped between the edge of the tentorium and the uncus of the temporal lobe. Oculomotor palsy can also occur from midbrain torsion and hemorrhages during herniation. In the cavernous sinus, oculomotor palsy arises from carotid aneurysm, carotid cavernous fistula, cavernous sinus thrombosis, tumor (pituitary adenoma, meningioma, metastasis), herpes zoster infection, and the Tolosa-Hunt syndrome.

The etiology of an isolated, pupil-sparing oculomotor palsy often remains an enigma, even after neuroimaging and extensive laboratory testing. Most cases are thought to result from microvascular infarction of the nerve, somewhere along its course from the brainstem to the orbit. Usually the patient complains of pain. Diabetes, hypertension, and vascular disease are major risk factors. Spontaneous recovery over a period of months is the rule. If this fails to occur, or if new findings develop, the diagnosis of microvascular oculomotor nerve palsy should be reconsidered. Aberrant regeneration is common when the oculomotor nerve is injured by trauma or compression (tumor, aneurysm). Miswiring of sprouting fibers to the levator muscle and the rectus muscles results in elevation of the eyelid upon downgaze or adduction. The pupil also constricts upon attempted adduction, elevation, or depression of the globe. Aberrant regeneration is not seen after oculomotor palsy from microvascular infarct and hence vitiates that diagnosis.

Trochlear Nerve

The fourth cranial nerve originates in the midbrain, just caudal to the oculomotor nerve complex. Fibers exit the brainstem dorsally and cross to innervate the contralateral superior oblique. The principal actions of this muscle are to depress and to intort the globe. A palsy therefore results in hypertropia and excyclotorsion. The cyclotorsion is seldom noticed by patients. Instead, they complain of vertical diplopia, especially upon reading or looking down. The vertical diplopia is also exacerbated by tilting the head toward the side with the muscle palsy, and alleviated by tilting it away. This "head tilt test" is a cardinal diagnostic feature.

Isolated trochlear nerve palsy occurs from all the causes listed above for the oculomotor nerve, except aneurysm. The trochlear nerve is particularly apt to suffer injury after closed head trauma. The free edge of the tentorium

is thought to impinge upon the nerve during a concussive blow. Most isolated trochlear nerve palsies are idiopathic and hence diagnosed by exclusion as "microvascular." Spontaneous improvement occurs over a period of months in most patients. A base-down prism (conveniently applied to the patient's glasses as a stick-on Fresnel lens) may serve as a temporary measure to alleviate diplopia. If the palsy does not resolve, the eyes can be realigned by weakening the inferior oblique muscle.

Abducens Nerve

The sixth cranial nerve innervates the lateral rectus muscle. A palsy produces horizontal diplopia, worse on gaze to the side of the lesion. A nuclear lesion has different consequences, because the abducens nucleus contains interneurons that project via the medial longitudinal fasciculus to the medial rectus subnucleus of the contralateral oculomotor complex. Therefore, an abducens nuclear lesion produces a complete lateral gaze palsy, from weakness of both the ipsilateral lateral rectus and the contralateral medial rectus. *Foville's syndrome* following dorsal pontine injury includes lateral gaze palsy, ipsilateral facial palsy, and contralateral hemiparesis incurred by damage to descending corticospinal fibers. *Millard-Gubler syndrome* from ventral pontine injury is similar, except for the eye findings. There is lateral rectus weakness only, instead of gaze palsy, because the abducens fascicle is injured rather than the nucleus. Infarct, tumor, hemorrhage, vascular malformation, and multiple sclerosis are the most common etiologies of brainstem abducens palsy.

After leaving the ventral pons, the abducens nerve runs forward along the clivus to pierce the dura at the petrous apex, where it enters the cavernous sinus. Along its subarachnoid course it is susceptible to meningitis, tumor (meningioma, chordoma, carcinomatous meningitis), subarachnoid hemorrhage, trauma, and compression by aneurysm or dolichoectatic vessels. At the petrous apex, mastoiditis can produce deafness, pain, and ipsilateral abducens palsy (*Gradenigo's syndrome*). In the cavernous sinus, the nerve can be affected by carotid aneurysm, carotid cavernous fistula, tumor (pituitary adenoma, meningioma, nasopharyngeal carcinoma), herpes infection, and Tolosa-Hunt syndrome.

Unilateral or bilateral abducens palsy is a classic sign of raised intracranial pressure. The diagnosis can be confirmed if papilledema is observed on fundus examination. The mechanism is still debated but is probably related to rostral-caudal displacement of the brainstem. The same phenomenon accounts for abducens palsy from low intracranial pressure (e.g., after lumbar puncture, spinal anesthesia, or spontaneous dural cerebrospinal fluid leak).

Treatment of abducens palsy is aimed at prompt correction of the underlying cause. However, the cause remains obscure in many instances, despite diligent evaluation. As mentioned above for isolated trochlear or oculomotor palsy, most cases are assumed to represent microvascular infarcts because they often occur in the setting of diabetes or other vascular risk factors. Some cases may develop as a postinfectious mononeuritis (e.g., following a viral flu). Patching one eye or applying a temporary prism will provide relief of diplopia until the palsy resolves. If recovery is incomplete, eye muscle surgery can nearly always realign the eyes, at least in primary position. A patient with an abducens palsy that fails to improve should be reevaluated for an occult etiology (e.g., chordoma, carcinomatous meningitis, carotid cavernous fistula, myasthenia gravis).

Multiple Ocular Motor Nerve Palsies

These should not be attributed to spontaneous microvascular events affecting more than one cranial nerve at a time. This remarkable coincidence does occur, especially in diabetic patients, but the diagnosis is made only in retrospect after exhausting all other diagnostic alternatives. Neuroimaging should focus on the cavernous sinus, superior orbital fissure, and orbital apex, where all three ocular motor nerves are in close proximity. In the diabetic or compromised host, fungal infection (*Aspergillus*, Mucorales, *Cryptococcus*) is a frequent cause of multiple nerve palsies. In the patient with systemic malignancy, carcinomatous meningitis is a likely diagnosis. Cytologic examination may be negative despite repeated sampling of the cerebrospinal fluid. The cancer-associated Lambert-Eaton myasthenic syndrome can also produce ophthalmoplegia. Giant cell (temporal) arteritis occasionally manifests as diplopia from ischemic palsies of extraocular muscles. Fisher syndrome, an ocular variant of Guillain-Barré, produces ophthalmoplegia with areflexia and ataxia. Often the ataxia is mild, and the reflexes are normal. Antiganglioside antibodies (GQ1b) can be detected in about 50% of cases.

Supranuclear Disorders of Gaze

These are often mistaken for multiple ocular motor nerve palsies. For example, Wernicke's encephalopathy can produce nystagmus and a partial deficit of horizontal and vertical gaze that mimics a combined abducens and oculomotor nerve palsy. The disorder occurs in malnourished or alcoholic patients and can be reversed by thiamine. Infarct, hemorrhage, tumor, multiple sclerosis, encephalitis, vasculitis, and Whipple's disease are other important causes of supranuclear gaze palsy. Disorders of vertical gaze, especially downwards saccades, are an early feature of progressive supranuclear palsy. Smooth pursuit is affected later in the course of the disease. Parkinson's disease, Huntington's chorea, and olivopontocerebellar degeneration can also affect vertical gaze.

The *frontal eye field* of the cerebral cortex is involved in generation of saccades to the contralateral side. After hemispheric stroke, the eyes usually deviate towards the lesioned side because of the unopposed action of the frontal eye field in the normal hemisphere. With time, this deficit resolves. Seizures generally have the opposite effect: the eyes deviate conjugately away from the irritative focus. *Parietal lesions* disrupt smooth pursuit of targets moving toward the side of the lesion. Bilateral parietal lesions produce *Balint's syndrome*, characterized by impaired eye-hand coordination (optic ataxia), difficulty initiating voluntary eye movements (ocular apraxia), and visuospatial disorientation (simultanagnosia).

Horizontal Gaze

Descending cortical inputs mediating horizontal gaze ultimately converge at the level of the pons. Neurons in the paramedian pontine reticular formation are responsible for controlling conjugate gaze toward the same side. They project directly to the ipsilateral abducens nucleus. A lesion of either the paramedian pontine reticular formation or the abducens nucleus causes an ipsilateral conjugate gaze palsy. Lesions at either locus produce nearly identical clinical syndromes, with the following exception: vestibular stimulation (oculocephalic maneuver or caloric irrigation) will succeed in driving the eyes conjugately to the side in a patient with a lesion of the paramedian pontine reticular formation, but not in a patient with a lesion of the abducens nucleus.

Internuclear Ophthalmoplegia

This results from damage to the medial longitudinal fasciculus ascending from the abducens nucleus in the pons to the oculomotor nucleus in the midbrain (hence, "internuclear"). Damage to fibers carrying the conjugate signal from abducens interneurons to the contralateral medial rectus motoneurons results in a failure of adduction on attempted lateral gaze. For example, a patient with a left internuclear ophthalmoplegia will have slowed or absent adducting movements of the left eye (**Fig. 17-19**). A patient with bilateral injury to the medial longitudinal fasciculus will have bilateral internuclear ophthalmoplegia. Multiple sclerosis is the most common cause, although tumor, stroke, trauma, or any brainstem process may be responsible. *One-and-a-half syndrome* is due to a combined lesion of the medial longitudinal fasciculus and the abducens nucleus on the same side. The patient's only horizontal eye movement is abduction of the eye on the other side.

Vertical Gaze

This is controlled at the level of the midbrain. The neuronal circuits affected in disorders of vertical gaze are not fully elucidated, but lesions of the rostral interstitial

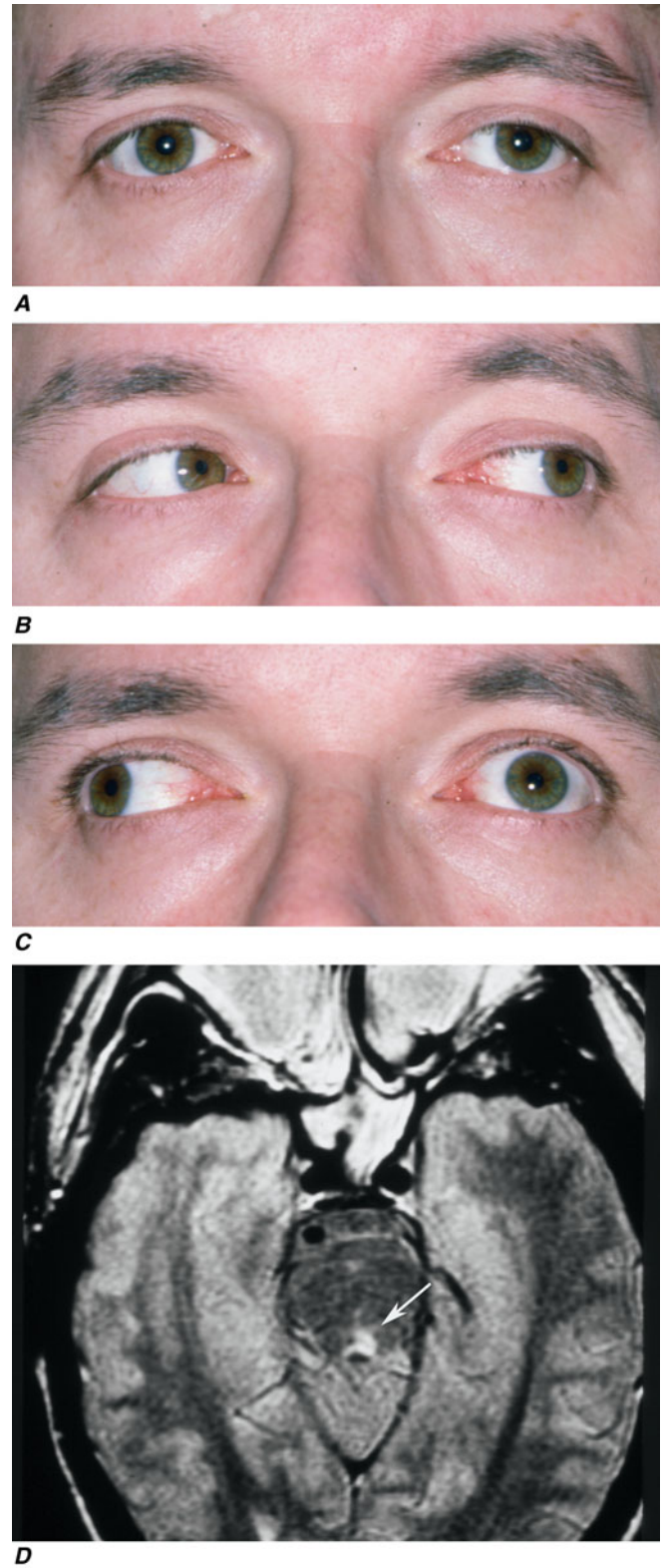

FIGURE 17-19

Left internuclear ophthalmoplegia (INO). *A.* In primary position of gaze the eyes appear normal. ***B.*** Horizontal gaze to the left is intact. ***C.*** On attempted horizontal gaze to the right, the left eye fails to adduct. In mildly affected patients the eye may adduct partially, or more slowly than normal. Nystagmus is usually present in the abducted eye. ***D.*** T2-weighted axial MRI image through the pons showing a demyelinating plaque in the left medial longitudinal fasciculus (*arrow*).

nucleus of the medial longitudinal fasciculus and the interstitial nucleus of Cajal cause supranuclear paresis of upgaze, downgaze, or all vertical eye movements. Distal basilar artery ischemia is the most common etiology. *Skew deviation* refers to a vertical misalignment of the eyes, usually constant in all positions of gaze. The finding has poor localizing value because skew deviation has been reported after lesions in widespread regions of the brainstem and cerebellum.

Parinaud's Syndrome

Also known as dorsal midbrain syndrome, this is a distinct supranuclear vertical gaze disorder from damage to the posterior commissure. It is a classic sign of hydrocephalus from aqueductal stenosis. Pineal region tumors, cysticercosis, and stroke also cause Parinaud's syndrome. Features include loss of upgaze (and sometimes downgaze), convergence-retraction nystagmus on attempted upgaze, downwards ocular deviation ("setting sun" sign), lid retraction (Collier's sign), skew deviation, pseudoabducens palsy, and light-near dissociation of the pupils.

Nystagmus

This is a rhythmical oscillation of the eyes, occurring physiologically from vestibular and optokinetic stimulation or pathologically in a wide variety of diseases (Chap. 9). Abnormalities of the eyes or optic nerves, present at birth or acquired in childhood, can produce a complex, searching nystagmus with irregular pendular (sinusoidal) and jerk features. This nystagmus is commonly referred to as *congenital sensory nystagmus*. It is a poor term, because even in children with congenital lesions, the nystagmus does not appear until several months of age. *Congenital motor nystagmus*, which looks similar to congenital sensory nystagmus, develops in the absence of any abnormality of the sensory visual system. Visual acuity is also reduced in congenital motor nystagmus, probably by the nystagmus itself, but seldom below a level of 20/200.

Jerk Nystagmus

This is characterized by a slow drift off the target, followed by a fast corrective saccade. By convention, the nystagmus is named after the quick phase. Jerk nystagmus can be downbeat, upbeat, horizontal (left or right), and torsional. The pattern of nystagmus may vary with gaze position. Some patients will be oblivious to their nystagmus. Others will complain of blurred vision, or a subjective, to-and-fro movement of the environment (oscillopsia) corresponding to their nystagmus. Fine nystagmus may be difficult to see upon gross examination of the eyes. Observation of nystagmoid movements of the optic disc on ophthalmoscopy is a sensitive way to detect subtle nystagmus.

Gaze-Evoked Nystagmus

This is the most common form of jerk nystagmus. When the eyes are held eccentrically in the orbits, they have a natural tendency to drift back to primary position. The subject compensates by making a corrective saccade to maintain the deviated eye position. Many normal patients have mild gaze-evoked nystagmus. Exaggerated gaze-evoked nystagmus can be induced by drugs (sedatives, anticonvulsants, alcohol); muscle paresis; myasthenia gravis; demyelinating disease; and cerebellopontine angle, brainstem, and cerebellar lesions.

Vestibular Nystagmus

Vestibular nystagmus results from dysfunction of the labyrinth (Ménière's disease), vestibular nerve, or vestibular nucleus in the brainstem. Peripheral vestibular nystagmus often occurs in discrete attacks, with symptoms of nausea and vertigo. There may be associated tinnitus and hearing loss. Sudden shifts in head position may provoke or exacerbate symptoms.

Downbeat Nystagmus

Downbeat nystagmus occurs from lesions near the craniocervical junction (Chiari malformation, basilar invagination). It has also been reported in brainstem or cerebellar stroke, lithium or anticonvulsant intoxication, alcoholism, and multiple sclerosis. Upbeat nystagmus is associated with damage to the pontine tegmentum, from stroke, demyelination, or tumor.

Opsoclonus

This rare, dramatic disorder of eye movements consists of bursts of consecutive saccades (saccadomania). When the saccades are confined to the horizontal plane, the term *ocular flutter* is preferred. It can occur from viral encephalitis, trauma, or a paraneoplastic effect of neuroblastoma, breast carcinoma, and other malignancies. It has also been reported as a benign, transient phenomenon in otherwise healthy patients.

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CHAPTER 18

DISORDERS OF SMELL, TASTE, AND HEARING

Anil K. Lalwani

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SMELL

The sense of smell determines the flavor and palatability of food and drink and serves, along with the trigeminal system, as a monitor of inhaled chemicals, including dangerous substances such as natural gas, smoke, and air pollutants. Olfactory dysfunction affects ~1% of individuals younger than 60 years and more than one-half of the population beyond this age.

DEFINITIONS

Smell is the perception of odor by the nose. *Taste* is the perception of salty, sweet, sour, or bitter by the tongue. Related sensations during eating such as somatic sensations of coolness, warmth, and irritation are mediated through the trigeminal, glossopharyngeal, and vagal afferents in the nose, oral cavity, tongue, pharynx, and larynx. *Flavor* is the complex interaction of taste, smell, and somatic sensation. Terms relating to disorders of smell include *anosmia*, an absence of the ability to smell; *hyposmia*, a decreased ability to smell; *hyperosmia*, an increased sensitivity to an odorant; *dysosmia*, distortion in the perception of an odor; *phantosmia*, perception of an odorant where none is present; and *agnosia*, inability to classify, contrast, or identify odor sensations verbally, even though the ability to distinguish between odorants or to recognize them may be normal. An odor stimulus is referred to as an *odorant*. Each category of smell dysfunction can be further subclassified as total (applying to all odorants) or partial (dysfunction of only select odorants).

PHYSIOLOGY OF SMELL

The *olfactory epithelium* is located in the superior part of the nasal cavities and is highly variable in its distribution between individuals. Over time the olfactory epithelium loses its homogeneity, as small areas undergo metaplasia producing islands of respiratory-like epithelium. This process is thought to be secondary to insults from environmental toxins, bacteria, and viruses. The primary sensory neuron in the olfactory epithelium is the bipolar cell. The dendritic process of the bipolar cell has a bulb-shaped vesicle that projects into the mucous layer and bears six to eight cilia containing odorant receptors. On average, each bipolar cell elaborates 56 cm^2 (9 $in.^2$) of surface area to receive olfactory stimuli. These primary sensory neurons are unique among sensory systems in that they are short-lived, regularly replaced, and regenerate and establish new central connections after injury. Basal stem cells, located on the basal surface of the olfactory epithelium, are the progenitors that differentiate into new bipolar cells (**Fig. 18-1**).

Between 50 and 200 unmyelinated axons of receptor cells form the fila of the olfactory nerve; they pass through the cribriform plate to terminate within spherical masses

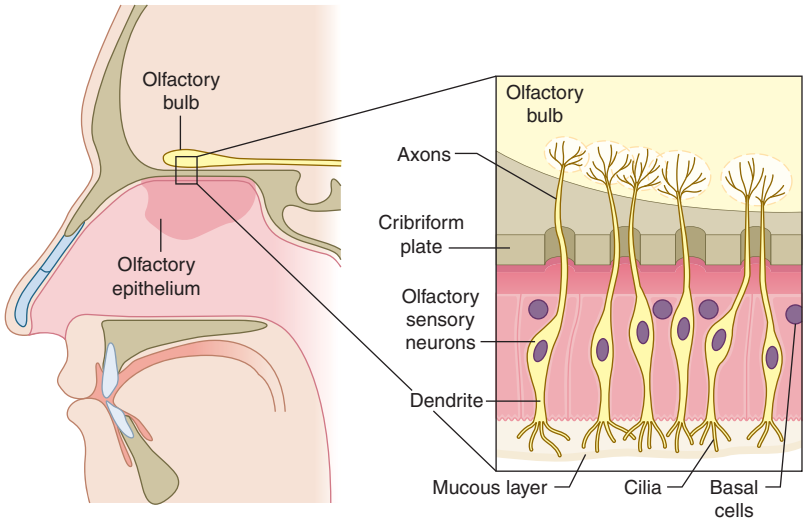

FIGURE 18-1
Olfaction. Olfactory sensory neurons (bipolar cells) are embedded in a small area of specialized epithelium in the dorsal posterior recess of the nasal cavity. These neurons project axons to the olfactory bulb of the brain, a small ovoid structure that rests on the cribriform plate of the ethmoid bone. Odorants bind to specific receptors on olfactory cilia and initiate a cascade of action potential events that lead to the production of action potentials in the sensory axons.

of neuropil, termed *glomeruli*, in the olfactory bulb. Olfactory ensheathing cells, which have features resembling glia of both the central and peripheral nervous systems, surround the axons along their course. The glomeruli are the focus of a high degree of convergence of information, since many more fibers enter than leave them. The main second-order neurons are mitral cells. The primary dendrite of each mitral cell extends into a single glomerulus. Axons of the mitral cells project along with the axons of adjacent tufted cells to the limbic system, including the anterior olfactory nucleus and the amygdala. Cognitive awareness of smell requires stimulation of the prepiriform cortex or amygdaloid nuclei.

A secondary site of olfactory chemosensation is located in the epithelium of the vomeronasal organ, a tubular structure that opens on the ventral aspect of the nasal septum. In humans, this structure is rudimentary and nonfunctional, without central projections. Sensory neurons located in the vomeronasal organ detect pheromones, nonvolatile chemical signals that in lower mammals trigger innate and stereotyped reproductive and social behaviors, as well as neuroendocrine changes.

The sensation of smell begins with introduction of an odorant to the cilia of the bipolar neuron. Most odorants are hydrophobic; as they move from the air phase of the nasal cavity to the aqueous phase of the olfactory mucous, they are transported toward the cilia by small water-soluble proteins called *odorant-binding proteins* and reversibly bind to receptors on the cilia surface. Binding leads to conformational changes in the receptor protein, activation of G protein–coupled second messengers, and generation of action potentials in the primary neurons. Intensity appears to be coded by the amount of firing in the afferent neurons.

Olfactory receptor proteins belong to the large family of G protein–coupled receptors that also includes rhodopsins; α- and β-adrenergic receptors; muscarinic acetylcholine receptors; and neurotransmitter receptors for dopamine, serotonin, and substance P. In humans, there are 300–1000 olfactory receptor genes belonging to 20 different families located in clusters at >25 different chromosomal locations. Each olfactory neuron expresses only one or, at most, a few receptor genes, thus providing the molecular basis of odor discrimination. Bipolar cells that express similar receptors appear to be scattered across discrete spatial zones. These similar cells converge on a select few glomeruli in the olfactory bulb. The result is a potential spatial map of how we receive odor stimuli, much like the tonotopic organization of how we perceive sound.

DISORDERS OF THE SENSE OF SMELL

These are caused by conditions that interfere with the access of the odorant to the olfactory neuroepithelium (transport loss), injure the receptor region (sensory loss), or damage central olfactory pathways (neural loss). Currently no clinical tests exist to differentiate these different types of olfactory losses. Fortunately, the history of the disease provides important clues to the cause. The leading causes of olfactory disorders are summarized in **Table 18-1**; the most common etiologies are head trauma in children and young adults, and viral infections in older adults.

Head trauma is followed by unilateral or bilateral impairment of smell in up to 15% of cases; anosmia is more common than hyposmia. Olfactory dysfunction is more common when trauma is associated with loss of consciousness, moderately severe head injury (grades II–V), and skull fracture. Frontal injuries and fractures disrupt the cribriform plate and olfactory axons that perforate it. Sometimes there is an associated cerebrospinal fluid (CSF) rhinorrhea resulting from a tearing of the dura overlying the cribriform plate and paranasal

TABLE 18-1

CAUSES OF OLFACTORY DYSFUNCTION

Transport Losses	Neural Losses
Allergic rhinitis	AIDS
Bacterial rhinitis and sinusitis	Alcoholism
Congenital abnormalities	Alzheimer's disease
Nasal neoplasms	Cigarette smoke
Nasal polyps	Depression
Nasal septal deviation	Diabetes mellitus
Nasal surgery	Drugs/toxins
Viral infections	Huntington's chorea
Sensory Losses	Hypothyroidism
Drugs	Kallmann syndrome
Neoplasms	Malnutrition
Radiation therapy	Neoplasms
Toxin exposure	Neurosurgery
Viral infections	Parkinson's disease
	Trauma
	Vitamin B_{12} deficiency
	Zinc deficiency

sinuses. Anosmia may also follow blows to the occiput. Once traumatic anosmia develops, it is usually permanent; only 10% of patients ever improve or recover. Perversion of the sense of smell may occur as a transient phase in the recovery process.

Viral infections can destroy the olfactory neuroepithelium, which is then replaced by respiratory epithelium. Parainfluenza virus type 3 appears to be especially detrimental to human olfaction. HIV infection is associated with subjective distortion of taste and smell, which may become more severe as the disease progresses. The loss of taste and smell may play an important role in the development and progression of HIV-associated wasting. Congenital anosmias are rare but important. Kallmann syndrome is an X-linked disorder characterized by congenital anosmia and hypogonadotropic hypogonadism resulting from a failure of migration from the olfactory placode of olfactory receptor neurons and neurons synthesizing gonadotropin-releasing hormone. Anosmia can also occur in albinos. The receptor cells are present but are hypoplastic, lack cilia, and do not project above the surrounding supporting cells.

Meningiomas of the inferior frontal region are the most frequent neoplastic cause of anosmia; loss of smell may be the only neurologic abnormality. Rarely, anosmia can occur with gliomas of the frontal lobe. Occasionally, pituitary adenomas, craniopharyngiomas, suprasellar meningiomas, and aneurysms of the anterior part of the circle of Willis extend forward and damage olfactory structures. These tumors and hamartomas may also induce seizures with olfactory hallucinations, indicating involvement of the uncus of the temporal lobe.

Olfactory dysfunction is common in a variety of neurologic diseases, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis. In Alzheimer's and Parkinson's, olfactory loss may be the first clinical sign of the disease. In Parkinson's disease, bilateral olfactory deficits occur more commonly than the cardinal signs of the disorder such as tremor. In multiple sclerosis, olfactory loss is related to lesions visible by MRI, in olfactory processing areas in the temporal and frontal lobes.

Dysosmia, subjective distortions of olfactory perception, may occur with intranasal diseases that partially impair smell or during recovery from a neurogenic anosmia. Most dysosmic disorders consist of disagreeable odors, sometimes accompanied by distortions of taste. Dysosmia also can occur with depression.

Approach to the Patient: DISORDERS OF THE SENSE OF SMELL

Unilateral anosmia is rarely a complaint and is only recognized by testing of smell in each nasal cavity separately. Bilateral anosmia, on the other hand, brings patients to medical attention. Anosmic patients usually complain of a loss of the sense of taste even though their taste thresholds may be within normal limits. In actuality, they are complaining of a loss of flavor detection, which is mainly an olfactory function. The physical examination should include a thorough inspection of the ears, upper respiratory tract, and head and neck. A neurologic examination emphasizing the cranial nerves and cerebellar and sensorimotor function is essential. Any signs of depression should be noted.

Sensory olfactory function can be assessed by several methods. The Odor Stix test uses a commercially available odor-producing magic marker–like pen held ~8–15 cm (3–6 in.) from the patient's nose. The 30-cm alcohol test uses a freshly opened isopropyl alcohol packet held ~30 cm (12 in.) from the patient's nose. There is a commercially available scratch-and-sniff card containing three odors available for gross testing of olfaction. A superior test is the University of Pennsylvania Smell Identification Test (UPSIT). This consists of a 40-item, forced choice, scratch-and-sniff paradigm. For example, one of the items reads, "This odor smells most like (a) chocolate, (b) banana, (c) onion, or (d) fruit punch." The test is highly reliable, is sensitive to age and sex differences, and provides an accurate quantitative determination of the olfactory deficit. The UPSIT, which is a forced-choice test, can also be used to identify malingerers who typically report fewer correct responses than would be expected by chance. The average score for total anosmics is slightly higher than that expected on the basis of chance because of the inclusion of some odorants that act by trigeminal stimulation.

Olfactory threshold testing is another method of assessing olfactory function. Following assessment of sensory olfactory function, the detection threshold for an odorant such as methyl ethyl carbinol is established using graduated concentrations for each side of the nose. Nasal resistance can also be measured with anterior rhinomanometry for each side of the nose.

CT or MRI of the head is required to rule out paranasal sinusitis; neoplasms of the anterior cranial fossa, nasal cavity, or paranasal sinuses; or unsuspected fractures of the anterior cranial fossa. Bone abnormalities are best seen with CT. MRI is the most sensitive method to visualize olfactory bulbs, ventricles, and other soft tissue of the brain. Coronal CT is optimal for assessing cribriform plate, anterior cranial fossa, and sinus anatomy.

Biopsy of the olfactory epithelium is possible. However, given the widespread degeneration of the olfactory epithelium and intercalation of respiratory epithelium in the olfactory area of adults with no apparent olfactory dysfunction, biopsy results must be interpreted with caution.

Rx Treatment: DISORDERS OF THE SENSE OF SMELL

Therapy for patients with transport olfactory losses due to allergic rhinitis, bacterial rhinitis and sinusitis, polyps, neoplasms, and structural abnormalities of the nasal cavities can be undertaken with a high likelihood for improvement. Allergy management; antibiotic therapy; topical and systemic glucocorticoid therapy; and surgery for nasal polyps, deviation of the nasal septum, and chronic hyperplastic sinusitis are frequently effective in restoring the sense of smell.

There is no proven treatment for sensorineural olfactory losses. Fortunately, spontaneous recovery often occurs. Zinc and vitamin therapy (especially with vitamin A) are advocated by some. Profound zinc deficiency can produce loss and distortion of the sense of smell but is not a clinically important problem except in very limited geographic areas. The epithelial degeneration associated with vitamin A deficiency can cause anosmia, but in western societies the prevalence of vitamin A deficiency is low. Exposure to cigarette smoke and other airborne toxic chemicals can cause metaplasia of the olfactory epithelium, and spontaneous recovery can occur if the insult is removed. Counseling of patients is therefore helpful in such cases.

More than one-half of people older than 60 years suffer from olfactory dysfunction. No effective treatment exists for presbyosmia, but patients are often reassured to learn that this problem is common in their age group. In addition, early recognition and counseling can help patients to compensate for the loss of smell. The incidence of natural gas–related accidents is disproportionately high in the elderly, perhaps due in part to the gradual loss of smell. Mercaptan, the pungent odor in natural gas, is an olfactory stimulant that does not activate taste receptors. Many elderly with olfactory dysfunction experience a decrease in flavor sensation and find it necessary to hyperflavor food, usually by increasing the amount of salt in their diet.

TASTE

Compared with disorders of smell, gustatory disorders are uncommon. Loss of olfactory sensitivity is often accompanied by complaints of loss of the sense of taste, usually with normal detection thresholds for taste.

DEFINITIONS

Disturbances of the sense of taste may be categorized as *total ageusia*, total absence of gustatory function or inability to detect the qualities of sweet, salt, bitter, or sour; *partial ageusia*, ability to detect some but not all of the qualitative gustatory sensations; *specific ageusia*, inability to detect the taste quality of certain substances; *total hypogeusia*, decreased sensitivity to all tastants; *partial hypogeusia*, decreased sensitivity to some tastants; and *dysgeusia* or *phantogeusia*, distortion in the perception of a tastant, i.e., the perception of the wrong quality when a tastant is presented or the perception of a taste when there has been no tastant ingested. Confusion between sour and bitter, and less commonly between salty and bitter, may represent a semantic misunderstanding or have a true pathophysiologic basis. It may be possible to differentiate between the loss of flavor recognition in patients with olfactory losses who complain of a loss of taste as well as smell by asking if they are able to taste sweetness in sodas, saltiness in potato chips, etc.

PHYSIOLOGY OF TASTE

The taste receptor cells are located in the taste buds, spherical groups of cells arranged in a pattern resembling the segments of a citrus fruit (**Fig. 18–2**). At the surface, the taste bud has a pore into which microvilli of the receptor cells project. Unlike the olfactory system, the receptor cell is not the primary neuron. Instead, gustatory afferent nerve fibers contact individual taste receptor cells. The papillae lie along the lateral margin and dorsum of the tongue; at the junction of the dorsum and the base of the tongue; and in the palate, epiglottis, larynx, and esophagus.

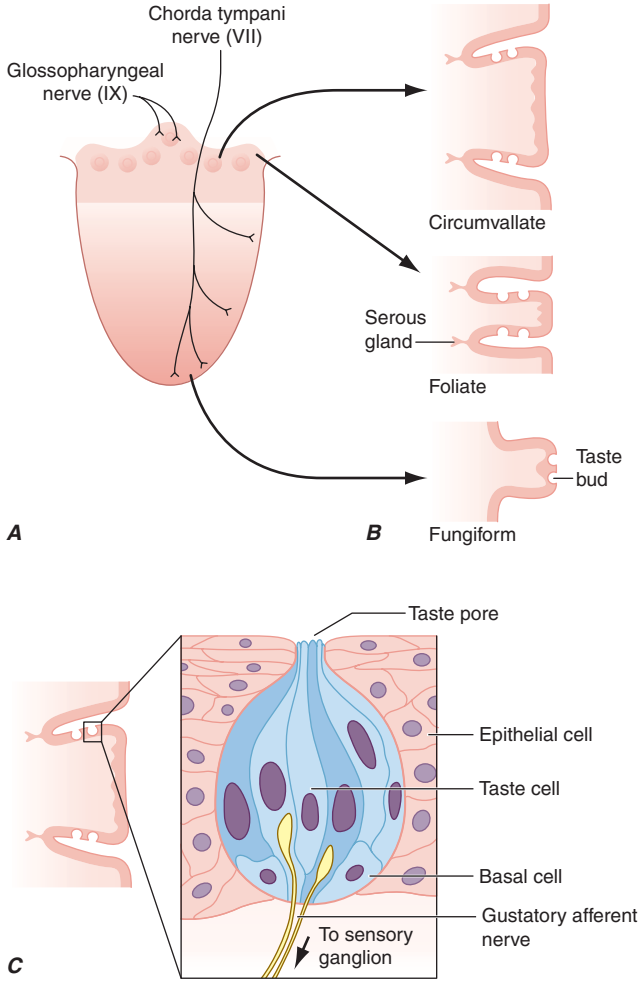

FIGURE 18-2

Taste. ***A.*** The taste buds of the anterior two-thirds of the tongue are innervated by the gustatory fibers that travel in a branch of the facial nerve (VII) called the chorda tympani. The taste buds of the posterior third of the tongue are innervated by gustatory fibers that travel in the lingual branch of the glossopharyngeal nerve (IX). *[Adapted from ER Kandel et al (eds): Principles of Neural Science, 4th ed., New York, McGraw-Hill, 2000; with permission.]* ***B.*** The main types of taste papillae are shown in schematic cross sections. Each type predominates in specific areas of the tongue, as indicated by the arrows from ***A.*** ***C.*** Each taste bud contains 50–150 taste cells that extend from the base of the taste bud to the taste pore, where the apical microvilli of taste cells have contact with tastants dissolved in saliva and taste pore mucus. Access of tastants to the basolateral regions of these cells is generally prevented by tight junctions between taste cells. Taste cells are short-lived cells that are replaced from stem cells at the base of the taste bud. Three types of taste cells in each taste bud (light cells, dark cells, and intermediate cells) may represent different stages of differentiation or different cell lineages. Taste stimuli, detected at the apical end of the taste cell, induce action potentials that cause the release of neurotransmitter at synapses formed at the base of the taste cell with gustatory fibers that transmit signals to the brain.

Tastants gain access to the receptor cells through the taste pore. Four classes of taste have been traditionally recognized: sweet, salt, sour, and bitter, and more recently "umami" (monosodium glutamate, disodium gluanylate, disodium inosinate). Tastants enter the taste pore in a solution and initiate transduction by either activating receptors coupled to G-proteins or by directly activating ion channels on the microvillae within the taste bud. Individual gustatory afferent fibers almost always respond to a number of different chemicals. As with olfaction and other sensory systems, intensity appears to be encoded by the quantity of neural activity.

The sense of taste is mediated through the facial, glossopharyngeal, and vagal nerves. The chorda tympani branch of the facial nerve subserves taste from the anterior two-thirds of the tongue. The posterior third of the tongue is supplied by the lingual branch of the glossopharyngeal nerve. Afferents from the palate travel with the greater superficial petrosal nerve to the geniculate ganglion and then via the facial nerve to the brainstem. The internal branch of the superior laryngeal nerve of the vagus nerve contains the taste afferents from the larynx, including the epiglottis and esophagus.

The central connections of the nerves terminate in the brainstem in the nucleus of the tractus solitarius. The central pathway from the nucleus of the tractus solitarius projects to the ipsilateral parabrachial nuclei of the pons. Two divergent pathways project from the parabrachial nuclei. One ascends to the gustatory relay in the dorsal thalamus, synapses, and continues to the cortex of the insula. There is also evidence for a direct pathway from the parabrachial nuclei to the cortex. (Olfaction and gustation appear to be unique among sensory systems in that at least some fibers bypass the thalamus.) The other pathway from the parabrachial nuclei goes to the ventral forebrain, including the lateral hypothalamus, substantia innominata, central nucleus of the amygdala, and the stria terminalis.

DISORDERS OF THE SENSE OF TASTE

Disorders of the sense of taste are caused by conditions that interfere with the access of the tastant to the receptor cells in the taste bud (transport loss), injure receptor cells (sensory loss), or damage gustatory afferent nerves and central gustatory pathways (neural loss) (Table 18-2). *Transport gustatory losses* result from xerostomia due to many causes, including Sjögren's syndrome, radiation therapy, heavy-metal intoxication, and bacterial colonization of the taste pore. *Sensory gustatory losses* are caused by inflammatory and degenerative diseases in the oral cavity; a vast number of drugs, particularly those that interfere with cell turnover such as antithyroid and antineoplastic agents; radiation therapy to the oral cavity and pharynx; viral infections; endocrine disorders; neoplasms; and aging. *Neural gustatory losses* occur with neoplasms, trauma, and

TABLE 18-2

CAUSES OF GUSTATORY DYSFUNCTION

Transport Gustatory Losses	Neural Gustatory Losses
Drugs	Diabetes mellitus
Heavy-metal intoxication	Hypothyroidism
Radiation therapy	Oral neoplasms
Sjögren's syndrome	Oral surgery
Xerostomia	Radiation therapy
Sensory Gustatory Losses	Renal disease
Aging	Stroke and other CNS disorders
Candidiasis	Trauma
Drugs (antithyroid and antineoplastic)	Upper respiratory tract infections
Endocrine disorders	
Oral neoplasms	
Pemphigus	
Radiation therapy	
Viral infections (especially with herpes viruses)	

surgical procedures in which the gustatory afferents are injured. Taste buds degenerate when their gustatory afferents are transected but remain when their somatosensory afferents are severed. Patients with renal disease have increased thresholds for sweet and sour tastes, which resolves with dialysis.

A side effect of medication is the single most common cause of taste dysfunction in clinical practice. Xerostomia, regardless of the etiology, can be associated with taste dysfunction. It is associated with poor oral clearance and poor dental hygiene and can adversely affect the oral mucosa, all leading to dysgeusia. However, severe salivary gland failure does not necessarily lead to taste complaints. Xerostomia, the use of antibiotics or glucocorticoids, or immunodeficiency can lead to overgrowth of *Candida*; overgrowth alone, without thrush or overt signs of infection, can be associated with bad taste or hypogeusia. When taste dysfunction occurs in a patient at risk for fungal overgrowth, a trial of nystatin or other antifungal medication is warranted.

Upper respiratory infections and head trauma can lead to both smell and taste dysfunction; taste is more likely to improve than smell. The mechanism of taste disturbance in these situations is not well understood. Trauma to the chorda tympani branch of the facial nerve during middle ear surgery or third molar extractions is relatively common and can cause dysgeusia. Bilateral chorda tympani injuries are usually associated with hypogeusia, whereas unilateral lesions produce only limited symptoms.

As noted above, aging itself may be associated with reduced taste sensitivity. The taste dysfunction may be limited to a single compound and may be mild.

Approach to the Patient: DISORDERS OF THE SENSE OF TASTE

Patients who complain of loss of taste should be evaluated for both gustatory and olfactory function. Clinical assessment of taste is not as well developed or standardized as that of smell. The first step is to perform suprathreshold whole-mouth taste testing for quality, intensity, and pleasantness perception of four taste qualities: sweet, salty, sour, and bitter. Most commonly used reagents for taste testing are sucrose, citric acid or hydrochloric acid, caffeine or quinine (sulfate or hydrochloride), and sodium chloride. The taste stimuli should be freshly prepared and have similar viscosity. For quantification, detection thresholds are obtained by applying graduated dilutions to the tongue quadrants or by whole-mouth sips. Electric taste testing (*electrogustometry*) is used clinically to identify taste deficits in specific quadrants of the tongue. Regional gustatory testing may also be performed to assess for the possibility of loss localized to one or several receptor fields as a result of a peripheral or central lesion. The history of the disease and localization studies provide important clues to the causes of the taste disturbance. For example, absence of taste on the anterior two-thirds of the tongue associated with a facial paralysis indicates that the lesion is proximal to the juncture of the chorda tympani branch with the facial nerve in the mastoid.

Rx Treatment: DISORDERS OF THE SENSE OF TASTE

Treatment of gustatory disorders is limited. No effective therapies exist for the sensorineural disorders of taste. Altered taste due to surgical stretch injury of the chorda tympani nerve usually improves within 3–4 months, while dysfunction is usually permanent with transection of the nerve. Taste dysfunction following trauma may resolve spontaneously without intervention and is more likely to do so than posttraumatic smell dysfunction. Idiopathic alterations of taste sensitivity usually remain stable or worsen; zinc and vitamin therapy are of unproven value. Directed therapy to address factors that affect taste perception can be of value. Xerostomia can be treated with artificial saliva, providing some benefit to patients with a disturbed salivary milieu. Oral pilocarpine may be beneficial for a variety of forms of xerostomia. Appropriate treatment of bacterial and fungal infections of the oral cavity can be of great help in improving taste function. Taste disturbance related to drugs can often be resolved by changing the prescribed medication.

HEARING

Hearing loss is one of the most common sensory disorders in humans and can present at any age. Nearly 10% of the adult population has some hearing loss, and one-third of individuals >65 years have a hearing loss of sufficient magnitude to require a hearing aid.

PHYSIOLOGY OF HEARING

(Fig. 18-3) The function of the external and middle ear is to amplify sound to facilitate mechanotransduction by hair cells in the inner ear. Sound waves enter the external auditory canal and set the tympanic membrane in motion, which in turn moves the malleus, incus, and stapes of the middle ear. Movement of the footplate of the stapes causes pressure changes in the fluid-filled inner ear eliciting a traveling wave in the basilar membrane of the cochlea. The tympanic membrane and the ossicular chain in the middle ear serve as an impedance-matching mechanism, improving the efficiency of energy transfer from air to the fluid-filled inner ear.

Stereocilia of the hair cells of the organ of Corti, which rests on the basilar membrane, are in contact with the tectorial membrane and are deformed by the traveling wave. A point of maximal displacement of the basilar membrane is determined by the frequency of the stimulating tone. High-frequency tones cause maximal displacement of the basilar membrane near the base of the cochlea. As the frequency of the stimulating tone decreases, the point of maximal displacement moves toward the apex of the cochlea.

The inner and outer hair cells of the organ of Corti have different innervation patterns, but both are mechanoreceptors. The afferent innervation relates principally to the inner hair cells, and the efferent innervation relates principally to outer hair cells. The motility of the outer hair cells alters the micromechanics of the inner hair cells, creating a cochlear amplifier, which explains the exquisite sensitivity and frequency selectivity of the cochlea.

Beginning in the cochlea, the frequency specificity is maintained at each point of the central auditory pathway: dorsal and ventral cochlear nuclei, trapezoid body, superior olivary complex, lateral lemniscus, inferior colliculus, medial geniculate body, and auditory cortex. At low frequencies, individual auditory nerve fibers can respond more or less synchronously with the stimulating tone. At higher frequencies, phase-locking occurs so that neurons alternate in response to particular phases of the cycle of the sound wave. Intensity is encoded by the amount of neural activity in individual neurons, the number of neurons that are active, and the specific neurons that are activated.

GENETIC CAUSES OF HEARING LOSS

More than half of childhood hearing impairment is thought to be hereditary; hereditary hearing impairment (HHI) can also manifest later in life. HHI may be classified as either nonsyndromic, when hearing loss is the only clinical abnormality, or syndromic, when hearing loss is associated with anomalies in other organ systems. Nearly two-thirds of HHIs are nonsyndromic, and the remaining one-third are syndromic. Between 70 and 80% of nonsyndromic HHI is inherited in an autosomal recessive manner and designated DFNB; another 15–20% is autosomal dominant (DFNA). Less than 5% is X-linked or maternally inherited via the mitochondria.

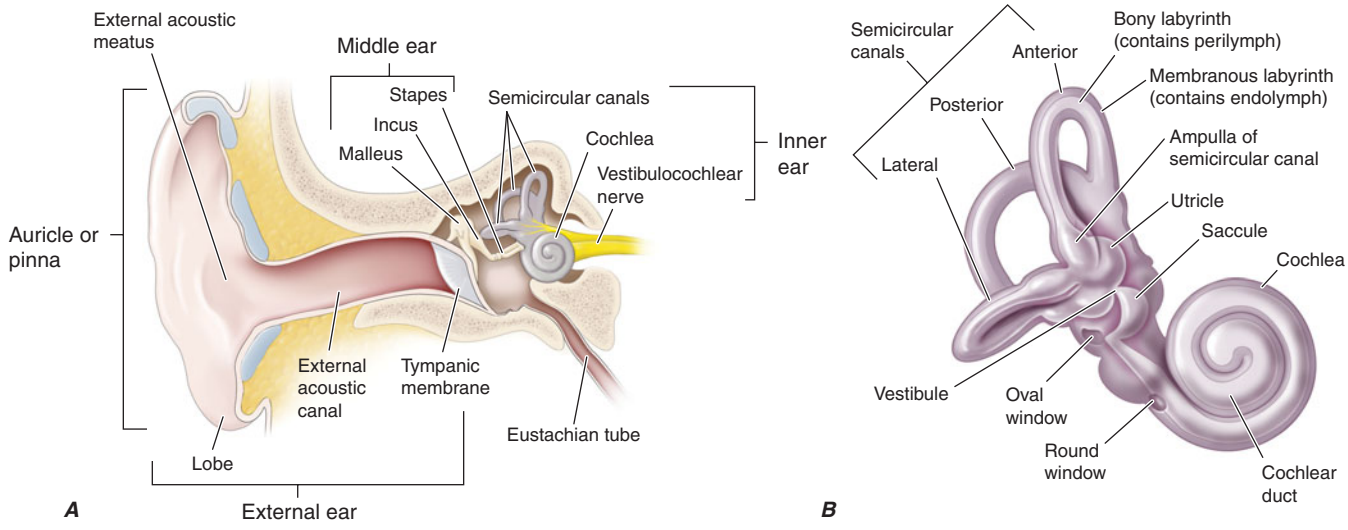

FIGURE 18-3

Ear anatomy. *A.* Drawing of modified coronal section through external ear and temporal bone, with structures of the middle and inner ear demonstrated. ***B.*** High-resolution view of inner ear.

Nearly 100 loci harboring genes for nonsyndromic HHI have been mapped, with equal numbers of dominant and recessive modes of inheritance; numerous genes have now been cloned (Table 18-3). The hearing genes fall into the categories of structural proteins (MYH9, MYO7A, MYO15, TECTA, DIAPH1), transcription factors (POU3F4, POU4F3), ion channels (KCNQ4, SLC26A4), and gap junction proteins (GJB2, GJB3, GJB6). Several of these genes, including connexin 26 (GJB2), TECTA, and TMC1, cause both autosomal dominant and recessive forms of nonsyndromic HHI. In general, the hearing loss associated with dominant genes has

TABLE 18-3

HEREDITARY HEARING IMPAIRMENT GENES

DESIGNATION	GENE	FUNCTION
Autosomal Dominant		
	CRYM	Thyroid hormone binding protein
DFNA1	*DIAPH1*	Cytoskeletal protein
DFNA2	*GJB3 (Cx31)*	Gap junctions
DFNA2	*KCNQ4*	Potassium channel
DFNA3	*GJB2 (Cx26)*	Gap junctions
DFNA3	*GJB6 (Cx30)*	Gap junctions
DFNA4	*MYH14*	Class II nonmuscle myosin
DFNA5	*DFNA5*	Unknown
DFNA6/14/38	*WFS*	Transmembrane protein
DFNA8/12	*TECTA*	Tectorial membrane protein
DFNA9	*COCH*	Unknown
DFNA10	*EYA4*	Developmental gene
DFNA11	*MYO7A*	Cytoskeletal protein
DFNA13	*COL11A2*	Cytoskeletal protein
DFNA15	*POU4F3*	Transcription factor
DFNA17	*MYH9*	Cytoskeletal protein
DFNA20/26	*ACTG1*	Cytoskeletal protein
DFNA22	*MYO6*	Unconventional myosin
DFNA28	*TFCP2L3*	Transcription factor
DFNA36	*TMC1*	Transmembrane protein
DFNA48	*MYO1A*	Unconventional myosin
Autosomal Recessive		
	SLC26A5 (Prestin)	Motor protein
DFNB1	*GJB2 (CX26)*	Gap junction
	GJB6(CX30)	Gap junction
DFNB2	*MYO7A*	Cytoskeletal protein
DFNB3	*MYO15*	Cytoskeletal protein
DFNB4	*PDS(SLC26A4)*	Chloride/iodide transporter
DFNB6	*TMIE*	Transmembrane protein
DFNB7/B11	*TMC1*	Transmembrane protein
DFNB9	*OTOF*	Trafficking of membrane vesicles
DFNB8/10	*TMPRSS3*	Transmembrane serine protease
DFNB12	*CDH23*	Intercellular adherence protein
DFNB16	*STRC*	Stereocilia protein
DFNB18	*USH1C*	Unknown
DFNB21	*TECTA*	Tectorial membrane protein
DFNB22	*OTOA*	Gel attachement to nonsensory cell
DFNB23	*PCDH15*	Morphogenesis and cohesion
DFNB28	*TRIOBP*	Cytoskeletal-organizing protein
DFNB29	*CLDN14*	Tight junctions
DFNB30	*MYO3A*	Hybrid motor-signaling myosin
DFNB31	*WHRN*	PDZ domain–containing protein
DFNB36	*ESPN*	Ca-insensitive actin-bundling protein
DFNB37	*MYO6*	Unconventional myosin
DFNB67	*TMHS*	Unknown function; tetraspan protein

its onset in adolescence or adulthood and varies in severity, whereas the hearing loss associated with recessive inheritance is congenital and profound. Connexin 26 is particularly important because it is associated with nearly 20% of cases of childhood deafness. Two frame-shift mutations, 35delG and 167delT, account for >50% of the cases; however, screening for these two mutations alone is insufficient to diagnose GJB2-related recessive deafness. The 167delT mutation is highly prevalent in Ashkenazi Jews; ~1 in 1765 individuals in this population are homozygous and affected. The hearing loss can also vary among the members of the same family, suggesting that other genes or factors influence the auditory phenotype.

The contribution of genetics to presbycusis (see later) is also becoming better understood. In addition to GJB2, several other nonsyndromic genes are associated with hearing loss that progresses with age. Sensitivity to aminoglycoside ototoxicity can be maternally transmitted through a mitochondrial mutation. Susceptibility to noise-induced hearing loss may also be genetically determined.

There are >400 syndromic forms of hearing loss. These include Usher syndrome (retinitis pigmentosa and hearing loss), Waardenburg syndrome (pigmentary abnormality and hearing loss), Pendred syndrome (thyroid organification defect and hearing loss), Alport syndrome (renal disease and hearing loss), Jervell and Lange-Nielsen syndrome (prolonged QT interval and hearing loss), neurofibromatosis type 2 (bilateral acoustic schwannoma), and mitochondrial disorders [mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS); myoclonic epilepsy and ragged red fibers (MERRF); progressive external ophthalmoplegia (PEO)] (**Table 18-4**).

DISORDERS OF THE SENSE OF HEARING

Hearing loss can result from disorders of the auricle, external auditory canal, middle ear, inner ear, or central auditory pathways (**Fig. 18-4**). *In general, lesions in the auricle, external auditory canal, or middle ear cause conductive hearing losses, whereas lesions in the inner ear or eighth nerve cause sensorineural hearing losses.*

Conductive Hearing Loss

This results from obstruction of the external auditory canal by cerumen, debris, and foreign bodies; swelling of the lining of the canal; atresia or neoplasms of the canal; perforations of the tympanic membrane; disruption of the ossicular chain, as occurs with necrosis of the long process of the incus in trauma or infection; otosclerosis; or fluid, scarring, or neoplasms in the middle ear. Rarely,

TABLE 18-4

SYNDROMIC HEREDITARY HEARING IMPAIRMENT GENES

SYNDROME	GENE	FUNCTION
Alport syndrome	*COL4A3-5*	Cytoskeletal protein
BOR syndrome	*EYA1*	Developmental gene
	SIX1	Developmental gene
Jervell and Lange-Nielsen syndrome	*KVLQT1*	Delayed rectifier K^+ channel
	KCNE1	Delayed rectifier K^+ channel
Norrie disease	*Norrin*	Cell-cell interactions
Pendred syndrome	*SLC26A4*	Chloride/iodide transporter
Treacher Collins	*TCOF1*	Nucleolar-cytoplasmic transport
Usher syndrome	*MYO7A*	Cytoskeletal protein
	USH1C	Unknown
	CDH23	Intercellular adherence protein
	PCDH15	Cell adhesion molecule
	SANS	Harmonin associated protein
	USH2A	Cell adhesion molecule
	VLGR1	G protein–coupled receptor
	USH3	Unknown
WS type I, III	*PAX3*	Transcription factor
WS type II	*MITF*	Transcription factor
	SLUG	Transcription factor
WS type IV	*EDNRB*	Endothelin-B receptor
	EDN3	Endothelin-B receptor ligand
	SOX10	Transcription factor

Note: BOR, branchio-oto-renal syndrome; WS, Waardenburg syndrome.

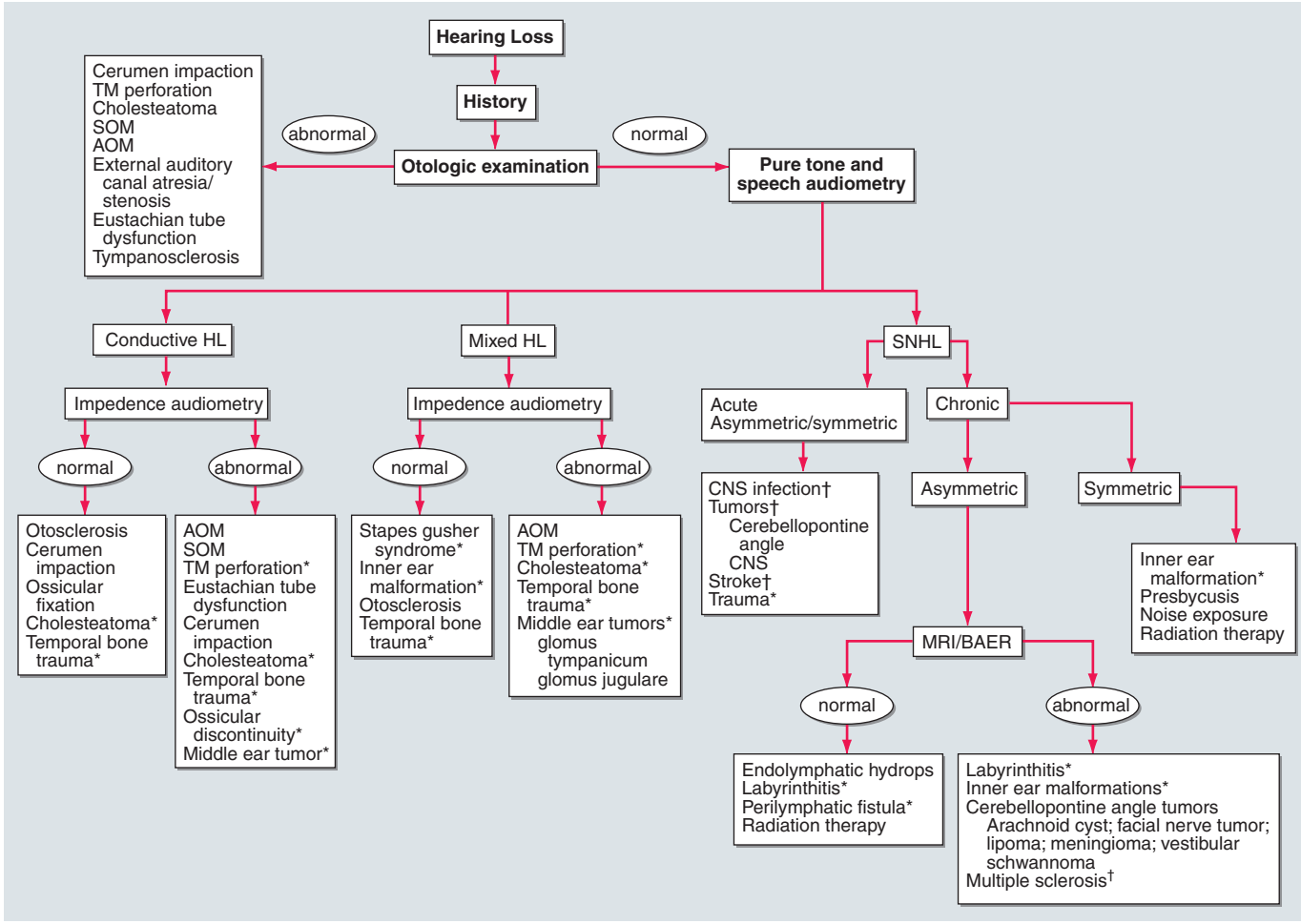

FIGURE 18-4

An algorithm for the approach to hearing loss. HL, hearing loss; SNHL, sensorineural hearing loss; TM, tympanic membrane; SOM, serous otitis media; AOM, acute otitis media; *, CT scan of temporal bone; †, MRI scan.

inner-ear malformations may present as conductive hearing loss beginning in adulthood.

Cholesteatoma, stratified squamous epithelium in the middle ear or mastoid, occurs frequently in adults. This is a benign, slowly growing lesion that destroys bone and normal ear tissue. Theories of pathogenesis include traumatic implantation and invasion, immigration and invasion through a perforation, and metaplasia following chronic infection and irritation. On examination, there is often a perforation of the tympanic membrane filled with cheesy white squamous debris. A chronically draining ear that fails to respond to appropriate antibiotic therapy should raise suspicion of a cholesteatoma. Conductive hearing loss secondary to ossicular erosion is common. Surgery is required to remove this destructive process.

Conductive hearing loss with a normal ear canal and intact tympanic membrane suggests ossicular pathology. Fixation of the stapes from *otosclerosis* is a common cause of low-frequency conductive hearing loss. It occurs equally in men and women and is inherited as an autosomal dominant trait with incomplete penetrance. Hearing impairment usually presents between the late teens to the forties. In women, the otosclerotic process is accelerated during pregnancy, and the hearing loss is often first noticeable at this time. A hearing aid or a simple outpatient surgical procedure (stapedectomy) can provide adequate auditory rehabilitation. Extension of otosclerosis beyond the stapes footplate to involve the cochlea (cochlear otosclerosis) can lead to mixed or sensorineural hearing loss. Fluoride therapy to prevent hearing loss from cochlear otosclerosis is of uncertain value.

Eustachian tube dysfunction is extremely common in adults and may predispose to acute otitis media (AOM) or serous otitis media (SOM). Trauma, AOM, or chronic otitis media are the usual factors responsible for tympanic membrane perforation. While small perforations often heal spontaneously, larger defects usually require surgical intervention. Tympanoplasty is highly effective (>90%) in the repair of tympanic membrane perforations. Otoscopy is usually sufficient to diagnose AOM, SOM, chronic otitis media, cerumen impaction, tympanic membrane perforation, and eustachian tube dysfunction.

Sensorineural Hearing Loss

Damage to the hair cells of the organ of Corti may be caused by intense noise, viral infections, ototoxic drugs (e.g., salicylates, quinine and its synthetic analogues, aminoglycoside antibiotics, loop diuretics such as furosemide and ethacrynic acid, and cancer chemotherapeutic agents such as cisplatin), fractures of the temporal bone, meningitis, cochlear otosclerosis (see earlier), Ménière's disease, and aging. Congenital malformations of the inner ear may be the cause of hearing loss in some adults. Genetic predisposition alone or in concert with environmental exposures may also be responsible.

Presbycusis (age-associated hearing loss) is the most common cause of sensorineural hearing loss in adults. In the early stages, it is characterized by symmetric, gentle to sharply sloping high-frequency hearing loss. With progression, the hearing loss involves all frequencies. More importantly, the hearing impairment is associated with significant loss in clarity. There is a loss of discrimination for phonemes, recruitment (abnormal growth of loudness), and particular difficulty in understanding speech in noisy environments. Hearing aids may provide limited rehabilitation once the word recognition score deteriorates below 50%. Cochlear implants are the treatment of choice when hearing aids prove inadequate, even when hearing loss is incomplete.

Ménière's disease is characterized by episodic vertigo, fluctuating sensorineural hearing loss, tinnitus, and aural fullness. Tinnitus and/or deafness may be absent during the initial attacks of vertigo, but invariably appear as the disease progresses and increase in severity during acute attacks. The annual incidence of Ménière's disease is 0.5–7.5 per 1000; onset is most frequently in the fifth decade of life but may also occur in young adults or the elderly. Histologically, there is distention of the endolymphatic system (endolymphatic hydrops) leading to degeneration of vestibular and cochlear hair cells. This may result from endolymphatic sac dysfunction secondary to infection, trauma, autoimmune disease, inflammatory causes, or tumor; an idiopathic etiology constitutes the largest category and is most accurately referred to as Ménière's disease. Although any pattern of hearing loss can be observed, typically, low-frequency, unilateral sensorineural hearing impairment is present. MRI should be obtained to exclude retrocochlear pathology such as a cerebellopontine angle tumor or demyelinating disorder. Therapy is directed toward the control of vertigo. A low-salt diet is the mainstay of treatment for control of rotatory vertigo. Diuretics, a short course of glucocorticoids, and intratympanic gentamicin may also be useful adjuncts in recalcitrant cases. Surgical therapy of vertigo is reserved for unresponsive cases and includes endolymphatic sac decompression, labyrinthectomy, and vestibular nerve section. Both labyrinthectomy and vestibular nerve section abolish rotatory vertigo in >90% of patients. Unfortunately, there is no effective therapy for hearing loss, tinnitus, or aural fullness from Ménière's disease.

Sensorineural hearing loss may also result from any neoplastic, vascular, demyelinating, infectious, or degenerative disease or trauma affecting the central auditory pathways. HIV leads to both peripheral and central auditory system pathology and is associated with sensorineural hearing impairment.

A finding of conductive and sensory hearing loss in combination is termed *mixed hearing loss*. Mixed hearing losses are due to pathology of both the middle and inner ear, as can occur in otosclerosis involving the ossicles and the cochlea, head trauma, chronic otitis media, cholesteatoma, middle ear tumors, and some inner ear malformations.

Trauma resulting in temporal bone fractures may be associated with conductive, sensorineural, or mixed hearing loss. If the fracture spares the inner ear, there may simply be conductive hearing loss due to rupture of the tympanic membrane or disruption of the ossicular chain. These abnormalities can be surgically corrected. Profound hearing loss and severe vertigo are associated with temporal bone fractures involving the inner ear. A perilymphatic fistula associated with leakage of inner-ear fluid into the middle ear can occur and may require surgical repair. An associated facial nerve injury is not uncommon. CT is best suited to assess fracture of the traumatized temporal bone, evaluate the ear canal, and determine the integrity of the ossicular chain and the involvement of the inner ear. CSF leaks that accompany temporal bone fractures are usually self-limited; the value of prophylactic antibiotics is uncertain.

Tinnitus is defined as the perception of a sound when there is no sound in the environment. It may have a buzzing, roaring, or ringing quality and may be pulsatile (synchronous with the heartbeat). Tinnitus is often associated with either a conductive or sensorineural hearing loss. The pathophysiology of tinnitus is not well understood. The cause of the tinnitus can usually be determined by finding the cause of the associated hearing loss. Tinnitus may be the first symptom of a serious condition such as a vestibular schwannoma. Pulsatile tinnitus requires evaluation of the vascular system of the head to exclude vascular tumors such as glomus jugulare tumors, aneurysms, and stenotic arterial lesions; it may also occur with SOM.

Approach to the Patient:
DISORDERS OF THE SENSE OF HEARING

The goal in the evaluation of a patient with auditory complaints is to determine (1) the nature of the hearing impairment (conductive vs. sensorineural vs. mixed), (2) the severity of the impairment (mild, moderate, severe, profound), (3) the anatomy of the impairment (external ear, middle ear, inner ear, or central auditory pathway),

and (4) the etiology. The history should elicit characteristics of the hearing loss, including the duration of deafness, unilateral vs. bilateral involvement, nature of onset (sudden vs. insidious), and rate of progression (rapid vs. slow). Symptoms of tinnitus, vertigo, imbalance, aural fullness, otorrhea, headache, facial nerve dysfunction, and head and neck paresthesias should be noted. Information regarding head trauma, exposure to ototoxins, occupational or recreational noise exposure, and family history of hearing impairment may also be important. A sudden onset of unilateral hearing loss, with or without tinnitus, may represent a viral infection of the inner ear or a stroke. Patients with unilateral hearing loss (sensory or conductive) usually complain of reduced hearing, poor sound localization, and difficulty hearing clearly with background noise. Gradual progression of a hearing deficit is common with otosclerosis, noise-induced hearing loss, vestibular schwannoma, or Ménière's disease. Small vestibular schwannomas typically present with asymmetric hearing impairment, tinnitus, and imbalance (rarely vertigo); cranial neuropathy, in particular of the trigeminal or facial nerve, may accompany larger tumors. In addition to hearing loss, Ménière's disease may be associated with episodic vertigo, tinnitus, and aural fullness. Hearing loss with otorrhea is most likely due to chronic otitis media or cholesteatoma.

Examination should include the auricle, external ear canal, and tympanic membrane. The external ear canal of the elderly is often dry and fragile; it is preferable to clean cerumen with wall-mounted suction and cerumen loops and to avoid irrigation. In examining the eardrum, the topography of the tympanic membrane is more important than the presence or absence of the light reflex. In addition to the pars tensa (the lower two-thirds of the eardrum), the pars flaccida above the short process of the malleus should also be examined for retraction pockets that may be evidence of chronic eustachian tube dysfunction or cholesteatoma. Insufflation of the ear canal is necessary to assess tympanic membrane mobility and compliance. Careful inspection of the nose, nasopharynx, and upper respiratory tract is indicated. Unilateral serous effusion should prompt a fiberoptic examination of the nasopharynx to exclude neoplasms. Cranial nerves should be evaluated with special attention to facial and trigeminal nerves, which are commonly affected with tumors involving the cerebellopontine angle.

The Rinne and Weber tuning fork tests, with a 512-Hz tuning fork, are used to screen for hearing loss, differentiate conductive from sensorineural hearing losses, and to confirm the findings of audiologic evaluation. Rinne's test compares the ability to hear by air conduction with the ability to hear by bone conduction. The tines of a vibrating tuning fork are held near the opening of the external auditory canal, and then the stem is placed on the mastoid process; for direct contact, it may be placed on teeth or dentures. The patient is asked to indicate whether the tone is louder by air conduction or bone conduction. Normally, and in the presence of sensorineural hearing loss, a tone is heard louder by air conduction than by bone conduction; however, with conductive hearing loss of ≥30 dB (see Audiologic Assessment, below), the bone-conduction stimulus is perceived as louder than the air-conduction stimulus. For the Weber test, the stem of a vibrating tuning fork is placed on the head in the midline and the patient asked whether the tone is heard in both ears or better in one ear than in the other. With a unilateral conductive hearing loss, the tone is perceived in the affected ear. With a unilateral sensorineural hearing loss, the tone is perceived in the unaffected ear. A 5-dB difference in hearing between the two ears is required for lateralization.

LABORATORY ASSESSMENT OF HEARING

Audiologic Assessment

The minimum audiologic assessment for hearing loss should include the measurement of pure tone air-conduction and bone-conduction thresholds, speech reception threshold, discrimination score, tympanometry, acoustic reflexes, and acoustic-reflex decay. This test battery provides a screening evaluation of the entire auditory system and allows one to determine whether further differentiation of a sensory (cochlear) from a neural (retrocochlear) hearing loss is indicated.

Pure tone audiometry assesses hearing acuity for pure tones. The test is administered by an audiologist and is performed in a sound-attenuated chamber. The pure tone stimulus is delivered with an audiometer, an electronic device that allows the presentation of specific frequencies (generally between 250 and 8000 Hz) at specific intensities. Air and bone conduction thresholds are established for each ear. Air conduction thresholds are determined by presenting the stimulus in air with the use of headphones. Bone conduction thresholds are determined by placing the stem of a vibrating tuning fork or an oscillator of an audiometer in contact with the head. In the presence of a hearing loss, broad-spectrum noise is presented to the nontest ear for *masking* purposes so that responses are based on perception from the ear under test.

The responses are measured in decibels. An *audiogram* is a plot of intensity in decibels of hearing threshold versus frequency. A decibel (dB) is equal to 20 times the logarithm of the ratio of the sound pressure required to achieve threshold in the patient to the sound pressure required to achieve threshold in a normal hearing person.

Therefore, a change of 6 dB represents doubling of sound pressure, and a change of 20 dB represents a tenfold change in sound pressure. Loudness, which depends on the frequency, intensity, and duration of a sound, doubles with approximately each 10-dB increase in sound pressure level. Pitch, on the other hand, does not directly correlate with frequency. The perception of pitch changes slowly in the low and high frequencies. In the middle tones, which are important for human speech, pitch varies more rapidly with changes in frequency.

Pure tone audiometry establishes the presence and severity of hearing impairment, unilateral vs. bilateral involvement, and the type of hearing loss. Conductive hearing losses with a large mass component, as is often seen in middle-ear effusions, produce elevation of thresholds that predominate in the higher frequencies. Conductive hearing losses with a large stiffness component, as in fixation of the footplate of the stapes in early otosclerosis, produce threshold elevations in the lower frequencies. Often, the conductive hearing loss involves all frequencies, suggesting involvement of both stiffness and mass. In general, sensorineural hearing losses such as presbycusis affect higher frequencies more than lower frequencies. An exception is Ménière's disease, which is characteristically associated with low-frequency sensorineural hearing loss. Noise-induced hearing loss has an unusual pattern of hearing impairment in which the loss at 4000 Hz is greater than at higher frequencies. Vestibular schwannomas characteristically affect the higher frequencies, but any pattern of hearing loss can be observed.

Speech recognition requires greater synchronous neural firing than is necessary for appreciation of pure tones. *Speech audiometry* tests the clarity with which one hears. The *speech reception threshold* (SRT) is defined as the intensity at which speech is recognized as a meaningful symbol and is obtained by presenting two-syllable words with an equal accent on each syllable. The intensity at which the patient can repeat 50% of the words correctly is the SRT. Once the SRT is determined, discrimination or word recognition ability is tested by presenting one-syllable words at 25–40 dB above the SRT. The words are phonetically balanced in that the phonemes (speech sounds) occur in the list of words at the same frequency that they occur in ordinary conversational English. An individual with normal hearing or conductive hearing loss can repeat 88–100% of the phonetically balanced words correctly. Patients with a sensorineural hearing loss have variable loss of discrimination. As a general rule, neural lesions produce greater deficits in discrimination than do lesions in the inner ear. For example, in a patient with mild asymmetric sensorineural hearing loss, a clue to the diagnosis of vestibular schwannoma is the presence of a substantial deterioration in discrimination ability. Deterioration in discrimination ability at higher intensities above the SRT also suggests a lesion in the eighth nerve or central auditory pathways.

Tympanometry measures the impedance of the middle ear to sound and is useful in diagnosis of middle-ear effusions. A *tympanogram* is the graphic representation of change in impedance or compliance as the pressure in the ear canal is changed. Normally, the middle ear is most compliant at atmospheric pressure, and the compliance decreases as the pressure is increased or decreased; this pattern is seen with normal hearing or in the presence of sensorineural hearing loss. Compliance that does not change with change in pressure suggests middle-ear effusion. With a negative pressure in the middle ear, as with eustachian tube obstruction, the point of maximal compliance occurs with negative pressure in the ear canal. A tympanogram in which no point of maximal compliance can be obtained is most commonly seen with discontinuity of the ossicular chain. A reduction in the maximal compliance peak can be seen in otosclerosis.

During tympanometry, an intense tone elicits contraction of the stapedius muscle. The change in compliance of the middle ear with contraction of the stapedius muscle can be detected. The presence or absence of this *acoustic reflex* is important in the anatomic localization of facial nerve paralysis as well as hearing loss. Normal or elevated acoustic reflex threshold in an individual with sensorineural hearing impairment suggests a cochlear hearing loss. Assessment of *acoustic reflex decay* helps differentiate sensory from neural hearing losses. In neural hearing loss, the reflex adapts or decays with time.

Otoacoustic emissions (OAE) can be measured with microphones inserted into the external auditory canal. The emissions may be spontaneous or evoked with sound stimulation. The presence of OAEs indicates that the outer hair cells of the organ of Corti are intact and can be used to assess auditory thresholds and to distinguish sensory from neural hearing losses.

Evoked Responses

Electrocochleography measures the earliest evoked potentials generated in the cochlea and the auditory nerve. Receptor potentials recorded include the cochlear microphonic, generated by the outer hair cells of the organ of Corti, and the summating potential, generated by the inner hair cells in response to sound. The whole nerve action potential representing the composite firing of the first-order neurons can also be recorded during electrocochleography. Clinically, the test is useful in the diagnosis of Ménière's disease, where an elevation of the ratio of summating potential to action potential is seen.

Brainstem auditory evoked responses (BAERs) are useful in differentiating the site of sensorineural hearing loss. In response to sound, five distinct electrical potentials arising from different stations along the peripheral and

central auditory pathway can be identified using computer averaging from scalp surface electrodes. BAERs are valuable in situations in which patients cannot or will not give reliable voluntary thresholds. They are also used to assess the integrity of the auditory nerve and brainstem in various clinical situations, including intraoperative monitoring and in determination of brain death.

The *vestibular-evoked myogenic potential (VEMP) test* elicits a vestibulocollic reflex whose afferent limb arises from acoustically sensitive cells in the saccule, with signals conducted via the inferior vestibular nerve. VEMP is a biphasic, short-latency response recorded from the tonically contracted sternocleidomastoid muscle in response to loud auditory clicks or tones. VEMPs may be diminished or absent in patients with early and late Ménière's disease, vestibular neuritis, benign paroxysmal positional vertigo, and vestibular schwannoma. On the other hand, the threshold for VEMPs may be lower in cases of superior canal dehiscence and perilymphatic fistula.

Imaging Studies

The choice of radiologic tests is largely determined by whether the goal is to evaluate the bony anatomy of the external, middle, and inner ear or to image the auditory nerve and brain. Axial and coronal CT of the temporal bone with fine 1-mm cuts is ideal for determining the caliber of the external auditory canal, integrity of the ossicular chain, and presence of middle-ear or mastoid disease; it can also detect inner-ear malformations. CT is also ideal for the detection of bone erosion with chronic otitis media and cholesteatoma. MRI is superior to CT for imaging of retrocochlear pathology such as vestibular schwannoma, meningioma, other lesions of the cerebellopontine angle, demyelinating lesions of the brainstem, and brain tumors. Both CT and MRI are equally capable of identifying inner-ear malformations and assessing cochlear patency for preoperative evaluation of patients for cochlear implantation.

℞ Treatment: DISORDERS OF THE SENSE OF HEARING

In general, conductive hearing losses are amenable to surgical correction, while sensorineural hearing losses are more difficult to manage. Atresia of the ear canal can be surgically repaired, often with significant improvement in hearing. Tympanic membrane perforations due to chronic otitis media or trauma can be repaired with an outpatient tympanoplasty. Likewise, conductive hearing loss associated with otosclerosis can be treated by stapedectomy, which is successful in 90–95% of cases. Tympanostomy tubes allow the prompt return of normal hearing in individuals with middle-ear effusions. Hearing aids are effective and well-tolerated in patients with conductive hearing losses.

Patients with mild, moderate, and severe sensorineural hearing losses are regularly rehabilitated with hearing aids of varying configuration and strength. Hearing aids have been improved to provide greater fidelity and have been miniaturized. The current generation of hearing aids can be placed entirely within the ear canal, thus reducing any stigma associated with their use. In general, the more severe the hearing impairment, the larger the hearing aid required for auditory rehabilitation. Digital hearing aids lend themselves to individual programming, and multiple and directional microphones at the ear level may be helpful in noisy surroundings. Since all hearing aids amplify noise as well as speech, the only absolute solution to the problem of noise is to place the microphone closer to the speaker than the noise source. This arrangement is not possible with a self-contained, cosmetically acceptable device.

In many situations, including lectures and the theater, hearing-impaired persons benefit from assistive devices that are based on the principle of having the speaker closer to the microphone than any source of noise. Assistive devices include infrared and frequency-modulated (FM) transmission as well as an electromagnetic loop around the room for transmission to the individual's hearing aid. Hearing aids with telecoils can also be used with properly equipped telephones in the same way.

In the event that the hearing aid provides inadequate rehabilitation, cochlear implants may be appropriate. Criteria for implantation include severe to profound hearing loss with word recognition score $\leq$ 30% under best aided conditions. Worldwide, >20,000 deaf individuals (including 4000 children) have received cochlear implants. Cochlear implants are neural prostheses that convert sound energy to electrical energy and can be used to stimulate the auditory division of the eighth nerve directly. In most cases of profound hearing impairment, the auditory hair cells are lost but the ganglionic cells of the auditory division of the eighth nerve are preserved. Cochlear implants consist of electrodes that are inserted into the cochlea through the round window, speech processors that extract acoustical elements of speech for conversion to electrical currents, and a means of transmitting the electrical energy through the skin. Patients with implants experience sound that helps with speech reading, allows open-set word recognition, and helps in modulating the person's own voice. Usually, within 3 months after implantation, adult patients can understand speech without visual cues. With the current generation of multichannel

cochlear implants, nearly 75% of patients are able to converse on the telephone. For individuals who have had both eighth nerves destroyed by trauma or bilateral vestibular schwannomas (e.g., neurofibromatosis type 2), brainstem auditory implants placed near the cochlear nucleus may provide auditory rehabilitation.

Tinnitus often accompanies hearing loss. As for background noise, tinnitus can degrade speech comprehension in individuals with hearing impairment. Therapy for tinnitus is usually directed toward minimizing the appreciation of tinnitus. Relief of the tinnitus may be obtained by masking it with background music. Hearing aids are also helpful in tinnitus suppression, as are tinnitus maskers, devices that present a sound to the affected ear that is more pleasant to listen to than the tinnitus. The use of a tinnitus masker is often followed by several hours of inhibition of the tinnitus. Antidepressants have been shown to be beneficial in helping patients cope with tinnitus.

Hard-of-hearing individuals often benefit from a reduction in unnecessary noise (e.g., radio or television) to enhance the signal-to-noise ratio. Speech comprehension is aided by lip reading; therefore the impaired listener should be seated so that the face of the speaker is well-illuminated and easily seen. Although speech should be in a loud, clear voice, one should be aware that in sensorineural hearing losses in general and in hard-of-hearing elderly in particular, recruitment (abnormal perception of loud sounds) may be troublesome. Above all, optimal communication cannot take place without both parties giving it their full and undivided attention.

PREVENTION

Conductive hearing losses may be prevented by prompt antibiotic therapy of adequate duration for AOM and by ventilation of the middle ear with tympanostomy tubes in middle-ear effusions lasting ≥12 weeks. Loss of vestibular function and deafness due to aminoglycoside antibiotics can largely be prevented by careful monitoring of serum peak and trough levels.

Some 10 million Americans have noise-induced hearing loss, and 20 million are exposed to hazardous noise in their employment. Noise-induced hearing loss can be prevented by avoidance of exposure to loud noise or by regular use of ear plugs or fluid-filled ear muffs to attenuate intense sound. High-risk activities for noise-induced hearing loss include wood and metal working with electrical equipment and target practice and hunting with small firearms. All internal-combustion and electric engines, including snow and leaf blowers, snowmobiles, outboard motors, and chain saws, require protection of the user with hearing protectors. Virtually all noise-induced hearing loss is preventable through education, which should begin before the teenage years. Programs of industrial conservation of hearing are required when the exposure over an 8-h period averages 85 dB. Workers in such noisy environments can be protected with preemployment audiologic assessment, the mandatory use of hearing protectors, and annual audiologic assessments.

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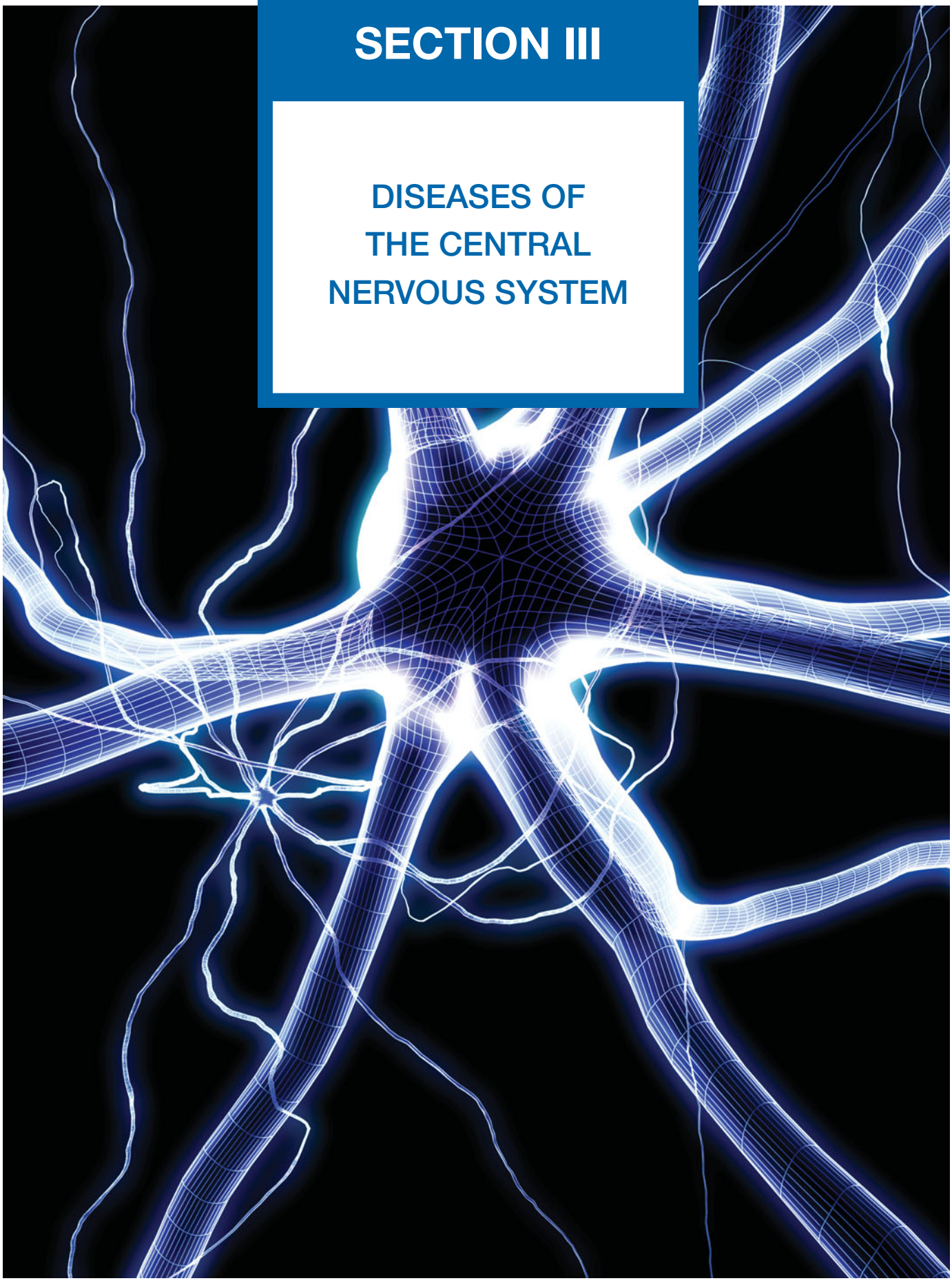
SECTION III

DISEASES OF THE CENTRAL NERVOUS SYSTEM



CHAPTER 19

MECHANISMS OF NEUROLOGIC DISEASES

Stephen L. Hauser ■ M. Flint Beal

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The human nervous system is the organ of consciousness, cognition, ethics, and behavior; as such, it is the most intricate structure known to exist. More than one-third of the 23,000 genes encoded in the human genome are expressed in the nervous system. Each mature brain is composed of 100 billion neurons, several million miles of axons and dendrites, and $>10^{15}$ synapses. Neurons exist within a dense parenchyma of multifunctional glial cells that synthesize myelin, preserve homeostasis, and regulate immune responses. Measured against this background of complexity, the achievements of molecular neuroscience have been extraordinary. This chapter reviews selected themes in neuroscience that provide a context for understanding fundamental mechanisms underlying neurologic disorders.

NEUROGENETICS

The landscape of neurology has been transformed by modern molecular genetics. More than 350 different disease-causing genes have now been identified, and >1000 neurologic disorders have been genetically mapped to various chromosomal locations. The vast majority of these represent highly penetrant mutations that cause rare neurologic disorders; alternatively, they represent rare monogenic causes of common phenotypes. Examples of the latter include mutations of the amyloid precursor protein in familial Alzheimer's disease, the microtubule-associated protein tau (MAPT) in frontotemporal dementia, and α-synuclein in Parkinson's disease. These discoveries have been profoundly important because the mutated gene in the familial disorder often encodes a protein that is also pathogenetically involved (although not mutated) in the typical, sporadic form. The common mechanism involves disordered processing and, ultimately, aggregation of the protein, leading to cell death (see Protein Aggregation and Neurodegeneration, later in the chapter).

There is great optimism that complex genetic disorders, caused by combinations of both genetic and environmental factors, have now become tractable problems. The development of new genetic approaches, such as haplotype mapping for the efficient screening of variants genome-wide along with advances in high-throughput sequencing, are beginning to delineate incompletely penetrant genetic variants that influence susceptibility to, or modify the expression of, complex diseases including age-related macular degeneration, type 2 diabetes mellitus, and Alzheimer's disease.

Not all genetic diseases of the nervous system are caused by simple changes in the linear nucleotide sequence of

genes. As the complex architecture of the human genome becomes better defined, many disorders that result from alterations in copy numbers of genes ("gene-dosage" effects) resulting from unequal crossing-over are likely to be identified. The first copy-number disorders to be recognized were Charcot-Marie-Tooth disease type 1A (CMT1A), caused by a duplication in the gene encoding the myelin protein PMP22, and the reciprocal deletion of the gene causing hereditary liability to pressure palsies (HNPP) (Chap. 40). Gene-dosage effects are causative in some cases of Parkinson's disease (α-synuclein), Alzheimer's disease (amyloid precursor protein), spinal muscular atrophy (survival motor neuron 2), the dysmyelinating disorder Pelizaeus-Merzbacher syndrome (proteolipid protein 1), late-onset leukodystrophy (lamin B1), and a variety of developmental neurologic disorders. It is now evident that copy-number variations contribute substantially to normal human genomic variation for numerous genes involved in neurologic function, regulation of cell growth, and regulation of metabolism. It is also likely that gene-dosage effects will influence many behavioral phenotypes, learning disorders, and autism spectrum disorders.

The role of splicing variation as a contributor to neurologic disease is another area of active investigation. *Alternative splicing* refers to the inclusion of different combinations of exons in mature mRNA, resulting in the potential for many different protein products encoded by a single gene. Alternative splicing represents a powerful mechanism for generation of complexity and variation, and this mechanism appears to be highly prevalent in the nervous system, affecting key processes such as neurotransmitter receptors and ion channels. Numerous diseases are already known to result from abnormalities in alternative splicing. Increased inclusion of exon 10-containing transcripts of MAPT can cause frontotemporal dementia. Aberrant splicing also contributes to the pathogenesis of Duchenne, myotonic, and fascioscapulohumeral muscular dystrophies; ataxia telangiectasia; neurofibromatosis; some inherited ataxias; and fragile X syndrome; among other disorders. It is also likely that subtle variations of splicing will influence many genetically complex disorders. Recently a splicing variant of the interleukin 7 receptor α chain, resulting in production of more soluble and less membrane-bound receptor, was found to be associated with susceptibility to multiple sclerosis (MS) in multiple different populations.

Epigenetics refers to the mechanisms by which levels of gene expression can be exquisitely modulated, not by variations in the primary genetic sequence of DNA but rather by postgenomic alterations in DNA and chromatin structure, which influence how, when, and where genes are expressed. DNA methylation, as well as methylation and acetylation of histone proteins that interact with nuclear DNA to form chromatin, are key mediators of these events. Epigenetic processes appear to be dynamically active even in postmitotic neurons. *Imprinting* refers to an epigenetic feature, present for a subset of genes, in which the predominant expression of one allele is determined by its parent-of-origin. The distinctive neurodevelopmental disorders Prader-Willi syndrome (mild mental retardation and endocrine abnormalities) and Angelman syndrome (cortical atrophy, cerebellar dysmyelination, Purkinje cell loss) are classic examples of imprinting disorders whose distinctive features are determined by whether the paternal or maternal copy of chromosome of the critical genetic region 15q11-13 was responsible. Preferential allelic expression, whether due to imprinting, resistance to X-inactivation, or other mechanisms, is likely to play a major role in determining complex behaviors and susceptibility to many neurologic and psychiatric disorders.

ION CHANNELS AND CHANNELOPATHIES

The resting potential of neurons and the action potentials responsible for impulse conduction are generated by ion currents and ion channels. Most ion channels are gated, meaning that they can transition between conformations that are open or closed to ion conductance. Individual ion channels are distinguished by the specific ions they conduct; by their kinetics; and by whether they directly sense voltage, are linked to receptors for neurotransmitters or other ligands such as neurotrophins, or are activated by second messengers. The diverse characteristics of different ion channels provide a means by which neuronal excitability can be exquisitely modulated at both the cellular and the subcellular levels. Disorders of ion channels—channelopathies—are responsible for a growing list of human neurologic diseases (**Table 19-1**). Most are caused by mutations in ion channel genes or by autoantibodies against ion channel proteins. One example is epilepsy, a syndrome of diverse causes characterized by repetitive, synchronous firing of neuronal action potentials. Action potentials are normally generated by the opening of sodium channels and the inward movement of sodium ions down the intracellular concentration gradient. Depolarization of the neuronal membrane opens potassium channels, resulting in outward movement of potassium ions, repolarization, closure of the sodium channel, and hyperpolarization. Sodium or potassium channel subunit genes have long been considered candidate disease genes in inherited epilepsy syndromes, and recently such mutations have been identified. These mutations appear to alter the normal gating function of these channels, increasing the inherent excitability of neuronal membranes in regions where the abnormal channels are expressed.

Whereas the specific clinical manifestations of channelopathies are quite variable, one common feature is

TABLE 19-1

EXAMPLES OF NEUROLOGIC CHANNELOPATHIES

CATEGORY	DISORDER	CHANNEL TYPE	MUTATED GENE	CHAP. REF.
Genetic				
Ataxias	Episodic ataxia-1	K	*KCNA1*	26
	Episodic ataxia-2	Ca	*CACNL1A*	
	Spinocerebellar ataxia-6	Ca	*CACNL1A*	
Migraine	Familial hemiplegic migraine 1	Ca	*CACNL1A*	6
	Familial hemiplegic migraine 2	Na	SCN1A	
Epilepsy	Benign neonatal familial convulsions			
	Generalized epilepsy with febrile convulsions plus	K Na	*KCNQ2*, *KCNQ3* *SCN1B*	20
Periodic paralysis	Hyperkalemic periodic paralysis	Na	*SCN4A*	43
	Hypokalemic periodic paralysis	Ca	*CACNL1A3*	
Myotonia	Myotonia congenita	Cl	*CLCN1*	43
	Paramyotonia congenita	Na	*SCN4A*	
Deafness	Jorvell and Lange-Nielsen syndrome (deafness, prolonged QT interval, and arrythmia)	K	*KCNQ1*, *KCNE1*	18
	Autosomal dominant progressive deafness	K	*KCNQ4*	
Autoimmune				
Paraneoplastic	Limbic encephalitis	Kv1	—	39
	Acquired neuromyotonia	Kv1	—	39
	Cerebellar ataxia	Ca (P/Q type)	—	39
	Lambert-Eaton syndrome	Ca (P/Q type)	—	39

that manifestations tend to be intermittent or paroxysmal, such as occurs in epilepsy, migraine, ataxia, myotonia, or periodic paralysis. Exceptions are clinically progressive channel disorders such as autosomal dominant hearing impairment. The genetic channelopathies identified to date are all uncommon disorders caused by obvious mutations in channel genes. As the full repertoire of human ion channels and related proteins is identified, it is likely that additional channelopathies will be discovered. In addition to rare disorders that result from obvious mutations, it is also likely that less penetrant allelic variations in channel genes or in their pattern of expression might underlie susceptibility to some common forms of epilepsy, migraine, or other disorders. For example, mutations in the T-type Ca channel gene *CACNA1H*, as well as a K channel (*KCND2*) and various GABA receptor genes, have been associated with an increased risk for epilepsy.

NEUROTRANSMITTERS AND NEUROTRANSMITTER RECEPTORS

Synaptic neurotransmission is the predominant means by which neurons communicate with each other. Classic neurotransmitters are synthesized in the presynaptic region of the nerve terminal; stored in vesicles; and released into the synaptic cleft, where they bind to receptors on the postsynaptic cell. Secreted neurotransmitters are eliminated by reuptake into the presynaptic neuron (or glia), by diffusion away from the synaptic cleft, and/or by specific inactivation. In addition to the classic neurotransmitters, many neuropeptides have been identified as definite or probable neurotransmitters; these include substance P, neurotensin, enkephalins, β-endorphin, histamine, vasoactive intestinal polypeptide, cholecystokinin, neuropeptide Y, and somatostatin. Peptide neurotransmitters are synthesized in the cell body rather than the nerve terminal and may colocalize with classic neurotransmitters in single neurons. Nitric oxide and carbon monoxide are gases that appear also to function as neurotransmitters, in part by signaling in a retrograde fashion from the postsynaptic to the presynaptic cell.

Neurotransmitters modulate the function of postsynaptic cells by binding to specific neurotransmitter receptors, of which there are two major types. *Ionotropic receptors* are direct ion channels that open after engagement by the neurotransmitter. *Metabotropic receptors* interact with G proteins, stimulating production of second messengers and activating protein kinases, which modulate a variety of cellular events. Ionotropic receptors are multiple subunit structures, whereas metabotropic receptors are composed of single subunits only. One important difference between ionotropic and metabotropic receptors is that

the kinetics of ionotropic receptor effects are fast (generally <1 ms) because neurotransmitter binding directly alters the electrical properties of the postsynaptic cell, whereas metabotropic receptors function over longer time periods. These different properties contribute to the potential for selective and finely modulated signaling by neurotransmitters.

Neurotransmitter systems are perturbed in a large number of clinical disorders, examples of which are highlighted in **Table19-2**. One example is the involvement of dopaminergic neurons originating in the substantia nigra of the midbrain and projecting to the striatum (nigrostriatal pathway) in Parkinson's disease and in heroin addicts after the ingestion of the toxin MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine).

A second important dopaminergic system arising in the midbrain is the mediocorticolimbic pathway, which is implicated in the pathogenesis of addictive behaviors including drug reward. Its key components include the midbrain ventral tegmental area (VTA), median forebrain bundle, and nucleus accumbens (Fig. 48-2). The cholinergic pathway originating in the nucleus basalis of Meynert plays a role in memory function in Alzheimer's disease.

Addictive drugs share the property of increasing dopamine release in the nucleus accumbens. Amphetamine increases intracellular release of dopamine from vesicles and reverses transport of dopamine through the dopamine transporters. Patients prone to addiction show increased activation of the nucleus accumbens following administration of amphetamine. Cocaine binds to dopamine transporters and inhibits dopamine reuptake. Ethanol inhibits inhibitory neurons in the VTA, leading to increased dopamine release in the nucleus accumbens. Opioids also disinhibit these dopaminergic neurons by binding to μ receptors expressed by GABA-containing interneurons in the VTA. Nicotine increases dopamine release by activating nicotinic acetylcholine receptors on cell bodies and nerve terminals of dopaminergic VTA neurons. Tetrahydrocannabinol, the active ingredient of cannabis, also increases dopamine levels in the nucleus accumbens. Blockade of dopamine in the nucleus accumbens can terminate the rewarding effects of addictive drugs.

Not all cell-to-cell communication in the nervous system occurs via neurotransmission. Gap junctions provide for direct neuron-neuron electrical conduction and also create openings for the diffusion of ions and metabolites between cells. In addition to neurons, gap junctions are also widespread in glia, creating a syncytium that protects neurons by removing glutamate and potassium from the extracellular environment. Gap junctions consist of membrane-spanning proteins, termed *connexins*, that pair across adjacent cells. Mechanisms that involve gap junctions have been related to a variety of neurologic disorders. Mutations in connexin 32, a gap junction protein expressed by Schwann cells, are responsible for the X-linked form of CMT disease (Chap. 40). Mutations in either of two gap junction proteins expressed in the inner ear—connexin 26 and connexin 31—result in autosomal dominant progressive hearing loss (Chap. 18). Glial calcium waves mediated through gap junctions also appear to explain the phenomenon of spreading depression associated with migraine auras and the march of epileptic discharges. Spreading depression is a neural response that follows a variety of different stimuli and is characterized by a circumferentially expanding negative potential that propagates at a characteristic speed of 20 m/s and is associated with an increase in extracellular potassium.

SIGNALING PATHWAYS AND GENE TRANSCRIPTION

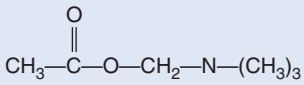
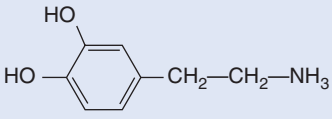
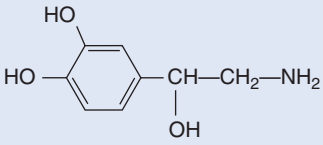
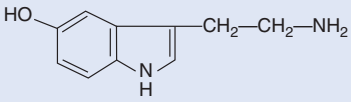
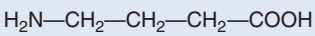
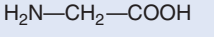
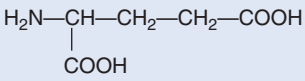
The fundamental issue of how memory, learning, and thinking are encoded in the nervous system is likely to be clarified by identifying the signaling pathways involved in neuronal differentiation, axon guidance, and synapse formation, and by understanding how these pathways are modulated by experience. Many families of transcription factors, each comprising multiple individual components, are expressed in the nervous system. Elucidation of these signaling pathways has already begun to provide insights into the cause of a variety of neurologic disorders, including inherited disorders of cognition such as X-linked mental retardation. This problem affects ~1 in 500 males, and linkage studies in different families suggest that as many as 60 different X-chromosome encoded genes may be responsible. Rett syndrome, a common cause of (dominant) X-linked progressive mental retardation in females, is due to a mutation in a gene (*MECP2*) encoding a DNA-binding protein involved in transcriptional repression. As the X chromosome comprises only ~3% of germline DNA, then by extrapolation the number of genes that potentially contribute to clinical disorders affecting intelligence in humans must be potentially very large. As discussed below, there is increasing evidence that abnormal gene transcription may play a role in neurodegenerative diseases, such as Huntington's disease, in which proteins with polyglutamine expansions bind to and sequester transcription factors. A critical transcription factor for neuronal survival is CREB (cyclic adenosine monophosphate responsive element-binding) protein, which also plays an important role in memory in the hippocampus.

MYELIN

Myelin is the multilayered insulating substance that surrounds axons and speeds impulse conduction by permitting action potentials to jump between naked regions of axons (nodes of Ranvier) and across myelinated segments.

TABLE 19-2

PRINCIPAL CLASSIC NEUROTRANSMITTERS

NEUROTRANSMITTER	ANATOMY	CLINICAL ASPECTS
Acetylcholine (ACh) 	Motor neurons in spinal cord → neuromuscular junction	Acetylcholinesterases (nerve gases) Myasthenia gravis (antibodies to ACh receptor) Congenital myasthenic syndromes (mutations in ACh receptor subunits) Lambert-Eaton syndrome (antibodies to Ca channels impair ACh release) Botulism (toxin disrupts ACh release by exocytosis)
	Basal forebrain →widespread cortex	Alzheimer's disease (selective cell death) Autosomal dominant frontal lobe epilepsy (mutations in CNS ACh receptor)
	Interneurons in striatum Autonomic nervous system (preganglionic and postganglionic parasympathetic; preganglionic sympathetic)	Parkinson's disease (tremor)
Dopamine 	Substantia nigra → striatum (nigrostriatal pathway) Substantia nigra → limbic system and widespread cortex Arcuate nucleus of hypothalamus → anterior pituitary (via portal veins)	Parkinson's disease (selective cell death) MPTP parkinsonism (toxin transported into neurons) Addiction, behavioral disorders Inhibits prolactin secretion
Norepinephrine (NE) 	Locus coeruleus (pons) → limbic system, hypothalamus, cortex Medulla → locus coeruleus, spinal cord Postganglionic neurons of sympathetic nervous system	Mood disorders (MAOA inhibitors and tricyclics increase NE and improve depression) Anxiety Orthostatic tachycardia syndrome (mutations in NE transporter)
Serotonin 	Pontine raphe nuclei → widespread projections Medulla/pons → dorsal horn of spinal cord	Mood disorders (SSRIs improve depression) Migraine pain pathway Pain pathway
γ-Aminobutyric acid (GABA) 	Major inhibitory neurotransmitter in brain; widespread cortical interneurons and long projection pathways	Stiff person syndrome (antibodies to glutamic acid decarboxylase, the biosynthetic enzyme for GABA) Epilepsy (gabapentin and valproic acid increase GABA)
Glycine 	Major inhibitory neurotransmitter in spinal cord	Spasticity Hyperekplexia (myoclonic startle syndrome) due to mutations in glycine receptor
Glutamate 	Major excitatory neurotransmitter; located throughout CNS, including cortical pyramidal cells	Seizures due to ingestion of domoic acid (a glutamate analogue) Rasmussen's encephalitis (antibody against glutamate receptor 3) Excitotoxic cell death

Note: CNS, central nervous system; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MAOA, monoamine oxidase A; SSRI, selective serotonin reuptake inhibitor.

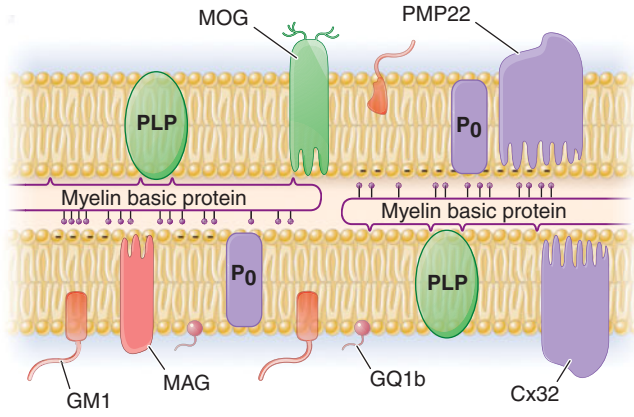


FIGURE 19-1

The molecular architecture of the myelin sheath illustrating the most important disease-related proteins. The illustration represents a composite of CNS and PNS myelin. Proteins restricted to CNS myelin are shown in green, proteins of PNS myelin are lavender, and proteins present in both CNS and PNS are red. In the CNS, the X-linked allelic disorders, Pelizaeus-Merzbacher disease and one variant of familial spastic paraplegia, are caused by mutations in the gene for proteolipid protein (PLP) that normally promotes extracellular compaction between adjacent myelin lamellae. The homologue of PLP in the PNS is the P_0 protein, mutations in which cause the neuropathy Charcot-Marie-Tooth disease (CMT) type 1B. The most common form of CMT is the 1A subtype caused by a duplication of the *PMP22* gene; deletions in *PMP22* are responsible for another inherited neuropathy termed *hereditary liability to pressure palsies* (Chap. 40).

In multiple sclerosis (MS), myelin basic protein (MBP) and the quantitatively minor CNS protein, myelin oligodendrocyte glycoprotein (MOG), are likely T cell and B cell antigens, respectively. The location of MOG at the outermost lamella of the CNS myelin membrane may facilitate its targeting by autoantibodies. In the PNS, autoantibodies against myelin gangliosides are implicated in a variety of disorders, including GQ1b in the Fisher variant of Guillain-Barré syndrome, GM1 in multifocal motor neuropathy, and sulfatide constituents of myelin-associated glycoprotein (MAG) in peripheral neuropathies associated with monoclonal gammopathies (Chap. 41).

Molecular interactions between the myelin membrane and axon are required to maintain the stability, function, and normal lifespan of both structures. A single oligodendrocyte usually ensheaths multiple axons in the central nervous system (CNS), whereas in the peripheral nervous system (PNS) each Schwann cell typically myelinates a single axon. Myelin is a lipid-rich material formed by a spiraling process of the membrane of the myelinating cell around the axon, creating multiple membrane bilayers that are tightly apposed (compact myelin) by charged protein interactions. Several inhibitors of axon growth are expressed on the innermost (periaxonal) lamellae of the myelin membrane (see Stem Cells and Transplantation, below). A number of clinically important neurologic disorders are caused by inherited mutations in myelin proteins of the CNS or PNS (**Fig. 19-1**). Constituents of myelin also have a propensity to be targeted as autoantigens in autoimmune demyelinating disorders (**Fig. 19-2**).

NEUROTROPHIC FACTORS

Neurotrophic factors (**Table 19-3**) are secreted proteins that modulate neuronal growth, differentiation, repair, and survival; some have additional functions, including roles in neurotransmission and in the synaptic reorganization involved in learning and memory. The neurotrophin (NT) family contains nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), NT3, and NT4/5. The neurotrophins act at TrK and p75 receptors to promote survival of neurons. Because of their survival-promoting and antiapoptotic effects, neurotrophic factors are in theory outstanding candidates for therapy of disorders characterized by premature death of neurons such as occurs in amyotrophic lateral sclerosis (ALS) and other degenerative motor neuron disorders. Knockout mice lacking receptors for ciliary neurotrophic factor (CNTF) or BDNF show loss of motor neurons, and experimental motor neuron death can be rescued by treatment with various neurotrophic factors including CNTF, BDNF, and vascular endothelial growth factor (VEGF). However, in phase 3 clinical trials, growth factors were ineffective in human ALS. The growth factor glial-derived neurotrophic factor (GDNF) is important for survival of dopaminergic neurons. It has shown promising neurorestorative effects in experimental models of Parkinson's disease and is being tested using gene therapy in early-stage human clinical trials.

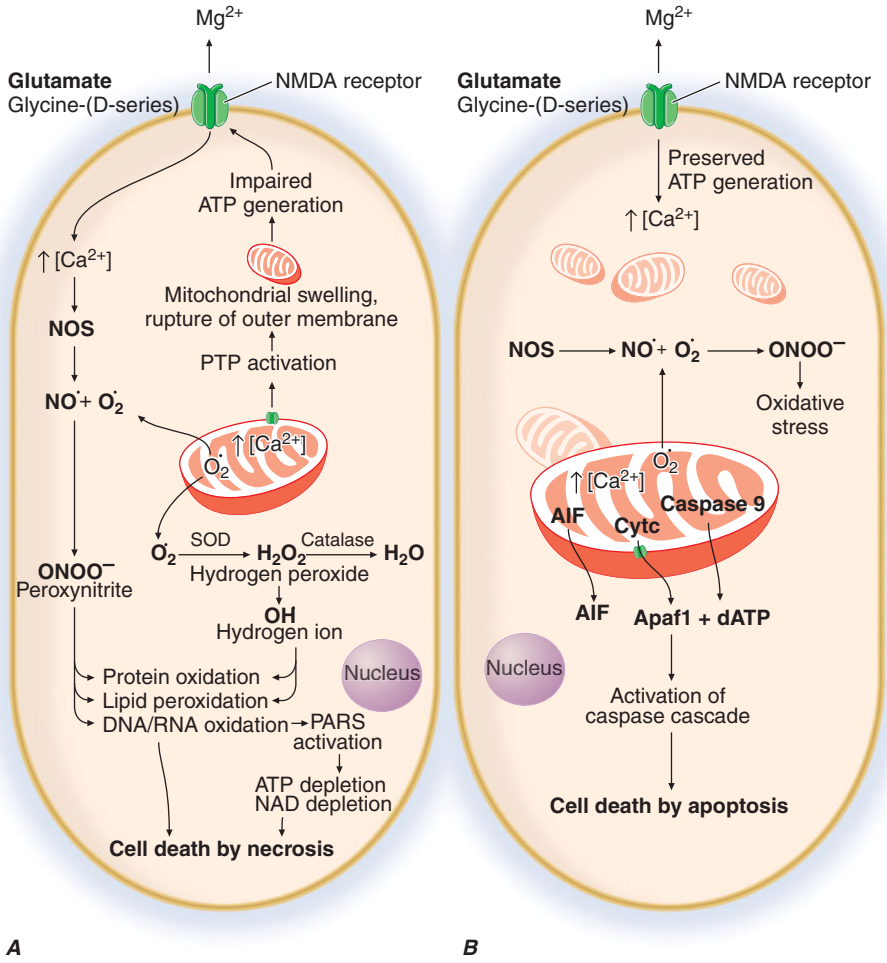


FIGURE 19-2

Involvement of mitochondria in cell death. A severe excitotoxic insult (***A***) results in cell death by necrosis, whereas a mild excitotoxic insult (***B***) results in apoptosis. After a severe insult (such as ischemia), there is a large increase in glutamate activation of NMDA receptors, an increase in intracellular Ca^{2+} concentrations, activation of nitric oxide synthase (NOS), and increased mitochondrial Ca^{2+} and superoxide generation followed by the formation of $ONOO^-$. This sequence results in damage to cellular macromolecules including DNA, leading to activation of poly-ADP-ribose polymerase (PARS). Both mitochondrial accumulation of Ca^{2+} and oxidative damage lead to activation of the permeability transition pore (PTP) that is linked to excitotoxic cell death. A mild excitotoxic insult can occur due either to an abnormality in an excitotoxicity amino acid receptor, allowing more Ca^{2+} flux, or to impaired functioning of other ionic channels or of energy production, which may allow the voltage-dependent NMDA receptor to be activated by ambient concentrations of glutamate. This event can then lead to increased mitochondrial Ca^{2+} and free radical production, yet relatively preserved ATP generation. The mitochondria may then release cytochrome c (Cytc), caspase 9, apoptosis-inducing factor (AIF), and perhaps other mediators that lead to apoptosis. The precise role of the PTP in this mode of cell death is still being clarified, but there does appear to be involvement of the adenine nucleotide transporter that is a key component of the PTP.

STEM CELLS AND TRANSPLANTATION

The nervous system is traditionally considered to be a nonmitotic organ, in particular with respect to neurons. These concepts have been challenged by the finding that neural progenitor or stem cells exist in the adult CNS that are capable of differentiation, migration over long distances, and extensive axonal arborization and synapse formation with appropriate targets. These capabilities also indicate that the repertoire of factors required for growth, survival, differentiation, and migration of these cells exists in the mature nervous system. In rodents, neural stem cells, defined as progenitor cells capable of differentiating into mature cells of neural or glial lineage, have been experimentally propagated from fetal CNS and neuroectodermal tissues and also from adult germinal matrix and ependyma regions. Human fetal CNS tissue is also capable of differentiation into cells with neuronal, astrocyte, and oligodendrocyte morphology when cultured in the presence of growth factors. Impressively,

TABLE 19-3

NEUROTROPHIC FACTORS	
Neurotrophin family	Transforming growth factor β family
Nerve growth factor	Glial-derived neurotrophic family
Brain-derived neurotrophic factor	Neurturin
Neurotrophin-3	Persephin
Neurotrophin-4	Fibroblast growth factor family
Neurotrophin-6	Hepatocyte growth factor
Cytokine family	Insulin-like growth factor (IGF) family
Ciliary neurotrophic factor	IGF-1
Leukemia inhibitory factor	IGF-2
Interleukin-6	
Cardiotrophin-1	

such cells could be stably engrafted into mouse CNS tissue, creating neural chimeras. Another approach is to use somatic cell nuclear transfer, in which cell nuclei are placed inside an enucleated oocyte and then differentiated into stem cells with an identical genetic background to the donor. This technique has been utilized successfully in animal models of Parkinson's disease. Once the repertoire of signals required for cell type specification is better understood, differentiation into specific neural or glial subpopulations can be directed in vitro; such cells could also be engineered to express therapeutic molecules. Another promising approach is to utilize growth factors, such as BDNF, to stimulate endogenous stem cells to proliferate and migrate to areas of neuronal damage. Administration of epidermal growth factor with fibroblast growth factor replenished up to 50% of hippocampal CA1 neurons a month after global ischemia in rats. The new neurons made connections and improved performance in a memory task.

Although stem cells hold tremendous promise for the treatment of debilitating neurologic diseases, such as Parkinson's disease and spinal cord injury, it should be emphasized that medical application is in its infancy. Major obstacles are the generation of position- and neurotransmitter-defined subtypes of neurons and their isolation as pure populations of the desired cells. This is crucial to avoid persistence of undifferentiated embryonic stem (ES) cells, which can generate tumors. The establishment of appropriate neural connections and afferent control is also critical. For instance, human ES motor neurons will need to be introduced at multiple segments in the neuraxis, and then their axons will need to regenerate from the spinal cord to distal musculature.

Experimental transplantation of human fetal dopaminergic neurons in patients with Parkinson's disease has shown that these transplanted cells can survive within the host striatum; however, some patients developed disabling dyskinesias and this approach is no longer in clinical development. Human ES cells can be differentiated into dopaminergic neurons, which reverse symptoms of Parkinson's disease in experimental animal models. Studies of transplantation for patients with Huntington's disease have also reported encouraging, although very preliminary, results. Oligodendrocyte precursor cells transplanted into mice with a dysmyelinating disorder effectively migrated in the new environment, interacted with axons, and mediated myelination; such experiments raise hope that similar transplantation strategies may be feasible in human disorders of myelin such as MS. The promise of stem cells for treatment of both neurodegenerative diseases and neural injury is great, but development has been slowed by unresolved concerns over safety (including the theoretical risk of malignant transformation of transplanted cells), ethics (particularly with respect to use of fetal tissue), and efficacy.

In developing brain, the extracellular matrix provides stimulatory and inhibitory signals that promote neuronal migration, neurite outgrowth, and axonal extension. After neuronal damage, reexpression of inhibitory molecules such as chondroitin sulfate proteoglycans may prevent tissue regeneration. Chondroitinase degraded these inhibitory molecules and enhanced axonal regeneration and motor recovery in a rat model of spinal cord injury. Several myelin proteins, specifically Nogo, oligodendrocyte myelin glycoprotein (OMGP), and myelin-associated glycoprotein (MAG), may also interfere with axon regeneration. Sialidase, which cleaves one class of receptors for MAG, enhances axonal outgrowth. Antibodies against Nogo promote regeneration after experimental focal ischemia or spinal cord injury. Nogo, OMGP, and MAG all bind to the same neural receptor, the Nogo receptor, which mediates its inhibitory function via the p75 neurotrophin receptor signaling.

CELL DEATH—EXCITOTOXICITY AND APOPTOSIS

Excitotoxicity refers to neuronal cell death caused by activation of excitatory amino acid receptors (**Fig. 19-3**). Compelling evidence for a role of excitotoxicity, especially in ischemic neuronal injury, is derived from experiments in animal models. Experimental models of stroke are associated with increased extracellular concentrations of the excitatory amino acid neurotransmitter glutamate, and neuronal damage is attenuated by denervation of glutamate-containing neurons or the administration of glutamate receptor antagonists. The distribution of cells sensitive to ischemia corresponds closely with that of *N*-methyl-D-aspartate (NMDA) receptors (except for cerebellar Purkinje cells, which are vulnerable to hypoxia-ischemia but lack NMDA receptors); and competitive and noncompetitive NMDA antagonists are effective in preventing focal ischemia. In global cerebral ischemia,

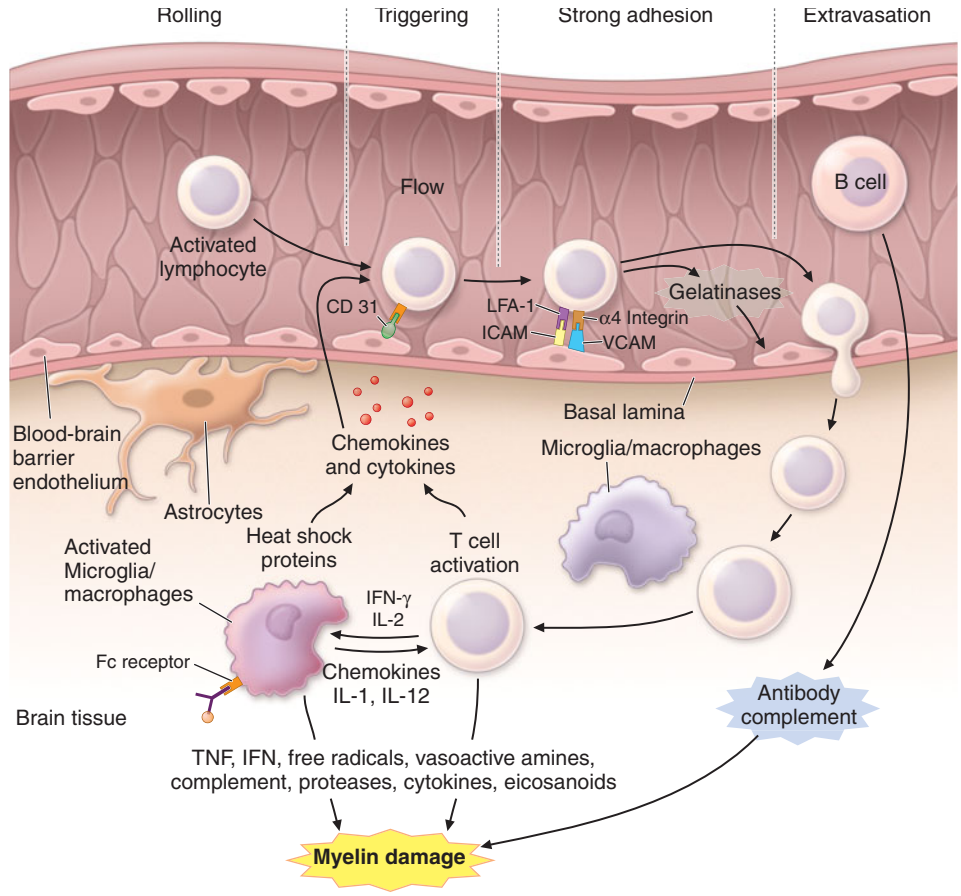


FIGURE 19-3
A model for experimental allergic encephalomyelitis (EAE). Crucial steps for disease initiation and progression include peripheral activation of preexisting autoreactive T cells; homing to the CNS and extravasation across the blood-brain barrier; reactivation of T cells by exposed autoantigens; secretion of cytokines; activation of microglia and astrocytes and recruitment of a secondary inflammatory wave; and immune-mediated myelin destruction. ICAM, intercellular adhesion molecule; LFA-1, leukocyte function-associated antigen-1; VCAM, vascular cell adhesion molecule; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

non-NMDA receptors (kainic acid and AMPA) are activated, and antagonists to these receptors are protective. Experimental brain damage induced by hypoglycemia is also attenuated by NMDA antagonists.

Excitotoxicity is not a single event but rather a cascade of cell injury. Excitotoxicity causes influx of calcium into cells, and much of the calcium is sequestered in mitochondria rather than in the cytoplasm. Increased cytoplasmic calcium causes metabolic dysfunction and free radical generation; activates protein kinases, phospholipases, nitric oxide synthase, proteases, and endonucleases; and inhibits protein synthesis. Activation of nitric oxide synthase generates nitric oxide (NO•), which can react with superoxide ($O^{\bullet}_2$) to generate peroxynitrite ($ONOO^-$), which may play a direct role in neuronal injury. Another critical pathway is activation of poly-ADP-ribose polymerase, which occurs in response to free radical–mediated DNA damage. Experimentally, mice with knockout mutations of neuronal nitric oxide synthase or poly-ADP-ribose polymerase, or those that overexpress superoxide dismutase, are resistant to focal ischemia.

Although excitotoxicity is clearly implicated in the pathogenesis of cell death in stroke, to date treatment with NMDA antagonists has not proven to be clinically useful. Transient receptor potentials (TRP) are calcium channels that are activated by oxidative stress in parallel with excitotoxic signal pathways. In addition, glutamate-independent pathways of calcium influx via acid-sensing ion channels have been identified. These channels transport calcium in the setting of acidosis and substrate depletion, and pharmacologic blockade of these channels markedly attenuates stroke injury. These channels offer a potential new therapeutic target for stroke.

Apoptosis, or programmed cell death, plays an important role in both physiologic and pathologic conditions. During embryogenesis, apoptotic pathways operate to destroy neurons that fail to differentiate appropriately or reach their intended targets. There is mounting evidence

for an increased rate of apoptotic cell death in a variety of acute and chronic neurologic diseases. Apoptosis is characterized by neuronal shrinkage, chromatin condensation, and DNA fragmentation, whereas necrotic cell death is associated with cytoplasmic and mitochondrial swelling followed by dissolution of the cell membrane. Apoptotic and necrotic cell death can coexist or be sequential events, depending on the severity of the initiating insult. Cellular energy reserves appear to have an important role in these two forms of cell death, with apoptosis favored under conditions in which ATP levels are preserved. Evidence of DNA fragmentation has been found in a number of degenerative neurologic disorders, including Alzheimer's disease, Huntington's disease, and ALS. The best characterized genetic neurologic disorder related to apoptosis is infantile spinal muscular atrophy (Werdnig-Hoffmann disease), in which two genes thought to be involved in the apoptosis pathways are causative.

Mitochondria are essential in controlling specific apoptosis pathways. The redistribution of cytochrome c, as well as apoptosis-inducing factor (AIF), from mitochondria during apoptosis leads to the activation of a cascade of intracellular proteases known as *caspases*. Caspase-independent apoptosis occurs after DNA damage, activation of poly-ADP-ribose polymerase, and translocation of AIF into the nucleus. Redistribution of cytochrome c is prevented by overproduction of the apoptotic protein BCL2 and is promoted by the proapoptotic protein BAX. These pathways may be triggered by activation of a large pore in the mitochondrial inner membrane known as the *permeability transition pore*, although in other circumstances they occur independently. Recent studies suggest that blocking the mitochondrial pore reduces both hypoglycemic and ischemic cell death. Mice deficient in cyclophilin D, a key protein involved in opening the permeability transition pore, are resistant to necrosis produced by focal cerebral ischemia.

PROTEIN AGGREGATION AND NEURODEGENERATION

The possibility that protein aggregation plays a role in the pathogenesis of neurodegenerative diseases is a major focus of current research. Protein aggregation is a major histopathologic hallmark of neurodegenerative diseases. Deposition of β-amyloid is strongly implicated in the pathogenesis of Alzheimer's disease. Genetic mutations in familial Alzheimer's disease cause increased production of β-amyloid with 42 amino acids, which has an increased propensity to aggregate, as compared to β-amyloid with 40 amino acids. Mutations in genes encoding the MAPT lead to altered splicing of tau and the production of neurofibrillary tangles in frontotemporal dementia and progressive supranuclear palsy. Familial Parkinson's disease is associated with mutations in α-synuclein, parkin, and the ubiquitin carboxy-terminal hydrolase. Parkin, which causes autosomal recessive early-onset Parkinson's disease, is a ubiquitin ligase. The characteristic histopathologic feature of Parkinson's disease is the Lewy body, an eosinophilic cytoplasmic inclusion that contains both neurofilaments and α-synuclein. Huntington's disease and cerebellar degenerations are associated with expansions of polyglutamine repeats in proteins, which aggregate to produce neuronal intranuclear inclusions. Familial ALS is associated with superoxide dismutase mutations and cytoplasmic inclusions containing superoxide dismutase. In autosomal dominant neurohypophyseal diabetes insipidus, mutations in vasopressin result in abnormal protein processing, accumulation in the endoplasmic reticulum, and cell death.

The current major scientific question is whether protein aggregates contribute to neuronal death or whether they are merely secondary bystanders. A major focus in all the neurodegenerative diseases is now on small protein aggregates termed *oligomers*. These may be the toxic species of β-amyloid, α-synuclein, and proteins with expanded polyglutamines such as are associated with Huntington's disease. Protein aggregates are usually ubiquinated, which targets them for degradation by the 26S component of the proteosome. An inability to degrade protein aggregates could lead to cellular dysfunction, impaired axonal transport, and cell death by apoptotic mechanisms.

In experimental models of Huntington's disease and cerebellar degeneration, protein aggregates are not well correlated with neuronal death and may be protective. A substantial body of evidence suggests that the mutant proteins with polyglutamine expansions in these diseases bind to transcription factors and that this contributes to disease pathogenesis. In Huntington's disease there is dysfunction of the transcriptional co-regulator, PGC-1α, a key regulator of mitochondrial biogenesis. Agents that upregulate gene transcription are neuroprotective in animal models of these diseases. A number of compounds have been developed to block β-amyloid production and/or aggregation, and these agents are being studied in early clinical trials in humans.

SYSTEMS NEUROSCIENCE

Systems neuroscience refers to study of the functions of neurocircuits and how they relate to brain function, behavior, motor activity, and cognition. Brain imaging techniques, primarily functional MRI (fMRI) and position emission tomography (PET), have made it possible to investigate cognitive processes such as perception, making judgments, paying attention, and thinking. This has allowed insights into how networks of neurons operate to produce behavior. Many of these studies at present are based on determining the connectivity of neural circuits and how they operate, and how this can

be then modeled to produce improved understanding of physiologic processes. fMRI uses contrast mechanisms related to physiologic changes in tissue, and brain perfusion can be studied by observing the time-course of changes in brain water signal as a bolus of injected paramagnetic gadolinium contrast moves through the brain. More recently, to study intrinsic contrast-related local changes in blood oxygenation with brain activity, blood-oxygen-level-dependent (BOLD) contrast has been used to provide a rapid noninvasive approach for functional assessment. These techniques have been reliably utilized in the field of both behavior and cognitive sciences. One example is the use of fMRI to demonstrate mirror neuron systems, imitative pathways activated when observing actions of others (**Fig. 19-4**). Mirror neurons are thought to be important for social conditioning and for many forms of learning, and abnormalities in mirror neurons may underlie some autism disorders. Data also suggest that enhancement of mirror neuron pathways might have potential for rehabilitation after stroke. Other examples of the use of fMRI include the study of memory. Recent studies have shown that not only is hippocampal activity correlated with declarative memory consolidation, but it also involves activation in the ventral medial prefrontal cortex. Consolidation of memory over time results in decreased activity of the hippocampus and progressively stronger activation in the ventral medial prefrontal region associated with retrieval of consolidated memories. An elegant study used MRI to identify the brain protein KIBRA as being significantly associated with human memory performance. This locus was initially identified in a genome-wide screen of three independent populations, which were studied in relation to the inability to perform verbal memory tasks. Several KIBRA alleles were associated with improved free recall performance. The authors then utilized fMRI to detect KIBRA allele–dependent differences in hippocampal activation during memory retrieval. These experiments provided strong evidence that KIBRA plays a direct role in human memory function. fMRI has also been utilized to identify sequences of brain activation involved in normal movements and alterations in their activation associated with both injury and recovery, and to plan neurosurgical operations. Diffusion tensor imaging is a recently developed MRI technique that can measure

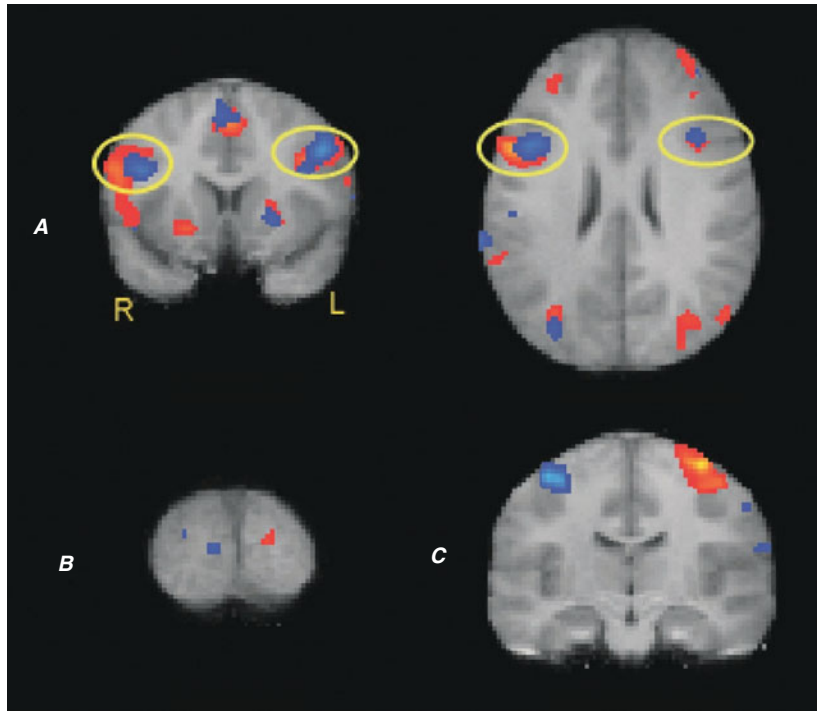


FIGURE 19-4

Mirror neuron systems are bilaterally activated during imitation. ***A.*** Bilateral activations (circled in yellow) in inferior frontal mirror neuron areas during imitation, as measured by BOLD fMRI signal changes. In red, activation during right hand imitation. In blue, activation during left hand imitation. ***B.*** In contrast, there is lateralized (contralateral) primary visual activation of the primary visual cortex for imitated actions presented to the right visual field (in red, left visual cortex) and to the left visual field (in blue, right visual cortex). ***C.*** Lateralized primary motor activation for hand actions imitated with the right hand (in red, left motor cortex) and with the left hand (in blue, right motor cortex). *(From L. Aziz-Zadeh et al: J Neurosci 26:2964, 2006.)*

macroscopic axonal organization in nervous system tissues; it appears to be useful in assessing myelin and axonal injuries as well as brain development.

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CHAPTER 20

SEIZURES AND EPILEPSY

Daniel H. Lowenstein

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A *seizure* (from the Latin *sacire*, "to take possession of") is a paroxysmal event due to abnormal, excessive, hypersynchronous discharges from an aggregate of central nervous system (CNS) neurons. Depending on the distribution of discharges, this abnormal CNS activity can have various manifestations, ranging from dramatic convulsive activity to experiential phenomena not readily discernible by an observer. Although a variety of factors influence the incidence and prevalence of seizures, ~5–10% of the population will have at least one seizure, with the highest incidence occurring in early childhood and late adulthood.

The meaning of the term *seizure* needs to be carefully distinguished from that of epilepsy. *Epilepsy* describes a condition in which a person has *recurrent* seizures due to a chronic, underlying process. This definition implies that a person with a single seizure, or recurrent seizures due to correctable or avoidable circumstances, does not necessarily have epilepsy. Epilepsy refers to a clinical phenomenon rather than a single disease entity, since there are many forms and causes of epilepsy. However, among the many causes of epilepsy there are various *epilepsy syndromes* in which the clinical and pathologic characteristics are distinctive and suggest a specific underlying etiology.

Using the definition of epilepsy as two or more unprovoked seizures, the incidence of epilepsy is ~0.3–0.5% in different populations throughout the world, and the prevalence of epilepsy has been estimated at 5–10 persons per 1000.

CLASSIFICATION OF SEIZURES

Determining the type of seizure that has occurred is essential for focusing the diagnostic approach on particular etiologies, selecting the appropriate therapy, and providing potentially vital information regarding prognosis. In 1981, the International League against Epilepsy (ILAE) published a modified version of the International Classification of Epileptic Seizures that has continued to be a useful classification system (**Table 20-1**).

TABLE 20-1

CLASSIFICATION OF SEIZURES

1. **Partial seizures**
   a. Simple partial seizures (with motor, sensory, autonomic, or psychic signs)
   b. Complex partial seizures
   c. Partial seizures with secondary generalization
2. **Primarily generalized seizures**
   a. Absence (petit mal)
   b. Tonic-clonic (grand mal)
   c. Tonic
   d. Atonic
   e. Myoclonic
3. **Unclassified seizures**
   a. Neonatal seizures
   b. Infantile spasms

This system is based on the clinical features of seizures and associated electroencephalographic findings. Other potentially distinctive features such as etiology or cellular substrate are not considered in this classification system, although this will undoubtedly change in the future as more is learned about the pathophysiologic mechanisms that underlie specific seizure types.

A fundamental principle is that seizures may be either partial (synonymous with focal) or generalized. *Partial seizures* are those in which the seizure activity is restricted to discrete areas of the cerebral cortex. *Generalized seizures* involve diffuse regions of the brain simultaneously. Partial seizures are usually associated with structural abnormalities of the brain. In contrast, generalized seizures may result from cellular, biochemical, or structural abnormalities that have a more widespread distribution.

PARTIAL SEIZURES

Partial seizures occur within discrete regions of the brain. If consciousness is fully preserved during the seizure, the clinical manifestations are considered relatively simple and the seizure is termed a *simple partial seizure*. If consciousness is impaired, the symptomatology is more complex and the seizure is termed a *complex partial seizure*. An important additional subgroup comprises those seizures that begin as partial seizures and then spread diffusely throughout the cortex, i.e., *partial seizures with secondary generalization*.

Simple Partial Seizures

Simple partial seizures cause motor, sensory, autonomic, or psychic symptoms without an obvious alteration in consciousness. For example, a patient having a partial motor seizure arising from the right primary motor cortex in the vicinity controlling hand movement will note the onset of involuntary movements of the contralateral, left hand. These movements are typically clonic (i.e., repetitive, flexion/extension movements) at a frequency of ~2–3 Hz; pure tonic posturing may be seen as well. Since the cortical region controlling hand movement is immediately adjacent to the region for facial expression, the seizure may also cause abnormal movements of the face synchronous with the movements of the hand. The electroencephalogram (EEG) recorded with scalp electrodes during the seizure (i.e., an ictal EEG) may show abnormal discharges in a very limited region over the appropriate area of cerebral cortex if the seizure focus involves the cerebral convexity. Seizure activity occurring within deeper brain structures is often not recorded by the standard EEG, however, and may require intracranial electrodes for its detection.

Three additional features of partial motor seizures are worth noting. First, in some patients the abnormal motor movements may begin in a very restricted region such as the fingers and gradually progress (over seconds to minutes) to include a larger portion of the extremity. This phenomenon, described by Hughlings Jackson and known as a "Jacksonian march," represents the spread of seizure activity over a progressively larger region of motor cortex. Second, patients may experience a localized paresis (Todd's paralysis) for minutes to many hours in the involved region following the seizure. Third, in rare instances the seizure may continue for hours or days. This condition, termed *epilepsia partialis continua*, is often refractory to medical therapy.

Simple partial seizures may also manifest as changes in somatic sensation (e.g., paresthesias), vision (flashing lights or formed hallucinations), equilibrium (sensation of falling or vertigo), or autonomic function (flushing, sweating, piloerection). Simple partial seizures arising from the temporal or frontal cortex may also cause alterations in hearing, olfaction, or higher cortical function (psychic symptoms). This includes the sensation of unusual, intense odors (e.g., burning rubber or kerosene) or sounds (crude or highly complex sounds), or an epigastric sensation that rises from the stomach or chest to the head. Some patients describe odd, internal feelings such as fear, a sense of impending change, detachment, depersonalization, déjà vu, or illusions that objects are growing smaller (micropsia) or larger (macropsia). When such symptoms precede a complex partial or secondarily generalized seizure, these simple partial seizures serve as a warning, or *aura*.

Complex Partial Seizures

Complex partial seizures are characterized by focal seizure activity accompanied by a transient impairment of the patient's ability to maintain normal contact with the environment. The patient is unable to respond appropriately to visual or verbal commands during the seizure and has impaired recollection or awareness of the

ictal phase. The seizures frequently begin with an aura (i.e., a simple partial seizure) that is stereotypic for the patient. The start of the ictal phase is often a sudden behavioral arrest or motionless stare, which marks the onset of the period of amnesia. The behavioral arrest is usually accompanied by *automatisms*, which are involuntary, automatic behaviors that have a wide range of manifestations. Automatisms may consist of very basic behaviors such as chewing, lip smacking, swallowing, or "picking" movements of the hands, or more elaborate behaviors such as a display of emotion or running. The patient is typically confused following the seizure, and the transition to full recovery of consciousness may range from seconds up to an hour. Examination immediately following the seizure may show an anterograde amnesia or, in cases involving the dominant hemisphere, a postictal aphasia.

The routine interictal (i.e., between seizures) EEG in patients with complex partial seizures is often normal or may show brief discharges termed *epileptiform spikes*, or *sharp waves*. Since complex partial seizures can arise from the medial temporal lobe or inferior frontal lobe, i.e., regions distant from the scalp, the EEG recorded during the seizure may be nonlocalizing. However, the seizure focus is often detected using sphenoidal or surgically placed intracranial electrodes.

The range of potential clinical behaviors linked to complex partial seizures is so broad that extreme caution is advised before concluding that stereotypic episodes of bizarre or atypical behavior are not due to seizure activity. In such cases additional, detailed EEG studies may be helpful.

Partial Seizures with Secondary Generalization

Partial seizures can spread to involve both cerebral hemispheres and produce a generalized seizure, usually of the tonic-clonic variety (discussed later). Secondary generalization is observed frequently following simple partial seizures, especially those with a focus in the frontal lobe, but may also be associated with partial seizures occurring elsewhere in the brain. A partial seizure with secondary generalization is often difficult to distinguish from a primary generalized tonic-clonic seizure, since bystanders tend to emphasize the more dramatic, generalized convulsive phase of the seizure and overlook the more subtle, focal symptoms present at onset. In some cases, the focal onset of the seizure becomes apparent only when a careful history identifies a preceding aura (i.e., simple partial seizure). Often, however, the focal onset is not clinically evident and may be established only through careful EEG analysis. Nonetheless, distinguishing between these two entities is extremely important, as there may be substantial differences in the evaluation and treatment of partial versus generalized seizure disorders.

GENERALIZED SEIZURES

By definition, generalized seizures arise from both cerebral hemispheres simultaneously. However, it is currently impossible to exclude entirely the existence of a focal region of abnormal activity that initiates the seizure prior to rapid secondary generalization. For this reason, generalized seizures may be practically defined as bilateral clinical and electrographic events without any detectable focal onset. Fortunately, several types of generalized seizures have distinctive features that facilitate clinical diagnosis.

Absence Seizures (Petit Mal)

Absence seizures are characterized by sudden, brief lapses of consciousness without loss of postural control. The seizure typically lasts for only seconds, consciousness returns as suddenly as it was lost, and there is no postictal confusion. Although the brief loss of consciousness may be clinically inapparent or the sole manifestation of the seizure discharge, absence seizures are usually accompanied by subtle, bilateral motor signs such as rapid blinking of the eyelids, chewing movements, or small-amplitude, clonic movements of the hands.

Absence seizures usually begin in childhood (4–8 years) or early adolescence and are the main seizure type in 15–20% of children with epilepsy. The seizures can occur hundreds of times per day, but the child may be unaware of or unable to convey their existence. Since the clinical signs of the seizures are subtle, especially to new parents, it is not surprising that the first clue to absence epilepsy is often unexplained "daydreaming" and a decline in school performance recognized by a teacher.

The electrophysiologic hallmark of typical absence seizures is a generalized, symmetric, 3-Hz spike-and-wave discharge that begins and ends suddenly, superimposed on a normal EEG background. Periods of spike-and-wave discharges lasting more than a few seconds usually correlate with clinical signs, but the EEG often shows many more brief bursts of abnormal cortical activity than were suspected clinically. Hyperventilation tends to provoke these electrographic discharges and even the seizures themselves and is routinely used when recording the EEG.

Typical absence seizures are often associated with generalized, tonic-clonic seizures, but patients usually have no other neurologic problems and respond well to treatment with specific anticonvulsants. Although estimates vary, ~60–70% of such patients will have a spontaneous remission during adolescence.

Atypical Absence Seizures

Atypical absence seizures have features that deviate both clinically and electrophysiologically from typical absence

seizures. For example, the lapse of consciousness is usually of longer duration and less abrupt in onset and cessation, and the seizure is accompanied by more obvious motor signs that may include focal or lateralizing features. The EEG shows a generalized, slow spike-and-wave pattern with a frequency of ≤2.5/s, as well as other abnormal activity. Atypical absence seizures are usually associated with diffuse or multifocal structural abnormalities of the brain and therefore may accompany other signs of neurologic dysfunction such as mental retardation. Furthermore, the seizures are less responsive to anticonvulsants compared to typical absence seizures.

Generalized, Tonic-Clonic Seizures (Grand Mal)

Primary generalized, tonic-clonic seizures are the main seizure type in ~10% of all persons with epilepsy. They are also the most common seizure type resulting from metabolic derangements and are therefore frequently encountered in many different clinical settings. The seizure usually begins abruptly without warning, although some patients describe vague premonitory symptoms in the hours leading up to the seizure. This prodrome is distinct from the stereotypic auras associated with focal seizures that secondarily generalize. The initial phase of the seizure is usually tonic contraction of muscles throughout the body, accounting for a number of the classic features of the event. Tonic contraction of the muscles of expiration and the larynx at the onset will produce a loud moan or "ictal cry." Respirations are impaired, secretions pool in the oropharynx, and cyanosis develops. Contraction of the jaw muscles may cause biting of the tongue. A marked enhancement of sympathetic tone leads to increases in heart rate, blood pressure, and pupillary size. After 10–20 s, the tonic phase of the seizure typically evolves into the clonic phase, produced by the superimposition of periods of muscle relaxation on the tonic muscle contraction. The periods of relaxation progressively increase until the end of the ictal phase, which usually lasts no more than 1 min. The postictal phase is characterized by unresponsiveness, muscular flaccidity, and excessive salivation that can cause stridorous breathing and partial airway obstruction. Bladder or bowel incontinence may occur at this point. Patients gradually regain consciousness over minutes to hours, and during this transition there is typically a period of postictal confusion. Patients subsequently complain of headache, fatigue, and muscle ache that can last for many hours. The duration of impaired consciousness in the postictal phase can be extremely long, i.e., many hours, in patients with prolonged seizures or underlying CNS diseases such as alcoholic cerebral atrophy.

The EEG during the tonic phase of the seizure shows a progressive increase in generalized low-voltage fast activity, followed by generalized high-amplitude, polyspike discharges. In the clonic phase, the high-amplitude activity is typically interrupted by slow waves to create a spike-and-wave pattern. The postictal EEG shows diffuse slowing that gradually recovers as the patient awakens.

There are many variants of the generalized tonic-clonic seizure, including pure tonic and pure clonic seizures. Brief tonic seizures lasting only a few seconds are especially noteworthy since they are usually associated with specific epileptic syndromes having mixed seizure phenotypes, such as the Lennox-Gastaut syndrome (discussed later).

Atonic Seizures

Atonic seizures are characterized by sudden loss of postural muscle tone lasting 1–2 s. Consciousness is briefly impaired, but there is usually no postictal confusion. A very brief seizure may cause only a quick head drop or nodding movement, while a longer seizure will cause the patient to collapse. This can be extremely dangerous, since there is a substantial risk of direct head injury with the fall. The EEG shows brief, generalized spike-and-wave discharges followed immediately by diffuse slow waves that correlate with the loss of muscle tone. Similar to pure tonic seizures, atonic seizures are usually seen in association with known epileptic syndromes.

Myoclonic Seizures

Myoclonus is a sudden and brief muscle contraction that may involve one part of the body or the entire body. A normal, common physiologic form of myoclonus is the sudden jerking movement observed while falling asleep. Pathologic myoclonus is most commonly seen in association with metabolic disorders, degenerative CNS diseases, or anoxic brain injury (Chap. 22). Although the distinction from other forms of myoclonus is imprecise, myoclonic seizures are considered to be true epileptic events since they are caused by cortical (versus subcortical or spinal) dysfunction. The EEG may show bilaterally synchronous spike-and-wave discharges synchronized with the myoclonus, although these can be obscured by movement artifact. Myoclonic seizures usually coexist with other forms of generalized seizure disorders but are the predominant feature of juvenile myoclonic epilepsy (discussed below).

UNCLASSIFIED SEIZURES

Not all seizure types can be classified as partial or generalized. This appears to be especially true of seizures that occur in neonates and infants. The distinctive phenotypes of seizures at these early ages likely result, in part, from differences in neuronal function and connectivity in the immature versus mature CNS.

EPILEPSY SYNDROMES

Epilepsy syndromes are disorders in which epilepsy is a predominant feature, and there is sufficient evidence (e.g., through clinical, EEG, radiologic, or genetic observations) to suggest a common underlying mechanism. Three important epilepsy syndromes are listed below; additional examples with a known genetic basis are given in **Table 20-2**.

JUVENILE MYOCLONIC EPILEPSY

Juvenile myoclonic epilepsy (JME) is a generalized seizure disorder of unknown cause that appears in early adolescence and is usually characterized by bilateral myoclonic jerks that may be single or repetitive. The myoclonic seizures are most frequent in the morning after awakening and can be provoked by sleep deprivation. Consciousness is preserved unless the myoclonus is especially severe. Many patients also experience generalized tonic-clonic seizures, and up to one-third have absence seizures. The condition is otherwise benign, and although complete remission is uncommon, the seizures respond well to appropriate anticonvulsant medication. There is often a family history of epilepsy, and genetic linkage studies suggest a polygenic cause.

LENNOX-GASTAUT SYNDROME

Lennox-Gastaut syndrome occurs in children and is defined by the following triad: (1) multiple seizure types (usually including generalized tonic-clonic, atonic, and atypical absence seizures); (2) an EEG showing slow (<3 Hz) spike-and-wave discharges and a variety of other abnormalities; and (3) impaired cognitive function in most but not all cases. Lennox-Gastaut syndrome is associated with CNS disease or dysfunction from a variety of causes, including developmental abnormalities, perinatal hypoxia/ischemia, trauma, infection, and other acquired lesions. The multifactorial nature of this syndrome suggests that it is a nonspecific response of the brain to diffuse neural injury. Unfortunately, many patients have a poor prognosis due to the underlying CNS disease and the physical and psychosocial consequences of severe, poorly controlled epilepsy.

MESIAL TEMPORAL LOBE EPILEPSY SYNDROME

Mesial temporal lobe epilepsy (MTLE) is the most common syndrome associated with complex partial seizures and is an example of a symptomatic, partial epilepsy with distinctive clinical, electroencephalographic, and pathologic features (**Table 20-3**). High-resolution MRI can detect the characteristic hippocampal sclerosis that appears to be essential in the pathophysiology of MTLE for many patients (**Fig. 20-1**). Recognition of this syndrome is especially important because it tends to be refractory to treatment with anticonvulsants but responds extremely well to surgical intervention. Advances in the understanding of basic mechanisms of epilepsy have come through studies of experimental models of MTLE, discussed later.

THE CAUSES OF SEIZURES AND EPILEPSY

Seizures are a result of a shift in the normal balance of excitation and inhibition within the CNS. Given the numerous properties that control neuronal excitability, it is not surprising that there are many different ways to perturb this normal balance, and therefore many different causes of both seizures and epilepsy. Three clinical observations emphasize how a variety of factors determine why certain conditions may cause seizures or epilepsy in a given patient.

1. *The normal brain is capable of having a seizure under the appropriate circumstances, and there are differences between individuals in the susceptibility or threshold for seizures.* For example, seizures may be induced by high fevers in children who are otherwise normal and who never develop other neurologic problems, including epilepsy. However, febrile seizures occur only in a relatively small proportion of children. This implies there are various underlying *endogenous factors* that influence the threshold for having a seizure. Some of these factors are clearly genetic, as it has been shown that a family history of epilepsy will influence the likelihood of seizures occurring in otherwise normal individuals. Normal development also plays an important role, since the brain appears to have different seizure thresholds at different maturational stages.
2. *There are a variety of conditions that have an extremely high likelihood of resulting in a chronic seizure disorder.* One of the best examples of this is severe, penetrating head trauma, which is associated with up to a 50% risk of subsequent epilepsy. The high propensity for severe traumatic brain injury to lead to epilepsy suggests that the injury results in a long-lasting pathologic change in the CNS that transforms a presumably normal neural network into one that is abnormally hyperexcitable. This process is known as *epileptogenesis*, and the specific changes that result in a lowered seizure threshold can be considered *epileptogenic factors*. Other processes associated with epileptogenesis include stroke, infections, and abnormalities of CNS development. Likewise, the genetic abnormalities associated with epilepsy likely

TABLE 20-2

EXAMPLES OF GENES ASSOCIATED WITH EPILEPSY SYNDROMES[a]

GENE (LOCUS)	FUNCTION OF GENE	CLINICAL SYNDROME	COMMENTS
CHRNA4 (20q13.2)	Nicotinic acetylcholine receptor subunit; mutations cause alterations in Ca^{2+} flux through the receptor; this may reduce amount of GABA release in presynaptic terminals	Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE); childhood onset; brief, nighttime seizures with prominent motor movements; often misdiagnosed as primary sleep disorder	Rare; first identified in a large Australian family; other families found to have mutations in CHRNA2 or CHRNB2, and some families appear to have mutations at other loci
KCNQ2 (20q13.3)	Voltage-gated potassium channel subunits; mutation in pore regions may cause a 20–40% reduction of potassium currents, which will lead to impaired repolarization	Benign familial neonatal convulsions (BFNC); autosomal dominant inheritance; onset in 1st week of life in infants who are otherwise normal; remission usually within weeks to months; long-term epilepsy in 10–15%	Rare; other families found to have mutations in KCNQ3; sequence and functional homology to KCNQ1, mutations of which cause long QT syndrome and a cardiac-auditory syndrome
SCN1B (19q12.1)	β subunit of a voltage-gated sodium channel; mutation disrupts disulfide bridge that is crucial for structure of extracellular domain; mutated β subunit leads to slower sodium channel inactivation	Generalized epilepsy with febrile seizures plus (GEFS+); autosomal dominant inheritance; presents with febrile seizures at median 1 year, which may persist >6 years, then variable seizure types not associated with fever	Incidence uncertain; GEFS+ identified in other families with mutations in other sodium channel subunits (SCN1A and SCN2A) and $GABA_A$ receptor subunit (GABRG2 and GABRA1); significant phenotypic heterogeneity within same family, including members with febrile seizures only
LGI1 (10q24)	Leucine-rich glioma-inactivated 1 gene; previous evidence for role in glial tumor progression; protein homology suggests a possible role in nervous system development	Autosomal dominant partial epilepsy with auditory features (ADPEAF); a form of idiopathic lateral temporal lobe epilepsy with auditory symptoms or aphasia as a major simple partial seizure manifestation; age of onset usually between 10 and 25 years	Mutations found in approximately 50% of families containing two or more subjects with idiopathic localization-related epilepsy with ictal auditory symptoms, suggesting that at least one other gene may underlie this syndrome. *LGI1* is the only gene identified so far in temporal lobe epilepsy
CSTB	Cystatin B, a noncaspase cysteine protease inhibitor; normal protein may block neuronal apoptosis by inhibiting caspases directly or indirectly (via cathepsins), or controlling proteolysis	Progressive myoclonus epilepsy (PME) (Unverricht-Lundborg disease); autosomal recessive inheritance; age of onset between 6 and 15 years, myoclonic seizures, ataxia, and progressive cognitive decline; brain shows neuronal degeneration	Overall rare, but relatively common in Finland and Western Mediterranean (>1 in 20,000); precise role of cystatin B in human disease unknown, although mice with null mutations of cystatin B have similar syndrome
EPM2A (6q24)	Laforin, a protein tyrosine phosphatase (PTP); may influence glycogen metabolism, which is known to be regulated by phosphatases	Progressive myoclonus epilepsy (Lafora's disease); autosomal recessive inheritance; onset age 6–19 years, death within 10 years; brain degeneration associated with polyglucosan intracellular inclusion bodies in numerous organs	Most common PME in Southern Europe, Middle East, Northern Africa, and Indian subcontinent; genetic heterogeneity; unknown whether seizure phenotype due to degeneration or direct effects of abnormal laforin expression.
Doublecortin (Xq21-24)	Doublecortin, expressed primarily in frontal lobes; function unknown; potentially an intracellular signaling molecule	Classic lissencephaly associated with severe mental retardation and seizures in men; subcortical band heterotopia with more subtle findings in women (presumably due to random X-inactivation); X-linked dominant	Relatively rare but of uncertain incidence, recent increased ascertainment due to improved imaging techniques; relationship between migration defect and seizure phenotype unknown

[a]The first four syndromes listed in the table (ADNFLE, BFNC, GEFS+, and ADPEAF) are examples of idiopathic epilepsies associated with identified gene mutations. The last three syndromes are examples of the numerous Mendelian disorders in which seizures are one part of the phenotype.
Note: GABA, γ-aminobutyric acid; PME, progressive myoclonus epilepsy.

TABLE 20-3

CHARACTERISTICS OF THE MESIAL TEMPORAL LOBE EPILEPSY SYNDROME

History	
History of febrile seizures	Rare secondarily generalized seizures
Family history of epilepsy	Seizures may remit and reappear
Early onset	Seizures often intractable
Clinical observations	
Aura common	Postictal disorientation, memory loss, dysphasia (with focus in dominant hemisphere)
Behavioral arrest/stare	
Complex automatisms	
Unilateral posturing	
Laboratory studies	
Unilateral or bilateral anterior temporal spikes on EEG	
Hypometabolism on interictal PET	
Hypoperfusion on interictal SPECT	
Material-specific memory deficits on intracranial amobarbital (Wada) test	
MRI findings	
Small hippocampus with increased signal on T2-weighted sequences	
Small temporal lobe	
Enlarged temporal horn	
Pathologic findings	
Highly selective loss of specific cell populations within hippocampus in most cases	

Note: EEG, electroencephalogram; PET, positron emission tomography; SPECT, single photon emission computed tomography.

involve processes that trigger the appearance of specific sets of epileptogenic factors.

3. *Seizures are episodic.* Patients with epilepsy have seizures intermittently and, depending on the underlying cause, many patients are completely normal for months or even years between seizures. This implies there are important provocative or *precipitating factors* that induce seizures in patients with epilepsy. Similarly, precipitating factors are responsible for causing the single seizure in someone without epilepsy. Precipitants include those due to intrinsic physiologic processes, such as psychological or physical stress, sleep deprivation, or hormonal changes associated with the menstrual cycle. They also include exogenous factors such as exposure to toxic substances and certain medications.

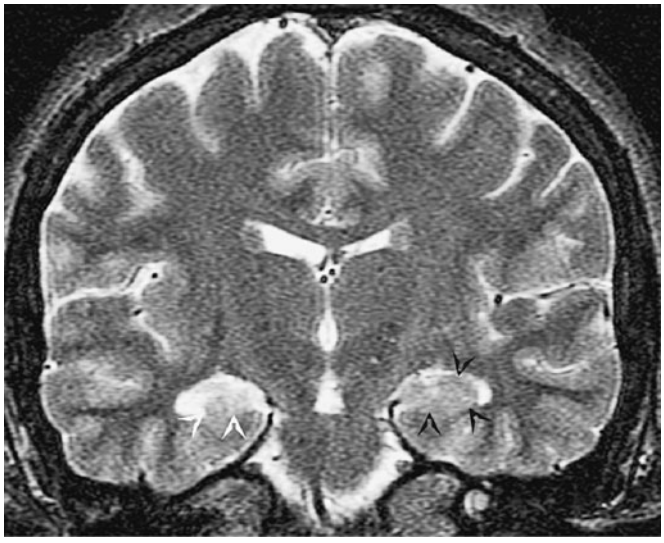

FIGURE 20-1

Mesial temporal lobe epilepsy. The EEG suggested a right temporal lobe focus. Coronal high-resolution T2-weighted fast spin echo magnetic resonance image obtained through the body of the hippocampus demonstrates abnormal high-signal intensity in the right hippocampus (*white arrows*; compare with the normal hippocampus on the left, *black arrows*) consistent with mesial temporal sclerosis.

These observations emphasize the concept that the many causes of seizures and epilepsy result from a dynamic interplay between endogenous factors, epileptogenic factors, and precipitating factors. The potential role of each needs to be carefully considered when determining the appropriate management of a patient with seizures. For example, the identification of predisposing factors (e.g., family history of epilepsy) in a patient with febrile seizures may increase the necessity for closer follow-up and a more aggressive diagnostic evaluation. Finding an epileptogenic lesion may help in the estimation of seizure recurrence and duration of therapy. Finally, removal or modification of a precipitating factor may be an effective and safer method for preventing further seizures than the prophylactic use of anticonvulsant drugs.

CAUSES ACCORDING TO AGE

In practice, it is useful to consider the etiologies of seizures based on the age of the patient, as age is one of the most

important factors determining both the incidence and the likely causes of seizures or epilepsy (Table 20-4). During the *neonatal period and early infancy*, potential causes include hypoxic-ischemic encephalopathy, trauma, CNS infection, congenital CNS abnormalities, and metabolic disorders. Babies born to mothers using neurotoxic drugs such as cocaine, heroin, or ethanol are susceptible to drug-withdrawal seizures in the first few days after delivery. Hypoglycemia and hypocalcemia, which can occur as secondary complications of perinatal injury, are also causes of seizures early after delivery. Seizures due to inborn errors of metabolism usually present once regular feeding begins, typically 2–3 days after birth. Pyridoxine (vitamin B_6) deficiency, an important cause of neonatal seizures, can be effectively treated with pyridoxine replacement. The idiopathic or inherited forms of benign neonatal convulsions are also seen during this time period.

TABLE 20-4

CAUSES OF SEIZURES	
Neonates (<1 month)	Perinatal hypoxia and ischemia
	Intracranial hemorrhage and trauma
	Acute CNS infection
	Metabolic disturbances (hypoglycemia, hypocalcemia, hypomagnesemia, pyridoxine deficiency)
	Drug withdrawal
	Developmental disorders
	Genetic disorders
Infants and children (>1 mo and <12 years)	Febrile seizures
	Genetic disorders (metabolic, degenerative, primary epilepsy syndromes)
	CNS infection
	Developmental disorders
	Trauma
	Idiopathic
Adolescents (12–18 years)	Trauma
	Genetic disorders
	Infection
	Brain tumor
	Illicit drug use
	Idiopathic
Young adults (18–35 years)	Trauma
	Alcohol withdrawal
	Illicit drug use
	Brain tumor
	Idiopathic
Older adults (>35 years)	Cerebrovascular disease
	Brain tumor
	Alcohol withdrawal
	Metabolic disorders (uremia, hepatic failure, electrolyte abnormalities, hypoglycemia)
	Alzheimer's disease and other degenerative CNS diseases
	Idiopathic

Note: CNS, central nervous system.

The most common seizures arising in *late infancy and early childhood* are febrile seizures, which are seizures associated with fevers but without evidence of CNS infection or other defined causes. The overall prevalence is 3–5% and even higher in some parts of the world, such as Asia. Patients often have a family history of febrile seizures or epilepsy. Febrile seizures usually occur between 3 months and 5 years of age and have a peak incidence between 18 and 24 months. The typical scenario is a child who has a generalized, tonic-clonic seizure during a febrile illness in the setting of a common childhood infection such as otitis media, respiratory infection, or gastroenteritis. The seizure is likely to occur during the rising phase of the temperature curve (i.e., during the first day) rather than well into the course of the illness. A *simple* febrile seizure is a single, isolated event, brief, and symmetric in appearance. *Complex* febrile seizures are characterized by repeated seizure activity, duration >15 min, or by focal features. Approximately one-third of patients with febrile seizures will have a recurrence, but <10% have three or more episodes. Recurrences are much more likely when the febrile seizure occurs in the first year of life. Simple febrile seizures are not associated with an increase in the risk of developing epilepsy, while complex febrile seizures have a risk of 2–5%; other risk factors include the presence of preexisting neurologic deficits and a family history of nonfebrile seizures.

Childhood marks the age at which many of the well-defined epilepsy syndromes present. Some children who are otherwise normal develop idiopathic, generalized tonic-clonic seizures without other features that fit into specific syndromes. Temporal lobe epilepsy usually presents in childhood and may be related to mesial temporal lobe sclerosis (as part of the MTLE syndrome) or other focal abnormalities such as cortical dysgenesis. Other types of partial seizures, including those with secondary generalization, may be the relatively late manifestation of a developmental disorder, an acquired lesion such as head trauma, CNS infection (especially viral encephalitis), or very rarely a CNS tumor.

The period of *adolescence and early adulthood* is one of transition during which the idiopathic or genetically based epilepsy syndromes, including JME and juvenile absence epilepsy, become less common, while epilepsies secondary to acquired CNS lesions begin to predominate. Seizures that begin in patients in this age range may be associated with head trauma, CNS infections (including parasitic infections such as cysticercosis), brain tumors, congenital CNS abnormalities, illicit drug use, or alcohol withdrawal.

Head trauma is a common cause of epilepsy in adolescents and adults. The head injury can be caused by a variety of mechanisms, and the likelihood of developing

epilepsy is strongly correlated with the severity of the injury. A patient with a penetrating head wound, depressed skull fracture, intracranial hemorrhage, or prolonged posttraumatic coma or amnesia has a 40–50% risk of developing epilepsy, while a patient with a closed head injury and cerebral contusion has a 5–25% risk. Recurrent seizures usually develop within 1 year after head trauma, although intervals of ≥10 years are well known. In controlled studies, mild head injury, defined as a concussion with amnesia or loss of consciousness of <30 min, was found to be associated with only a slightly increased likelihood of epilepsy. Nonetheless, most epileptologists know of patients who have partial seizures within hours or days of a mild head injury and subsequently develop chronic seizures of the same type; such cases may represent rare examples of chronic epilepsy resulting from mild head injury.

The causes of seizures in *older adults* include cerebrovascular disease, trauma (including subdural hematoma), CNS tumors, and degenerative diseases. Cerebrovascular disease may account for ~50% of new cases of epilepsy in patients older than 65 years. Acute seizures (i.e., occurring at the time of the stroke) are seen more often with embolic rather than hemorrhagic or thrombotic stroke. Chronic seizures typically appear months to years after the initial event and are associated with all forms of stroke.

Metabolic disturbances such as electrolyte imbalance, hypo- or hyperglycemia, renal failure, and hepatic failure may cause seizures at any age. Similarly, endocrine disorders, hematologic disorders, vasculitides, and many other systemic diseases may cause seizures over a broad age range. A wide variety of medications and abused substances are known to precipitate seizures as well (Table 20-5).

TABLE 20-5

DRUGS AND OTHER SUBSTANCES THAT CAN CAUSE SEIZURES

- Alkylating agents (e.g., busulfan, chlorambucil)
- Antimalarials (chloroquine, mefloquine)
- Antimicrobials/antivirals
  - β-lactam and related compounds
  - Quinolones
  - Acyclovir
  - Isoniazid
  - Ganciclovir
- Anesthetics and analgesics
  - Meperidine
  - Tramadol
  - Local anesthetics
- Dietary supplements
  - Ephedra (ma huang)
  - Gingko
- Immunomodulatory drugs
  - Cyclosporine
  - OKT3 (monoclonal antibodies to T cells)
  - Tacrolimus
  - Interferons
- Psychotropics
  - Antidepressants
  - Antipsychotics
  - Lithium
- Radiographic contrast agents
- Theophylline
- Sedative-hypnotic drug withdrawal
  - Alcohol
  - Barbiturates (short-acting)
  - Benzodiazepines (short-acting)
- Drugs of abuse
  - Amphetamine
  - Cocaine
  - Phencyclidine
  - Methylphenidate
- Flumazenil[a]

[a]In benzodiazepine-dependent patients.

BASIC MECHANISMS

MECHANISMS OF SEIZURE INITIATION AND PROPAGATION

Partial seizure activity can begin in a very discrete region of cortex and then spread to neighboring regions, i.e., there is a *seizure initiation* phase and a *seizure propagation* phase. The initiation phase is characterized by two concurrent events in an aggregate of neurons: (1) high-frequency bursts of action potentials and (2) hypersynchronization. The bursting activity is caused by a relatively long-lasting depolarization of the neuronal membrane due to influx of extracellular calcium (Ca^{2+}), which leads to the opening of voltage-dependent sodium (Na^+) channels, influx of Na^+, and generation of repetitive action potentials. This is followed by a hyperpolarizing afterpotential mediated by γ-aminobutyric acid (GABA) receptors or potassium (K^+) channels, depending on the cell type. The synchronized bursts from a sufficient number of neurons result in a so-called spike discharge on the EEG.

Normally, the spread of bursting activity is prevented by intact hyperpolarization and a region of surrounding inhibition created by inhibitory neurons. With sufficient activation there is a recruitment of surrounding neurons via a number of mechanisms. Repetitive discharges lead to the following: (1) an increase in extracellular K^+, which blunts hyperpolarization and depolarizes neighboring neurons; (2) accumulation of Ca^{2+} in presynaptic terminals, leading to enhanced neurotransmitter release; and (3) depolarization-induced activation of the *N*-methyl-D-aspartate (NMDA) subtype of the excitatory amino acid receptor, which causes Ca^{2+} influx and

neuronal activation. The recruitment of a sufficient number of neurons leads to a loss of the surrounding inhibition and propagation of seizure activity into contiguous areas via local cortical connections, and to more distant areas via long commissural pathways such as the corpus callosum.

Many factors control neuronal excitability, and thus there are many potential mechanisms for altering a neuron's propensity to have bursting activity. Mechanisms *intrinsic* to the neuron include changes in the conductance of ion channels, response characteristics of membrane receptors, cytoplasmic buffering, second-messenger systems, and protein expression as determined by gene transcription, translation, and posttranslational modification. Mechanisms *extrinsic* to the neuron include changes in the amount or type of neurotransmitters present at the synapse, modulation of receptors by extracellular ions and other molecules, and temporal and spatial properties of synaptic and nonsynaptic input. Nonneural cells, such as astrocytes and oligodendrocytes, have an important role in many of these mechanisms as well.

Certain recognized causes of seizures are explained by these mechanisms. For example, accidental ingestion of domoic acid, which is an analogue of glutamate (the principal excitatory neurotransmitter in the brain), causes profound seizures via direct activation of excitatory amino acid receptors throughout the CNS. Penicillin, which can lower the seizure threshold in humans and is a potent convulsant in experimental models, reduces inhibition by antagonizing the effects of GABA at its receptor. The basic mechanisms of other precipitating factors of seizures, such as sleep deprivation, fever, alcohol withdrawal, hypoxia, and infection, are not as well understood but presumably involve analogous perturbations in neuronal excitability. Similarly, the endogenous factors that determine an individual's seizure threshold may relate to these properties as well.

Knowledge of the mechanisms responsible for initiation and propagation of most generalized seizures (including tonic-clonic, myoclonic, and atonic types) remains rudimentary and reflects the limited understanding of the connectivity of the brain at a systems level. Much more is understood about the origin of generalized spike-and-wave discharges in absence seizures. These appear to be related to oscillatory rhythms normally generated during sleep by circuits connecting the thalamus and cortex. This oscillatory behavior involves an interaction between $GABA_B$ receptors, T-type Ca^{2+} channels, and K^+ channels located within the thalamus. Pharmacologic studies indicate that modulation of these receptors and channels can induce absence seizures, and there is speculation that the genetic forms of absence epilepsy may be associated with mutations of components of this system.

MECHANISMS OF EPILEPTOGENESIS

Epileptogenesis refers to the transformation of a normal neuronal network into one that is chronically hyperexcitable. There is often a delay of months to years between an initial CNS injury such as trauma, stroke, or infection and the first seizure. The injury appears to initiate a process that gradually lowers the seizure threshold in the affected region until a spontaneous seizure occurs. In many genetic and idiopathic forms of epilepsy, epileptogenesis is presumably determined by developmentally regulated events.

Pathologic studies of the hippocampus from patients with temporal lobe epilepsy have led to the suggestion that some forms of epileptogenesis are related to *structural changes in neuronal networks*. For example, many patients with MTLE have a highly selective loss of neurons that may contribute to inhibition of the main excitatory neurons within the dentate gyrus. There is also evidence that, in response to the loss of neurons, there is reorganization or "sprouting" of surviving neurons in a way that affects the excitability of the network. Some of these changes can be seen in experimental models of prolonged electrical seizures or traumatic brain injury. Thus, an initial injury such as head injury may lead to a very focal, confined region of structural change that causes local hyperexcitability. The local hyperexcitability leads to further structural changes that evolve over time until the focal lesion produces clinically evident seizures. Similar models have also provided strong evidence for long-term alterations in *intrinsic, biochemical properties of cells* within the network, such as chronic changes in glutamate or GABA receptor function.

GENETIC CAUSES OF EPILEPSY

The most important recent progress in epilepsy research has been the identification of genetic mutations associated with a variety of epilepsy syndromes (Table 20-2). Although all of the mutations identified to date cause rare forms of epilepsy, their discovery has led to extremely important conceptual advances. For example, it appears that many of the inherited, idiopathic epilepsies (i.e., the relatively "pure" forms of epilepsy in which seizures are the phenotypic abnormality and brain structure and function are otherwise normal) are due to mutations affecting ion channel function. These syndromes are therefore part of the larger group of channelopathies causing paroxysmal disorders such as cardiac arrhythmias, episodic ataxia, periodic weakness, and familial hemiplegic migraine. In contrast, gene mutations observed in symptomatic epilepsies (i.e., disorders in which other neurologic abnormalities, such as cognitive impairment, coexist with seizures) are proving to be associated with pathways influencing CNS development or neuronal homeostasis. A current challenge is to identify the multiple susceptibility

genes that underlie the more common forms of idiopathic epilepsies.

MECHANISMS OF ACTION OF ANTIEPILEPTIC DRUGS

Antiepileptic drugs appear to act primarily by blocking the initiation or spread of seizures. This occurs through a variety of mechanisms that modify the activity of ion channels or neurotransmitters, and in most cases the drugs have pleiotropic effects. The mechanisms include inhibition of Na^+-dependent action potentials in a frequency-dependent manner (e.g., phenytoin, carbamazepine, lamotrigine, topiramate, zonisamide), inhibition of voltage-gated Ca^{2+} channels (phenytoin), decrease of glutamate release (lamotrigine), potentiation of GABA receptor function (benzodiazepines and barbiturates), increase in the availability of GABA (valproic acid, gabapentin, tiagabine), and modulation of release of synaptic vesicles (levetiracetam). The two most effective drugs for absence seizures, ethosuximide and valproic acid, probably act by inhibiting T-type Ca^{2+} channels in thalamic neurons.

In contrast to the relatively large number of antiepileptic drugs that can attenuate seizure activity, there are currently no drugs known to prevent the formation of a seizure focus following CNS injury. The eventual development of such "antiepileptogenic" drugs will provide an important means of preventing the emergence of epilepsy following injuries such as head trauma, stroke, and CNS infection.

Approach to the Patient: SEIZURE

When a patient presents shortly after a seizure, the first priorities are attention to vital signs, respiratory and cardiovascular support, and treatment of seizures if they resume (see Rx: Seizures and Epilepsy). Life-threatening conditions such as CNS infection, metabolic derangement, or drug toxicity must be recognized and managed appropriately.

When the patient is not acutely ill, the evaluation will initially focus on whether there is a history of earlier seizures (**Fig. 20-2**). If this is the first seizure, then the emphasis will be to (1) establish whether the reported episode was a seizure rather than another paroxysmal event, (2) determine the cause of the seizure by identifying risk factors and precipitating events, and (3) decide whether anticonvulsant therapy is required in addition to treatment for any underlying illness.

In the patient with prior seizures or a known history of epilepsy, the evaluation is directed toward (1) identification of the underlying cause and precipitating factors, and (2) determination of the adequacy of the patient's current therapy.

HISTORY AND EXAMINATION

The first goal is to determine whether the event was truly a seizure. An in-depth history is essential, for *in many cases the diagnosis of a seizure is based solely on clinical grounds—the examination and laboratory studies are often normal*. Questions should focus on the symptoms before, during, and after the episode in order to differentiate a seizure from other paroxysmal events (see Differential Diagnosis of Seizures later). Seizures frequently occur out-of-hospital, and the patient may be unaware of the ictal and immediate postictal phases; thus, witnesses to the event should be interviewed carefully.

The history should also focus on risk factors and predisposing events. Clues for a predisposition to seizures include a history of febrile seizures, earlier auras or brief seizures not recognized as such, and a family history of seizures. Epileptogenic factors such as prior head trauma, stroke, tumor, or infection of the nervous system should be identified. In children, a careful assessment of developmental milestones may provide evidence for underlying CNS disease. Precipitating factors such as sleep deprivation, systemic diseases, electrolyte or metabolic derangements, acute infection, drugs that lower the seizure threshold (Table 20-5), or alcohol or illicit drug use should also be identified.

The general physical examination includes a search for signs of infection or systemic illness. Careful examination of the skin may reveal signs of neurocutaneous disorders, such as tuberous sclerosis or neurofibromatosis, or chronic liver or renal disease. A finding of organomegaly may indicate a metabolic storage disease, and limb asymmetry may provide a clue to brain injury early in development. Signs of head trauma and use of alcohol or illicit drugs should be sought. Auscultation of the heart and carotid arteries may identify an abnormality that predisposes to cerebrovascular disease.

All patients require a complete neurologic examination, with particular emphasis on eliciting signs of cerebral hemispheric disease (Chap. 1). Careful assessment of mental status (including memory, language function, and abstract thinking) may suggest lesions in the anterior frontal, parietal, or temporal lobes. Testing of visual fields will help screen for lesions in the optic pathways and occipital lobes. Screening tests of motor function such as pronator drift, deep tendon reflexes, gait, and coordination may suggest lesions in motor (frontal) cortex, and cortical sensory testing (e.g., double simultaneous stimulation) may detect lesions in the parietal cortex.

LABORATORY STUDIES

Routine blood studies are indicated to identify the more common metabolic causes of seizures, such as abnormalities in electrolytes, glucose, calcium, or magnesium, and hepatic or renal disease. A screen for toxins in blood and

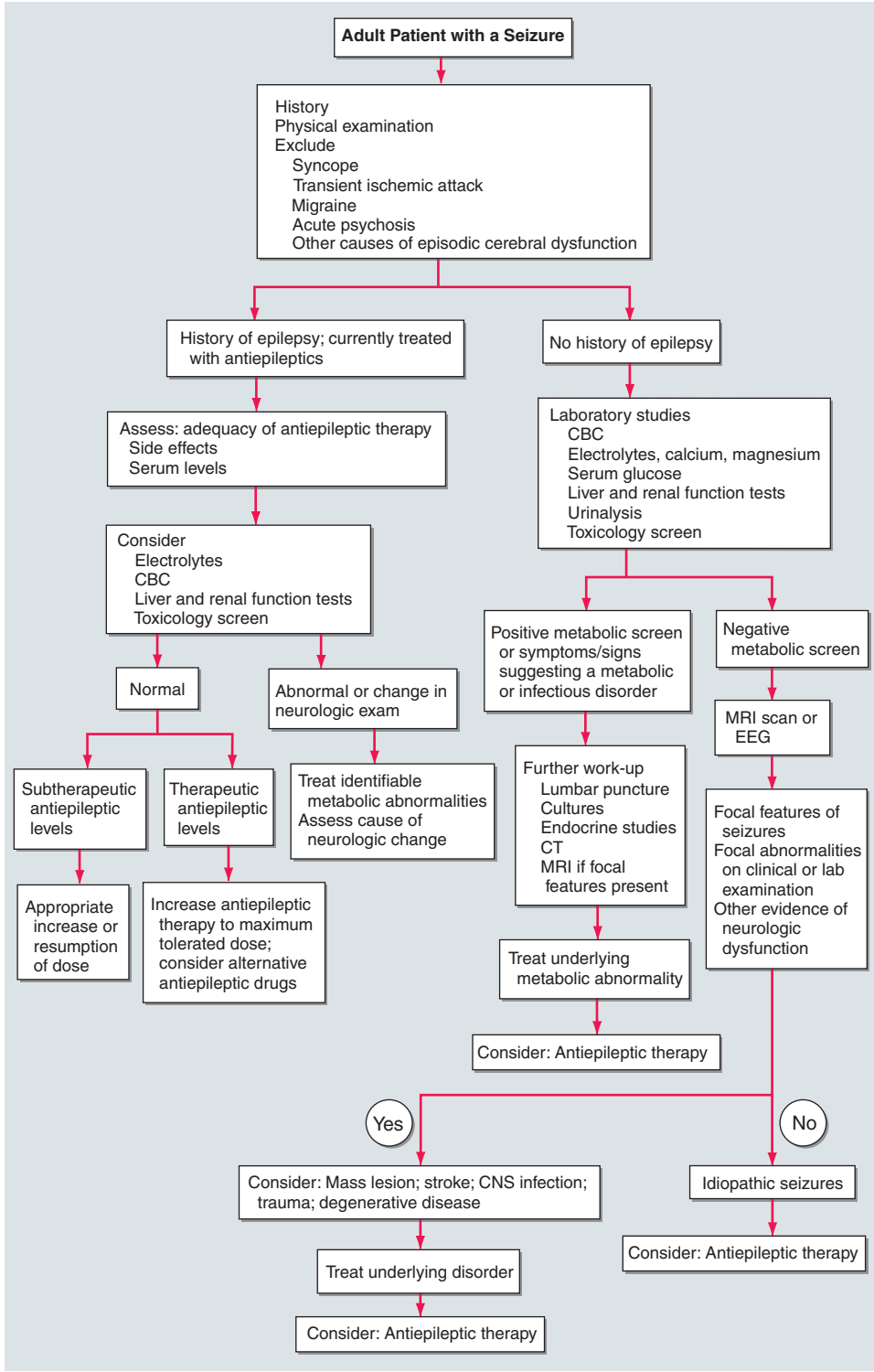

FIGURE 20-2

Evaluation of the adult patient with a seizure. CBC, complete blood count; CT, computed tomography; MRI, magnetic resonance imaging; EEG, electroencephalogram; CNS, central nervous system.

urine should also be obtained from all patients in appropriate risk groups, especially when no clear precipitating factor has been identified. A lumbar puncture is indicated if there is any suspicion of meningitis or encephalitis, and it is mandatory in all patients infected with HIV, even in the absence of symptoms or signs suggesting infection.

ELECTROPHYSIOLOGIC STUDIES

All patients who have a possible seizure disorder should be evaluated with an EEG as soon as possible. Details about the EEG are covered in Chap. 3.

In the evaluation of a patient with suspected epilepsy, the presence of *electrographic seizure activity* during the

clinically evident event—i.e., abnormal, repetitive, rhythmic activity having an abrupt onset and termination—clearly establishes the diagnosis. The absence of electrographic seizure activity does not exclude a seizure disorder, however, because simple or complex seizures may originate from a region of the cortex that is not within range of the scalp electrodes. The EEG is always abnormal during generalized tonic-clonic seizures. Since seizures are typically infrequent and unpredictable, it is often not possible to obtain the EEG during a clinical event. Continuous monitoring for prolonged periods in video-EEG telemetry units for hospitalized patients or the use of portable equipment to record the EEG continuously on cassettes for ≥24 h in ambulatory patients has made it easier to capture the electrophysiologic accompaniments of clinical events. In particular, video-EEG telemetry is now a routine approach for the accurate diagnosis of epilepsy in patients with poorly characterized events or seizures that are difficult to control.

Magnetoencephalography (MEG) provides another way of looking noninvasively at cortical activity. Instead of measuring electrical activity of the brain, it measures the small magnetic fields that are generated by this activity. Epileptiform activity seen on the MEG can be analyzed, and its source in the brain can be estimated using a variety of mathematical techniques. These source estimates can then be plotted on an anatomic image of the brain, such as an MRI (discussed later), to generate a magnetic source image (MSI). MSI can be useful to localize potential seizure foci.

The EEG may also be helpful in the interictal period by showing certain abnormalities that are highly supportive of the diagnosis of epilepsy. Such *epileptiform activity* consists of bursts of abnormal discharges containing spikes or sharp waves. The presence of epileptiform activity is not specific for epilepsy, but it has a much greater prevalence in patients with epilepsy than in normal individuals. However, even in an individual who is known to have epilepsy, the initial routine interictal EEG may be normal up to 60% of the time. Thus, the EEG cannot establish the diagnosis of epilepsy in many cases.

The EEG is also used for classifying seizure disorders and aiding in the selection of anticonvulsant medications. For example, episodic generalized spike-wave activity is usually seen in patients with typical absence epilepsy and may be seen with other generalized epilepsy syndromes. Focal interictal epileptiform discharges would support the diagnosis of a partial seizure disorder such as temporal lobe epilepsy or frontal lobe seizures, depending on the location of the discharges.

The routine scalp-recorded EEG may also be used to assess the prognosis of seizure disorders; in general, a normal EEG implies a better prognosis, whereas an abnormal background or profuse epileptiform activity suggests a poor outlook. Unfortunately, the EEG has not proved to be useful in predicting which patients with predisposing conditions, such as head injury or brain tumor, will go on to develop epilepsy, because in such circumstances epileptiform activity is commonly encountered regardless of whether seizures occur.

BRAIN IMAGING

Almost all patients with new-onset seizures should have a brain imaging study to determine whether there is an underlying structural abnormality that is responsible. The only potential exception to this rule is children who have an unambiguous history and examination suggestive of a benign, generalized seizure disorder such as absence epilepsy. MRI has been shown to be superior to CT for the detection of cerebral lesions associated with epilepsy. In some cases MRI will identify lesions such as tumors, vascular malformations, or other pathologies that need immediate therapy. The use of newer MRI methods, such as fluid-attenuated inversion recovery (FLAIR), has increased the sensitivity for detection of abnormalities of cortical architecture, including hippocampal atrophy associated with mesial temporal sclerosis, as well as abnormalities of cortical neuronal migration. In such cases the findings may not lead to immediate therapy, but they do provide an explanation for the patient's seizures and point to the need for chronic anticonvulsant therapy or possible surgical resection.

In the patient with a suspected CNS infection or mass lesion, CT scanning should be performed emergently when MRI is not immediately available. Otherwise, it is usually appropriate to obtain an MRI study within a few days of the initial evaluation. Functional imaging procedures such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) are also used to evaluate certain patients with medically refractory seizures (discussed below).

DIFFERENTIAL DIAGNOSIS OF SEIZURES

Disorders that may mimic seizures are listed in **Table 20-6**. In most cases seizures can be distinguished from other conditions by meticulous attention to the history and relevant laboratory studies. On occasion, additional studies, such as video-EEG monitoring, sleep studies, tilt-table analysis, or cardiac electrophysiology, may be required to reach a correct diagnosis. Two of the more common nonepileptic syndromes in the differential diagnosis are detailed below.

SYNCOPE

(See also Chap. 8) The diagnostic dilemma encountered most frequently is the distinction between a generalized seizure and syncope. Observations by the patient and

TABLE 20-6

DIFFERENTIAL DIAGNOSIS OF SEIZURES

- Syncope
  - Vasovagal syncope
  - Cardiac arrhythmia
  - Valvular heart disease
  - Cardiac failure
  - Orthostatic hypotension
- Psychological disorders
  - Psychogenic seizure
  - Hyperventilation
  - Panic attack
- Metabolic disturbances
  - Alcoholic blackouts
  - Delirium tremens
  - Hypoglycemia
  - Hypoxia
  - Psychoactive drugs (e.g., hallucinogens)
- Migraine
  - Confusional migraine
  - Basilar migraine
- Transient ischemic attack (TIA)
  - Basilar artery TIA
- Sleep disorders
  - Narcolepsy/cataplexy
  - Benign sleep myoclonus
- Movement disorders
  - Tics
  - Nonepileptic myoclonus
  - Paroxysmal choreoathetosis
- Special considerations in children
  - Breath-holding spells
  - Migraine with recurrent abdominal pain and cyclic vomiting
  - Benign paroxysmal vertigo
  - Apnea
  - Night terrors
  - Sleepwalking

bystanders that can help differentiate between the two are listed in **Table 20-7**. Characteristics of a seizure include the presence of an aura, cyanosis, unconsciousness, motor manifestations lasting >30 s, postictal disorientation, muscle soreness, and sleepiness. In contrast, a syncopal episode is more likely if the event was provoked by acute pain or anxiety or occurred immediately after arising from the lying or sitting position. Patients with syncope often describe a stereotyped transition from consciousness to unconsciousness that includes tiredness, sweating, nausea, and tunneling of vision, and they experience a relatively brief loss of consciousness. Headache or incontinence usually suggests a seizure but may on occasion also occur with syncope. A brief period (i.e., 1–10 s) of convulsive motor activity is frequently seen immediately at the onset of a syncopal episode, especially if the patient remains in an upright posture after fainting (e.g., in a dentist's chair) and therefore has a sustained decrease in cerebral perfusion. Rarely, a syncopal episode can induce a full tonic-clonic seizure. In such cases the evaluation must focus on both the cause of the syncopal event as well as the possibility that the patient has a propensity for recurrent seizures.

PSYCHOGENIC SEIZURES

Psychogenic seizures are nonepileptic behaviors that resemble seizures. They are often part of a conversion reaction precipitated by underlying psychological distress. Certain behaviors, such as side-to-side turning of the head, asymmetric and large-amplitude shaking movements of the limbs, twitching of all four extremities without loss of consciousness, and pelvic thrusting are more commonly associated with psychogenic rather than epileptic seizures. Psychogenic seizures often last longer than epileptic seizures and may wax and wane over minutes to hours. However, the distinction is sometimes difficult on clinical grounds alone, and there are many examples of diagnostic errors made by experienced epileptologists. This is especially true for psychogenic seizures that resemble complex partial seizures, since the behavioral manifestations of complex partial seizures (especially of frontal lobe origin) can be extremely unusual, and in both cases the routine surface EEG may be normal. Video-EEG monitoring is very useful when historic features are nondiagnostic. Generalized tonic-clonic seizures always produce marked EEG abnormalities during and after the seizure. For suspected complex partial seizures of temporal lobe origin, the use of additional electrodes beyond the standard scalp locations (e.g., sphenoidal electrodes) may be required to localize a seizure focus. Measurement of serum prolactin levels may also help to distinguish between organic and psychogenic seizures, since most generalized seizures and many complex partial seizures are accompanied by rises in serum prolactin (during the immediate 30-min postictal period), whereas psychogenic seizures are not. The diagnosis of psychogenic seizures does not exclude a concurrent diagnosis of epilepsy, since the two often coexist.

℞ Treatment: SEIZURES AND EPILEPSY

Therapy for a patient with a seizure disorder is almost always multimodal and includes treatment of underlying conditions that cause or contribute to the seizures, avoidance of precipitating factors, suppression of recurrent seizures by prophylactic therapy with antiepileptic medications or surgery, and addressing a variety of psychological and social issues. Treatment plans must be individualized, given the many different types and causes of seizures as well as the differences in efficacy and toxicity of antiepileptic medications for each patient. In almost all cases a neurologist with experience

TABLE 20-7

FEATURES THAT DISTINGUISH GENERALIZED TONIC-CLONIC SEIZURE FROM SYNCOPE

FEATURES	SEIZURE	SYNCOPE
Immediate precipitating factors	Usually none	Emotional stress, Valsalva, orthostatic hypotension, cardiac etiologies
Premonitory symptoms	None or aura (e.g., odd odor)	Tiredness, nausea, diaphoresis, tunneling of vision
Posture at onset	Variable	Usually erect
Transition to unconsciousness	Often immediate	Gradual over seconds[a]
Duration of unconsciousness	Minutes	Seconds
Duration of tonic or clonic movements	30–60 s	Never more than 15 s
Facial appearance during event	Cyanosis, frothing at mouth	Pallor
Disorientation and sleepiness after event	Many minutes to hours	<5 min
Aching of muscles after event	Often	Sometimes
Biting of tongue	Sometimes	Rarely
Incontinence	Sometimes	Sometimes
Headache	Sometimes	Rarely

[a]May be sudden with certain cardiac arrhythmias.

in the treatment of epilepsy should design and oversee implementation of the treatment strategy. Furthermore, patients with refractory epilepsy or those who require polypharmacy with antiepileptic drugs should remain under the regular care of a neurologist.

TREATMENT OF UNDERLYING CONDITIONS

If the sole cause of a seizure is a metabolic disturbance such as an abnormality of serum electrolytes or glucose, then treatment is aimed at reversing the metabolic problem and preventing its recurrence. Therapy with antiepileptic drugs is usually unnecessary unless the metabolic disorder cannot be corrected promptly and the patient is at risk of having further seizures. If the apparent cause of a seizure was a medication (e.g., theophylline) or illicit drug use (e.g., cocaine), then appropriate therapy is avoidance of the drug; there is usually no need for antiepileptic medications unless subsequent seizures occur in the absence of these precipitants.

Seizures caused by a structural CNS lesion such as a brain tumor, vascular malformation, or brain abscess may not recur after appropriate treatment of the underlying lesion. However, despite removal of the structural lesion, there is a risk that the seizure focus will remain in the surrounding tissue or develop *de novo* as a result of gliosis and other processes induced by surgery, radiation, or other therapies. Most patients are therefore maintained on an antiepileptic medication for at least 1 year, and an attempt is made to withdraw medications only if the patient has been completely seizure-free. If seizures are refractory to medication, the patient may benefit from surgical removal of the epileptic brain region (see later).

AVOIDANCE OF PRECIPITATING FACTORS

Unfortunately, little is known about the specific factors that determine precisely when a seizure will occur in a patient with epilepsy. Some patients can identify particular situations that appear to lower their seizure threshold; these situations should be avoided. For example, a patient who has seizures in the setting of sleep deprivation should obviously be advised to maintain a normal sleep schedule. Many patients note an association between alcohol intake and seizures, and they should be encouraged to modify their drinking habits accordingly. There are also relatively rare cases of patients with seizures that are induced by highly specific stimuli such as a video game monitor, music, or an individual's voice ("reflex epilepsy"). If there is an association between stress and seizures, stress reduction techniques such as physical exercise, meditation, or counseling may be helpful.

ANTIEPILEPTIC DRUG THERAPY Antiepileptic drug therapy is the mainstay of treatment for most patients with epilepsy. The overall goal is to completely prevent seizures without causing any untoward side effects, preferably with a single medication and a dosing schedule that is easy for the patient to follow. Seizure classification is an important element in designing the treatment plan, since some antiepileptic drugs have different activities against various seizure types. However,

there is considerable overlap between many antiepileptic drugs, such that the choice of therapy is often determined more by the patient's specific needs, especially his/her assessment of side effects.

When to Initiate Antiepileptic Drug Therapy Antiepileptic drug therapy should be started in any patient with recurrent seizures of unknown etiology or a known cause that cannot be reversed. Whether to initiate therapy in a patient with a single seizure is controversial. Patients with a single seizure due to an identified lesion such as a CNS tumor, infection, or trauma, in which there is strong evidence that the lesion is epileptogenic, should be treated. The risk of seizure recurrence in a patient with an apparently unprovoked or idiopathic seizure is uncertain, with estimates ranging from 31 to 71% in the first 12 months after the initial seizure. This uncertainty arises from differences in the underlying seizure types and etiologies in various published epidemiologic studies. Generally accepted risk factors associated with recurrent seizures include the following: (1) an abnormal neurologic examination, (2) seizures presenting as status epilepticus, (3) postictal Todd's paralysis, (4) a strong family history of seizures, or (5) an abnormal EEG. Most patients with one or more of these risk factors should be treated. Issues such as employment or driving may influence the decision whether to start medications as well. For example, a patient with a single, idiopathic seizure whose job depends on driving may prefer taking antiepileptic drugs rather than risk a seizure recurrence and the potential loss of driving privileges.

Selection of Antiepileptic Drugs Antiepileptic drugs available in the United States are shown in Table 20-8, and the main pharmacologic characteristics of commonly used drugs are listed in Table 20-9. Worldwide, older medications such as phenytoin, valproic acid, carbamazepine, and ethosuximide are generally used as first-line therapy for most seizure disorders since, overall, they are as effective as recently marketed drugs and significantly less expensive. Most of the new drugs that have become available in the past decade are used as add-on or alternative therapy, although some are now being used as first-line monotherapy.

In addition to efficacy, factors influencing the choice of an initial medication include the convenience of dosing (e.g., once daily versus three or four times daily) and potential side effects. In this regard, a number of the newer drugs have the advantage of a relative lack of drug-drug interactions and easier dosing. Almost all of the commonly used antiepileptic drugs can cause similar, dose-related side effects such as sedation, ataxia, and diplopia. Close follow-up is required to ensure these are promptly recognized and reversed. Most of the older drugs and some of the newer ones can also cause idiosyncratic toxicity such as rash, bone marrow suppression, or hepatotoxicity. Although rare, these side effects should be considered during drug selection, and patients must be instructed about symptoms or signs that should signal the need to alert their health care provider. For some drugs, laboratory tests (e.g., complete blood count and liver function tests) are recommended prior to the institution of therapy (to establish

TABLE 20-8

SELECTION OF ANTIEPILEPTIC DRUGS

PRIMARY GENERALIZED TONIC-CLONIC	PARTIAL[a]	ABSENCE	ATYPICAL ABSENCE, MYOCLONIC, ATONIC
First-Line			
Valproic acid Lamotrigine Topiramate	Carbamazepine Phenytoin Lamotrigine Oxcarbazepine Valproic acid	Valproic acid Ethosuximide	Valproic acid Lamotrigine Topiramate
Alternatives			
Zonisamide[b] Phenytoin Carbamazepine Oxcarbazepine Phenobarbital Primidone Felbamate	Levetiracetam[b] Topiramate Tiagabine[b] Zonisamide[b] Gabapentin[b] Phenobarbital Primidone Felbamate	Lamotrigine Clonazepam	Clonazepam Felbamate

[a]Includes simple partial, complex partial, and secondarily generalized seizures.
[b]As adjunctive therapy.

TABLE 20-9

DOSAGE AND ADVERSE EFFECTS OF COMMONLY USED ANTIEPILEPTIC DRUGS

GENERIC NAME	TRADE NAME	PRINCIPAL USES	TYPICAL DOSE; DOSE INTERVAL	HALF-LIFE	THERAPEUTIC RANGE	ADVERSE EFFECTS		DRUG INTERACTIONS
						NEUROLOGIC	SYSTEMIC	
Phenytoin (diphenyl-hydantoin	Dilantin	Tonic-clonic (grand mal) Focal-onset	300–400 mg/d (3–6 mg/kg, adult; 4–8 mg/kg, child); qd-bid	24 h (wide variation, dose-dependent)	10–20 μg/mL	Dizziness Diplopia Ataxia Incoordination Confusion	Gum hyperplasia Lymphade-nopathy Hirsutism Osteomalacia Facial coarsening Skin rash	Level increased by isoniazid, sulfonamides, fluoxetine Level decreased by enzyme-inducing drugs[a] Altered folate metabolism
Carba mazepine	Tegretol Carbatrol	Tonic-clonic Focal-onset	600–1800 mg/d (15–35 mg/kg, child); bid-qid	10–17 h	6–12 μg/mL	Ataxia Dizziness Diplopia Vertigo	Aplastic anemia Leukopenia Gastrointesti-nal irritation Hepatotoxicity Hyponatremia	Level decreased by enzyme-inducing drugs[a] Level increased by erythromycin, propoxyphene, isoniazid, cimeti-dine, fluoxetine
Valproic acid	Depakene Depakote Depakote ER	Tonic-clonic Absence Atypical absence Myoclonic Focal-onset	750–2000 mg/d (20–60 mg/kg); bid-qid	15 h	50–125 μg/mL	Ataxia Sedation Tremor	Hepatotoxicity Thrombocyto-penia Gastrointesti-nal irritation Weight gain Transient alopecia Hyperamm-onemia	Level decreased by enzyme-inducing drugs[a]
Lamotrigine	Lamictal	Focal-onset Tonic-clonic Atypical absence Myoclonic Lennox-Gastaut syndrome	150–500 mg/d; bid	25 h 14 h (with enzyme-inducers) 59 h (with val-proic acid)	Not established	Dizziness Diplopia Sedation Ataxia Headache	Skin rash Stevens-Johnson syndrome	Level decreased by enzyme-inducing drugs[a] and oral contraceptives Level increased by valproic acid
Ethosuxi mide	Zarontin	Absence (petit mal)	750–1250 mg/d (20-40 mg/kg); qd-bid	60 h, adult 30 h, child	40–100 μg/mL	Ataxia Lethargy Headache	Gastrointesti-nal irritation Skin rash Bone marrow suppression	
Gabapentin	Neurontin	Focal-onset	900–2400 mg/d; tid-qid	5–9 h	Not established	Sedation Dizziness Ataxia Fatigue	Gastrointesti-nal irritation Weight gain Edema	No known significant interactions
Topiramate	Topamax	Focal-onset Tonic-clonic Lennox-Gastaut syndrome	200–400 mg/d; bid	20–30 h	Not established	Psychomotor slowing Sedation Speech or language problems Fatigue Paresthesias	Renal stones (avoid use with other carbonic anhydrase inhibitors) Glaucoma Weight loss Hypohydrosis	Level decreased by enzyme-inducing drugs[a]
Tiagabine	Gabitril	Focal-onset Tonic-clonic	32–56 mg/d; bid-qid	7–9 h	Not established	Confusion Sedation Depression Dizziness Speech or language problems Paresthesias Psychosis	Gastrointesti-nal irritation	Level decreased by enzyme-inducing drugs[a]

TABLE 20-9 (*CONTINUED*)

DOSAGE AND ADVERSE EFFECTS OF COMMONLY USED ANTIEPILEPTIC DRUGS

GENERIC NAME	TRADE NAME	PRINCIPAL USES	TYPICAL DOSE; DOSE INTERVAL	HALF-LIFE	THERAPEUTIC RANGE	ADVERSE EFFECTS		DRUG INTERACTIONS
						NEUROLOGIC	SYSTEMIC	
Phenobarbital	Luminol	Tonic-clonic Focal-onset	60–180 mg/d (1–4 mg/kg, adult); (3–6 mg/kg, child); qd	90 h (70 h in children)	10–40 µg/mL	Sedation Ataxia Confusion Dizziness Decreased libido Depression	Skin rash	Level increased by valproic acid, phenytoin
Primidone	Mysoline	Tonic-clonic Focal-onset	750–1000 mg/d (10–25 mg/kg); bid-tid	Primidone, 8–15 h Phenobarbital, 90 h	Primidone, 4–12 µg/mL Phenobarbital, 10–40 µg/mL	Same as phenobarbital		
Clonazepam	Klonopin	Absence Atypical absence Myoclonic	1–12 mg/d (0.1–0.2 mg/kg); qd-tid	24–48 h	10–70 ng/mL	Ataxia Sedation Lethargy	Anorexia	Level decreased by enzyme-inducing drugs[a]
Felbamate	Felbatol	Focal-onset Lennox-Gastaut syndrome	2400–3600 mg/d, (45 mg/kg, child); tid-qid	16–22 h	Not established	Insomnia Dizziness Sedation Headache	Aplastic anemia Hepatic failure Weight loss Gastrointestinal irritation	Increases phenytoin, valproic acid, active carbamazepine metabolite
Levetiracetam	Keppra	Focal-onset	1000–3000 mg/d; bid	6–8 h	Not established	Sedation Fatigue Incoordination Psychosis	Anemia Leukopenia	None known
Zonisamide	Zonegran	Focal-onset	200–400 mg/d; qd-bid	50–68 h	Not established	Sedation Dizziness Confusion Headache Psychosis	Anorexia Renal stones Hypohydrosis	Level decreased by enzyme-inducing drugs[a]
Oxcarbazepine	Trileptal	Focal-onset	900–2400 mg/d (30–45 mg/kg, child); bid	10–17 h (for active metabolite)	Not established	Fatigue Ataxia Dizziness Diplopia Vertigo Headache	See carbamazepine	Level decreased by enzyme-inducing drugs[a] May increase phenytoin

[a]Phenytoin, carbamazepine, phenobarbital.

baseline values) and during initial dosing and titration of the agent.

Antiepileptic Drug Selection for Partial Seizures Carbamazepine (or a related drug, oxcarbazepine), phenytoin, lamotrigine and topiramate are currently the drugs of choice approved for the initial treatment of partial seizures, including those that secondarily generalize. Overall they have very similar efficacy, but differences in pharmacokinetics and toxicity are the main determinants for use in a given patient. For example, phenytoin has a relatively long half-life and offers the advantage of once or twice daily dosing in comparison with two or three times daily dosing for many of the other drugs. However, phenytoin shows properties of saturation kinetics, such that small increases in phenytoin doses above a standard maintenance dose can precipitate marked side effects. This is one of the main causes of acute phenytoin toxicity. Long-term use of phenytoin is associated with untoward cosmetic effects (e.g., hirsutism, coarsening of facial features, and gingival hypertrophy), and effects on bone metabolism, so it is often avoided in young patients who are likely to require the drug for many years. An advantage of carbamazepine (which is also available in an extended-release form) is that its metabolism follows first-order pharmacokinetics, and the relationship between drug dose, serum levels, and toxicity is linear. Carbamazepine

can cause leukopenia, aplastic anemia, or hepatotoxicity and would therefore be contraindicated in patients with predispositions to these problems. Asian individuals carrying the HLA allele HLA-B*1502 are at particularly high risk of developing fatal skin reactions including Stevens Johnson syndrome and should be tested for this allele prior to initiation of carbamazepine. Oxcarbazepine has the advantage of being metabolized in a way that avoids an intermediate metabolite associated with some of the side effects of carbamazepine. Oxcarbazepine also has fewer drug interactions than carbamazepine. Lamotrigine tends to be well-tolerated in terms of side effects. However, patients need to be particularly vigilant about the possibility of a skin rash during the initiation of therapy. This can be extremely severe and lead to Stevens-Johnson syndrome if unrecognized and if the medication is not discontinued immediately. This risk can be reduced by slow introduction and titration. Lamotrigine must be started slowly when used as add-on therapy with valproic acid, since valproic acid inhibits lamotrigine metabolism, thereby substantially prolonging its half-life. Topiramate has recently been approved as monotherapy for partial and primary generalized seizures. Similar to some of the other antiepileptic drugs, topiramate can cause significant psychomotor slowing and other cognitive problems, and it should not be used in patients at risk for the development of glaucoma or renal stones.

Valproic acid is an effective alternative for some patients with partial seizures, especially when the seizures secondarily generalize. Gastrointestinal side effects are fewer when using the valproate semisodium formulation (Depakote). Valproic acid also rarely causes reversible bone marrow suppression and hepatotoxicity, and laboratory testing is required to monitor toxicity. This drug should generally be avoided in patients with preexisting bone marrow or liver disease. Irreversible, fatal hepatic failure appearing as an idiosyncratic rather than dose-related side effect is a relatively rare complication; its risk is highest in children <2 years, especially those taking other antiepileptic drugs or with inborn errors of metabolism.

Levetiracetam, tiagabine, zonisamide, and gabapentin are additional drugs currently used for the treatment of partial seizures with or without secondary generalization. Phenobarbital and other barbiturate compounds were commonly used in the past as first-line therapy for many forms of epilepsy. However, the barbiturates frequently cause sedation in adults, hyperactivity in children, and other more subtle cognitive changes; thus, their use should be limited to situations in which no other suitable treatment alternatives exist.

Antiepileptic Drug Selection for Generalized Seizures Valproic acid and lamotrigine are currently considered the best initial choice for the treatment of primary generalized, tonic-clonic seizures. Phenytoin, followed by topiramate, carbamazepine, and zonisamide are suitable alternatives. Valproic acid is also particularly effective in absence, myoclonic, and atonic seizures and is therefore the drug of choice in patients with generalized epilepsy syndromes having mixed seizure types. Importantly, both carbamazepine and phenytoin can worsen certain types of generalized seizures, including absence, myoclonic, tonic, and atonic seizures. Ethosuximide is a particularly effective drug for the treatment of uncomplicated absence seizures, but it is not useful for tonic-clonic or partial seizures. Ethosuximide rarely causes bone marrow suppression, so that periodic monitoring of blood cell counts is required. Lamotrigine appears to be particularly effective in epilepsy syndromes with mixed, generalized seizure types such as JME and Lennox-Gastaut syndrome. Topiramate, zonisamide, and felbamate may have similar broad efficacy.

Initiation and Monitoring of Therapy Because the response to any antiepileptic drug is unpredictable, patients should be carefully educated about the approach to therapy. The goal is to prevent seizures and minimize the side effects of therapy; determination of the optimal dose is often a matter of trial and error. This process may take months or longer if the baseline seizure frequency is low. Most anticonvulsant drugs need to be introduced relatively slowly to minimize side effects, and patients should expect that minor side effects such as mild sedation, slight changes in cognition, or imbalance will typically resolve within a few days. Starting doses are usually the lowest value listed under the dosage column in Table 20-9. Subsequent increases should be made only after achieving a steady state with the previous dose (i.e., after an interval of five or more half-lives).

Monitoring of serum antiepileptic drug levels can be very useful for establishing the initial dosing schedule. However, the published therapeutic ranges of serum drug concentrations are only an approximate guide for determining the proper dose for a given patient. The key determinants are the clinical measures of seizure frequency and presence of side effects, not the laboratory values. Conventional assays of serum drug levels measure the total drug (i.e., both free and protein-bound). However, it is the concentration of free drug that reflects extracellular levels in the brain and correlates best with efficacy. Thus, patients with decreased levels of serum proteins (e.g., decreased serum albumin due to impaired liver or renal function) may have an increased ratio of free to bound drug, yet the concentration of free drug may be adequate for seizure control. These patients may have a "subtherapeutic" drug level, but the dose should be changed only if seizures remain

uncontrolled, not just to achieve a "therapeutic" level. It is also useful to monitor free drug levels in such patients. In practice, other than during the initiation or modification of therapy, monitoring of antiepileptic drug levels is most useful for documenting compliance.

If seizures continue despite gradual increases to the maximum tolerated dose and documented compliance, then it becomes necessary to switch to another antiepileptic drug. This is usually done by maintaining the patient on the first drug while a second drug is added. The dose of the second drug should be adjusted to decrease seizure frequency without causing toxicity. Once this is achieved, the first drug can be gradually withdrawn (usually over weeks unless there is significant toxicity). The dose of the second drug is then further optimized based on seizure response and side effects. Monotherapy should be the goal whenever possible.

When to Discontinue Therapy Overall, about 70% of children and 60% of adults who have their seizures completely controlled with antiepileptic drugs can eventually discontinue therapy. The following patient profile yields the greatest chance of remaining seizure-free after drug withdrawal: (1) complete medical control of seizures for 1–5 years; (2) single seizure type, either partial or generalized; (3) normal neurologic examination, including intelligence; and (4) normal EEG. The appropriate seizure-free interval is unknown and undoubtedly varies for different forms of epilepsy. However, it seems reasonable to attempt withdrawal of therapy after 2 years in a patient who meets all of the above criteria, is motivated to discontinue the medication, and clearly understands the potential risks and benefits. In most cases it is preferable to reduce the dose of the drug gradually over 2–3 months. Most recurrences occur in the first 3 months after discontinuing therapy, and patients should be advised to avoid potentially dangerous situations such as driving or swimming during this period.

Treatment of Refractory Epilepsy Approximately one-third of patients with epilepsy do not respond to treatment with a single antiepileptic drug, and it becomes necessary to try a combination of drugs to control seizures. Patients who have focal epilepsy related to an underlying structural lesion or those with multiple seizure types and developmental delay are particularly likely to require multiple drugs. There are currently no clear guidelines for rational polypharmacy, although in theory a combination of drugs with different mechanisms of action may be most useful. In most cases the initial combination therapy combines first-line drugs, i.e., carbamazepine, phenytoin, valproic acid, and lamotrigine. If these drugs are unsuccessful, then the addition of a newer drug such as levetiracetam or topiramate is indicated. Patients with myoclonic seizures resistant to valproic acid may benefit from the addition of clonazepam, and those with absence seizures may respond to a combination of valproic acid and ethosuximide. The same principles concerning the monitoring of therapeutic response, toxicity, and serum levels for monotherapy apply to polypharmacy, and potential drug interactions need to be recognized. If there is no improvement, a third drug can be added while the first two are maintained. If there is a response, the less effective or less well-tolerated of the first two drugs should be gradually withdrawn.

SURGICAL TREATMENT OF REFRACTORY EPILEPSY Approximately 20–30% of patients with epilepsy are resistant to medical therapy despite efforts to find an effective combination of antiepileptic drugs. For some, surgery can be extremely effective in substantially reducing seizure frequency and even providing complete seizure control. Understanding the potential value of surgery is especially important when, at the time of diagnosis, a patient has an epilepsy syndrome that is considered likely to be drug-resistant. Rather than submitting the patient to years of unsuccessful medical therapy and the psychosocial trauma and increased mortality associated with ongoing seizures, the patient should have an efficient but relatively brief attempt at medical therapy and then be referred for surgical evaluation.

The most common surgical procedure for patients with temporal lobe epilepsy involves resection of the anteromedial temporal lobe (temporal lobectomy) or a more limited removal of the underlying hippocampus and amygdala (amygdalohippocampectomy). Focal seizures arising from extratemporal regions may be abolished by a focal neocortical resection with precise removal of an identified lesion (lesionectomy). When the cortical region cannot be removed, multiple subpial transection, which disrupts intracortical connections, is sometimes used to prevent seizure spread. Hemispherectomy or multilobar resection is useful for some patients with severe seizures due to hemispheric abnormalities such as hemimegalencephaly or other dysplastic abnormalities, and corpus callosotomy has been shown to be effective for disabling tonic or atonic seizures, usually when they are part of a mixed-seizure syndrome (e.g., Lennox-Gastaut syndrome).

Presurgical evaluation is designed to identify the functional and structural basis of the patient's seizure disorder. Inpatient video-EEG monitoring is used to define the anatomic location of the seizure focus and to correlate the abnormal electrophysiologic activity with behavioral manifestations of the seizure. Routine scalp or scalp-sphenoidal recordings are usually sufficient for localization, and advances in neuroimaging have made the use of invasive electrophysiologic monitoring such as implanted depth electrodes or subdural electrodes less common. A high-resolution MRI scan is routinely

used to identify structural lesions, and this is sometimes augmented with MEG. Functional imaging studies such as SPECT and PET are adjunctive tests that may help verify the localization of an apparent epileptogenic region. Once the presumed location of the seizure onset is identified, additional studies, including neuropsychological testing and the intracarotid amobarbital test (Wada test) may be used to assess language and memory localization and to determine the possible functional consequences of surgical removal of the epileptogenic region. In some cases, the exact extent of the resection to be undertaken is determined by performing cortical mapping at the time of the surgical procedure, allowing for a tailored resection. This involves electrocorticographic recordings made with electrodes on the surface of the brain to identify the extent of epileptiform disturbances. If the region to be resected is within or near brain regions suspected of having sensorimotor or language function, electrical cortical stimulation mapping is performed on the awake patient to determine the function of cortical regions in question in order to avoid resection of so-called eloquent cortex and thereby minimize postsurgical deficits.

Advances in presurgical evaluation and microsurgical techniques have led to a steady increase in the success of epilepsy surgery. Clinically significant complications of surgery are <5%, and the use of functional mapping procedures has markedly reduced the neurologic sequelae due to removal or sectioning of brain tissue. For example, about 70% of patients treated with temporal lobectomy will become seizure-free, and another 15–25% will have at least a 90% reduction in seizure frequency. Marked improvement is also usually seen in patients treated with hemispherectomy for catastrophic seizure disorders due to large hemispheric abnormalities. Postoperatively, patients generally need to remain on antiepileptic drug therapy, but the marked reduction of seizures following resective surgery can have a very beneficial effect on quality of life. Recently, focal radiosurgery as emerged as a potential alternative to resective procedures.

Not all medically refractory patients are suitable candidates for resective surgery. For example, some patients have seizures arising from more than one site, making the risk of ongoing seizures or potential harm from the surgery unacceptably high. Vagus nerve stimulation (VNS) may be useful in some of these cases, although the benefit for most patients seems to be very limited; i.e., the efficacy of VNS appears to be no greater than trying another drug, which rarely works if a patient has proved to be refractory to the first two to three drugs. The precise mechanism of action of VNS is unknown, although experimental studies have shown that stimulation of vagal nuclei leads to widespread activation of cortical and subcortical pathways and an associated increased seizure threshold. Adverse effects of the surgery are rare, and stimulation-induced side effects, including transient hoarseness, cough, and dyspnea, are usually mild.

Although still in development, there are some additional therapies that will likely be of benefit to patients with medically refractory epilepsy. Preliminary studies suggest that stereotactic radiosurgery may be effective in certain partial seizure disorders. There has also been great interest in the development of implantable devices that can detect the onset of a seizure (in some instances, before the seizure becomes clinically apparent) and deliver either an electrical stimulation or drug directly to the seizure focus to abort the event.

STATUS EPILEPTICUS

Status epilepticus refers to continuous seizures or repetitive, discrete seizures with impaired consciousness in the interictal period. Status epilepticus has numerous subtypes, including generalized convulsive status epilepticus (GCSE) (e.g., persistent, generalized electrographic seizures, coma, and tonic-clonic movements), and nonconvulsive status epilepticus (e.g., persistent absence seizures or partial seizures, confusion or partially impaired consciousness, and minimal motor abnormalities). The duration of seizure activity sufficient to meet the definition of status epilepticus has traditionally been specified as 15–30 min. However, a more practical definition is to consider status epilepticus as a situation in which the duration of seizures prompts the acute use of anticonvulsant therapy. For GCSE, this is typically when seizures last beyond 5 min.

GCSE is an emergency and must be treated immediately, since cardiorespiratory dysfunction, hyperthermia, and metabolic derangements can develop as a consequence of prolonged seizures, and these can lead to irreversible neuronal injury. Furthermore, CNS injury can occur even when the patient is paralyzed with neuromuscular blockade but continues to have electrographic seizures. The most common causes of GCSE are anticonvulsant withdrawal or noncompliance, metabolic disturbances, drug toxicity, CNS infection, CNS tumors, refractory epilepsy, and head trauma.

GCSE is obvious when the patient is having overt convulsions. However, after 30–45 min of uninterrupted seizures, the signs may become increasingly subtle. Patients may have mild clonic movements of only the fingers or fine, rapid movements of the eyes. There may be paroxysmal episodes of tachycardia, hypertension, and pupillary dilation. In such cases, the EEG may be the only method of establishing the diagnosis. Thus, if the patient stops having overt seizures, yet remains comatose, an EEG should be performed to rule out ongoing status

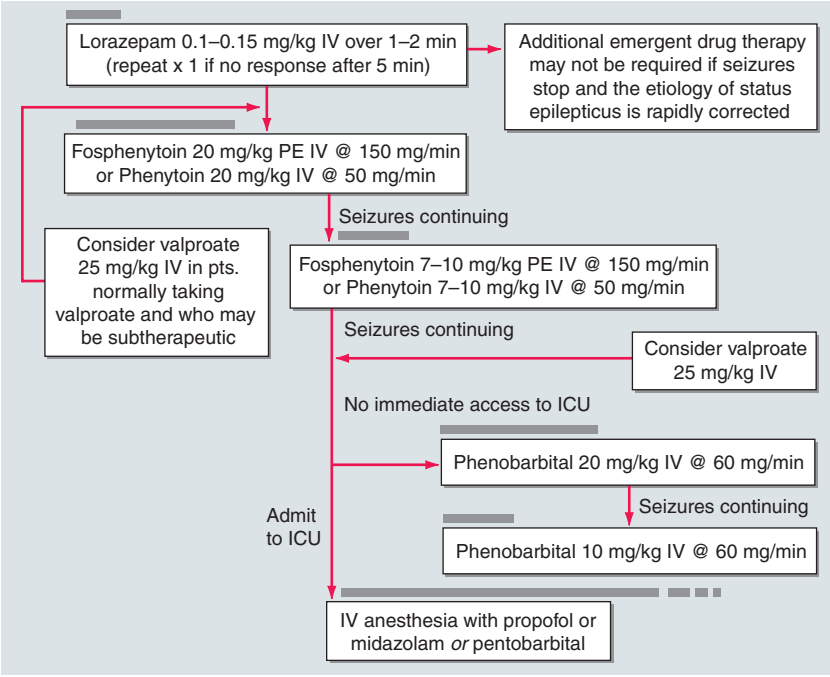

FIGURE 20-3
Pharmacologic treatment of generalized tonic-clonic status epilepticus in adults. The horizontal bars indicate the approximate duration of drug infusions. IV, intravenous; PE, phenytoin equivalents.

epilepticus. This is obviously also essential when a patient with GCSE has been paralyzed with neuromuscular blockade in the process of protecting the airway.

The first step in the management of a patient in GCSE is to attend to any acute cardiorespiratory problems or hyperthermia, perform a brief medical and neurologic examination, establish venous access, and send samples for laboratory studies to identify metabolic abnormalities. Anticonvulsant therapy should then begin without delay; a treatment approach is shown in Fig. 20-3.

The treatment of nonconvulsive status epilepticus is somewhat less urgent than GCSE, since the ongoing seizures are not accompanied by the severe metabolic disturbances seen with GCSE. However, evidence suggests that nonconvulsive status epilepticus, especially that caused by ongoing, focal seizure activity, is associated with cellular injury in the region of the seizure focus, so that the condition should be treated as promptly as possible using the general approach described for GCSE.

BEYOND SEIZURES: OTHER MANAGEMENT ISSUES

INTERICTAL BEHAVIOR

The adverse effects of epilepsy often go beyond the occurrence of clinical seizures, and the extent of these effects largely depends on the etiology of the seizure disorder, the degree to which the seizures are controlled, and the presence of side effects from antiepileptic therapy. Many patients with epilepsy are completely normal between seizures and able to live highly successful and productive lives. In contrast, patients with seizures secondary to developmental abnormalities or acquired brain injury may have impaired cognitive function and other neurologic deficits. Frequent interictal EEG abnormalities have been shown to be associated with subtle dysfunction of memory and attention. Patients with many seizures, especially those emanating from the temporal lobe, often note an impairment of short-term memory that may progress over time.

Patients with epilepsy are at risk of developing a variety of psychiatric problems, including depression, anxiety, and psychosis. This risk varies considerably depending on many factors, including the etiology, frequency, and severity of seizures and the patient's age and previous history. Depression occurs in ~20% of patients, and the incidence of suicide is higher in epileptic patients than in the general population. Depression should be treated through counseling or medication. The selective serotonin reuptake inhibitors typically have no effect on seizures, while the tricyclic antidepressants may lower the seizure threshold. Anxiety can appear as a manifestation of a seizure, and anxious or psychotic behavior can sometimes be observed as part of a postictal delirium. Postictal psychosis is a rare phenomenon that typically occurs after a period of increased seizure frequency. There is usually a brief lucid interval lasting up to a week, followed by days to weeks of agitated, psychotic behavior. The psychosis will usually resolve spontaneously but may require treatment with antipsychotic or anxiolytic medications.

There is ongoing controversy as to whether some patients with epilepsy (especially temporal lobe epilepsy)

have a stereotypical "interictal personality." The predominant view is that the unusual or abnormal personality traits observed in such patients are, in most cases, not due to epilepsy but result from an underlying structural brain lesion, the effects of antiepileptic drugs, or psychosocial factors related to suffering from a chronic disease.

MORTALITY OF EPILEPSY

Patients with epilepsy have a risk of death that is roughly two to three times greater than expected in a matched population without epilepsy. Most of the increased mortality is due to the underlying etiology of epilepsy, e.g., tumors or strokes in older adults. However, a significant number of patients die from accidents, status epilepticus, and a syndrome known as *sudden unexpected death in epileptic patients* (SUDEP), which usually affects young people with convulsive seizures and tends to occur at night. The cause of SUDEP is unknown; it may result from brainstem-mediated effects of seizures on cardiac rhythms or pulmonary function.

PSYCHOSOCIAL ISSUES

There continues to be a cultural stigma about epilepsy, although it is slowly declining in societies with effective health education programs. Many patients with epilepsy harbor fears, such as the fear of becoming mentally retarded or dying during a seizure. These issues need to be carefully addressed by educating the patient about epilepsy and by ensuring that family members, teachers, fellow employees, and other associates are equally well informed. The Epilepsy Foundation of America (1-800-EFA-1000) is a patient advocacy organization and a useful source of educational material.

EMPLOYMENT, DRIVING, AND OTHER ACTIVITIES

Many patients with epilepsy face difficulty in obtaining or maintaining employment, even when their seizures are well controlled. Federal and state legislation is designed to prevent employers from discriminating against patients with epilepsy, and patients should be encouraged to understand and claim their legal rights. Patients in these circumstances also benefit greatly from the assistance of health providers who act as strong patient advocates.

Loss of driving privileges is one of the most disruptive social consequences of epilepsy. Physicians should be very clear about local regulations concerning driving and epilepsy, since the laws vary considerably among states and countries. In all cases, it is the physician's responsibility to warn patients of the danger imposed on themselves and others while driving if their seizures are uncontrolled (unless the seizures are not associated with impairment of consciousness or motor control). In general, most states allow patients to drive after a seizure-free interval (on or off medications) of between 3 months and 2 years.

Patients with incompletely controlled seizures must also contend with the risk of being in situations where an impairment of consciousness or loss of motor control could lead to major injury or death. Thus, depending on the type and frequency of seizures, many patients need to be instructed to avoid working at heights or with machinery, or to have someone close by for activities such as bathing and swimming.

SPECIAL ISSUES RELATED TO WOMEN AND EPILEPSY

CATAMENIAL EPILEPSY

Some women experience a marked increase in seizure frequency around the time of menses. This is thought to reflect either the effects of estrogen and progesterone on neuronal excitability or changes in antiepileptic drug levels due to altered protein binding. Acetazolamide (250–500 mg/d) may be effective as adjunctive therapy in some cases when started 7–10 days prior to the onset of menses and continued until bleeding stops. Some patients may benefit from increases in antiepileptic drug dosages during this time or from control of the menstrual cycle through the use of oral contraceptives. Natural progestins may be of benefit to a subset of women.

PREGNANCY

Most women with epilepsy who become pregnant will have an uncomplicated gestation and deliver a normal baby. However, epilepsy poses some important risks to a pregnancy. Seizure frequency during pregnancy will remain unchanged in ~50% of women, increase in 30%, and decrease in 20%. Changes in seizure frequency are attributed to endocrine effects on the CNS, variations in antiepileptic drug pharmacokinetics (such as acceleration of hepatic drug metabolism or effects on plasma protein binding), and changes in medication compliance. It is useful to see patients at frequent intervals during pregnancy and monitor serum antiepileptic drug levels. Measurement of the unbound drug concentrations may be useful if there is an increase in seizure frequency or worsening of side effects of antiepileptic drugs.

The overall incidence of fetal abnormalities in children born to mothers with epilepsy is 5–6%, in comparison with 2–3% in healthy women. Part of the higher incidence is due to teratogenic effects of antiepileptic drugs, and the risk increases with the number of medications

used (e.g., 10% risk of malformations with three drugs). A syndrome comprising facial dysmorphism, cleft lip, cleft palate, cardiac defects, digital hypoplasia, and nail dysplasia was originally ascribed to phenytoin therapy, but it is now known to occur with other first-line antiepileptic drugs (i.e., valproic acid and carbamazepine) as well. Also, valproic acid and carbamazepine are associated with a 1–2% incidence of neural tube defects compared with a baseline of 0.5–1%. Little is currently known about the safety of newer drugs, although very recent reports suggest a higher than expected incidence of cleft lip with the use of lamotrigine during pregnancy.

Because the potential harm of uncontrolled seizures on the mother and fetus is considered greater than the teratogenic effects of antiepileptic drugs, it is currently recommended that pregnant women be maintained on effective drug therapy. When possible, it seems prudent to have the patient on monotherapy at the lowest effective dose, especially during the first trimester. Patients should also take folate (1–4 mg/d), since the antifolate effects of anticonvulsants are thought to play a role in the development of neural tube defects, although the benefits of this treatment remain unproved in this setting.

Enzyme-inducing drugs such as phenytoin, phenobarbital, and primidone cause a transient and reversible deficiency of vitamin K–dependent clotting factors in ~50% of newborn infants. Although neonatal hemorrhage is uncommon, the mother should be treated with oral vitamin K (20 mg/d) in the last 2 weeks of pregnancy, and the infant should receive vitamin K (1 mg) at birth.

CONTRACEPTION

Special care should be taken when prescribing antiepileptic medications for women who are taking oral contraceptive agents. Drugs such as carbamazepine, phenytoin, phenobarbital, and topiramate can significantly antagonize the effects of oral contraceptives via enzyme induction and other mechanisms. Patients should be advised to consider alternative forms of contraception, or their contraceptive medications should be modified to offset the effects of the antiepileptic medications.

BREAST-FEEDING

Antiepileptic medications are excreted into breast milk to a variable degree. The ratio of drug concentration in breast milk relative to serum is ~80% for ethosuximide, 40–60% for phenobarbital, 40% for carbamazepine, 15% for phenytoin, and 5% for valproic acid. Given the overall benefits of breast-feeding and the lack of evidence for long-term harm to the infant by being exposed to antiepileptic drugs, mothers with epilepsy can be encouraged to breast-feed. This should be reconsidered, however, if there is any evidence of drug effects on the infant, such as lethargy or poor feeding.

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CHAPTER 21

CEREBROVASCULAR DISEASES

Wade S. Smith ■ Joey D. English ■ S. Claiborne Johnston

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Cerebrovascular diseases include some of the most common and devastating disorders: ischemic stroke, hemorrhagic stroke, and cerebrovascular anomalies such as intracranial aneurysms and arteriovenous malformations (AVMs). They cause ~200,000 deaths each year in the United States and are a major cause of disability. The incidence of cerebrovascular diseases increases with age, and the number of strokes is projected to increase as the elderly population grows, with a doubling in stroke deaths in the United States by 2030. Most cerebrovascular diseases are manifest by the abrupt onset of a focal neurologic deficit, as if the patient was "struck by the hand of God." A stroke, or cerebrovascular accident, is defined by this abrupt onset of a neurologic deficit that is attributable to a focal vascular cause. Thus, the definition of stroke is clinical, and laboratory studies including brain imaging are used to support the diagnosis. The clinical manifestations of stroke are highly variable because of the complex anatomy of the brain and its vasculature. *Cerebral ischemia* is caused by a reduction in blood flow that lasts longer than several seconds. Neurologic symptoms are manifest within seconds because neurons lack glycogen, so energy failure is rapid. If the cessation of flow lasts for more than a few minutes, *infarction* or death of brain tissue results. When blood flow is quickly restored, brain tissue can recover fully and the patient's symptoms are only transient: this is called a *transient ischemic attack* (TIA). The standard definition of TIA requires that all neurologic signs and symptoms resolve within 24 h regardless of whether there is imaging evidence of new permanent brain injury; stroke has occurred if the neurologic signs and symptoms last for >24 h. However, a newly proposed definition classifies those with new brain infarction as ischemic strokes regardless of whether symptoms persist. A generalized reduction in cerebral blood flow due to systemic hypotension (e.g., cardiac arrhythmia, myocardial infarction, or hemorrhagic shock) usually produces syncope (Chap. 8). If low cerebral blood flow persists for a longer duration, then infarction in the border zones between the major cerebral artery distributions may develop. In more severe instances, *global hypoxia-ischemia* causes widespread brain injury; the constellation of cognitive sequelae that ensues is called *hypoxic-ischemic encephalopathy* (Chap. 22). *Focal ischemia* or infarction, on the other hand, is usually caused by thrombosis of the cerebral vessels themselves or by emboli from a proximal arterial source or the heart. *Intracranial hemorrhage* is caused by bleeding directly into or around the brain; it produces neurologic symptoms by producing a mass effect on neural structures, from the toxic effects of blood itself, or by increasing intracranial pressure.

Approach to the Patient: CEREBROVASCULAR DISEASE

Rapid evaluation is essential for use of time-sensitive treatments such as thrombolysis. However, nearly half of patients with acute stroke often do not seek medical assistance on their own, both because they are rarely in pain, as well as because they may lose the appreciation that something is wrong (anosognosia); it is often a family member or a bystander who calls for help. Therefore, patients and their family members should be counseled to call emergency medical services immediately if they experience or witness the sudden onset of any of the following: loss of sensory and/or motor function on one side of the body (nearly 85% of ischemic stroke patients have hemiparesis); change in vision, gait, or ability to speak or understand; or if they experience a sudden, severe headache.

There are several common causes of sudden-onset neurologic symptoms that may mimic stroke, including seizure, intracranial tumor, migraine, and metabolic encephalopathy. An adequate history from an observer that no convulsive activity occurred at the onset reasonably excludes seizure. Tumors may present with acute neurologic symptoms due to hemorrhage, seizure, or hydrocephalus. Surprisingly, migraine can mimic stroke, even in patients without a significant migraine history. When it develops without head pain (*acephalgic migraine*), the diagnosis may remain elusive. Patients without any prior history of migraine may develop acephalgic migraine even older than 65 years. A sensory disturbance is often prominent, and the sensory deficit, as well as any motor deficits, tends to migrate slowly across a limb over minutes rather than seconds as with stroke. The diagnosis of migraine becomes more secure as the cortical disturbance begins to cross vascular boundaries or if typical visual symptoms are present, such as scintillating scotomata (Chap. 6). At times it may be difficult to make the diagnosis until multiple episodes have occurred leaving behind no residual symptoms and with a normal MRI study of the brain. Classically, metabolic encephalopathies produce fluctuating mental status without focal neurologic findings. However, in the setting of prior stroke or brain injury, a patient with fever or sepsis may manifest hemiparesis, which clears rapidly when the infection is remedied. The metabolic process serves to "unmask" a prior deficit.

Once the diagnosis of stroke is made, a brain imaging study is necessary to determine if the cause of stroke is ischemia or hemorrhage (Fig. 21-1). CT imaging of the brain is the standard imaging modality to detect the presence or absence of intracranial hemorrhage (see Imaging Studies, later). If the stroke is ischemic, administration of recombinant tissue plasminogen activator (rtPA) or endovascular mechanical thrombectomy may be beneficial in restoring cerebral perfusion (see Rx: Acute Ischemic Stroke). Medical management to reduce the risk of complications becomes the next priority, followed by plans for secondary prevention. For ischemic stroke, several strategies can reduce the risk of subsequent stroke in all patients, while other strategies are effective for patients with specific causes of stroke such as cardiac embolus and carotid atherosclerosis. For hemorrhagic stroke, aneurysmal subarachnoid hemorrhage (SAH) and hypertensive intracranial hemorrhage are two important causes. The treatment and prevention of hypertensive intracranial hemorrhage are discussed later in this chapter. SAH is discussed in Chap. 22.

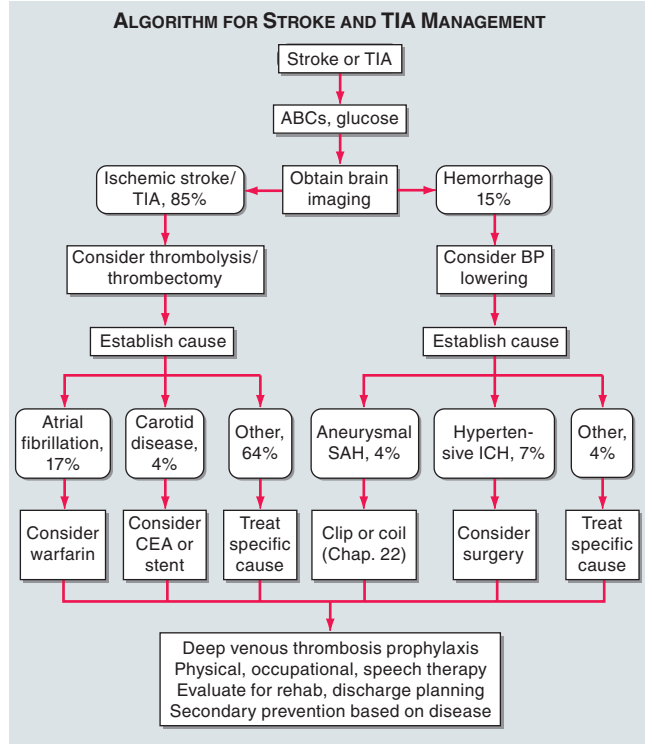

FIGURE 21-1

Medical management of stroke and TIA. Rounded boxes are diagnoses; rectangles are interventions. Numbers are percentages of stroke overall. TIA, transient ischemic attack; ABCs, airway, breathing, circulation; BP, blood pressure; CEA, carotid endarterectomy, SAH, subarachnoid hemorrhage; ICH, intracerebral hemorrhage.

ISCHEMIC STROKE

PATHOPHYSIOLOGY OF ISCHEMIC STROKE

Acute occlusion of an intracranial vessel causes reduction in blood flow to the brain region it supplies. The magnitude of flow reduction is a function of collateral blood

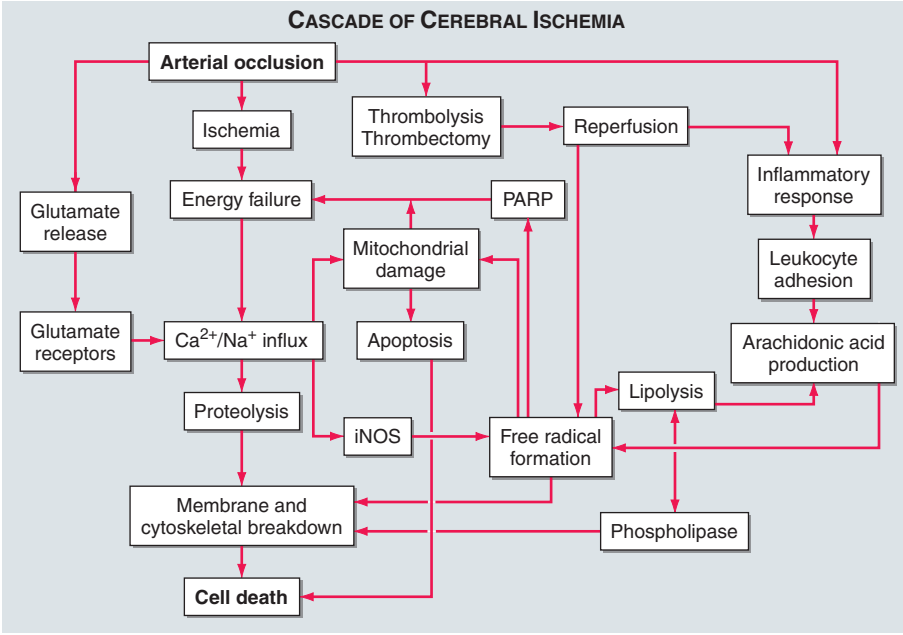

FIGURE 21-2
Major steps in the cascade of cerebral ischemia. See text for details. PARP, poly-A ribose polymerase; iNOS, inducible nitric oxide synthase.

flow and this depends on individual vascular anatomy and the site of occlusion. A fall in cerebral blood flow to zero causes death of brain tissue within 4–10 min; values <16–18 mL/100 g tissue per min cause infarction within an hour; and values <20 mL/100 g tissue per min cause ischemia without infarction unless prolonged for several hours or days. If blood flow is restored prior to a significant amount of cell death, the patient may experience only transient symptoms, i.e., a TIA. Tissue surrounding the core region of infarction is ischemic but reversibly dysfunctional and is referred to as the *ischemic penumbra*. The penumbra may be imaged by using perfusion-diffusion imaging with MRI (see later and Fig. 21-16). The ischemic penumbra will eventually infarct if no change in flow occurs, and hence saving the ischemic penumbra is the goal of revascularization therapies.

Focal cerebral infarction occurs via two distinct pathways (**Fig. 21-2**): (1) a necrotic pathway in which cellular cytoskeletal breakdown is rapid, due principally to energy failure of the cell; and (2) an apoptotic pathway in which cells become programmed to die. Ischemia produces necrosis by starving neurons of glucose, which in turn results in failure of mitochondria to produce ATP. Without ATP, membrane ion pumps stop functioning and neurons depolarize, allowing intracellular calcium to rise. Cellular depolarization also causes glutamate release from synaptic terminals; excess extracellular glutamate produces neurotoxicity by activating postsynaptic glutamate receptors that increase neuronal calcium influx. Free radicals are produced by membrane lipid degradation and mitochondrial dysfunction. Free radicals cause catalytic destruction of membranes and likely damage other vital functions of cells. Lesser degrees of ischemia, as are seen within the ischemic penumbra, favor apoptotic cellular death causing cells to die days to weeks later. Fever dramatically worsens ischemia, as does hyperglycemia [glucose >11.1 mmol/L (200 mg/dL)], so it is reasonable to suppress fever and prevent hyperglycemia as much as possible. Induced moderate hypothermia to mitigate stroke is the subject of continuing clinical research.

℞ Treatment: ACUTE ISCHEMIC STROKE

After the clinical diagnosis of stroke is made, an orderly process of evaluation and treatment should follow (Fig. 21-1). The first goal is to prevent or reverse brain injury. Attend to the patient's airway, breathing, circulation, and treat hypoglycemia or hyperglycemia if identified. Perform an emergency noncontrast head CT scan in order to differentiate between ischemic stroke and hemorrhagic stroke; there are no reliable clinical findings that conclusively separate ischemia from hemorrhage, although a more depressed level of consciousness, higher initial blood pressure, or worsening of symptoms after onset favor hemorrhage, and a deficit that remits suggests ischemia. Treatments designed to reverse or lessen the amount of tissue infarction and improve clinical outcome fall within six categories: (1) medical support (2) intravenous thrombolysis, (3) endovascular techniques, (4) antithrombotic treatment, (5) neuroprotection, and (6) stroke centers and rehabilitation.

MEDICAL SUPPORT When ischemic stroke occurs, the immediate goal is to optimize cerebral perfusion in the surrounding ischemic penumbra. Attention is also

directed toward preventing the common complications of bedridden patients—infections (pneumonia, urinary tract, and skin) and deep venous thrombosis (DVT) with pulmonary embolism. Many physicians use pneumatic compression stockings to prevent DVT; subcutaneous heparin appears to be safe as well and can be used concomitantly.

Because collateral blood flow within the ischemic brain is blood pressure dependent, there is controversy about whether blood pressure should be lowered acutely. Blood pressure should be lowered if there is malignant hypertension or concomitant myocardial ischemia or if blood pressure is >185/110 mmHg and thrombolytic therapy is anticipated. When faced with the competing demands of myocardium and brain, lowering the heart rate with a β_1-adrenergic blocker (such as esmolol) can be a first step to decrease cardiac work and maintain blood pressure. Fever is detrimental and should be treated with antipyretics and surface cooling. Serum glucose should be monitored and kept at <6.1 mmol/L (110 mg/dL) using an insulin infusion.

Between 5 and 10% of patients develop enough cerebral edema to cause obtundation or brain herniation. Edema peaks on the second or third day but can cause mass effect for ~10 days. The larger the infarct, the greater the likelihood that clinically significant edema will develop. Water restriction and IV mannitol may be used to raise the serum osmolarity, but hypovolemia should be avoided as this may contribute to hypotension and worsening infarction. Combined analysis of three randomized European trials of hemicraniectomy (craniotomy and temporary removal of part of the skull) shows that this procedure markedly reduces mortality, and the clinical outcomes of survivors are acceptable.

Special vigilance is warranted for patients with cerebellar infarction. Such strokes may mimic labyrinthitis because of prominent vertigo and vomiting; the presence of head or neck pain should alert the physician to consider cerebellar stroke from vertebral artery dissection. Even small amounts of cerebellar edema can acutely increase intracranial pressure (ICP) or directly compress the brainstem. The resulting brainstem compression can result in coma and respiratory arrest and require emergency surgical decompression. Prophylactic suboccipital decompression of large cerebellar infarcts before brainstem compression, although not tested rigorously in a clinical trial, is practiced at most stroke centers.

INTRAVENOUS THROMBOLYSIS The National Institute of Neurological Disorders and Stroke (NINDS) recombinant tPA (rtPA) Stroke Study showed a clear benefit for IV rtPA in selected patients with acute stroke. The NINDS study used IV rtPA (0.9 mg/kg to a 90-mg max; 10% as a bolus, then the remainder over 60 min) vs. placebo in patients with ischemic stroke within 3 h of onset. Half of the patients were treated within 90 min. Symptomatic intracerebral hemorrhage occurred in 6.4% of patients on rtPA and 0.6% on placebo. There was a nonsignificant 4% reduction in mortality in patients on rtPA (21% on placebo and 17% on rtPA); there was a significant 12% absolute increase in the number of patients with only minimal disability (32% on placebo and 44% on rtPA.) Thus, despite an increased incidence of symptomatic intracerebral hemorrhage, treatment with IV rtPA within 3 h of the onset of ischemic stroke improved clinical outcome.

Results of other trials of rtPA have been negative, perhaps because of the dose of rtPA and timing of its delivery. The European Cooperative Acute Stroke Study (ECASS) I used a higher dose of rtPA (1.2 mg/kg), and ECASS-II tested the NINDS dose of rtPA (0.9 mg/kg; maximum dose, 90 mg) but allowed patients to receive drug up to the sixth hour. No significant benefit was found, but improvement was found in post hoc analyses. ATLANTIS tested the NINDS dosing of rtPA between 3 and 5 h and found no benefit. Because of the marked differences in trial design, including drug and dose used, time to thrombolysis, and severity of stroke, the precise efficacy of IV thrombolytics for acute ischemic stroke remains unclear. The risk of intracranial hemorrhage appears to rise with larger strokes, longer times from onset of symptoms, and higher doses of rtPA administered. The established dose of 0.9 mg/kg administered IV within 3 h of stroke onset appears safe. The ECASS-III trial established efficacy of IV tPA in a 4.5-h window, although with less robust results compared to 3-hour trials. When data from all randomized IV rtPA trails are combined, efficacy is confirmed in the <3-h time window, and efficacy likely extends to 4.5 h. One may be able to select patients beyond the usual time windows who will benefit from thrombolysis using advanced neuroimaging (see neuroimaging section later), but this is currently investigational. The drug is now approved in the United States, Canada, and Europe for acute stroke when given within 3 h from the time the stroke symptoms began, and efforts should be made to give it as early in this 3-h window as possible. The time of stroke onset is defined as the time the patient's symptoms began or the time the patient was last seen as normal. Patients who awaken with stroke have the onset defined as when they went to bed. **Table 21-1** summarizes eligibility criteria and instructions for administration of IV rtPA.

ENDOVASCULAR TECHNIQUES Ischemic stroke from large-vessel intracranial occlusion results in high rates of mortality and morbidity. Occlusions in such large vessels [middle cerebral artery (MCA), internal

TABLE 21-1

ADMINISTRATION OF INTRAVENOUS RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR (rtPA) FOR ACUTE ISCHEMIC STROKE[a]

INDICATION	CONTRAINDICATION
Clinical diagnosis of stroke	Sustained BP >185/110 despite treatment
Onset of symptoms to time of drug administration ≤3 h	Platelets <100,000; HCT <25%; glucose <50 or >400 mg/dL
CT scan showing no hemorrhage or edema of $>^1/_3$ of the MCA territory	Use of heparin within 48 h and prolonged PTT, or elevated INR
Age ≥18 years	Rapidly improving symptoms
Consent by patient or surrogate	Prior stroke or head injury within 3 months; prior intracranial hemorrhage
	Major surgery in preceding 14 days
	Minor stroke symptoms
	Gastrointestinal bleeding in preceding 21 days
	Recent myocardial infarction
	Coma or stupor

Administration of rtPA

Intravenous access with two peripheral IV lines (avoid arterial or central line placement)
Review eligibility for rtPA
Administer 0.9 mg/kg intravenously (maximum 90 mg) IV as 10% of total dose by bolus, followed by remainder of total dose over 1 h
Frequent cuff blood pressure monitoring
No other antithrombotic treatment for 24 h
For decline in neurologic status or uncontrolled blood pressure, stop infusion, give cryoprecipitate, and reimage brain emergently
Avoid urethral catheterization for ≥2 h

[a]See Activase (tissue plasminogen activator) package insert for complete list of contraindications and dosing.
Note: BP, blood pressure; HCT, hematocrit; INR, international normalized ratio; MCA, middle cerebral artery; PTT, partial thromboplastin time.

carotid artery, and the basilar artery] generally involve a large clot volume and often fail to open with IV rtPA alone. Therefore, there is growing interest in using thrombolytics via an intraarterial route to increase the concentration of drug at the clot and minimize systemic bleeding complications. The Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial found benefit for intraarterial pro-urokinase for acute MCA occlusions up to the sixth hour following onset of stroke. Intra-arterial treatment of basilar artery occlusions may also be beneficial for selected patients. Intra-arterial administration of a thrombolytic agent for acute ischemic stroke is not approved by the U.S. Food and Drug Administration (FDA); however, many stroke centers offer this treatment based on these data.

Endovascular mechanical thrombectomy has recently shown promise as an alternative treatment of acute stroke in patients who are ineligible for, or have contraindications to, thrombolytics or in those who have failed to have vascular recanalization with IV thrombolytics (Fig. 21-15). The MERCI (Mechanical Embolus Removal in Cerebral Ischemia) single-arm trial investigated the ability of a novel endovascular thrombectomy device to restore patency of occluded intracranial vessels within 8 h of ischemic stroke symptoms. Recanalization of the target vessel occurred in 48% of treated patients and in 60% following use of adjuvant endovascular methods, and successful recanalization at 90 days correlated well with favorable outcome. Based upon these nonrandomized data, the FDA approved this device for revascularization of occluded vessels in acute ischemic stroke within 8 h of symptom onset. Recent trials have shown that it is safe to use this technique even in patients who have been given IV rtPA yet have failed to recanalize. Such a strategy allows primary stroke centers to administer rtPA to eligible patients, then rapidly refer such patients to comprehensive stroke centers that have endovascular capability.

ANTITHROMBOTIC TREATMENT

Platelet Inhibition Aspirin is the only antiplatelet agent that has been proven effective for the acute treatment of ischemic stroke; there are several antiplatelet agents proven for the secondary prevention of stroke (see later). Two large trials, the International Stroke Trial (IST) and the Chinese Acute Stroke Trial

(CAST), found that the use of aspirin within 48 h of stroke onset reduced both stroke recurrence risk and mortality minimally. Among 19,435 patients in IST, those allocated to aspirin, 300 mg/d, had slightly fewer deaths within 14 days (9.0 vs. 9.4%), significantly fewer recurrent ischemic strokes (2.8 vs. 3.9%), no excess of hemorrhagic strokes (0.9 vs. 0.8%), and a trend toward a reduction in death or dependence at 6 months (61.2 vs. 63.5%). In CAST, 21,106 patients with ischemic stroke received 160 mg/d of aspirin or a placebo for up to 4 weeks. There were very small reductions in the aspirin group in early mortality (3.3 vs. 3.9%), recurrent ischemic strokes (1.6 vs. 2.1%), and dependency at discharge or death (30.5 vs. 31.6%). These trials demonstrate that the use of aspirin in the treatment of acute ischemic stroke is safe and produces a small net benefit. For every 1000 acute strokes treated with aspirin, about 9 deaths or nonfatal stroke recurrences will be prevented in the first few weeks and ~13 fewer patients will be dead or dependent at 6 months.

The glycoprotein IIb/IIIa receptor inhibitor abciximab held promise as an acute treatment, but a recent clinical trial was stopped because of excess intracranial hemorrhage.

Anticoagulation Numerous clinical trials have failed to demonstrate any benefit of anticoagulation in the primary treatment of atherothrombotic cerebral ischemia. Several trials have investigated antiplatelet versus anticoagulant medications given within 12–24 h of the initial event. The U.S. Trial of Organon 10172 in Acute Stroke Treatment (TOAST), an investigational low-molecular-weight heparin, failed to show any benefit over aspirin. Use of SC unfractionated heparin versus aspirin was tested in IST. Heparin given SC afforded no additional benefit over aspirin and increased bleeding rates. Several trials of low-molecular-weight heparins have also shown no consistent benefit in acute ischemic stroke. Furthermore, trials generally have shown an excess risk of brain and systemic hemorrhage with acute anticoagulation. Therefore, trials do not support the use of heparin or other anticoagulants for patients with atherothrombotic stroke.

NEUROPROTECTION Neuroprotection is the concept of providing a treatment that prolongs the brain's tolerance to ischemia. Drugs that block the excitatory amino acid pathways have been shown to protect neurons and glia in animals, but despite multiple clinical trials, they have not yet been proven to be beneficial in humans. Hypothermia is a powerful neuroprotective treatment in patients with cardiac arrest (Chap. 22) and is neuroprotective in animal models of stroke, but it has not been adequately studied in patients with ischemic stroke.

STROKE CENTERS AND REHABILITATION Patient care in comprehensive stroke units followed by rehabilitation services improves neurologic outcomes and reduces mortality. Use of clinical pathways and staff dedicated to the stroke patient can improve care. Stroke teams that provide emergency 24-h evaluation of acute stroke patients for acute medical management and consideration of thrombolysis or endovascular treatments are important.

Proper rehabilitation of the stroke patient includes early physical, occupational, and speech therapy. It is directed toward educating the patient and family about the patient's neurologic deficit, preventing the complications of immobility (e.g., pneumonia, DVT and pulmonary embolism, pressure sores of the skin, and muscle contractures), and providing encouragement and instruction in overcoming the deficit. The goal of rehabilitation is to return the patient to home and to maximize recovery by providing a safe, progressive regimen suited to the individual patient. Additionally, the use of restraint therapy (immobilizing the unaffected side) has been shown to improve hemiparesis following stroke, even years following the stroke, suggesting that physical therapy can recruit unused neural pathways. This finding suggests that the human nervous system is more adaptable than originally thought and has stimulated active research into physical and pharmacologic strategies that can enhance long-term neural recovery.

ETIOLOGY OF ISCHEMIC STROKE

(**Figs.** 21-1 and **21-3** and **Table 21-2**) Although the initial management of acute ischemic stroke often does not depend on the etiology, establishing a cause is essential in reducing the risk of recurrence. Particular focus should be on atrial fibrillation and carotid atherosclerosis, as these etiologies have proved secondary prevention strategies. The clinical presentation and examination findings often establish the cause of stroke or narrow the possibilities to a few. Judicious use of laboratory testing and imaging studies completes the initial evaluation. Nevertheless, nearly 30% of strokes remain unexplained despite extensive evaluation.

Clinical examination should focus on the peripheral and cervical vascular system (carotid auscultation for bruits, blood pressure, and pressure comparison between arms), the heart (dysrhythmia, murmurs), extremities (peripheral emboli), and retina [effects of hypertension and cholesterol emboli (Hollenhorst plaques)]. A complete neurologic examination is performed to localize the site of stroke. An imaging study of the brain is nearly always indicated and is required for patients being considered for thrombolysis; it may be combined with CT- or MRI-based angiography to interrogate the neck and

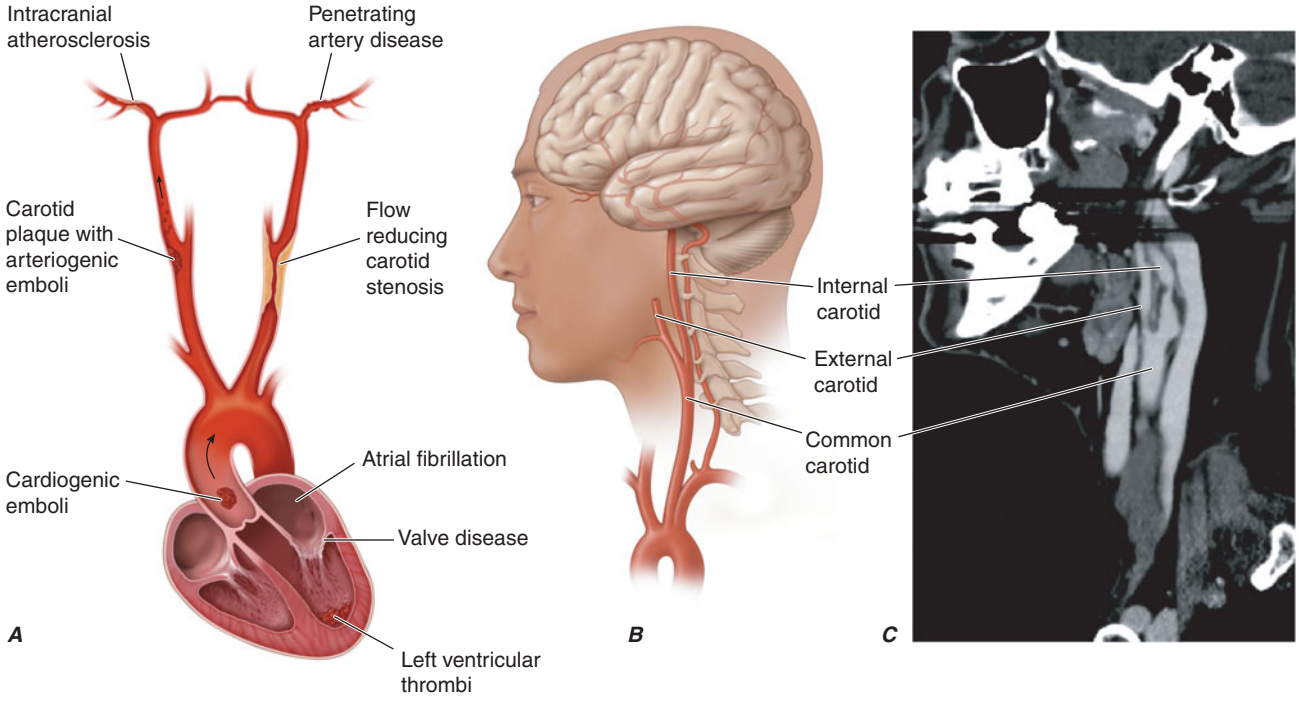

FIGURE 21-3

Pathophysiology of ischemic stroke. ***A.*** Diagram illustrating the three major mechanisms that underlie ischemic stroke: (1) occlusion of an intracranial vessel by an embolus that arises at a distant site (e.g., cardiogenic sources such as atrial fibrillation or artery-to-artery emboli from carotid atherosclerotic plaque), often affecting the large intracranial vessels; (2) in situ thrombosis of an intracranial vessel, typically affecting the small penetrating arteries that arise from the major intracranial arteries; (3) hypoperfusion caused by flow-limiting stenosis of a major extracranial (e.g., internal carotid) or intracranial vessel, often producing "watershed" ischemia. ***B*** and ***C.*** Diagram and reformatted CT angiogram of the common, internal, and external carotid arteries. High-grade stenosis of the internal carotid artery, which may be associated with either cerebral emboli or flow-limiting ischemia, was identified in this patient.

intracranial vessels (see Imaging Studies, later). A chest x-ray, electrocardiogram (ECG), urinalysis, complete blood count, erythrocyte sedimentation rate, serum electrolytes, blood urea nitrogen, creatinine, blood sugar, serologic test for syphilis, serum lipid profile, prothrombin time, and partial thromboplastin time (PTT) are often useful and should be considered in all patients. An ECG may demonstrate arrhythmias or reveal evidence of recent myocardial infarction (MI).

Cardioembolic Stroke

Cardioembolism is responsible for ~20% of all ischemic strokes. Stroke caused by heart disease is primarily due to embolism of thrombotic material forming on the atrial or ventricular wall or the left heart valves. These thrombi then detach and embolize into the arterial circulation. The thrombus may fragment or lyse quickly, producing only a TIA. Alternatively, the arterial occlusion may last longer, producing stroke. Embolic strokes tend to be sudden in onset, with maximum neurologic deficit at once. With reperfusion following more prolonged ischemia, petechial hemorrhage can occur within the ischemic territory. This is usually of no clinical significance and should be distinguished from frank intracranial hemorrhage into a region of ischemic stroke where the mass effect from the hemorrhage can cause a decline in neurologic function.

Emboli from the heart most often lodge in the MCA, the posterior cerebral artery (PCA), or one of their branches; infrequently, the anterior cerebral artery (ACA) territory is involved. Emboli large enough to occlude the stem of the MCA (3–4 mm) lead to large infarcts that involve both deep gray and white matter and some portions of the cortical surface and its underlying white matter. A smaller embolus may occlude a small cortical or penetrating arterial branch. The location and size of an infarct within a vascular territory depend on the extent of the collateral circulation.

The most significant causes of cardioembolic stroke in most of the world are nonrheumatic (often called nonvalvular) atrial fibrillation, MI, prosthetic valves, rheumatic heart disease, and ischemic cardiomyopathy (Table 21-2). Cardiac disorders causing brain embolism are discussed in the respective chapters on heart diseases. A few pertinent aspects are highlighted here.

TABLE 21-2

CAUSES OF ISCHEMIC STROKE

COMMON CAUSES	UNCOMMON CAUSES
Thrombosis	Hypercoagulable disorders
Lacunar stroke (small vessel)	Protein C deficiency
Large vessel thrombosis	Protein S deficiency
Dehydration	Antithrombin III deficiency
Embolic occlusion	Antiphospholipid syndrome
Artery-to-artery	Factor V Leiden mutation[a]
Carotid bifurcation	Prothrombin G20210 mutation[a]
Aortic arch	Systemic malignancy
Arterial dissection	Sickle cell anemia
Cardioembolic	β-Thalassemia
Atrial fibrillation	Polycythemia vera
Mural thrombus	Systemic lupus erythematosus
Myocardial infarction	Homocysteinemia
Dilated cardiomyopathy	Thrombotic thrombocytopenic purpura
Valvular lesions	Disseminated intravascular coagulation
Mitral stenosis	Dysproteinemias
Mechanical valve	Nephrotic syndrome
Bacterial endocarditis	Inflammatory bowel disease
Paradoxical embolus	Oral contraceptives
Atrial septal defect	Venous sinous thrombosis[b]
Patent foramen ovale	Fibromuscular dysplasia
Atrial septal aneurysm	Vasculitis
Spontaneous echo contrast	Systemic vasculitis (PAN, Wegener's, Takayasu's, giant cell arteritis)
	Primary CNS vasculitis
	Meningitis (syphilis, tuberculosis, fungal, bacterial, zoster)
	Cardiogenic
	Mitral valve calcification
	Atrial myxoma
	Intracardiac tumor
	Marantic endocarditis
	Libman-Sacks endocarditis
	Subarachnoid hemorrhage vasospasm
	Drugs: cocaine, amphetamine
	Moyamoya disease
	Eclampsia

[a]Chiefly cause venous sinus thrombosis.
[b]May be associated with any hypercoagulable disorder.
Note: CNS, central nervous system; PAN, polyarteritis nodosa.

Nonrheumatic atrial fibrillation is the most common cause of cerebral embolism overall. The presumed stroke mechanism is thrombus formation in the fibrillating atrium or atrial appendage, with subsequent embolization. Patients with atrial fibrillation have an average annual risk of stroke of ~5%. The risk varies according to the presence of certain risk factors, including older age, hypertension, poor left ventricular function, prior cardioembolism, mitral stenosis, prosthetic heart valve, or diabetes. Patients <65 years with none of these risk factors have an annual risk for stroke of ~0.5%, while those with most of the factors have a rate of ~15% per year. Left atrial enlargement and congestive heart failure are additional risk factors for formation of atrial thrombi. Rheumatic heart disease usually causes ischemic stroke when there is prominent mitral stenosis or atrial fibrillation. Guidelines for the use of warfarin and aspirin for secondary prevention are based on risk factors (**Table 21-3**).

Recent MI may be a source of emboli, especially when transmural and involving the anteroapical ventricular wall, and prophylactic anticoagulation following MI has been shown to reduce stroke risk. Mitral valve prolapse is not usually a source of emboli unless the prolapse is severe.

Paradoxical embolization occurs when venous thrombi migrate to the arterial circulation, usually via a patent

TABLE 21-3

CONSENSUS RECOMMENDATION FOR ANTITHROMBOTIC PROPHYLAXIS IN ATRIAL FIBRILLATION

AGE	RISK FACTORS[a]	RECOMMENDATION
≤65 years	≥1	Warfarin INR 2–3
	0	Aspirin
65–75 years	≥1	Warfarin INR 2–3
	0	Warfarin INR 2–3 or aspirin
>75 years		Warfarin INR 2–3

[a]Risk factors include previous transient ischemic attack or stroke, hypertension, heart failure, diabetes, systemic embolism, mitral stenosis, or prosthetic heart valve.

Source: Modified from DE Singer et al: Antithrombotic therapy in atrial fibrillation. Chest 126:429S, 2004; with permission.

foramen ovale or atrial septal defect. Bubble-contrast echocardiography (IV injection of agitated saline coupled with either transthoracic or transesophageal echocardiography) can demonstrate a right-to-left cardiac shunt, revealing the conduit for paradoxical embolization. Alternatively, a right-to-left shunt is implied if immediately following IV injection of agitated saline, the ultrasound signature of bubbles is observed during transcranial Doppler insonation of the MCA; pulmonary AVMs should be considered if this test is positive yet an echocardiogram fails to reveal an intracardiac shunt. Both techniques are highly sensitive for detection of right-to-left shunts. Besides venous clot, fat and tumor emboli, bacterial endocarditis, IV air, and amniotic fluid emboli at childbirth may occasionally be responsible for paradoxical embolization. The importance of right-to-left shunt as a cause of stroke is debated, particularly because such shunts are present in ~15% of the general population. Some studies have suggested that the risk is only elevated in the presence of a coexisting atrial septal aneurysm. The presence of a venous source of embolus, most commonly a deep venous thrombus, may provide confirmation of the importance of a right-to-left shunt in a particular case.

Bacterial endocarditis can cause valvular vegetations that can give rise to septic emboli. The appearance of multifocal symptoms and signs in a patient with stroke makes bacterial endocarditis more likely. Infarcts of microscopic size occur, and large septic infarcts may evolve into brain abscesses or cause hemorrhage into the infarct, which generally precludes use of anticoagulation or thrombolytics. Mycotic aneurysms caused by septic emboli give rise to SAH or intracerebral hemorrhage.

Artery-to-Artery Embolic Stroke

Thrombus formation on atherosclerotic plaques may embolize to intracranial arteries producing an artery-to-artery embolic stroke. Alternatively, a diseased vessel may acutely thrombose; the resulting blockage causes stroke by producing ischemia within the region of brain it supplied. Unlike the myocardial vessels, artery-to-artery embolism, rather than local thrombosis, appears to be the dominant vascular mechanism causing ischemia. Any diseased vessel may be a source, including the aortic arch, common carotid, internal carotid, vertebral, and basilar arteries. Carotid bifurcation atherosclerosis is the most common source of artery-to-artery embolus, and specific treatments have proven efficacy in reducing risk.

Carotid Atherosclerosis

Atherosclerosis within the carotid artery occurs most frequently within the common carotid bifurcation and proximal internal carotid artery. Additionally, the carotid siphon (portion within the cavernous sinus) is also vulnerable to atherosclerosis. Male gender, older age, smoking, hypertension, diabetes, and hypercholesterolemia are risk factors for carotid disease, as they are for stroke in general (**Table 21-4**). Carotid atherosclerosis produces an estimated 10% of ischemic stroke.

Carotid disease can be classified by whether the stenosis is symptomatic or asymptomatic and by the degree of stenosis (percent narrowing of the narrowest segment compared to a more distal internal carotid segment). Symptomatic carotid disease implies that the patient has experienced a stroke or TIA within the vascular distribution of the artery, and it is associated with a greater risk of subsequent stroke than asymptomatic stenosis, in which the patient is symptom free and the stenosis is detected through screening. Greater degrees of arterial narrowing are generally associated with a greater risk of stroke, except that those with near occlusions are at lower risk of stroke.

℞ Treatment: CAROTID ATHEROSCLEROSIS

Carotid atherosclerosis can be removed surgically (endarterectomy) or mitigated with endovascular stenting with or without balloon angioplasty.

SURGICAL THERAPY *Symptomatic carotid stenosis* was studied in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST). Both showed a substantial benefit for surgery in patients with a stenosis of ≥70%. In NASCET, the average cumulative ipsilateral stroke risk at 2 years was 26% for patients treated medically and 9% for those receiving the same medical treatment plus a carotid endarterectomy. This 17% *absolute* reduction in the surgical group is a 65% *relative* risk reduction favoring surgery (Table 21-4). NASCET also showed a significant, although less robust, benefit for

TABLE 21-4

RISK FACTORS FOR STROKE

RISK FACTOR	RELATIVE RISK	RELATIVE RISK REDUCTION WITH TREATMENT	NUMBER NEEDED TO TREAT[a]	
			PRIMARY PREVENTION	SECONDARY PREVENTION
Hypertension	2–5	38%	100–300	50–100
Atrial fibrillation	1.8–2.9	68% warfarin, 21% aspirin	20–83	13
Diabetes	1.8–6	No proven effect		
Smoking	1.8	50% at 1 year, baseline risk at 5 years post cessation		
Hyperlipidemia	1.8–2.6	16–30%	560	230
Asymptomatic carotid stenosis	2.0	53%	85	N/A
Symptomatic carotid stenosis (70–99%)		65% at 2 years	N/A	12
Symptomatic carotid stenosis (50–69%)		29% at 5 years	N/A	77

[a]Number needed to treat to prevent one stroke annually. Prevention of other cardiovascular outcomes is not considered here.
Note: N/A, not applicable.

patients with 50–70% stenosis. ECST found harm for patients with stenosis <30% treated surgically.

A patient's risk of stroke and possible benefit from surgery are related to the presence of retinal versus hemispheric symptoms, degree of arterial stenosis, extent of associated medical conditions (of note, NASCET and ECST excluded "high-risk" patients with significant cardiac, pulmonary, or renal disease), institutional surgical morbidity and mortality, timing of surgery relative to symptoms, and other factors. A recent meta-analysis of the NASCET and ECST trials demonstrated that endarterectomy is most beneficial when performed within 2 weeks of symptom onset. In addition, benefit is more pronounced in patients >75 years, and men appear to benefit more than women.

In summary, a patient with recent symptomatic hemispheric ischemia, high-grade stenosis in the appropriate internal carotid artery, and an institutional perioperative morbidity and mortality rate of ≤6% generally should undergo carotid endarterectomy. If the perioperative stroke rate is >6% for any particular surgeon, however, the benefits of carotid endarterectomy are questionable.

The indications for surgical treatment of *asymptomatic carotid disease* have been clarified by the results of the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST). ACAS randomized asymptomatic patients with ≥60% stenosis to medical treatment with aspirin or the same medical treatment plus carotid endarterectomy. The surgical group had a risk over 5 years for ipsilateral stroke (and any perioperative stroke or death) of 5.1%, compared to a risk in the medical group of 11%. While this demonstrates a 53% *relative* risk reduction, the *absolute* risk reduction is only 5.9% over 5 years, or 1.2% annually (Table 21-4). Nearly half of the strokes in the surgery group were caused by preoperative angiograms. The recently published ACST randomized 3120 asymptomatic patients with >60% carotid stenosis to endarterectomy or medical therapy. The 5-year risk of stroke in the surgical group (including perioperative stroke or death) was 6.4%, in comparison with 11.8% in the medically treated group (46% relative risk reduction and 5.4% absolute risk reduction).

In both ACAS and ACST, the perioperative complication rate was higher in women, perhaps negating any benefit in the reduction of stroke risk within 5 years. It is possible that with longer follow-up, a clear benefit in women will emerge. At present, carotid endarterectomy in asymptomatic women remains particularly controversial.

In summary, the natural history of asymptomatic stenosis is a ~2% per year stroke rate, while symptomatic patients experience a 13% per year risk of stroke. Whether to recommend carotid revascularization for an asymptomatic patient is somewhat controversial and depends on many factors, including patient preference, degree of stenosis, age, gender, and comorbidities. Medical therapy for reduction of atherosclerosis risk factors, including cholesterol-lowering agents and antiplatelet medications, is generally recommended for patients with asymptomatic carotid stenosis. As with atrial fibrillation, it is imperative to counsel the patient about TIAs so that therapy can be revised if symptoms develop.

ENDOVASCULAR THERAPY Balloon angioplasty coupled with stenting is being used with increasing frequency to open stenotic carotid arteries and maintain

their patency. These techniques can treat carotid stenosis not only at the bifurcation but also near the skull base and in the intracranial segments. The SAPPHIRE trial (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) randomized high-risk patients (defined as patients with clinically significant coronary or pulmonary disease, contralateral carotid occlusion, restenosis after endarterectomy, contralateral laryngeal-nerve palsy, prior radical neck surgery or radiation, or age >80) with symptomatic carotid stenosis >50% or asymptomatic stenosis >80% to either stenting combined with a distal embolic-protection device or endarterectomy. The risk of death, stroke, or MI within 30 days and ipsilateral stroke or death within 1 year was 12.2% in the stenting group and 20.1% in the endarterectomy group (p = .055), suggesting that stenting is at the very least comparable to endarterectomy as a treatment option for this patient group at high risk of surgery. However, the outcomes with both interventions may not have been better than leaving the carotid stenoses untreated, particularly for the asymptomatic patients, and much of the benefit seen in the stenting group was due to a reduction in peri-procedure MI. Multicenter trials are currently underway comparing stenting with endarterectomy in lower-risk patients, the population previously studied in the NASCET, ECST, ACAS, and ACST trials (see above).

BYPASS SURGERY Extracranial-to-intracranial (EC-IC) bypass surgery has been proven ineffective for atherosclerotic stenoses that are inaccessible to conven-tional carotid endarterectomy. However, a trial is underway to evaluate whether patients with decreased brain perfusion based on positron emission tomography (PET) imaging will benefit from EC-IC bypass.

Other Causes of Artery-to-Artery Embolic Stroke

Intracranial atherosclerosis produces stroke either by an embolic mechanism or by in situ thrombosis of a diseased vessel. It is more common in patients of Asian and African-American descent. The WASID (Warfarin-Aspirin Symptomatic Intracranial Disease) trial randomized patients with symptomatic stenosis (50–99%) of a major intracranial vessel to either high-dose aspirin (1300 mg/d) or warfarin (target INR, 2.0–3.0), with a combined primary endpoint of ischemic stroke, brain hemorrhage, or death from vascular cause other than stroke. The trial was terminated early because of an increased risk of adverse events related to warfarin anticoagulation. With a mean follow-up of 1.8 years, the primary endpoint was seen in 22.1% in the aspirin group and 21.8% of the warfarin group. Death from any cause was seen in 4.3% of the aspirin group and 9.7% of the warfarin group; 3.2% of patients on aspirin experienced major hemorrhage, compared to 8.3% of patients taking warfarin.

Given the worrisome natural history of symptomatic intracranial atherosclerosis (in the aspirin arm of the WASID trial, 15% of patients experienced a stroke within the first year, despite current standard aggressive medical therapy), some centers treat symptomatic lesions with intracranial angioplasty and stenting. This intervention has not been compared with medical therapy for stroke prevention in this patient population, but such clinical trials will likely be conducted in the near future. Likewise, it is unclear whether EC-IC bypass, or other grafting procedures of extracranial blood supply to the pial arteries, is of value in such patients.

Dissection of the internal carotid or vertebral arteries or even vessels beyond the circle of Willis is a common source of embolic stroke in young (<60 years) patients. The dissection is usually painful and precedes the stroke by several hours or days. Extracranial dissections do not cause hemorrhage because of the tough adventitia of these vessels. Intracranial dissections, on the other hand, may produce SAH because the adventitia of intracranial vessels is thin and pseudoaneurysms may form, requiring treatment to prevent rerupture. Treating asymptomatic pseudoaneurysms following dissection is controversial. The cause of dissection is usually unknown and recurrence is rare. Ehlers-Danlos type IV, Marfan's disease, cystic medial necrosis, and fibromuscular dysplasia are associated with dissections. Trauma (usually a motor vehicle accident or a sports injury) can cause carotid and vertebral artery dissections. Spinal manipulative therapy is independently associated with vertebral artery dissection and stroke. Most dissections heal spontaneously, and stroke or TIA is uncommon beyond 2 weeks. Although there are no trials comparing anticoagulation to antiplatelet agents, many physicians treat acutely with anticoagulants for 3–6 months then convert to 6–9 months of antiplatelet therapy after demonstration of vascular recanalization; a recent observational study questioned the superiority of anticoagulants versus antiplatelets in carotid dissection.

Small-Vessel Stroke

The term *lacunar infarction* refers to infarction following atherothrombotic or lipohyalinotic occlusion of a small artery (30–300 μm) in the brain. The term *small-vessel stroke* denotes occlusion of such a small penetrating artery and is now the preferred term. Small-vessel strokes account for ~20% of all strokes.

Pathophysiology

The MCA stem, the arteries comprising the circle of Willis (A1 segment, anterior and posterior communicating arteries, and P1 segment), and the basilar and vertebral arteries all give rise to 30- to 300-μm branches that

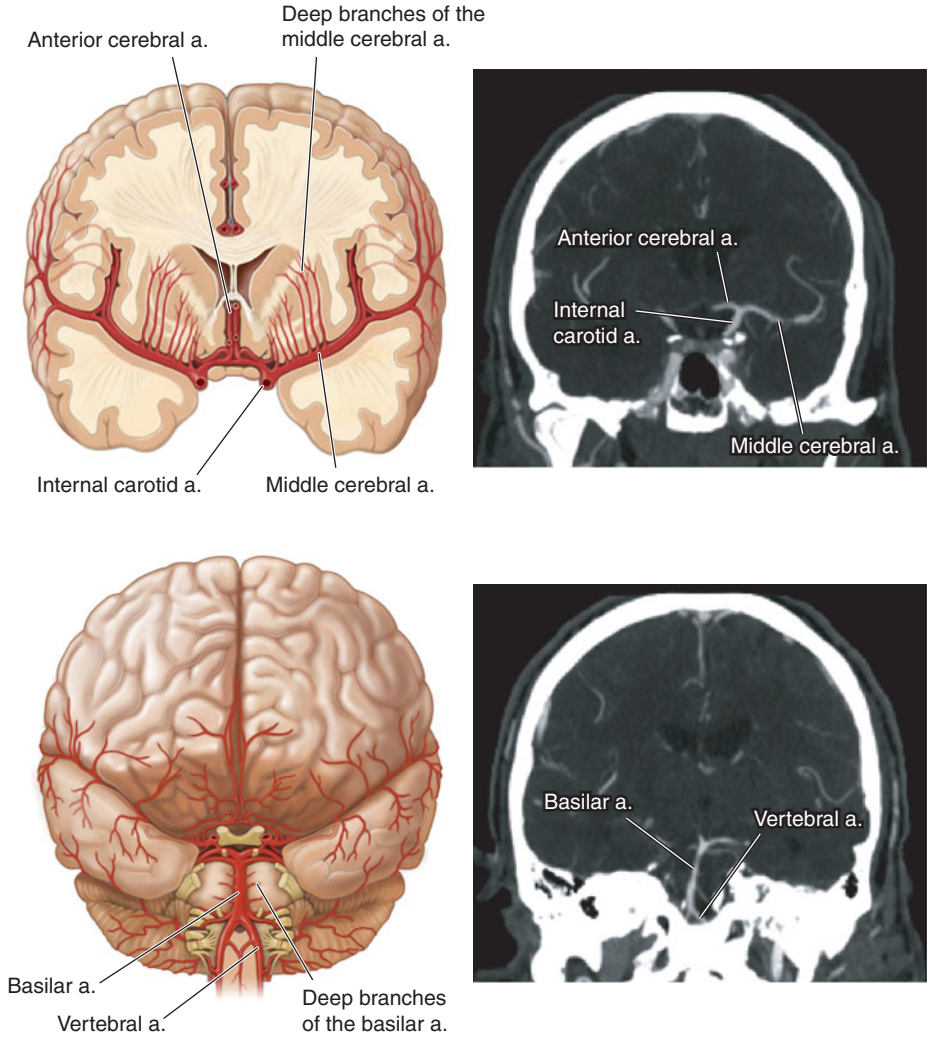

FIGURE 21-4

Diagrams and reformatted CT angiograms in the coronal section illustrating the deep penetrating arteries involved in small-vessel strokes. In the anterior circulation, small penetrating arteries called lenticulostriates arise from the proximal portion of the anterior and middle cerebral arteries and supply deep subcortical structures (***upper panels***). In the posterior circulation, similar arteries arise directly from the vertebral and basilar arteries to supply the brainstem (***lower panels***). Occlusion of a single penetrating artery gives rise to a discrete area of infarct (pathologically termed a "lacune," or lake). Note that these vessels are too small to be visualized on CT angiography.

penetrate the deep gray and white matter of the cerebrum or brainstem (Fig. 21-4). Each of these small branches can occlude either by atherothrombotic disease at its origin or by the development of lipohyalinotic thickening. Thrombosis of these vessels causes small infarcts that are referred to as *lacunes* (Latin for "lake" of fluid noted at autopsy). These infarcts range in size from 3 mm to 2 cm in diameter. Hypertension and age are the principal risk factors.

Clinical Manifestations

The most common *lacunar syndromes* are the following: (1) *Pure motor hemiparesis* from an infarct in the posterior limb of the internal capsule or basis pontis; the face, arm, and leg are almost always involved; (2) *pure sensory stroke* from an infarct in the ventral thalamus; (3) *ataxic hemiparesis* from an infarct in the ventral pons or internal capsule; (4) and *dysarthria and a clumsy hand* or arm due to infarction in the ventral pons or in the genu of the internal capsule.

Transient symptoms (small vessel TIAs) may herald a small-vessel infarct; they may occur several times a day and last only a few minutes. Recovery from small-vessel strokes tends to be more rapid and complete than recovery from large-vessel strokes; in some cases, however, there is severe permanent disability. Often, institution of combined antithrombotic treatments does not prevent eventual stroke in "stuttering lacunes."

A large-vessel source (either thrombosis or embolism) may manifest initially as a lacunar syndrome with

small-vessel infarction. Therefore, the search for embolic sources (carotid and heart) should not be completely abandoned in the evaluation of these patients. Secondary prevention of lacunar stroke involves risk factor modification, specifically reduction in blood pressure (see Primary and Secondary Prevention, later).

LESS COMMON CAUSES OF STROKE

(Table 21-2) *Hypercoagulable disorders* primarily cause increased risk of venous thrombosis and therefore may cause venous sinus thrombosis. Protein S deficiency and homocysteinemia may cause arterial thromboses as well. Systemic lupus erythematosus with Libman-Sacks endocarditis can be a cause of embolic stroke. These conditions overlap with the antiphospholipid syndrome, which probably requires long-term anticoagulation to prevent further stroke.

Venous sinus thrombosis of the lateral or sagittal sinus or of small cortical veins (cortical vein thrombosis) occurs as a complication of oral contraceptive use, pregnancy and the postpartum period, inflammatory bowel disease, intracranial infections (meningitis), and dehydration. It is also seen with increased incidence in patients with laboratory-confirmed thrombophilia (Table 21-2) including polycythemia, sickle cell anemia, deficiencies of proteins C and S, factor V Leiden mutation (resistance to activated protein C), antithrombin III deficiency, homocysteinemia, and the prothrombin G20210 mutation. Women who take oral contraceptives and have the prothrombin G20210 mutation may be at particularly high risk for sinus thrombosis. Patients present with headache and may also have focal neurologic signs (especially paraparesis) and seizures. Often, CT imaging is normal unless an intracranial venous hemorrhage has occurred, but the venous sinus occlusion is readily visualized using magnetic resonance (MR) venography or conventional x-ray angiography. With greater degrees of sinus thrombosis, the patient may develop signs of increased ICP and coma. Intravenous heparin, regardless of the presence of intracranial hemorrhage, has been shown to reduce morbidity and mortality, and the long-term outcome is generally good. Heparin prevents further thrombosis and reduces venous hypertension and ischemia. If an underlying hypercoagulable state is not found, many physicians treat with warfarin sodium for 3–6 months then convert to aspirin, depending on the degree of resolution of the venous sinus thrombus. Anticoagulation is often continued indefinitely if thrombophilia is diagnosed.

Sickle cell anemia (SS disease) is a common cause of stroke in children. A subset of homozygous carriers of this hemoglobin mutation develop stroke in childhood and this may be predicted by documenting high-velocity blood flow within the MCAs using transcranial Doppler ultrasonography. In children who are identified to have high velocities, treatment with aggressive exchange transfusion dramatically reduces risk of stroke, and if exchange transfusion is ceased, their stroke rate increases again along with MCA velocities.

Fibromuscular dysplasia affects the cervical arteries and occurs mainly in women. The carotid or vertebral arteries show multiple rings of segmental narrowing alternating with dilatation. Occlusion is usually incomplete. The process is often asymptomatic but occasionally is associated with an audible bruit, TIAs, or stroke. Involvement of the renal arteries is common and may result in hypertension. The cause and natural history of fibromuscular dysplasia are unknown. TIA or stroke generally occurs only when the artery is severely narrowed or dissects. Anticoagulation or antiplatelet therapy may be helpful.

Temporal (giant cell) arteritis is a relatively common affliction of elderly persons in which the external carotid system, particularly the temporal arteries, becomes the site of a subacute granulomatous inflammation with giant cells. Occlusion of posterior ciliary arteries derived from the ophthalmic artery results in blindness in one or both eyes and can be prevented with glucocorticoids. It rarely causes stroke as the internal carotid artery is usually not inflamed. Idiopathic giant cell arteritis involving the great vessels arising from the aortic arch (*Takayasu's arteritis*) may cause carotid or vertebral thrombosis; it is rare in the western hemisphere.

Necrotizing (or granulomatous) arteritis, occurring alone or in association with generalized polyarteritis nodosa or Wegener's granulomatosis, involves the distal small branches (<2 mm diameter) of the main intracranial arteries and produces small ischemic infarcts in the brain, optic nerve, and spinal cord. The cerebrospinal fluid (CSF) often shows pleocytosis, and the protein level is elevated. *Primary central nervous system vasculitis* is rare; small or medium-sized vessels are usually affected, without apparent systemic vasculitis. Brain biopsy or high-resolution conventional x-ray angiography is usually required to make the diagnosis (**Fig. 21-5**). The differential diagnosis includes infection (tubercular, fungal), atherosclerosis, emboli, connective tissue disease, sarcoidosis, angiocentric lymphoma, carcinomatous meningitis, vasospasm, and drug-associated causes. Some cases follow the postpartum period and are self-limited. Patients with any form of vasculitis may present with insidious progression of combined white and gray matter infarctions, prominent headache, and cognitive decline. Aggressive immunosuppression with glucocorticoids, and often cyclophosphamide, is usually necessary to prevent progression; a diligent investigation for infectious causes such as tuberculosis is essential prior to immunosuppression. Depending upon the duration of the disease, many patients can make an excellent recovery.

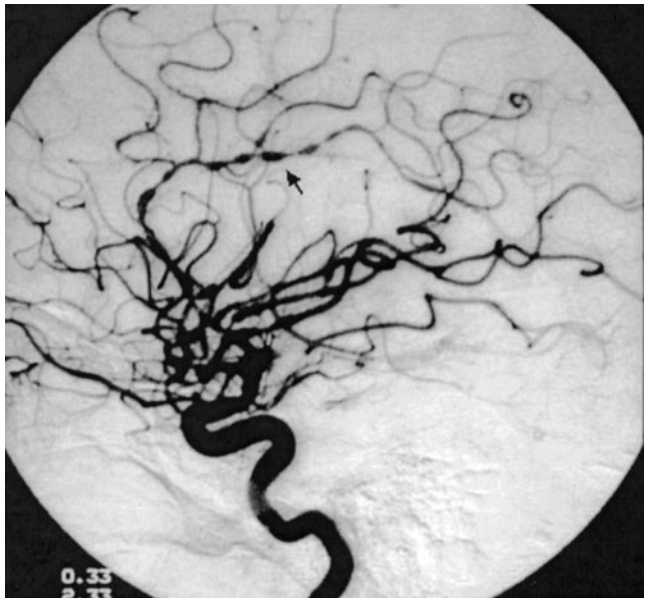

FIGURE 21-5
Cerebral angiogram from a 32-year-old male with central nervous system vasculitis. Dramatic beading (*arrow*) typical of vasculitis is seen.

Drugs, in particular amphetamines and perhaps cocaine, may cause stroke on the basis of acute hypertension or drug-induced vasculitis. Abstinence appears to be the best treatment, as no data exist on use of any treatment. Phenylpropanolamine has been linked with intracranial hemorrhage, as has cocaine, perhaps related to a drug-induced vasculitis. Arteritis can also occur as a consequence of bacterial, tuberculous, and syphilitic meningitis.

Moyamoya disease is a poorly understood occlusive disease involving large intracranial arteries, especially the distal internal carotid artery and the stem of the MCA and ACA. Vascular inflammation is absent. The lenticulostriate arteries develop a rich collateral circulation around the occlusive lesion, which gives the impression of a "puff of smoke" (*moyamoya* in Japanese) on conventional x-ray angiography. Other collaterals include transdural anastomoses between the cortical surface branches of the meningeal and scalp arteries. The disease occurs mainly in Asian children or young adults, but the appearance may be identical in adults who have atherosclerosis, particularly in association with diabetes. The etiology of the childhood form is unknown. Because of the occurrence of intracranial hemorrhage from rupture of the transdural and pial anastomotic channels, anticoagulation is risky. Breakdown of dilated lenticulostriate arteries may produce parenchymal hemorrhage, and progressive occlusion of large surface arteries can occur, producing large-artery distribution strokes. Bypass of extracranial carotid arteries to the dura or MCAs may prevent stroke and hemorrhage.

Reversible posterior leukoencephalopathy can occur in head injury, migraine, sympathomimetic drug use, eclampsia, and the postpartum period. The etiology is unclear but likely involves widespread cerebral segmental vasoconstriction and cerebral edema. Patients complain of headache and manifest fluctuating neurologic symptoms and signs, especially visual symptoms. Sometimes cerebral infarction ensues, but typically the clinical and imaging findings suggest that ischemia reverses completely. Conventional x-ray angiography is the only means of establishing the diagnosis, but MRI findings are characteristic.

Leukoariosis, or *periventricular white matter disease,* is the result of multiple small-vessel infarcts within the subcortical white matter. It is readily seen on CT or MRI scans as areas of white matter injury surrounding the ventricles and within the corona radiata. Areas of lacunar infarction are often seen also. The pathophysiologic basis of the disease is lipohyalinosis of small penetrating arteries within the white matter, likely produced by chronic hypertension. Patients with periventricular white matter disease may develop a subcortical dementia syndrome, depending on the amount of white matter infarction.

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is an inherited disorder that presents as small-vessel strokes, progressive dementia, and extensive symmetric white matter changes visualized by MRI. Approximately 40% of patients have migraine with aura, often manifest as transient motor or sensory deficits. Onset is usually in the fourth or fifth decade of life. This autosomal dominant condition is caused by one of several mutations in Notch-3, a member of a highly conserved gene family characterized by epidermal growth factor repeats in its extracellular domain. Other monogenic ischemic stroke syndromes include cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) and hereditary endotheliopathy, retinopathy, nephropathy, and stroke (HERNS). Fabry's disease also produces both large-vessel arteriopathy and small-vessel infarcts by an unknown mechanism.

TRANSIENT ISCHEMIC ATTACKS

TIAs are episodes of stroke symptoms that last only briefly; the standard definition of duration is <24 h, but most TIAs last <1 h. The causes of TIA are similar to the causes of ischemic stroke, but because TIAs may herald stroke they are an important risk factor that should be considered separately. TIAs may arise from emboli to the brain or from in situ thrombosis of an intracranial vessel. With a TIA, the occluded blood vessel reopens and neurologic function is restored. However, infarcts of the brain do occur in 15–50% of TIAs even though neurologic signs and symptoms are absent. Newer definitions

of TIA categorize those with new infarct as having ischemic stroke rather than TIA regardless of symptom duration, but the vast majority of studies have used the standard, time-based definition.

In addition to the stroke syndromes discussed later, one specific TIA symptom should receive special notice. *Amaurosis fugax*, or transient monocular blindness, occurs from emboli to the central retinal artery of one eye. This may indicate carotid stenosis as the cause or local ophthalmic artery disease.

The risk of stroke after a TIA is ~10–15% in the first 3 months, with most events occurring in the first 2 days. Therefore, urgent evaluation and treatment are justified. Since etiologies for stroke and TIA are identical, evaluation for TIA should parallel that of stroke (Figs. 21-1 and 21-3). The improvement characteristic of TIA is a contraindication to thrombolysis. However, since the risk of subsequent stroke in the first few days after a TIA is high, the opportunity to give rtPA more frequently and rapidly if a stroke occurs probably justifies hospital admission for most patients. Acute antiplatelet therapy has not been tested specifically after TIA but is likely to be effective and is recommended. No large-scale trial has evaluated acute anticoagulation after TIA, a setting in which the risk of hemorrhage may be lower than for other categories of stroke.

RISK FACTORS FOR ISCHEMIC STROKE AND TIA

Identification and control of modifiable risk factors is the best strategy to reduce the burden of stroke, and the total number of strokes could be reduced substantially by these means (Table 21-4).

PRIMARY AND SECONDARY PREVENTION OF STROKE AND TIA

General Principles

A number of medical and surgical interventions, as well as lifestyle modifications, are available for preventing stroke. Some of these can be widely applied because of their low cost and minimal risk; others are expensive and carry substantial risk but may be valuable for selected high-risk patients.

Evaluation of a patient's *clinical risk profile* can help determine which preventive treatments to offer. In addition to known risk factors for ischemic stroke (above), certain clinical characteristics also contribute to an increased risk of stroke (Table 21-4).

Atherosclerosis Risk Factors

There are a number of factors that are associated with the risk of atherosclerosis. Older age, family history of thrombotic stroke, diabetes mellitus, hypertension, tobacco smoking, abnormal blood cholesterol [particularly, low high-density lipoprotein (HDL) and/or high low-density lipoprotein (LDL)], and other factors are either proven or probable risk factors for ischemic stroke, largely by their link to atherosclerosis. Risk of stroke is much greater in those with prior stroke or TIA. Many cardiac conditions predispose to stroke, including atrial fibrillation and recent MI. Oral contraceptives and hormone replacement therapy increase stroke risk, and certain inherited and acquired hypercoagulable states predispose to stroke. Hypertension is the most significant of the risk factors; in general, all hypertension should be treated. The presence of known cerebrovascular disease is not a contraindication to treatment aimed at achieving normotension. Also, the value of treating systolic hypertension in older patients has been clearly established. Lowering blood pressure to levels below those traditionally defining hypertension appears to reduce the risk of stroke even further. Data are particularly strong in support of thiazide diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.

Several trials have confirmed that statin drugs reduce the risk of stroke even in patients without elevated LDL or low HDL. The recently reported SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial showed benefit in secondary stroke reduction for patients with recent stroke or TIA who were prescribed atorvastatin, 80 mg/d. Although studies specifically targeting primary prevention of stroke are still underway, results for patients with cardiovascular risk factors or dyslipidemia have been compelling, with a 16–30% relative risk reduction for stroke. Therefore, a statin should be considered in all patients with prior ischemic stroke. Tobacco smoking should be discouraged in all patients. Whether tight control of blood sugar in patients with diabetes lowers stroke risk is uncertain, but statins, more aggressive blood pressure control, and pioglitazone (an agonist of peroxisome proliferator-activated receptor gamma) are effective.

Antiplatelet Agents

Platelet antiaggregation agents can prevent atherothrombotic events, including TIA and stroke, by inhibiting the formation of intraarterial platelet aggregates. These can form on diseased arteries, induce thrombus formation, and occlude the artery or embolize into the distal circulation. Aspirin, clopidogrel, and the combination of aspirin plus extended-release dipyridamole are the antiplatelet agents most commonly used for this purpose. Ticlopidine has been largely abandoned because of its adverse effects.

Aspirin is the most widely studied antiplatelet agent. Aspirin acetylates platelet cyclooxygenase, which

irreversibly inhibits the formation in platelets of thromboxane A_2, a platelet aggregating and vasoconstricting prostaglandin. This effect is permanent and lasts for the usual 8-day life of the platelet. Paradoxically, aspirin also inhibits the formation in endothelial cells of prostacyclin, an antiaggregating and vasodilating prostaglandin. This effect is transient. As soon as aspirin is cleared from the blood, the nucleated endothelial cells again produce prostacyclin. Aspirin in low doses given once daily inhibits the production of thromboxane A_2 in platelets without substantially inhibiting prostacyclin formation. Higher doses of aspirin have not been proven to be more effective than lower doses, and 50–325 mg/d of aspirin is generally recommended for stroke prevention.

Ticlopidine and clopidogrel block the ADP receptor on platelets and thus prevent the cascade resulting in activation of the glycoprotein IIb/IIIa receptor that leads to fibrinogen binding to the platelet and consequent platelet aggregation. Ticlopidine is more effective than aspirin; however, it has the disadvantage of causing diarrhea, skin rash, and, in rare instances, neutropenia and thrombotic thrombocytopenic purpura. Clopidogrel is not associated with these important side effects. However, the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial, which led to FDA approval, found that it was only marginally more effective than aspirin in reducing risk of stroke. The MATCH (Management of Atherothrombosis with Clopidogrel in High-Risk Patients) trial was a large multicenter, randomized double-blind study that compared clopidogrel in combination with aspirin to clopidogrel alone in the secondary prevention of TIA or stroke. The MATCH trial found no difference in TIA or stroke prevention with this combination, but did show a small but significant increase in major bleeding complications (3% vs. 1%). In the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial, which included a subgroup of patients with prior stroke or TIA along with other groups at high risk of cardiovascular events, there was no benefit of clopidogrel combined with aspirin compared to aspirin alone. Thus, the use of clopidogrel in combination with aspirin is not generally recommended for stroke prevention. However, these trials did not enroll patients immediately after the stroke or TIA, and the benefits of combination therapy were greater among those treated earlier, so it is possible that clopidogrel combined with aspirin may be beneficial in this acute period. Ongoing studies are currently addressing this question.

Dipyridamole is an antiplatelet agent that inhibits the uptake of adenosine by a variety of cells, including those of the vascular endothelium. The accumulated adenosine is an inhibitor of aggregation. At least in part through its effects on platelet and vessel wall phosphodiesterases, dipyridamole also potentiates the antiaggregatory effects of prostacyclin and nitric oxide produced by the endothelium and acts by inhibiting platelet phosphodiesterase, which is responsible for the breakdown of cyclic AMP. The resulting elevation in cyclic AMP inhibits aggregation of platelets. Dipyridamole is erratically absorbed depending on stomach pH, but a newer formulation combines timed-release dipyridamole, 200 mg, with aspirin, 25 mg, and has better oral bioavailability. This combination drug was studied in two trials. The European Stroke Prevention Study (ESPS) II showed efficacy of both 50 mg/d of aspirin and extended-release dipyridamole in preventing stroke, and a significantly better risk reduction when the two agents were combined. The ESPRIT (European/Australasian Stroke Prevention in Reversible Ischaemia Trial) trial confirmed the ESPS-II results. This was an open-label, academic trial in which 2739 patients with stroke or TIA treated with aspirin were randomized to dipyridamole, 200 mg twice daily, or no dipyridamole. Primary outcome was the composite of death from all vascular causes, non-fatal stroke, non-fatal MI, or major bleeding complication. After 3.5 years of follow-up, 13% patients on aspirin and dipyridamole and 16% on aspirin alone (hazard ratio 0.80, 95% CI 0.66–0.98) met the primary outcome. A meta-analysis of all dypridamole data on secondary stroke prevention found an overall risk ratio for the composite of vascular death, stroke, or MI of 0.82 (95% CI 0.74–0.91). The principal side effect of the drug is headache. A combination capsule of extended-release dipyridamole and aspirin is approved for prevention of stroke.

Many large clinical trials have demonstrated clearly that most antiplatelet agents reduce the risk of all important vascular atherothrombotic events (i.e., ischemic stroke, MI, and death due to all vascular causes) in patients at risk for these events. The overall *relative* reduction in risk of nonfatal stroke is about 25–30% and of all vascular events is about 25%. The *absolute* reduction varies considerably, depending on the particular patient's risk. Individuals at very low risk for stroke seem to experience the same relative reduction, but their risk may be so low that the "benefit" is meaningless. On the other hand, individuals with a 10–15% risk of vascular events per year experience a reduction to about 7.5–11%.

Aspirin is inexpensive, can be given in low doses, and could be recommended for all adults to prevent both stroke and MI. However, it causes epigastric discomfort, gastric ulceration, and gastrointestinal hemorrhage, which may be asymptomatic or life-threatening. Consequently, not every 40- or 50-year-old should be advised to take aspirin regularly because the risk of atherothrombotic stroke is extremely low and is outweighed by the risk of adverse side effects. Conversely, every patient who has experienced an atherothrombotic stroke or TIA and has no contraindication should

be taking an antiplatelet agent regularly because the average annual risk of another stroke is 8–10%; another few percent will experience a MI or vascular death. Clearly, the likelihood of benefit far outweighs the risks of treatment.

The choice of antiplatelet agent and dose must balance the risk of stroke, the expected benefit, and the risk and cost of treatment. However, there are no definitive data, and opinions vary. Many authorities believe low-dose (30–75 mg/d) and high-dose (650–1300 mg/d) aspirin are about equally effective. Some advocate very low doses to avoid adverse effects, and still others advocate very high doses to be sure the benefit is maximal. Most physicians in North America recommend 81–325 mg/d, while most in Europe recommend 50–100 mg. Similarly, the choice of aspirin, clopidogrel, or dipyridamole plus aspirin must balance the fact that the latter are more effective than aspirin but the cost is higher, and this is likely to affect long-term patient adherence. The Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) study was a large randomized secondary prevention trial of over 20,000 patients that demonstrated equal efficacy of clopidogrel and the combination of low-dose aspirin and extended-release dipyridamole, suggesting that either is a reasonable choice for secondary stroke prevention.

Anticoagulation Therapy and Embolic Stroke

Several trials have shown that anticoagulation (INR range, 2–3) in patients with chronic nonvalvular (nonrheumatic) atrial fibrillation prevents cerebral embolism and is safe. For primary prevention and for patients who have experienced stroke or TIA, anticoagulation with warfarin reduces the risk by about 67%, which clearly outweighs the 1% risk per year of a major bleeding complication. In those patients who cannot tolerate warfarin, the combination of aspirin and clopidogrel appears superior to aspirin alone.

The decision to use anticoagulation for primary prevention is based primarily on risk factors (Table 21-3). The presence of any risk factor tips the balance in favor of anticoagulation.

Because of the high annual stroke risk in untreated rheumatic heart disease, primary prophylaxis against stroke has not been studied in a double-blind fashion. These patients generally should receive long-term anticoagulation.

Anticoagulation also reduces the risk of embolism in acute MI. Most clinicians recommend a 3-month course of anticoagulation when there is anterior Q-wave infarction, substantial left ventricular dysfunction, congestive heart failure, mural thrombosis, or atrial fibrillation. Warfarin is recommended long-term if atrial fibrillation persists. Warfarin is currently being studied in patients with congestive heart failure.

Stroke secondary to thromboembolism is one of the most serious complications of prosthetic heart valve implantation. The intensity of anticoagulation and/or antiplatelet therapy is dictated by the type of prosthetic valve and its location. The Seventh American College of Chest Physicians Conference on Antithrombotic Therapy for Valvular Heart Disease published the following guidelines in 2004: (1) for St. Jude Medical bileaflet valves in the aortic position, long-term warfarin with a target INR of 2.5 (range 2.0–3.0), (2) for tilting disk valves and bileaflet mechanical valves in the mitral position, long-term warfarin with a target INR of 3.0; (range 2.5–3.5); (3) for caged ball or caged disk valves, long-term warfarin with target INR of 3.0 (range 2.5–3.5) in combination with aspirin (75–100 mg/d); (4) for bioprosthetic valves, warfarin anticoagulation with target INR 2.5 for 3 months, followed by long-term aspirin alone (75–100 mg/d), assuming there is no history of atrial fibrillation.

If the embolic source cannot be eliminated, anticoagulation should in most cases be continued indefinitely. Many neurologists recommend combining antiplatelet agents with anticoagulants for patients who "fail" anticoagulation (i.e., have another stroke or TIA).

Anticoagulation Therapy and Noncardiogenic Stroke

Data do not support the use of long-term warfarin for preventing atherothrombotic stroke, for either intracranial or extracranial cerebrovascular disease. The WARSS (Warfarin-Aspirin Reinfarction Stroke Study) study found no benefit of warfarin sodium (INR, 1.4–2.8) over aspirin, 325 mg, for secondary prevention of stroke but did find a slightly higher bleeding rate in the warfarin group. A recent European study confirmed this finding. The WASID study (see earlier) demonstrated no benefit of warfarin (INR, 2–3) over aspirin in patients with symptomatic intracranial atherosclerosis, and also found higher bleeding complications.

Other Causes of Stroke

Carotid Disease

Surgical or endovascular repair of carotid atherosclerosis is preferred over medical therapy for symptomatic carotid artery disease (see earlier section). Anticoagulation has not been directly compared with antiplatelet therapy for carotid disease.

Dural Sinus Thrombosis

Limited evidence exists to support short-term usage of anticoagulants, regardless of the presence of intracranial

hemorrhage for venous infarction following sinus thrombosis.

STROKE SYNDROMES

A careful history and neurologic examination can often localize the region of brain dysfunction; if this region corresponds to a particular arterial distribution, the possible causes responsible for the syndrome can be narrowed. This is of particular importance when the patient presents with a TIA and a normal examination. For example, if a patient develops language loss and a right homonymous hemianopia, a search for causes of left middle cerebral emboli should be performed. A finding of an isolated stenosis of the right internal carotid artery in that patient, for example, suggests an asymptomatic carotid stenosis, and the search for other causes of stroke should continue. The following sections describe the clinical findings of cerebral ischemia associated with cerebral vascular territories depicted in Figs. 21-4, and 21-6 through 21-14. Stroke syndromes are divided into: (1) large-vessel stroke within the anterior circulation, (2) large-vessel stroke within the posterior circulation, and (3) small-vessel disease of either vascular bed.

Stroke within the Anterior Circulation

The internal carotid artery and its branches comprise the anterior circulation of the brain. These vessels can be occluded by intrinsic disease of the vessel (e.g., atherosclerosis or dissection) or by embolic occlusion from a proximal source as discussed earlier. Occlusion of each major intracranial vessel has distinct clinical manifestations.

Middle Cerebral Artery

Occlusion of the proximal MCA or one of its major branches is most often due to an embolus (artery-to-artery, cardiac, or of unknown source) rather than intracranial atherothrombosis. Atherosclerosis of the proximal MCA may cause distal emboli to the middle cerebral territory or, less commonly, may produce low-flow TIAs. Collateral formation via leptomeningeal vessels often prevents MCA stenosis from becoming symptomatic.

The cortical branches of the MCA supply the lateral surface of the hemisphere except for (1) the frontal pole and a strip along the superomedial border of the frontal and parietal lobes supplied by the ACA, and (2) the lower temporal and occipital pole convolutions supplied by the PCA (Figs. 21-6, 21-7, 21-8, and 21-9).

The proximal MCA (M1 segment) gives rise to penetrating branches (termed *lenticulostriate arteries*) that supply the putamen, outer globus pallidus, posterior limb of the internal capsule, the adjacent corona radiata, and most of the caudate nucleus (Fig. 21-6). In the sylvian fissure, the MCA in most patients divides into *superior* and *inferior* divisions (M2 branches). Branches of the inferior division supply the inferior parietal and temporal cortex, and those from the superior division supply the frontal and superior parietal cortex (Fig. 21-7).

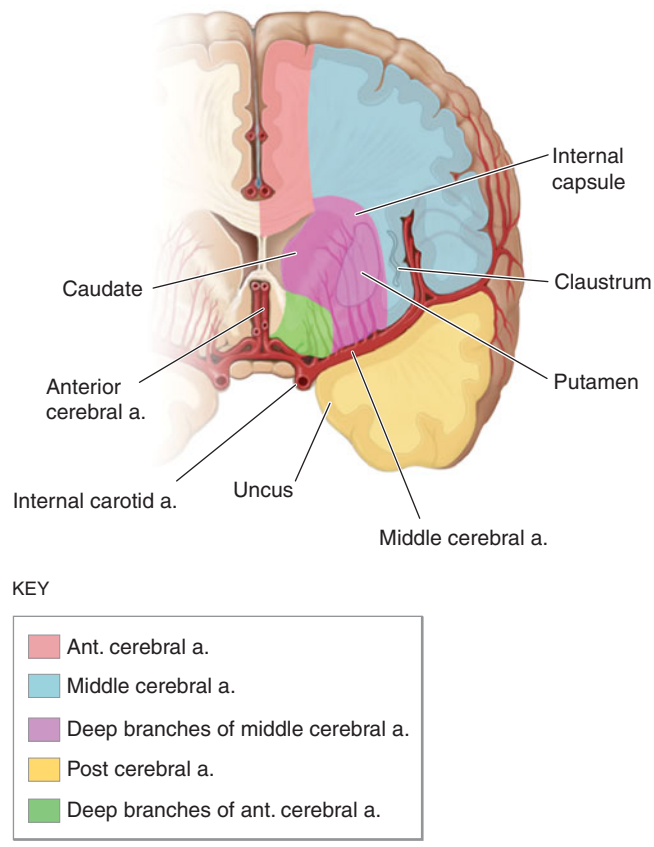

FIGURE 21-6
Diagram of a cerebral hemisphere in coronal section showing the territories of the major cerebral vessels that branch from the internal carotid arteries.

If the entire MCA is occluded at its origin (blocking both its penetrating and cortical branches) and the distal collaterals are limited, the clinical findings are contralateral hemiplegia, hemianesthesia, homonymous hemianopia, and a day or two of gaze preference to the ipsilateral side. Dysarthria is common because of facial weakness. When the dominant hemisphere is involved, global aphasia is present also, and when the nondominant hemisphere is affected, anosognosia, constructional apraxia, and neglect are found (Chap. 15).

Complete MCA syndromes occur most often when an embolus occludes the stem of the artery. Cortical collateral blood flow and differing arterial configurations are probably responsible for the development of many partial syndromes. Partial syndromes may also be due to emboli that enter the proximal MCA without complete occlusion, occlude distal MCA branches, or fragment and move distally.

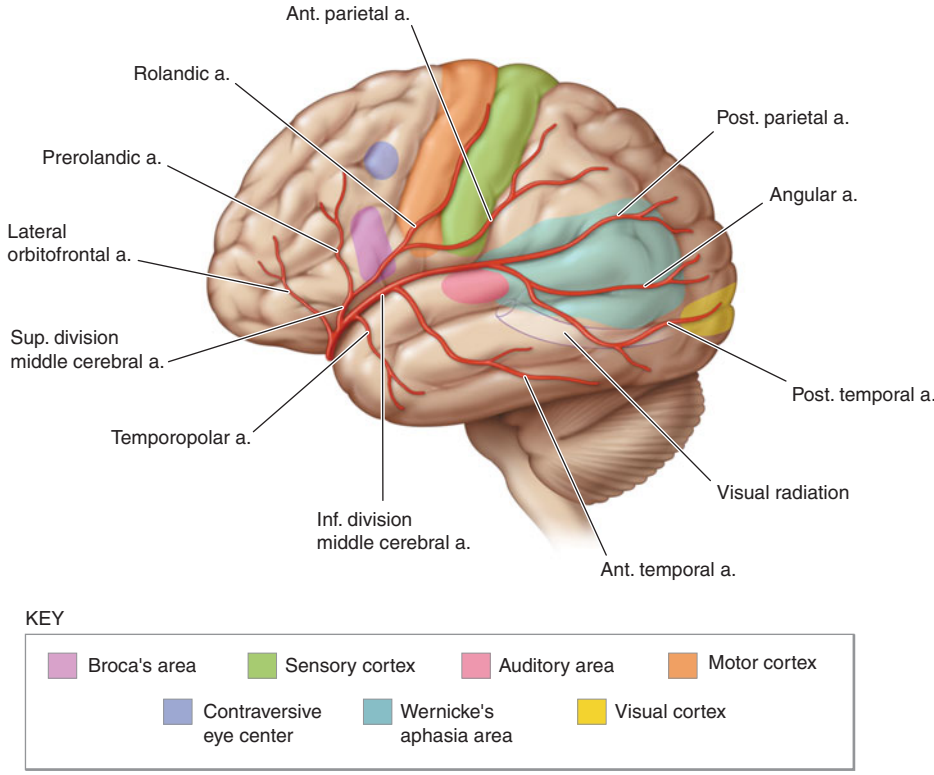

FIGURE 21-7

Diagram of a cerebral hemisphere, lateral aspect, showing the branches and distribution of the middle cerebral artery and the principal regions of cerebral localization. Note the bifurcation of the middle cerebral artery into a superior and inferior division.

Signs and symptoms: *Structures involved*

Paralysis of the contralateral face, arm, and leg; sensory impairment over the same area (pinprick, cotton touch, vibration, position, two-point discrimination, stereognosis, tactile localization, barognosis, cutaneographia): *Somatic motor area for face and arm and the fibers descending from the leg area to enter the corona radiata and corresponding somatic sensory system*

Motor aphasia: *Motor speech area of the dominant hemisphere*

Central aphasia, word deafness, anomia, jargon speech, sensory agraphia, acalculia, alexia, finger agnosia, right-left confusion (the last four comprise the Gerstmann syndrome): *Central, suprasylvian speech area and parietooccipital cortex of the dominant hemisphere*

Conduction aphasia: *Central speech area (parietal operculum)*

Apractognosia of the nondominant hemisphere, anosognosia, hemiasomatognosia, unilateral neglect, agnosia for the left half of external space, dressing "apraxia," constructional "apraxia," distortion of visual coordinates, inaccurate localization in the half field, impaired ability to judge distance, upside-down reading, visual illusions (e.g., it may appear that another person walks through a table): *Nondominant parietal lobe (area corresponding to speech area in dominant hemisphere); loss of topographic memory is usually due to a nondominant lesion, occasionally to a dominant one*

Homonymous hemianopia (often homonymous inferior quadrantanopia): *Optic radiation deep to second temporal convolution*

Paralysis of conjugate gaze to the opposite side: *Frontal contraversive eye field or projecting fibers*

Partial syndromes due to embolic occlusion of a single branch include hand, or arm and hand, weakness alone (brachial syndrome) or facial weakness with nonfluent (Broca) aphasia (Chap. 15), with or without arm weakness (frontal opercular syndrome). A combination of sensory disturbance, motor weakness, and nonfluent aphasia suggests that an embolus has occluded the proximal superior division and infarcted large portions of the frontal and parietal cortices (Fig. 21-7). If a fluent (Wernicke's) aphasia occurs without weakness, the inferior division of the MCA supplying the posterior part (temporal cortex) of the dominant hemisphere is probably involved. Jargon speech and an inability to comprehend written and spoken language are prominent features, often accompanied by a contralateral, homonymous superior quadrantanopia. Hemineglect or spatial agnosia without weakness indicates that the inferior division of the MCA in the nondominant hemisphere is involved.

Occlusion of a lenticulostriate vessel produces small-vessel (lacunar) stroke within the internal capsule (Fig. 21-6). This produces pure motor stroke or sensory-motor stroke contralateral to the lesion. Ischemia within the genu of

the internal capsule causes primarily facial weakness followed by arm then leg weakness as the ischemia moves posterior within the capsule. Alternatively, the contralateral hand may become ataxic and dysarthria will be prominent (clumsy hand, dysarthria lacunar syndrome). Lacunar infarction affecting the globus pallidus and putamen often has few clinical signs, but parkinsonism and hemiballismus have been reported.

Anterior Cerebral Artery

The ACA is divided into two segments: the precommunal (A1) circle of Willis, or stem, which connects the internal carotid artery to the anterior communicating artery, and the postcommunal (A2) segment distal to the anterior communicating artery (Figs. 21-4, 21-6, and 21-8). The A1 segment gives rise to several deep penetrating branches that supply the anterior limb of the internal capsule, the anterior perforate substance, amygdala, anterior hypothalamus, and the inferior part of the head of the caudate nucleus (Fig. 21-6).

Occlusion of the proximal ACA is usually well tolerated because of collateral flow through the anterior communicating artery and collaterals through the MCA and PCA. Occlusion of a single A2 segment results in the contralateral symptoms noted in Fig. 21-8. If both A2 segments arise from a single anterior cerebral stem (contralateral A1 segment atresia), the occlusion may affect both hemispheres. Profound abulia (a delay in verbal and motor response) and bilateral pyramidal signs with paraparesis and urinary incontinence result.

Anterior Choroidal Artery

This artery arises from the internal carotid artery and supplies the posterior limb of the internal capsule and the white matter posterolateral to it, through which pass some of the geniculocalcarine fibers (Fig. 21-9). The

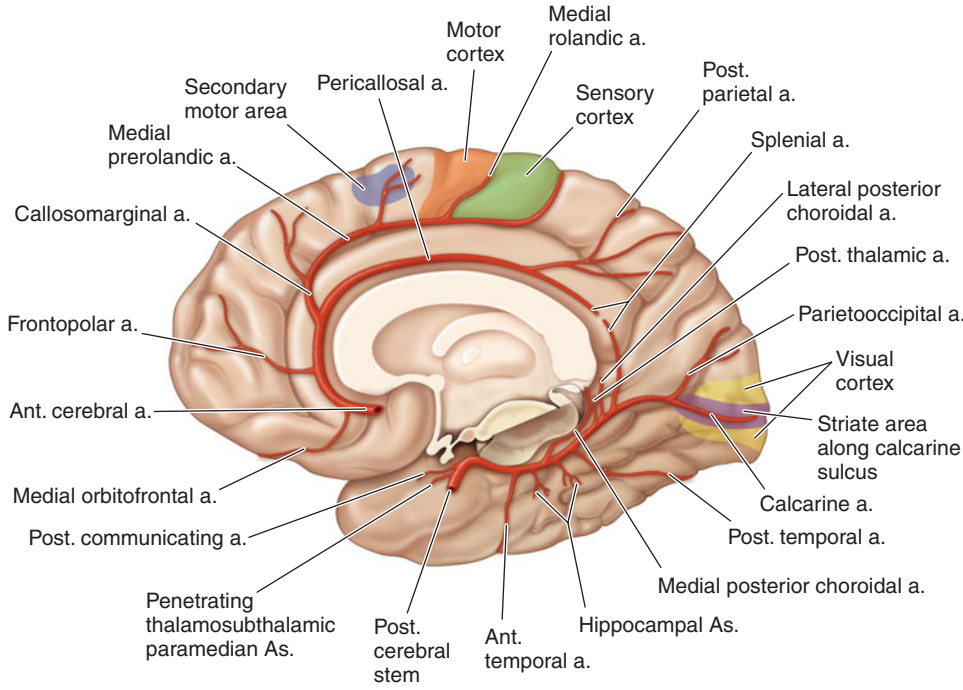

FIGURE 21-8

Diagram of a cerebral hemisphere, medial aspect, showing the branches and distribution of the anterior cerebral artery and the principal regions of cerebral localization.

Signs and symptoms: *Structures involved*

Paralysis of opposite foot and leg: *Motor leg area*

A lesser degree of paresis of opposite arm: *Arm area of cortex or fibers descending to corona radiata*

Cortical sensory loss over toes, foot, and leg: *Sensory area for foot and leg*

Urinary incontinence: *Sensorimotor area in paracentral lobule*

Contralateral grasp reflex, sucking reflex, gegenhalten (paratonic rigidity): *Medial surface of the posterior frontal lobe; likely supplemental motor area*

Abulia (akinetic mutism), slowness, delay, intermittent interruption, lack of spontaneity, whispering, reflex distraction to sights and sounds: *Uncertain localization—probably cingulate gyrus and medial inferior portion of frontal, parietal, and temporal lobes*

Impairment of gait and stance (gait apraxia): *Frontal cortex near leg motor area*

Dyspraxia of left limbs, tactile aphasia in left limbs: *Corpus callosum*

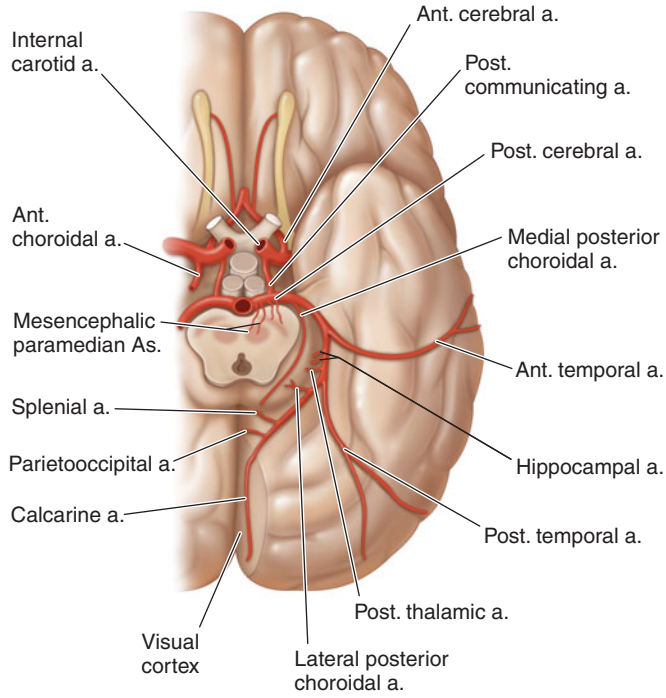

FIGURE 21-9

Inferior aspect of the brain with the branches and distribution of the posterior cerebral artery and the principal anatomic structures shown.

Signs and symptoms: *Structures involved*

Peripheral territory (see also Fig. 21-12). Homonymous hemianopia (often upper quadrantic): *Calcarine cortex or optic radiation nearby*. Bilateral homonymous hemianopia, cortical blindness, awareness or denial of blindness; tactile naming, achromatopia (color blindness), failure to see to-and-fro movements, inability to perceive objects not centrally located, apraxia of ocular movements, inability to count or enumerate objects, tendency to run into things that the patient sees and tries to avoid: *Bilateral occipital lobe with possibly the parietal lobe involved*. Verbal dyslexia without agraphia, color anomia: *Dominant calcarine lesion and posterior part of corpus callosum*. Memory defect: *Hippocampal lesion bilaterally or on the dominant side only*. Topographic disorientation and prosopagnosia: *Usually with lesions of nondominant, calcarine, and lingual gyrus*. Simultanagnosia, hemivisual neglect: *Dominant visual cortex, contralateral hemisphere*. Unformed visual hallucinations, peduncular hallucinosis, metamorphopsia, teleopsia, illusory visual spread, palinopsia, distortion of outlines, central photophobia: *Calcarine cortex*. Complex hallucinations: *Usually nondominant hemisphere*.

Central territory. Thalamic syndrome: sensory loss (all modalities), spontaneous pain and dysesthesias, choreoathetosis, intention tremor, spasms of hand, mild hemiparesis: *Posteroventral nucleus of thalamus; involvement of the adjacent subthalamus body or its afferent tracts*. Thalamoperforate syndrome: crossed cerebellar ataxia with ipsilateral third nerve palsy (Claude's syndrome): *Dentatothalamic tract and issuing third nerve*. Weber's syndrome: Third nerve palsy and contralateral hemiplegia: *Third nerve and cerebral peduncle*. Contralateral hemiplegia: *Cerebral peduncle*. Paralysis or paresis of vertical eye movement, skew deviation, sluggish pupillary responses to light, slight miosis and ptosis (retraction nystagmus and "tucking" of the eyelids may be associated): *Supranuclear fibers to third nerve, interstitial nucleus of Cajal, nucleus of Darkschewitsch, and posterior commissure*. Contralateral rhythmic, ataxic action tremor; rhythmic postural or "holding" tremor (rubral tremor): *Dentatothalamic tract*.

complete syndrome of anterior choroidal artery occlusion consists of contralateral hemiplegia, hemianesthesia (hypesthesia), and homonymous hemianopia. However, because this territory is also supplied by penetrating vessels of the proximal MCA and the posterior communicating and posterior choroidal arteries, minimal deficits may occur, and patients frequently recover substantially. Anterior choroidal strokes are usually the result of in situ thrombosis of the vessel, and the vessel is particularly vulnerable to iatrogenic occlusion during surgical clipping of aneurysms arising from the internal carotid artery.

Internal Carotid Artery

The clinical picture of internal carotid occlusion varies depending on whether the cause of ischemia is propagated thrombus, embolism, or low flow. The cortex supplied by the MCA territory is affected most often. With a competent circle of Willis, occlusion may go unnoticed. If the thrombus propagates up the internal carotid artery into the MCA or embolizes it, symptoms are identical to proximal MCA occlusion (see earlier). Sometimes there is massive infarction of the entire deep white matter and cortical surface. When the origins of both the

ACA and MCA are occluded at the top of the carotid artery, abulia or stupor occurs with hemiplegia, hemianesthesia, and aphasia or anosognosia. When the PCA arises from the internal carotid artery (a configuration called a *fetal posterior cerebral artery*), it may also become occluded and give rise to symptoms referable to its peripheral territory (Figs. 21-8 and 21-9).

In addition to supplying the ipsilateral brain, the internal carotid artery perfuses the optic nerve and retina via the ophthalmic artery. In ~25% of symptomatic internal carotid disease, recurrent transient monocular blindness (amaurosis fugax) warns of the lesion. Patients typically describe a horizontal shade that sweeps down or up across the field of vision. They may also complain that their vision was blurred in that eye or that the upper or lower half of vision disappeared. In most cases, these symptoms last only a few minutes. Rarely, ischemia or infarction of the ophthalmic artery or central retinal arteries occurs at the time of cerebral TIA or infarction.

A high-pitched prolonged carotid bruit fading into diastole is often associated with tightly stenotic lesions. As the stenosis grows tighter and flow distal to the stenosis becomes reduced, the bruit becomes fainter and may disappear when occlusion is imminent.

Common Carotid Artery

All symptoms and signs of internal carotid occlusion may also be present with occlusion of the common carotid artery. Bilateral common carotid artery occlusions at their origin may occur in Takayasu's arteritis.

Stroke within the Posterior Circulation

The posterior circulation is composed of the paired vertebral arteries, the basilar artery, and the paired posterior cerebral arteries. The vertebral arteries join to form the basilar artery at the pontomedullary junction. The basilar artery divides into two posterior cerebral arteries in the interpeduncular fossa (Figs. 21-4, 21-8, and 21-9). These major arteries give rise to long and short circumferential branches and to smaller deep penetrating branches that supply the cerebellum, medulla, pons, midbrain, subthalamus, thalamus, hippocampus, and medial temporal and occipital lobes. Occlusion of each vessel produces its own distinctive syndrome.

Posterior Cerebral Artery

In 75% of cases, both PCAs arise from the bifurcation of the basilar artery; in 20%, one has its origin from the ipsilateral internal carotid artery via the posterior communicating artery; in 5%, both originate from the respective ipsilateral internal carotid arteries (Figs. 21-8 and 21-9). The precommunal, or P1, segment of the true posterior cerebral artery is atretic in such cases.

PCA syndromes usually result from atheroma formation or emboli that lodge at the top of the basilar artery; posterior circulation disease may also be caused by dissection of either vertebral artery and fibromuscular dysplasia.

Two clinical syndromes are commonly observed with occlusion of the PCA: (1) *P1 syndrome*: midbrain, subthalamic, and thalamic signs, which are due to disease of the proximal P1 segment of the PCA or its penetrating branches (thalamogeniculate, Percheron, and posterior choroidal arteries); and (2) *P2 syndrome*: cortical temporal and occipital lobe signs, due to occlusion of the P2 segment distal to the junction of the PCA with the posterior communicating artery.

P1 Syndromes

Infarction usually occurs in the ipsilateral subthalamus and medial thalamus and in the ipsilateral cerebral peduncle and midbrain (Figs. 21-9 and 21-14). A third nerve palsy with contralateral ataxia (Claude's syndrome) or with contralateral hemiplegia (Weber's syndrome) may result. The ataxia indicates involvement of the red nucleus or dentatorubrothalamic tract; the hemiplegia is localized to the cerebral peduncle (Fig. 21-14). If the subthalamic nucleus is involved, contralateral hemiballismus may occur. Occlusion of the artery of Percheron produces paresis of upward gaze and drowsiness, and often abulia. Extensive infarction in the midbrain and subthalamus occurring with bilateral proximal PCA occlusion presents as coma, unreactive pupils, bilateral pyramidal signs, and decerebrate rigidity.

Occlusion of the penetrating branches of thalamic and thalamogeniculate arteries produces less extensive thalamic and thalamocapsular lacunar syndromes. The *thalamic Déjerine-Roussy syndrome* consists of contralateral hemisensory loss followed later by an agonizing, searing or burning pain in the affected areas. It is persistent and responds poorly to analgesics. Anticonvulsants (carbamazepine or gabapentin) or tricyclic antidepressants may be beneficial.

P2 Syndromes

(See also Figs. 21-8 and 21-9) Occlusion of the distal PCA causes infarction of the medial temporal and occipital lobes. Contralateral homonymous hemianopia with macula sparing is the usual manifestation. Occasionally, only the upper quadrant of visual field is involved. If the visual association areas are spared and only the calcarine cortex is involved, the patient may be aware of visual defects. Medial temporal lobe and hippocampal involvement may cause an acute disturbance in memory, particularly if it occurs in the dominant hemisphere. The defect usually clears because memory has bilateral representation. If the dominant hemisphere is affected and the infarct extends to involve the splenium

of the corpus callosum, the patient may demonstrate alexia without agraphia. Visual agnosia for faces, objects, mathematical symbols, and colors and anomia with paraphasic errors (amnestic aphasia) may also occur in this setting, even without callosal involvement. Occlusion of the posterior cerebral artery can produce *peduncular hallucinosis* (visual hallucinations of brightly colored scenes and objects).

Bilateral infarction in the distal PCAs produces cortical blindness (blindness with preserved pupillary light reaction). The patient is often unaware of the blindness or may even deny it (*Anton's syndrome*). Tiny islands of vision may persist, and the patient may report that vision fluctuates as images are captured in the preserved portions. Rarely, only peripheral vision is lost and central vision is spared, resulting in "gun-barrel" vision. Bilateral visual association area lesions may result in *Balint's syndrome*, a disorder of the orderly visual scanning of the environment (Chap. 15), usually resulting from infarctions secondary to low flow in the "watershed" between the distal PCA and MCA territories, as occurs after cardiac arrest. Patients may experience persistence of a visual image for several minutes despite gazing at another scene (*palinopia*) or an inability to synthesize the whole of an image (*asimultanagnosia*). Embolic occlusion of the top of the basilar artery can produce any or all of the central or peripheral territory symptoms. The hallmark is the sudden onset of bilateral signs, including ptosis, pupillary asymmetry or lack of reaction to light, and somnolence.

Vertebral and Posterior Inferior Cerebellar Arteries

The vertebral artery, which arises from the innominate artery on the right and the subclavian artery on the left, consists of four segments. The first (V1) extends from its origin to its entrance into the sixth or fifth transverse vertebral foramen. The second segment (V2) traverses the vertebral foramina from C6 to C2. The third (V3) passes through the transverse foramen and circles around the arch of the atlas to pierce the dura at the foramen magnum. The fourth (V4) segment courses upward to join the other vertebral artery to form the basilar artery; only the fourth segment gives rise to branches that supply the brainstem and cerebellum. The posterior inferior cerebellar artery (PICA) in its proximal segment supplies the lateral medulla and, in its distal branches, the inferior surface of the cerebellum.

Atherothrombotic lesions have a predilection for V1 and V4 segments of the vertebral artery. The first segment may become diseased at the origin of the vessel and may produce posterior circulation emboli; collateral flow from the contralateral vertebral artery or the ascending cervical, thyrocervical, or occipital arteries is usually sufficient to prevent low-flow TIAs or stroke. When one vertebral artery is atretic and an atherothrombotic lesion threatens the origin of the other, the collateral circulation, which may also include retrograde flow down the basilar artery, is often insufficient (Figs. 21-4 and 21-9). In this setting, low-flow TIAs may occur, consisting of syncope, vertigo, and alternating hemiplegia; this state also sets the stage for thrombosis. Disease of the distal fourth segment of the vertebral artery can promote thrombus formation manifest as embolism or with propagation as basilar artery thrombosis. Stenosis proximal to the origin of the PICA can threaten the lateral medulla and posterior inferior surface of the cerebellum.

If the subclavian artery is occluded proximal to the origin of the vertebral artery, there is a reversal in the direction of blood flow in the ipsilateral vertebral artery. Exercise of the ipsilateral arm may increase demand on vertebral flow, producing posterior circulation TIAs, or "subclavian steal."

Although atheromatous disease rarely narrows the second and third segments of the vertebral artery, this region is subject to dissection, fibromuscular dysplasia, and, rarely, encroachment by osteophytic spurs within the vertebral foramina.

Embolic occlusion or thrombosis of a V4 segment causes ischemia of the lateral medulla. The constellation of vertigo, numbness of the ipsilateral face and contralateral limbs, diplopia, hoarseness, dysarthria, dysphagia, and ipsilateral Horner's syndrome is called the *lateral medullary (or Wallenberg's) syndrome* (**Fig. 21-10**). Most cases result from ipsilateral vertebral artery occlusion; in the remainder, PICA occlusion is responsible. Occlusion of the medullary penetrating branches of the vertebral artery or PICA results in partial syndromes. *Hemiparesis is not a feature of vertebral artery occlusion, however, quadriparesis may result from occlusion of the anterior spinal artery.*

Rarely, a *medial medullary syndrome* occurs with infarction of the pyramid and contralateral hemiparesis of the arm and leg, sparing the face. If the medial lemniscus and emerging hypoglossal nerve fibers are involved, contralateral loss of joint position sense and ipsilateral tongue weakness occur.

Cerebellar infarction with edema can lead to *sudden respiratory arrest* due to raised ICP in the posterior fossa. Drowsiness, Babinski signs, dysarthria, and bifacial weakness may be absent, or present only briefly, before respiratory arrest ensues. Gait unsteadiness, headache, dizziness, nausea, and vomiting may be the only early symptoms and signs and should arouse suspicion of this impending complication, which may require neurosurgical decompression, often with an excellent outcome. Separating these symptoms from those of viral labrynthitis can be a challenge, but headache, neck stiffness, and unilateral dysmetria favor stroke.

Basilar Artery

Branches of the basilar artery supply the base of the pons and superior cerebellum and fall into three groups:

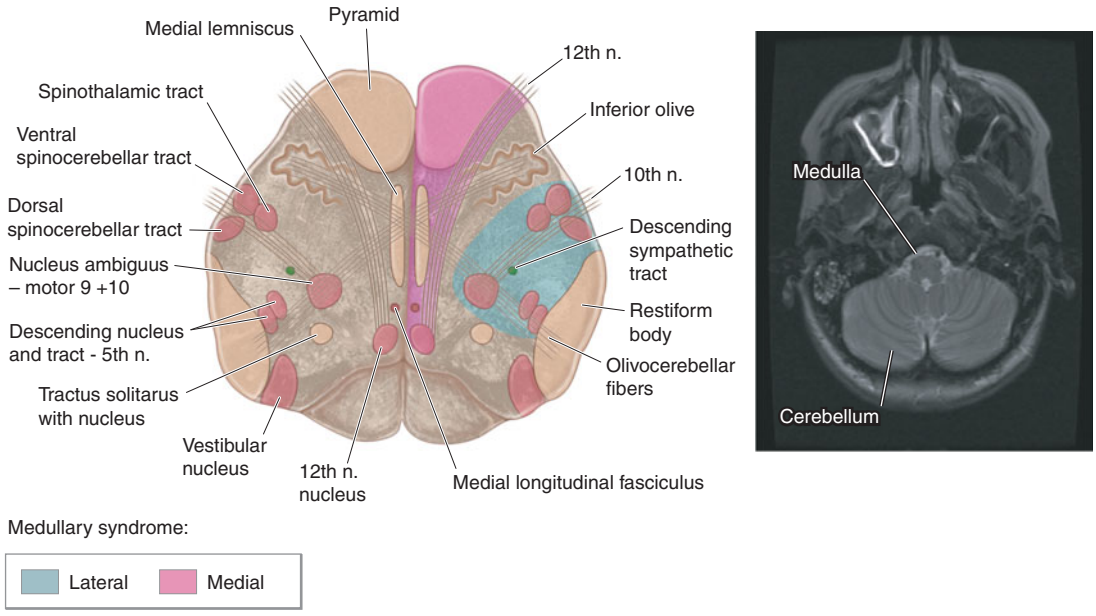

FIGURE 21-10

Axial section at the level of the medulla, depicted schematically on the left, with a corresponding MR image on the right. Note that in Figs. 21-10 through 21-14, all drawings are oriented with the dorsal surface at the bottom, matching the orientation of the brainstem that is commonly seen in all modern neuroimaging studies. Approximate regions involved in medial and lateral medullary stroke syndromes are shown.

Signs and symptoms: *Structures involved*

1. Medial medullary syndrome (occlusion of vertebral artery or of branch of vertebral or lower basilar artery)
   - On side of lesion
     - Paralysis with atrophy of half the tongue: *Ipsilateral twelfth nerve*
   - On side opposite lesion
     - Paralysis of arm and leg, sparing face; impaired tactile and proprioceptive sense over half the body: *Contralateral pyramidal tract and medial lemniscus*
2. Lateral medullary syndrome (occlusion of any of five vessels may be responsible—vertebral, posterior inferior cerebellar, superior, middle, or inferior lateral medullary arteries)
   - On side of lesion
     - Pain, numbness, impaired sensation over half the face: *Descending tract and nucleus fifth nerve*
     - Ataxia of limbs, falling to side of lesion: *Uncertain—restiform body, cerebellar hemisphere, cerebellar fibers, spinocerebellar tract (?)*
     - Nystagmus, diplopia, oscillopsia, vertigo, nausea, vomiting: *Vestibular nucleus*
     - Horner's syndrome (miosis, ptosis, decreased sweating): *Descending sympathetic tract*
     - Dysphagia, hoarseness, paralysis of palate, paralysis of vocal cord, diminished gag reflex: *Issuing fibers ninth and tenth nerves*
     - Loss of taste: *Nucleus and tractus solitarius*
     - Numbness of ipsilateral arm, trunk, or leg: *Cuneate and gracile nuclei*
     - Weakness of lower face: *Genuflected upper motor neuron fibers to ipsilateral facial nucleus*
   - On side opposite lesion
     - Impaired pain and thermal sense over half the body, sometimes face: *Spinothalamic tract*
3. Total unilateral medullary syndrome (occlusion of vertebral artery): Combination of medial and lateral syndromes
4. Lateral pontomedullary syndrome (occlusion of vertebral artery): Combination of lateral medullary and lateral inferior pontine syndrome
5. Basilar artery syndrome (the syndrome of the lone vertebral artery is equivalent): A combination of the various brainstem syndromes plus those arising in the posterior cerebral artery distribution.
   - Bilateral long tract signs (sensory and motor; cerebellar and peripheral cranial nerve abnormalities): *Bilateral long tract; cerebellar and peripheral cranial nerves*
   - Paralysis or weakness of all extremities, plus all bulbar musculature: *Corticobulbar and corticospinal tracts bilaterally*

(1) paramedian, 7–10 in number, which supply a wedge of pons on either side of the midline; (2) short circumferential, 5–7 in number, which supply the lateral two-thirds of the pons and middle and superior cerebellar peduncles; and (3) bilateral long circumferential (superior cerebellar and anterior inferior cerebellar arteries), which course around the pons to supply the cerebellar hemispheres.

Atheromatous lesions can occur anywhere along the basilar trunk but are most frequent in the proximal

basilar and distal vertebral segments. Typically, lesions occlude either the proximal basilar and one or both vertebral arteries. The clinical picture varies depending on the availability of retrograde collateral flow from the posterior communicating arteries. Rarely, dissection of a vertebral artery may involve the basilar artery and, depending on the location of true and false lumen, may produce multiple penetrating artery strokes.

Although atherothrombosis occasionally occludes the distal portion of the basilar artery, emboli from the heart or proximal vertebral or basilar segments are more commonly responsible for "top of the basilar" syndromes.

Because the brainstem contains many structures in close apposition, a diversity of clinical syndromes may emerge with ischemia, reflecting involvement of the corticospinal and corticobulbar tracts, ascending sensory tracts, and cranial nerve nuclei (**Figs. 21-11**, **21-12**, **21-13**, and **21-14**).

The symptoms of transient ischemia or infarction in the territory of the basilar artery often do not indicate whether the basilar artery itself or one of its branches is diseased, yet this distinction has important implications for therapy. *The picture of complete basilar occlusion, however, is easy to recognize as a constellation of bilateral long tract signs (sensory and motor) with signs of cranial nerve and cerebellar dysfunction.* A "locked-in" state of preserved consciousness with quadriplegia and cranial nerve signs suggests complete pontine and lower midbrain infarction. The

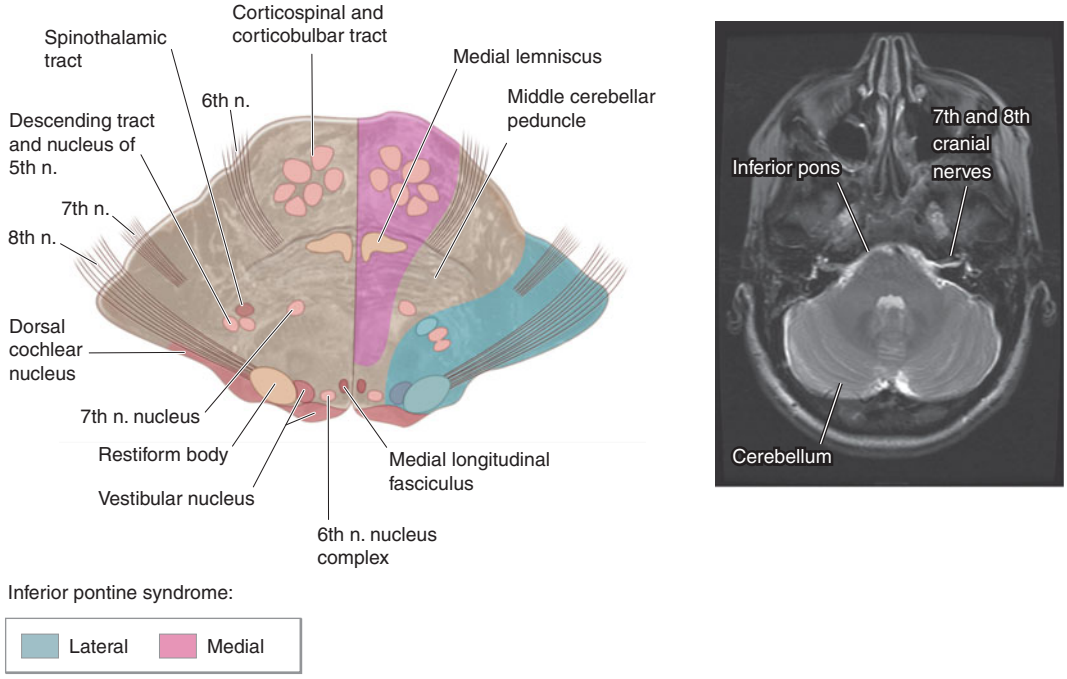

FIGURE 21-11

Axial section at the level of the inferior pons, depicted schematically on the left, with a corresponding MR image on the right. Approximate regions involved in medial and lateral inferior pontine stroke syndromes are shown.

Signs and symptoms: *Structures involved*

1. Medial inferior pontine syndrome (occlusion of paramedian branch of basilar artery)
   - On side of lesion
     - Paralysis of conjugate gaze to side of lesion (preservation of convergence): *Center for conjugate lateral gaze*
     - Nystagmus: *Vestibular nucleus*
     - Ataxia of limbs and gait: Likely *middle cerebellar peduncle*
     - Diplopia on lateral gaze: *Abducens nerve*
   - On side opposite lesion
     - Paralysis of face, arm, and leg: *Corticobulbar and corticospinal tract in lower pons*
     - Impaired tactile and proprioceptive sense over half of the body: *Medial lemniscus*
2. Lateral inferior pontine syndrome (occlusion of anterior inferior cerebellar artery)
   - On side of lesion
     - Horizontal and vertical nystagmus, vertigo, nausea, vomiting, oscillopia: *Vestibular nerve or nucleus*
     - Facial paralysis: *Seventh nerve*
     - Paralysis of conjugate gaze to side of lesion: *Center for conjugate lateral gaze*
     - Deafness, tinnitus: *Auditory nerve or cochlear nucleus*
     - Ataxia: *Middle cerebellar peduncle and cerebellar hemisphere*
     - Impaired sensation over face: *Descending tract and nucleus fifth nerve*
   - On side opposite lesion
     - Impaired pain and thermal sense over half the body (may include face): *Spinothalamic tract*

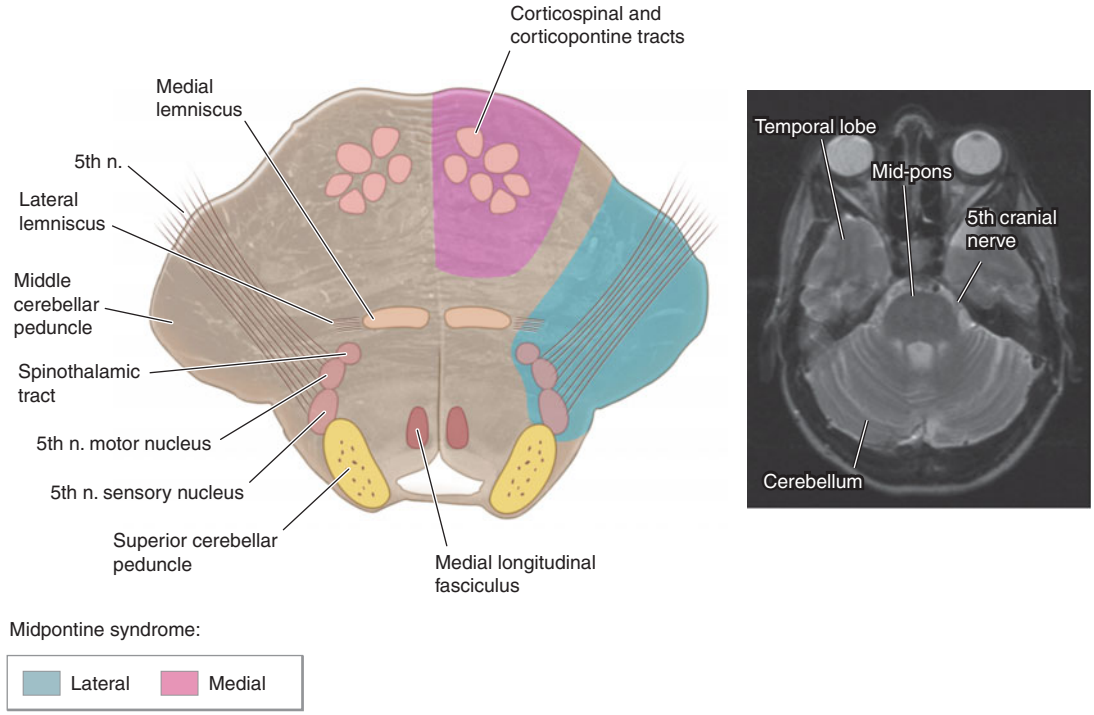

FIGURE 21-12

Axial section at the level of the mid pons, depicted schematically on the left, with a corresponding MR image on the right. Approximate regions involved in medial and lateral midpontine stroke syndromes are shown.

Signs and symptoms: *Structures involved*

1. Medial midpontine syndrome (paramedian branch of midbasilar artery)
   - On side of lesion
     - Ataxia of limbs and gait (more prominent in bilateral involvement): *Pontine nuclei*
   - On side opposite lesion
     - Paralysis of face, arm, and leg: *Corticobulbar and corticospinal tract*
     - Variable impaired touch and proprioception when lesion extends posteriorly: *Medial lemniscus*
2. Lateral midpontine syndrome (short circumferential artery)
   - On side of lesion
     - Ataxia of limbs: *Middle cerebellar peduncle*
     - Paralysis of muscles of mastication: *Motor fibers or nucleus of fifth nerve*
     - Impaired sensation over side of face: *Sensory fibers or nucleus of fifth nerve*
   - On side opposite lesion
     - Impaired pain and thermal sense on limbs and trunk: *Spinothalamic tract*

therapeutic goal is to identify *impending* basilar occlusion before devastating infarction occurs. A series of TIAs and a slowly progressive, fluctuating stroke are extremely significant, as they often herald an atherothrombotic occlusion of the distal vertebral or proximal basilar artery.

TIAs in the proximal basilar distribution may produce vertigo (often described by patients as "swimming," "swaying," "moving," "unsteadiness," or "light-headedness"). Other symptoms that warn of basilar thrombosis include diplopia, dysarthria, facial or circumoral numbness, and hemisensory symptoms. In general, symptoms of basilar branch TIAs affect one side of the brainstem, whereas symptoms of basilar artery TIAs usually affect both sides, though a "herald" hemiparesis has been emphasized as an initial symptom of basilar occlusion. Most often TIAs, whether due to impending occlusion of the basilar artery or a basilar branch, are short-lived (5–30 min) and repetitive, occurring several times a day. The pattern suggests intermittent reduction of flow. Many neurologists treat with heparin to prevent clot propagation.

Atherothrombotic occlusion of the basilar artery with infarction usually causes *bilateral* brainstem signs. A gaze paresis or internuclear ophthalmoplegia associated with ipsilateral hemiparesis may be the only manifestation of bilateral brainstem ischemia. More often, unequivocal signs of bilateral pontine disease are present. Complete basilar thrombosis carries a high mortality.

Occlusion of a branch of the basilar artery usually causes *unilateral* symptoms and signs involving motor, sensory, and cranial nerves. As long as symptoms remain unilateral, concern over pending basilar occlusion should be reduced.

Occlusion of the superior cerebellar artery results in severe ipsilateral cerebellar ataxia, nausea and vomiting, dysarthria, and contralateral loss of pain and temperature sensation over the extremities, body, and face (spino- and

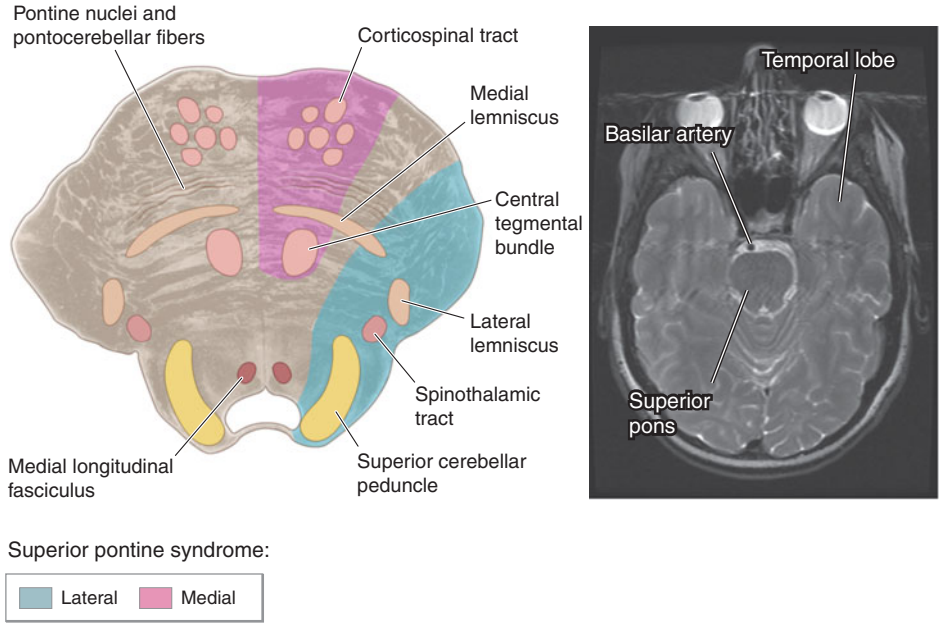

FIGURE 21-13

Axial section at the level of the superior pons, depicted schematically on the left, with a corresponding MR image on the right. Approximate regions involved in medial and lateral superior pontine stroke syndromes are shown.

Signs and symptoms: *Structures involved*

1. Medial superior pontine syndrome (paramedian branches of upper basilar artery)
   On side of lesion
   - Cerebellar ataxia (probably): *Superior and/or middle cerebellar peduncle*
   - Internuclear ophthalmoplegia: *Medial longitudinal fasciculus*
   - Myoclonic syndrome, palate, pharynx, vocal cords, respiratory apparatus, face, oculomotor apparatus, etc.: *Localization uncertain—central tegmental bundle, dentate projection, inferior olivary nucleus*

   On side opposite lesion
   - Paralysis of face, arm, and leg: *Corticobulbar and corticospinal tract*
   - Rarely touch, vibration, and position are affected: *Medial lemniscus*

2. Lateral superior pontine syndrome (syndrome of superior cerebellar artery)
   On side of lesion
   - Ataxia of limbs and gait, falling to side of lesion: *Middle and superior cerebellar peduncles, superior surface of cerebellum, dentate nucleus*
   - Dizziness, nausea, vomiting; horizontal nystagmus: *Vestibular nucleus*
   - Paresis of conjugate gaze (ipsilateral): *Pontine contralateral gaze*
   - Skew deviation: *Uncertain*
   - Miosis, ptosis, decreased sweating over face (Horner's syndrome): *Descending sympathetic fibers*
   - Tremor: Localization unclear—*Dentate nucleus, superior cerebellar peduncle*

   On side opposite lesion
   - Impaired pain and thermal sense on face, limbs, and trunk: *Spinothalamic tract*
   - Impaired touch, vibration, and position sense, more in leg than arm (there is a tendency to incongruity of pain and touch deficits): *Medial lemniscus (lateral portion)*

trigeminothalamic tract). Partial deafness, ataxic tremor of the ipsilateral upper extremity, Horner's syndrome, and palatal myoclonus may occur rarely. Partial syndromes occur frequently (Fig. 21-13). With large strokes, swelling and mass effects may compress the midbrain or produce hydrocephalus; these symptoms may evolve rapidly. Neurosurgical intervention may be lifesaving in such cases.

Occlusion of the anterior inferior cerebellar artery produces variable degrees of infarction because the size of this artery and the territory it supplies vary inversely with those of the PICA. The principal symptoms include: (1) ipsilateral deafness, facial weakness, vertigo, nausea and vomiting, nystagmus, tinnitus, cerebellar ataxia, Horner's syndrome, and paresis of conjugate lateral gaze; and (2) contralateral loss of pain and temperature sensation. An occlusion close to the origin of the artery may cause corticospinal tract signs (Fig. 21-11).

Occlusion of one of the short circumferential branches of the basilar artery affects the lateral two-thirds of the pons and middle or superior cerebellar peduncle, whereas occlusion of one of the paramedian branches affects a wedge-shaped area on either side of the medial pons (Figs. 21-11 through 21-13).

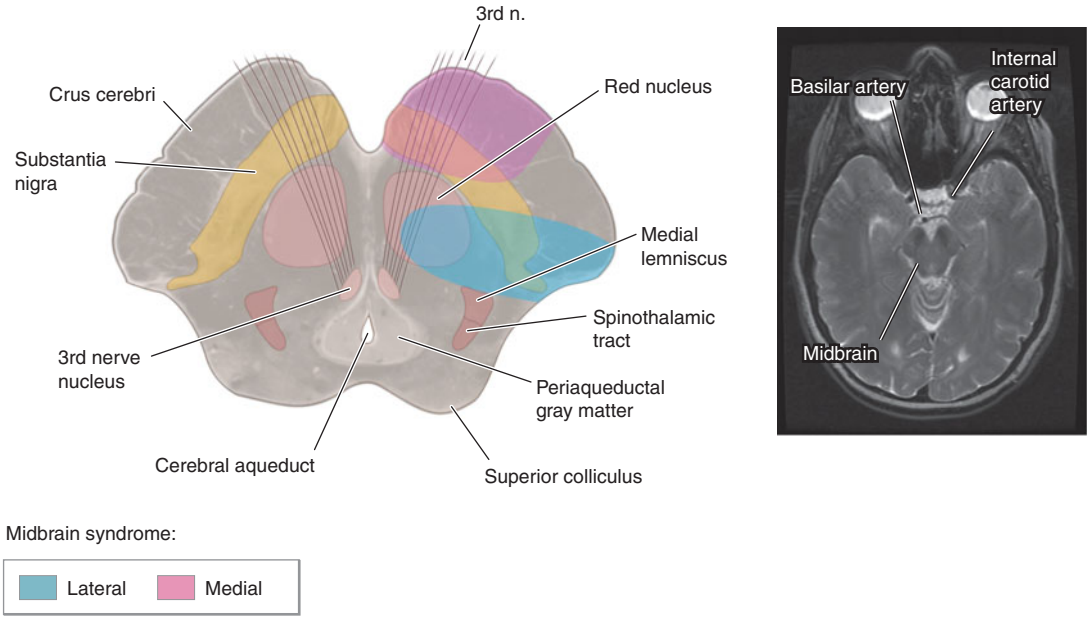

FIGURE 21-14

Axial section at the level of the midbrain, depicted schematically on the left, with a corresponding MR image on the right. Approximate regions involved in medial and lateral midbrain stroke syndromes are shown.

Signs and symptoms: *Structures involved*

1. Medial midbrain syndrome (paramedian branches of upper basilar and proximal posterior cerebral arteries)
   On side of lesion
   Eye "down and out" secondary to unopposed action of fourth and sixth cranial nerves, with dilated and unresponsive pupil: *Third nerve fibers*
   On side opposite lesion
   Paralysis of face, arm, and leg: *Corticobulbar and corticospinal tract descending in crus cerebri*
2. Lateral midbrain syndrome (syndrome of small penetrating arteries arising from posterior cerebral artery)
   On side of lesion
   Eye "down and out" secondary to unopposed action of fourth and sixth cranial nerves, with dilated and unresponsive pupil: *Third nerve fibers and/or third nerve nucleus*
   On side opposite lesion
   Hemiataxia, hyperkinesias, tremor: *Red nucleus, dentatorubrothalamic pathway*

IMAGING STUDIES

See also Chap. 2.

CT Scans

CT radiographic images identify or exclude hemorrhage as the cause of stroke, and they identify extraparenchymal hemorrhages, neoplasms, abscesses, and other conditions masquerading as stroke. Scans obtained in the first several hours after an infarction generally show no abnormality, and the infarct may not be seen reliably for 24–48 h. CT may fail to show small ischemic strokes in the posterior fossa because of bone artifact; small infarcts on the cortical surface may also be missed.

Contrast-enhanced CT scans add specificity by showing contrast enhancement of subacute infarcts and allow visualization of venous structures. Coupled with newer generation multi-detector scanners, CT angiography (CTA) can be performed with administration of IV iodinated contrast allowing visualization of the cervical and intracranial arteries, intracranial veins, aortic arch, and even the coronary arteries in one imaging session. Carotid disease and intracranial vascular occlusions are readily identified with this method (Fig. 21-3). After an IV bolus of contrast, deficits in brain perfusion produced by vascular occlusion can also be demonstrated (**Fig. 21-15**) and used to predict the region of infarcted brain and the brain at risk of further infarction (i.e., the ischemic penumbra). CT imaging is also sensitive for detecting SAH (though by itself does not rule it out), and CTA can readily identify intracranial aneurysms (Chap. 22). Because of its speed and wide availability, noncontrast head CT is the imaging modality of choice in patients with acute stroke (Fig. 21-1), and CTA and CT perfusion imaging may also be useful and convenient adjuncts.

MRI

MRI reliably documents the extent and location of infarction in all areas of the brain, including the posterior fossa and cortical surface. It also identifies intracranial hemorrhage and other abnormalities but is less sensitive than CT for detecting acute blood. MRI scanners with

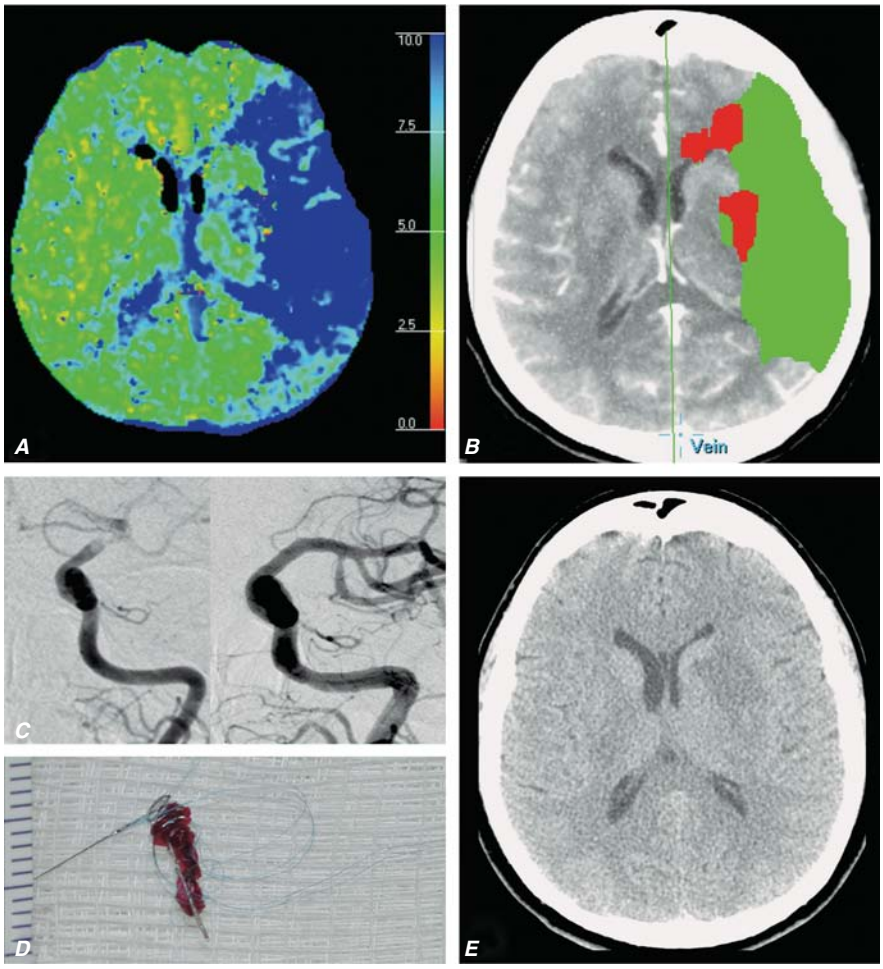

FIGURE 21-15

Acute left middle cerebral artery (MCA) stroke with right hemiplegia but preserved language. ***A.*** CT perfusion mean-transit time map showing delayed perfusion of the left MCA distribution (blue). ***B.*** Predicted region of infarct (red) and penumbra (green) based on CT perfusion data. ***C.*** Conventional angiogram showing occlusion of the left internal carotid–MCA bifurcation (*left panel*), and revascularization of the vessels following successful thrombectomy 8 h after stroke symptom onset (*right panel*). ***D.*** The clot removed with a thrombectomy device (L5, Concentric Medical, Inc). ***E.*** CT scan of the brain 2 days later; note infarction in the region predicted in ***B*** but preservation of the penumbral region by successful revascularization.

magnets of higher field strength produce more reliable and precise images. Diffusion-weighted imaging is more sensitive for early brain infarction than standard MR sequences or CT (**Fig. 21-16**), as is FLAIR (fluid-attenuated inversion recovery) imaging (Chap. 2). Using IV administration of gadolinium contrast, MR perfusion studies can be performed. Brain regions showing poor perfusion but no abnormality on diffusion are considered equivalent to the ischemic penumbra (see Pathophysiology of Ischemic Stroke, earlier and Fig. 21-16), and patients showing large regions of mismatch may be better candidates for acute revascularization. MR angiography is highly sensitive for stenosis of extracranial internal carotid arteries and of large intracranial vessels. With higher degrees of stenosis, MR angiography tends to overestimate the degree of stenosis when compared to conventional x-ray angiography. MRI with fat saturation is an imaging sequence used to visualize extra- or intracranial arterial dissection. This sensitive technique images clotted blood within the dissected vessel wall.

MRI is less sensitive for acute blood products than CT and is more expensive and time consuming and less readily available. Claustrophobia also limits its application. Most acute stroke protocols use CT because of these limitations. However, MRI may be useful outside the acute period by more clearly defining the extent of tissue injury and discriminating new from old regions of brain infarction. MRI may have particular utility in patients with TIA: it is also more likely to identify new infarction, which is a strong predictor of subsequent stroke.

Cerebral Angiography

Conventional x-ray cerebral angiography is the "gold standard" for identifying and quantifying atherosclerotic stenoses of the cerebral arteries and for identifying and characterizing other pathologies, including aneurysms, vasospasm, intraluminal thrombi, fibromuscular dysplasia, arteriovenous fistula, vasculitis, and collateral channels of blood flow. Endovascular techniques, which are evolving rapidly, can be used to deploy stents within delicate intracranial vessels, to perform balloon angioplasty of stenotic lesions, to treat intracranial aneurysms by embolization, and to open occluded vessels in acute stroke with mechanical thrombectomy devices. Recent studies have also documented that intraarterial delivery of thrombolytic agents to patients with acute MCA stroke can effectively recanalize vessels and improve clinical outcomes. Although its use

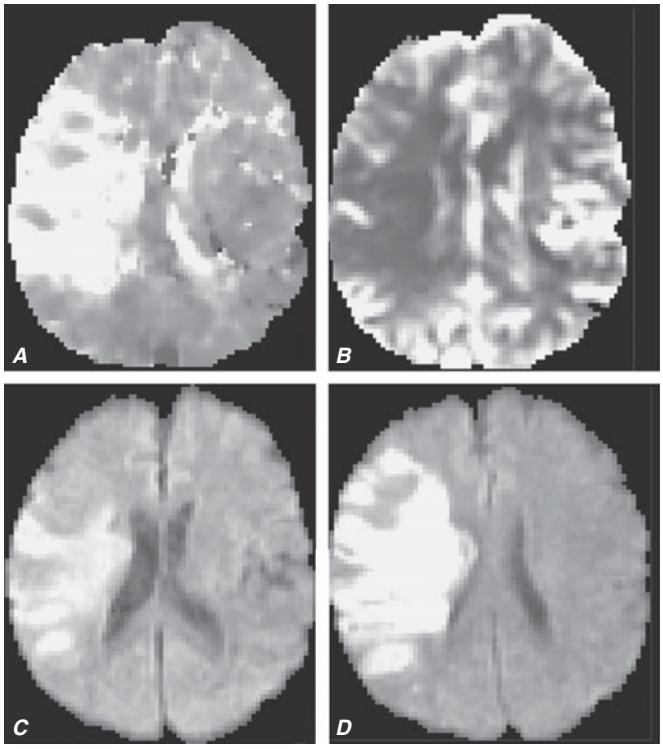

FIGURE 21-16

MRI of acute stroke. ***A.*** Perfusion defect within the right hemisphere (bright signal) imaged after administration of an IV bolus of gadolinium contrast. ***B.*** Cerebral blood flow measured at the same time as in ***A***; darker signal reflects decreased blood flow. ***C.*** Diffusion-weighted image obtained 5 h after onset of a right middle cerebral artery stroke; bright signal indicates regions of restricted diffusion that will progress to infarction. The discrepancy between the region of poor perfusion shown in ***A*** and ***B*** and the diffusion deficit is called *diffusion-perfusion mismatch* and is a measure of the ischemic penumbra. Without specific therapy (as shown in Fig. 21-15) the region of infarction will expand to match the perfusion deficit, as shown in the diffusion weighted image in ***D*** obtained 5 days later. *(Courtesy of Gregory Albers and Vincent Thijs, MD, Stanford University; with permission.)*

is investigational in many centers, cerebral angiography coupled with endovascular techniques for cerebral revascularization may become routine in the near future. Centers capable of these techniques are termed *comprehensive stroke centers* to distinguish them from primary stroke centers that can administer IV rtPA but not perform endovascular therapy. Conventional angiography carries risks of arterial damage, groin hemorrhage, embolic stroke, and renal failure from contrast nephropathy, so it should be reserved for situations where less invasive means are inadequate.

Ultrasound Techniques

Stenosis at the origin of the internal carotid artery can be identified and quantified reliably by ultrasonography that combines a B-mode ultrasound image with a Doppler ultrasound assessment of flow velocity ("duplex" ultrasound). Transcranial Doppler (TCD) assessment of MCA, ACA, and PCA flow and of vertebrobasilar flow is also useful. This latter technique can detect stenotic lesions in the large intracranial arteries because such lesions increase systolic flow velocity. In many cases, MR angiography combined with carotid and transcranial ultrasound studies eliminates the need for conventional x-ray angiography in evaluating vascular stenosis. Alternatively, CT angiography of the entire head and neck can be performed during the initial imaging of acute stroke. Because this images the entire arterial system relevant to stroke, with the exception of the heart, much of the clinician's stroke workup can be completed with one imaging study.

Perfusion Techniques

Both xenon techniques (principally xenon-CT) and PET can quantify cerebral blood flow. These tools are generally used for research (Chap. 2) but can be useful for determining the significance of arterial stenosis and planning for revascularization surgery. Single photon emission tomography (SPECT) and MR perfusion techniques report relative cerebral blood flow. Since CT imaging is used as the initial imaging modality for acute stroke, some centers now combine both CT angiography and CT perfusion imaging together with the noncontrast CT scan. CT perfusion imaging increases the sensitivity for detecting ischemia, and can measure the ischemic penumbra (Fig. 21-15). Alternatively, MR perfusion can be combined with MR diffusion imaging to identify the ischemic penumbra as the mismatch between these two imaging sequences (Fig. 21-16). The ability to image the ischemic penumbra allows more judicious selection of patients who may or may not benefit from acute interventions such as thrombolysis, thrombectomy, or investigational neuroprotective strategies.

INTRACRANIAL HEMORRHAGE

Hemorrhages are classified by their location and the underlying vascular pathology. Bleeding into subdural and epidural spaces is principally produced by trauma. SAHs are produced by trauma and rupture of intracranial aneurysms (Chap. 22). Intraparenchymal and intraventricular hemorrhage will be considered here.

DIAGNOSIS

Intracranial hemorrhage is often discovered on noncontrast CT imaging of the brain during the acute evaluation of stroke. Since CT is more sensitive than routine MRI for acute blood, CT imaging is the preferred

TABLE 21-5

CAUSES OF INTRACRANIAL HEMORRHAGE

CAUSE	LOCATION	COMMENTS
Head trauma	Intraparenchymal: frontal lobes, anterior temporal lobes; subarachnoid	Coup and contracoup injury during brain deceleration
Hypertensive hemorrhage	Putamen, globus pallidus, thalamus, cerebellar hemisphere, pons	Chronic hypertension produces hemorrhage from small (~100 μm) vessels in these regions
Transformation of prior ischemic infarction	Basal ganglion, subcortical regions, lobar	Occurs in 1–6% of ischemic strokes with predilection for large hemispheric infarctions
Metastatic brain tumor	Lobar	Lung, choriocarcinoma, melanoma, renal cell carcinoma, thyroid, atrial myxoma
Coagulopathy	Any	Uncommon cause; often associated with prior stroke or underlying vascular anomaly
Drug	Lobar, subarachnoid	Cocaine, amphetamine, phenylpropranolamine
Arteriovenous malformation	Lobar, intraventricular, subarachnoid	Risk is ~2–4% per year for bleeding
Aneurysm	Subarachnoid, intraparenchymal, rarely subdural	Mycotic and nonmycotic forms of aneurysms
Amyloid angiopathy	Lobar	Degenerative disease of intracranial vessels; linkage to Alzheimer's disease, rare in patients <60
Cavernous angioma	Intraparenchymal	Multiple cavernous angiomas linked to mutations in KRIT1, CCM2, and PDCD10 genes
Dural arteriovenous fistula	Lobar, subarachnoid	Produces bleeding by venous hypertension
Capillary telangiectasias	Usually brainstem	Rare cause of hemorrhage

method for acute stroke evaluation (Fig. 21-1). The location of the hemorrhage narrows the differential diagnosis to a few entities. Table 21-5 lists the causes and anatomic spaces involved in hemorrhages.

EMERGENCY MANAGEMENT

Close attention should be paid to airway management since a reduction in the level of consciousness is common and often progressive. The initial blood pressure should be maintained until the results of the CT scan are reviewed. There is growing evidence that intraparenchymal hemorrhage may be exacerbated by acutely elevated blood pressure, and current recommendations are to lower mean arterial blood pressure to <130 mmHg. Blood pressure should be lowered with nonvasodilating IV drugs such as nicardipine, labetalol, or esmolol. Patients with cerebellar hemorrhages or with depressed mental status and radiographic evidence of hydrocephalus should undergo urgent neurosurgical evaluation. Based on the clinical examination and CT findings, further imaging studies may be necessary, including MRI or conventional x-ray angiography. Stuporous or comatose patients generally are treated presumptively for elevated ICP, with tracheal intubation and hyperventilation, mannitol administration, and elevation of the head of the bed while surgical consultation is obtained (Chap. 22).

INTRAPARENCHYMAL HEMORRHAGE

Intraparenchymal hemorrhage is the most common type of intracranial hemorrhage. It accounts for ~10% of all strokes and is associated with a 50% case fatality rate. Incidence rates are particularly high in Asians and African Americans. Hypertension, trauma, and cerebral amyloid angiopathy cause the majority of these hemorrhages. Advanced age and heavy alcohol consumption increase the risk, and cocaine use is one of the most important causes in the young.

Hypertensive Intraparenchymal Hemorrhage

Pathophysiology

Hypertensive intraparenchymal hemorrhage (hypertensive hemorrhage or hypertensive intracerebral hemorrhage) usually results from spontaneous rupture of a small penetrating artery deep in the brain. The most common sites are the basal ganglia (especially the putamen), thalamus, cerebellum, and pons. When hemorrhages occur in other brain areas or in nonhypertensive patients, greater consideration should be given to hemorrhagic disorders,

neoplasms, vascular malformations, and other causes. The small arteries in these areas seem most prone to hypertension-induced vascular injury. The hemorrhage may be small or a large clot may form and compress adjacent tissue, causing herniation and death. Blood may dissect into the ventricular space, which substantially increases morbidity and may cause hydrocephalus.

Most hypertensive intraparenchymal hemorrhages develop over 30–90 min, whereas those associated with anticoagulant therapy may evolve for as long as 24–48 h. Within 48 h macrophages begin to phagocytize the hemorrhage at its outer surface. After 1–6 months, the hemorrhage is generally resolved to a slitlike orange cavity lined with glial scar and hemosiderin-laden macrophages.

Clinical Manifestations

Although not particularly associated with exertion, intracerebral hemorrhages almost always occur while the patient is awake and sometimes when stressed. The hemorrhage generally presents as the abrupt onset of focal neurologic deficit. Seizures are uncommon. The focal deficit typically worsens steadily over 30–90 min and is associated with a diminishing level of consciousness and signs of increased ICP, such as headache and vomiting.

The putamen is the most common site for hypertensive hemorrhage, and the adjacent internal capsule is usually damaged (**Fig. 21-17**). Contralateral hemiparesis is therefore the sentinel sign. When mild, the face sags on one side over 5–30 min, speech becomes slurred, the arm and leg gradually weaken, and the eyes deviate away from the side of the hemiparesis. The paralysis may worsen until the affected limbs become flaccid or extend rigidly. When hemorrhages are large, drowsiness gives way to stupor as signs of upper brainstem compression appear. Coma ensues, accompanied by deep, irregular, or intermittent respiration, a dilated and fixed ipsilateral pupil, and decerebrate rigidity. In milder cases, edema in adjacent brain tissue may cause progressive deterioration over 12–72 h.

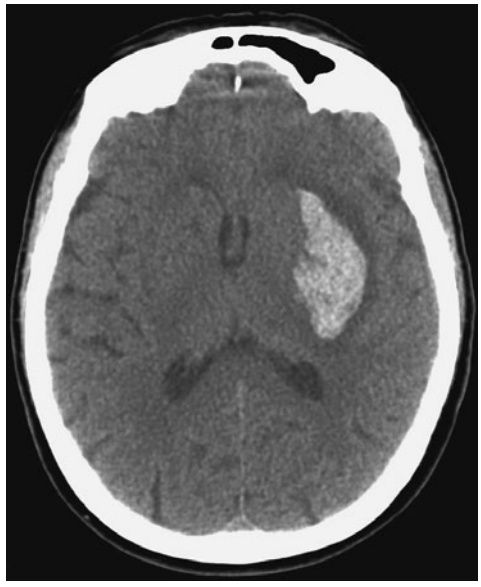

FIGURE 21-17

Hypertensive hemorrhage. Transaxial noncontrast CT scan through the region of the basal ganglia reveals a hematoma involving the left putamen in a patient with rapidly progressive onset of right hemiparesis.

Thalamic hemorrhages also produce a contralateral hemiplegia or hemiparesis from pressure on, or dissection into, the adjacent internal capsule. A prominent sensory deficit involving all modalities is usually present. Aphasia, often with preserved verbal repetition, may occur after hemorrhage into the dominant thalamus, and constructional apraxia or mutism occurs in some cases of nondominant hemorrhage. There may also be a homonymous visual field defect. Thalamic hemorrhages cause several typical ocular disturbances by virtue of extension inferiorly into the upper midbrain. These include deviation of the eyes downward and inward so that they appear to be looking at the nose, unequal pupils with absence of light reaction, skew deviation with the eye opposite the hemorrhage displaced downward and medially, ipsilateral Horner's syndrome, absence of convergence, paralysis of vertical gaze, and retraction nystagmus. Patients may later develop a chronic, contralateral pain syndrome (Déjerine-Roussy syndrome).

In pontine hemorrhages, deep coma with quadriplegia usually occurs over a few minutes. There is often prominent decerebrate rigidity and "pin-point" (1 mm) pupils that react to light. There is impairment of reflex horizontal eye movements evoked by head turning (doll's-head or oculocephalic maneuver) or by irrigation of the ears with ice water (Chap. 14). Hyperpnea, severe hypertension, and hyperhidrosis are common. Death often occurs within a few hours, but small hemorrhages are compatible with survival.

Cerebellar hemorrhages usually develop over several hours and are characterized by occipital headache, repeated vomiting, and ataxia of gait. In mild cases there may be no other neurologic signs other than gait ataxia. Dizziness or vertigo may be prominent. There is often paresis of conjugate lateral gaze toward the side of the hemorrhage, forced deviation of the eyes to the opposite side, or an ipsilateral sixth nerve palsy. Less frequent ocular signs include blepharospasm, involuntary closure of one eye, ocular bobbing, and skew deviation. Dysarthria and dysphagia may occur. As the hours pass, the patient often becomes stuporous and then comatose from brainstem compression or obstructive hydrocephalus; immediate surgical evacuation before brainstem compression occurs may be lifesaving. Hydrocephalus from fourth ventricle compression can be relieved by external ventricular drainage, but definitive hematoma evacuation is essential for survival. If the deep cerebellar nuclei are spared, full recovery is common.

Lobar Hemorrhage

Symptoms and signs appear over several minutes. Most lobar hemorrhages are small and cause a restricted clinical syndrome that simulates an embolus to an artery supplying one lobe. For example, the major neurologic deficit with an occipital hemorrhage is hemianopia; with a left temporal hemorrhage, aphasia and delirium; with a parietal hemorrhage, hemisensory loss; and with frontal hemorrhage, arm weakness. Large hemorrhages may be associated with stupor or coma if they compress the thalamus or midbrain. Most patients with lobar hemorrhages have focal headaches, and more than half vomit or are drowsy. Stiff neck and seizures are uncommon.

Other Causes of Intracerebral Hemorrhage

Cerebral amyloid angiopathy is a disease of the elderly in which arteriolar degeneration occurs and amyloid is deposited in the walls of the cerebral arteries. Amyloid angiopathy causes both single and recurrent lobar hemorrhages and is probably the most common cause of lobar hemorrhage in the elderly. It accounts for some intracranial hemorrhages associated with IV thrombolysis given for MI. This disorder can be suspected in patients who present with multiple hemorrhages (and infarcts) over several months or years, or in patients with "micro-bleeds" seen on brain MRI sequences sensitive for hemosiderin, but it is definitively diagnosed by pathologic demonstration of Congo red staining of amyloid in cerebral vessels. The ε2 and ε4 allelic variations of the apolipoprotein E gene are associated with increased risk of recurrent lobar hemorrhage and may therefore be markers of amyloid angiopathy. Currently, there is no specific therapy, though antiplatelet and anticoagulating agents are typically avoided.

Cocaine is a frequent cause of stroke in young (<45 years) patients. Intracerebral hemorrhage, ischemic stroke, and SAH are all associated with cocaine use. Angiographic findings vary from completely normal arteries to large-vessel occlusion or stenosis, vasospasm, or changes consistent with vasculitis. The mechanism of cocaine-related stroke is not known, but cocaine enhances sympathetic activity causing acute, sometimes severe, hypertension, and this may lead to hemorrhage. Slightly more than half of cocaine-related intracranial hemorrhages are intracerebral, and the rest are subarachnoid. In cases of SAH, a saccular aneurysm is usually identified. Presumably, acute hypertension causes aneurysmal rupture.

Head injury often causes intracranial bleeding. The common sites are intracerebral (especially temporal and inferior frontal lobes) and into the subarachnoid, subdural, and epidural spaces. Trauma must be considered in any patient with an unexplained acute neurologic deficit (hemiparesis, stupor, or confusion), particularly if the deficit occurred in the context of a fall (Chap. 31).

Intracranial hemorrhages associated with *anticoagulant therapy* can occur at any location; they are often lobar or subdural. Anticoagulant-related intracerebral hemorrhages may evolve slowly, over 24–48 h. Coagulopathy and thrombocytopenia should be reversed rapidly, as discussed below. Intracerebral hemorrhage associated with *hematologic disorders* (leukemia, aplastic anemia, thrombocytopenic purpura) can occur at any site and may present as multiple intracerebral hemorrhages. Skin and mucous membrane bleeding is usually evident and offers a diagnostic clue.

Hemorrhage into a *brain tumor* may be the first manifestation of neoplasm. Choriocarcinoma, malignant melanoma, renal cell carcinoma, and bronchogenic carcinoma are among the most common metastatic tumors associated with intracerebral hemorrhage. Glioblastoma multiforme in adults and medulloblastoma in children may also have areas of intracerebral hemorrhage.

Hypertensive encephalopathy is a complication of malignant hypertension. In this acute syndrome, severe hypertension is associated with headache, nausea, vomiting, convulsions, confusion, stupor, and coma. Focal or lateralizing neurologic signs, either transitory or permanent, may occur but are infrequent and therefore suggest some other vascular disease (hemorrhage, embolism, or atherosclerotic thrombosis). There are retinal hemorrhages, exudates, papilledema (hypertensive retinopathy), and evidence of renal and cardiac disease. In most cases ICP and CSF protein levels are elevated. The hypertension may be essential or due to chronic renal disease, acute glomerulonephritis, acute toxemia of pregnancy, pheochromocytoma, or other causes. Lowering the blood pressure reverses the process, but stroke can occur, especially if blood pressure is lowered too rapidly. Neuropathologic examination reveals multifocal to diffuse cerebral edema and hemorrhages of various sizes from petechial to massive. Microscopically, there are necrosis of arterioles, minute cerebral infarcts, and hemorrhages. The term *hypertensive encephalopathy* should be reserved for this syndrome and not for chronic recurrent headaches, dizziness, recurrent TIAs, or small strokes that often occur in association with high blood pressure.

Primary intraventricular hemorrhage is rare. It usually begins within the substance of the brain and dissects into the ventricular system without leaving signs of intraparenchymal hemorrhage. Alternatively, bleeding can arise from periependymal veins. Vasculitis, usually polyarteritis nodosa or lupus erythematosus, can produce hemorrhage into any region of the central nervous system; most hemorrhages are associated with hypertension, but the arteritis itself may cause bleeding by disrupting the vessel wall. *Sepsis* can cause small petechial hemorrhages throughout the cerebral white matter. *Moyamoya disease*, mainly an occlusive arterial disease that causes ischemic symptoms, may on occasion produce intraparenchymal hemorrhage, particularly in the

young. Hemorrhages into the spinal cord are usually the result of an AVM or metastatic tumor. *Epidural spinal hemorrhage* produces a rapidly evolving syndrome of spinal cord or nerve root compression (Chap. 30). Spinal hemorrhages usually present with sudden back pain and some manifestation of myelopathy.

Laboratory and Imaging Evaluation

Patients should have routine blood chemistries and hematologic studies. Specific attention to the platelet count and PT/PTT are important to identify coagulopathy. CT imaging reliably detects acute focal hemorrhages in the supratentorial space. Small pontine hemorrhages may not be identified because of motion and bone-induced artifact that obscure structures in the posterior fossa. After the first 2 weeks, x-ray attenuation values of clotted blood diminish until they become isodense with surrounding brain. Mass effect and edema may remain. In some cases, a surrounding rim of contrast enhancement appears after 2–4 weeks and may persist for months. MRI, though more sensitive for delineating posterior fossa lesions, is generally not necessary in most instances. Images of flowing blood on MRI scan may identify AVMs as the cause of the hemorrhage. MRI, CT angiography, and conventional x-ray angiography are used when the cause of intracranial hemorrhage is uncertain, particularly if the patient is young or not hypertensive and the hematoma is not in one of the four usual sites for hypertensive hemorrhage. For example, hemorrhage into the temporal lobe suggests rupture of a MCA saccular aneurysm.

Since patients typically have focal neurologic signs and obtundation, and often show signs of increased ICP, a lumbar puncture should be avoided as it may induce cerebral herniation.

℞ Treatment: INTRACRANIAL HEMORRHAGE

ACUTE MANAGEMENT Nearly 50% of patients with a hypertensive intracerebral hemorrhage die, but others may have a good to complete recovery if they survive the initial hemorrhage. The volume and location of the hematoma determine the prognosis. In general, supratentorial hematomas with volumes <30 mL have a good prognosis; 30–60 mL, an intermediate prognosis; and >60 mL, a poor prognosis during initial hospitalization. Extension into the ventricular system worsens the prognosis, as does advanced age, location within the posterior fossa, and depressed level of consciousness at initial presentation. Any identified coagulopathy should be reversed as soon as possible. For patients taking warfarin sodium, more rapid reversal of coagulopathy can be achieved by infusing prothrombin complex concentrates followed by fresh-frozen plasma and vitamin K. When intracerebral hemorrhage is associated with thrombocytopenia (platelet count <50,000/μL), transfusion of fresh platelets is indicated. At present, little can be done about the hemorrhage itself. Hematomas may expand for several hours following the initial hemorrhage, so treating severe hypertension seems reasonable to prevent hematoma progression. Preliminary data suggested that treatment with recombinant factor VIIa, even in patients without coagulopathy, may decrease risk of hematoma expansion and improve clinical outcome; however, a multicenter randomized trial of this approach did not show clinical benefit despite a decrease in hematoma expansion.

Evacuation of supratentorial hematomas does not appear to improve outcome. The International Surgical Trial in Intracerebral Hemorrhage (STICH) randomized 1033 patients with supratentorial intracerebral hemorrhage to either early surgical evacuation or initial medical management. No benefit was found in the early surgery arm, though analysis was complicated by the fact that 26% of patients in the initial medical management group ultimately had surgery for neurologic deterioration. Overall, these data do not support routine surgical evacuation of supratentorial hemorrhages; however, many centers operate on patients with progressive neurologic deterioration. Surgical techniques continue to evolve, and minimally invasive endoscopic hematoma evacuation may prove beneficial in future trials.

For cerebellar hemorrhages, a neurosurgeon should be consulted immediately to assist with the evaluation; most cerebellar hematomas >3 cm in diameter will require surgical evacuation. If the patient is alert without focal brainstem signs and if the hematoma is <1 cm in diameter, surgical removal is usually unnecessary. Patients with hematomas between 1 and 3 cm require careful observation for signs of impaired consciousness and precipitous respiratory failure.

Tissue surrounding hematomas is displaced and compressed but not necessarily infarcted. Hence, in survivors, major improvement commonly occurs as the hematoma is reabsorbed and the adjacent tissue regains its function. Careful management of the patient during the acute phase of the hemorrhage can lead to considerable recovery.

Surprisingly, ICP is often normal even with large intraparenchymal hemorrhages. However, if the hematoma causes marked midline shift of structures with consequent obtundation, coma, or hydrocephalus, osmotic agents coupled with induced hyperventilation can be instituted to lower ICP (Chap. 22). These maneuvers will provide enough time to place a ventriculostomy or ICP monitor. Once ICP is recorded, further hyperventilation

and osmotic therapy can be tailored to the individual patient. For example, if ICP is found to be high, CSF can be drained from the ventricular space and osmotic therapy continued; persistent or progressive elevation in ICP may prompt surgical evacuation of the clot or withdrawal of support. Alternately, if ICP is normal or only mildly elevated, induced hyperventilation can be reversed and osmotic therapy tapered. Since hyperventilation may actually produce ischemia by cerebral vasoconstriction, induced hyperventilation should be limited to acute resuscitation of the patient with presumptive high ICP and eliminated once other treatments (osmotic therapy or surgical treatments) have been instituted. Glucocorticoids are not helpful for the edema from intracerebral hematoma.

PREVENTION Hypertension is the leading cause of primary intracerebral hemorrhage. Prevention is aimed at reducing hypertension, excessive alcohol use, and use of illicit drugs such as cocaine and amphetamines.

VASCULAR ANOMALIES

Vascular anomalies can be divided into congenital vascular malformations and acquired vascular lesions.

CONGENITAL VASCULAR MALFORMATIONS

True *arteriovenous malformations* (AVMs), venous anomalies, and capillary telangiectasias are lesions that usually remain clinically silent through life. Although most AVMs are congenital, cases of acquired lesions have been reported.

True AVMs are congenital shunts between the arterial and venous systems that may present as headache, seizures, and intracranial hemorrhage. AVMs consist of a tangle of abnormal vessels across the cortical surface or deep within the brain substance. AVMs vary in size from a small blemish a few millimeters in diameter to a large mass of tortuous channels composing an arteriovenous shunt of sufficient magnitude to raise cardiac output. The blood vessels forming the tangle interposed between arteries and veins are usually abnormally thin and do not have a normal structure. AVMs occur in all parts of the cerebral hemispheres, brainstem, and spinal cord, but the largest ones are most frequently in the posterior half of the hemispheres, commonly forming a wedge-shaped lesion extending from the cortex to the ventricle.

Although the lesion is thought to be present from birth in most patients, bleeding or other symptoms are most common between 10 and 30 years of age, occasionally as late as the 50s. AVMs are more frequent in men, and rare familial cases have been described.

Headache (without bleeding) may be hemicranial and throbbing, like migraine, or diffuse. Focal seizures, with or without generalization, occur in ~30% of cases. Half of AVMs become evident as intracerebral hemorrhages. In most, the hemorrhage is mainly intraparenchymal with extension into the subarachnoid space in some cases. Blood is usually not deposited in the basal cisterns, and symptomatic cerebral vasospasm is rare. The risk of rerupture is ~2–4% per year and is particularly high in the first few weeks. Hemorrhages may be massive, leading to death, or may be as small as 1 cm in diameter, leading to minor focal symptoms or no deficit. The AVM may be large enough to steal blood away from adjacent normal brain tissue or to increase venous pressure significantly to produce venous ischemia locally and in remote areas of the brain. This is seen most often with large AVMs in the territory of the MCA.

Large AVMs of the anterior circulation may be associated with a systolic and diastolic bruit (sometimes self-audible) over the eye, forehead, or neck and a bounding carotid pulse. Headache at the onset of AVM rupture is not generally as explosive as with aneurysmal rupture. MRI is better than CT for diagnosis, although noncontrast CT scanning sometimes detects calcification of the AVM and contrast may demonstrate the abnormal blood vessels. Once identified, conventional x-ray angiography is the gold standard for evaluating the precise anatomy of the AVM.

Surgical treatment of symptomatic AVMs, often with preoperative embolization to reduce operative bleeding, is usually indicated for accessible lesions. Stereotaxic radiation, an alternative to surgery, can produce a slow sclerosis of arterial channels over 2–3 years.

Patients with asymptomatic AVMs have about a ~2–4% per year risk for hemorrhage. Several angiographic features of the AVM can be used to help predict future bleeding risk. Paradoxically, smaller lesions seem to have a higher hemorrhage rate. The impact of recurrent hemorrhage on disability is relatively modest, so the indication for surgery in asymptomatic AVMs is debated. A large-scale randomized trial is currently addressing this question.

Venous anomalies are the result of development of anomalous cerebral, cerebellar, or brainstem drainage. These structures, unlike AVMs, are functional venous channels. They are of little clinical significance and should be ignored if found incidentally on brain imaging studies. Surgical resection of these anomalies may result in venous infarction and hemorrhage. Venous anomalies may be associated with cavernous malformations (see below), which do carry some bleeding risk. If resection of a cavernous malformation is attempted, the venous anomaly should not be disturbed.

Capillary telangiectasias are true capillary malformations that often form extensive vascular networks through an otherwise normal brain structure. The pons and deep cerebral white matter are typical locations, and these capillary malformations can be seen in patients with hereditary

hemorrhagic telangiectasia (Osler-Rendu-Weber) syndrome. If bleeding does occur, it rarely produces mass effect or significant symptoms. No treatment options exist.

ACQUIRED VASCULAR LESIONS

Cavernous angiomas are tufts of capillary sinusoids that form within the deep hemispheric white matter and brainstem with no normal intervening neural structures. The pathogenesis is unclear. Familial cavernous angiomas have been mapped to several different chromosomal loci: KRIT1 (7q21-q22), CCM2 (7p13), and PDCD10 (3q26.1). Both KRIT1 and CCM2 are instrumental in blood vessel formation while PDCD10 is an apoptotic gene. Cavernous angiomas are typically <1 cm in diameter and are often associated with a venous anomaly. Bleeding is usually of small volume, causing slight mass effect only. The bleeding risk for single cavernous malformations is 0.7–1.5% per year and may be higher for patients with prior clinical hemorrhage or multiple malformations. Seizures may occur if the malformation is located near the cerebral cortex. Surgical resection eliminates bleeding risk and may reduce seizure risk, but it is reserved for those malformations that form near the brain surface. Radiation treatment has not been shown to be of benefit.

Dural arteriovenous fistulas are acquired connections usually from a dural artery to a dural sinus. Patients may complain of a pulse-synchronous cephalic bruit ("pulsatile tinnitus") and headache. Depending on the magnitude of the shunt, venous pressures may rise high enough to cause cortical ischemia or venous hypertension and hemorrhage, particularly subarachnoid hemorrhage. Surgical and endovascular techniques are usually curative. These fistulas may form because of trauma, but most are idiopathic. There is an association between fistulas and dural sinus thrombosis. Fistulas have been observed to appear months to years following venous sinus thrombosis, suggesting that angiogenesis factors elaborated from the thrombotic process may cause these anomalous connections to form. Alternatively, dural arteriovenous fistulas can produce venous sinus occlusion over time, perhaps from the high pressure and high flow through a venous structure.

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CHAPTER 22

NEUROLOGIC CRITICAL CARE, INCLUDING HYPOXIC-ISCHEMIC ENCEPHALOPATHY AND SUBARACHNOID HEMORRHAGE

J. Claude Hemphill, III ■ Wade S. Smith

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Life-threatening neurologic illness may be caused by a primary disorder affecting any region of the neuraxis or may occur as a consequence of a systemic disorder such as hepatic failure, multisystem organ failure, or cardiac arrest (**Table 22-1**). Neurologic critical care focuses on preservation of neurologic tissue and prevention of secondary brain injury caused by ischemia, edema, and elevated intracranial pressure (ICP).

PATHOPHYSIOLOGY

Brain Edema

Swelling, or edema, of brain tissue occurs with many types of brain injury. The two principal types of edema are vasogenic and cytotoxic. *Vasogenic edema* refers to the influx of fluid and solutes into the brain through an incompetent blood-brain barrier (BBB). In the normal cerebral vasculature, endothelial tight junctions associated with astrocytes create an impermeable barrier (the BBB), through which access into the brain interstitium is dependent upon specific transport mechanisms (Chap. 19). The BBB may be compromised in ischemia, trauma, infection, and metabolic derangements. Typically, vasogenic edema develops rapidly following injury. *Cytotoxic edema* refers to cellular swelling and occurs in a variety of settings including brain ischemia and trauma. Early astrocytic swelling is a hallmark of ischemia. Brain edema that is clinically significant usually represents a combination of vasogenic and cellular components. Edema can lead to increased ICP as well as tissue shifts and brain displacement from focal processes (Chap. 14). These tissue shifts can cause injury by mechanical distraction and compression in addition to the ischemia of impaired perfusion consequent to the elevated ICP.

Ischemic Cascade and Cellular Injury

When delivery of substrates, principally oxygen and glucose, is inadequate to sustain cellular function, a series of interrelated biochemical reactions known as the *ischemic cascade* is initiated (see Fig. 21-2). The release of excitatory amino acids, especially glutamate, leads to influx of calcium and sodium ions, which disrupt cellular homeostasis. An increased intracellular calcium concentration may activate proteases and lipases, which then lead to lipid peroxidation and free radical–mediated cell membrane injury. Cytotoxic edema ensues, and ultimately necrotic cell death and tissue infarction occur. This pathway to irreversible cell death is common to ischemic stroke, global cerebral ischemia, and traumatic brain injury. *Penumbra* refers to ischemic brain tissue that has not yet undergone irreversible infarction, implying that the region is potentially salvageable if ischemia can be reversed. Factors that may

TABLE 22-1

NEUROLOGIC DISORDERS IN CRITICAL ILLNESS

LOCALIZATION ALONG NEUROAXIS	SYNDROME
Central Nervous System	
Brain: Cerebral hemispheres	Global encephalopathy
	Sepsis
	Organ failure—hepatic, renal
	Medication related
	Sedatives/hypnotics/analgesics
	H_2 blockers, antihypertensives
	Drug overdose
	Electrolyte disturbance—hyponatremia, hypoglycemia
	Hypotension/hypoperfusion
	Hypoxia
	Meningitis
	Subarachnoid hemorrhage
	Wernicke's disease
	Seizure—postictal or nonconvulsive status
	Hypertensive encephalopathy
	Hypothyroidism—myxedema
	Focal deficits
	Ischemic stroke
	Tumor
	Abscess, subdural empyema
	Subdural/epidural hematoma
Brainstem	Mass effect and compression
	Ischemic stroke, intraparenchymal hemorrhage
	Hypoxia
Spinal cord	Mass effect and compression
	Disc herniation
	Epidural hematoma
	Ischemia—hypotension/embolic
	Subdural empyema
	Trauma, central cord syndrome
Peripheral Nervous System	
Peripheral nerve	Critical illness polyneuropathy
Axonal	Possible neuromuscular blocking agent complication
	Metabolic disturbances, uremia, hyperglycemia
	Medication effects—chemotherapeutic, antiretroviral
Demyelinating	Guillian-Barré syndrome
	Chronic inflammatory demyelinating polyneuropathy
Neuromuscular junction	Prolonged effect of neuromuscular blockade
	Medication effects—aminoglycosides
	Myasthenia-gravis, Lambert-Eaton syndrome
Muscle	Critical illness myopathy
	Septic myopathy
	Cachectic myopathy—with or without disuse atrophy
	Electrolyte disturbances—hypokalemia/hyperkalemia, hypophosphatemia
	Acute quadriplegic myopathy

exacerbate ischemic brain injury include systemic hypotension and hypoxia, which further reduce substrate delivery to vulnerable brain tissue, and fever, seizures, and hyperglycemia, which can increase cellular metabolism outstripping compensatory processes. Clinically, these events are known as *secondary brain insults* because they lead to exacerbation of the primary brain injury. Prevention, identification, and treatment of secondary brain insults are fundamental goals of management.

An alternative pathway of cellular injury is *apoptosis*. This process implies programmed cell death, which may occur in the setting of ischemic stroke, global cerebral

ischemia, traumatic brain injury, and possibly intracerebral hemorrhage. Apoptotic cell death can be distinguished histologically from the necrotic cell death of ischemia and is mediated through a different set of biochemical pathways. At present, interventions for prevention and treatment of apoptotic cell death remain less well defined than those for ischemia. Excitotoxicity and mechanisms of cell death are discussed in more detail in Chap. 19.

Cerebral Perfusion and Autoregulation

Brain tissue requires constant perfusion in order to ensure adequate delivery of substrate. The hemodynamic response of the brain has the capacity to preserve perfusion across a wide range of systemic blood pressures. Cerebral perfusion pressure (CPP), defined as the mean systemic arterial pressure (MAP) minus the ICP, provides the driving force for circulation across the capillary beds of the brain. *Autoregulation* refers to the physiologic response whereby cerebral blood flow (CBF) remains relatively constant over a wide range of blood pressures as a consequence of alterations of cerebrovascular resistance (**Fig. 22-1**). If systemic blood pressure drops, cerebral perfusion is preserved through vasodilatation of arterioles in the brain; likewise, arteriolar vasoconstriction occurs at high systemic pressures to prevent hyperperfusion. At the extreme limits of MAP or CPP (high or low), flow becomes directly related to perfusion pressure. These autoregulatory changes occur in the microcirculation and are mediated by vessels below the resolution of those seen on angiography. CBF is also strongly influenced by pH and P_{CO2}. CBF increases with hypercapnia and acidosis and decreases with hypocapnia and alkalosis. This forms the basis for the use of hyperventilation to lower ICP, and this effect on ICP is mediated through a decrease in intracranial blood volume. Cerebral autoregulation is critical to the normal homeostatic functioning of the brain, and this process may be disordered focally and unpredictably in disease states such as traumatic brain injury and severe focal cerebral ischemia.

Cerebrospinal Fluid and Intracranial Pressure

The cranial contents consist essentially of brain, cerebrospinal fluid (CSF), and blood. CSF is produced principally in the choroid plexus of each lateral ventricle, exits the brain via the foramina of Luschka and Magendi, and flows over the cortex to be absorbed into the venous system along the superior sagittal sinus. Approximately 150 mL of CSF are contained within the ventricles and surrounding the brain and spinal cord; the cerebral blood volume is also ~150 mL. The bony skull offers excellent protection for the brain but allows little tolerance for additional volume. Significant increases in volume eventually result in increased ICP. Obstruction of CSF outflow, edema of cerebral tissue, or increases in volume from tumor or hematoma may increase ICP. Elevated ICP diminishes cerebral perfusion and can lead to tissue ischemia. Ischemia in turn may lead to vasodilatation via autoregulatory mechanisms designed to restore cerebral perfusion. However, vasodilatation also increases cerebral blood volume, which in turn then increases ICP, lowers CPP, and provokes further ischemia (**Fig. 22-2**). This vicious cycle is commonly seen in traumatic brain injury, massive intracerebral hemorrhage, and large hemispheric infarcts with significant tissue shifts.

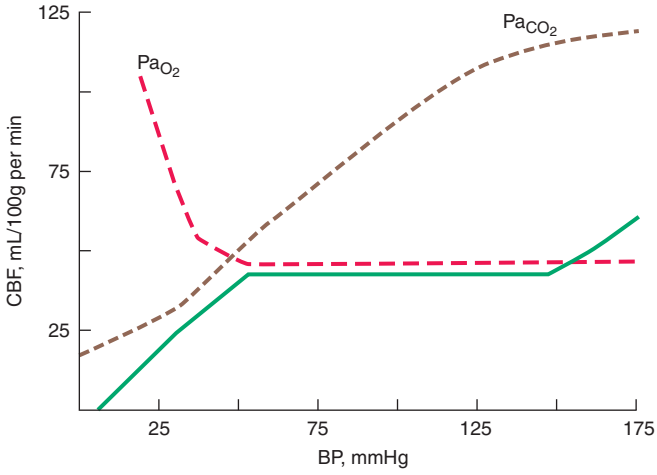

FIGURE 22-1

Autoregulation of cerebral blood flow (solid line). Cerebral perfusion is constant over a wide range of systemic blood pressure. Perfusion is increased in the setting of hypoxia or hypercarbia. BP, blood pressure; CBF, cerebral blood flow. *(Reprinted with permission from Anesthesiology 43:447, 1975. Copyright 1975, Lippincott Company.)*

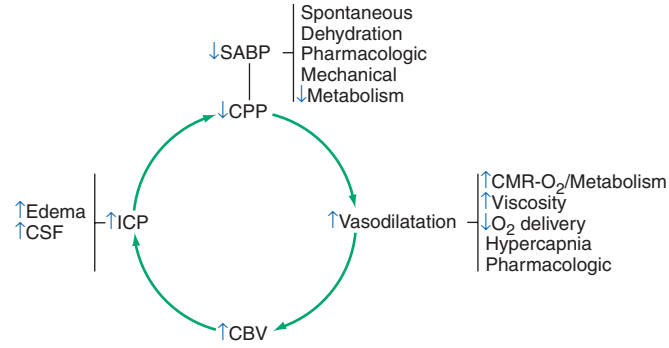

FIGURE 22-2

Ischemia and vasodilatation. Reduced cerebral perfusion pressure (CPP) leads to increased ischemia, vasodilatation, increased intracranial pressure (ICP), and further reductions in CPP, a cycle leading to further neurologic injury. CBV, cerebral blood volume; CMR, cerebral metabolic rate; CSF, cerebrospinal fluid; SABP, systolic arterial blood pressure. *(Adapted from MJ Rosner et al: J Neurosurg 83:949, 1995; with permission.)*

Approach to the Patient: SEVERE CNS DYSFUNCTION

Critically ill patients with severe central nervous system dysfunction require rapid evaluation and intervention in order to limit primary and secondary brain injury. Initial neurologic evaluation should be performed concurrent with stabilization of basic respiratory, cardiac, and hemodynamic parameters. Significant barriers may exist to neurologic assessment in the critical care unit, including endotracheal intubation and the use of sedative or paralytic agents to facilitate procedures.

An impaired level of consciousness is common in critically ill patients. The essential first task in assessment is to determine whether the cause of dysfunction is related to a diffuse, usually metabolic, process or whether a focal, usually structural, process is implicated. Examples of diffuse processes include metabolic encephalopathies related to organ failure, drug overdose, or hypoxia-ischemia. Focal processes include ischemic and hemorrhagic stroke and traumatic brain injury, especially with intracranial hematomas. Since these two categories of disorders have fundamentally different causes, treatments, and prognoses, the initial focus is on making this distinction rapidly and accurately. The approach to the comatose patient is discussed in Chap. 14; etiologies are listed in Table 14-1.

Minor focal deficits may be present on the neurologic examination in patients with metabolic encephalopathies. However, the finding of prominent focal signs such as pupillary asymmetry, hemiparesis, gaze palsy, or paraplegia should suggest the possibility of a structural lesion. All patients with a decreased level of consciousness associated with focal findings should undergo an urgent neuroimaging procedure, as should all patients with coma of unknown etiology. CT scanning is usually the most appropriate initial study because it can be performed quickly in critically ill patients and demonstrates hemorrhage, hydrocephalus, and intracranial tissue shifts well. MRI may provide more specific information in some situations, such as acute ischemic stroke (diffusion-weighted imaging, DWI) and cerebral venous sinus thrombosis (magnetic resonance venography, MRV). Any suggestion of trauma from the history or examination should alert the examiner to the possibility of cervical spine injury and prompt an imaging evaluation using plain x-rays, MRI, or CT.

Other diagnostic studies are best utilized in specific circumstances, usually when neuroimaging studies fail to reveal a structural lesion and the etiology of the altered mental state remains uncertain. Electroencephalography (EEG) can be important in the evaluation of critically ill patients with severe brain dysfunction. The EEG of metabolic encephalopathy typically reveals generalized slowing. One of the most important uses of EEG is to help exclude inapparent seizures, especially nonconvulsive status epilepticus. Untreated continuous or frequently recurrent seizures may cause neuronal injury, making the diagnosis and treatment of seizures crucial in this patient group. Lumbar puncture (LP) may be necessary to exclude infectious processes, and an elevated opening pressure may be an important clue to cerebral venous sinus thrombosis. In patients with coma or profound encephalopathy, it is preferable to perform a neuroimaging study prior to LP. If bacterial meningitis is suspected, an LP may be performed first or antibiotics may be empirically administered before the diagnostic studies are completed. Standard laboratory evaluation of critically ill patients should include assessment of serum electrolytes (especially sodium and calcium), glucose, renal and hepatic function, complete blood count, and coagulation. Serum or urine toxicology screens should be performed in patients with encephalopathy of unknown cause. EEG, LP, and other specific laboratory tests are most useful when the mechanism of the altered level of consciousness is uncertain; they are not routinely performed in clear-cut cases of stroke or traumatic brain injury.

Monitoring of ICP can be an important tool in selected patients. In general, patients who should be considered for ICP monitoring are those with primary neurologic disorders, such as stroke or traumatic brain injury, who are at significant risk for secondary brain injury due to elevated ICP and decreased CPP. Included are patients with the following: severe traumatic brain injury [Glasgow Coma Scale (GCS) score $\leq$8 (Table 31-2)]; large tissue shifts from supratentorial ischemic or hemorrhagic stroke; or hydrocephalus from subarachnoid hemorrhage (SAH), intraventricular hemorrhage, or posterior fossa stroke. An additional disorder in which ICP monitoring can add important information is fulminant hepatic failure, in which elevated ICP may be treated with barbiturates or, eventually, liver transplantation. In general, ventriculostomy is preferable to ICP monitoring devices that are placed in the brain parenchyma, because ventriculostomy allows CSF drainage as a method of treating elevated ICP. However, parenchymal ICP monitoring is most appropriate for patients with diffuse edema and small ventricles (which may make ventriculostomy placement more difficult) or any degree of coagulopathy (in which ventriculostomy carries a higher risk of hemorrhagic complications) (**Fig 22-3**).

TREATMENT OF ELEVATED ICP Elevated ICP may occur in a wide range of disorders including head trauma, intracerebral hemorrhage, SAH with hydrocephalus, and fulminant hepatic failure. Because

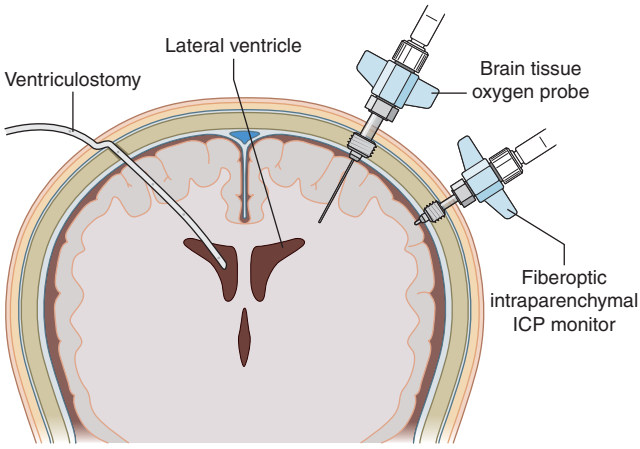

FIGURE 22-3

Intracranial pressure and brain tissue oxygen monitoring. A ventriculostomy allows for drainage of cerebrospinal fluid to treat elevated intracranial pressure (ICP). Fiberoptic ICP and brain tissue oxygen monitors are usually secured using a screwlike skull bolt. Cerebral blood flow and microdialysis probes (not shown) may be placed in a manner similar to the brain tissue oxygen probe.

CSF and blood volume can be redistributed initially, by the time elevated ICP occurs intracranial compliance is severely impaired. At this point, any small increase in the volume of CSF, intravascular blood, edema, or a mass lesion may result in a significant increase in ICP and a decrease in cerebral perfusion. This is a fundamental mechanism of secondary ischemic brain injury and constitutes an emergency that requires immediate attention. In general, ICP should be maintained at <20 mm Hg and CPP should be maintained at >60 mm Hg.

Interventions to lower ICP are ideally based on the underlying mechanism responsible for the elevated ICP (Table 22-2). For example, in hydrocephalus from SAH, the principal cause of elevated ICP is impairment of CSF drainage. In this setting, ventricular drainage of CSF is likely to be sufficient and most appropriate. In head trauma and stroke, cytotoxic edema may be most responsible, and the use of osmotic diuretics such as mannitol becomes an appropriate early step. As described above, elevated ICP may cause tissue ischemia, and, if cerebral autoregulation is intact, the resulting vasodilatation can lead to a cycle of worsening ischemia. Paradoxically, administration of vasopressor agents to increase mean arterial pressure may actually lower ICP by improving perfusion, thereby allowing autoregulatory vasoconstriction as ischemia is relieved and ultimately decreasing intracranial blood volume.

Early signs of elevated ICP include drowsiness and a diminished level of consciousness. Neuroimaging studies may reveal evidence of edema and mass effect. Hypotonic IV fluids should be avoided, and elevation of the head of the bed is recommended. Patients must be carefully observed for risk of aspiration and compromise of the airway as the level of alertness declines. Coma and unilateral pupillary changes are late signs and require immediate intervention. Emergent treatment of elevated ICP is most quickly achieved by intubation and hyperventilation, which causes vasoconstriction and reduces cerebral blood volume. In order to avoid provoking or worsening cerebral ischemia, hyperventilation is best used for short periods of time until a more definitive treatment can be instituted. Furthermore, the effects of hyperventilation on ICP are short-lived, often lasting only for several hours because of the buffering capacity of the cerebral interstitium, and rebound elevations of ICP may accompany abrupt discontinuation

TABLE 22-2

STEPWISE APPROACH TO TREATMENT OF ELEVATED INTRACRANIAL PRESSURE[a]

Insert ICP monitor—ventriculostomy versus parenchymal device
General goals: maintain ICP <20 mmHg and CPP ≥60 mmHg
For ICP > 20–25 mmHg for >5 min:

1. Drain CSF via ventriculostomy (if in place)
2. Elevate head of the bed; midline head position
3. Osmotherapy—mannitol 25–100 g q4h as needed—(maintain serum osmolality <320 mosmol) or hypertonic saline (30 mL, 23.4% NaCl bolus)
4. Glucocorticoids—dexamethasone 4 mg q6h for vasogenic edema from tumor, abscess (avoid glucocorticoids in head trauma, ischemic and hemorrhagic stroke)
5. Sedation (e.g., morphine, propofol, or midazolam); add neuromuscular paralysis if necessary (patient will require endotracheal intubation and mechanical ventilation at this point, if not before)
6. Hyperventilation—to Pa_{co_2} 30–35 mmHg
7. Pressor therapy—phenylephrine, dopamine, or norepinephrine to maintain adequate MAP to ensure CPP ≥60 mmHg (maintain euvolemia to minimize deleterious systemic effects of pressors)
8. Consider second-tier therapies for refractory elevated ICP
   a. High-dose barbiturate therapy ("pentobarb coma")
   b. Aggressive hyperventilation to Pa_{co_2} <30 mmHg
   c. Hypothermia
   d. Hemicraniectomy

[a]Throughout ICP treatment algorithm, consider repeat head CT to identify mass lesions amenable to surgical evacuation.

Note: CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; MAP, mean arterial pressure; Pa_{co_2}, arterial partial pressure of carbon dioxide.

of hyperventilation. As the level of consciousness declines to coma, the ability to follow the neurologic status of the patient by examination deteriorates and measurement of ICP assumes greater importance. If a ventriculostomy device is in place, direct drainage of CSF to reduce ICP is possible. Finally, high-dose barbiturates, decompressive hemicraniectomy, or hypothermia are sometimes used for refractory elevations of ICP, although these have significant side effects and have not been proven to improve outcome.

SECONDARY BRAIN INSULTS Patients with primary brain injuries, whether due to trauma or stroke, are at risk for ongoing secondary ischemic brain injury. Because secondary brain injury can be a major determinant of a poor outcome, strategies for minimizing secondary brain insults are an integral part of the critical care of all patients. While elevated ICP may lead to secondary ischemia, most secondary brain injury is mediated through other clinical events that exacerbate the ischemic cascade already initiated by the primary brain injury. Episodes of secondary brain insults are usually not associated with apparent neurologic worsening. Rather, they lead to cumulative injury, which manifests as higher mortality or worsened long-term functional outcome. Thus, close monitoring of vital signs is important, as is early intervention to prevent secondary ischemia. Avoiding hypotension and hypoxia is critical, as significant hypotensive events (systolic blood pressure <90 mm Hg) as short as 10 min in duration have been shown to adversely influence outcome after traumatic brain injury. Even in patients with stroke or head trauma who do not require ICP monitoring, close attention to adequate cerebral perfusion is warranted. Hypoxia (pulse oximetry saturation < 90%), particularly in combination with hypotension, also leads to secondary brain injury. Likewise, fever and hyperglycemia both worsen experimental ischemia and have been associated with worsened clinical outcome after stroke and head trauma. Aggressive control of fever with a goal of normothermia is warranted but may be difficult to achieve with antipyretic medications and cooling blankets. The value of newer surface or intravascular temperature control devices for the management of refractory fever is under investigation. The use of IV insulin infusion is encouraged for control of hyperglycemia as this allows better regulation of serum glucose levels than subcutaneous insulin. A reasonable goal is to maintain the serum glucose level at <7.8 mmol/L (<140 mg/dL), although some have suggested that even tighter control is warranted. New cerebral monitoring tools that allow continuous evaluation of brain tissue oxygen tension, CBF, and metabolism (via microdialysis) may further improve the management of secondary brain injury.

CRITICAL CARE DISORDERS OF THE CENTRAL NERVOUS SYSTEM

HYPOXIC-ISCHEMIC ENCEPHALOPATHY

This occurs from lack of delivery of oxygen to the brain because of hypotension or respiratory failure. Causes include myocardial infarction, cardiac arrest, shock, asphyxiation, paralysis of respiration, and carbon monoxide or cyanide poisoning. In some circumstances, hypoxia may predominate. Carbon monoxide and cyanide poisoning are termed *histotoxic hypoxia* since they cause a direct impairment of the respiratory chain.

Clinical Manifestations

Mild degrees of pure hypoxia, such as occur at high altitudes, cause impaired judgment, inattentiveness, motor incoordination, and, at times, euphoria. However, with hypoxia-ischemia, such as occurs with circulatory arrest, consciousness is lost within seconds. If circulation is restored within 3–5 min, full recovery may occur, but if hypoxia-ischemia lasts beyond 3–5 min, some degree of permanent cerebral damage is the rule. Except in extreme cases, it may be difficult to judge the precise degree of hypoxia-ischemia, and some patients make a relatively full recovery after even 8–10 min of global cerebral ischemia. The distinction between pure hypoxia and hypoxia-ischemia is important, since a Pa_{O_2} as low as 20 mmHg (2.7 kPa) can be well tolerated if it develops gradually and normal blood pressure is maintained, but short durations of very low or absent cerebral circulation may result in permanent impairment.

Clinical examination at different time points after a hypoxic-ischemic insult (especially cardiac arrest) is useful in assessing prognosis for long-term neurologic outcome. The prognosis is better for patients with intact brainstem function, as indicated by normal pupillary light responses and intact oculocephalic (doll's-eyes), oculovestibular (caloric), and corneal reflexes (**Fig. 22-4**). Absence of these reflexes and the presence of persistently dilated pupils that do not react to light are grave prognostic signs. A uniformly dismal prognosis from hypoxic-ischemic coma is conveyed by an absent pupillary light reflex or extensor or absent motor response to pain on day 3 following the injury. Electrophysiologically, the bilateral absence of the N20 component of the somatosensory evoked response (SSEPs) in the first several days also conveys a poor prognosis. A very elevated serum level (>33 μg/L) of the biochemical marker neuron-specific enolase (NSE) is indicative of brain damage after resuscitation from cardiac arrest and predicts a poor outcome. However, at present, SSEPs and NSE levels may be difficult to obtain in a timely fashion, with SSEP testing requiring substantial expertise in interpretation and NSE measurements not yet standardized. Whether administration of mild hypothermia

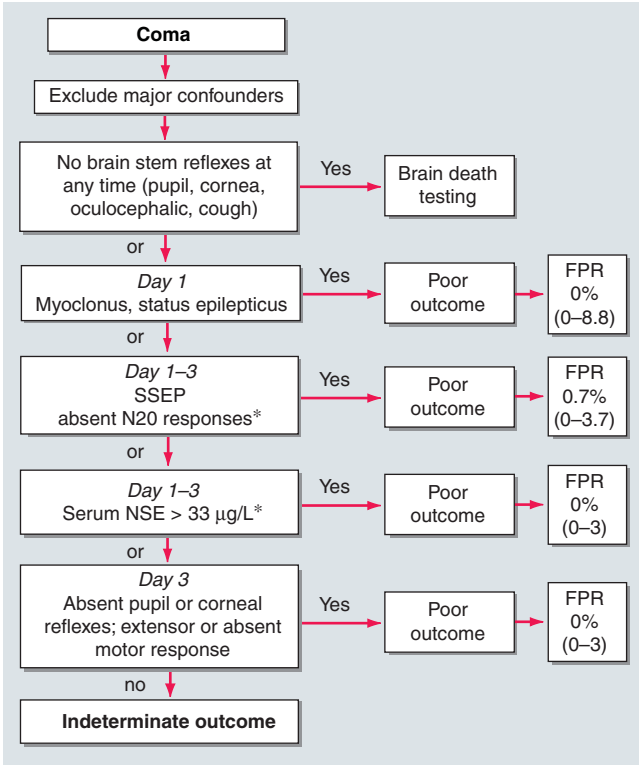

FIGURE 22-4

Prognostication of outcome in comatose survivors of cardiopulmonary resuscitation. Numbers in parentheses are 95% confidence intervals. Confounders could include use of sedatives or neuromuscular blocking agents, hypothermia therapy, organ failure, or shock. Tests denoted with an * may not be available in a timely and standardized manner. SSEP, somatosensory evoked potentials; NSE, neuron-specific enolase; FPR, false-positive rate. *(From Wijdicks et al, with permission.)*

after cardiac arrest (see Treatment) will alter the usefulness of these clinical and electrophysiologic predictors is unknown. Long-term consequences of hypoxic-ischemic encephalopathy include persistent coma or a vegetative state (Chap. 14), dementia, visual agnosia (Chap. 15), parkinsonism, choreoathetosis, cerebellar ataxia, myoclonus, seizures, and an amnestic state, which may be a consequence of selective damage to the hippocampus.

Pathology

Principal histologic findings are extensive multifocal or diffuse laminar cortical necrosis (Fig. 22-5), with almost invariable involvement of the hippocampus. The hippocampal CA1 neurons are vulnerable to even brief episodes of hypoxia-ischemia, perhaps explaining why selective persistent memory deficits may occur after brief cardiac arrest. Scattered small areas of infarction or neuronal loss may be present in the basal ganglia, hypothalamus, or brainstem. In some cases, extensive bilateral thalamic scarring may affect pathways that mediate arousal, and this pathology may be responsible for the persistent vegetative state. A specific form of hypoxic-ischemic encephalopathy, so-called watershed infarcts, occurs at the distal territories between the major cerebral arteries and can cause cognitive deficits, including visual agnosia, and weakness that is greater in proximal than in distal muscle groups.

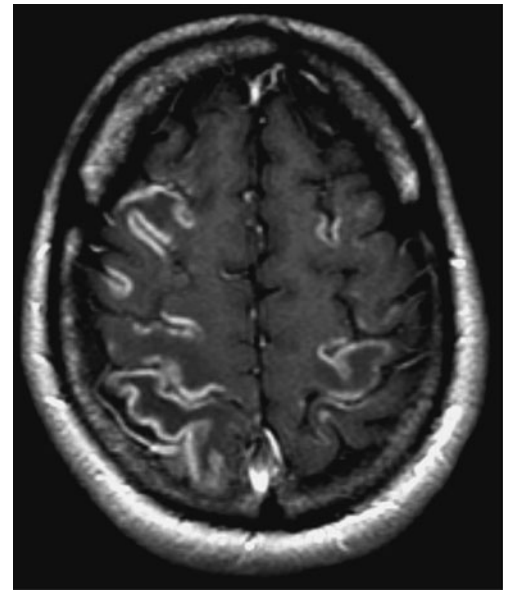

FIGURE 22-5

Cortical laminar necrosis in hypoxic-ischemic encephalopathy. T1-weighted postcontrast MRI shows cortical enhancement in a watershed distribution consistent with laminar necrosis.

Diagnosis

Diagnosis is based upon the history of a hypoxic-ischemic event such as cardiac arrest. Blood pressure <70 mmHg systolic or Pa_{o_2} <40 mmHg is usually necessary, although both absolute levels as well as duration of exposure are important determinants of cellular injury. Carbon monoxide intoxication can be confirmed by measurement of carboxyhemoglobin and is suggested by a cherry red color of the skin, although the latter is an inconsistent clinical finding.

Rx Treatment: HYPOXIC-ISCHEMIC ENCEPHALOPATHY

Treatment should be directed at restoration of normal cardiorespiratory function. This includes securing a clear airway, ensuring adequate oxygenation and ventilation, and restoring cerebral perfusion, whether by cardiopulmonary resuscitation, fluid, pressors, or cardiac pacing.

Hypothermia may target the neuronal cell injury cascade and has substantial neuroprotective properties in experimental models of brain injury. In two trials, mild hypothermia (33°C) improved functional outcome in patients who remained comatose after resuscitation from a cardiac arrest. Treatment was initiated within minutes of cardiac resuscitation and continued for 12 h in one study and 24 h in the other. Potential complications of hypothermia include coagulopathy and an increased risk of infection. Based upon these studies, the International Liaison Committee on Resuscitation issued the following advisory statement in 2003: "Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°–34°C for 12–24 h when the initial rhythm was ventricular fibrillation."

Severe carbon monoxide intoxication may be treated with hyperbaric oxygen. Anticonvulsants may be needed to control seizures, although these are not usually given prophylactically. Posthypoxic myoclonus may respond to oral administration of clonazepam at doses of 1.5–10 mg daily or valproate at doses of 300–1200 mg daily in divided doses. Myoclonic status epilepticus within 24 h after a primary circulatory arrest portends a universally poor prognosis, even if seizures are controlled.

DELAYED POSTANOXIC ENCEPHALOPATHY

Delayed postanoxic encephalopathy is an uncommon phenomenon in which patients appear to make an initial recovery from hypoxic-ischemic insult but then develop a relapse characterized by apathy, confusion, and agitation. Progressive neurologic deficits may include shuffling gait, diffuse rigidity and spasticity, persistent parkinsonism or myoclonus, and, on occasion, coma and death after 1–2 weeks. Widespread cerebral demyelination may be present.

Carbon monoxide and cyanide intoxication can also cause a delayed encephalopathy. Little clinical impairment is evident when the patient first regains consciousness, but a parkinsonian syndrome characterized by akinesia and rigidity without tremor may develop. Symptoms can worsen over months, accompanied by increasing evidence of damage in the basal ganglia as seen on both CT and MRI.

METABOLIC ENCEPHALOPATHIES

Altered mental states, variously described as confusion, delirium, disorientation, and encephalopathy, are present in many patients with severe illness in an intensive care unit (ICU). Older patients are particularly vulnerable to delirium, a confusional state characterized by disordered perception, frequent hallucinations, delusions, and sleep disturbance. This is often attributed to medication effects, sleep deprivation, pain, and anxiety. The term *ICU psychosis* has been used to describe a mental state with profound agitation occurring in this setting. The presence of family members in the ICU may help to calm and orient agitated patients, and in severe cases, low doses of neuroleptics (e.g., haloperidol 0.5–1 mg) can be useful. Ultimately, the psychosis resolves with improvement in the underlying illness and a return to familiar surroundings.

In the ICU setting, several metabolic causes of an altered level of consciousness predominate. Hypercarbic encephalopathy can present with headache, confusion, stupor, or coma. Hypoventilation syndrome occurs most frequently in patients with a history of chronic CO_2 retention who are receiving oxygen therapy for emphysema or chronic pulmonary disease. The elevated Pa_{co_2} leading to CO_2 narcosis may have a direct anesthetic effect, and cerebral vasodilatation from increased Pa_{co_2} can lead to increased ICP. Hepatic encephalopathy is suggested by asterixis and can occur in chronic liver failure or acute fulminant hepatic failure. Both hyperglycemia and hypoglycemia can cause encephalopathy, as can hypernatremia and hyponatremia. Confusion, impairment of eye movements, and gait ataxia are the hallmarks of acute Wernicke's disease (see later in the chapter).

SEPTIC ENCEPHALOPATHY

Pathogenesis

In patients with sepsis, the systemic response to infectious agents leads to the release of circulating inflammatory mediators that appear to contribute to encephalopathy. Critical illness, in association with the systemic inflammatory response syndrome (SIRS), can lead to multisystem organ failure. This syndrome can occur in the setting of apparent sepsis, severe burns, or trauma, even without clear identification of an infectious agent. Many patients with critical illness, sepsis, or SIRS develop encephalopathy without obvious explanation. This condition is broadly termed *septic encephalopathy*. While the specific mediators leading to neurologic dysfunction remain uncertain, it is clear that the encephalopathy is not simply the result of metabolic derangements of multiorgan failure. The cytokines tumor necrosis factor , interleukin (IL) 1, IL-2, and IL-6 are thought to play a role in this syndrome.

Diagnosis

Septic encephalopathy presents clinically as a diffuse dysfunction of the brain without prominent focal findings. Confusion, disorientation, agitation, and fluctuations in level of alertness are typical. In more profound cases, especially with hemodynamic compromise, the decrease in level of alertness can be more prominent, at times

resulting in coma. Hyperreflexia and frontal release signs such as a grasp or snout reflex (Chap. 15) can be seen. Abnormal movements such as myoclonus, tremor, or asterixis can occur. Septic encephalopathy is quite common, occurring in the majority of patients with sepsis and multisystem organ failure. Diagnosis is often difficult because of the multiple potential causes of neurologic dysfunction in critically ill patients and requires exclusion of structural, metabolic, toxic, and infectious (e.g., meningitis or encephalitis) causes. The mortality of patients with septic encephalopathy severe enough to produce coma approaches 50%, although this principally reflects the severity of the underlying critical illness and is not a singular result of the septic encephalopathy. Patients dying from severe sepsis or septic shock may have elevated levels of the serum brain injury biomarker S-100β and neuropathologic findings of neuronal apoptosis and cerebral ischemic injury. However, successful treatment of the underlying critical illness almost always results in complete resolution of the encephalopathy, with profound long-term cognitive disability being uncommon.

CENTRAL PONTINE MYELINOLYSIS

This disorder typically presents in a devastating fashion as quadriplegia and pseudobulbar palsy. Predisposing factors include severe underlying medical illness or nutritional deficiency; most cases are associated with rapid correction of hyponatremia or with hyperosmolar states. The pathology consists of demyelination without inflammation in the base of the pons, with relative sparing of axons and nerve cells. MRI is useful in establishing the diagnosis (Fig. 22-6) and may also identify partial forms that present as confusion, dysarthria, and/or disturbances of conjugate gaze without quadriplegia. Occasional cases present with lesions outside of the brainstem. Therapeutic guidelines for the restoration of severe hyponatremia should aim for gradual correction, i.e., by ≥10 mmol/L (10 meq/L) within 24 h and 20 mmol/L (20 meq/L) within 48 h.

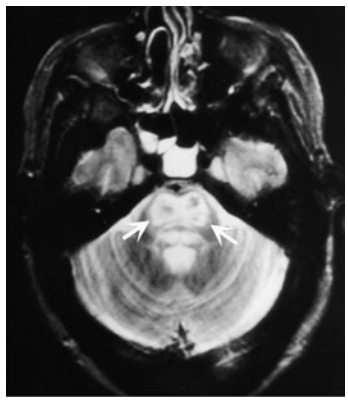

FIGURE 22-6

Central pontine myelinolysis. Axial T2-weighted MR scan through the pons reveals a symmetric area of abnormal high signal intensity within the basis pontis (*arrows*).

WERNICKE'S DISEASE

Wernicke's disease is a common and preventable disorder due to a deficiency of thiamine. In the United States, alcoholics account for most cases, but patients with malnutrition due to hyperemesis, starvation, renal dialysis, cancer, AIDS, or rarely gastric surgery are also at risk. The characteristic clinical triad is that of ophthalmoplegia, ataxia, and global confusion. However, only one-third of patients with acute Wernicke's disease present with the classic clinical triad. Most patients are profoundly disoriented, indifferent, and inattentive, although rarely they have an agitated delirium related to ethanol withdrawal. If the disease is not treated, stupor, coma, and death may ensue. Ocular motor abnormalities include horizontal nystagmus on lateral gaze, lateral rectus palsy (usually bilateral), conjugate gaze palsies, and rarely ptosis. Gait ataxia probably results from a combination of polyneuropathy, cerebellar involvement, and vestibular paresis. The pupils are usually spared, but they may become miotic with advanced disease.

Wernicke's disease is usually associated with other manifestations of nutritional disease, such as polyneuropathy. Rarely, amblyopia or myelopathy occurs. Tachycardia and postural hypotension may be related to impaired function of the autonomic nervous system or to the coexistence of cardiovascular beriberi. Patients who recover show improvement in ocular palsies within hours after the administration of thiamine, but horizontal nystagmus may persist. Ataxia improves more slowly than the ocular motor abnormalities. Approximately half recover incompletely and are left with a slow, shuffling, wide-based gait and an inability to tandem walk. Apathy, drowsiness, and confusion improve more gradually. As these symptoms recede, an amnestic state with impairment in recent memory and learning may become more apparent (*Korsakoff's psychosis*). Korsakoff's psychosis is frequently persistent; the residual mental state is characterized by gaps in memory, confabulation, and disordered temporal sequencing.

Pathology

Periventricular lesions surround the third ventricle, aqueduct, and fourth ventricle, with petechial hemorrhages in occasional acute cases and atrophy of the mammillary bodies in most chronic cases. There is frequently endothelial proliferation, demyelination, and some neuronal loss. These changes may be detected by MRI scanning (Fig. 22-7). The amnestic defect is related to lesions in the dorsal medial nuclei of the thalamus.

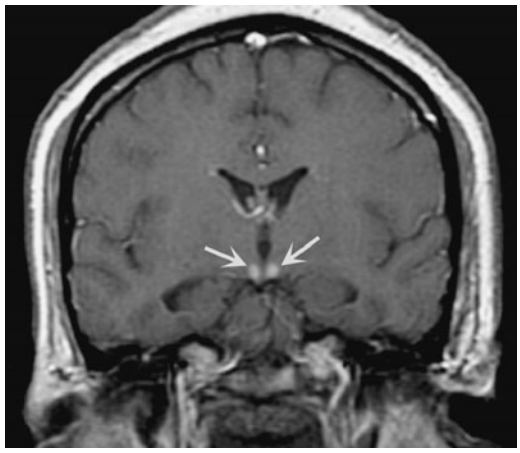

FIGURE 22-7
Wernicke's disease. Coronal T1-weighted postcontrast MRI reveals abnormal enhancement of the mammillary bodies (*arrows*), typical of acute Wernicke's encephalopathy.

Pathogenesis

Thiamine is a cofactor of several enzymes, including transketolase, pyruvate dehydrogenase, and α-ketoglutarate dehydrogenase. Thiamine deficiency produces a diffuse decrease in cerebral glucose utilization and results in mitochondrial damage. Glutamate accumulates owing to impairment of α-ketoglutarate dehydrogenase activity and, in combination with the energy deficiency, may result in excitotoxic cell damage.

℞ Treatment: WERNICKE'S DISEASE

Wernicke's disease is a medical emergency and requires immediate administration of thiamine, in a dose of 100 mg either IV or IM. The dose should be given daily until the patient resumes a normal diet and should be begun prior to treatment with IV glucose solutions. Glucose infusions may precipitate Wernicke's disease in a previously unaffected patient or cause a rapid worsening of an early form of the disease. For this reason, thiamine should be administered to all alcoholic patients requiring parenteral glucose.

CRITICAL CARE DISORDERS OF THE PERIPHERAL NERVOUS SYSTEM

Critical illness with disorders of the peripheral nervous system (PNS) arises in two contexts: (1) primary neurologic diseases that require critical care interventions such as intubation and mechanical ventilation, and (2) secondary PNS manifestations of systemic critical illness, often involving multisystem organ failure. The former include acute polyneuropathies such as Guillain-Barré syndrome (Chap. 41), neuromuscular junction disorders including myasthenia gravis (Chap. 42) and botulism, and primary muscle disorders such as polymyositis (Chap. 44). The latter result either from the systemic disease itself or as a consequence of interventions.

General principles of respiratory evaluation in patients with PNS involvement, regardless of cause, include assessment of pulmonary mechanics, such as maximal inspiratory force (MIF) and vital capacity (VC), and evaluation of strength of bulbar muscles. Regardless of the cause of weakness, endotracheal intubation should be considered when the MIF falls to <25 cmH_2O or the VC is <1 L. Also, patients with severe palatal weakness may require endotracheal intubation in order to prevent acute upper airway obstruction or recurrent aspiration. Arterial blood gases and oxygen saturation from pulse oximetry are used to follow patients with potential respiratory compromise from PNS dysfunction. However, intubation and mechanical ventilation should be undertaken based on clinical assessment rather than waiting until oxygen saturation drops or CO_2 retention develops from hypoventilation. Noninvasive mechanical ventilation may be considered initially in lieu of endotracheal intubation but is generally insufficient in patients with severe bulbar weakness or ventilatory failure with hypercarbia.

NEUROPATHY

Although encephalopathy may be the most obvious neurologic dysfunction in critically ill patients, dysfunction of the PNS is also quite common. It is typically present in patients with prolonged critical illnesses lasting several weeks and involving sepsis; clinical suspicion is aroused when there is failure to wean from mechanical ventilation despite improvement of the underlying sepsis and critical illness. *Critical illness polyneuropathy* refers to the most common PNS complication related to critical illness; it is seen in the setting of prolonged critical illness, sepsis, and multisystem organ failure. Neurologic findings include diffuse weakness, decreased reflexes, and distal sensory loss. Electrophysiologic studies demonstrate a diffuse, symmetric, distal axonal sensorimotor neuropathy, and pathologic studies have confirmed axonal degeneration. The precise mechanism of critical illness polyneuropathy remains unclear, but circulating factors such as cytokines, which are associated with sepsis and SIRS, are thought to play a role. It has been reported that up to 70% of patients with the sepsis syndrome have some degree of neuropathy, although far fewer have a clinical syndrome profound enough to cause severe respiratory muscle weakness requiring prolonged mechanical ventilation or resulting in failure to wean. Recent studies suggest that aggressive glycemic control

with insulin infusions decreases the risk of critical illness polyneuropathy. Treatment is supportive, with specific intervention directed at treating the underlying illness. While spontaneous recovery is usually seen, the time course may extend over weeks to months and necessitate long-term ventilatory support and care even after the underlying critical illness has resolved.

DISORDERS OF NEUROMUSCULAR TRANSMISSION

A defect in neuromuscular transmission may be a source of weakness in critically ill patients. Myasthenia gravis may be a consideration; however, persistent weakness secondary to impaired neuromuscular junction transmission is almost always due to administration of drugs. A number of medications impair neuromuscular transmission; these include antibiotics, especially aminoglycosides, and beta-blocking agents. In the ICU, the nondepolarizing neuromuscular blocking agents (nd-NMBAs), also known as muscle relaxants, are most commonly responsible. Included in this group of drugs are such agents as pancuronium, vecuronium, rocuronium, and atracurium. They are often used to facilitate mechanical ventilation or other critical care procedures, but with prolonged use persistent neuromuscular blockade may result in weakness even after discontinuation of these agents hours or days earlier. Risk factors for this prolonged action of neuromuscular blocking agents include female sex, metabolic acidosis, and renal failure.

Prolonged neuromuscular blockade does not appear to produce permanent damage to the PNS. Once the offending medications are discontinued, full strength is restored, although this may take days. In general, the lowest dose of neuromuscular blocking agent should be used to achieve the desired result, and, when these agents are used in the ICU, a peripheral nerve stimulator should be used to monitor neuromuscular junction function.

MYOPATHY

Critically ill patients, especially those with sepsis, frequently develop muscle wasting, often in the face of seemingly adequate nutritional support. The assumption has been that this represents a catabolic myopathy brought about as a result of multiple factors, including elevated cortisol and catecholamine release and other circulating factors induced by the SIRS. In this syndrome, known as *cachectic myopathy*, serum creatine kinase levels and electromyography (EMG) are normal. Muscle biopsy shows type II fiber atrophy. Panfascicular muscle fiber necrosis may also occur in the setting of profound sepsis. This so-called *septic myopathy* is characterized clinically by weakness progressing to a profound level over just a few days. There may be associated elevations in serum creatine kinase and urine myoglobin. Both EMG and muscle biopsy may be normal initially but eventually show abnormal spontaneous activity and panfascicular necrosis with an accompanying inflammatory reaction. Both of these myopathic syndromes may be considered under the broader heading of *critical illness myopathy*.

Acute quadriplegic myopathy describes a clinical syndrome of severe weakness seen in the setting of glucocorticoid and nd-NMBA use. The most frequent scenario in which this is encountered is the asthmatic patient who requires high-dose glucocorticoids and nd-NMBA to facilitate mechanical ventilation. This muscle disorder is not due to prolonged action of nd-NMBAs at the neuromuscular junction but, rather, is an actual myopathy with muscle damage; it has occasionally been described with high-dose glucocorticoid use alone. Clinically this syndrome is most often recognized when a patient fails to wean from mechanical ventilation despite resolution of the primary pulmonary process. Pathologically, there may be vacuolar changes in both type I and type II muscle fibers with evidence of regeneration. Acute quadriplegic myopathy has a good prognosis. If patients survive their underlying critical illness, the myopathy invariably improves and most patients return to normal. However, because this syndrome is a result of true muscle damage, not just prolonged blockade at the neuromuscular junction, this process may take weeks or months, and tracheostomy with prolonged ventilatory support may be necessary. Some patients do have residual long-term weakness, with atrophy and fatigue limiting ambulation. At present, it is unclear how to prevent this myopathic complication, except by avoiding use of nd-NMBAs, a strategy not always possible. Monitoring with a peripheral nerve stimulator can help to avoid the overuse of these agents. However, this is more likely to prevent the complication of prolonged neuromuscular junction blockade than it is to prevent this myopathy.

SUBARACHNOID HEMORRHAGE

Subarachnoid hemorrhage (SAH) renders the brain critically ill from both primary and secondary brain insults. Excluding head trauma, the most common cause of SAH is rupture of a saccular aneurysm. Other causes include bleeding from a vascular malformation (arteriovenous malformation or dural arterial-venous fistula) and extension into the subarachnoid space from a primary intracerebral hemorrhage. Some idiopathic SAHs are localized to the perimesencephalic cisterns and are benign; they probably have a venous or capillary source, and angiography is unrevealing.

Saccular ("Berry") Aneurysm

Autopsy and angiography studies have found that about 2% of adults harbor intracranial aneurysms, for a prevalence

of 4 million persons in the United States; the aneurysm will rupture, producing SAH, in 25,000–30,000 cases per year. For patients who arrive alive at hospital, the mortality rate over the next month is about 45%. Of those who survive, more than half are left with major neurologic deficits as a result of the initial hemorrhage, cerebral vasospasm with infarction, or hydrocephalus. If the patient survives but the aneurysm is not obliterated, the rate of rebleeding is about 20% in the first 2 weeks, 30% in the first month, and about 3% per year afterwards. Given these alarming figures, the major therapeutic emphasis is on preventing the predictable early complications of the SAH.

Unruptured, asymptomatic aneurysms are much less dangerous than a recently ruptured aneurysm. The annual risk of rupture for aneurysms <10 mm in size is ~0.1%, and for aneurysms ≥10 mm in size is ~0.5–1%; the surgical morbidity far exceeds these percentages. Because of the longer length of exposure to risk of rupture, younger patients with aneurysms >10 mm in size may benefit from prophylactic treatment. As with the treatment of asymptomatic carotid stenosis, this risk-benefit strongly depends on the complication rate of treatment.

Giant aneurysms, those >2.5 cm in diameter, occur at the same sites (see later) as small aneurysms and account for 5% of cases. The three most common locations are the terminal internal carotid artery, middle cerebral artery (MCA) bifurcation, and top of the basilar artery. Their risk of rupture is ~6% in the first year after identification and may remain high indefinitely. They often cause symptoms by compressing the adjacent brain or cranial nerves.

Mycotic aneurysms are usually located distal to the first bifurcation of major arteries of the circle of Willis. Most result from infected emboli due to bacterial endocarditis causing septic degeneration of arteries and subsequent dilatation and rupture. Whether these lesions should be sought and repaired prior to rupture or left to heal spontaneously is controversial.

Pathophysiology

Saccular aneurysms occur at the bifurcations of the large to medium-sized intracranial arteries; rupture is into the subarachnoid space in the basal cisterns and often into the parenchyma of the adjacent brain. Approximately 85% of aneurysms occur in the anterior circulation, mostly on the circle of Willis. About 20% of patients have multiple aneurysms, many at mirror sites bilaterally. As an aneurysm develops, it typically forms a neck with a dome. The length of the neck and the size of the dome vary greatly and are factors that are important in planning neurosurgical obliteration or endovascular embolization. The arterial internal elastic lamina disappears at the base of the neck. The media thins, and connective tissue replaces smooth-muscle cells. At the site of rupture (most often the dome) the wall thins, and the tear that allows bleeding is often ≤0.5 mm long. Aneurysm size and site are important in predicting risk of rupture. Those >7 mm in diameter and those at the top of the basilar artery and at the origin of the posterior communicating artery are at greater risk of rupture.

Clinical Manifestations

Most unruptured intracranial aneurysms are completely asymptomatic. Symptoms are usually due to rupture and resultant SAH, although some present with mass effect on cranial nerves or brain parenchyma. At the moment of aneurysmal rupture with major SAH, the ICP suddenly rises. This may account for the sudden transient loss of consciousness that occurs in nearly half of patients. Sudden loss of consciousness may be preceded by a brief moment of excruciating headache, but most patients first complain of headache upon regaining consciousness. In 10% of cases, aneurysmal bleeding is severe enough to cause loss of consciousness for several days. In ~45% of cases, severe headache associated with exertion is the presenting complaint. The patient often calls the headache "the worst headache of my life"; however, the most important characteristic is sudden onset. Occasionally these ruptures may present as headache of only moderate intensity or as a change in the patient's usual headache pattern. The headache is usually generalized, often with neck stiffness, and vomiting is common.

Although sudden headache in the absence of focal neurologic symptoms is the hallmark of aneurysmal rupture, focal neurologic deficits may occur. Anterior communicating artery or MCA bifurcation aneurysms may rupture into the adjacent brain or subdural space and form a hematoma large enough to produce mass effect. The common deficits that result include hemiparesis, aphasia, and abulia.

Occasionally, prodromal symptoms suggest the location of a progressively enlarging unruptured aneurysm. A third cranial nerve palsy, particularly when associated with pupillary dilatation, loss of ipsilateral (but retained contralateral) light reflex, and focal pain above or behind the eye, may occur with an expanding aneurysm at the junction of the posterior communicating artery and the internal carotid artery. A sixth nerve palsy may indicate an aneurysm in the cavernous sinus, and visual field defects can occur with an expanding supraclinoid carotid or anterior cerebral artery aneurysm. Occipital and posterior cervical pain may signal a posterior inferior cerebellar artery or anterior inferior cerebellar artery aneurysm. Pain in or behind the eye and in the low temple can occur with an expanding MCA aneurysm. Thunderclap headache is a variant of migraine that simulates a SAH. Before concluding that a patient with sudden, severe headache has thunderclap migraine,

TABLE 22-3

GRADING SCALES FOR SUBARACHNOID HEMORRHAGE

GRADE	HUNT-HESS SCALE	WORLD FEDERATION OF NEUROSURGICAL SOCIETIES (WFNS) SCALE
1	Mild headache, normal mental status, no cranial nerve or motor findings	Glasgow Coma Scale[a] (GCS) score 15, no motor deficits
2	Severe headache, normal mental status, may have cranial nerve deficit	GCS 13–14, no motor deficits
3	Somnolent, confused, may have cranial nerve or mild motor deficit	GCS 13–14, with motor deficits
4	Stupor, moderate to severe motor deficit, may have intermittent reflex posturing	GCS 7–12, with or without motor deficits
5	Coma, reflex posturing or flaccid	GCS 3–6, with or without motor deficits

[a]Glasgow Coma Scale: See Table 31-2.

a definitive workup for aneurysm or other intracranial pathology is required.

Aneurysms can undergo small ruptures and leaks of blood into the subarachnoid space, so-called *sentinel bleeds*. Sudden unexplained headache at any location should raise suspicion of SAH and be investigated, because a major hemorrhage may be imminent.

The initial clinical manifestations of SAH can be graded using the Hunt-Hess or World Federation of Neurosurgical Societies classification schemes (**Table 22–3**). For ruptured aneurysms, prognosis for good outcomes falls as the grade increases. For example it is unusual for a Hunt-Hess grade 1 patient to die if the aneurysm is treated, but the mortality for grade 4 and 5 patients may be as high as 80%.

Delayed Neurologic Deficits

There are four major causes of delayed neurologic deficits: rerupture, hydrocephalus, vasospasm, and hyponatremia.

1. *Rerupture*. The incidence of rerupture of an untreated aneurysm in the first month following SAH is ~30%, with the peak in the first 7 days. Rerupture is associated with a 60% mortality and poor outcome. Early treatment eliminates this risk.
2. *Hydrocephalus*. Acute hydrocephalus can cause stupor and coma and can be mitigated by placement of an external ventricular drain. More often, subacute hydrocephalus may develop over a few days or weeks and causes progressive drowsiness or slowed mentation (abulia) with incontinence. Hydrocephalus is differentiated from cerebral vasospasm with a CT scan, CT angiogram, transcranial Doppler (TCD) ultrasound, or conventional x-ray angiography. Hydrocephalus may clear spontaneously or require temporary ventricular drainage. Chronic hydrocephalus may develop weeks to months after SAH and manifest as gait difficulty, incontinence, or impaired mentation. Subtle signs may be a lack of initiative in conversation or a failure to recover independence.
3. *Vasospasm*. Narrowing of the arteries at the base of the brain following SAH causes symptomatic ischemia and infarction in ~30% of patients and is the major cause of delayed morbidity and death. Signs of ischemia appear 4–14 days after the hemorrhage, most often at 7 days. The severity and distribution of vasospasm determine whether infarction will occur.

   Delayed vasospasm is believed to result from direct effects of clotted blood and its breakdown products on the arteries within the subarachnoid space. In general, the more blood that surrounds the arteries, the greater the chance of symptomatic vasospasm. Spasm of major arteries produces symptoms referable to the appropriate vascular territory (Chap. 21). All of these focal symptoms may present abruptly, fluctuate, or develop over a few days. In most cases, focal spasm is preceded by a decline in mental status.

   Vasospasm can be detected reliably with conventional x-ray angiography, but this invasive procedure is expensive and carries the risk of stroke and other complications. TCD ultrasound is based on the principle that the velocity of blood flow within an artery will rise as the lumen diameter is narrowed. By directing the probe along the MCA and proximal anterior cerebral artery (ACA), carotid terminus, and vertebral and basilar arteries on a daily or every-other-day basis, vasospasm can be reliably detected and treatments initiated to prevent cerebral ischemia (see later). CT angiography is another method that can detect vasospasm.

Severe cerebral edema in patients with infarction from vasospasm may increase the ICP enough to reduce cerebral perfusion pressure. Treatment may include mannitol, hyperventilation, and hemicraniectomy; moderate hypothermia may have a role as well.

4. *Hyponatremia.* Hyponatremia may be profound and can develop quickly in the first 2 weeks following SAH. There is both natriuresis and volume depletion with SAH, so that patients become both hyponatremic and hypovolemic. Both atrial natriuretic peptide and brain natriuretic peptide have a role in producing this "cerebral salt-wasting syndrome." Typically it clears over the course of 1–2 weeks and, in the setting of SAH, should not be treated with free-water restriction as this may increase the risk of stroke (see later).

Laboratory Evaluation and Imaging

(**Fig. 22-8**) The hallmark of aneurysmal rupture is blood in the CSF. More than 95% of cases have enough blood to be visualized on a high-quality noncontrast CT scan obtained within 72 h. If the scan fails to establish the diagnosis of SAH and no mass lesion or obstructive hydrocephalus is found, a lumbar puncture should be performed to establish the presence of subarachnoid blood. Lysis of the red blood cells and subsequent conversion of hemoglobin to bilirubin stains the spinal fluid yellow within 6–12 h. This xanthochromic spinal fluid peaks in intensity at 48 h and lasts for 1–4 weeks, depending on the amount of subarachnoid blood.

The extent and location of subarachnoid blood on noncontrast CT scan help locate the underlying aneurysm, identify the cause of any neurologic deficit, and predict delayed vasospasm. A high incidence of symptomatic vasospasm in the MCA and ACA has been found when early CT scans show subarachnoid clots >5 × 3 mm in the basal cisterns or layers of blood >1 mm thick in the cerebral fissures. CT scans less reliably predict vasospasm in the vertebral, basilar, or posterior cerebral arteries.

Lumbar puncture prior to an imaging procedure is indicated only if a CT scan is not available at the time of the suspected SAH. Once the diagnosis of hemorrhage from a ruptured saccular aneurysm is suspected, four-vessel conventional x-ray angiography (both carotids and both vertebrals) is generally performed to localize and define the anatomic details of the aneurysm and to determine if other unruptured aneurysms exist (Fig. 22-8*C*). At some centers, the ruptured aneurysm can be treated using endovascular techniques at the time of the initial angiogram as a way to expedite treatment and minimize the number of invasive procedures. CT angiography is an alternative method for locating the aneurysm and may be sufficient to plan definitive therapy.

Close monitoring (daily or twice daily) of electrolytes is important because hyponatremia can occur precipitously during the first 2 weeks following SAH (see above).

The electrocardiogram (ECG) frequently shows ST-segment and T-wave changes similar to those associated with cardiac ischemia. Prolonged QRS complex, increased QT interval, and prominent "peaked" or deeply inverted symmetric T waves are usually secondary to the intracranial hemorrhage. There is evidence that structural myocardial lesions produced by circulating catecholamines and excessive discharge of sympathetic neurons may occur after SAH, causing these ECG changes and a reversible cardiomyopathy sufficient to cause shock or congestive heart failure. Echocardiography reveals a pattern of regional wall motion abnormalities that follow the distribution of sympathetic nerves rather than the major coronary arteries, with relative sparing of the ventricular wall apex. The sympathetic nerves themselves appear to be injured by direct toxicity from the excessive catecholamine release. An asymptomatic troponin elevation is common. Serious ventricular dysrhythmias are unusual.

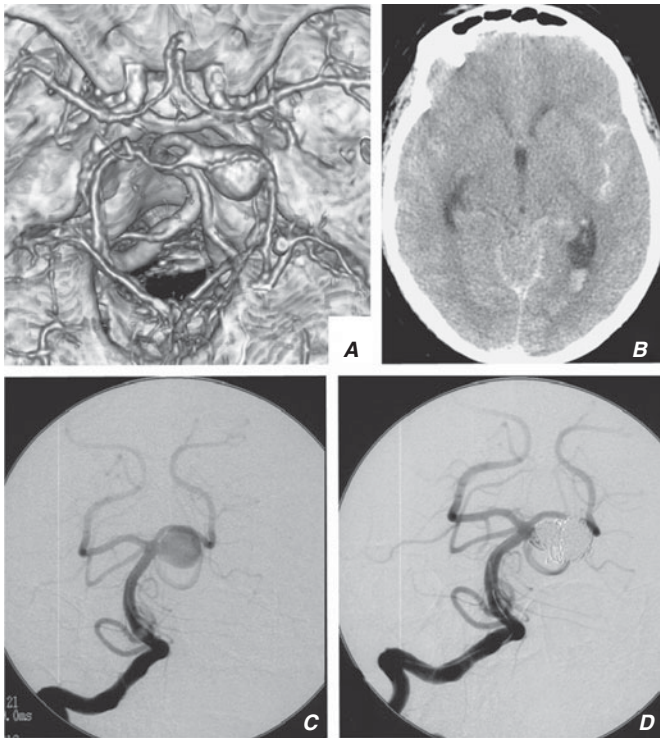

FIGURE 22-8

Subarachnoid hemorrhage. ***A.*** CT angiography revealing an aneurysm of the left superior cerebellar artery. ***B.*** Noncontrast CT scan at the level of the third ventricle revealing subarachnoid blood (bright) in the left sylvian fissure and within the left lateral ventricle. ***C.*** Conventional anteroposterior x-ray angiogram of the right vertebral and basilar artery showing the large aneurysm. ***D.*** Conventional angiogram following coil embolization of the aneurysm, whereby the aneurysm body is filled with platinum coils delivered through a microcatheter navigated from the femoral artery into the aneurysm neck.

Rx Treatment: SUBARACHNOID HEMORRHAGE

Early aneurysm repair prevents rerupture and allows the safe application of techniques to improve blood flow (e.g., induced hypertension and hypervolemia) should symptomatic vasospasm develop. An aneurysm can be "clipped" by a neurosurgeon or "coiled" by an endovascular surgeon. Surgical repair involves placing a metal clip across the aneurysm neck, thereby immediately eliminating the risk of rebleeding. This approach requires craniotomy and brain retraction, which is associated with neurologic morbidity. Endovascular techniques involve placing platinum coils, or other embolic material, within the aneurysm via a catheter that is passed from the femoral artery. The aneurysm is packed tightly to enhance thrombosis and over time is walled-off from the circulation (Fig. 22-8D). The only prospective randomized trial of surgery versus endovascular treatment for ruptured aneurysm, the International Subarachnoid Aneurysm Trial (ISAT), was terminated early when 24% of patients treated with endovascular therapy were dead or dependent at 1 year compared to 31% treated with surgery, a significant 23% relative reduction. Follow-up for these patients, now complete, reveals that the benefit of endovascular therapy is durable. However, some aneurysms have a morphology that is not amenable to endovascular treatment. Thus, surgery remains an important treatment option. Centers that combine both endovascular and neurosurgical expertise likely offer the best outcomes for patients, and there are good data showing that centers that specialize in aneurysm treatment have improved mortality rates.

The medical management of SAH focuses on protecting the airway, managing blood pressure before and after aneurysm treatment, preventing rebleeding prior to treatment, managing vasospasm, treating hydrocephalus, treating hyponatremia, and preventing pulmonary embolus.

Intracranial hypertension following aneurysmal rupture occurs secondary to subarachnoid blood, parenchymal hematoma, acute hydrocephalus, or loss of vascular autoregulation. Patients who are stuporous should undergo emergent ventriculostomy to measure ICP and to treat high ICP in order to prevent cerebral ischemia. Medical therapies designed to combat raised ICP (e.g., mild hyperventilation, mannitol, and sedation) can also be used as needed. High ICP refractory to treatment is a poor prognostic sign.

Prior to definitive treatment of the ruptured aneurysm, care is required to maintain adequate cerebral perfusion pressure while avoiding excessive elevation of arterial pressure. If the patient is alert, it is reasonable to lower the blood pressure to normal using nicardipine, labetolol, or esmolol. If the patient has a depressed level of consciousness, ICP should be measured and the cerebral perfusion pressure targeted to 60–70 mm Hg.

Because rebleeding is common, all patients who are not candidates for early aneurysm repair are put on bed rest in a quiet room and are given stool softeners to prevent straining. If headache or neck pain is severe, mild sedation and analgesia are prescribed. Extreme sedation is avoided because it can obscure changes in neurologic status. Adequate hydration is necessary to avoid a decrease in blood volume predisposing to brain ischemia.

Seizures are uncommon at the onset of aneurysmal rupture. The quivering, jerking, and extensor posturing that often accompany loss of consciousness with SAH are probably related to the sharp rise in ICP or, perhaps, acute generalized vasospasm rather than seizure. However, phenytoin is often given as prophylactic therapy since a seizure may promote rebleeding.

Glucocorticoids may help reduce the head and neck ache caused by the irritative effect of the subarachnoid blood. There is no good evidence that they reduce cerebral edema, are neuroprotective, or reduce vascular injury, and their routine use therefore is not recommended.

Antifibrinolytic agents are not routinely prescribed but may be considered in patients in whom aneurysm treatment cannot proceed immediately. They are associated with a reduced incidence of aneurysmal rerupture but may also increase the risk of delayed cerebral infarction and deep vein thrombosis (DVT).

Vasospasm remains the leading cause of morbidity and mortality following aneurysmal SAH. Treatment with the calcium channel antagonist nimodipine (60 mg PO every 4 h) improves outcome, perhaps by preventing ischemic injury rather than reducing the risk of vasospasm. Nimodipine can cause significant hypotension in some patients, which may worsen cerebral ischemia in patients with vasospasm. Symptomatic cerebral vasospasm can also be treated by increasing the cerebral perfusion pressure by raising mean arterial pressure through plasma volume expansion and the judicious use of IV vasopressor agents, usually phenylephrine or norepinephrine. Raised perfusion pressure has been associated with clinical improvement in many patients, but high arterial pressure may promote rebleeding in unprotected aneurysms. Treatment with induced hypertension and hypervolemia generally requires monitoring of arterial and central venous pressures; it is best to infuse pressors through a central venous line as well. Volume expansion helps prevent hypotension, augments cardiac output, and reduces blood viscosity by reducing the hematocrit. This method is called "triple-H" (hypertension, hemodilution, and hypervolemic) therapy.

If symptomatic vasospasm persists despite optimal medical therapy, intraarterial vasodilators and percutaneous transluminal angioplasty are considered. Vasodilatation by direct angioplasty appears to be permanent, allowing triple-H therapy to be tapered sooner. The pharmacologic vasodilators (verapamil and nicardipine) do not last more than 8–24 h, and therefore multiple treatments may be required until the subarachnoid blood is reabsorbed. Although intraarterial papaverine is an effective vasodilator, there is evidence that papaverine may be neurotoxic so its use should be reserved for refractory cases.

Acute hydrocephalus can cause stupor or coma. It may clear spontaneously or require temporary ventricular drainage. When chronic hydrocephalus develops, ventricular shunting is the treatment of choice.

Free-water restriction is contraindicated in patients with SAH at risk for vasospasm because hypovolemia and hypotension may occur and precipitate cerebral ischemia. Many patients continue to experience a decline in serum sodium despite receiving parenteral fluids containing normal saline. Frequently, supplemental oral salt coupled with normal saline will mitigate hyponatremia, but often patients also require hypertonic saline. Care must be taken not to correct serum sodium too quickly in patients with marked hyponatremia of several days' duration, as central pontine myelinolysis may occur.

All patients should have pneumatic compression stockings applied to prevent pulmonary embolism. Unfractionated heparin administered subcutaneously for DVT prophylaxis can be initiated immediately following endovascular treatment and within days following craniotomy and surgical clipping and is a useful adjunct to pneumatic compression stockings. Treatment of pulmonary embolus depends on whether the aneurysm has been treated and whether or not the patient has had a craniotomy. Systemic anticoagulation with heparin is contraindicated in patients with ruptured and untreated aneurysms. It is a relative contraindication following craniotomy for several days or perhaps weeks, and it may delay thrombosis of a coiled aneurysm. Following craniotomy, use of inferior vena cava filters is preferred to prevent further pulmonary emboli, while systemic anticoagulation with heparin is preferred following successful endovascular treatment.

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CHAPTER 23

ALZHEIMER'S DISEASE AND OTHER DEMENTIAS

Thomas D. Bird ■ Bruce L. Miller

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Dementia, a syndrome with many causes, affects >4 million Americans and results in a total health care cost of >$100 billion annually. It is defined as an acquired deterioration in cognitive abilities that impairs the successful performance of activities of daily living. Memory is the most common cognitive ability lost with dementia; 10% of persons >70 years and 20–40% of individuals >85 years have clinically identifiable memory loss. In addition to memory, other mental faculties are also affected in dementia; these include language, visuospatial ability, calculation, judgment, and problem solving. Neuropsychiatric and social deficits also develop in many dementia syndromes, resulting in depression, withdrawal, hallucinations, delusions, agitation, insomnia, and disinhibition. The most common forms of dementia are progressive, but some dementing illnesses are static and unchanging or fluctuate dramatically from day to day. Most diagnoses of dementia require some sort of memory deficit, although there are many dementias, such as frontotemporal dementia, where memory loss is not a presenting feature.

FUNCTIONAL ANATOMY OF THE DEMENTIAS

Dementia results from the disruption of cerebral neuronal circuits; the quantity of neuronal loss and the location of affected regions are factors that combine to cause the specific disorder (Chap. 15). Behavior and mood are modulated by noradrenergic, serotonergic, and dopaminergic pathways, while acetylcholine seems to be particularly important for memory. Therefore, the loss of cholinergic neurons in Alzheimer's disease (AD) may underlie the memory impairment, while in patients with non-AD dementias, the loss of serotonergic and glutaminergic neurons causes primarily behavioral symptoms, leaving memory relatively spared. Neurotrophins (Chap. 19) are also postulated to play a role in memory function, in part by preserving cholinergic neurons, and therefore represent a pharmacologic pathway toward slowing or reversing the effects of AD.

Dementias have anatomically specific patterns of neuronal degeneration that dictate the clinical symptomatology. AD begins in the entorhinal cortex, spreads to the hippocampus, and then moves to posterior temporal and parietal neocortex, eventually causing a relatively diffuse degeneration throughout the cerebral cortex. *Multi-infarct dementia* is associated with focal damage in a random patchwork of cortical regions. Diffuse white matter damage may disrupt intracerebral connections and cause dementia syndromes similar to those associated with leukodystrophies, multiple sclerosis, and Binswanger's disease (see later). Subcortical structures, including the caudate, putamen, thalamus, and substantia

nigra, also modulate cognition and behavior in ways that are not yet well understood. The effect that these patterns of cortical degeneration have on disease symptomatology is clear: AD primarily presents as memory loss and is often associated with aphasia or other disturbances of language. In contrast, patients with frontal lobe or subcortical dementias such as *frontotemporal dementia* (FTD) or *Huntington's disease* (HD) are less likely to begin with memory problems and more likely to have difficulties with attention, judgment, awareness, and behavior.

Lesions of specific cortical-subcortical pathways have equally specific effects on behavior. The dorsolateral prefrontal cortex has connections with dorsolateral caudate, globus pallidus, and thalamus. Lesions of these pathways result in poor organization and planning, decreased cognitive flexibility, and impaired judgment. The lateral orbital frontal cortex connects with the ventromedial caudate, globus pallidus, and thalamus. Lesions of these connections cause irritability, impulsiveness, and distractibility. The anterior cingulate cortex connects with the nucleus accumbens, globus pallidus, and thalamus. Interruption of these connections produces apathy and poverty of speech or even akinetic mutism.

The single strongest risk factor for dementia is increasing age. The prevalence of disabling memory loss increases with each decade after 50 years of age and is associated most often with the microscopic changes of AD at autopsy. Slow accumulation of mutations in neuronal mitochondria is also hypothesized to contribute to the increasing prevalence of dementia with age. Yet some centenarians have intact memory function and no evidence of clinically significant dementia. Whether dementia is an inevitable consequence of normal human aging remains controversial.

THE CAUSES OF DEMENTIA

The many causes of dementia are listed in **Table 23-1**. The frequency of each condition depends on the age group under study, the access of the group to medical care, the country of origin, and perhaps racial or ethnic background. AD is the most common cause of dementia in Western countries, representing more than half of demented patients. Vascular disease is the second most common cause of dementia in the United States, representing 10–20%. In populations with limited access to medical care, where vascular risk factors are undertreated, the prevalence of vascular dementia can be much higher. Dementia associated with Parkinson's disease (PD) is the next most common category, and in many instances these patients suffer from dementia with Lewy bodies (DLB). In patients younger than 60 years, FTD rivals AD as the most common cause of dementia. Chronic intoxications, including those resulting from alcohol and prescription drugs, are an important and often treatable cause of dementia. Other disorders listed in the table are uncommon but important because many are reversible. The classification of dementing illnesses into two broad groups of reversible and irreversible disorders is a useful approach to the differential diagnosis of dementia.

In a study of 1000 persons attending a memory disorders clinic, 19% had a potentially reversible cause of the cognitive impairment and 23% had a potentially reversible concomitant condition. The three most common potentially reversible diagnoses were depression, hydrocephalus, and alcohol dependence (Table 23-1).

Subtle cumulative decline in episodic memory is a natural part of aging. This frustrating experience, often the source of jokes and humor, is referred to as *benign forgetfulness of the elderly*. *Benign* means that it is not so progressive or serious that it impairs reasonably successful and productive daily functioning, although the distinction between benign and more significant memory loss can be difficult to make. At 85 years, the average person is able to learn and recall approximately one-half the number of items (e.g., words on a list) that he or she could at 18 years. A cognitive problem that has begun to subtly interfere with daily activities is referred to as *mild cognitive impairment* (MCI). A sizeable proportion of persons with MCI will progress to frank dementia, usually caused by AD. The conversion rate from MCI to AD is ~12% per year. It remains unclear why some individuals show progression and others do not. Factors that predict progression from MCI to AD include a memory deficit >1.5 standard deviations from the norm, family history of dementia, the presence of an apolipoprotein ε4 (Apo ε4), and small hippocampal volumes. There is optimism that new positron emission tomography (PET) imaging techniques that label amyloid or tau in vivo might aid in early diagnosis of AD in the future.

The major degenerative dementias include AD, FTD and related disorders, DLB, HD, and prion disorders including Creutzfeldt-Jakob disease (CJD). These disorders are all associated with the abnormal aggregation of a specific protein: $A\beta_{42}$ in AD, tau or TDP-43 in FTD, α-synuclein in DLB, polyglutamine repeats in HD, and prions in CJD (**Table 23-2**).

Approach to the Patient: DEMENTIA

Three major issues should be kept in the forefront: (1) What is the most accurate diagnosis? (2) Is there a treatable or reversible component to the dementia? (3) Can the physician help to alleviate the burden on caregivers? A broad overview of the approach to dementia is shown in **Table 23-3**. The major degenerative dementias can usually be distinguished by the

TABLE 23-1

DIFFERENTIAL DIAGNOSIS OF DEMENTIA

Most Common Causes of Dementia

- Alzheimer's disease
- Vascular dementia
  - Multi-infarct
  - Diffuse white matter disease (Binswanger's)
- Alcoholism[a]
- Parkinson's disease
- Drug/medication intoxication[a]

Less Common Causes of Dementia

- Vitamin deficiencies
  - Thiamine (B_1): Wernicke's encephalopathy[a]
  - B_{12} (pernicious anemia)[a]
  - Nicotinic acid (pellagra)[a]
- Endocrine and other organ failure
  - Hypothyroidism[a]
  - Adrenal insufficiency and Cushing's syndrome[a]
  - Hypo- and hyperparathyroidism[a]
  - Renal failure[a]
  - Liver failure[a]
  - Pulmonary failure[a]
- Chronic infections
  - HIV
  - Neurosyphilis[a]
  - Papovavirus (progressive multifocal leukoencephalopathy)
  - Prion (Creutzfeldt-Jakob and Gerstmann-Sträussler-Scheinker diseases)
  - Tuberculosis, fungal, and protozoal[a]
  - Whipple's disease[a]
- Head trauma and diffuse brain damage
  - Dementia pugilistica
  - Chronic subdural hematoma[a]
  - Postanoxia
  - Postencephalitis
  - Normal-pressure hydrocephalus[a]
- Neoplastic
  - Primary brain tumor[a]
  - Metastatic brain tumor[a]
  - Paraneoplastic limbic encephalitis
- Toxic disorders
  - Drug, medication, and narcotic poisoning[a]
  - Heavy metal intoxication[a]
  - Dialysis dementia (aluminum)
  - Organic toxins
- Psychiatric
  - Depression (pseudodementia)[a]
  - Schizophrenia[a]
  - Conversion reaction[a]
- Degenerative disorders
  - Huntington's disease
  - Pick's disease
  - Dementia with Lewy bodies
  - Progressive supranuclear palsy (Steel-Richardson syndrome)
  - Multisystem degeneration (Shy-Drager syndrome)
  - Hereditary ataxias (some forms)
  - Motor neuron disease [amyotrophic lateral sclerosis (ALS); some forms]
  - Frontotemporal dementia
  - Cortical basal degeneration
  - Multiple sclerosis
  - Adult Down's syndrome with Alzheimer's
  - ALS–Parkinson's–Dementia complex of Guam
- Miscellaneous
  - Sarcoidosis[a]
  - Vasculitis[a]
  - CADASIL etc
  - Acute intermittent porphyria[a]
  - Recurrent nonconvulsive seizures[a]
- Additional conditions in children or adolescents
  - Hallervorden-Spatz disease
  - Subacute sclerosing panencephalitis
  - Metabolic disorders (e.g., Wilson's and Leigh's diseases, leukodystrophies, lipid storage diseases, mitochondrial mutations)

[a]Potentially reversible dementia.

initial symptoms; neuropsychological, neuropsychiatric, and neurologic findings; and neuroimaging features (Table 23-4).

HISTORY The history should concentrate on the onset, duration, and tempo of progression of the dementia. An acute or subacute onset of confusion may represent delirium and should trigger the search for intoxication, infection, or metabolic derangement. An elderly person with slowly progressive memory loss over several years is likely to suffer from AD. Nearly 75% of AD patients begin with memory symptoms, but other early symptoms include difficulty with managing money, driving, shopping, following instructions, finding words, or navigating. A change in personality, disinhibition, and gain of weight or food obsession suggests FTD, not AD. FTD is also suggested by the finding of apathy, loss of executive function, or progressive abnormalities in speech, or by a relative sparing of memory or spatial abilities. The diagnosis

TABLE 23-2

THE MOLECULAR BASIS FOR DEGENERATIVE DEMENTIA

DEMENTIA	MOLECULAR BASIS	CAUSAL GENES AND (CHROMOSOME)	SUSCEPTIBILITY GENES	PATHOLOGY
AD	Aβ	<2% carry these mutations. *APP* (21), *PS-1* (14), *PS-2* (1) (most mutations are in *PS-1*)	*Apo ε4* (19)	Amyloid plaques, neurofibrillary tangles
FTD	Tau	Tau exon and intron mutations (17) (about 10% of familial cases) Progranulin (17) (10% of familial cases)	H1 tau haplotypes	Tau inclusions, Pick bodies, neurofibrillary tangles
DLB	α-synuclein	Very rare α-synuclein (4) (dominant)	Unknown	α-synuclein inclusions (Lewy bodies)
CJD	PrP^{SC} proteins	Prion (20) (up to 15% of cases carry these dominant mutations)	Codon 129 homozygosity for methionine or valine	Tau inclusions, spongiform changes, gliosis

Note: AD, Alzheimer's disease; FTD, frontotemporal dementia; DLB, dementia with Lewy bodies; CJD, Creutzfeldt-Jakob disease.

TABLE 23-3

EVALUATION OF THE PATIENT WITH DEMENTIA

ROUTINE EVALUATION	OPTIONAL FOCUSED TESTS	OCCASIONALLY HELPFUL TESTS
History	Psychometric testing	EEG
Physical examination	Chest x-ray	Parathyroid function
Laboratory tests	Lumbar puncture	Adrenal function
Thyroid function (TSH)	Liver function	Urine heavy metals
Vitamin B_{12}	Renal function	RBC sedimentation rate
Complete blood count	Urine toxin screen	Angiogram
Electrolytes	HIV	Brain biopsy
CT/MRI	Apolipoprotein E	SPECT
	RPR or VDRL	PET
Diagnostic Categories		
REVERSIBLE CAUSES	**IRREVERSIBLE/ DEGENERATIVE DEMENTIAS**	**PSYCHIATRIC DISORDERS**
Examples	Examples	Depression
Hypothyroidism	Alzheimer's	Schizophrenia
Thiamine deficiency	Frontotemporal dementia	Conversion reaction
Vitamin B_{12} deficiency	Huntington's	
Normal-pressure hydrocephalus	Dementia with Lewy bodies	
Subdural hematoma	Vascular	
Chronic infection	Leukoencephalopathies	
Brain tumor	Parkinson's	
Drug intoxication		
Associated Treatable Conditions		
Depression	Agitation	
Seizures	Caregiver "burnout"	
Insomnia	Drug side effects	

Note: PET, positron emission tomography; RPR, rapid plasma reagin (test); SPECT, single photon emission CT; VDRL, Venereal Disease Research Laboratory (test for syphilis).

TABLE 23-4

CLINICAL DIFFERENTIATION OF THE MAJOR DEMENTIAS

DISEASE	FIRST SYMPTOM	MENTAL STATUS	NEUROPSYCHIATRY	NEUROLOGY	IMAGING
AD	Memory loss	Episodic memory loss	Initially normal	Initially normal	Entorhinal cortex and hippocampal atrophy
FTD	Apathy; poor judgment/insight, speech/language; hyperorality	Frontal/executive, language; spares drawing	Apathy, disinhibition, hyperorality, euphoria, depression	Due to PSP/CBD overlap; vertical gaze palsy, axial rigidity, dystonia, alien hand	Frontal and/or temporal atrophy; spares posterior parietal lobe
DLB	Visual hallucinations, REM sleep disorder, delirium, Capgras' syndrome, parkinsonism	Drawing and frontal/executive; spares memory; delirium prone	Visual hallucinations, depression, sleep disorder, delusions	Parkinsonism	Posterior parietal atrophy; hippocampi larger than in AD
CJD	Dementia, mood, anxiety, movement disorders	Variable, frontal/executive, focal cortical, memory	Depression, anxiety	Myoclonus, rigidity, parkinsonism	Cortical ribboning and basal ganglia or thalamus hyperintensity on diffusion/flare MRI
Vascular	Often but not always sudden; variable; apathy, falls, focal weakness	Frontal/executive, cognitive slowing; can spare memory	Apathy, delusions, anxiety	Usually motor slowing, spasticity; can be normal	Cortical and/or subcortical infarctions, confluent white matter disease

Note: AD, Alzheimer's disease; FTD, frontotemporal dementia; PSP, progressive supranuclear palsy; CBD, cortical basal degeneration; DLB, dementia with Lewy bodies; CJD, Creutzfeldt-Jakob disease.

of DLB is suggested by the early presence of visual hallucinations; parkinsonism; delirium; REM sleep disorder (the merging of dream-states into wakefulness); or Capgras' syndrome, the delusion that a familiar person has been replaced by an impostor.

A history of sudden stroke with irregular stepwise progression suggests multi-infarct dementia. Multi-infarct dementia is also commonly seen in the setting of hypertension, atrial fibrillation, peripheral vascular disease, and diabetes. In patients suffering from cerebrovascular disease, it can be difficult to determine whether the dementia is due to AD, multi-infarct dementia, or a mixture of the two as many of the risk factors for vascular dementia, including diabetes, high cholesterol, elevated homocysteine and low exercise, are also risk factors for AD. Rapid progression of the dementia in association with motor rigidity and myoclonus suggests CJD. Seizures may indicate strokes or neoplasm. Gait disturbance is commonly seen with multi-infarct dementia, PD, or normal-pressure hydrocephalus (NPH). Multiple sex partners or intravenous drug use should trigger a search for central nervous system (CNS) infection, especially for HIV. A history of recurrent head trauma could indicate chronic subdural hematoma, dementia pugilistica, or NPH. Alcoholism may suggest malnutrition and thiamine deficiency. A remote history of gastric surgery resulting in loss of intrinsic factor can bring about vitamin B_{12} deficiency. Certain occupations such as working in a battery or chemical factory might indicate heavy metal intoxication. Careful review of medication intake, especially of sedatives and tranquilizers, may raise the issue of chronic drug intoxication. A positive family of dementia is found in HD and in forms of familial Alzheimer's disease (FAD), FTD, or prion disorders. The recent death of a loved one, or depressive signs such as insomnia or weight loss, raises the possibility of pseudodementia due to depression.

PHYSICAL AND NEUROLOGIC EXAMINATION

A thorough general and neurologic examination is essential to document dementia, look for other signs of nervous system involvement, and search for clues suggesting a systemic disease that might be responsible for the cognitive disorder. AD does not affect

motor systems until later in the course. In contrast, FTD patients often develop axial rigidity, supranuclear gaze palsy, or features of amyotrophic lateral sclerosis (ALS). In DLB, initial symptoms may be the new onset of a parkinsonian syndrome (resting tremor, cogwheel rigidity, bradykinesia, festinating gait) with the dementia following later, or vice versa. Corticobasal degeneration (CBD) is associated with dystonia, alien hand, and asymmetric extrapyramidal, pyramidal, or sensory deficits or myoclonus. Progressive supranuclear palsy (PSP) is associated with unexplained falls, axial rigidity, dysphagia, and vertical gaze deficits. CJD is suggested by the presence of diffuse rigidity, an akinetic state, and myoclonus.

Hemiparesis or other focal neurologic deficits may occur in multi-infarct dementia or brain tumor. Dementia with a myelopathy and peripheral neuropathy suggests vitamin B_{12} deficiency. A peripheral neuropathy could also indicate an underlying vitamin deficiency or heavy metal intoxication. Dry, cool skin, hair loss, and bradycardia suggest hypothyroidism. Confusion associated with repetitive stereotyped movements may indicate ongoing seizure activity. Hearing impairment or visual loss may produce confusion and disorientation misinterpreted as dementia. Such sensory deficits are common in the elderly but can be a manifestation of mitochondrial disorders.

COGNITIVE AND NEUROPSYCHIATRIC EXAMINATION Brief screening tools such as the mini-mental state examination (MMSE) help to confirm the presence of cognitive impairment and to follow the progression of dementia (**Table 23-5**). The MMSE, an easily administered 30-point test of cognitive function, contains tests of orientation, working memory (e.g., spell *world* backwards), episodic memory (orientation and recall), language comprehension, naming, and copying. In most patients with MCI and some with clinically apparent AD, the MMSE may be normal and a more rigorous set of neuropsychological tests will be required. Additionally, when the etiology for the dementia syndrome remains in doubt, a specially tailored evaluation should be performed that includes tasks of working and episodic memory, frontal executive function, language, and visuospatial and perceptual abilities. In AD the deficits involve episodic memory, category generation ("name as many animals as you can in one minute"), and visuoconstructive ability. Deficits in verbal or visual episodic memory are often the first neuropsychological abnormalities seen with AD, and tasks that require the patient to recall a long list of words or a series of pictures after a predetermined delay will demonstrate deficits in most AD patients. In FTD, the earliest deficits often involve frontal executive or language

TABLE 23-5

THE MINI-MENTAL STATUS EXAMINATION

	POINTS
Orientation	
Name: season/date/day/month/year	5 (1 for each name)
Name: hospital/floor/town/state/country	5 (1 for each name)
Registration	
Identify three objects by name and ask patient to repeat	3 (1 for each object)
Attention and calculation	
Serial 7s; subtract from 100 (e.g., 93–86–79–72–65)	5 (1 for each subtraction)
Recall	
Recall the three objects presented earlier	3 (1 for each object)
Language	
Name pencil and watch	2 (1 for each object)
Repeat "No ifs, ands, or buts"	1
Follow a 3-step command (e.g., "Take this paper, fold it in half, and place it on the table")	3 (1 for each command)
Write "close your eyes" and ask patient to obey written command	1
Ask patient to write a sentence	1
Ask patient to copy a design (e.g., intersecting pentagons)	1
Total	30

(speech or naming) function. DLB patients have more severe deficits in visuospatial function but do better on episodic memory tasks than patients with AD. Patients with vascular dementia often demonstrate a mixture of frontal executive and visuospatial deficits. In delirium, deficits tend to fall in the area of attention, working memory, and frontal function.

A functional assessment should also be performed. The physician should determine the day-to-day impact of the disorder on the patient's memory, community affairs, hobbies, judgment, dressing, and eating. Knowledge of the patient's day-to-day function will help the clinician and the family to organize a therapeutic approach.

Neuropsychiatric assessment is important for diagnosis, prognosis, and treatment. In the early stages of AD, mild depressive features, social withdrawal, and denial of illness are the most prominent psychiatric changes. However, patients often maintain their social skills into the middle stages of the illness, when delusions, agitation, and sleep disturbance become more common. In FTD, dramatic personality change, apathy, overeating, repetitive compulsions, disinhibition, euphoria, and loss of empathy are common. DLB shows visual hallucinations, delusions related to personal identity, and day-to-day fluctuation. Vascular dementia can present with psychiatric symptoms such as depression, delusions, disinhibition, or apathy.

LABORATORY TESTS The choice of laboratory tests in the evaluation of dementia is complex. The physician does not want to miss a reversible or treatable cause, yet no single etiology is common; thus, a screen must employ multiple tests, each of which has a low yield. Cost/benefit ratios are difficult to assess, and many laboratory screening algorithms for dementia discourage multiple tests. Nevertheless, even a test with only a 1–2% positive rate is probably worth undertaking if the alternative is missing a treatable cause of dementia. Table 23-3 lists most screening tests for dementia. Recently the American Academy of Neurology recommended the routine measurement of thyroid function, a vitamin B_{12} level test, and a neuroimaging study (CT or MRI).

Neuroimaging studies will identify primary and secondary neoplasms, locate areas of infarction, diagnose subdural hematomas, and suggest NPH or diffuse white matter disease. They also lend support to the diagnosis of AD, especially if there is hippocampal atrophy in addition to diffuse cortical atrophy. Focal frontal and/or anterior temporal atrophy suggests FTD. There is no specific pattern yet determined for DLB, although these patients tend to have less hippocampal atrophy than patients with AD. The use of diffusion-weighted imaging with MRI will detect abnormalities in the cortical ribbon and basal ganglia in the vast majority of patients with CJD. Large white-matter abnormalities correlate with a vascular etiology for dementia. The role of functional imaging in the diagnosis of dementia is still under study. Single photon emission computed tomography (SPECT) and PET scanning will show temporal-parietal hypoperfusion or hypometabolism in AD and frontotemporal hypoperfusion or hypometabolism in FTD, but most of these changes reflect atrophy. Recently, amyloid imaging has shown promise for the diagnosis of AD, and Pittsburgh Agent B appears to be a reliable agent for detecting brain amyloid due to the accumulation of $A\beta_{42}$ within plaques (Fig. 23-1). Similarly, MRI perfusion and brain activation studies using functional MRI are under active study as potential early diagnostic tools.

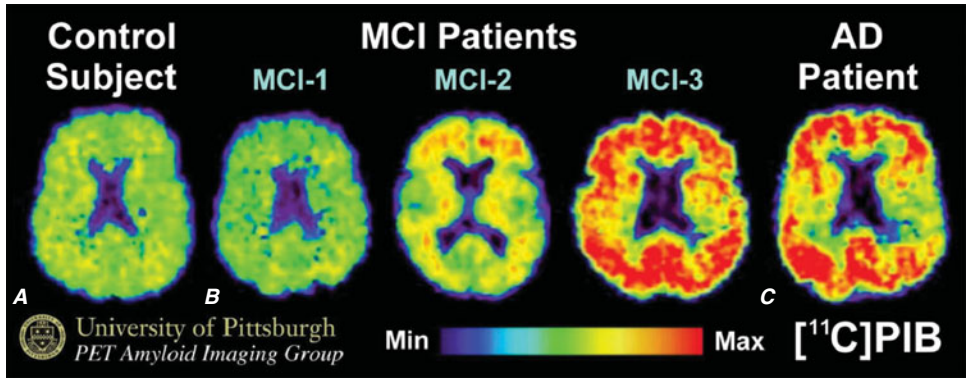


FIGURE 23-1

PET images obtained with the amyloid-imaging agent Pittsburgh Compound-B ([^{11}C]PIB) in a normal control (***A***); three different patients with mild cognitive impairment (MCI, ***B***); and a mild AD patient (***C***). Some MCI patients have control-like levels of amyloid, some have AD-like levels of amyloid, and some have intermediate levels. PET, positron emission tomography; MCI, mild cognitive impairment; AD, Alzheimer's disease.

Lumbar puncture need not be done routinely in the evaluation of dementia, but it is indicated if CNS infection is a serious consideration. Cerebrospinal fluid (CSF) levels of tau protein and $A\beta_{42}$ amyloid show differing patterns with the various dementias; however, the sensitivity and specificity of these measures are not sufficiently high to warrant routine measurement. Formal psychometric testing, though not necessary in every patient with dementia, helps to document the severity of dementia, suggest psychogenic causes, and provide a semiquantitative method for following the disease course. EEG is rarely helpful except to suggest CJD (repetitive bursts of diffuse high voltage sharp waves) or an underlying nonconvulsive seizure disorder (epileptiform discharges). Brain biopsy (including meninges) is not advised except to diagnose vasculitis, potentially treatable neoplasms, unusual infections, or systemic disorders such as vasculitis or sarcoid, or in young persons where the diagnosis is uncertain. Angiography should be considered when cerebral vasculitis is a possible cause of the dementia.

SPECIFIC DEMENTIAS

ALZHEIMER'S DISEASE

Approximately 10% of all persons older than 70 years have significant memory loss and in more than one-half the cause is AD. It is estimated that the annual total cost of caring for a single AD patient in an advanced stage of the disease is >$50,000. The disease also exacts a heavy emotional toll on family members and caregivers. AD can occur in any decade of adulthood, but it is the most common cause of dementia in the elderly. AD most often presents with subtle onset of memory loss followed by a slowly progressive dementia that has a course of several years. Pathologically, there is diffuse atrophy of the cerebral cortex with secondary enlargement of the ventricular system. Microscopically, there are neuritic plaques containing Aβ amyloid, silver-staining neurofibrillary tangles (NFTs) in neuronal cytoplasm, and accumulation of $A\beta^{42}$ amyloid in arterial walls of cerebral blood vessels (see Pathogenesis, later). The identification of four different susceptibility genes for AD has provided a foundation for rapid progress in understanding AD's biologic basis.

Clinical Manifestations

The cognitive changes with AD tend to follow a characteristic pattern, beginning with memory impairment and spreading to language and visuospatial deficits. However, ~20% of AD patients present with nonmemory complaints such as word-finding, organizational, or navigational difficulty. In the early stages of the disease, the memory loss may go unrecognized or be ascribed to benign forgetfulness. Once the memory loss begins to affect day-to-day activities or falls below 1.5 standard deviations from normal on standardized memory tasks, the disease is defined as MCI. Approximately 50% of MCI individuals will progress to AD within 5 years. Slowly the cognitive problems begin to interfere with daily activities, such as keeping track of finances, following instructions on the job, driving, shopping, and housekeeping. Some patients are unaware of these difficulties (*anosognosia*), while others have considerable insight. Change of environment may be bewildering, and the patient may become lost on walks or while driving an automobile. In the middle stages of AD, the patient is unable to work, is easily lost and confused, and requires daily supervision. Social graces, routine behavior, and superficial conversation may be surprisingly intact. Language becomes impaired—first naming, then comprehension, and finally fluency. In some patients, *aphasia* is an early and prominent feature. Word finding difficulties and circumlocution may be a problem even when formal testing demonstrates intact naming and fluency. *Apraxia* emerges, and patients have trouble performing sequential motor tasks. Visuospatial deficits begin to interfere with dressing, eating, solving simple puzzles, and copying geometric figures. Patients may be unable to do simple calculations or tell time.

In the late stages of the disease, some persons remain ambulatory but wander aimlessly. Loss of judgment, reason, and cognitive abilities is inevitable. Delusions are common and usually simple in quality, such as delusions of theft, infidelity, or misidentification. Approximately 10% of AD patients develop *Capgras' syndrome*, believing that a caregiver has been replaced by an impostor. In contrast to DLB, where Capgras' syndrome is an early feature, in AD this syndrome emerges later in the course of the illness. Loss of inhibitions and aggression may occur and alternate with passivity and withdrawal. Sleep-wake patterns are prone to disruption, and nighttime wandering becomes disturbing to the household. Some patients develop a shuffling gait with generalized muscle rigidity associated with slowness and awkwardness of movement. Patients often look parkinsonian (Chap. 24) but rarely have a rapid, rhythmic, resting tremor. In end-stage AD, patients become rigid, mute, incontinent, and bedridden. Help may be needed with the simplest tasks, such as eating, dressing, and toilet function. They may show hyperactive tendon reflexes. Myoclonic jerks (sudden brief contractions of various muscles or the whole body) may occur spontaneously or in response to physical or auditory stimulation. Myoclonus raises the possibility of CJD (Chap. 38), but the course of AD is much more prolonged. Generalized

seizures may also occur. Often death results from malnutrition, secondary infections, pulmonary emboli, or heart disease. The typical duration of AD is 8–10 years, but the course can range from 1 to 25 years. For unknown reasons, some AD patients show a steady downhill decline in function, while others have prolonged plateaus without major deterioration.

Differential Diagnosis

Early in the disease course, other etiologies of dementia should be excluded. These include treatable entities such as thyroid disease, vitamin deficiencies, brain tumor, drug and medication intoxication, chronic infection, and severe depression (pseudodementia). Neuroimaging studies (CT and MRI) do not show a single specific pattern with AD and may be normal early in the course of the disease. As AD progresses, diffuse cortical atrophy becomes apparent, and MRI scans show atrophy of the hippocampus (**Fig. 23-2*A*, *B***). Imaging helps to exclude other disorders, such as primary and secondary neoplasms, multiinfarct dementia, diffuse white matter disease, and NPH; it also helps to distinguish AD from other degenerative disorders with distinctive imaging patterns such as FTD or CJD. Functional imaging studies in AD reveal hypoperfusion or hypometabolism in the posterior temporal-parietal cortex (Fig. 23-2*C, D*). The EEG in AD is normal or shows nonspecific slowing. Routine spinal fluid examination is also normal. CSF Aβ amyloid levels are reduced, whereas levels of tau protein are increased, but the considerable overlap of these levels with those of the normal aged population limits the usefulness of these measurements in diagnosis. The use of blood Apo ε genotyping is discussed under Pathogenesis, later. *Slowly progressive decline in memory and orientation, normal results on laboratory tests, and an MRI or CT scan showing only diffuse or posteriorly predominant cortical and hippocampal atrophy is highly suggestive of AD.* A clinical diagnosis of AD reached after careful evaluation is confirmed at autopsy about 90% of the time, with misdiagnosed cases usually representing one of the other dementing disorders described later in this chapter, a mixture of AD with vascular pathology, or DLB.

Relatively simple clinical clues are useful in the differential diagnosis. Early prominent gait disturbance with only mild memory loss suggests vascular dementia or, rarely, NPH (see later). Resting tremor with stooped posture, bradykinesia, and masked facies suggest PD (Chap. 24). The early appearance of parkinsonian features, visual hallucinations, delusional misidentification, or REM sleep disorders suggest DLB. Chronic alcoholism should prompt the search for vitamin deficiency. Loss of sensibility to position and vibration stimuli accompanied by Babinski responses suggests vitamin B_{12} deficiency (Chap. 30). Early onset of a seizure suggests a metastatic or primary brain neoplasm (Chap. 32). A past history of depression suggests pseudodementia (see later). A history of treatment for insomnia, anxiety, psychiatric disturbance, or epilepsy suggests chronic drug intoxication. Rapid progression over a few weeks or months associated with rigidity and myoclonus suggests CJD (Chap. 38). Prominent behavioral changes with intact memory and lobar atrophy on brain imaging are typical of FTD. A positive family history of dementia suggests either one of the familial forms of AD or one of the other genetic disorders associated with dementia, such as HD (see later), FTD (see later), familial forms of prion diseases, or rare forms of hereditary ataxias (Chap. 26).

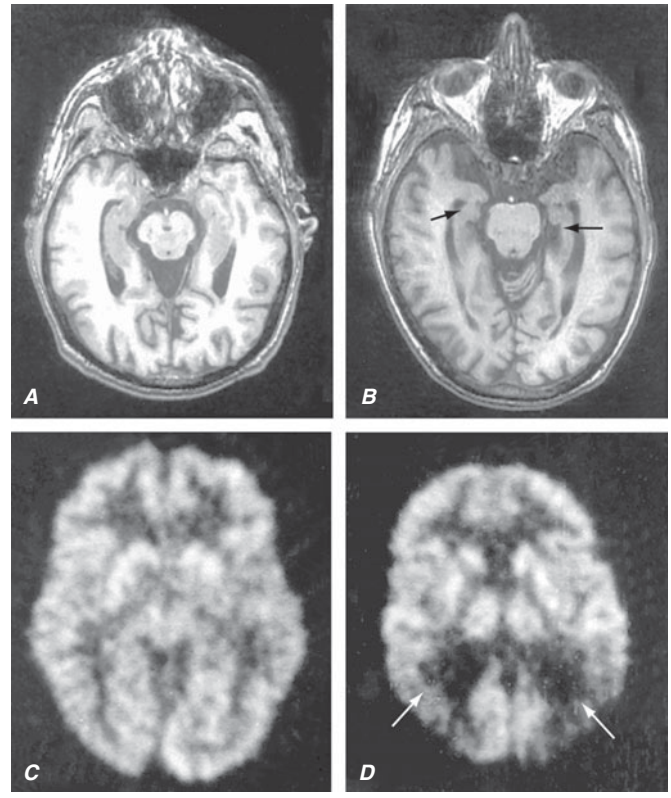


FIGURE 23-2

Alzheimer's disease. Axial T1weighted MR images through the midbrain of a normal 86-year-old athlete (***A***) and a 77-year-old male (***B***) with AD. Note that both individuals have prominent sulci and slight dilatation of the lateral ventricles. However, there is a reduction in the volume of the hippocampus of the patient with AD (*arrows*) compared with that of the normal-for-age hippocampus (***A***). Fluorodeoxyglucose PET scans of a normal control (***C***) and a patient with AD (***D***). Note that the patient with AD has decreased activity in the parietal lobes bilaterally (*arrows*), a typical finding in this condition. AD, Alzheimer's disease; PET, positron emission tomography. *(Images courtesy of TF Budinger, University of California; with permission.)*

Epidemiology

The most important risk factors for AD are old age and a positive family history. The frequency of AD increases

with each decade of adult life, reaching 20–40% of the population older than 85 years. A positive family history of dementia suggests a genetic cause of AD. Female gender may also be a risk factor independent of the greater longevity of women. Some AD patients have a past history of head trauma with concussion, but this appears to be a relatively minor risk factor. AD is more common in groups with very low educational attainment, but education influences test-taking ability, and it is clear that AD can affect persons of all intellectual levels. One study found that the capacity to express complex written language in early adulthood correlated with a decreased risk for AD. Numerous environmental factors, including aluminum, mercury, and viruses, have been proposed as causes of AD, but none has been demonstrated to play a significant role. Similarly, several studies suggest that the use of nonsteroidal anti-inflammatory agents is associated with a decreased risk of AD, but this has not been confirmed in large prospective studies. Vascular disease, in particular stroke, seems to lower the threshold for the clinical expression of AD. Also, in many AD patients, amyloid angiopathy can lead to ischemic infarctions or hemorrhages. Diabetes increases the risk of AD threefold. Elevated homocysteine and cholesterol levels; hypertension; diminished serum levels of folic acid; low dietary intake of fruits, vegetables, and red wine; and low levels of exercise are all being explored as potential risk factors for AD.

Pathology

At autopsy, the most severe pathology is usually found in the hippocampus, temporal cortex, and nucleus basalis of Meynert (lateral septum). The most important microscopic findings are neuritic "senile" plaques and NFTs. These lesions accumulate in small numbers during normal aging of the brain but occur in excess in AD. There is increasing evidence to suggest that soluble amyloid fibrils called *oligomers* lead to the dysfunction of the cell and may be the first biochemical injury in AD. Misfolded $A\beta_{42}$ molecules may be the most toxic form of this protein. Accumulation of oligomers eventually leads to formation of neuritic plaques (**Fig. 23-3**). The neuritic plaques contain a central core that includes Aβ amyloid, proteoglycans, Apo ε4, α_1 antichymotrypsin, and other proteins. Aβ amyloid is a protein of 39–42 amino acids that is derived proteolytically from a larger transmembrane protein named *amyloid precursor protein* (APP) when APP is cleaved by β and γ secretases. The normal function of Aβ amyloid is unknown. APP has neurotrophic and neuroprotective activities. The plaque core is surrounded by the debris of degenerating neurons, microglia, and macrophages. The accumulation of Aβ amyloid in cerebral arterioles is termed *amyloid angiopathy*. NFTs are silverstaining, twisted neurofilaments in neuronal cytoplasm that represent abnormally

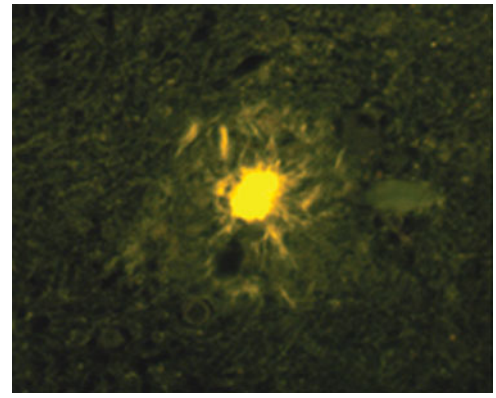


FIGURE 23-3
Mature neuritic plaque with a dense central amyloid core surrounded by dystrophic neurites (thioflavin S stain). *(Image courtesy of S DeArmond, University of California; with permission.)*

phosphorylated tau (τ) protein and appear as paired helical filaments by electron microscopy. Tau is a microtubule associated protein that may function to assemble and stabilize the microtubules that convey cell organelles, glycoproteins, and other important materials throughout the neuron. The ability of tau protein to bind to microtubule segments is determined partly by the number of phosphate groups attached to it. Increased phosphorylation of tau protein disturbs this normal process. Finally, the co-association of AD with DLB and vascular pathology is extremely common.

Biochemically, AD is associated with a decrease in the cerebral cortical levels of several proteins and neurotransmitters, especially acetylcholine, its synthetic enzyme choline acetyltransferase, and nicotinic cholinergic receptors. Reduction of acetylcholine may be related in part to degeneration of cholinergic neurons in the nucleus basalis of Meynert that project to many areas of cortex. There is also reduction in norepinephrine levels in brainstem nuclei such as the locus coeruleus.

GENETIC CONSIDERATIONS

Several genetic factors play important roles in the pathogenesis of at least some cases of AD. One is the *APP* gene on chromosome 21. Adults with trisomy 21 (Down's syndrome) consistently develop the typical neuropathologic hallmarks of AD if they survive beyond age 40. Many develop a progressive dementia superimposed on their baseline mental retardation. APP is a membrane-spanning protein that is subsequently processed into smaller units, including Aβ amyloid that is deposited in neuritic plaques. Aβ peptide results from cleavage of APP by β and γ secretases (**Fig. 23-4**). Presumably the extra dose of the *APP* gene on chromosome 21 is the initiating cause of AD in adult Down's syndrome

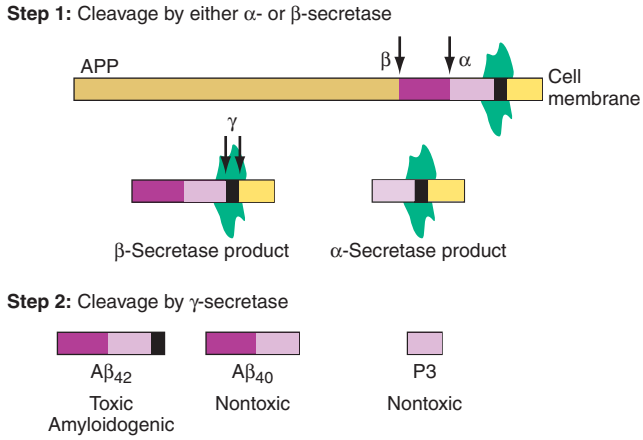


FIGURE 23-4

Amyloid precursor protein (APP) is catabolized by α-, β-, and γ-secretases. A key initial step is the digestion by either β-secretase (BASE) or α-secretase [ADAM10 or ADAM17 (TACE)], producing smaller nontoxic products. Cleavage of the β-secretase product by γ-secretase (step 2) results in either the toxic $A\beta_{42}$ or the nontoxic $A\beta_{40}$ peptide; cleavage of the α-secretase product by γ-secretase produces the nontoxic P3 peptide. Excess production of $A\beta_{42}$ is a key initiator of cellular damage in Alzheimer's disease. Current AD research is focused on developing therapies designed to reduce accumulation of $A\beta_{42}$ by antagonizing β- or γ-secretases, promoting α-secretase, or clearing $A\beta_{42}$ that has already formed by use of specific antibodies.

and results in an excess of cerebral amyloid. Furthermore, a few families with early onset FAD have been discovered to have point mutations in the *APP* gene. Although very rare, these families were the first examples of a single-gene autosomal dominant genetic transmission of AD.

Investigation of large families with multigenerational FAD led to the discovery of two additional AD genes, termed the *presenilins*. Presenilin-1 (*PS-1*) is on chromosome 14 and encodes a protein called S182. Mutations in this gene cause an early-onset AD (onset before age 60 and often before age 50) transmitted in an autosomal dominant, highly penetrant fashion. More than 100 different mutations have been found in the *PS-1* gene in families from a wide range of ethnic backgrounds. Presenilin-2 (*PS-2*) is on chromosome 1 and encodes a protein called STM2. A mutation in the *PS-2* gene was first found in a group of American families with Volga German ethnic background. Mutations in *PS-1* are much more common than those in *PS-2*. The two genes (*PS-1* and *PS-2*) are highly homologous and encode similar proteins that at first appeared to have seven transmembrane domains (hence the designation *STM*), but subsequent studies have suggested eight such domains, with a ninth submembrane region. Both S182 and STM2 are cytoplasmic neuronal proteins that are widely expressed throughout the nervous system. They are homologous to a cell-trafficking protein, sel 12, found in the nematode *Coenorhabditis elegans*. Patients with mutations in these genes have elevated plasma levels of $A\beta_{42}$ amyloid, and *PS-1* mutations in cell cultures produce increased $A\beta_{42}$ amyloid in the media. There is evidence that *PS-1* is involved in the cleavage of APP at the gamma secretase site and mutations in either gene (*PS-1* or *APP*) may disturb this function. Mutations in *PS-1* have thus far proved to be the most common cause of earlyonset FAD, representing perhaps 40–70% of this relatively rare syndrome. Mutations in *PS-1* tend to produce AD with an earlier age of onset (mean onset 45 years) and a shorter, more rapidly progressive course (mean duration 6–7 years) than the disease caused by mutations in *PS-2* (mean onset 53 years; duration 11 years). Some carriers of uncommon *PS-2* mutations have had onset of dementia after the age of 70. Mutations in the presenilins are rarely involved in the more common sporadic cases of late-onset AD occurring in the general population. Molecular DNA blood testing for these uncommon mutations is now possible on a research basis, and mutation analysis of *PS-1* is commercially available. Such testing is likely to be positive only in early-onset familial cases of AD. Any testing of asymptomatic persons at risk must be done in the context of formal, thoughtful genetic counseling.

A discovery of great importance has implicated the *Apo* ε gene on chromosome 19 in the pathogenesis of late onset familial and sporadic forms of AD. *Apo* ε is involved in cholesterol transport and has three alleles: 2, 3, and 4. The Apo ε4 allele has a strong association with AD in the general population, including sporadic and late-onset familial cases. Approximately 24–30% of the nondemented white population has at least one ε4 allele (12–15% allele frequency), and about 2% are ε4/4 homozygotes. Approximately 40–65% of AD patients have at least one ε4 allele, a highly significant difference compared with controls. On the other hand, many AD patients have no ε4 allele, and individuals with ε4 may never develop AD. Therefore, ε4 is neither necessary nor sufficient as a cause of AD. Nevertheless, it is clear that the Apo ε4 allele, especially in the homozygous 4/4 state, is an important risk factor for AD. It appears to act as a dose-dependent modifier of age of onset, with the earliest onset associated with the ε4/4 homozygous state. It is unknown how Apo ε functions as a risk factor modifying age of onset, but it may be involved with the clearance of amyloid, less efficiently in the case of Apo ε4. Apo ε is present in the neuritic amyloid plaques of AD, and it may also be involved in neurofibrillary tangle formation, because it binds to tau protein. Apo ε4 decreases neurite outgrowth in cultures of dorsal root ganglion neurons, perhaps indicating a deleterious role in the brain's response to injury. There is some evidence that the ε2 allele may be "protective," but that remains to be clarified. The use of Apo ε testing in the diagnosis

of AD is controversial. It is not indicated as a predictive test in normal persons because its precise predictive value is unclear, and many individuals with the ε4 allele never develop dementia. However, some cognitively normal ε4 heterozygotes and homozygotes have been found by PET to have decreased cerebral cortical metabolic rates, suggesting possible presymptomatic abnormalities compatible with the earliest stage of AD. In demented persons who meet clinical criteria for AD, the finding of an ε4 allele increases the reliability of diagnosis. However, the absence of an ε4 allele does not eliminate the diagnosis of AD. Furthermore, all patients with dementia, including those with an ε4 allele, require a search for reversible causes of their cognitive impairment. Nevertheless, Apo ε4 remains the single most important biologic marker associated with risk for AD, and studies of its functional role and diagnostic usefulness are progressing rapidly. Its association (or lack thereof) with other dementing illnesses needs to be fully evaluated. The ε4 allele is not associated with FTD, DLB, or CJD. Additional genes are also likely to be involved in AD, but none have been reliably identified.

Rx Treatment: ALZHEIMER'S DISEASE

The management of AD is challenging and gratifying, despite the absence of a cure or a robust pharmacologic treatment. The primary focus is on long-term amelioration of associated behavioral and neurologic problems.

Building rapport with the patient, family members, and other caregivers is essential to successful management. In the early stages of AD, memory aids such as notebooks and posted daily reminders can be helpful. Common sense and clinical studies show that family members should emphasize activities that are pleasant and deemphasize those that are unpleasant. Kitchens, bathrooms, and bedrooms need to be made safe, and eventually patients must stop driving. Loss of independence and change of environment may worsen confusion, agitation, and anger. Communication and repeated calm reassurance are necessary. Caregiver "burnout" is common, often resulting in nursing home placement of the patient, and respite breaks for the caregiver help to maintain successful long-term management of the patient. Use of adult day-care centers can be most helpful. Local and national support groups, such as the Alzheimer's Association, are valuable resources.

Donepezil, rivastigmine, galantamine, memantine, and tacrine are the drugs presently approved by the Food and Drug Administration (FDA) for treatment of AD. Due to hepatotoxicity, tacrine is no longer used. The pharmacologic action of donepezil, rivastigmine, and galantamine is inhibition of cholinesterase, with a resulting increase in cerebral levels of acetylcholine. Memantine appears to act by blocking overexcited N-methyl-D-aspartate (NMDA) channels. Double-blind, placebo-controlled, crossover studies with cholinesterase inhibitors and memantine have shown them to be associated with improved caregiver ratings of patients' functioning and with an apparent decreased rate of decline in cognitive test scores over periods of up to 3 years. The average patient on an anticholinesterase compound maintains his or her MMSE score for close to a year, whereas a placebo-treated patient declines 2–3 points over the same time period. Memantine, used in conjunction with cholinesterase inhibitors or by itself, seems to slow cognitive deterioration in patients with moderate to severe AD and is not approved for mild AD. These compounds have only modest efficacy for AD and offer even less benefit in the late stages. All the cholinesterase inhibitors are relatively easy to administer, and their major side effects are gastrointestinal symptoms (nausea, diarrhea, cramps), altered sleep with bad dreams, bradycardia (usually benign), and sometimes muscle cramps.

In a prospective observational study, the use of estrogen replacement therapy appeared to protect—by about 50%—against development of AD in women. This study seemed to confirm the results of two earlier case-controlled studies. Sadly, a prospective placebo-controlled study of a combined estrogen-progesterone therapy for asymptomatic postmenopausal women increased, rather than decreased, the prevalence of dementia. This study markedly dampened enthusiasm for hormone treatments for the prevention of dementia. Additionally, no benefit has been found in the treatment of AD with estrogen.

In patients with moderately advanced AD, a prospective trial of the antioxidants selegiline, α-tocopherol (vitamin E), or both, slowed institutionalization and progression to death. Because vitamin E has less potential for toxicity than selegiline and is cheaper, the doses used in this study of 1000 IU twice daily are offered to many patients with AD. However, the beneficial effects of vitamin E remain controversial, and most investigators no longer give it in these high doses because of potential cardiovascular complications.

A randomized, double-blind, placebo-controlled trial of an extract of *Ginkgo biloba* found modest improvement in cognitive function in subjects with AD and vascular dementia. This study requires confirmation before *Ginkgo biloba* is used as a treatment for dementia because there was a high subject dropout rate and no improvement on a clinician's judgment scale. A comprehensive 6-year multicenter prevention study using *Ginkgo biloba* is underway.

Vaccination against $A\beta_{42}$ has proved highly efficacious in mouse models of AD; it helped to clear amyloid from the brain and prevent further accumulation of amyloid. However, in human trials this approach led to life-threatening complications, including meningoencephalitis. Modifications of the vaccine approach using passive immunization with monoclonal antibodies are currently being evaluated in phase 3 trials. Another experimental approach to the treatment of AD has been the use of β and γ secretase inhibitors that diminish the production of $A\beta_{42}$.

Several retrospective studies suggest that nonsteroidal anti-inflammatory agents and statins (HMG-CoA reductase inhibitors) may have a protective effect on dementia, and controlled prospective studies are being conducted. Similarly, prospective studies with the goal of lowering serum homocysteine levels are underway, suggesting an association of elevated homocysteine with dementia progression based on epidemiologic studies. Finally, there is now a strong interest in the relationship between diabetes and AD, and insulin-regulating studies are being conducted.

Mild to moderate depression is common in the early stages of AD and responds to antidepressants or cholinesterase inhibitors. Selective serotonin reuptake inhibitors (SSRIs) are commonly used due to their low anticholinergic side effects. Generalized seizures should be treated with an appropriate anticonvulsant, such as phenytoin or carbamazepine. Agitation, insomnia, hallucinations, and belligerence are especially troublesome characteristics of some AD patients, and these behaviors can lead to nursing home placement. The newer generation of atypical antipsychotics, such as risperidone, quetiapine, and olanzapine, are being used in low doses to treat these neuropsychiatric symptoms. The few controlled studies comparing drugs against behavioral intervention in the treatment of agitation suggest mild efficacy with significant side effects related to sleep, gait, and cardiovascular complications. All of the antipsychotics carry a black-box warning and are associated with increased deaths in AD patients; therefore, they should be used with caution. However, careful, daily, nonpharmacologic behavior management is often not available, rendering medications necessary.

VASCULAR DEMENTIA

Dementia associated with cerebral vascular disease can be divided into two general categories: multi-infarct dementia and diffuse white matter disease (also called *leukoaraiosis, subcortical arteriosclerotic encephalopathy* or *Binswanger's disease*). Cerebral vascular disease appears to be a more common cause of dementia in Asia than in Europe and North America. Individuals who have had several strokes may develop chronic cognitive deficits, commonly called *multi-infarct dementia*. The strokes may be large or small (sometimes lacunar) and usually involve several different brain regions. The occurrence of dementia depends partly on the total volume of damaged cortex, but it is also more common in individuals with left-hemisphere lesions, independent of any language disturbance. Patients typically report a history of discrete episodes of sudden neurologic deterioration. Many multi-infarct dementia patients have a history of hypertension, diabetes, coronary artery disease, or other manifestations of widespread atherosclerosis. Physical examination usually shows focal neurologic deficits such as hemiparesis, a unilateral Babinski reflex, a visual field defect, or pseudobulbar palsy. Recurrent strokes result in a stepwise progression of disease. Neuroimaging studies show multiple areas of infarction. Thus, the history and neuroimaging findings differentiate this condition from AD. However, both AD and multiple infarctions are common and sometimes occur together. With normal aging, there is also an accumulation of amyloid in cerebral blood vessels, leading to a condition called *cerebral amyloid angiopathy of aging* (not associated with dementia), which predisposes older persons to hemorrhagic lobar stroke. AD patients with amyloid angiopathy may be at increased risk for cerebral infarction.

Some individuals with dementia are discovered on MRI to have bilateral abnormalities of subcortical white matter, termed *diffuse white matter disease*, often occurring in association with lacunar infarctions (**Fig. 23-5**). The dementia may be insidious in onset and progress slowly, features that distinguish it from multi-infarct dementia, but other patients show a stepwise deterioration more typical of multi-infarct dementia. Early symptoms are mild confusion, apathy, changes in personality, depression, psychosis, memory, and spatial or executive deficits. Marked difficulties in judgment and orientation and dependence on others for daily activities develop later. Euphoria, elation, depression, or aggressive behaviors are common as the disease progresses. Both pyramidal and cerebellar signs may be present in the same patient. A gait disorder is present in at least half of these patients. With advanced disease, urinary incontinence and dysarthria with or without other pseudobulbar features (e.g., dysphagia, emotional lability) are frequent. Seizures and myoclonic jerks appear in a minority of patients. This disorder appears to result from chronic ischemia due to occlusive disease of small, penetrating cerebral arteries and arterioles (microangiopathy). Any disease-causing stenosis of small cerebral vessels may be the critical underlying factor, though most typically hypertension is the main cause. The term *Binswanger's disease* should be used with caution, because it does not really identify a single entity.

Other rare causes of white matter disease also present with dementia, such as adult metachromatic leukodystrophy

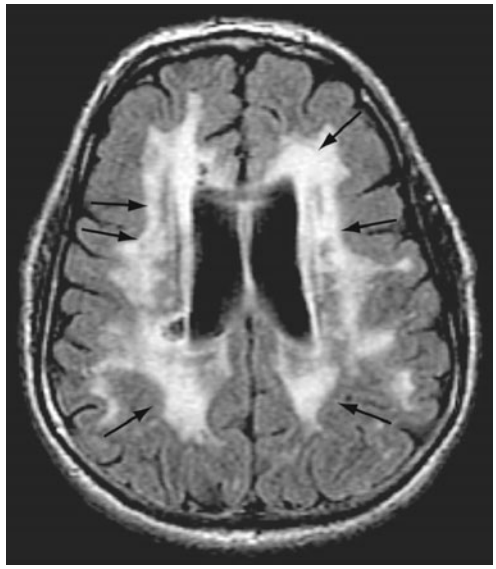


FIGURE 23-5

Diffuse white matter disease (Binswanger's disease). Axial T2-weighted MR image through the lateral ventricles reveals multiple areas of abnormal high signal intensity involving the periventricular white matter as well as the corona radiata and lentiform nuclei (*arrows*). While seen in some individuals with normal cognition, this appearance is more pronounced in patients with dementia of a vascular etiology.

(arylsulfatase A deficiency) and progressive multifocal leukoencephalopathy (papovavirus infection). A dominantly inherited form of diffuse white matter disease is known as *cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy* (CADASIL). Clinically, there is a progressive dementia developing in the fifth to seventh decades in multiple family members who may also have a history of migraine and recurrent stroke without hypertension. Skin biopsy may show characteristic dense bodies in the media of arterioles. The disease is caused by mutations in the *notch 3* gene, and there is a commercially available genetic test. The frequency of this disorder is unknown, and there are no known treatments.

Mitochondrial disorders can present with strokelike episodes and can selectively injure basal ganglia or cortex. Many such patients show other findings suggestive of a neurologic or systemic disorder such as ophthalmoplegia, retinal degeneration, deafness, myopathy, neuropathy, or diabetes. Diagnosis is difficult but serum—especially CSF—levels of lactate and pyruvate may be abnormal, and biopsy of affected tissue is often diagnostic.

Treatment of vascular dementia must be focused on the underlying causes, such as hypertension, atherosclerosis, and diabetes. Recovery of lost cognitive function is not likely to occur, although fluctuations with periods of improvement are common. Anticholinesterase compounds are being studied as a treatment for vascular dementia.

FRONTOTEMPORAL DEMENTIA, PROGRESSIVE SUPRANUCLEAR PALSY, AND CORTICOBASAL DEGENERATION

Frontotemporal dementia (FTD) often begins when the patient is in the fifth to seventh decades, and in this age group it is nearly as common as AD. Most studies suggest that FTD is twice as common in men as it is in women. *Unlike AD, behavioral symptoms predominate in the early stages of FTD.* Genetics play a significant role in a sizable minority of cases. The clinical heterogeneity in familial and sporadic forms of FTD is remarkable, with patients demonstrating variable mixtures of disinhibition, dementia, PSP, CBD, and motor neuron disease. The most common genetic mutations that cause an autosomal dominant form of FTD involve the *tau* or *progranulin* genes, both on chromosome 17. *Tau* mutations lead to a change in the alternate splicing of tau or cause loss of function in the tau molecule. With *progranulin*, a missense mutation in the coding sequence of the gene is the underlying cause for the neurodegeneration. Progranulin appears to be a rare example of an autosomal dominant mutation leading to haploinsufficiency—too little of the progranulin protein. Both *tau* and *progranulin* mutations are associated with parkinsonian features, while ALS is rare in the setting of these mutations. In contrast, familial FTD with ALS has been linked to chromosome 9. Mutations in the valosin (chromosome 9) and ESCRTII molecules (chromosome 3) also lead to autosomal dominant forms of familial FTD.

In FTD, early symptoms are divided among cognitive, behavioral, and sometimes motor abnormalities, reflecting degeneration of the anterior frontal and temporal regions, basal ganglia, and motor neurons. Cognitive testing typically reveals spared memory but impaired planning, judgment, or language. Poor business decisions and difficulty organizing work tasks are common, and speech and language deficits often emerge. Patients with FTD often show an absence of insight into their condition. Common behavioral deficits include apathy, disinhibition, weight gain, food fetishes, compulsions, and euphoria.

Findings at the bedside are dictated by the anatomic localization of the disorder. Asymmetric left-frontal cases present with nonfluent aphasias, while left anterior temporal degeneration is characterized by loss of words and concepts related to language (semantic dementia). Nonfluent patients quickly progress to mutism, while those with semantic dementia develop features of multimodality agnosia, losing the ability to recognize faces, objects, words, and the emotions of others. Copying, calculating, and navigation often remain normal into later in the illness. Recently it has become apparent that many if not most patients with nonfluent aphasia progress to clinical syndromes that overlap with PSP and CBD and show these pathologies at autopsy. This left-hemisphere

presentation of FTD has been called *primary progressive aphasia*. In contrast, right-frontal or temporal cases show profound alterations in social conduct, with loss of empathy, disinhibition, and antisocial behaviors predominating. Memory and visuospatial skills are relatively spared in most FTD patients. There is a striking overlap among FTD, PSP, CBD, and motor neuron disease; ophthalmoplegia, dystonia, swallowing symptoms, and fasciculations are common at presentation of FTD or emerge during the course of the illness.

The distinguishing anatomic hallmark of FTD is a marked lobar atrophy of temporal and/or frontal lobes, which can be visualized by neuroimaging studies and is readily apparent at autopsy (**Figs. 23-6** and **23-7**). The atrophy is sometimes asymmetric and may involve the basal ganglia. Two major pathologies have been linked to the clinical syndrome, one associated with tau inclusions, the other with inclusions that stain negatively for tau but positively for ubiquitin and TDP-43. Microscopic findings that are seen across all FTD cases include gliosis, neuronal loss, and spongiosus.

Approximately one-half of all cases show swollen or ballooned neurons containing cytoplasmic inclusions that stain positively for tau. These aggregates sometimes resemble those found in PSP and CBD, and tau plays a major role in the pathogenesis of all three conditions. A toxic gain of function related to tau underlies the pathogenesis of many familial cases and is presumed to be a factor in sporadic cases as well. Nearly 80% of FTD patients show involvement of the basal ganglia at autopsy, and 15% go on to develop motor neuron disease, underscoring the multisystem nature of this illness. Serotonergic losses are seen in many patients, and glutaminergic neurons are depleted. In contrast to AD, the cholinergic system is relatively spared in FTD, whereas serotonergic and glutaminergic neurons are depleted in many patients.

Historically, *Pick's disease* was described as a progressive degenerative disorder characterized clinically by selective involvement of the anterior frontal and temporal neocortex and pathologically by intracellular inclusions (*Pick bodies*). Classic Pick bodies stain positive with silver (argyrophilic) and tau, but many of the tau-positive

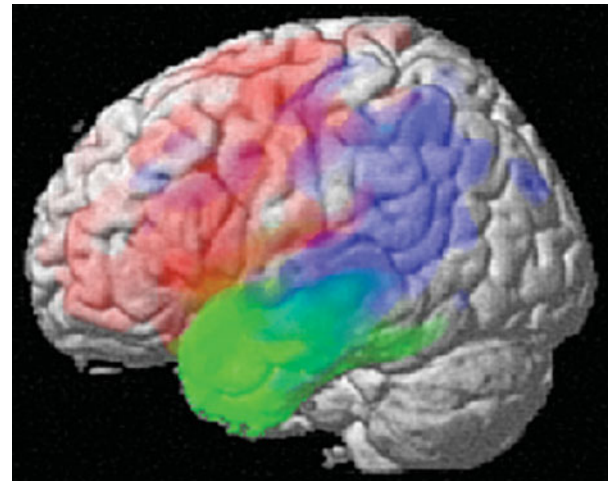
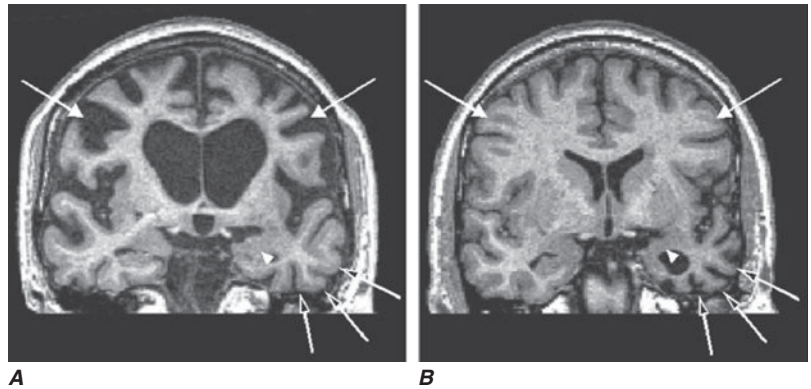


FIGURE 23-7

Voxel-based morphometry analysis showing differing patterns of brain atrophy in the frontal variant of frontotemporal dementia (red), temporal variant of frontotemporal dementia (green), and Alzheimer's disease (blue). This technique allows comparison of MRI gray matter volumes between groups of subjects. *(Image courtesy of M Gorno-Tempini, University of California at San Francisco; with permission.*



A ***B***

FIGURE 23-6

Frontotemporal dementia (FTD). Coronal MRI sections from one patient with frontally predominant FTD (***A***) and another with temporally predominant FTD (***B***). Prominent atrophy affecting the frontal gyri (*white arrows*) is present in frontally predominant FTD, particularly affecting the right frontal region; note also the thinning of the corpus callosum superior to the lateral ventricles. This patient presented with disinhibition and antisocial behavior. In the temporally predominant patient, severe atrophy in the left temporal lobe (*open arrows*) and amygdala (*white arrowheads*) is present; this patient presented with progressive aphasia. *(Images courtesy of H Rosen and G Schauer, University of California at San Francisco; with permission.)*

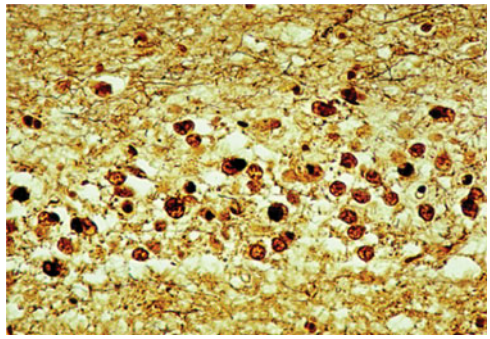


FIGURE 23-8

Classic intraneuronal Pick body (tau2 stain). These consist of loosely arranged paired and straight-helical filaments and stain positive for tau. Classic Pick bodies are seen in ~20% of all frontotemporal dementia cases.

inclusions in FTD cases are not labeled with silver stains (Fig. 23-8). Although the nomenclature for these patients has remained controversial, the term *FTD* is increasingly used to describe the clinical syndrome, while *Pick's disease* is used to classify patients in whom the pathology shows classic Pick bodies (only a minority of patients with the clinical features of FTD).

The burden on caregivers of FTD patients is extremely high. Treatment is symptomatic, and there are currently no therapies known to slow progression or improve cognitive symptoms. Many of the behaviors that accompany FTD, such as depression, hyperorality, compulsions, and irritability, can be ameliorated with serotonin-modifying antidepressants. The co-association with motor disorders necessitates the careful use of antipsychotics, which can exacerbate this problem.

Progressive supranuclear palsy (PSP) is a degenerative disease that involves the brainstem, basal ganglia, and neocortex. Clinically, this disorder begins with falls and vertical supranuclear gaze paresis and progresses to symmetrical rigidity and dementia. A stiff, unstable posture with hyperextension of the neck and slow gait with frequent falls is characteristic of PSP. Early in the disease, patients have difficulty with downgaze and lose vertical opticokinetic nystagmus on downward movement of a target. Frequent unexplained and sometimes spectacular falls are common secondary to a combination of axial rigidity, inability to look down, and bad judgment. Although the patients have very limited voluntary eye movements, their eyes still retain oculocephalic reflexes (doll's head maneuver); thus, the eye-movement disorder is supranuclear. The dementia is similar to FTD with apathy, frontal/executive dysfunction, poor judgment, slowed thought processes, impaired verbal fluency, and difficulty with sequential actions and with shifting from one task to another all common at the time of presentation and often preceding the motor syndrome. Some patients begin with a nonfluent aphasia and progress to classical PSP. There is only a limited response to L-dopa; no other effective treatments exist. Death occurs within 5–10 years of onset. At autopsy, abnormal accumulation of tau is found within neurons and glia, often in the form of neurofibrillary tangles (NFTs). These tangles are found in multiple subcortical structures (including the subthalamus, globus pallidus, substantia nigra, locus coeruleus, periaqueductal gray, superior colliculi, and oculomotor nuclei) as well as in the neocortex. The NFTs have similar staining characteristics to those of AD, but on electron microscopy they are generally seen to consist of straight tubules rather than the paired helical filaments found in AD.

In addition to its overlap with FTD and CBD (see below), PSP is often confused with idiopathic *Parkinson's disease* (PD). Although elderly Parkinson's patients may have some difficulty with upgaze, they do not develop downgaze paresis or other abnormalities of voluntary eye movements typical of PSP. Dementia does occur in ~20% of PD patients, often secondary to DLB. Furthermore, the behavioral syndromes seen with DLB differ from PSP (see later). The occurrence of dementia in PD is more likely with increasing age, increasing severity of extrapyramidal signs, a long duration of disease, and the presence of depression. These patients also show cortical atrophy on brain imaging. Neuropathologically, there may be Alzheimer changes in the cortex (amyloid plaques and NFTs), neuronal Lewy body inclusions in both the substantia nigra and the cortex, or no specific microscopic changes other than gliosis and neuronal loss. Progressive supranuclear palsy and Parkinson's disease are discussed in detail in Chap. 24.

Cortical basal degeneration (CBD) is a slowly progressive dementing illness associated with severe gliosis and neuronal loss in both the neocortex and basal ganglia (substantia nigra and striatum). Occasionally there is a unilateral onset with rigidity, dystonia, and apraxia of one arm and hand, sometimes called the *alien hand*, while in other instances the disease presents as a progressive frontal syndrome or as progressive symmetrical parkinsonism. Some patients begin with a progressive nonfluent aphasia or a progressive motor disorder of speech. Eventually CBD becomes bilateral and leads to dysarthria, slow gait, action tremor, and dementia. The microscopic features include enlarged, achromatic neurons in the cortex with tau inclusions. Glial plaques with tau inclusions are pathognomonic of CBD. The condition is rarely familial, the cause is unknown, and there is no specific treatment.

DEMENTIA WITH LEWY BODIES

The parkinsonian dementia syndromes are under increasing study, with many cases unified by the presence of Lewy bodies in both the substantia nigra and the cortex at pathology. The clinical syndrome is characterized by visual hallucinations, parkinsonism, fluctuating alertness,

falls, and often REM sleep behavior disorder. Dementia can precede or follow the appearance of parkinsonism. Hence, one pathway to DLB occurs in patients with longstanding PD without cognitive impairment who slowly develop a dementia that is associated with visual hallucinations, parkinsonism, and fluctuating alertness. In others, the dementia and neuropsychiatric syndrome precede the parkinsonism. DLB patients are highly susceptible to metabolic perturbations, and in some patients the first manifestation of illness is a delirium, often precipitated by an infection or other systemic disturbance. A delirium induced by L-dopa, prescribed for parkinsonian symptoms attributed to PD, may be the initial clue that the correct diagnosis is DLB. Even without an underlying precipitant, fluctuations can be marked in DLB patients, with the occurrence of episodic confusion admixed with lucid intervals. However, despite the fluctuating pattern, the clinical features persist over a long period of time, unlike delirium, which resolves following correction of the underlying precipitant. Cognitively, DLB patients tend to have relatively better memory but more severe visuospatial deficits than individuals with AD.

The key neuropathologic feature is the presence of Lewy bodies throughout the cortex, amygdala, cingulate cortex, and substantia nigra. Lewy bodies are intraneuronal cytoplasmic inclusions that stain with periodic acid–Schiff (PAS) and ubiquitin. They are composed of straight neurofilaments 7–20 nm long with surrounding amorphous material. They contain epitopes recognized by antibodies against phosphorylated and nonphosphorylated neurofilament proteins, ubiquitin, and a presynaptic protein called α-synuclein. Lewy bodies are traditionally found in the substantia nigra of patients with idiopathic PD. A profound cholinergic deficit is present in many patients with DLB and may be a factor responsible for the fluctuations and visual hallucinations present in these patients. In patients without other pathologic features, the condition is referred to as *diffuse Lewy body disease*. In patients whose brains also contain excessive amounts of amyloid plaques and NFTs, the condition is called the *Lewy body variant of Alzheimer's disease*. The quantity of Lewy bodies required to establish the diagnosis is controversial, but a definite diagnosis requires pathology. At autopsy, 10–30% of demented patients show cortical Lewy bodies.

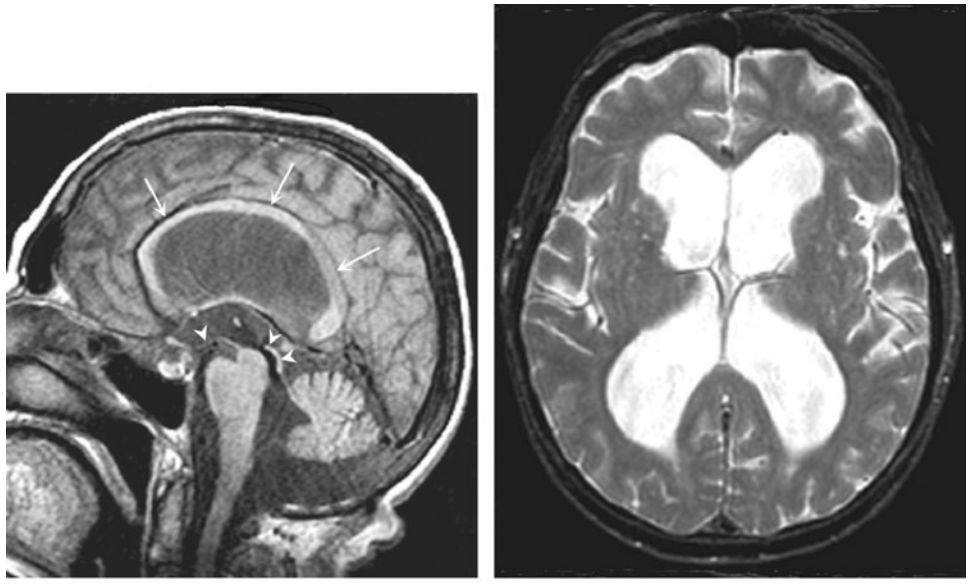
Due to the overlap with AD and the cholinergic deficit in DLB, anticholinesterase compounds may be helpful. Exercise programs maximize the motor function of these patients. Similarly, antidepressants are often necessary to treat the depressive syndromes that accompany DLB. Atypical antipsychotics in low doses are sometimes needed to alleviate psychosis, although even low doses can increase extrapyramidal syndromes and may rarely lead to death. As noted above, patients with DLB are extremely sensitive to dopaminergic medications, which must be carefully titrated; tolerability may be improved by concomitant AD medications.

OTHER CAUSES OF DEMENTIA

Prion disorders such as *Creutzfeldt-Jakob disease* (CJD) are rare conditions (~1 per million population) that produce dementia. CJD is a rapidly progressive disorder associated with dementia, focal cortical signs, rigidity, and myoclonus, causing death in <1 year from the first symptoms. The rapidity of progression seen with CJD is uncommon in AD so that distinction between the two disorders is usually possible. However, CBD and DLB, more rapid degenerative dementias with prominent abnormalities in movement, are more likely to be mistaken for CJD. The differential diagnosis for CJD usually includes other rapidly progressive dementing conditions such as viral or bacterial encephalitides, Hashimoto's encephalitis, CNS vasculitis, lymphoma, or paraneoplastic syndromes. The markedly abnormal periodic EEG discharges and cortical and basal ganglia abnormalities on diffusion-weighted MRI are unique diagnostic features of CJD. Transmission from infected cattle to the human population in the United Kingdom has caused a small epidemic of atypical CJD in young adults. Prion diseases are discussed in detail in Chap. 38.

Huntington's disease (HD) (Chap. 25) is an autosomal dominant, degenerative brain disorder. A DNA repeat expansion (CAG repeat) of the mutant gene on chromosome 4 forms the basis of a diagnostic blood test for the disease gene. The clinical hallmarks of the disease are chorea, behavioral disturbance, and frontal executive disorder. Onset is usually in the fourth or fifth decade, but there is a wide range in age of onset, from childhood to >70 years. Memory is frequently not impaired until late in the disease, but attention, judgment, awareness, and executive functions may be seriously deficient at an early stage. Depression, apathy, social withdrawal, irritability, and intermittent disinhibition are common. Delusions and obsessive compulsive behavior may occur. The disease duration is typically about 15 years but is quite variable. There is no specific treatment, but the adventitious movements may partially respond to first- and second-generation antipsychotics. Treatment of behavioral changes are discussed in "General Symptomatic Treatment of the Patient with Dementia," later. Asymptomatic adult children at risk for HD should receive careful genetic counseling prior to DNA testing, because a positive result may have serious emotional and social consequences.

Normal-pressure hydrocephalus (NPH) is a relatively uncommon syndrome with clinical, physiologic, and neuroimaging characteristics. Historically, many of the individuals who have been treated for NPH have suffered from other dementias, particularly AD, multi-infarct



A B

FIGURE 23-9

Normal-pressure hydrocephalus. ***A.*** Sagittal T1-weighted MR image demonstrates dilatation of the lateral ventricle and stretching of the corpus callosum (*arrows*), depression of the floor of the third ventricle (*single arrowhead*), and enlargement of the aqueduct (*double arrowheads*). Note the diffuse dilatation of the lateral, third, and fourth ventricles with a patent aqueduct, typical of communicating hydrocephalus. ***B.*** Axial T2-weighted MR images demonstrate dilatation of the lateral ventricles. This patient underwent successful ventriculoperitoneal shunting.

dementia, and DLB. For NPH the clinical triad includes an abnormal gait (ataxic or apractic), dementia (usually mild to moderate), and urinary incontinence. Neuroimaging studies reveal enlarged lateral ventricles (hydrocephalus) with little or no cortical atrophy. This syndrome is a communicating hydrocephalus with a patent aqueduct of Sylvius (Fig. 23-9), in contrast to congenital aqueductal stenosis, where the aqueduct is small. In many cases, periventricular edema is present. Lumbar puncture opening pressure is in the high normal range, and the CSF protein, sugar concentrations, and cell count are normal. NPH is presumed to be caused by obstruction to normal flow of CSF over the cerebral convexity and delayed absorption into the venous system. The indolent nature of the process results in enlarged lateral ventricles but relatively little increase in CSF pressure. There is presumed stretching and distortion of white matter tracts in the corona radiata, but the exact physiologic cause of the clinical syndrome is unclear. Some patients have a history of conditions producing scarring of the basilar meninges (blocking upward flow of CSF) such as previous meningitis, subarachnoid hemorrhage, or head trauma. Others with longstanding but asymptomatic congenital hydrocephalus may have adult-onset deterioration in gait or memory that is confused with NPH. In contrast to AD, the NPH patient has an early and prominent gait disturbance and no evidence of cortical atrophy on CT or MRI. A number of attempts have been made to use various special studies to improve the diagnosis of NPH and predict the success of ventricular shunting. These include radionuclide cisternography (showing a delay in CSF absorption over the convexity) and various attempts to monitor and alter CSF flow dynamics, including a constant-pressure infusion test. None has proven to be specific or consistently useful. There is sometimes a transient improvement in gait or cognition following lumbar puncture (or serial punctures) with removal of 30–50 mL of CSF, but this finding also has not proven to be consistently predictive of post-shunt improvement. AD often masquerades as NPH, because the gait may be abnormal in AD and cortical atrophy sometimes is difficult to determine by CT or MRI early in the disease. Hippocampal atrophy on MRI is a clue favoring AD. Approximately 30–50% of patients identified by careful diagnosis as having NPH will show improvement with a ventricular shunting procedure. Gait may improve more than memory. Transient, short-lasting improvement is common. Patients should be carefully selected for this operation, because subdural hematoma and infection are known complications.

Dementia can accompany *chronic alcoholism* (Chap. 50). This may be a result of associated malnutrition, especially of B vitamins and particularly thiamine. However, other poorly defined aspects of chronic alcohol ingestion may also produce cerebral damage. A rare idiopathic syndrome

of dementia and seizures with degeneration of the corpus callosum has been reported primarily in male Italian drinkers of red wine (Marchiafava-Bignami disease).

Thiamine (vitamin B_1) deficiency causes Wernicke's encephalopathy (Chap. 22). The clinical presentation is a malnourished individual (frequently but not necessarily alcoholic) with confusion, ataxia, and diplopia from ophthalmoplegia. Thiamine deficiency damages the thalamus, mammillary bodies, midline cerebellum, periaqueductal grey matter of the midbrain, and peripheral nerves. Damage to the dorsomedial thalamic region correlates most closely with the memory loss. Prompt administration of parenteral thiamine (100 mg intravenously for 3 days followed by daily oral dosage) may reverse the disease if given in the first days of symptom onset. However, prolonged untreated thiamine deficiency can result in an irreversible dementia/amnestic syndrome (Korsakoff's psychosis) or even death.

In *Korsakoff's syndrome*, the patient is unable to recall new information despite normal immediate memory, attention span, and level of consciousness. Memory for new events is seriously impaired, whereas memory of knowledge prior to the illness is relatively intact. Patients are easily confused, disoriented, and incapable of recalling new information for more than a brief interval. Superficially, they may be conversant, entertaining, and able to perform simple tasks and follow immediate commands. Confabulation is common, although not always present, and may result in obviously erroneous statements and elaborations. There is no specific treatment because the previous thiamine deficiency has produced irreversible damage to the medial thalamic nuclei and mammillary bodies. Mammillary body atrophy may be visible on high-resolution MRI.

Vitamin B_{12} deficiency, as can occur in pernicious anemia, causes a macrocytic anemia and may also damage the nervous system (Chap. 30). Neurologically, it most commonly produces a spinal cord syndrome (myelopathy) affecting the posterior columns (loss of position and vibratory sense) and corticospinal tracts (hyperactive tendon reflexes with Babinski responses); it also damages peripheral nerves, resulting in sensory loss with depressed tendon reflexes. Damage to cerebral myelinated fibers may also cause dementia. The mechanism of neurologic damage is unclear but may be related to a deficiency of *S*-adenosylmethionine (required for methylation of myelin phospholipids) due to reduced methionine synthase activity or accumulation of methylmalonate, homocysteine, and propionate, providing abnormal substrates for fatty acids synthesis in myelin. The neurologic signs of vitamin B_{12} deficiency are usually associated with macrocytic anemia but on occasion may occur in its absence. Treatment with parenteral vitamin B_{12} (1000 μg intramuscularly daily for a week, weekly for a month, and monthly for life for pernicious anemia) stops progression of the disease if instituted promptly, but reversal of advanced nervous system damage will not occur.

Deficiency of nicotinic acid (*pellagra*) is associated with sun-exposed skin rash, glossitis, and angular stomatitis. Severe dietary deficiency of nicotinic acid along with other B vitamins such as pyridoxine may result in spastic paraparesis, peripheral neuropathy, fatigue, irritability, and dementia. This syndrome has been seen in prisoner-of-war and concentration camps. Low serum folate levels appear to be a rough index of malnutrition, but isolated folate deficiency has not been proven to be specific cause of dementia.

Infections of the CNS usually cause delirium and other acute neurologic syndromes (Chap. 13). However, some chronic CNS infections, particularly those associated with chronic meningitis (Chap. 36), may produce a dementing illness. The possibility of chronic infectious meningitis should be suspected in patients presenting with a dementia or behavioral syndrome who also have headache, meningismus, cranial neuropathy, and/or radiculopathy. Between 20 and 30% of patients in the advanced stages of infection with HIV become demented (Chap. 37). Cardinal features include psychomotor retardation, apathy, and impaired memory. This syndrome may result from secondary opportunistic infections but can also be caused by direct infection of CNS neurons with HIV. CNS syphilis was a common cause of dementia in the preantibiotic era; it is uncommon nowadays but can still be encountered in patients with multiple sex partners. Characteristic CSF changes consist of pleocytosis, increased protein, and a positive venereal disease research laboratory (VDRL) test.

Primary and metastatic *neoplasms of the CNS* (Chap. 32) usually produce focal neurologic findings and seizures rather than dementia. However, if tumor growth begins in the frontal or temporal lobes, the initial manifestations may be memory loss or behavioral changes. A paraneoplastic syndrome of dementia associated with occult carcinoma (often small cell lung cancer) is termed *limbic encephalitis* (Chap. 39). In this syndrome, confusion, agitation, seizures, poor memory, movement disorders, and frank dementia may occur in association with sensory neuropathy.

A *nonconvulsive seizure disorder* may underlie a syndrome of confusion, clouding of consciousness, and garbled speech. Psychiatric disease is often suspected, but an EEG demonstrates the seizure discharges. If recurrent or persistent, the condition may be termed *complex partial status epilepticus*. The cognitive disturbance often responds to anticonvulsant therapy. The etiology may be previous small strokes or head trauma; some cases are idiopathic.

It is important to recognize *systemic diseases* that indirectly affect the brain and produce chronic confusion or dementia. Such conditions include hypothyroidism; vasculitis; and hepatic, renal, or pulmonary disease. Hepatic encephalopathy may begin with irritability and confusion and slowly progress to agitation, lethargy, and coma (Chaps. 14, 45).

Isolated vasculitis of the CNS (CNS granulomatous vasculitis) (Chap. 21) occasionally causes a chronic encephalopathy associated with confusion, disorientation, and cloudiness of consciousness. Headache is common, and strokes and cranial neuropathies may occur. Brain imaging studies may be normal or nonspecifically abnormal. CSF studies reveal a mild pleocytosis or elevation in the protein level. Cerebral angiography often shows multifocal stenosis and narrowing of vessels. A few patients have only small-vessel disease that is not revealed on angiography. The angiographic appearance is not specific and may be mimicked by atherosclerosis, infection, or other causes of vascular disease. Brain or meningeal biopsy demonstrates abnormal arteries with endothelial cell proliferation and infiltrates of mononuclear cells. The prognosis is often poor, although the disorder may remit spontaneously. Some patients respond to glucocorticoids or chemotherapy.

Chronic metal exposure may produce a dementing syndrome. The key to diagnosis is to elicit a history of exposure at work or home, or even as a consequence of a medical procedure such as dialysis. Chronic lead poisoning from inadequately fired glazed pottery has been reported. Fatigue, depression, and confusion may be associated with episodic abdominal pain and peripheral neuropathy. Gray lead lines appear in the gums. There is usually an anemia with basophilic stippling of red cells. The clinical presentation can resemble that of acute intermittent porphyria, including elevated levels of urine porphyrins as a result of the inhibition of δ-aminolevulinic acid dehydrase. The treatment is chelation therapy with agents such as ethylenediamine tetraacetic acid (EDTA). Chronic mercury poisoning produces dementia, peripheral neuropathy, ataxia, and tremulousness that may progress to a cerebellar intention tremor or choreoathetosis. The confusion and memory loss of chronic arsenic intoxication is also associated with nausea, weight loss, peripheral neuropathy, pigmentation and scaling of the skin, and transverse white lines of the fingernails (Mees' lines). Treatment is chelation therapy with dimercaprol (BAL). Aluminum poisoning has been best documented with the dialysis dementia syndrome, in which water used during renal dialysis was contaminated with excessive amounts of aluminum. This poisoning resulted in a progressive encephalopathy associated with confusion, nonfluent aphasia, memory loss, agitation, and, later, lethargy and stupor. Speech arrest and myoclonic jerks were common and associated with severe and generalized EEG changes. The condition has been eliminated by the use of deionized water for dialysis.

Recurrent head trauma in professional boxers may lead to a dementia sometimes called the "punch drunk" syndrome, or *dementia pugilistica*. The symptoms can be progressive, beginning late in a boxer's career or even long after retirement. The severity of the syndrome correlates with the length of the boxing career and number of bouts. Early in the condition, a personality change associated with social instability and sometimes paranoia and delusions occurs. Later, memory loss progresses to full dementia, often associated with parkinsonian signs and ataxia or intention tremor. At autopsy, the cerebral cortex may show changes similar to AD, although NFTs are usually more prominent than amyloid plaques (which are usually diffuse rather than neuritic). There may also be loss of neurons in the substantia nigra. Chronic subdural hematoma (Chap. 31) is also occasionally associated with dementia, often in the context of underlying cortical atrophy from conditions such as AD or HD. In these latter cases, evacuation of subdural hematoma will not alter the underlying degenerative process.

Transient global amnesia (TGA) is characterized by the sudden onset of a severe episodic memory deficit, usually occurring in persons >50 years. Often the memory loss occurs in the setting of an emotional stimulus or physical exertion. During the attack, the individual is alert and communicative, general cognition seems intact, and there are no other neurologic signs or symptoms. The patient may seem confused and repeatedly ask about present events. The ability to form new memories returns after a period of hours, and the individual returns to normal with no recall for the period of the attack. Frequently no cause is determined, but cerebrovascular disease, epilepsy (7% in one study), migraine, or cardiac arrhythmias have all been implicated. A Mayo Clinic review of 277 patients with TGA found a past history of migraine in 14% and cerebrovascular disease in 11%, but these conditions were not temporally related to the TGA episodes. Approximately one-quarter of the patients had recurrent attacks, but they were not at increased risk for subsequent stroke. Rare instances of permanent memory loss after sudden onset have been reported, usually representing ischemic infarction of the hippocampi or medial thalamic nuclei bilaterally.

The *ALS/parkinsonian/dementia complex of Guam* is a rare degenerative disease that has occurred in the Chamorro natives on the island of Guam. Individuals may have any combination of parkinsonian features, dementia, and motor neuron disease. The most characteristic pathologic features are the presence of NFTs in degenerating neurons of the cortex and substantia nigra and loss of motor neurons in the spinal cord. Epidemiologic evidence supports a possible environmental cause, such as exposure to a neurotoxin with a long latency period. One interesting but unproven candidate neurotoxin occurs in the seed of the false palm tree, which Guamanians traditionally used to make flour. The ALS syndrome is decreasing in frequency in Guam, but a dementing illness with rigidity continues to be seen.

Rarely, adult-onset leukodystrophies, neuronal storage diseases, and other genetic disorders can present as dementia late in life. Metachromatic leukodystrophy can

present as a dementia associated with large frontal white matter lesions. This syndrome is diagnosed by measuring arylsulfatase A enzyme activity in white blood cells. Adult presentations of adrenal leukodystrophy have been reported, and in these cases involvement of the spinal cord and posterior white matter is common. Adrenoleukodystrophy is diagnosed with measurement of plasma very long-chain fatty acids. CADASIL is another genetic syndrome associated with white matter disease, often frontally and temporally predominant. Diagnosis is made with biopsy of skin which shows osmophilic granules in arterioles; genetic testing for mutations in notch 3 is also possible (see earlier). The neuronal cerebrolipofuscinoses are a genetically heterogeneous group of disorders associated with myoclonus, seizures, and progressive dementia. Diagnosis is made by finding curvilinear inclusions within white blood cells or neuronal tissue.

Psychogenic amnesia for personally important memories is common, although whether this results from deliberate avoidance of unpleasant memories or from unconscious repression is currently unknown. The event-specific amnesia is more likely to occur after violent crimes such as homicide of a close relative or friend or sexual abuse. It may also develop in association with severe drug or alcohol intoxication and sometimes with schizophrenia. More prolonged psychogenic amnesia occurs in fugue states that also commonly follow severe emotional stress. The patient with a fugue state suffers from a sudden loss of personal identity and may be found wandering far from home. *In contrast to organic amnesia, fugue states are associated with amnesia for personal identity and events closely associated with the personal past.* At the same time, memory for other recent events and the ability to learn and use new information are preserved. The episodes usually last hours or days and occasionally weeks or months while the patient takes on a new identity. On recovery, there is a residual amnesia gap for the period of the fugue. Very rarely, selective loss of autobiographic information represents a focal injury in the brain areas involved with these functions.

Psychiatric diseases may mimic dementia. Severely depressed individuals may appear demented, a phenomenon called *pseudodementia*. Memory and language are usually intact when carefully tested in depressed persons, and a significant memory disturbance usually suggests an underlying dementia, even if the patient is depressed. The pseudodemented patient may feel confused and unable to accomplish routine tasks. Vegetative symptoms, such as insomnia, lack of energy, poor appetite, and concern with bowel function, are common. The onset is often abrupt, and the psychosocial milieu may suggest prominent reasons for depression. Such patients respond to treatment of the depression. Schizophrenia is usually not difficult to distinguish from dementia, but occasionally the distinction can be problematic. Schizophrenia generally has a much earlier age of onset (second and third decades) than most dementing illnesses, and is associated with intact memory. The delusions and hallucinations of schizophrenia are usually more complex and bizarre than those of dementia. Some chronic schizophrenics develop an unexplained progressive dementia late in life that is not related to AD. Conversely, FTD, HD, vascular dementia, DLB, AD, or leukoencephalopathy can begin with schizophrenia-like features, leading to the misdiagnosis of a psychiatric condition. The later age of onset, presence of significant deficits on cognitive testing, or the presence of abnormal neuroimaging findings point toward a degenerative condition. Memory loss may also be part of a conversion reaction. In this situation, patients commonly complain bitterly of memory loss, but careful cognitive testing either does not confirm the deficits or demonstrates inconsistent or unusual patterns of cognitive problems. The patient's behavior and "wrong" answers to questions often indicate that he or she understands the question and knows the correct answer.

Clouding of cognition by *chronic drug or medication use*, often prescribed by physicians, is an important cause of dementia. Sedatives, tranquilizers, and analgesics used to treat insomnia, pain, anxiety, or agitation may cause confusion, memory loss, and lethargy, especially in the elderly. Discontinuation of the offending medication often improves mentation.

Rx Treatment: DEMENTIA

The major goals of management are to treat any correctable causes of the dementia and to provide comfort and support to the patient and caregivers. Treatment of underlying causes might include thyroid replacement for hypothyroidism; vitamin therapy for thiamine or B_{12} deficiency or for elevated serum homocysteine; antibiotics for opportunistic infections; ventricular shunting for NPH; and appropriate surgical, radiation, and/or chemotherapeutic treatment for CNS neoplasms. Removal of sedating or cognition-impairing drugs and medications is often beneficial. If the patient is depressed rather than demented (pseudodementia), the depression should be vigorously treated. Patients with degenerative diseases may also be depressed, and that portion of their condition may respond to antidepressant therapy. Antidepressants that are low in cognitive side effects, such as SSRIs (Chap. 49), are advisable when treatment is necessary. Anticonvulsants are used to control seizures.

Agitation, hallucinations, delusions, and confusion are difficult to treat. These behavioral problems represent major causes for nursing home placement and institutionalization. Before treating these behaviors with medications, a thorough search for potentially modifiable

environmental or metabolic factors should be sought. Hunger, lack of exercise, toothache, constipation, urinary tract infection, or drug toxicity all represent easily correctable factors that can be treated without psychoactive drugs. Drugs such as phenothiazines and benzodiazepines may ameliorate the behavior problems but have untoward side effects such as sedation, rigidity, and dyskinesias. Despite their unfavorable side-effect profile, second-generation antipsychotics such as quetiapine (25 mg qd starting dose) are increasingly being used for patients with agitation, aggression, and psychosis. When patients do not respond to treatment, it is usually a mistake to advance to higher doses or to use anticholinergics or sedatives (such as barbiturates or benzodiazepines). It is important to recognize and treat depression; initial treatment can be with a low dose of an SSRI (e.g., escitalopram 10 mg/d) while monitoring for efficacy and toxicity. Sometimes apathy, visual hallucinations, depression, and other psychiatric symptoms respond to the cholinesterase inhibitors, obviating the need for other more toxic therapies.

Cholinesterase inhibitors are being used to treat AD, and other drugs, such as anti-inflammatory agents, are being investigated in the treatment or prevention of AD. Depression should be recognized and treated, initially with a low dose of an SSRI (Lexapro 10 mg), closely monitoring for efficacy and toxicity. These approaches are reviewed in the treatment section for AD, earlier.

A proactive strategy has been shown to reduce the occurrence of delirium in hospitalized patients. This strategy includes frequent orientation, cognitive activities, sleep-enhancement measures, vision and hearing aids, and correction of dehydration.

Nondrug behavior therapy has an important place in the management of dementia. The primary goal is to make the demented patient's life comfortable, uncomplicated, and safe. Preparing lists, schedules, calendars, and labels can be helpful. It is also useful to stress familiar routines, short-term tasks, walks, and simple physical exercises. For many demented patients, memory for facts is worse than that for routine activities, and they may still be able to take part in preserved physical activities such as walking, bowling, dancing, and golf. Demented patients usually object to losing control over familiar tasks such as driving, cooking, and handling finances. Attempts to help or take over may be greeted with complaints, depression, or anger. Hostile responses on the part of the caretaker are useless and sometimes harmful. Explanation, reassurance, distraction, and calm statements are more productive responses in this setting. Eventually, tasks such as finances and driving must be assumed by others, and the patient will conform and adjust. Safety is an important issue that includes not only driving but the environment of the kitchen, bathroom, and sleeping area. These areas need to be monitored, supervised, and made as safe as possible. A move to a retirement home, assisted-living center, or nursing home can initially increase confusion and agitation. Repeated reassurance, reorientation, and careful introduction to the new personnel will help to smooth the process. Provision of activities that are known to be enjoyable to the patient can be of considerable benefit. Attention should also be paid to frustration and depression in family members and caregivers. Caregiver guilt and burnout are common. Family members often feel overwhelmed and helpless and may vent their frustrations on the patient, each other, and health care providers. Caregivers should be encouraged to take advantage of day-care facilities and respite breaks. Education and counseling about dementia are important. Local and national support groups can be of considerable help, such as the Alzheimer's Association (*www.alz.org*).

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CHAPTER 24
PARKINSON'S DISEASE AND OTHER EXTRAPYRAMIDAL MOVEMENT DISORDERS

Mahlon R. DeLong ■ Jorge L. Juncos

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PARKINSON'S DISEASE

Parkinson's disease (PD) is the most common form of a group of progressive neurodegenerative disorders characterized by the clinical features of parkinsonism, including bradykinesia (a paucity and slowness of movement), rest tremor, muscular rigidity, shuffling gait, and flexed posture. Although defined clinically as a movement disorder, it is now widely appreciated that PD can be accompanied by a variety of non-motor symptoms, including autonomic, sensory, sleep, cognitive, and psychiatric disturbances. Nearly all forms of parkinsonism result from a reduction of dopaminergic transmission within the basal ganglia. The discovery of dopamine in the brain, the demonstration of its depletion in PD, and the success of dopamine replacement therapy by its precursor, levodopa, are all major landmarks in the field of neurology.

EPIDEMIOLOGY

PD afflicts ~1 million individuals in the United States (~1% of those older than 55 years). Its peak age of onset is in the early 60s (range 35–85 years), and the course of the illness ranges between 10 and 25 years. PD accounts for ~75% of all cases of parkinsonism; the remaining cases result from other neurodegenerative disorders, cerebrovascular disease, and drugs. Familial forms of known autosomal dominant and recessive forms of PD (now numbering >10) comprise ~5% of cases (**Table 24–1**). These are generally characterized by an earlier age of onset (typically <45 years) and a longer course than cases of "sporadic" PD, although one genetic form, LLRK-2, causes PD in the same age range as sporadic PD. Although most patients with PD appear to have no strong genetic determinant, epidemiologic evidence points to a complex interaction between genetic vulnerability and environmental factors. Risk factors include a positive family history, male gender, head injury, exposure to pesticides, consumption of well water, and rural living. Factors associated with a reduced incidence of PD include coffee drinking, smoking, use of nonsteroidal anti-inflammatory drugs, and estrogen replacement in postmenopausal women.

CLINICAL FEATURES

A diagnosis of PD can be made with some confidence in patients who present with at least two of the three cardinal signs—rest tremor, rigidity, and bradykinesia. Tremor is particularly important, as it is present in 85% of patients with true PD; a diagnosis of PD is particularly difficult when tremor is absent. A unilateral and gradual onset of symptoms further supports the diagnosis. Masked facies, decreased eye blinking, stooped posture, and decreased arm swing complete the early picture. The onset may also be heralded by vague feelings of weakness, fatigue, aching, and discomfort.

TABLE 24-1

GENETICALLY BASED PARKINSON'S DISEASE

LOCUS	GENE	PROTEIN	FUNCTION	INHERITANCE
PARK1	*SNCA*	α-Synuclein	Uncertain; vesicle trafficking	AD
PARK2	*PRKN*	Parkin	E3 ubiquitin ligase	AR
PARK4	*SNCA*	α-Synuclein (triplication or duplication)	Uncertain; vesicle trafficking	AD
PARK5	*UCH-L1*	UCH-L1 (Ubiquitin carboxy-terminal hydroxylase L1)	Proteosomal processing	AD
PARK6	*PINK1*	PINK1	Mitochondrial kinase	AR
PARK7	*DJ-1*	DJ-1	Oxidative stress response	AR
PARK8	*LRRK2*	Dardarin	Cytosolic kinase	AD

Note: See text for details. AD, autosomal dominant; AR, autosomal recessive.

MOTOR FEATURES

The most disabling motor feature of PD is bradykinesia, which interferes with all aspects of daily living including rising from a chair, walking, turning in bed, and dressing. Fine motor control is also impaired, as evidenced by decreased manual dexterity and micrographia. Soft speech (hypophonia) and sialorrhea are other troubling manifestations of (bulbar) bradykinesia. Rest tremor, at a frequency of 4–6 Hz, typically appears unilaterally, first distally, involving the digits and wrist, where it may have a "pill-rolling" character. Tremor usually spreads proximally and occasionally to the ipsilateral leg before appearing on the other side after a year or more. It may appear later in the lips, tongue, and jaw but spares the head and neck. Rigidity is felt as a uniform resistance to passive movement about a joint throughout the full range of motion, accompanied by a characteristic "plastic" quality to the movement. Brief, regular interruptions of resistance during passive movement, due to subclinical tremor, may give rise to a "cogwheeling" sensation. Dystonia involving the distal arm or leg may occur early in the disease, unrelated to treatment, especially in younger patients. It can also be provoked by antiparkinsonian drug therapy.

Gait disturbance with shuffling short steps and a tendency to turn en bloc is a prominent feature of PD. Festinating gait, a classic sign of parkinsonism, results from the combination of flexed posture and loss of postural reflexes, which cause the patient to accelerate in an effort to "catch up" with the body's center of gravity. Freezing of gait, a feature of more advanced PD, occurs commonly at the onset of locomotion (start hesitation), when attempting to change direction or turn around, and upon entering a crowded room or narrow space such as a doorway.

Abnormalities of balance and posture tend to increase as the disease progresses. Flexion of the head, stooping and tilting of the upper trunk, and a tendency to hold the arm in a flexed posture while walking are common, as are changes in the posture of the fingers, hand, and arm. Postural instability is one of the most disabling features of advanced PD, contributing to falls and injuries and leading to major morbidity and mortality. It can be tested in the office with the "pull test" (Fig. 24-1). The development of postural instability and falls in the first years of the illness, however, strongly suggest a diagnosis of atypical PD. Patients are also at risk for hip fractures, which are associated with osteoporosis and vitamin D deficiency.

Testing for Postural Instability

I. Practice session

Explanation must be given that the patient will be pulled forcefully backward to test balance and that the patient must prevent himself or herself from falling, if necessary, by taking a step backward after he or she is pulled. At least one good practice session is carried out before the final test.

II. Patient stance

Patient must be upright and cannot lean forward in any way unless axial flexion prevents upright posture. Patient must not be pulled while off balance from a previous pull. Stance should be with feet comfortably apart.

III. Pull

Patient is pulled briskly and forcefully enough to trigger one step back.

IV. Examiner's response

Examiner is ready to catch the patient but allows enough space to move backward with the patient for at least three steps of recovery. The test is to be performed in a space long enough to differentiate between persistent but recovering retropulsion and no recovery.

FIGURE 24-1

Testing for postural instability. *(From: RP Munhox et al. Neurology 62:125, 2004; with permission.)*

NON-MOTOR FEATURES

Non-motor aspects of PD include depression and anxiety, cognitive impairment, sleep disturbances, sensory abnormalities and pain, loss of smell (anosmia), and disturbances of autonomic function. Together these may contribute as much to the burden of the disease as the more obvious motor abnormalities. Some of these non-motor disturbances may be present long before the onset of motor signs. The physiologic basis of the non-motor signs and symptoms are explained in part by widespread involvement of brainstem, olfactory, thalamic, and cortical structures, as discussed later in the chapter.

Sensory symptoms often manifest as a distressing sensation of inner restlessness presumed to be a form of akathisia. Aching pain and discomfort in the extremities can be a prominent presenting symptom or develop when antiparkinsonian medications are wearing off. Some patients may develop a subjective shortness of breath in the absence of any underlying cardiorespiratory pathology.

Sleep disorders and impaired daytime alertness are common in PD. Factors that disrupt sleep include nighttime reemergence of bradykinesia and rigidity, with difficulty turning in bed, as well as tremor and involuntary movements (e.g., myoclonic jerks or periodic leg movements). Restless legs and rapid eye movement behavioral disorder often precede the onset of motor signs of PD. Vivid dreams and hallucinations related to dopaminomimetic therapy may also contribute to sleep disruption. Finally, sleep apnea and other sleep disturbances can also occur. Correction of these sleep disorders may improve daytime functioning, but often alertness remains impaired, pointing to a separate disorder of arousal or to drug-induced sedation.

Autonomic dysfunction can produce diverse manifestations, including orthostatic hypotension, constipation, urinary urgency and frequency, excessive sweating, and seborrhea. Orthostatic hypotension is present in many patients resulting from impaired vasomotor reflexes, sympathetic denervation of the heart, or as a side effect of dopaminomimetic therapy. This rarely leads to syncope unless the patient has developed true autonomic failure or has an unrelated cardiac problem. Paroxysms of drenching sweats may occur in advanced PD, often related to the wearing off of antiparkinsonian medications.

NEUROPSYCHIATRIC SYMPTOMS

Changes in mood, cognition, and behavior are common accompaniments of PD, especially in its later stages, and may be the direct result of PD or its comorbid pathologies [e.g., Alzheimer's disease (AD), cortical dementia with Lewy bodies (DLB)] or may occur as a side effect of antiparkinsonian or concomitant therapy.

Depression affects approximately one-half of patients with PD and can occur at any phase of the illness. It is often difficult to diagnose due to the overlap between the somatic and vegetative symptoms of PD and depression. As a result, depression may go unrecognized and untreated. There is compelling evidence that depression in PD is an intrinsic part of the illness and not simply a reaction to disability. Recognizing even mild depression is particularly important since it can account for otherwise unexplained albeit reversible worsening of parkinsonian motor symptoms, new somatic symptoms, and sleep disruption. Depression can also be induced or aggravated iatrogenically by antiparkinsonian and psychotropic agents used to treat other symptoms. Finally, other causes for depressive symptoms and refractory depression should always be considered, including hypothyroidism, hypogonadism, and vitamin B_{12} deficiency.

Anxiety disorders in PD can appear in isolation or as an accompaniment of depression or progressive cognitive impairment. They can also be due to an akathisia equivalent provoked in part by undertreatment of motor symptoms. The development of drug-induced motor fluctuations can compound the problem by precipitating anxiety during the off periods that, in severe cases, may mimic panic attacks.

Mild or moderate cognitive abnormalities affect many patients with PD. These occur in the later stages of the illness and present as frontal lobe dysfunction. Difficulties with complex tasks, long-term planning, and memorizing or retrieving new information are common. Although some of these symptoms represent bradyphrenia (the cognitive equivalent of bradykinesia), it is now clear that the dysfunction also includes working memory, executive function, attention, mental flexibility, visuospatial function, and word fluency. In contrast, language and simple mathematical skills are relatively spared, unlike in patients with AD. Iatrogenic contributors to cognitive decline in vulnerable patients include the use of anticholinergics, amantadine, psychotropics, and even dopaminomimetic medications. Depression and intercurrent medical illnesses, especially infections (of the urinary tract or elsewhere) and dehydration, are important reversible causes of an acute change in cognitive function in PD.

The incidence of significant dementia in PD may be as high as six times that in age-matched controls and, in subspecialty clinics, can be as high as 70% or greater with long-term observation (≥8 years). In late stages the presence of substantial cognitive impairment may limit therapeutic options and contribute more to overall disability than the motor symptoms in PD. Predictors of dementia include late age of onset, akinetic-rigid phenotype, presence of severe depression, persistent hallucinations, and advanced stages of disease. In most instances, accumulating amyloid and α-synuclein pathologies in the frontal lobes, basal forebrain, hippocampus, and amygdala account for the progression of these symptoms (see Pathology, below).

Psychotic symptoms affect up to 40% of patients with PD, depending on the age, disease duration, and prevalence

of dementia in the population surveyed. Early symptoms include visual illusions (e.g., shadows of the edge of the visual field) and formed visual hallucinations (usually people and animals), both with retained insight. Although depression and dementia are the most important risk factors for psychotic symptoms in PD, the symptoms are often triggered by drug therapy. Dopaminomimetics (especially dopamine agonists), anticholinergics, amantadine, and psychotropics are the chief drug offenders. Delusions are more disturbing than hallucinations because they place an even heavier burden on the family and caregivers. The prodrome to these psychotic symptoms includes sleep disturbances and subtle erratic behaviors with temperamental and sometimes unreasonable outbursts.

In recent years there has been increased recognition of insidious behavioral disturbances in a subset of patients with PD, referred to collectively as *impulse control disorders* (ICDs); these include pathologic gambling, hypersexuality, compulsive shopping, and compulsive eating and are associated primarily with the use of dopaminergic agents. A related disorder, termed *punding*, consists of stereotypical motor behavior in which there is an intense fascination with repetitive handling and examining of mechanical objects, such as picking at oneself, taking apart watches and radios, or sorting and arranging common objects. Current therapeutic approaches to these disorders include reduction or discontinuation of dopamine agonist therapy, psychosocial interventions, and in some cases consideration of deep brain stimulation with a goal of reducing the requirement for drugs.

PATHOLOGY

Gross examination of the brain in PD reveals mild frontal atrophy with loss of the normal dark melanin pigment of the midbrain. Microscopically there is degeneration of the dopaminergic cells with the presence of Lewy bodies (LBs) in the remaining neurons and processes of the substantia nigra pars compacta (SNpc); other brainstem nuclei; and regions such as the medial temporal, limbic, and frontal cortices. LBs have a high concentration of α-synuclein and are the pathologic hallmark of the disorder. Mutations in the α-synuclein gene can cause familial PD by promoting the formation of α-synuclein-positive filaments that aggregate into LBs and Lewy neurites (Fig. 24-2). It is now generally accepted that this pathology appears first in the anterior olfactory nuclei and lower brainstem (glossopharyngeal and vagal nerve nuclei), with ascending brainstem involvement of the locus coeruleus, n. gigantocellularis, and the raphe, before extending to the magnocellular nuclei of the basal forebrain, the central nucleus of the amygdala, and the SNpc. Further progression extends to the thalamus and cerebral cortex. Involvement of these extranigral areas is postulated to play a role in the non-motor (e.g., autonomic, sleep, emotional, and cognitive) and levodopa unresponsive motor aspects (e.g., postural instability, gait, and bulbar disturbances) of PD.

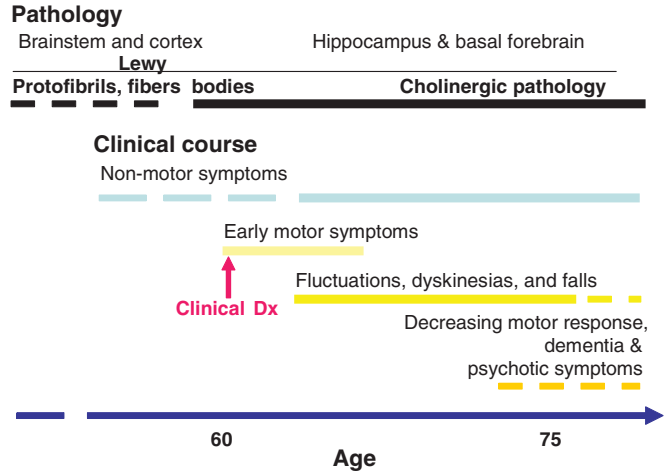

FIGURE 24-2

Proposed stages of Parkinson's disease (PD) based on extrapolations from pathologic, clinical and brain imaging studies. Broken black lines indicate that, by itself, Lewy (α-synuclein) protofibril or fiber pathology is not sufficient to make the pathologic diagnosis of PD. Broken blue lines represent non-motor signs that usually precede clinical recognition of PD, including impaired olfaction, sleep and mood disturbances, and constipation. Broken yellow lines indicate that fluctuations may be less apparent in the late stages of PD.

The biochemical consequence of dopaminergic cell loss in the SNpc is gradual denervation of the striatum, the main target projection for the SNpc neurons. Other target regions of these neurons include the intralaminar and parafascicular nuclei of the thalamus, the globus pallidus, and the subthalamic nucleus (STN). Dopamine denervation of the putamen, the motor portion of the striatum, leads to many of the motor symptoms of PD. Symptoms develop when striatal dopamine depletion reaches 50–70% of normal. Pharmacologic restoration of dopamine transmission is the basis for symptomatic drug treatment of PD.

GENETIC CONSIDERATIONS

Although the vast majority of cases of PD appear to be sporadic, increasing evidence indicates that genetic factors play an important role in many forms of PD. Much of this evidence comes from studies of the concordance rates for PD among monozygotic and dizygotic twins. These studies suggest that heredity plays an important role in cases with age of onset <45 years and a less important role in older patients. Eight genes have been clearly linked to familial forms of PD (Table 24-1), and a number of other candidate genes or

genetic loci have been identified as possibly causative of PD. Among the former, *PARK1*, *PARK4*, and *PARK5* lead to an autosomal dominant form of PD with atypical features such as early age of onset and rapid progression of symptoms. *PARK1* is due to a mutation in the gene for α-synuclein leading to abnormal aggregation of this protein (**Fig. 24-3**). *PARK2* and *PARK7* lead to autosomal recessive disorders also with atypical features, including juvenile forms of parkinsonism. *PARK2* encodes *parkin*, an E3 ubiquitin protein ligase. Mutations in parkin appear to be the major cause of autosomal recessive PD. Remarkably, *PARK5* codes for the ubiquitin carboxy-terminal hydroxylase L1 (UCH-L1), another component of the ubiquitin proteasomal system. Because ubiquitination of proteins targets them for degradation in the proteasome system, these findings suggest that abnormal proteasomal processing is important in the pathogenesis of at least some forms of PD. The most recently identified mutation is the gene for LRRK2. Most cases are slowly progressive and begin in late adulthood, closely resembling sporadic PD. The prevalence of causative LRRK2 mutations is highly dependent on the population under study, ranging from 1 to 2% of all PD cases, except in isolated pockets where

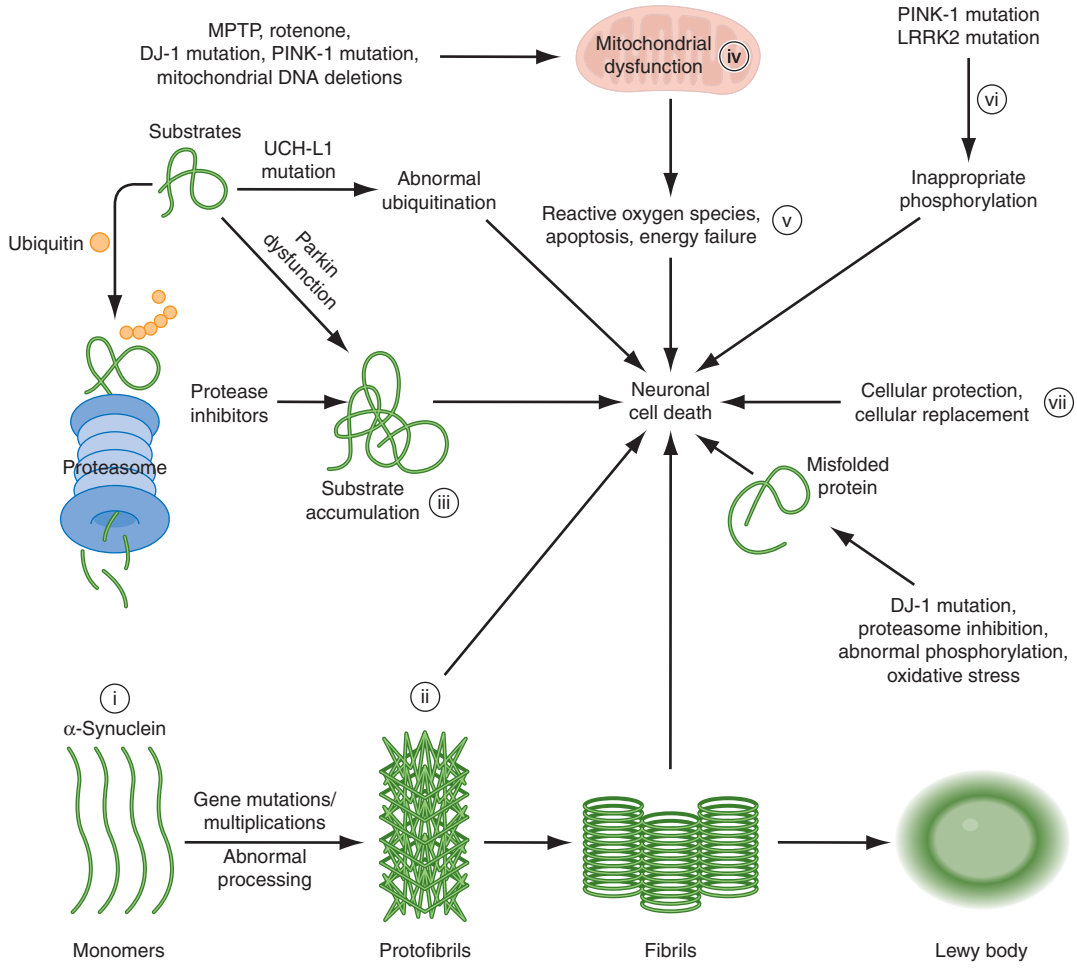

FIGURE 24-3

Pathogenesis of dopamine cell death in Parkinson's disease (PD) and possible sites for therapeutic intervention in PD. Studies on inherited forms of PD (see text) have led to the identification of genes that, when mutated, lead to dopaminergic cell loss. These genes are involved in cellular processes that include protein ubiquitination and degradation via the proteasomal system, response to oxidative stress, mitochondrial function, protein phosphorylation, and protein folding. Potential points for therapeutic intervention are highlighted: gene silencing therapies, to reduce synuclein levels (*i*); inhibition of synuclein aggregation and/or processing (*ii*); interventions to down-regulate toxic substrates or up-regulate parkin or proteasomal function (*iii*); interventions to enhance mitochondrial function with factors such as CoQ_{10}, DJ-1, or PINK-1 (*iv*); free radical scavengers and antioxidants (*v*); kinase inhibitors to block LRRK2 activity or interventions to increase PINK-1 function (*vi*); and other therapies using tropic factors such as GDNF (see text), survival genes, or fetal/stem cell replacement that would protect or replace susceptible cells (*vii*). MPTP, 1-methyl-1,2,4,6 tetrahydropyridine. *(Reprinted from JM Savitt et al, with permission.)*

the prevalence can be higher. Although the mechanism of action of the LRRK2 mutation is not certain, evidence suggests that abnormal kinase activity may mediate dopamine cell death; a similar mechanism may be operative in *PARK6*, resulting from mutations in *PINK1* (Fig. 24-3). Other mutations with yet-to-be-identified genes include *PARK10*, a late-onset PD susceptibility gene. The identification of these and other mutations are proving invaluable in refining the correlation between genotypes and phenotypes, in generating animal models to study pathogenesis, and in identifying target pathways for possible therapeutic intervention.

PATHOGENESIS

In PD, nigral dopamine neurons and other cells die from a combination of factors, including: (1) genetic vulnerability (e.g., abnormal processing or folding of α-synuclein; Fig. 24-3, steps i, ii); (2) oxidative stress (steps iv, v); (3) proteasomal dysfunction (step iii); (4) abnormal kinase activity (step vi); and (5) environmental factors, most of which have yet to be identified.

Oxidative stress appears to play an important role in the sporadic forms of PD. Endogenous sources of oxidative stress include the free radicals produced by the metabolism of dopamine and melanin. Additional stress may come from defects in mitochondrial complex I of the oxidative phosphorylation chain. This defect has been detected in platelets and muscle and in postmortem tissue from the substantia nigra. Several agents have been shown to cause oxidative toxicity and dopamine cell death in animal models of PD, further strengthening the above hypothesis. The most important of these are MPTP, a meperidine derivative, and rotenone, a commonly used insecticide. Both cause oxidative damage by inhibiting complex I. In vitro, oxidative stress can lead to aggregation of α-synuclein and proteasomal dysfunction. Proteasomal system abnormalities have also been described in the substantia nigra from sporadic cases of PD. Other contributors to the selective dopamine neuron degeneration in PD are abnormal phosphorylation of proteins, microglial activation, low-grade inflammation, and apoptosis; each represents a potential target for therapeutic intervention.

DIFFERENTIAL DIAGNOSIS AND SCREENING EVALUATION

Primary and secondary causes must be considered in the differential diagnosis of parkinsonism (**Table 24-2**). Essential tremor (ET) is sometimes confused with rest tremor in PD, but the absence of other signs of parkinsonism, the bilaterality, higher frequency (8–10 Hz), and postural dependency of ET help differentiate this from the rest tremor of PD (Chap. 25). In individuals younger than 40 years, it is important to rule out Wilson disease. In younger individuals, Huntington's disease (HD) sometimes presents with prominent parkinsonian features (Chap. 25). Although parkinsonian features are often present in AD, they occur late in the course and are greatly outweighed by cognitive and behavioral disturbances (Chap. 23). In DLB the parkinsonian features are compounded by the early appearance of hallucinations and disturbances in arousal and behavior (Chap. 23). Parkinsonism may also develop following exposure to certain neurotoxins such as carbon monoxide or manganese. MRI is useful in selected cases to rule out disorders such as normal pressure hydrocephalus, vascular disease, or mass lesions. Positron emission tomography (PET) is helpful in confirming the diagnosis but cannot reliably separate PD from the most common atypical forms. As yet, genetic screening has little place in general practice.

In evaluating individuals with PD, it is also important to rule out treatable conditions that may contribute to the disability, such as B_{12} deficiency, hypothyroidism, testosterone deficiency, and vitamin D deficiency.

At present the frequency of misdiagnosis is still 10–25% even in the best of hands. The differentiation of sporadic (idiopathic) PD from atypical parkinsonism (see later) is often difficult, since early in their course these atypical forms may meet diagnostic criteria for PD (**Table 24-3**). Accordingly, it is important to watch for the development of early imbalance, falls, and characteristic abnormalities of vertical gaze that suggest progressive supranuclear palsy (PSP); and early urinary incontinence, orthostatic hypotension, and dysarthria suggestive of multiple system atrophy (MSA). The early appearance of drug-induced hallucinations strongly favors the diagnosis of DLB. As a rule, the different forms of atypical PD can be reliably differentiated from sporadic PD within the first 3–4 years of the illness.

℞ Treatment: PARKINSON'S DISEASE

GENERAL CONSIDERATIONS The goals of therapy in PD are to maintain function and quality of life and to avoid drug-induced complications. Bradykinesia, tremor, rigidity, and abnormal posture respond well to symptomatic therapy early in the course of the illness. In contrast, cognitive symptoms, hypophonia, autonomic dysfunction, and imbalance tend to respond poorly. Primary motor disability in PD is often aggravated by secondary disability resulting from physical deconditioning following a sedentary lifestyle. Prevention of secondary disability requires a consistent program of physical exercise. Multiple open-label studies of exercise in PD

TABLE 24-2

DIFFERENTIAL DIAGNOSIS OF PARKINSONISM

Primary Parkinsonism

Genetically based PD (see Table 24-1)
Idiopathic ("sporadic") PD (most common form)
  Phenotype may be influenced by "vulnerability" genes and environmental factors
Other neurodegenerative disorders
  Disorders associated with α-synuclein pathology
    Multiple system atrophies (glial and neuronal inclusions)
      Striatonigral degeneration
      Olivopontocerebellar atrophy
      Shy-Drager syndrome
      Motor neuron disease with PD features
    Dementia with Lewy bodies (cortical and brainstem neuronal inclusions)
  Disorders associated with primary tau pathology ("tauopathies")
    Progressive supranuclear palsy
    Corticobasal degeneration
    Frontotemporal dementia
  Disorders associated with primary amyloid pathology ("amyloidopathies")
    Alzheimer's disease with parkinsonism
Genetically mediated disorders with occasional parkinsonian features
  Wilson's disease
  Hallervorden-Spatz disease
  Chédiak-Hagashi syndrome
  SCA-3 spinocerebellar ataxia
  X-linked dystonia-parkinsonism (DYT3)
  Fragile X premutation associated ataxia-tremor-parkinsonism syndrome
  Huntington's disease (Westphalt variant)
  Prion disease
Miscellaneous acquired conditions
  Vascular parkinsonism
  Normal pressure hydrocephalus
  Catatonia
  Cerebral palsy

Secondary Parkinsonism

Repeated head trauma ("Dementia pugilistica" with parkinsonian features)
Infectious and postinfectious diseases
  Postencephalitic PD
  Neurosyphillis
Metabolic conditions
  Hypoparathyroidism or pseudohypoparathyroidism with basal ganglia calcifications
  Non-Wilsonian hepatolenticular degeneration
Drugs
  Neuroleptics (typical antipsychotics)
  Selected atypical antipsychotics (see text)
  Antiemetics (e.g., compazine, metoclopramide)
  Dopamine-depleting agents (reserpine, tetrabenazine)
  α-Methyldopa
  Lithium carbonate
  Valproic acid
  Fluoxetine
Toxins
  1-Methyl-1,2,4,6 tetrahydropyridine (MPTP)
  Manganese
  Cyanide
  Methanol
  Carbon monoxide
  Carbon disulfide
  Hexane

TABLE 24-3

HISTORY AND EXAMINATION FEATURES SUGGESTING DIAGNOSES OTHER THAN PARKINSON'S DISEASE

SYMPTOMS/SIGNS	ALTERNATIVE DIAGNOSIS TO CONSIDER
History	
Falls as the first symptom	PSP
Exposure to neuroleptics	Drug-induced parkinsonism
Onset prior to 40 years	If PD, think genetic causes
Associated unexplained liver disease	Wilson's disease
Early hallucinations	Lewy body dementia
Sudden onset of parkinsonian symptoms	Vascular parkinsonism
Physical Exam	
Dementia as first symptom	Dementia with Lewy bodies
Prominent orthostasis	MSA-p
Early dysarthria	MSA-c
Lack of tremor	Various Parkinson's-plus syndromes
High frequency (8–10 Hz) symmetric tremor	Essential tremor

support the importance of regular activity; one controlled epidemiologic study revealed a hazard ratio of observed/expected deaths during the 4-year observation period of 1.8 in patients who did not exercise compared to those who did. Remaining mentally active is probably equally important for preservation of cognition in general.

As a general principle, patients should be treated as soon as symptoms begin to interfere with function in any way. Most specialists now have a low threshold for initiating symptomatic therapy. The concern that symptomatic therapy should be delayed as long as possible since the available compounds are effective for only a limited number of years is unfounded. Early initiation of therapy is often necessary to maintain an adequate level of physical and mental activity. Another common concern, that dyskinesias will develop sooner if levodopa is introduced "too early," is also unfounded. Recent studies (see later) have shown that the risk of "troublesome dyskinesias" in patients receiving levodopa therapy (up to 300 mg/d) appears to be considerably lower than previously reported.

A current priority is to move beyond symptom control to neuroprotective therapies. Unfortunately, no such therapy is yet available. High doses of coenzyme Q_{10}, oral creatine supplementation, intrastriatal infusion (or delivery via viral vectors) of neurotrophic factors, and possibly the use of newer monoamine oxidase B (MAO-B) inhibitors may hold promise in this regard and are under investigation. In animal models of PD, forced exercise (e.g., treadmill running) at moderate intensities appears to promote neuroprotection in dopamine neurons.

INITIATION OF THERAPY (Fig. 24-4) From a practical standpoint, dopaminomimetic therapy (Table 24-4) should be initiated as soon as the patient's symptoms begin to interfere with quality of life. The ideal first-line agent depends on the age and cognitive

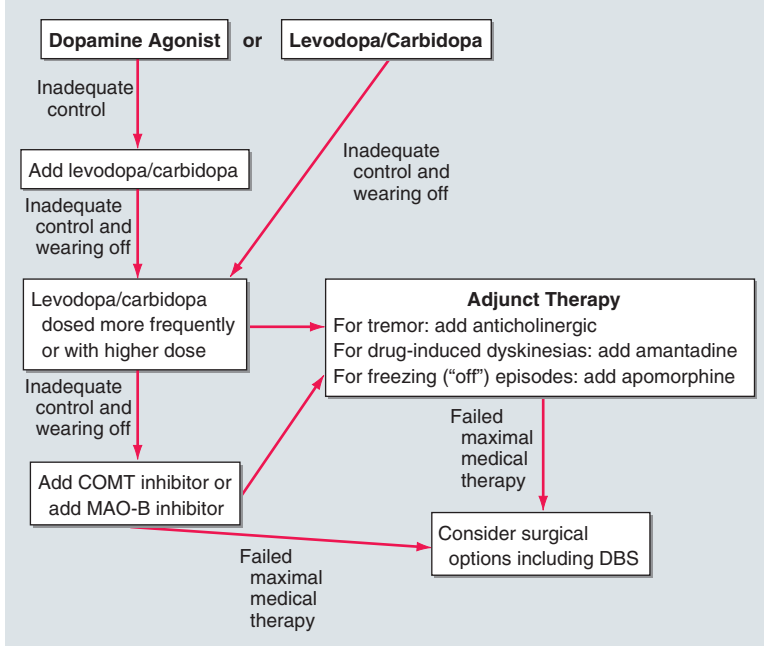

FIGURE 24-4
Treatment approaches to newly diagnosed idiopathic PD.

TABLE 24-4

LEVODOPA FORMULATIONS AND DOPAMINE AGONISTS USED IN PARKINSON'S DISEASE

AGENTS	LD DOSE EQUIVALENCY	AVAILABLE STRENGTHS (MG)	INITIAL DOSING	COMMENTS
Carbidopa/Levodopa (Typical Initial Strength)				
Carbidopa/levodopa IR 25/100	100 mg (levodopa anchor dose)	10/100 25/100 25/250	25/100; 0.5–1 tab tid	Usual range = 300–800 mg/d with typical schedules being q8h to q3h.
Carbidopa/levodopa CR 50/200	150 mg	25/100 50/200	50/200; 1 tab bid to tid	Increased bioavailability with food. Splitting the tablet negates the CR properties. Usual schedule is q8h to q4h.
Carbidopa/levodopa/ entacapone 25/100/200	120 mg	12.5/50/200 25/100/200 37.5/150/200	25/100/200; 1 tab bid to tid	Do not split tablets. May combine with Sinemet IR. Usual schedule is q8h to q4h.
Parcopa 25/100	100 mg	25/100 25/250	25/100; 1 tab tid	Can be used as regular or supplemental rescue doses in cases of regular dose failure. Orally dissolved without water.

Dopamine Agonists	Approximate Target Doses					
	DA EQUIVALENT TO ABOVE LD ANCHOR DOSE	AVAILABLE STRENGTHS (MG)	INITIAL DOSING	MONOTHERAPY	AS ADJUNCTS TO LD	OTHER CONSIDERATIONS
Non-ergot alkaloids Pramipexole	1 mg	0.125, 0.25, 1, 1.5	0.125 mg tid	1.5–4.5 mg/d	0.375–3.0 mg/d	Renal metabolism; dose adjustments needed in renal insufficiency. Occasionally associated with "sleep attacks."
Ropinirole	5 mg	0.25, 0.5, 1, 2, 3, 4, 5	0.25 mg tid	12–24 mg/d	6–16 mg/d	Hepatic metabolism; potential drug-drug interactions. Occasionally associated with "sleep attacks."
Ropinirole extended release	Availability pending.					
Rotigotine		2, 4, 6	2 mg/24 h	6 mg/d	2–6 mg/d	Available as transdermal patch.
Ergot alkaloids Bromocriptine	2 mg	2.5, 5.0	1.25 mg bid to tid	7.5–15 mg/d	3.75–7.5 mg/d	Rare reports of pulmonary and retroperitoneal fibrosis. Relative incidence of sleep attacks not well studied.
Pergolide	Removed from U.S. market in 2007. See text.					
Cabergoline	Used in select cases of PD in Europe. Not approved for the treatment of PD in the U.S.					

Note: Equivalency doses are approximations based on clinical experience, may not be accurate in individual patients, and are not intended to correlate with the in vitro binding affinities of these compounds.
DA, dopamine agonist; IR, immediate release; CR, controlled release; LD, levodopa (with carbidopa).
Carbidopa/levodopa/entacapone = Stalevo.

status of the patient and, to a lesser extent, the patient's clinical type and finances. The choices consist of either, a dopamine agonist, a levodopa preparation, or one of the MAO-B inhibitors. Controlled studies support the view that, in early PD, monotherapy with any of the dopamine agonists is well tolerated and significantly improves motor function and disability. Using this approach, patients experience ~50% lower risk of dyskinesias and 25% lower risk of motor fluctuations compared to levodopa-treated patients. This difference lasts as long

as the patient remains on monotherapy. Once a levodopa preparation is added, dyskinesias and motor fluctuations begin to emerge, suggesting that dopamine agonists delay the onset but do not prevent the development of these problems. In fact, about two-thirds of patients on agonist monotherapy require levodopa therapy by year 5 in order to maintain motor function.

Motor fluctuations, also known as "on-off" phenomena, are the exaggerated ebb and flow of parkinsonian signs experienced by many patients between doses of antiparkinsonian medications. *Dyskinesias* refer to choreiform and dystonic movements that can occur as a peak dose effect or at the beginning or end of the dose (diphasic dyskinesias). More than 50% of patients with PD treated over 5 years with levodopa will develop these complications.

Successful dopamine agonist monotherapy requires a higher dose of the agonist than is typically needed when the agonist is used to supplement levodopa (Table 24-4). In both cases, titration has to be slow and cautious to avoid unnecessary side effects. Patients benefit greatly from education and support during this titration. Most patients will require the addition of levodopa or another agent within 1–3 years of initiating dopamine agonist monotherapy. Preclinical studies suggest that the advantages of dopamine agonist monotherapy can be maintained with agonist-dominant therapy. In this case, dopamine agonists continue to provide the bulk of dopaminomimetic therapy, with levodopa playing a supplementary role.

Although dopamine agonist monotherapy is considered the initial treatment of choice for most patients with PD, the long-term benefits noted above must be balanced against a higher incidence of non-motor side effects and a slightly higher level of motor disability than with levodopa. These recommendations may need to be modified in patients with psychotic symptoms, behavioral disturbances, or severe daytime sleep disturbances. Older patients and those with akinetic rigid forms of PD have a lower risk of motor complications and dyskinesias compared to the average PD patient and may be satisfactorily treated with levodopa.

PHARMACOTHERAPY OF MOTOR SYMPTOMS

The above practices in the initiation of therapy notwithstanding, levodopa remains the most effective treatment for PD. It significantly improves motor symptoms and increases quality of life and independence. The aim of all dopaminomimetic strategies is to restore dopamine transmission in the striatum. This is accomplished by stimulating postsynaptic receptors (directly with dopamine agonists), increasing dopamine precursor availability (levodopa), blocking the metabolism of levodopa in the periphery and in the brain, and blocking the catabolism of dopamine at the synapse.

Dopamine Agonists Dopamine agonists readily cross the blood-brain barrier and act directly on postsynaptic dopamine receptors (primarily D_2 type). Compared to levodopa, they are longer-acting and thus provide a more uniform stimulation of dopamine receptors. They are effective as monotherapeutic agents and as adjuncts to carbidopa/levodopa therapy. They can also be used in combination with anticholinergics and amantadine. Table 24-4 provides a guide to the doses and uses of these agents.

Available agents for PD include three non-ergot alkaloids—pramipexole, ropinirole, and, more recently, rotigotine—plus the ergot alkaloids bromocriptine, cabergoline, and lisuride (the latter two only in Europe). Pergolide is a dopamine agonist recently removed from the U.S. market due to its association with asymptomatic valvular heart disease in 28% of patients treated chronically. The incidence of symptomatic valvular disease is far lower, perhaps as low as <1%. Nonetheless, patients currently on pergolide need to be transferred to alternative therapy, perhaps equivalent doses of non-ergot dopamine agonists (Table 24-4). The dose equivalency of pergolide is ~1:1 with pramipexole.

Subcutaneous injectable apomorphine is approved in the United States as a "rescue therapy" for dose failure (usually due to erratic gastric emptying), motor fluctuations, and especially for the debilitating "off" spells that affect many patients with moderate to advanced disease. Finally, sumanirole is another potent experimental dopamine agonist that in a recent controlled study proved to be comparable in efficacy to ropinirole and better tolerated.

A long-acting formulation of ropinirole and a transdermal patch delivery system of rotigotine will soon be approved for use in PD. Based on pharmacokinetic data, these formulations can achieve levels of continuous dopaminergic stimulation that are closer to those achieved with subcutaneous infusions of apomorphine (not available in the United States). In comparison with oral dopaminomimetics, infusion therapy has proved superior at controlling motor fluctuations and reducing dyskinesias over time. The convenience of these new formulations should overcome the major limitation of infusions: cost and site reactions. Experience with the patch delivery system thus far indicates that it is safe and well tolerated except for occasional skin reactions to the adhesive.

Dopamine agonists have been approved for the treatment of PD at every stage of disease and in combination with other antiparkinsonian agents; however, the use of two dopamine agonists simultaneously cannot be recommended. Agonists are particularly effective in treating bradykinesia, loss of fine motor dexterity, tremor, and gait disturbances. When used as monotherapy, they are less effective than levodopa-based

formulations. Accordingly, it is imperative to titrate the dose as needed to control motor function; the maximum dose provided in titration packs may be insufficient in some patients. As the dose is escalated it is equally important to remain vigilant to potential dose-dependent side effects, particularly when combining these drugs with carbidopa/levodopa and psychotropics.

Side effects of dopamine agonists include nausea, postural hypotension, psychiatric symptoms, daytime sedation, and occasional sleep attacks. These can be managed by decreasing the dose; by decreasing concomitant medication with similar side effects; or, in the case of nausea, by the introduction of peripheral dopamine blockers such as domperidone (not available in the United States) or a short course of trimethobenzamide or dronabinol until the patient develops tolerance to these symptoms. Patients should be cautioned about the potential for sleep attacks associated with dopamine agonists (and to a lesser extent with carbidopa/levodopa). These can occur without warning and have resulted in traffic accidents. When used as adjuncts to levodopa therapy, dopamine agonists can aggravate dyskinesias if the doses of carbidopa/levodopa are not adjusted accordingly. Furthermore, dopamine agonists are more expensive than carbidopa/levodopa, which is now available in generic form. Dopamine agonist–induced impulse control disorders (pathologic gambling, etc.) are discussed earlier under Neuropsychiatric Symptoms.

Carbidopa/Levodopa Formulations Carbidopa/levodopa is available in regular, immediate release (IR) formulations (Sinemet, Atamet, and others; 10/100 mg, 25/100 mg, and 25/250 mg), controlled release (CR) formulations (Sinemet CR 25/100 mg, 50/200 mg), or more recently as Stalevo (Table 24-4). The latter combines variable doses of IR-carbidopa/levodopa (12.5/50, 25/100, 37.5/150) with 200 mg of entacapone (see later). In most individuals, at least 75 mg/d of carbidopa is necessary to block the peripheral decarboxylation of levodopa to dopamine, and to limit the symptoms of nausea and orthostasis associated with initiation of therapy. Initial target doses of these medications are summarized in Table 24-4. Individualized dosing and gradual dose escalation is recommended. Initiation of dosing at mealtimes will reduce the incidence and severity of nausea. As patients develop tolerance to nausea and other side effects, these medications can be administered on an empty stomach, which generally leads to a more brisk and predictable absorption.

Etilevodopa, the ethyl-ester pro-drug of levodopa, has greater solubility than levodopa in the stomach and a more rapid transit time to the duodenum, where it is quickly absorbed after being hydrolyzed to levodopa. In spite of these pharmacokinetic advantages, in a controlled study oral administration of etilevodopa (with carbidopa) proved no different from oral carbidopa/levodopa with respect to mean dose requirements, treatment failures, and hours of daily "off" time.

Levodopa Augmentation Strategies A number of drugs can augment dopamine transmission by blocking the breakdown of dopamine at the level of the synapse.

MAO-B Inhibitors These are selective and irreversible inhibitors of the catabolic breakdown of dopamine; they work by inhibiting MAO-B at the synapse. These compounds offer a modest symptomatic motor benefit when used as monotherapy and enhance the efficacy of carbidopa/levodopa formulations when used as adjuncts. Their potential additional role as neuroprotective agents remains unproven. Unlike patients taking unselective or MAO-A inhibitors who are subject to hypertensive crises from consumption of large doses of tyramine (the amino acid precursor of norepinephrine), patients taking MAO-B inhibitors do not require dietary tyramine restrictions. At the approved doses, rasagiline and oral zydis selegiline (i.e., orally disintegrating) carry little risk of a hypertensive complication.

Selegiline, a selective MAO-B inhibitor, was approved in 1989 for the treatment of PD. As monotherapy, it has a small symptomatic effect. As an adjunct to levodopa therapy, it increases "on" time while reducing motor fluctuations; the dose is 5 mg with breakfast and lunch. A significant side effect of selegiline is insomnia, probably due to an amphetamine-like metabolite.

In 2006, two additional, more potent MAO-B inhibitors with once-daily dosing were introduced for the treatment of PD. Rasagiline was approved for use as initial monotherapy and as adjunctive therapy. It is metabolized to an aminoindan metabolite that lacks the amphetamine-like properties of selegiline. As monotherapy in treatment-naïve patients it improves motor function compared to placebo, and as an adjunct it increases daily "on" time by about 1.8 h. The usual dose is 0.5–1 mg/d. A recent trial suggested that rasagiline may alter the course of the disease (i.e. provide benefit other than symptomatic treatment), but this will need to be confirmed as the trial demonstrated this effect for only one of two doses tested.

Zydis selegiline is an orally disintegrating, freeze-dried tablet that is absorbed through the oral mucosa; this results in higher levels of selegiline and lower levels of the plasma amphetamine-like metabolites compared with the usual oral route. Its usual dose is 1.25–2.5 mg/d in the morning. In a 2004 controlled study, Zydis selegiline in patients with PD and motor fluctuations increased dyskinesias-free "on" time by 1–1.5 h/d in comparison with placebo.

Although these compounds are generally well tolerated, side effects include dose-dependent nausea, dyspepsia, dizziness, insomnia, dyskinesias, orthostatic hypotension, confusion, and hallucinations. They should not be used with meperidine, tramadol, methadone, or propoxyphene. Rarely, a hyperserotonergic syndrome may result from use in combination with tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). This syndrome is characterized by anxiety, tremulousness, myoclonus, and alterations in mental status. Although the risk of this complication in PD appears to be small at the approved doses, it is judicious to remain vigilant to these possible side effects until more Phase IV safety information is available. In the interim, the lower dose of these compounds should be considered in older individuals with active cardiac disease, or in those who are prescribed concomitant antidepressant drugs.

COMT Inhibitors The catechol-*O*-methyltransferase (COMT) inhibitors entacapone and tolcapone offer yet another strategy to augment the effects of levodopa by blocking the enzymatic degradation of levodopa and dopamine. Entacapone is preferred to tolcapone because of the low but potentially serious incidence of hepatic and hematologic side effects of the latter. When used in conjunction with carbidopa/levodopa, these agents increase the plasma levodopa levels by >30% and alleviate wearing-off symptoms. Entacaprone (200 mg with each dose of carbidopa/levodopa) increases "on" time by <1 h/d, whereas tolcapone (100–200 mg tid) increases "on" time by about 1.8 h/d.

The more common side effects are gastrointestinal and hyperdopaminergic, including sleep disturbances and increased dyskinesias that may require reductions in the dose of carbidopa/levodopa. Hyperdopaminergic symptoms can be managed with appropriate decreases in the dose of other dopaminomimetics. Tolcapone can be associated with a dose-dependent increase in hepatic aminotransferase levels in 1–3% of cases and rare instances of acute fulminant liver failure. ALT/AST levels should be monitored every 2–4 weeks for the first 6 months and periodically thereafter. Tolcapone should not be used in patients with preexisting liver disease and should be discontinued if the ALT/AST levels exceed two times the upper limit of normal.

Other Well-Established Agents Anticholinergics and amantadine are appropriate adjuncts to dopaminomimetic therapy. Anticholinergics are particularly useful for controlling rest tremor and dystonia, and amantadine can reduce drug-induced dyskinesias by up to 70%. The mechanisms of action of amantadine are unknown, although there is evidence it has both anticholinergic and dopaminomimetic properties. Recently amantadine has been shown to have weak glutamate antagonist properties, a mechanism thought responsible for reducing drug-induced dyskinesias. The side effects of amantadine are nausea, headaches, edema, erythema, and livedo reticularis. In older patients, it may aggravate confusion and psychosis. Doses need to be decreased in patients with renal insufficiency.

THERAPY OF NON-MOTOR SYMPTOMS

Patients with frequent nighttime awakenings due to nocturnal akinesia or tremor can be treated with supplemental doses of carbidopa/levodopa at night. A bedtime dose of a dopamine agonist helps restless leg symptoms and urinary urgency. Treatment of bladder symptoms will improve sleep in many elderly patients with PD. Depression typically responds to antidepressants (either TCAs or SSRIs). As discussed earlier, the combination of SSRIs and selegiline carries an exceedingly low risk of a hyperserotonergic syndrome (delirium with myoclonus and hyperpyrexia). Electroconvulsive therapy (ECT) is highly effective in drug-refractory cases or in patients intolerant of oral antidepressants. There are several reports indicating that ECT also has short-term benefit for parkinsonian motor symptoms.

In patients with psychotic symptoms or confusion, anticholinergics and amantadine should be eliminated first. Following this, MAO-B inhibitors and dopamine agonists should be reduced or discontinued as needed to control symptoms. This should be followed by gradual reductions as needed in nocturnal and then daytime doses of Sinemet CR, and finally carbidopa/levodopa. If the patient improves after only a modest reduction of antiparkinsonian therapy, the overall impact on the parkinsonian motor symptoms may be negligible. If in the process parkinsonian symptoms worsen, most specialists initiate treatment with an atypical antipsychotic that has a low incidence of extrapyramidal side effects rather than continuing to lower dopaminomimetic therapy. Clozapine (12.5–100 mg/d) is the best established agent for treatment of psychotic symptoms in PD. Quetiapine (12.5–100 mg) is sometimes used first because it lacks the small risk of agranulocytosis associated with clozapine. Both are dosed at night to promote sleep and minimize daytime sedation and orthostasis. Their use and that of all antipsychotics in PD are limited by dose-dependent sedation, orthostatic hypotension, dizziness, and confusion. Other atypical antipsychotics such as risperidone, olanzapine, and, more recently, aripiprazole are not well tolerated by most patients with PD due to a higher incidence of drug-induced parkinsonism (DIP) and akathisia.

Centrally acting acetylcholinesterase inhibitors can improve dementia symptoms in PD, providing the same stabilization of cognitive decline noted in AD. Rivastigmine is approved by the Food and Drug Administration for the treatment of dementia in PD, and

donepezil also appears to be effective. Both appear to be well tolerated by most patients with PD and may also be useful for treatment of psychotic symptoms such as hallucinations and delusions.

Given the complexity of the above polypharmacy, the management of non-motor symptoms is best carried out in an interdisciplinary setting, coordinated by a neurologist who specializes in PD together with a psychiatrist and the patient's primary care physician.

NEUROPROTECTIVE THERAPY Slowing the progression of PD through neuroprotective or restorative therapy is a major focus of research. Epidemiologic studies suggest that the chronic use of nonsteroidal anti-inflammatory agents or the use of estrogen replacement in postmenopausal women may delay or prevent the onset of PD through yet-unclear mechanisms. Similarly, in large populations, the long-term use of nicotine and caffeine has been associated with a lower risk of PD.

From a pharmacologic standpoint, current strategies involve interrupting the cascade of biochemical events that leads to death of dopaminergic cells (Fig. 24-3). The first such clinical trial in PD was the large multicenter DATATOP study in which selegiline monotherapy delayed the need for levodopa therapy by 9–12 months in newly diagnosed patients. Most evidence indicates that this delay was due to a mild symptomatic effect of selegiline. The antioxidant vitamin E had no effect. Long-term follow-up of the DATATOP cohort revealed that patients who remained on selegiline for 7 years experienced slower motor decline compared to those who were changed to placebo after 5 years. The 7-year patient group was more likely to develop dyskinesias but less likely to develop freezing gait.

Coenzyme Q_{10}, an antioxidant and a cofactor of complex I of the mitochondrial oxidative chain, has been shown to have neuroprotective effects against multiple toxic agents in vitro and in animal models of PD. In a large controlled phase 2 trial, a dose of 1200 mg/d appeared to delay progression of disability in untreated patients with PD. Coenzyme Q_{10} was well tolerated and devoid of toxicity. A phase 3 trial will examine the disease-modifying effect of this compound in untreated patients receiving up to 2400 mg/d. Other potential neuroprotective agents under investigation are creatine monohydrate and acetyl-levo-carnitine. A phase 2 trial of creatine in early PD demonstrated promising results, and a phase 3 trial is now under way.

Dopamine agonists are also under investigation as putative agents to slow disease progression in PD, based on their possible antioxidant properties resulting in part from their in vitro ability to decrease dopamine turnover, scavenge free radicals, and interfere with proapoptotic cell signaling. Other promising agents include nitric oxide synthetase inhibitors and antiapoptotic agents such as Jun N-terminal kinase inhibitors and desmethylselegiline. The latter, a metabolite of selegiline, has been shown experimentally to have neuroprotective effects on dopamine neurons, possibly through modulation of cellular antiapoptotic mechanisms, including Bcl-2, glyceraldehyde-3-phosphate dehydrogenase (GAPDH); activation of the proteasome-ubiquitin complex; and the prevention of caspase 3 activation. Clinical trials to test the putative new effects of dopamine agonists are now under way.

SURGICAL TREATMENTS Over the past decade there has been a renaissance in the surgical treatment of PD and other movement disorders. Although both pallidotomy and thalamotomy were performed widely in the 1950s, the introduction of levodopa in the 1960s led to the virtual abandonment of surgery. The resurgence in the use of surgery has been motivated by the fact that after 5 or more years of treatment, many patients develop significant drug-induced motor fluctuations and dyskinesias. Advances in understanding the functional organization of the basal ganglia and the pathophysiologic basis of parkinsonism have provided a clearer rationale for the effectiveness of these procedures and guidance for targeting specific structures (**Fig. 24-5**). The most common indications for surgery in PD are intractable tremor and drug-induced motor fluctuations or dyskinesias. The best candidates are patients with clear levodopa-responsive parkinsonism who are free of significant dementia or psychiatric comorbidities. In general, patients with atypical parkinsonism or dementia benefit little, or not at all. Currently the subthalamic nucleus is the preferred target, but controlled clinical trials comparing the pallidal and subthalamic targets are nearing completion. Deep brain stimulation (DBS) is most often performed bilaterally and simultaneously, but unilateral DBS can be highly effective for asymmetric cases. DBS in these areas alleviates parkinsonian motor signs, particularly during "off" periods, and reduces troublesome dyskinesias, dystonia, and motor fluctuations that result from drug administration. Both procedures have been shown to strongly improve the patient's quality of life, and both are more effective than medical management in the target population of patients with advanced PD. Signs and symptoms not responding to levodopa, such as postural instability and falling, hypophonia, micrographia, drooling, and autonomic dysfunction, are unlikely to benefit from surgery. As a rule of thumb, the benefits from surgery are unlikely to exceed the best results from antiparkinsonian medications but provide relief from motor fluctuations, dyskinesias, and dystonia. In general, the decision for surgery should be made by a movement-disorder neurologist

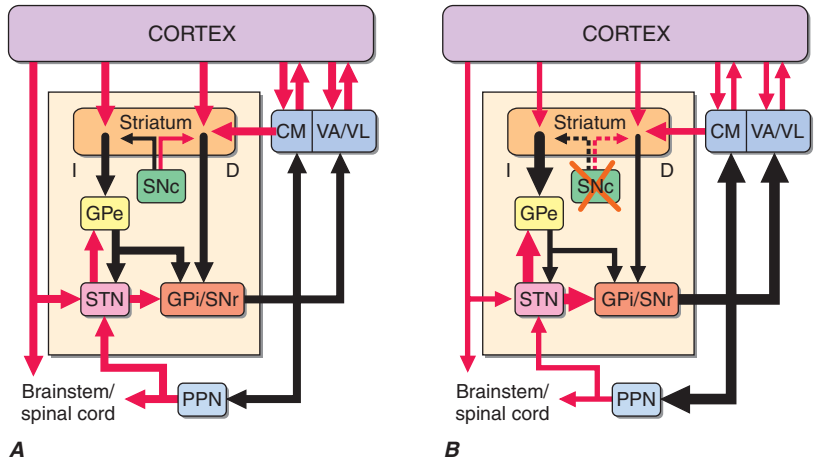

FIGURE 24-5

Schematic diagram of the basal ganglia–thalamocortical circuitry under normal conditions (*A*) and in Parkinson's disease (PD) (*B*). Inhibitory connections are shown as black arrows and excitatory connections as red arrows. Note that in PD, striatal dopamine denervation results in increased traffic in the indirect pathway and decreased traffic in the direct pathway. The downstream consequence of this is increased activity in striatal outflow stemming from the increased activity of STN and ultimately GPi/SNr neurons. Because striatal outflow is inhibitory to the thalamus (main neurotransmitter = γ-aminobutyric acid), there is a decrease in the ability of the thalamus to activate the frontal cortex leading to signs of parkinsonism. As discussed, changes in discharge pattern are also a major factor. D, direct pathway; I, indirect pathway; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; SNr, substantia nigra, pars reticulata; SNc, substantia nigra, pars compacta; STN, subthalamic nucleus; VA/VL, ventral anterior/ventrolateral thalamus; CM, centromedian nucleus; PPN, pedunculopontine nucleus. *(Courtesy of T Wichmann, MD, Emory University School of Medicine; with permission.)*

who is part of a team, including the neurosurgeon, neuropsychologist, and programmer.

The mechanism of action of DBS remains controversial. Because clinically it appears that ablation and stimulation of a given target have a similar effect, it has been assumed that stimulation causes a functional blockade. It is likely, however, that multiple factors are involved. The basis for improvement appears to be the replacement of abnormal neural activity by a more tolerable pattern of activity. Whatever the mechanism, it is clear that these approaches can offer impressive and enduring results in properly selected patients.

Neurotransplantation and Other Surgical Approaches Despite highly encouraging open-label pilot studies of fetal cell transplantation, this approach has produced considerable disappointment with the recent publication of the results from two large, well-controlled clinical trials. The first, using sham surgery, showed only modest benefit in patients <60 years and no benefit in those >60 years. An unexpected complication in a number of patients was the development of symptomatic dyskinesias, occurring off medication. The second study has shown similar findings with regard to benefit and the development of dyskinesias. A puzzling feature of these studies is the apparent successful grafting observed by PET and at autopsy. Because of these disappointing results, the considerable obstacles to obtaining sufficient fetal tissue, and opposition to the use of fetal tissue on ethical grounds, this approach is now viewed as purely investigational. It is hoped that these issues can be addressed with the development of other strategies to enhance dopaminergic cell function (e.g., carotid body cells; stem cells; encapsulated and genetically engineered cells capable of producing levodopa, dopamine, and/or trophic factors). One approach uses genetically engineered retinal epithelial cells in gelatin capsules to ensure their survival following implantation, typically into the putamen. The cells produce levodopa, which then diffuses into the cerebral microenvironment, providing dopamine reinnervation to surrounding tissue. A controlled clinical trial is under way to examine the potential benefit of this approach in PD following positive results in a small open-label study.

The favorable response from direct infusion of glial cell–derived neurotrophic factor (GDNF) to the putamen in two small open-label trials in patients with PD raised hopes that this approach may offer neuroprotection. However, a well-controlled trial using bilateral GDNF infusion to the putamen failed to demonstrate significant improvement. There is currently a moratorium on further

trials with GDNF due to the development of GDNF-neutralizing antibodies in four patients and to a toxicologic study revealing cerebellar degeneration in an exposed primate. However, trials are currently under way using alternative vehicles for these and other neurotrophins with actions similar to GDNF. These vehicles include recombinant adeno-associated virus, lentivirus, and pseudorabies virus. Stem cell transplantation in PD will need to await successful application of this technology in other areas of medicine.

DEMENTIA IN PARKINSON'S DISEASE

The incidence of dementia in PD may be as high as six times that in the general non-PD population. Approximately a quarter of patients will develop dementia of the Alzheimer type due to overlap of these two age-related pathologies. Pathologically, the incidence of AD-type findings in postmortem tissue from patients dying with PD is as high as 40%. Conversely, 25% of AD patients have at least mild clinical parkinsonian features such as rigidity and bradykinesia, and ≥60% have coexistent -synuclein pathology in the cortex. Patients with PD dementia (PDD) are more likely to have the akinetic/rigid PD phenotype rather than the tremor-predominant phenotype. In this population the presence of dementia makes management of the motor symptoms of PD more difficult due to the high incidence of cognitive side effects from antiparkinsonian therapy, particularly anticholinergics and amantadine. Central dopaminomimetic toxicity can present in many ways, ranging from sleep disruption with daytime sleepiness, personality changes, depression, and executive dysfunction (e.g., organization, planning, multitasking) to episodic confusion, hallucinations, and disruptive behaviors.

DLB is an increasingly recognized form of dementia with prominent parkinsonian features. The dementia may precede or follow the parkinsonian syndrome. In patients presenting with parkinsonian features, the dementia is often heralded by levodopa-induced sedation, myoclonus, and hallucinations. Early on, the phenotype can be indistinguishable from PD. Features that help differentiate this entity from PD include the presence of an action rather than a rest tremor; a rapidly fading response to levodopa; and rapidly fluctuating, spontaneous, and drug-induced problems with arousal. Another feature of DLB is the higher incidence of neuropsychiatric symptoms than in idiopathic PD. These symptoms include apathy, personality changes, depression, fixed delusions, and hallucinations. Finally, patients with DLB exhibit a heightened sensitivity to DIP when exposed to any dopamine blocker. The progression of symptoms in DLB is intermediate between the PD and PD/AD overlap. DLB is discussed in detail in Chap. 23.

OTHER PARKINSONIAN DISORDERS

PARKINSONIAN DISORDERS ASSOCIATED WITH ABNORMAL METABOLISM OF α-SYNUCLEIN (α-SYNUCLEINOPATHIES)

Multiple System Atrophy

MSA comprises a group of sporadic disorders characterized by varying degrees of parkinsonism and cerebellar, corticospinal, and autonomic dysfunction. The average age of onset is 50 years (earlier than in PD) and the median survival 6–9 years. The clinical presentation is highly varied and may begin with any of the above clinical manifestations. The unifying pathologic hallmark is the presence of α-synuclein-positive inclusions located in various brain regions.

Clinical Phenotypes

With disease progression, 90% of patients exhibit parkinsonian signs and 80% signs of autonomic failure; a similarly high percentage exhibit upper motor neuron signs. Tremor is common, but unlike in PD, this and other parkinsonian signs are more likely to present symmetrically. Parkinsonian symptoms are typically poorly responsive to dopaminergic therapy, although some patients may respond favorably for years. Drug-induced dyskinesias typically involve the face and neck rather than the trunk and limbs, as is the case in PD. Corticospinal signs consist of spasticity, involving the legs more than the arms, and pseudobulbar palsy. This aspect of the illness may mimic primary lateral sclerosis with lower motor neurons being occasionally involved. A few patients develop myoclonus.

Signs of autonomic failure include orthostatic hypotension, leg swelling not due to drug therapy, changes in sweating patterns, and autonomic storms with diaphoresis and flushing. Orthostatic hypotension can present with dizziness, faintness, or syncope. Once patients are successfully treated for syncope, they often develop fatigue and lassitude. This is due in part to chronic tissue hypoperfusion caused by marginal blood pressures while sitting or standing. More aggressive management of the blood pressure is warranted but not always successful. Urinary symptoms include urgency, retention, and incontinence. In men, impotence is one of the earliest and most prominent signs. The autonomic dysfunction can precede or follow the development of other neurologic signs by several years. Dementia may not be as frequent as in PD.

The clinical phenotype of MSA can fall into one of two broad categories, termed *MSA-p* (prominent parkinsonism at onset) and *MSA-c* (prominent cerebellar involvement at onset). Disorders that have now been reclassified as part of this new naming scheme include *striatonigral degeneration* (SND), *olivopontocerebellar atrophy* (OPCA), and *progressive autonomic failure* (PAF), either without parkinsonism or with parkinsonism (Shy-Drager

syndrome). Patients presenting with a relatively pure form of akinetic rigid parkinsonism and a limited response to levodopa are designated as having MSA-p. Distinguishing these conditions from PD and each other can be difficult, particularly in the early stages of illness. Individuals with other signs such as ataxia, upper motor neuron and corticobulbar involvement, myoclonus, oculomotor abnormalities, peripheral neuropathy, and deafness fit into the category of MSA-c. This phenotype is notably heterogeneous, with both sporadic and hereditary forms. The sporadic forms tend to form part of the spectrum discussed in this section, while the hereditary forms usually represent one of the spinocerebellar ataxias (Chap. 26). Although MSA categories are clinically useful, as disease progresses there tends to be more clinical and pathologic overlap than separation between the different entities.

The spectrum of disease in MSA is determined by the location and density of the LB pathology. For instance, the LBs are confined to neurons in the brainstem in PD and to the brainstem, cortex, and hippocampus in DLB. In MSA these deposits take the form of glial α-synuclein-positive intracytoplasmic inclusions in the substantia nigra, putamen, inferior olives, pontine nuclei, pigmented nuclei of the brainstem, intermediolateral nucleus of the spinal cord, and the cerebellum. In addition, in MSA there is myelin degeneration and oligodendroglia containing argyrophilic glial cytoplasmic inclusions that are immunoreactive for ubiquitin and α-synuclein. Similar inclusions can be found in neuronal cell bodies and processes.

Several diagnostic tests help differentiate MSA from PD and other parkinsonian syndromes. In MSA-c, brain MRI reveals prominent atrophy of the cerebellum, pons, and olivary eminence of the medulla. In MSA-p, prominent volume loss and T2-weighted image hyperintensity in the putamen, globus pallidus, and white matter may be present. Electrodiagnostic studies may reveal rectal sphincter abnormalities with signs of degeneration with reinnervation due to anterior horn cell loss. Commercially available genetic tests are available for many of the spinocerebellar ataxias (Chap. 26) that present with features that overlap OPCA.

℞ Treatment: PARKINSONIAN DISORDERS OF α-SYNUCLEIN ABNORMAL METABOLISM

Early in the course of the illness, parkinsonian features may respond to dopaminomimetic agents. These have to be used with caution due to their tendency to provoke orthostatic hypotension. Treatment of orthostatic hypotension and other autonomic symptoms is discussed in Chap. 28.

PARKINSONIAN DISORDERS ASSOCIATED WITH ABNORMALITIES OF TAU METABOLISM (TAUOPATHIES)

As in the synucleopathies, the discovery of a group of familial and sporadic disorders with pathology involving the microtubule-associated protein tau has helped classify a group of disorders characterized by atypical parkinsonism and dementia. In the familial forms of these disorders, mutations in the *tau* gene have been linked to rare forms of parkinsonism and to frontotemporal dementia (Chap. 23). The two entities discussed below typically present as movement disorders. The first, progressive supranuclear palsy (PSP), has not been linked to mutations in the *tau* gene but is associated with overrepresentation of the H1 tau gene haplotype. These and other findings support the view that abnormal processing of tau may be directly linked to the pathogenesis of sporadic and familial tauopathies.

Progressive Supranuclear Palsy

This is a sporadic neurodegenerative disorder of unknown etiology associated with tau pathology. It presents in the sixth to seventh decades and progresses more rapidly than PD, with death in 5–10 years. Risk factors include head trauma, vascular disease, dietary exposure to benzyltetrahydroisoquinolines (TIQ, reticuline), and beta-carbolines (reports from the West Indies).

PSP is characterized by akinetic rigid parkinsonism, dizziness, unsteadiness, slowness, falls, and pseudobulbar dysarthria. Tremor is distinctly uncommon. Supranuclear eye movement abnormalities affecting downgaze occur first, followed by variable limitations of upward and horizontal eye movement. Because the vestibular ocular reflex ("doll's eyes" maneuver) and the Bell's reflex (elevation and abduction of eyes on attempted lid closure) are intact, these abnormalities are termed *supranuclear*. Neurologic examination often reveals prominent stare and furrowed brow, axial (especially nuchal) and proximal limb rigidity and dystonia, as well as upper motor neuron and occasional cerebellar signs. Virtually all patients develop frontal-type cognitive dysfunction (Chaps. 15, 23), and a significant number may develop dementia with distinct subcortical features (e.g., abulia, mental inflexibility, and defects in memory retrieval). Brain MRI reveals midbrain atrophy (superior colliculus), and PET studies show symmetric frontal and striatal hypometabolism. The diagnosis is made on clinical grounds. Although some response may occur to levodopa and other antiparkinson medications, especially early in the course, treatment is generally not highly effective.

Pathologically, PSP is characterized by deposition of neurofibrillary tangles histochemically positive for tau (mostly 4-repeat tau) and negative for amyloid or α-synuclein. The deposits are associated with varying degrees of

degeneration in the brainstem, basal ganglia, and cerebellum. There is loss of dopamine and dopamine receptors due to intrinsic striatal damage. This is thought to account for the poor response to therapy.

Corticobasal Degeneration (CBD)

CBD, another sporadic tauopathy, is less common but has a broader range of clinical presentations than PSP. As with most atypical forms of parkinsonism, it begins insidiously in the sixth to seventh decades with varying degrees of asymmetric progressive apraxia, rigidity, dystonia, bradykinesia, and myoclonic jerks, with or without cortical sensory loss. The "alien limb" phenomenon, consisting of involuntary purposeful movements of a hand or limb, is a characteristic sign. The disorder progresses to become bilateral over 2–5 years, leading to total incapacity with, ultimately, paraplegia in flexion. A significant number of cases present with frontotemporal dementia or progressive aphasia, followed by asymmetric cortical sensory signs, including abnormalities of graphesthesia and astereognosis (Chaps. 15, 23). Brain MRI reveals focal cortical loss in the contralateral superior frontal and parietal lobes with corresponding hypometabolic changes on PET scan as well as hyperintense signal abnormalities in white matter and sometimes atrophy of the corpus callosum. Treatment is largely ineffective.

Grossly, CBD is a focal cortical degenerative process with asymmetric pathology and volume loss in the parietal and frontal regions. Most of the damage is in the dorsal peri-Rolandic, superior frontal, and superior parietal cortices, whereas cases with aphasia show abnormalities in the peri-Sylvian regions. Histologically, gliosis and swollen (ballooned) achromatic neurons and neuronal loss are present in these cortical regions as well as in the nigra, caudate, putamen, and thalamus. Recent clinicopathologic evidence indicates that the syndrome can occur in the absence of basal ganglia or nigral degeneration.

SECONDARY PARKINSONISM

Drug-Induced Parkinsonism

DIP typically presents bilaterally with bradykinesia or tremor. Asymmetry is far less prominent than in PD. It is commonly due to neuroleptics, some atypical antipsychotics, lithium carbonate, or antiemetic agents (especially metoclopramide). Less common causes include valproic acid and fluoxetine. DIP can also be induced by the chronic administration of antihypertensive agents such as reserpine and α-methyldopa. Exposure to manganese, carbon monoxide or disulfides, cyanide, and methanol can also lead to a parkinsonian state. The severity of the parkinsonian symptoms usually correlates with the dose or exposure to a medication or toxin. If due to medication, the symptoms tend to disappear within days to weeks after stopping the offending agent but may be permanent. Patients with permanent symptoms may have been in the process of developing parkinsonism. DIP may respond to anticholinergic agents, amantadine, and levodopa.

Vascular Parkinsonism

The concept of vascular or atherosclerotic parkinsonism remains a topic of controversy. Generally, patients with vascular parkinsonism exhibit an akinetic-rigid syndrome with short mincing steps without tremor. Most have neurologic signs distinguishable from those associated with PD, including upper motor neuron signs, pseudobulbar palsy, or dementia. A poor response to levodopa therapy is characteristic. Imaging studies are heterogeneous and may reveal basal ganglia lacunes or multiple infarcts. The hypertensive and diabetic microangiopathy and diffuse white matter disease (Chap. 21) typically present with patchy, confluent, or diffuse white matter in the centrum semiovale. Other causes of microangiopathy can also rarely be responsible. The premortem diagnosis of these disorders is difficult to make with certainty, given the absence of disease markers.

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CHAPTER 25

HYPERKINETIC MOVEMENT DISORDERS

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HYPERKINETIC DISORDERS

Hyperkinetic movement disorders are characterized by the presence of a variety of different involuntary movements (Table 25-1). The major hyperkinetic movement disorders and the diseases with which they are associated are considered in this chapter.

ESSENTIAL TREMOR

Clinical Features

Essential tremor (ET) is the most common involuntary movement disorder, affecting ~5–10 million individuals in the United States alone. It is a progressive disorder which can present in childhood but dramatically increases in prevalence over the age of 70. ET is characterized by a high-frequency tremor (up to 11Hz) that predominantly affects the upper extremities. The tremor is most prominent when trying to maintain a posture (postural tremor) or perform an action such as touching the finger to an object (kinetic tremor). It is typically bilateral and symmetric, but one side can be predominantly affected. Tremor may also affect the head (horizontal or vertical), and speech may be tremulous. The tremor characteristically improves with alcohol and may worsen with stress. Occasionally, subtle impairment of coordination or tandem walking may be present, but the neurologic examination is otherwise normal. ET can be differentiated from Parkinson's disease (PD) by the absence of resting tremor, bradykinesia, rigidity, micrographia, and other parkinsonian features. Tremor can also be observed with a variety of drugs, multiple sclerosis, degenerative disorders, and metabolic alterations.

Etiology and Pathophysiology

The specific etiology and pathophysiology of ET are not known. Approximately 50% of cases have a positive family history with an autosomal dominant pattern of inheritance. Linkage studies have detected loci at chromosome 3q13 (*ETM-1*) and 2p22-25 (*ETM-2*), and it is likely that there are many other undiscovered loci. The cerebellum and inferior olives have been implicated as possible sites of a "tremor pacemaker" based on the presence of cerebellar signs in some patients and findings of increased metabolic activity and blood flow in these regions.

℞ Treatment: ESSENTIAL TREMOR

Many cases are mild and require no treatment other than reassurance. Occasionally, tremor can be severe and interfere with eating, writing, and activities of daily living. Primidone (25–1000 mg/d) and propranolol

TABLE 25-1

HYPERKINETIC MOVEMENT DISORDERS

DISORDERS	MOVEMENT CHARACTERISTICS
Athetosis	Slow, distal, writhing, involuntary movements with a propensity to affect the arms and hands.
Chorea	Rapid, semipurposeful, graceful, dancelike, nonpatterned involuntary movements involving distal or proximal muscle groups.
Dystonia	Involuntary patterned sustained or repeated muscle contractions, often leading to twisting movements and abnormal posture.
Myoclonus	Sudden, brief (<100 ms), shocklike, arrhythmic muscle twitches.
Tics	Brief, repeated, stereotyped muscle contractions that are often suppressible. Can be simple and involve a single muscle group or complex and affect a range of motor activities.
Tremor	Rhythmic oscillation of a body part due to intermittent muscle contractions.

(20–80 mg/d) are the standard drug therapies and can be administered alone or in combination. Primidone frequently causes sedation and should be started at low doses (12.5 mg) and gradually titrated to an effective dose. Propranolol and other beta blockers are contraindicated in patients with cardiac arrhythmias or asthma. Benefits with these drugs are attained in ~50% of patients but may not be sustained. Alprazolam, gabapentin, topiramate, clonazepam, clozapine, and nimodipine have been reported to improve tremor in some patients. Botulinum toxin injections may be helpful for limb or voice tremor, but treatment can be associated with muscle weakness. Surgical therapies targeting the VIM nucleus of the thalamus can be very effective in severe and drug-resistant cases.

DYSTONIA

Clinical Features

Dystonia consists of sustained or repetitive involuntary muscle contractions, frequently causing twisting movements with abnormal postures. Dystonia can range from minor contractions in an individual muscle group to severe and disabling involvement of multiple muscle groups. The frequency is estimated at 300,000 cases in the United States but is likely greater since many cases are not recognized. Dystonia is often initially brought out by voluntary movements (action dystonia) and can later become sustained and extend to other body regions. It can be aggravated by stress and fatigue and attenuated by relaxation and sensory tricks such as touching the affected body part. Dystonia can be classified based on age of onset (childhood vs. adult), distribution (focal, multifocal, segmental, or generalized), or etiology (primary or secondary).

Primary Dystonias

Idiopathic torsion dystonia (ITD), or Oppenheim's dystonia, is predominantly a childhood-onset form of dystonia with an autosomal dominant pattern of inheritance that primarily affects Ashkenazi Jewish families. The majority of patients have an age of onset younger than 26 years (mean 14 years). In young-onset patients, dystonia typically begins in a foot or arm and can progress to involve the other limbs as well as the head and neck. In severe cases, patients can suffer disabling postural deformities. Severity can vary even within a family, with some affected relatives having mild dystonia that may not even have been appreciated. Several gene mutations are associated with ITD. Most cases are linked to a mutation in the *DYT1* gene located on chromosome 9q34, which results in a trinucleotide GAG deletion with loss of one of a pair of glutamic acid residues in the protein torsin A. *DYT1* mutations are found in 90% of Ashkenazi Jewish patients with ITD and are probably related to a founder effect that occurred about 350 years ago. There is variable penetrance, with only about 30% of *DYT1* gene carriers expressing a clinical phenotype. The function of torsin A is not known, but it is a member of the AAA^+ (ATPase) family of proteins that resemble heat shock proteins and may thus be related to protein regulation. Indeed, postmortem studies have shown protein aggregates and inclusions in the region of the pedunculopontine nucleus (PPN). Transgenic mice that carry the DYT1 dystonia mutation express a hyperkinetic and dystonic phenotype and a similar pathology to human DYT1.

Dopa responsive dystonia (DRD) or the Segawa variant (DYT5) is a dominantly inherited form of childhood-onset dystonia due to a mutation in the gene that encodes for guanosine triphosphate (GTP) cyclohydrolase I, the rate-limiting enzyme for the synthesis of tetrahydrobiopterin. This mutation leads to a defect in the biochemical synthesis of tyrosine hydroxylase and dopamine. DRD typically presents in early childhood (1–12 years) and is characterized by foot dystonia that interferes with walking. Patients often experience diurnal fluctuations, with worsening of gait as the day progresses and improvement with sleep. DRD is typified by an excellent and sustained response to small doses of levodopa. Some patients may present with parkinsonian features but can be differentiated from juvenile PD by

normal striatal fluorodopa uptake on positron emission tomography and the absence of levodopa-induced dyskinesias. DRD patients may occasionally present with spasticity, increased reflexes, and Babinski responses and be misdiagnosed as cerebral palsy. A mutation has also been identified in the epsilon-sarcoglycan gene on chromosome 7q21. These patients typically suffer from myoclonic dystonia frequently accompanied by psychiatric disturbances.

Focal Dystonias

These are the most common forms of dystonia. They typically present in the fourth to sixth decades and affect women more than men. The major types are:

1. *Blepharospasm*: dystonic contractions of the eyelids with increased blinking that can interfere with reading, watching TV, and driving.
2. *Oromandibular dystonia* (OMD): contractions of muscles of the lower face, lips, tongue, and jaw (opening or closing). Meige's syndrome is a combination of OMD and blepharospasm that predominantly affects women older than 60 years.
3. *Spasmodic dysphonia*: dystonic contractions of the vocal cords during phonation, causing impaired speech. Most cases affect the adductor muscles and cause speech to have a choking or strained quality. Less commonly, the abductors are affected, leading to speech with a breathy or whispering quality.
4. *Cervical dystonia*: dystonic contractions of neck muscles, causing the head to deviate to one side (*torticollis*), in a forward direction (*anterocollis*), or in a backward direction *(retrocollis)*. Muscle contractions can be painful and associated with dystonic tremor and a secondary cervical radiculopathy.
5. *Limb dystonias*: these can be present in either arms or legs and are often brought out by task-specific activities such as handwriting (writer's cramp), playing a musical instrument (musician's cramp), or putting in golf (the yips).

   Focal dystonias can extend to involve other body regions (~30% of cases) and are frequently misdiagnosed as psychiatric or orthopedic problems. Their cause is not known, but genetic factors, autoimmunity, and repeated trauma have been implicated.

Secondary Dystonias

These occur as a consequence of drugs or other neurologic problems. Drug-induced dystonia is most commonly seen with neuroleptic drugs or after chronic levodopa treatment in PD patients (see later). Secondary dystonia can also be observed following discrete lesions in the striatum, pallidum, thalamus, cortex, and brainstem due to infarction, anoxia, trauma, tumor, infection, toxins such as manganese, or carbon monoxide. In these cases, dystonia often assumes a segmental distribution. More rarely, dystonia can develop following peripheral nerve injury.

Dystonia-Plus Syndromes

Dystonia may occur as a part of neurodegenerative conditions such as Huntington's disease (HD), PD, Wilson's disease, corticobasal degeneration, progressive supranuclear palsy, the Lubag form of dystonia-parkinsonism (DYT3), and mitochondrial encephalopathies. In contrast to the primary dystonias, dystonia is usually not the dominant neurologic feature in these conditions.

Pathophysiology of Dystonia

The pathophysiologic basis of dystonia is not known. The phenomenon is characterized by cocontracting bursts in agonist and antagonist muscle groups. This is associated with a loss of inhibition at multiple levels of the nervous system as well as increased cortical excitability and reorganization. Attention has focused on the basal ganglia as the site of origin of at least some types of dystonia as there are alterations in blood flow and metabolism in basal ganglia structures. Further, ablation or stimulation of the globus pallidus can both induce and ameliorate dystonia. The dopamine system has also been implicated in the pathogenesis of dystonia, as dopaminergic therapies can both induce and treat some forms of dystonia. Recent studies have demonstrated pathologic changes in the PPN, and electrical stimulation in this region induces dystonic muscle contractures, suggesting that the PPN might also be involved.

℞ Treatment: DYSTONIA

Treatment is symptomatic for the most part, except in rare cases where treatment of a primary underlying condition is available. Wilson's disease should be ruled out in young patients with dystonia as well as in any young patient with a movement disorder. Levodopa should be tried in all cases of childhood-onset dystonia. High-dose anticholinergics (e.g., trihexyphenidyl 20–120 mg/d) may be beneficial in children but are less helpful in adults who can rarely tolerate such high doses because of cognitive impairment with hallucinations. Oral baclofen (25–120 mg) may be helpful, but benefits are usually modest, and side effects of sedation, weakness, and memory loss can be problematic. Intrathecal infusion of baclofen is more likely to be helpful, particularly with leg and trunk dystonia, but benefits are frequently

not sustained and complications can be serious, including infection, seizures, and coma. Tetrabenazine (12.5–200 mg/d) may be helpful, but the drug is not readily available in the United States. Neuroleptics typically are not recommended because of the risk of extrapyramidal side effects. Clonazepam and diazepam are rarely effective. In general, dystonic patients are not satisfactorily controlled with drug therapies, particularly if they have a generalized dystonia.

On the other hand, botulinum toxin can be of great benefit for patients with focal dystonia, particularly if involvement is limited to small muscle groups such as in blepharospasm, torticollis, and spasmodic dysphonia. Botulinum toxin acts by blocking the release of acetylcholine at the neuromuscular junction, leading to muscle weakness and reduced dystonia. Two serotypes of botulinum toxin are available (A and B). Both are effective, and it is not clear if there are advantages of one over the other. No systemic side effects are encountered with the doses typically employed, but benefits are transient and repeat injections are required at 2- to 5-month intervals. Some patients fail to respond after having experienced an initial benefit. This has been attributed to induction of antibodies, but improper muscle selection, injection technique, and inadequate dose should be excluded.

Surgical therapy is an alternative for patients with severe dystonia who are not responsive to other treatments. Peripheral procedures such as rhizotomy and myotomy were used in the past to treat cervical dystonia but have been rarely employed since the introduction of botulinum toxin therapy. Bilateral deep brain stimulation (DBS) of the pallidum can provide dramatic benefits for patients with primary (DYT1) dystonia. This represents a major therapeutic advance as previously there was no consistently effective therapy for these patients. Patients with secondary dystonia are less likely to benefit from DBS. The value of DBS in patients with focal dystonia is currently being explored. Supportive treatments such as physical therapy and education are important and should be a part of the treatment regimen for all dystonia patients.

Physicians should be aware of dystonic storm, a potentially fatal condition that typically occurs in response to a stress situation such as surgery in patients with a preexisting history of dystonia. It consists of the acute onset of generalized and persistent dystonic contractions that can involve the vocal cords or laryngeal muscles, leading to airway obstruction. Patients may experience rhabdomyolysis with renal failure. Patients should be managed in an ICU and treated with one or a combination of anticholinergics, diphenhydramine, baclofen, benzodiazepines, or dopamine blockers. Spasms may be difficult to control, and anesthesia with muscle paralysis may be required.

CHOREAS

Huntington's Disease

HD is a progressive, fatal, autosomal dominant disorder characterized by motor, behavioral, and cognitive dysfunction. The disease is named for George Huntington, a family physician who described cases on Long Island, New York, in the nineteenth century. Onset is typically between 25 and 45 years of age (range 3–70 years) with a prevalence of two to eight cases per 100,000. HD is characterized by rapid, nonpatterned, semipurposeful, involuntary choreiform movements. In the early stages the chorea tends to be focal or segmental, but it progresses over time to involve multiple body regions. Dysarthria, gait disturbance, and oculomotor abnormalities are common features. With advancing disease, there is a reduction in the chorea and emergence of dystonia, rigidity, bradykinesia, myoclonus, and spasticity. In younger patients (about 10% of cases), HD can present as an akinetic-rigid or parkinsonian syndrome (Westphall variant). HD patients eventually develop behavioral and cognitive disturbances which can be a major source of disability. Depression with suicidal tendencies, aggressive behavior, and psychosis can be prominent, and the majority of patients develop dementia. A clinical diagnosis of HD can be strongly suspected in cases of chorea with a positive family history. Neuropathologically, the disease predominantly strikes the striatum. Atrophy of the caudate nuclei, which form the lateral margins of the lateral ventricles, can be visualized on neuroimaging studies in the middle and late stages of the disease (**Fig. 25-1**). More diffuse cortical atrophy can be seen late in the disease. Genetic testing can be used to confirm the diagnosis and to detect affected individuals in the family, but this should be performed with caution and in conjunction with trained counselors, as positive results can lead to depressive and suicidal reactions.

Etiology

HD is caused by an increase in the number of polyglutamine (CAG) repeats (>40) in the coding sequence of the Huntington gene located on the short arm of chromosome 4. The larger the number of repeats, the earlier the disease is manifest. Anticipation occurs, particularly in males, with subsequent generations having larger numbers of repeats and earlier age of disease onset. The gene encodes the highly conserved cytoplasmic protein huntingtin, which is widely distributed in neurons throughout the CNS, but whose function is not known. Models of HD with striatal pathology can be induced by excitotoxic agents such as kianic acid and 3-nitroproprionic acid, which promote calcium entry into the cell and cytotoxicity. Mitochondrial dysfunction has been observed in HD and has been theorized to promote "weak excitotoxicity" by reducing ATP formation necessary for maintaining the voltage-dependent magnesium blockade of

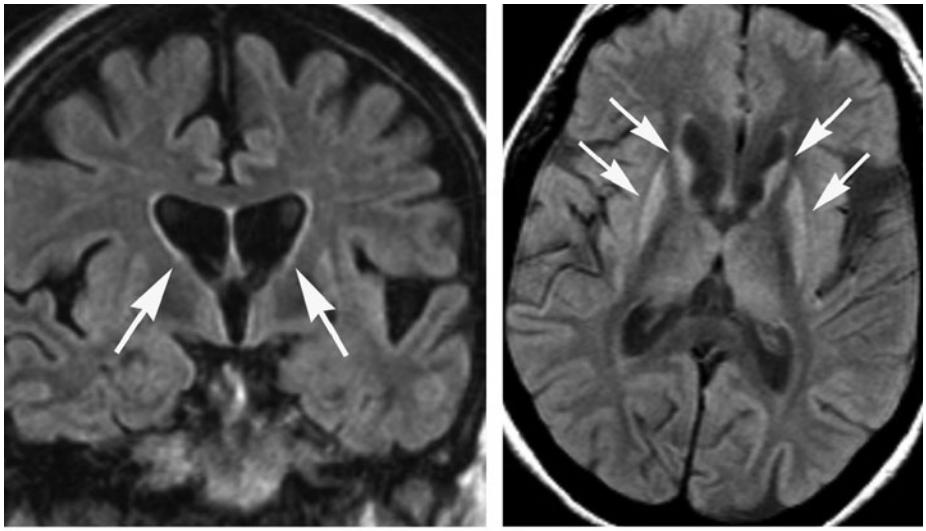

FIGURE 25-1
Huntington's disease. ***A.*** Coronal FLAIR MRI shows enlargement of the lateral ventricles reflecting typical caudate atrophy (*arrows*). ***B.*** Axial FLAIR image demonstrates abnormal high signal in the caudate and putamen (*arrows*).

calcium channels. Recent evidence indicates that fragments of the mutant huntingtin protein can be toxic, possibly by translocating into the nucleus and interfering with transcriptional regulatory proteins. Intraneuronal inclusions containing aggregates of ubiquitin and the mutant protein huntingtin are found in nuclei of neurons in the striatum and cerebral cortex. Neuronal inclusions found in affected regions in HD may represent a protective mechanism aimed at segregating and facilitating the clearance of these toxic proteins.

℞ Treatment: HUNTINGTON'S DISEASE

Treatment involves a multidisciplinary approach with medical, neuropsychiatric, social, and genetic counseling for patients and their families. Dopamine-blocking agents may control the chorea but are generally not recommended because of their side-effect profile and potential to aggravate motor symptoms, and because the chorea tends to be self-limited and is usually not disabling. Depression and anxiety can be greater problems, and patients should be treated with appropriate antidepressant and antianxiety drugs and monitored for mania and suicidal ideations. Psychosis can be treated with atypical neuroleptics such as clozapine (50–600 mg/d), quetiapine (50–600 mg/d), and risperidone (2–8 mg/d). There is no adequate treatment for the cognitive or motor decline. A neuroprotective therapy that slows or stops disease progression is the major unmet medical need in HD. Antiglutamate agents, bioenergetics, caspase inhibitors, inhibitors of protein aggregation, intracerebral delivery of neurotrophic factors, and transplantation of fetal striatal cells are all areas of active research, but none has as yet been demonstrated to have a disease-modifying effect.

Other Choreas

Chorea can be seen in a number of disorders. Sydenham's chorea (originally called Saint Vitus' dance) is more common in females and is typically seen in childhood (5–15 years). It often develops in association with prior exposure to a group A streptococcal infection and is thought to be the result of an autoimmune-mediated inflammatory disorder. With the reduction in the incidence of rheumatic fever, the incidence of Sydenham's chorea has fallen, but it can still be seen in developing countries. It is characterized by the acute onset of choreiform movements, behavioral disturbances, and occasionally other motor dysfunctions. Chorea generally responds to dopamine-blocking agents, valproic acid, and carbamazepine but it tends to be self-limited, and treatment is generally restricted to those with severe chorea. Chorea may recur in later life, particularly in association with pregnancy (chorea gravidarum) or treatment with sex hormones. Neuroacanthocytosis is a progressive and typically fatal autosomal recessive disorder that is characterized by chorea coupled with red cell abnormalities on peripheral blood smear (acanthocytes). The chorea can be severe and associated with self-mutilating behavior, dystonia, tics, seizures, and a polyneuropathy. The cause is unknown, but linkage to chromosome 9q21 has been described. A phenotypically similar X-linked form of the disorder has been described in older individuals who have reactivity with Kell blood group antigens (McLeod syndrome).

Paroxysmal forms of chorea have been described in association with vascular diseases, hypo- and hyperglycemia, and a variety of infections and degenerative disorders. Paroxysmal kinesigenic dyskinesia is rare and characterized by brief episodes of chorea triggered by sudden voluntary movements. A benign senile chorea in older individuals and a benign inherited chorea of childhood have also

been described. These conditions are somewhat controversial, and it is important to ensure that patients do not have HD.

Systemic lupus erythematosus is the most common systemic disorder that causes chorea; the chorea can last for days to years. Choreas can also be seen in patients with hyperthyroidism, various autoimmune disorders, infections including HIV, metabolic alterations, polycythemia rubra vera, following open heart surgery in the pediatric population, and in association with a wide variety of medications (especially anticonvulsants, cocaine, CNS stimulants, estrogens, and lithium).

Rx Treatment: CHOREA

Diagnosis and treatment of the underlying condition, where possible, is the first priority. Tetrabenazine (not available in the United States), neuroleptics, dopamine-blocking agents, propranolol, clonazepam, and baclofen may be helpful. Treatment is not indicated if the condition is mild and self-limited.

Levodopa-Induced Dyskinesia

Chronic levodopa treatment in PD patients is frequently associated with choreiform dyskinesias that affect the head, neck, torso, and extremities. They are usually associated with the peak plasma levodopa level and maximal clinical effect (peak dose dyskinesia) but may occur at the onset and wearing off of the levodopa effect (diphasic dyskinesia). The dyskinesias can be disabling and can also limit the ability to fully utilize levodopa to control PD features. Levodopa-induced dyskinesias are thought to relate to plastic changes in basal ganglia neurons induced by intermittent nonphysiologic activation of striatal dopamine receptors due to the drug's short half-life. Medical management with levodopa dose manipulations, dopamine agonists, and amantadine may be helpful but frequently do not provide satisfactory control. Surgical therapies (ablation and stimulation) directed at the pallidum and subthalamic nucleus (STN) can be very effective in severe cases (Chap. 24). Recent studies suggest that dyskinesias can be prevented by more continuous delivery of levodopa or other dopaminergic agents. Levodopa does not cause dyskinesias in normal individuals.

Hemiballismus

Hemiballismus is a violent form of chorea that comprises wild, flinging, large-amplitude movements on one side of the body. Proximal limb muscles tend to be predominantly affected. The movements may be so severe as to cause exhaustion, dehydration, local injury, and, in extreme cases, death. The most common cause is a partial lesion (infarct or hemorrhage) in the STN, but cases can also be seen with lesions in the putamen (**Fig. 25-2**). Fortunately, hemiballismus is usually self-limiting and tends to resolve spontaneously after weeks or months. The condition is difficult to treat pharmacologically. The drugs most consistently beneficial are tetrabenazine (not available in the United States), haloperidol, propranolol, phenytoin, clonazepam, and baclofen. In extreme cases, pallidotomy can be very effective. Interestingly, surgically induced lesions of the STN in PD are usually not associated with hemiballismus.

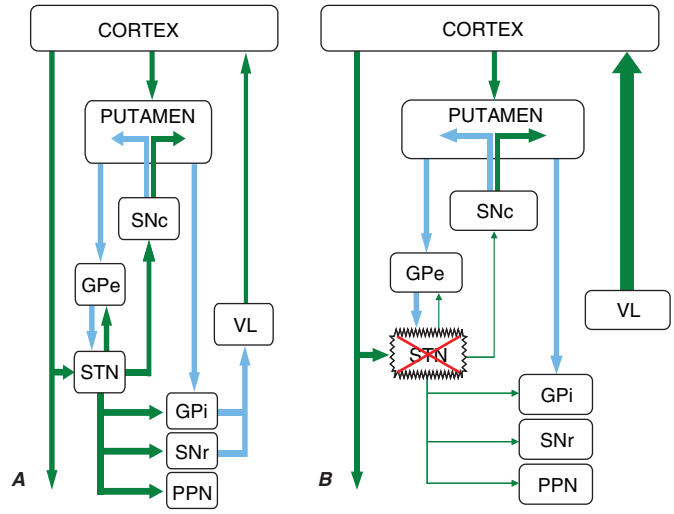

FIGURE 25-2

Schematic diagram of the basal ganglia–thalamocortical circuitry in normal (*A*) and hemiballismus (*B*) conditions. Inhibitory connections are shown as blue arrows and excitatory connections as green arrows. ***A.*** In the normal condition, the putamen connects to the GPi/SNr by direct and indirect pathways. Output neurons from the globus pallidus provide an inhibitory input to the VL thalamus and modulate its excitatory effect on cortical motor neurons. ***B.*** In hemiballismus, the lesion of the STN results in reduced excitatory input to the GPi/SNr and, in turn, reduced inhibition of thalamocortical neurons, leading to excessive activation of the cortex and the emergence of choreiform movements. Dopamine agonists may provide benefit in hemiballismus or chorea by blocking excitation of inhibitory neurons in the direct pathway (e.g., putamen → GPi/SNr) and preventing inhibition of remaining neurons in the excitatory indirect pathway (putamen → GPe → STN → GPi/SNr), thus increasing neuronal activity in GPi and inhibiting thalamic excitation of the cortex. Surgical lesions of the GPi are also beneficial, suggesting that abnormal neuronal discharge patterns in basal ganglia output neurons are an important contributing factor in the development of chorea. GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; SNr, substantia nigra, pars reticulata; SNc, substantia nigra, pars compacta; STN, subthalamic nucleus; VL, ventrolateral thalamus; PPN, pedunculopontine nucleus.

TICS

Tourette Syndrome (TS)

TS is a neurobehavioral disorder named after the French neurologist Georges Gilles de la Tourette. It predominantly affects males, and prevalence is estimated to be 0.03–1.6%, but it is likely that many mild cases do not come to medical attention. TS is characterized by multiple motor tics and vocalizations. A *tic* is a brief, rapid, recurrent, and seemingly purposeless stereotyped motor contraction. Motor tics can be "simple," with movement only affecting an individual muscle group (e.g., blinking, twitching of the nose, jerking of the neck), or "complex," with coordinated involvement of multiple muscle groups [e.g., jumping, sniffing, head banging, and echopraxia (mimicking movements)]. Vocal tics can also be simple (e.g., grunting) or complex [e.g., echolalia (repeating other peoples words), palilalia (repeating your own words), and coprolalia (expression of obscene words)]. Patients may also experience sensory tics, consisting of unpleasant focal sensations in the face, head, or neck. Patients may experience an irresistible urge to express tics but characteristically can voluntarily suppress them for short periods of time. Tics vary in intensity and may be absent for days or weeks only to recur, occasionally in a different pattern. Tics tend to present between ages 2–15 years (mean 7 years) and often lessen or even disappear in adulthood. Associated behavioral disturbances include anxiety, depression, attention-deficit hyperactivity disorder and obsessive compulsive disorder. Patients may experience personality disorders, self-destructive behaviors, difficulties in school, and impaired interpersonal relationships. Tics may present in adulthood and can be seen in association with a variety of other disorders, including PD, HD, trauma, dystonia, drugs (e.g., levodopa, neuroleptics), and toxins.

Etiology and Pathophysiology

TS is thought to be a genetic disorder, but no specific gene has been identified as yet. Current evidence supports a complex inheritance pattern with one or more major genes, multiple loci, low penetrance, and environmental influences. The risk of a family with one affected child having a second is about 25%. The pathophysiology of TS is not known, but alterations in dopamine neurotransmission, opioids, and second messenger systems have been proposed.

℞ Treatment: TOURETTE SYNDROME

Patients with mild disease often only require education and counseling (for themselves and family members). Drug treatment is indicated only when the tics are disabling and interfere with quality of life. Therapy is generally initiated with the α agonist clonidine, starting at low doses and gradually increasing the dose and frequency until satisfactory control is achieved. Guanfacine (0.5–2 mg/d) is a new α agonist that is preferred by many clinicians because it only requires once-a-day dosing. If these agents are not effective, antipsychotics can be employed. Atypical neuroleptics (risperidone 0.25–16 mg/d, olanzapine 2.5–15 mg/d, ziprasidone 20–200 mg/d) are preferred as they are associated with a reduced risk of extrapyramidal side effects. If they are not effective, classical neuroleptics such as haloperidol, fluphenazine, or pimozide can be tried. Botulinum toxin injections can be effective in controlling focal tics that involve small muscle groups. Behavioral features, and particularly anxiety and compulsions, can be a disabling feature of TS and should be treated. The potential value of DBS targeting the anterior portion of the internal capsule is currently being explored.

MYOCLONUS

Myoclonus is a brief, rapid (<100 ms), shocklike, jerky movement consisting of single or repetitive muscle discharges. Myoclonic jerks can be focal, multifocal, segmental, or generalized and can occur spontaneously, in association with voluntary movement (action myoclonus), or in response to an external stimulus (reflex or startle myoclonus). Negative myoclonus consists of a twitch due to a brief loss of muscle activity (e.g., asterixis in hepatic failure). Myoclonic jerks differ from tics in that they interfere with normal movement and are not suppressible. They can be seen in association with pathology in cortical, subcortical, or spinal cord regions, associated with hypoxic damage (especially following cardiac arrest), encephalopathy, and neurodegenerative disorders. Reversible myoclonus can be seen with metabolic disturbances (renal failure, electrolyte imbalance, hypocalcemia), toxins, and many medications. Essential myoclonus is a relatively benign familial condition characterized by multifocal lightning-like movements. Myoclonic jerks can be disabling when they interfere with normal movement. They can also be innocent and are commonly observed in normal people when waking up or falling asleep.

℞ Treatment: MYOCLONUS

Treatment primarily consists of treating the underlying condition or removing an offending agent. Pharmacologic therapy involves one or a combination of GABAergic agents such as valproic acid (1200–3000 mg/d), piracetam (8–20 g/d), clonazepam (2–15 mg/d), or primidone (500–1000 mg/d). Recent studies suggest that levetiracetam may be particularly effective.

DRUG-INDUCED MOVEMENT DISORDERS

This important group of movement disorders is primarily associated with drugs that block dopamine receptors (neuroleptics) or central dopaminergic transmission. These drugs are mostly used in psychiatry but are also important in the treatment of nausea or vomiting (e.g., Compazine) or gastroesophageal disorders (e.g., metoclopramide). Hyperkinetic movement disorders secondary to neuroleptic drugs can be divided into those which present acutely, subacutely, or after prolonged exposure (tardive syndromes). Dopamine-blocking drugs can also be associated with a reversible parkinsonian syndrome for which anticholinergics are often concomitantly prescribed, but there is concern that this may increase the risk of developing a tardive syndrome.

Acute

Dystonia is the most common acute hyperkinetic drug reaction. It is typically generalized in children and focal (e.g., blepharospasm, torticollis, or oromandibular dystonia) in adults. The reaction can develop within minutes of exposure and can be successfully treated in most cases with parenteral administration of anticholinergics (benztropine or diphenhydramine) or benzodiazepines (lorazepam or diazepam). Choreas, stereotypic behaviors, and tics may also be seen, particularly following acute exposure to CNS stimulants such as methylphenidate, cocaine, or amphetamines.

Subacute

Akathisia is the commonest reaction in this category. It consists of motor restlessness with a need to move that is alleviated by movement. Therapy consists of removing the offending agent(s). When this is not possible, symptoms may be ameliorated with benzodiazepines, anticholinergics, beta blockers, or dopamine agonists.

Tardive Syndromes

These disorders develop months to years after initiation of neuroleptic treatment. Tardive dyskinesia (TD) is the commonest and typically comprises choreiform movements involving the mouth, lips, and tongue. In severe cases the trunk, limbs, and respiratory muscles may be affected. Patients with affective disorders are more likely to develop TD than are patients with schizophrenia. In approximately one-third of patients, TD remits within 3 months of stopping the drug, and most patients gradually improve over the course of several years. The movements are often mild and more upsetting to the family than to the patient, but they can be severe and disabling, particularly in the context of an underlying psychiatric disorder. Atypical antipsychotics (e.g., clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole) are associated with a significantly lower risk of TD in comparison to traditional antipsychotics. Younger patients have a lower risk of developing neuroleptic-induced TD, while the elderly, the edentulous, and those with underlying organic cerebral dysfunction are at greater risk. Since TD can be permanent and resistant to treatment, antipsychotics should be used judiciously; atypical neuroleptics should be employed whenever possible, and the need for their continued use should be regularly monitored.

Treatment primarily consists of stopping the antipsychotic. If the patient is receiving a traditional antipsychotic and withdrawal is not possible, replacement with an atypical antipsychotic should be tried. Abrupt cessation of a neuroleptic should be avoided as acute withdrawal can induce transient worsening. TD can persist after withdrawal of antipsychotics and can be difficult to treat. Benefits may be achieved with valproic acid, anticholinergics, or botulinum toxin injections. In refractory cases, catecholamine depletors such as reserpine and tetrabenazine may be helpful. Tetrabenazine can be associated with dose-dependent sedation and orthostatic hypotension. Reserpine is an alternative, but it is frequently associated with depression and not often employed. Other approaches include baclofen (40–80 mg/d), clonazepam (1–8 mg/d), or valproic acid (750–3000 mg/d).

Chronic neuroleptic exposure can also be associated with tardive dystonia with preferential involvement of axial muscles and characteristic rocking movements of the trunk and pelvis. Tardive dystonia frequently persists despite stopping medication, and patients are often refractory to medical therapy. Valproic acid, anticholinergics, and botulinum toxin may occasionally be beneficial. Tardive akathisia and tardive Tourette syndromes are rare but may also occur after neuroleptic exposure.

Neuroleptic medications can also be associated with a neuroleptic malignant syndrome (NMS). NMS is characterized by muscle rigidity, elevated temperature, altered mental status, hyperthermia, tachycardia, labile blood pressure, and renal failure. Symptoms typically evolve within days or weeks after initiating the drug. NMS can also be precipitated by the abrupt withdrawal of antiparkinsonian medications in PD patients. Treatment involves immediate cessation of the offending antipsychotic drug and the introduction of a dopaminergic agent (e.g., dopamine agonists, levodopa), dantrolene, or benzodiazepines. Treatment also includes supportive measures such as control of body temperature (antipyretics and cooling blankets), hydration, electrolyte replacement, and control of renal function and blood pressure.

Drugs that have serotonin-like activity (tryptophan; MDMA, or "ecstasy"; meperidine) or that block serotonin reuptake can induce a rare, but potentially fatal, serotonin syndrome that is characterized by confusion, hyperthermia, tachycardia, and coma as well as rigidity, ataxia, and tremor. Myoclonus is often a prominent

feature, in contrast to NMS, which it resembles. Patients can be managed with propranolol, diazepam, diphenhydramine, chlorpromazine, or cyproheptadine as well as supportive measures.

A variety of other drugs can also be associated with hyperkinetic movement disorders. Some examples include phenytoin (chorea, dystonia, tremor, myoclonus); carbamazepine (tics and dystonia); tricyclic antidepressants (dyskinesias, tremor, myoclonus); fluoxetine (myoclonus, chorea, dystonia); oral contraceptives (dyskinesia); adrenergics (tremor); buspirone (akathisia, dyskinesias, myoclonus); and digoxin, cimetidine, diazoxide, lithium, methadone, and fentanyl (dyskinesias).

PSYCHOGENIC DISORDERS

Virtually all movement disorders, including tremor, tics, dystonia, myoclonus, chorea, ballismus, and parkinsonism, can be psychogenic in origin. Tremor affecting the upper limbs is the most common psychogenic movement disorder. Psychogenic movements can result from a somatoform or conversion disorder, malingering (e.g., seeking financial gain), or a factitious disorder (e.g., seeking psychological gain). Psychogenic movement disorders are common (estimated 2–3% of patients in a movement disorder clinic), more prominent in women, disabling for the patient and family, and expensive for society (estimated $20 billion annually). Clinical features suggesting a psychogenic movement disorder include an acute onset and a pattern of abnormal movement that is inconsistent with a known movement disorder. Diagnosis is based on the nonorganic quality of the movement, the absence of findings of an organic disease process, and positive features that specifically point to a psychogenic illness such as variability and distractibility. For example, the magnitude of a psychogenic tremor is increased with attention and diminishes or even disappears when the patient is distracted by being asked to perform a different task or is unaware that he or she is being observed. This is the opposite of what occurs with organic movement disorders, which tend to worsen when the patient is distracted and abate with attention. Other positive features that suggest a psychogenic problem include a tremor frequency that is variable or entrains with the frequency of tapping in the contralateral limb and a positive response to placebo medication. Comorbid psychiatric problems such as anxiety, depression, and emotional trauma may be present but are not necessary for the diagnosis of a psychogenic movement disorder to be made. Psychogenic movement disorders can occur as an isolated entity or in association with an underlying organic problem. The diagnosis can often be made based on clinical features alone, and unnecessary tests or medications should be avoided. Underlying psychiatric problems should be identified and treated. Psychotherapy and hypnosis may be of value for patients with conversion reaction, and cognitive behavioral therapy may be helpful for patients with somatoform disorders. Patients with hypochondriasis, factitious disorders, and malingering have a poor prognosis.

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CHAPTER 26

ATAXIC DISORDERS

Roger N. Rosenberg

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Approach to the Patient: ATAXIC DISORDERS

Symptoms and signs of ataxia consist of gait impairment, unclear ("scanning") speech, visual blurring due to nystagmus, hand incoordination, and tremor with movement. These result from the involvement of the cerebellum and its afferent and efferent pathways, including the spinocerebellar pathways, and the frontopontocerebellar pathway originating in the rostral frontal lobe. True cerebellar ataxia must be distinguished from ataxia associated with vestibular nerve or labyrinthine disease, as the latter results in a disorder of gait associated with a significant degree of dizziness, light-headedness, or the perception of movement (Chap. 9). True cerebellar ataxia is devoid of these vertiginous complaints and is clearly an unsteady gait due to imbalance. Sensory disturbances can also on occasion simulate the imbalance of cerebellar disease; with sensory ataxia, imbalance dramatically worsens when visual input is removed (Romberg sign). Rarely, weakness of proximal leg muscles mimics cerebellar disease. In the patient who presents with ataxia, the rate and pattern of the development of cerebellar symptoms help to narrow the diagnostic possibilities (**Table 26-1**). A gradual and progressive increase in symptoms with bilateral and symmetric involvement suggests a biochemical, metabolic, immune, or toxic etiology. Conversely, focal, unilateral symptoms with headache and impaired level of consciousness accompanied by ipsilateral cranial nerve palsies and contralateral weakness imply a space-occupying cerebellar lesion.

SYMMETRIC ATAXIA Progressive and symmetric ataxia can be classified with respect to onset as acute (over hours or days), subacute (weeks or months), or chronic (months to years). Acute and reversible ataxias include those caused by intoxication with alcohol, phenytoin, lithium, barbiturates, and other drugs. Intoxication caused by toluene exposure, gasoline sniffing, glue sniffing, spray painting, or exposure to methyl mercury or bismuth are additional causes of acute or subacute ataxia, as is treatment with cytotoxic chemotherapeutic drugs such as fluorouracil and paclitaxel. Patients with a postinfectious syndrome (especially after varicella) may develop gait ataxia and mild dysarthria, both of which are reversible (Chap. 34). Rare infectious causes of acquired ataxia include poliovirus, coxsackievirus, echovirus, Epstein-Barr virus, toxoplasmosis, *Legionella*, and Lyme disease.

The subacute development of ataxia of gait over weeks to months (degeneration of the cerebellar vermis) may be due to the combined effects of alcoholism and malnutrition, particularly with deficiencies of vitamins B_1 and B_{12}. Hyponatremia has also been

TABLE 26-1

ETIOLOGY OF CEREBELLAR ATAXIA

SYMMETRIC AND PROGRESSIVE SIGNS			FOCAL AND IPSILATERAL CEREBELLAR SIGNS		
ACUTE (HOURS TO DAYS)	**SUBACUTE (DAYS TO WEEKS)**	**CHRONIC (MONTHS TO YEARS)**	**ACUTE (HOURS TO DAYS)**	**SUBACUTE (DAYS TO WEEKS)**	**CHRONIC (MONTHS TO YEARS)**
Intoxication: alcohol, lithium, diphenylhydantoin, barbiturates (positive history and toxicology screen)	Intoxication: mercury, solvents, gasoline, glue; cytotoxic chemotherapeutic drugs	Paraneoplastic syndrome Anti-gliadin antibody syndrome Hypothyroidism	Vascular: cerebellar infarction, hemorrhage, or subdural hematoma Infectious: cerebellar abscess (mass lesion on MRI/CT, history in support of lesion)	Neoplastic: cerebellar glioma or metastatic tumor (positive for neoplasm on MRI/CT) Demyelinating: multiple sclerosis (history, CSF, and MRI are consistent)	Stable gliosis secondary to vascular lesion or demyelinating plaque (stable lesion on MRI/CT older than several months)
Acute viral cerebellitis (CSF supportive of acute viral infection)	Alcoholic-nutritional (vitamin B_1 and B_{12} deficiency)	Inherited diseases Tabes dorsalis (tertiary syphilis)		AIDS-related multifocal leuko-encephalopathy (positive HIV test and CD4+ cell count for AIDS)	Congenital lesion: Chiari or Dandy-Walker malforma-tions (malformation noted on MRI/CT)
Postinfection syndrome	Lyme disease	Phenytoin toxicity			

Note: CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging.

associated with ataxia. Paraneoplastic cerebellar ataxia is associated with a number of different tumors (and autoantibodies) such as breast and ovarian cancers (anti-Yo), small-cell lung cancer (anti-PQ type voltage-gated calcium channel), and Hodgkin's disease (anti-Tr) (Chap. 39). Another paraneoplastic syndrome associated with myoclonus and opsoclonus occurs with breast (anti-Ri) and lung cancers and neuroblastoma. Elevated serum anti-glutamic acid decarboxylase (GAD) antibodies have been associated with a progressive ataxic syndrome affecting speech and gait. For all of these paraneoplastic ataxias, the neurologic syndrome may be the presenting symptom of the cancer. Another immune-mediated progressive ataxia is associated with anti-gliadin (and anti-endomysium) antibodies and the HLA DQB1* 0201 haplotype; in some affected patients, biopsy of the small intestine reveals villous atrophy consistent with gluten-sensitive enteropathy. Finally, subacute progressive ataxia may be caused by a prion disorder, especially when an infectious etiology, such as transmission from contaminated human growth hormone, is responsible (Chap. 38).

Chronic symmetric gait ataxia suggests an inherited ataxia (discussed below), a metabolic disorder, or a chronic infection. Hypothyroidism must always be considered as a readily treatable and reversible form of gait ataxia. Infectious diseases that can present with ataxia are meningovascular syphilis and tabes dorsalis due to degeneration of the posterior columns and spinocerebellar pathways in the spinal cord.

FOCAL ATAXIA Acute focal ataxia commonly results from cerebrovascular disease, usually ischemic infarction, or cerebellar hemorrhage. These lesions typically produce cerebellar symptoms ipsilateral to the injured cerebellum and may be associated with an impaired level of consciousness due to brainstem compression and increased intracranial pressure; ipsilateral pontine signs, including sixth and seventh nerve palsies, may be present. Focal and worsening signs of acute ataxia should also prompt consideration of a posterior fossa subdural hematoma, bacterial abscess, or primary or metastatic cerebellar tumor. CT or MRI studies will reveal clinically significant processes of this type. Many of these lesions represent true neurologic emergencies, as sudden herniation, either rostrally through the tentorium or caudal herniation of cerebellar tonsils through the foramen magnum, can occur and is usually devastating. Acute surgical decompression may be required (Chap. 22). Lymphoma or progressive multifocal leukoencephalopathy (PML) in a patient with AIDS

may present with an acute or subacute focal cerebellar syndrome. Chronic etiologies of progressive ataxia include multiple sclerosis (Chap. 34) and congenital lesions such as a Chiari malformation (Chap. 30) or a congenital cyst of the posterior fossa (Dandy-Walker syndrome).

THE INHERITED ATAXIAS

These may show autosomal dominant, autosomal recessive, or maternal (mitochondrial) modes of inheritance. A genomic classification (**Table 26-2**) has now largely superseded previous ones based on clinical expression alone.

Although the clinical manifestations and neuropathologic findings of cerebellar disease dominate the clinical picture, there may also be characteristic changes in the basal ganglia, brainstem, spinal cord, optic nerves, retina, and peripheral nerves. In large families with dominantly inherited ataxias, many gradations are observed from purely cerebellar manifestations to mixed cerebellar and brainstem disorders, cerebellar and basal ganglia syndromes, and spinal cord or peripheral nerve disease. Rarely, dementia is present as well. The clinical picture may be homogeneous within a family with dominantly inherited ataxia, but sometimes most affected family members show one characteristic syndrome, while one or several members have an entirely different phenotype.

AUTOSOMAL DOMINANT ATAXIAS

The autosomal spinocerebellar ataxias (SCAs) include SCA types 1 through SCA28, dentatorubropallidoluysian atrophy (DRPLA), and episodic ataxia (EA) types 1 and 2 (Table 26-2). SCA1, SCA2, SCA3 [Machado-Joseph disease (MJD)], SCA6, SCA7, and SCA17 are caused by CAG triplet repeat expansions in different genes. SCA8 is due to an untranslated CTG repeat expansion, SCA12 is linked to an untranslated CAG repeat, and SCA10 is caused by an untranslated pentanucleotide repeat. The clinical phenotypes of these SCAs overlap. The genotype has become the "gold standard" for diagnosis and classification. CAG encodes glutamine, and these expanded CAG triplet repeat expansions result in expanded polyglutamine proteins, termed *ataxins*, that produce a toxic gain of function with autosomal dominant inheritance. Although the phenotype is variable for any given disease gene, a pattern of neuronal loss with gliosis is produced that is relatively unique for each ataxia. Immunohistochemical and biochemical studies have shown cytoplasmic (SCA2), neuronal (SCA1, MJD, SCA7), and nucleolar (SCA7) accumulation of the specific mutant polyglutamine-containing ataxin proteins. Expanded polyglutamine ataxins with more than ~40 glutamines are potentially toxic to neurons for a variety of reasons including the following: high levels of gene expression for the mutant polyglutamine ataxin in affected neurons; conformational change of the aggregated protein to a β-pleated structure; abnormal transport of the ataxin into the nucleus (SCA1, MJD, SCA7); binding to other polyglutamine proteins, including the TATA-binding transcription protein and the CREB-binding protein, impairing their functions; altering the efficiency of the ubiquitin-proteosome system of protein turnover; and inducing neuronal apoptosis. An earlier age of onset (anticipation) and more aggressive disease in subsequent generations are due to further expansion of the CAG triplet repeat and increased polyglutamine number in the mutant ataxin. The most common disorders are discussed below.

SCA1

SCA1 was previously referred to as *olivopontocerebellar atrophy*, but genomic data have shown that entity represents several different genotypes with overlapping clinical features.

Symptoms and Signs

SCA1 is characterized by the development in early or middle adult life of progressive cerebellar ataxia of the trunk and limbs, impairment of equilibrium and gait, slowness of voluntary movements, scanning speech, nystagmoid eye movements, and oscillatory tremor of the head and trunk. Dysarthria, dysphagia, and oculomotor and facial palsies may also occur. Extrapyramidal symptoms include rigidity, an immobile face, and parkinsonian tremor. The reflexes are usually normal, but knee and ankle jerks may be lost, and extensor plantar responses may occur. Dementia may be noted but is usually mild. Impairment of sphincter function is common, with urinary and sometimes fecal incontinence. Cerebellar and brainstem atrophy are evident on MRI (**Fig. 26-1**).

Marked shrinkage of the ventral half of the pons, disappearance of the olivary eminence on the ventral surface of the medulla, and atrophy of the cerebellum are evident on gross postmortem inspection of the brain. Variable loss of Purkinje cells, reduced numbers of cells in the molecular and granular layer, demyelination of the middle cerebellar peduncle and the cerebellar hemispheres, and severe loss of cells in the pontine nuclei and olives are found on histologic examination. Degenerative changes in the striatum, especially the putamen, and loss of the pigmented cells of the substantia nigra may be found in cases with extrapyramidal features. More widespread degeneration in the central nervous system (CNS), including involvement of the posterior columns and the spinocerebellar fibers, is often present.

TABLE 26-2

CLASSIFICATION OF THE SPINOCEREBELLAR ATAXIAS

NAME	LOCUS	PHENOTYPE
SCA1 (autosomal dominant type 1)	6p22-p23 with CAG repeats (exonic); leucine-rich acidic nuclear protein (LANP), region-specific interaction protein Ataxin-1	Ataxia with ophthalmoparesis, pyramidal and extrapyramidal findings
SCA2 (autosomal dominant type 2)	12q23-q24.1 with CAG repeats (exonic) Ataxin-2	Ataxia with slow saccades and minimal pyramidal and extrapyramidal findings
Machado-Joseph disease/SCA3 (autosomal dominant type 3)	14q24.3-q32 with CAG repeats (exonic); codes for ubiquitin protease (inactive with polyglutamine expansion); altered turnover of cellular proteins due to proteosome dysfunction MJD–ataxin-3	Ataxia with ophthalmoparesis and variable pyramidal, extrapyramidal, and amyotrophic signs
SCA4 (autosomal dominant type 4)	16q22.1-ter; pleckstrin homology domain-containing protein, family G, member 4; (PLEKHG4; puratrophin-1: Purkinke cell atrophy associated protein-1, including spectrin repeat and the guanine-nucleotide exchange factor, GEF for Rho GTPases)	Ataxia with normal eye movements, sensory axonal neuropathy, and pyramidal signs
SCA5 (autosomal dominant type 5)	11p12-q12; β-III spectrin mutations; (SPTBN2); stabilizes glutamate transporter EAAT4; descendants of President Abraham Lincoln	Ataxia and dysarthria
SCA6 (autosomal dominant type 6)	19p13.2 with CAG repeats in α_{1A}-voltage–dependent calcium channel gene (exonic); CACNA1A protein, P/Q type calcium channel subunit	Ataxia and dysarthria, nystagmus, mild proprioceptive sensory loss
SCA7 (autosomal dominant type 7)	3p14.1-p21.1 with CAG repeats (exonic); Ataxin-7; subunit of GCN5, histone acetyltransferase-containing complexes; ataxin 7 binding protein; Cbl-associated protein (CAP; SH3D5)	Ophthalmoparesis, visual loss, ataxia, dysarthria, extensor plantar response, pigmentary retinal degeneration
SCA8 (autosomal dominant type 8)	13q21 with CTG repeats; noncoding; 3′ untranslated region of transcribed RNA	Gait ataxia, dysarthria, nystagmus, leg spasticity, and reduced vibratory sensation
SCA10 (autosomal dominant type 10)	22q13; pentanucleotide repeat ATTCT repeat; noncoding, intron 9	Gait ataxia, dysarthria, nystagmus; partial complex and generalized motor seizures; polyneuropathy
SCA11 (autosomal dominant type 11)	15q14-q21.3 by linkage	Slowly progressive gait and extremity ataxia, dysarthria, vertical nystagmus, hyperreflexia
SCA12 (autosomal dominant type 12)	5q31-q33 by linkage; CAG repeat; protein phosphatase 2A, regulatory subunit B, (PPP2R2B); protein PP2A, serine/threonine phosphatase	Tremor, decreased movement, increased reflexes, dystonia, ataxia, dysautonomia, dementia, dysarthria
SCA13 (autosomal dominant type 13)	19q13.3-q14.4	Ataxia, legs>arms; dysarthria, horizontal nystagmus; delayed motor development; mental developmental delay; tendon reflexes increased; MRI: cerebellar and pontine atrophy
SCA14 (autosomal dominant type 14)	19q-13.4; protein kinase Cγ (PRKCG), missense mutations including in-frame deletion and a splice site mutation among others; serine/threonine kinase	Gait ataxia; leg>arm ataxia; dysarthria; pure ataxia with later onset; myoclonus; tremor of head and extremities; increased deep tendon reflexes at ankles; occasional dystonia and sensory neuropathy
SCA15 (autosomal dominant type 15)	3p24.2-3pter	Gait and extremity ataxia, dysarthria; nystagmus; MRI: superior vermis atrophy; sparing of hemispheres and tonsils
SCA16 (autosomal dominant type 16)	8q22.1-24.1	Pure cerebellar ataxia and head tremor, gait ataxia, and dysarthria; horizontal gaze–evoked nystagmus; MRI, cerebellar atrophy; no brainstem changes
SCA17 (autosomal dominant type 17)	6q27; CAG expansion in the TATA-binding protein (*TBP*) gene	Gait ataxia, dementia, parkinsonism, dystonia, chorea, seizures; hyperreflexia; dysarthria and dysphagia; MRI shows cerebral & cerebellar atrophy

(*Continued*)

TABLE 26-2 (*CONTINUED*)

CLASSIFICATION OF THE SPINOCEREBELLAR ATAXIAS

NAME	LOCUS	PHENOTYPE
SCA18 (autosomal dominant type 18)	7q22-q32	Ataxia; motor/sensory neuropathy; head tremor; dysarthria; extensor plantar responses in some patients; sensory axonal neuropathy; EMG denervation; MRI: cerebellar atrophy
SCA19 (autosomal dominant type 19)	1p21-q21	Ataxia, tremor, cognitive impairment, myoclonus; MRI: atrophy of cerebellum
SCA20 (assigned)	Chromosome 11	Dysarthria; gait ataxia; ocular gaze evoked saccades; palatal tremor; dentate calcification on CT; MRI: cerebral atrophy
SCA21 (autosomal dominant type 21)	7p21.3-p15.1	Ataxia, dysarthria, extrapyramidal features of akinesia, rigidity, tremor, cognitive defect; reduced deep tendon reflexes; MRI, cerebellar atrophy, normal basal ganglia and brainstem
SCA22 (autosomal dominant)	1p21-q23	Pure cerebellar ataxia; dysarthria; dysphagia; nystagmus; MRI: cerebellar atrophy
SCA23 (autosomal dominant)	20p13-12.3	Gait ataxia; dysarthria; extremity ataxia; ocular nystagmus, dysmetria; leg vibration loss; extensor plantar responses; MRI: cerebellar atrophy
SCA25 (autosomal dominant)	2p15-p21	Ataxia, nystagmus; vibratory loss in the feet; pain loss in some; abdominal pain; nausea and vomiting may be prominent; absent ankle reflexes; sensory nerve action potentials are absent; MRI: cerebellar atrophy, normal brainstem
SCA26 (autosomal dominant)	19p13.3	Gait ataxia; extremity ataxia; dysarthria; nystagmus; MRI: cerebellar atrophy
SCA27 (autosomal dominant)	13q34; fibroblast growth factor 14 protein; mutation F145S; produces reduced protein stability	Tremor extremities and head and orofacial dyskinesia; ataxia of arms>legs, gait ataxia; dysarthria; nystagmus; psychiatric symptoms; cognitive defect; MRI: cerebellar atrophy
SCA28 (autosomal dominant)	18p11.22-q11.2	Extremity and gait ataxia; dysarthria; nystagmus; ophthalmoparesis; leg hyperreflexia and extensor plantar responses; MRI: cerebellar atrophy
Dentatorubropal-lidoluysian atrophy (autosomal dominant)	12p13.31 with CAG repeats (exonic) Atrophin	Ataxia, choreoathetosis, dystonia, seizures, myoclonus, dementia
Friedreich's ataxia (autosomal recessive)	9q13-q21.1 with intronic GAA repeats, in intron at end of exon 1 Frataxin defective; abnormal regulation of mitochondrial iron metabolism; iron accumulates in mitochondria in yeast mutants	Ataxia, areflexia, extensor plantar responses, position sense deficits, cardiomyopathy, diabetes mellitus, scoliosis, foot deformities; optic atrophy; late onset form, as late as 50 years with preserved deep tendon reflexes, slower progression, reduced skeletal deformities, associated with an intermediate number of GAA repeats and missense mutations in one allele of frataxin
Friedreich's ataxia (autosomal recessive)	8q13.1-q13.3 (α-TTP deficiency)	Same as phenotype that maps to 9q but associated with vitamin E deficiency
Sensory ataxic neuropathy and ophthalmoparesis (SANDO) with dysarthria (autosomal recessive)	15q25; mutations in DNA polymerase-gamma (POLG) gene that leads to mtDNA deletions	Young-adult onset ataxia, sensory neuropathy, ophthalmoparesis, hearing loss, gastric symptoms; a variant of progressive external ophthalmoplegia; MRI: cerebellar and thalamic abnormalities; mildly increased lactate and creatine kinase
Von Hippel-Lindau syndrome (autosomal dominant)	3p26-p25	Cerebellar hemangioblastoma; pheochromocytoma
Baltic myoclonus (Unverricht-Lundborg recessive)	21q22.3; cystatin B; extra repeats of 12 base pair tandem repeats	Myoclonus epilepsy; late onset ataxia; responds to valproic acid, Clonazepam; phenobarbital

TABLE 26-2 (*CONTINUED*)

CLASSIFICATION OF THE SPINOCEREBELLAR ATAXIAS

NAME	LOCUS	PHENOTYPE
Marinesco-Sjogren syndrome (recessive)	5q31; SIL 1 protein, nucleotide exchange factor for the heat-shock protein 70 (HSP70); chaperone HSPA5; homozygous 4-nucleotide duplication in exon 6; also compound heterozygote	Ataxia, dysarthria; nystagmus; retarded motor and mental maturation; rhabdomyolysis after viral illness; weakness; hypotonia; areflexia; cataracts in childhood; short stature; kyphoscoliosis; contractures; hypogonadism
Autosomal recessive spastic ataxia of Charlevoix-Saguenay(ARSACS)	Chromosome 13q12; SACS gene; loss of Sacsin peptide activity	Childhood onset of ataxia, spasticity, dysarthria, distal muscle wasting, foot deformity, retinal striations, mitral valve prolapse
Kearns-Sayre syndrome (sporadic)	mtDNA deletion and duplication mutations	Ptosis, ophthalmoplegia, pigmentary retinal degeneration, cardiomyopathy, diabetes mellitus, deafness, heart block, increased CSF protein, ataxia
Myoclonic epilepsy and ragged red fiber syndrome (MERRF) (maternal inheritance)	Mutation in mtDNA of the $tRNA^{lys}$ at 8344; also mutation at 8356	Myoclonic epilepsy, ragged red fiber myopathy, ataxia
Mitochondrial encephalopathy, lactic acidosis, and stroke syndrome (MELAS) (maternal inheritance)	$tRNA^{leu}$ mutation at 3243; also at 3271 and 3252	Headache, stroke, lactic acidosis, ataxia
Neuropathy; ataxia; retinitis pigmentosa (NARP)	ATPase6 (Complex 5); mtDNA point mutation at 8993	Neuropathy; ataxia; retinitis pigmentosa; dementia; seizures
Episodic ataxia, type 1 (EA-1) (autosomal dominant)	12p13; potassium voltage-gated channel gene, *KCNA1*; Phe249Leu mutation; variable syndrome	Episodic ataxia for minutes; provoked by startle or exercise; with facial and hand myokymia; cerebellar signs are not progressive; choreoathetotic movements; responds to phenytoin
Episodic ataxia, type 2 (EA-2) (autosomal dominant)	19p-13(*CACNA1A*) (allelic with SCA6) (α_{1A}-voltage–dependent calcium channel subunit); point mutations or small deletions; allelic with SCA6 and familial hemiplegic migraine	Episodic ataxia for days; provoked by stress, fatigue; with down-gaze nystagmus; nystagmus; vertigo; vomiting; headache; cerebellar atrophy results; progressive cerebellar signs; responds to acetazolamide
Episodic ataxia, type 3 (autosomal dominant)	1q42	Episodic ataxia; 1 min. to over 6 hrs.; induced by movement; vertigo and tinnitus; headache; responds to acetazolamide
Episodic ataxia, type 4 (autosomal dominant)	Not mapped	Episodic ataxia; vertigo; diplopia; ocular slow pursuit defect; no response to acetazolamide
Episodic ataxia, type 5 (autosomal dominant)	2q22-q23; CACNB4β4 protein	Episodic ataxia; hours to weeks; seizures
Episodic ataxia, type 6	5p13; SLC1A3; glutamate transporter in astrocytes	Episodic ataxia; seizures; cognitive impairment; under 24 h
Episodic ataxia, type 7 (autosomal dominant)	19q13	Episodic ataxia; vertigo, weakness; less than 24 h
Episodic ataxia with seizures, migraine, and alternating hemiplegia (autosomal dominant)	SLC1A3; 5p13; EAAT1 protein; missense mutations; glial glutamate transporter (GLAST); 1047 C to G; proline to arginine	Ataxia, duration 2–4 days; episodic hypotonia; delayed motor milestones; seizures; migraine; alternating hemiplegia; mild truncal ataxia; coma; febrile illness as a trigger; MRI: cerebellar atrophy

(*Continued*)

TABLE 26-2 (*CONTINUED*)

CLASSIFICATION OF THE SPINOCEREBELLAR ATAXIAS

NAME	LOCUS	PHENOTYPE
Fragile X tremor/ ataxia syndrome (FXTAS) X-linked dominant	Xq27.3; CGG premutation expansion in FMR1 gene; expansions of 55–200 repeats in 5′ UTR of the FMR-1 mRNA; presumed dominant toxic RNA effect	Late onset ataxia with tremor, cognitive impairment, occasional parkinsonism; males typically affected, although affected females also reported; syndrome is of high concern if affected male has grandson with mental retardation; MRI shows increased T2 signal in middle cerebellar peduncles, cerebellar atrophy and occasional widespread brain atrophy
Ataxia telangiectasia (autosomal recessive)	11q22-23; *ATM* gene for regulation of cell cycle; mitogenic signal transduction and meiotic recombination	Telangiectasia, ataxia, dysarthria, pulmonary infections, neoplasms of lymphatic system; IgA and IgG deficiencies; diabetes mellitus, breast cancer
Early onset cerebellar ataxia with retained deep tendon reflexes (autosomal recessive)	13q11-12	Ataxia; neuropathy; preserved deep tendon reflexes; impaired cognitive and visuospatial functions; MRI: cerebellar atrophy
Ataxia with oculomotor apraxia (AOA1) (autosomal recessive)	9p13; protein is member of histidine triad superfamily, role in DNA repair	Ataxia; dysarthria; limb dysmetria; dystonia; oculomotor apraxia; optic atrophy; motor neuropathy; late sensory loss (vibration)
Ataxia with oculomotor apraxia 2 (AOA2) (autosomal recessive)	9q34; senataxin protein, involved in RNA maturation and termination; helicase superfamily 1	Gait ataxia; choreoathetosis; dystonia; oculomotor apraxia; neuropathy, vibration loss, position sense loss, and mild light touch loss; absent leg deep tendon reflexes; extensor plantar response
Cerebellar ataxia with muscle coenzyme Q10 deficiency (autosomal recessive)	9p13	Ataxia; hypotonia; seizures; mental retardation; increased deep tendon reflexes; extensor plantar responses; coenzyme Q10 levels reduced with about 25% of patients with a block in transfer of electrons to complex 3; may respond to coenzyme 10
Joubert syndrome (autosomal recessive)	9q34.3	Ataxia; ptosis; mental retardation; oculomotor apraxia; nystagmus; retinopathy; rhythmic tongue protrusion; episodic hyperpnea or apnea; dimples at wrists and elbows; telecanthus; micrognathia
Sideroblastic anemia and spinocerebellar ataxia (X-linked recessive)	Xq13; ATP-binding cassette 7 (ABCB7; ABC7) transporter; mitochondrial inner membrane; iron homeostasis; export from matrix to the intermembrane space	Ataxia; elevated free erythrocyte protoporphyrin levels; ring sideroblasts in bone marrow; heterozygous females may have mild anemia but not ataxia
Infantile-onset spinocerebellar ataxia of Nikali et al (autosomal recessive)	10q23.3-q24.1; twinkle protein (gene); homozygous for Tyr508Cys missense mutations	Infantile ataxia, sensory neuropathy; athetosis, hearing deficit, reduced deep tendon reflexes; ophthalmoplegia, optic atrophy; seizures; primary hypogonadism in females
Hypoceruloplasminemia with ataxia and dysarthria (autosomal recessive)	Ceruloplasmin gene; 3q23-q25 (trp 858 ter)	Gait ataxia and dysarthria; hyperreflexia; cerebellar atrophy by MRI; iron deposition in cerebellum, basal ganglia, thalamus, and liver; onset in the 4th decade
Spinocerebellar ataxia with neuropathy (SCAN1) (autosomal recessive)	Tryosyl-DNA phosphodiesterase-1 (TDP-1) 14q31-q32	Onset in 2nd decade; gait ataxia, dysarthria, seizures, cerebellar vermis atrophy on MRI, dysmetria

Note: MRI, magnetic resonance imaging; CSF, cerebrospinal fluid.

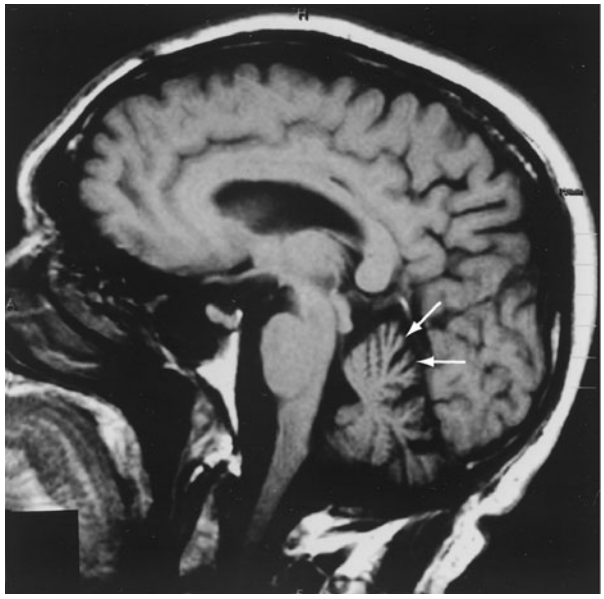

FIGURE 26-1
Sagittal MRI of the brain of a 60-year-old man with gait ataxia and dysarthria due to SCA1, illustrating cerebellar atrophy (*arrows*).

GENETIC CONSIDERATIONS

SCA1 encodes a gene product, called ataxin-1, which is a novel protein of unknown function. The mutant allele has 40 CAG repeats located within the coding region, whereas alleles from unaffected individuals have ≤36 repeats. A few patients with 38–40 CAG repeats have been described. There is a direct correlation between a larger number of repeats and a younger age of onset for SCA1. Juvenile patients have higher numbers of repeats, and anticipation is present in subsequent generations. Transgenic mice carrying SCA1 developed ataxia and Purkinje cell pathology. Nuclear localization, but not aggregation, of ataxin-1 appears to be required for cell death initiated by the mutant protein.

SCA2

Symptoms and Signs

Another clinical phenotype, SCA2, has been described in patients from Cuba and India. Cuban patients probably are descendants of a common ancestor, and the population may be the largest homogeneous group of patients with ataxia yet described. The age of onset ranges from 2 to 65 years, and there is considerable clinical variability within families. Although neuropathologic and clinical findings are compatible with a diagnosis of SCA1, including slow saccadic eye movements, ataxia, dysarthria, parkinsonian rigidity, optic disk pallor, mild spasticity, and retinal degeneration, SCA2 is a unique form of cerebellar degenerative disease.

GENETIC CONSIDERATIONS

The gene in SCA2 families also contains CAG repeat expansions coding for a polyglutamine-containing protein, ataxin-2. Normal alleles contain 15–32 repeats; mutant alleles have 35–77 repeats.

Machado-Joseph Disease/SCA3

MJD was first described among the Portuguese and their descendants in New England and California. Subsequently, MJD has been found in families from Portugal, Australia, Brazil, Canada, China, England, France, India, Israel, Italy, Japan, Spain, Taiwan, and the United States. In most populations, it is the most common autosomal dominant ataxia.

Symptoms and Signs

MJD has been classified into three clinical types. In type I MJD (amyotrophic lateral sclerosis–parkinsonism–dystonia type), neurologic deficits appear in the first two decades and involve weakness and spasticity of extremities, especially the legs, often with dystonia of the face, neck, trunk, and extremities. Patellar and ankle clonus are common, as are extensor plantar responses. The gait is slow and stiff, with a slightly broadened base and lurching from side to side; this gait results from spasticity, not true ataxia. There is no truncal titubation. Pharyngeal weakness and spasticity cause difficulty with speech and swallowing. Of note is the prominence of horizontal and vertical nystagmus, loss of fast saccadic eye movements, hypermetric and hypometric saccades, and impairment of upward vertical gaze. Facial fasciculations, facial myokymia, lingual fasciculations without atrophy, ophthalmoparesis, and ocular prominence are common early manifestations.

In type II MJD (ataxic type), true cerebellar deficits of dysarthria and gait and extremity ataxia begin in the second to fourth decades along with corticospinal and extrapyramidal deficits of spasticity, rigidity, and dystonia. Type II is the most common form of MJD. Ophthalmoparesis, upward vertical gaze deficits, and facial and lingual fasciculations are also present. Type II MJD can be distinguished from the clinically similar disorders SCA1 and SCA2.

Type III MJD (ataxic-amyotrophic type) presents in the fifth to the seventh decades with a pancerebellar disorder that includes dysarthria and gait and extremity ataxia. Distal sensory loss involving pain, touch, vibration, and position senses and distal atrophy are prominent, indicating the presence of peripheral neuropathy. The deep tendon reflexes are depressed to absent, and there are no corticospinal or extrapyramidal findings.

The mean age of onset of symptoms in MJD is 25 years. Neurologic deficits invariably progress and lead to death from debilitation within 15 years of onset, especially in patients with types I and II disease. Usually, patients retain full intellectual function.

The major pathologic findings are variable loss of neurons and glial replacement in the corpus striatum and severe loss of neurons in the pars compacta of the substantia nigra. A moderate loss of neurons occurs in the dentate nucleus of the cerebellum and in the red nucleus. Purkinje cell loss and granule cell loss occur in the cerebellar cortex. Cell loss also occurs in the dentate nucleus and in the cranial nerve motor nuclei. Sparing of the inferior olives distinguishes MJD from other dominantly inherited ataxias.

GENETIC CONSIDERATIONS

The gene for MJD maps to 14q24.3-q32. Unstable CAG repeat expansions are present in the MJD gene coding for a polyglutamine-containing protein named ataxin-3, or MJD-ataxin. An earlier age of onset is associated with longer repeats. Alleles from normal individuals have between 12 and 37 CAG repeats, while MJD alleles have 60–84 CAG repeats. Polyglutamine-containing aggregates of ataxin-3 (MJD-ataxin) have been described in neuronal nuclei undergoing degeneration. MJD ataxin codes for a ubiquitin protease, which is inactive due to expanded polyglutamines. Proteosome function is impaired, resulting in altered clearance of proteins and cerebellar neuronal loss.

SCA6

Genomic screening for CAG repeats in other families with autosomal dominant ataxia and vibratory and proprioceptive sensory loss have yielded another locus. Of interest is that different mutations in the same gene for the α_{1A} voltage-dependent calcium channel subunit (CACNLIA4; also referred to as the *CACNA1A* gene) at 19p13 result in different clinical disorders. CAG repeat expansions (21–27 in patients; 4–16 triplets in normal individuals) result in late-onset progressive ataxia with cerebellar degeneration. Missense mutations in this gene result in familial hemiplegic migraine. Nonsense mutations resulting in termination of protein synthesis of the gene product yield hereditary paroxysmal cerebellar ataxia or EA. Some patients with familial hemiplegic migraine develop progressive ataxia and also have cerebellar atrophy.

SCA7

This disorder is distinguished from all other SCAs by the presence of retinal pigmentary degeneration. The visual abnormalities first appear as blue-yellow color blindness and proceed to frank visual loss with macular degeneration. In almost all other respects, SCA7 resembles several other SCAs in which ataxia is accompanied by various noncerebellar findings, including ophthalmoparesis and extensor plantar responses. The genetic defect is an expanded CAG repeat in the SCA7 gene at 3p14-p21.1. The expanded repeat size in SCA7 is highly variable. Consistent with this, the severity of clinical findings varies from essentially asymptomatic to mild late-onset symptoms to severe, aggressive disease in childhood with rapid progression. Marked anticipation has been recorded, especially with paternal transmission. The disease protein, ataxin-7, forms aggregates in nuclei of affected neurons, as has also been described for SCA1 and SCA3/MJD.

SCA8

This form of ataxia is caused by a CTG repeat expansion in an untranslated region of a gene on chromosome 13q21. There is marked maternal bias in transmission, perhaps reflecting contractions of the repeat during spermatogenesis. The mutation is not fully penetrant. Symptoms include slowly progressive dysarthria and gait ataxia beginning at ~40 years of age with a range between 20 and 65 years. Other features include nystagmus, leg spasticity, and reduced vibratory sensation. Severely affected individuals are nonambulatory by the fourth to sixth decades. MRI shows cerebellar atrophy. The mechanism of disease may involve a dominant "toxic" effect occurring at the RNA level, as occurs in myotonic dystrophy.

Dentatorubropallidoluysian Atrophy

DRPLA has a variable presentation that may include progressive ataxia, choreoathetosis, dystonia, seizures, myoclonus, and dementia. DRPLA is due to unstable CAG triplet repeats in the open reading frame of a gene named *atrophin* located on chromosome 12p12-ter. Larger expansions are found in patients with earlier onset. The number of repeats is 49 in patients with DRPLA and ≤26 in normal individuals. Anticipation occurs in successive generations, with earlier onset of disease in association with an increasing CAG repeat number in children who inherit the disease from their father. One well-characterized family in North Carolina has a phenotypic variant known as the *Haw River syndrome*, now recognized to be due to the DRPLA mutation.

Episodic Ataxia

EA types 1 and 2 are two rare dominantly inherited disorders that have been mapped to chromosomes 12p (a potassium channel gene) for type 1 and 19p for type 2. Patients with EA-1 have brief episodes of ataxia with myokymia and nystagmus that last only minutes. Startle, sudden change in posture, and exercise can induce episodes. Acetazolamide or anticonvulsants may be therapeutic.

Patients with EA-2 have episodes of ataxia with nystagmus that can last for hours or days. Stress, exercise, or excessive fatigue may be precipitants. Acetazolamide may be therapeutic and can reverse the relative intracellular alkalosis detected by magnetic resonance spectroscopy. Stop codon, nonsense mutations causing EA-2 have been found in the *CACNA1A* gene, encoding the α_{1A} voltage-dependent calcium channel subunit (see "SCA6," above).

AUTOSOMAL RECESSIVE ATAXIAS

Friedreich's Ataxia

This is the most common form of inherited ataxia, comprising one-half of all hereditary ataxias. It can occur in a classic form or in association with a genetically determined vitamin E deficiency syndrome; the two forms are clinically indistinguishable.

Symptoms and Signs

Friedreich's ataxia presents before 25 years of age with progressive staggering gait, frequent falling, and titubation. The lower extremities are more severely involved than the upper ones. Dysarthria occasionally is the presenting symptom; rarely, progressive scoliosis, foot deformity, nystagmus, or cardiopathy is the initial sign.

The neurologic examination reveals nystagmus, loss of fast saccadic eye movements, truncal titubation, dysarthria, dysmetria, and ataxia of trunk and limb movements. Extensor plantar responses (with normal tone in trunk and extremities), absence of deep tendon reflexes, and weakness (greater distally than proximally) are usually found. Loss of vibratory and proprioceptive sensation occurs. The median age of death is 35 years. Women have a significantly better prognosis than men.

Cardiac involvement occurs in 90% of patients. Cardiomegaly, symmetric hypertrophy, murmurs, and conduction defects are reported. Moderate mental retardation or psychiatric syndromes are present in a small percentage of patients. A high incidence of diabetes mellitus (20%) is found and is associated with insulin resistance and pancreatic β-cell dysfunction. Musculoskeletal deformities are common and include pes cavus, pes equinovarus, and scoliosis. MRI of the spinal cord shows atrophy (**Fig. 26-2**).

The primary sites of pathology are the spinal cord, dorsal root ganglion cells, and the peripheral nerves. Slight atrophy of the cerebellum and cerebral gyri may occur. Sclerosis and degeneration occur predominantly in the spinocerebellar tracts, lateral corticospinal tracts, and posterior columns. Degeneration of the glossopharyngeal, vagus, hypoglossal, and deep cerebellar nuclei is described. The cerebral cortex is histologically normal except for loss of Betz cells in the precentral gyri. The peripheral nerves are extensively involved, with a loss of large myelinated fibers. Cardiac pathology consists of myocytic hypertrophy and fibrosis, focal vascular fibromuscular dysplasia with subintimal or medial deposition of periodic acid–Schiff (PAS)–positive material, myocytopathy with unusual pleomorphic nuclei, and focal degeneration of nerves and cardiac ganglia.

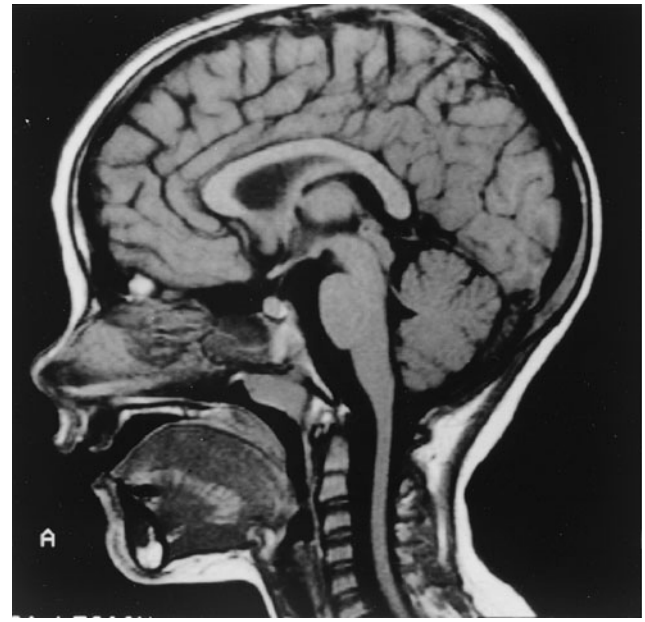

FIGURE 26-2
Sagittal MRI of the brain and spinal cord of a patient with Friedreich's ataxia, demonstrating spinal cord atrophy.

GENETIC CONSIDERATIONS

The classic form of Friedreich's ataxia has been mapped to 9q13-q21.1, and the mutant gene, *frataxin*, contains expanded GAA triplet repeats in the first intron. There is homozygosity for expanded GAA repeats in >95% of patients. Normal persons have 7–22 GAA repeats, and patients have 200–900 GAA repeats. A more varied clinical syndrome has been described in compound heterozygotes who have one copy of the GAA expansion and the other copy a point mutation in the *frataxin* gene. When the point mutation is located in the region of the gene that encodes the amino-terminal half of frataxin, the phenotype is milder, often consisting of a spastic gait, retained or exaggerated reflexes, no dysarthria, and mild or absent ataxia.

Patients with Friedreich's ataxia have undetectable or extremely low levels of *frataxin* mRNA, as compared with carriers and unrelated individuals; thus, disease appears to be caused by a loss of expression of the frataxin protein. Frataxin is a mitochondrial protein involved in iron homeostasis. Mitochondrial iron accumulation due to loss

of the iron transporter coded by the mutant *frataxin* gene results in oxidized intramitochondrial iron. Excess oxidized iron results in turn in the oxidation of cellular components and irreversible cell injury.

Two forms of hereditary ataxia associated with abnormalities in the interactions of vitamin E (α-tocopherol) with very low density lipoprotein (VLDL) have been delineated. These are abetalipoproteinemia (Bassen-Kornzweig syndrome) and ataxia with vitamin E deficiency (AVED). Abetalipoproteinemia is caused by mutations in the gene coding for the larger subunit of the microsomal triglyceride transfer protein (MTP). Defects in MTP result in impairment of formation and secretion of VLDL in liver. This defect results in a deficiency of delivery of vitamin E to tissues, including the central and peripheral nervous system, as VLDL is the transport molecule for vitamin E and other fat-soluble substitutes. AVED is due to mutations in the gene for α-tocopherol transfer protein (α-TTP). These patients have an impaired ability to bind vitamin E into the VLDL produced and secreted by the liver, resulting in a deficiency of vitamin E in peripheral tissues. Hence, either absence of VLDL (abetalipoproteinemia) or impaired binding of vitamin E to VLDL (AVED) causes an ataxic syndrome. Once again, a genotype classification has proved to be essential in sorting out the various forms of the Friedreich's disease syndrome, which may be clinically indistinguishable.

Ataxia Telangiectasia

Symptoms and Signs

Patients with ataxia telangiectasia (AT) present in the first decade of life with progressive telangiectatic lesions associated with deficits in cerebellar function and nystagmus. The neurologic manifestations correspond to those in Friedreich's disease, which should be included in the differential diagnosis. Truncal and limb ataxia, dysarthria, extensor plantar responses, myoclonic jerks, areflexia, and distal sensory deficits may develop. There is a high incidence of recurrent pulmonary infections and neoplasms of the lymphatic and reticuloendothelial system in patients with AT. Thymic hypoplasia with cellular and humoral (IgA and IgG2) immunodeficiencies, premature aging, and endocrine disorders such as type 1 diabetes mellitus are described. There is an increased incidence of lymphomas, Hodgkin's disease, acute leukemias of the T cell type, and breast cancer.

The most striking neuropathologic changes include loss of Purkinje, granule, and basket cells in the cerebellar cortex as well as of neurons in the deep cerebellar nuclei. The inferior olives of the medulla may also have neuronal loss. There is a loss of anterior horn neurons in the spinal cord and of dorsal root ganglion cells associated with posterior column spinal cord demyelination. A poorly developed or absent thymus gland is the most consistent defect of the lymphoid system.

GENETIC CONSIDERATIONS

The gene for AT (the *ATM* gene) encodes a protein that is similar to several yeast and mammalian phosphatidylinositol-3′-kinases involved in mitogenic signal transduction, meiotic recombination, and cell cycle control. Defective DNA repair in AT fibroblasts exposed to ultraviolet light has been demonstrated. The discovery of *ATM* will make possible the identification of heterozygotes who are at risk for cancer (e.g., breast cancer) and permit early diagnosis.

Mitochondrial Ataxias

Spinocerebellar syndromes have been identified with mutations in mitochondrial DNA (mtDNA). Thirty pathogenic mtDNA point mutations and 60 different types of mtDNA deletions are known, several of which cause or are associated with ataxia (Chap. 43).

℞ Treatment: ATAXIC DISORDERS

The most important goal in management of patients with ataxia is to identify treatable disease entities. Mass lesions must be recognized promptly and treated appropriately. Paraneoplastic disorders can often be identified by the clinical patterns of disease that they produce, measurement of specific autoantibodies, and uncovering the primary cancer; these disorders are often refractory to therapy, but some patients improve following removal of the tumor or immunotherapy (Chap. 39). Ataxia with antigliadin antibodies and gluten-sensitive enteropathy may improve with a gluten-free diet. Malabsorption syndromes leading to vitamin E deficiency may lead to ataxia. The vitamin E deficiency form of Friedreich's ataxia must be considered, and serum vitamin E levels measured. Vitamin E therapy is indicated for these rare patients. Vitamin B_1 and B_{12} levels in serum should be measured, and the vitamins administered to patients having deficient levels. Hypothyroidism is easily treated. The cerebrospinal fluid should be tested for a syphilitic infection in patients with progressive ataxia and other features of tabes dorsalis. Similarly, antibody titers for Lyme disease and *Legionella* should be measured and appropriate antibiotic therapy should be instituted in antibody-positive patients. Aminoacidopathies, leukodystrophies, urea-cycle abnormalities, and mitochondrial encephalomyopathies

may produce ataxia, and some dietary or metabolic therapies are available for these disorders. The deleterious effects of diphenylhydantoin and alcohol on the cerebellum are well known and these exposures should be avoided in patients with ataxia of any cause.

There is no proven therapy for any of the autosomal dominant ataxias (SCA1 to -28). There is preliminary evidence that idebenone, a free-radical scavenger, can improve myocardial hypertrophy in patients with classic Friedreich ataxia; there is no current evidence, however, that it improves neurologic function. Iron chelators and antioxidant drugs are potentially harmful in Friedreich's patients as they may increase heart muscle injury. Acetazolamide can reduce the duration of symptoms of episodic ataxia. At present, identification of an at-risk person's genotype, together with appropriate family and genetic counseling, can reduce the incidence of these cerebellar syndromes in future generations.

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CHAPTER 27

AMYOTROPHIC LATERAL SCLEROSIS AND OTHER MOTOR NEURON DISEASES

Robert H. Brown, Jr.

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AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is the most common form of progressive motor neuron disease. It is a prime example of a neurodegenerative disease and is arguably the most devastating of the neurodegenerative disorders.

Pathology

The pathologic hallmark of motor neuron degenerative disorders is death of lower motor neurons (consisting of anterior horn cells in the spinal cord and their brainstem homologues innervating bulbar muscles) and upper, or corticospinal, motor neurons (originating in layer five of the motor cortex and descending via the pyramidal tract to synapse with lower motor neurons, either directly or indirectly via interneurons) (Chap. 10). Although at its onset ALS may involve selective loss of function of only upper or lower motor neurons, it ultimately causes progressive loss of both categories of motor neurons. Indeed, in the absence of clear involvement of both motor neuron types, the diagnosis of ALS is questionable.

Other motor neuron diseases involve only particular subsets of motor neurons (**Tables 27-1** and **27-2**). Thus, in bulbar palsy and spinal muscular atrophy (SMA; also called progressive muscular atrophy), the lower motor neurons of brainstem and spinal cord, respectively, are most severely involved. By contrast, pseudobulbar palsy, primary lateral sclerosis (PLS), and familial spastic paraplegia (FSP) affect only upper motor neurons innervating the brainstem and spinal cord.

In each of these diseases, the affected motor neurons undergo shrinkage, often with accumulation of the pigmented lipid (lipofuscin) that normally develops in these cells with advancing age. In ALS, the motor neuron cytoskeleton is typically affected early in the illness. Focal enlargements are frequent in proximal motor axons; ultrastructurally, these "spheroids" are composed of accumulations of neurofilaments and other proteins. Also seen is proliferation of astroglia and microglia, the inevitable accompaniment of all degenerative processes in the central nervous system (CNS).

The death of the peripheral motor neurons in the brainstem and spinal cord leads to denervation and consequent atrophy of the corresponding muscle fibers. Histochemical and electrophysiologic evidence indicates that in the early phases of the illness denervated muscle can be reinnervated by sprouting of nearby distal motor nerve terminals, although reinnervation in this disease is considerably less extensive than in most other disorders affecting motor neurons (e.g., poliomyelitis, peripheral neuropathy). As denervation progresses, muscle atrophy is readily recognized in muscle biopsies and on clinical examination. This is the basis for the term *amyotrophy*. The loss of cortical motor neurons results in thinning of the corticospinal tracts that travel via the internal capsule (**Fig. 27-1**) and brainstem to the lateral and anterior white matter columns of the spinal cord. The loss of

TABLE 27-1

ETIOLOGY AND INVESTIGATION OF MOTOR NEURON DISORDERS

DIAGNOSTIC CATEGORY	INVESTIGATIONS
Structural lesions	MRI scan of head (including foramen magnum), cervical spine[a]
Parasagittal or foramen magnum tumors	
Cervical spondylosis	
Chiari malformation or syrinx	
Spinal cord arteriovenous malformation	
Infections	CSF exam, culture[a]
Bacterial—tetanus, Lyme	Lyme antibody titer[a]
Viral—poliomyelitis, herpes zoster	Antiviral antibody titers
Retroviral myelopathy	HTLV-I titers
Intoxications, physical agents	
Toxins—lead, aluminum, others	24-h urine for heavy metals[a]
Drugs—strychnine, phenytoin	Serum for lead level[a]
Electric shock, x-irradiation	
Immunologic mechanisms	Complete blood count[a]
Plasma cell dyscrasias	Sedimentation rate[a]
Autoimmune polyradiculoneuropathy	Protein immunoelectrophoresis[a]
Motor neuropathy with conduction block	Anti-GM1 antibodies[a]
Paraneoplastic	Anti-Hu antibody
Paracarcinomatous/lymphoma	MRI scan, bone marrow biopsy
Metabolic	
Hypoglycemia	Fasting blood sugar (FBS), routine chemistries including calcium[a]
Hyperparathyroidism	PTH, calcium, phosphate
Hyperthyroidism	Thyroid function[a]
Deficiency of folate, vitamin B_{12}, vitamin E	Vitamin B_{12}, vitamin E, folate levels[a]
Malabsorption	24-h stool fat, carotene, prothrombin time
Mitochondrial dysfunction	Fasting lactate, pyruvate, ammonia Consider mtDNA analysis
Hereditary biochemical disorders	
Superoxide dismutase 1 gene mutation	White blood cell DNA analysis
Androgen receptor defect (Kennedy's disease)	Abnormal CAG insert in androgen receptor gene
Hexosaminidase deficiency	Lysosomal enzyme screen
Infantile (α-glucosidase deficiency/ Pompe's disease)	α-glucosidase level
Hyperlipidemia	Lipid electrophoresis
Hyperglycinuria	Urine and serum amino acids
Methylcrotonylglycinuria	CSF amino acids

[a]Denotes studies that should be obtained in all cases.
Note: CSF, cerebrospinal fluid; HTLV, human T cell lymphotropic virus; PTH, parathyroid hormone.

fibers in the lateral columns and resulting fibrillary gliosis impart a particular firmness (*lateral sclerosis*). A remarkable feature of the disease is the selectivity of neuronal cell death. By light microscopy, the entire sensory apparatus, the regulatory mechanisms for the control and coordination of movement, and the components of the brain that are needed for cognitive processes, remain intact. However, immunostaining indicates that neurons bearing ubiquitin, a marker for degeneration, are also detected in nonmotor systems. Moreover, studies of glucose metabolism in the illness also indicate that there is neuronal dysfunction outside of the motor system. Within the motor system, there is some selectivity of involvement. Thus, motor neurons required for ocular motility remain unaffected, as do the parasympathetic neurons in the sacral spinal cord (the nucleus of Onufrowicz, or Onuf) that innervate the sphincters of the bowel and bladder.

Clinical Manifestations

The manifestations of ALS are somewhat variable depending on whether corticospinal neurons or lower motor neurons in the brainstem and spinal cord are more prominently involved. With lower motor neuron dysfunction

TABLE 27-2

SPORADIC MOTOR NEURON DISEASES
Chronic
Upper and lower motor neurons
Amyotrophic lateral sclerosis
Predominantly upper motor neurons
Primary lateral sclerosis
Predominantly lower motor neurons
Multifocal motor neuropathy with conduction block
Motor neuropathy with paraproteinemia or cancer
Motor-predominant peripheral neuropathies
Other
Associated with other degenerative disorders
Secondary motor neuron disorders (see Table 27-1)
Acute
Poliomyelitis
Herpes zoster
Coxsackie virus

and early denervation, typically the first evidence of the disease is insidiously developing asymmetric weakness, usually first evident distally in one of the limbs. A detailed history often discloses recent development of cramping with volitional movements, typically in the early hours of the morning (e.g., while stretching in bed). Weakness caused by denervation is associated with progressive wasting and atrophy of muscles and, particularly early in the illness, spontaneous twitching of motor units, or fasciculations. In the hands, a preponderance of extensor over flexor weakness is common. When the initial denervation involves bulbar rather than limb muscles, the problem at onset is difficulty with chewing, swallowing, and movements of the face and tongue. Early involvement of the muscles of respiration may lead to death before the disease is far advanced elsewhere. With prominent corticospinal involvement, there is hyperactivity of the muscle-stretch reflexes (tendon jerks) and, often, spastic resistance to passive movements of the affected limbs. Patients with significant reflex hyperactivity complain of muscle stiffness often out of proportion to weakness. Degeneration of the corticobulbar projections innervating the brainstem results in dysarthria and exaggeration of the motor expressions of emotion. The latter leads to involuntary excess in weeping or laughing (so-called pseudobulbar affect).

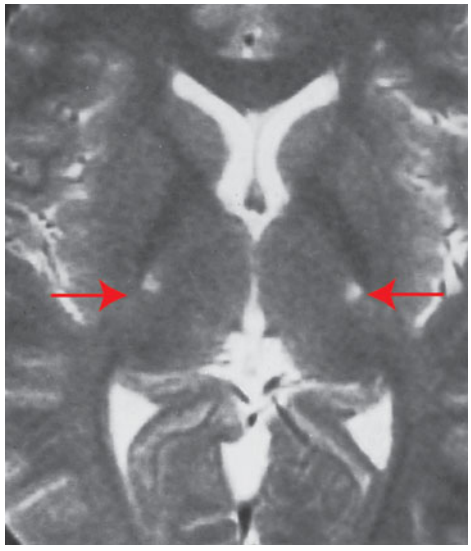

FIGURE 27-1

Amyotrophic lateral sclerosis. Axial T2-weighted MRI scan through the lateral ventricles of the brain reveals abnormal high signal intensity within the corticospinal tracts (*arrows*). This MRI feature represents an increase in water content in myelin tracts undergoing Wallerian degeneration secondary to cortical motor neuronal loss. This finding is commonly present in ALS, but can also be seen in AIDS-related encephalopathy, infarction, or other disease processes that produce corticospinal neuronal loss in a symmetric fashion.

Virtually any muscle group may be the first to show signs of disease, but, as time passes, more and more muscles become involved until ultimately the disorder takes on a symmetric distribution in all regions. It is characteristic of ALS that, regardless of whether the initial disease involves upper or lower motor neurons, both will eventually be implicated. Even in the late stages of the illness, sensory, bowel and bladder, and cognitive functions are preserved. Even when there is severe brainstem disease, ocular motility is spared until the very late stages of the illness. Dementia is not a component of sporadic ALS. In some families, ALS is co-inherited with frontotemporal dementia, characterized by early behavioral abnormalities with prominent behavioral features indicative of frontal lobe dysfunction.

A committee of the World Federation of Neurology has established diagnostic guidelines for ALS. Essential for the diagnosis is simultaneous upper and lower motor neuron involvement with progressive weakness, and the exclusion of all alternative diagnoses. The disorder is ranked as "definite" ALS when three or four of the following are involved: bulbar, cervical, thoracic, and lumbosacral motor neurons. When two sites are involved, the diagnosis is "probable," and when only one site is implicated, the diagnosis is "possible." An exception is made for those who have progressive upper and lower motor neuron signs at only one site and a mutation in the gene encoding superoxide dismutase (SOD1; later).

Epidemiology

The illness is relentlessly progressive, leading to death from respiratory paralysis; the median survival is from 3–5 years. There are very rare reports of stabilization or even regression of ALS. In most societies there is an incidence of 1–3 per 100,000 and a prevalence of 3–5 per 100,000. Several endemic foci of higher prevalence

exist in the western Pacific (e.g., in specific regions of Guam or Papua New Guinea). In the United States and Europe, males are somewhat more frequently affected than females. Epidemiologic studies have incriminated risk factors for this disease including exposure to pesticides and insecticides, smoking and, in one report, service in the military. While ALS is overwhelmingly a sporadic disorder, some 5–10% of cases are inherited as an autosomal dominant trait.

Familial ALS

Several forms of selective motor neuron disease are inheritable (Table 27-3). Two involve both corticospinal and lower motor neurons. The most common is familial ALS (FALS). Apart from its inheritance as an autosomal dominant trait, it is clinically indistinguishable from sporadic ALS. Genetic studies have identified mutations in the gene encoding the cytosolic, copper- and zinc-binding enzyme SOD1 as the cause of one form of FALS. However, this accounts for only 20% of inherited cases of ALS.

Rare mutations in other genes are also clearly implicated in ALS-like diseases. Thus, a familial, dominantly inherited motor disorder that in some individuals closely mimics the ALS phenotype arises from mutations in a gene that encodes a vesicle-binding protein. A predominantly lower motor neuron disease with early hoarseness due to laryngeal dysfunction has been ascribed to mutations in the gene encoding the cellular motor protein dynactin. Mutations in senataxin, a helicase, cause an early adult-onset, slowly evolving ALS variant. Kennedy's syndrome is an X-linked, adult-onset disorder that may mimic ALS, as described below.

Genetic analyses are also beginning to illuminate the pathogenesis of some childhood-onset motor neuron diseases. For example, a slowly disabling degenerative,

TABLE 27-3

GENETIC MOTOR NEURON DISEASES

DISEASE	LOCUS	GENE
I. Upper and lower motor neurons (familial ALS)		
A. Autosomal dominant	2p	Dynactin
	9q	Senataxin
	20q	Vesicle-associated protein B
	21q	Superoxide dismutase
	22q	Neurofilament heavy chain
B. Autosomal recessive	2q	Alsin
C. Mitochondrial	mtDNA	Cytochrome c oxidase
	mtDNA	tRNA-isoleucine
II. Lower motor neurons		
A. Spinal muscular atrophies	5q	Survival motor neuron protein
B. X-linked spinobulbar muscular atrophy	Xq	Androgen receptor
C. GM2 gangliosidosis		
1. Sandhoff disease	5q	Hexosaminidase B
2. AB variant	5q	GM2 activator protein
3. Adult Tay-Sach's disease	15q	Hexosaminidase A
III. Upper motor neuron (selected FSP's)		
A. Autosomal dominant	2p	Spastin
	11q	BSCL2
	12q	Kinesin heavy-chain KIF5A
	14q	Atlastin
	15q	NIPA1
B. Autosomal recessive	13q	Spartin
	15q	Maspardin
	16q	Paraplegin
C. X-linked	Xq	Proteolipid protein
	Xq	L1-CAM
D. Adrenomyeloneuropathy	Xq	Adrenoleukodystrophy protein
IV. ALS-plus syndromes		
Amyotrophy with behavioral disorder and Parkinsonism	17q	Tau protein

Note: ALS, amyotrophic lateral sclerosis; BSCL2, Bernadelli-Seip congenital lipodystrophy, 2B; FSP, familial spastic paraplegia

predominantly upper motor neuron disease that starts in the first decade is caused by mutations in a gene that expresses a novel signaling molecule with properties of a guanine-exchange factor, termed *alsin*.

Differential Diagnosis

Because ALS is currently untreatable, it is imperative that potentially remediable causes of motor neuron dysfunction be excluded (Table 27-1). This is particularly true in cases that are atypical by virtue of (1) restriction to either upper or lower motor neurons, (2) involvement of neurons other than motor neurons, and (3) evidence of motor neuronal conduction block on electrophysiologic testing. Compression of the cervical spinal cord or cervicomedullary junction from tumors in the cervical regions or at the foramen magnum or from cervical spondylosis with osteophytes projecting into the vertebral canal can produce weakness, wasting, and fasciculations in the upper limbs and spasticity in the legs, closely resembling ALS. The absence of cranial nerve involvement may be helpful in differentiation, although some foramen magnum lesions may compress the twelfth cranial (hypoglossal) nerve, with resulting paralysis of the tongue. Absence of pain or of sensory changes, normal bowel and bladder function, normal roentgenographic studies of the spine, and normal cerebrospinal fluid (CSF) all favor ALS. Where doubt exists, MRI scans and contrast myelography should be performed to visualize the cervical spinal cord.

Another important entity in the differential diagnosis of ALS is *multifocal motor neuropathy with conduction block* (MMCB), discussed later. A diffuse, lower motor axonal neuropathy mimicking ALS sometimes evolves in association with hematopoietic disorders such as lymphoma or multiple myeloma. In this clinical setting, the presence of an M-component in serum should prompt consideration of a bone marrow biopsy. Lyme disease may also cause an axonal, lower motor neuropathy, although typically with intense proximal limb pain and a CSF pleocytosis.

Other treatable disorders that occasionally mimic ALS are chronic lead poisoning and thyrotoxicosis. These disorders may be suggested by the patient's social or occupational history or by unusual clinical features. When the family history is positive, disorders involving the genes encoding cytosolic SOD1, hexosaminidase A, or α-glucosidase deficiency must be excluded. These are readily identified by appropriate laboratory tests. Benign fasciculations are occasionally a source of concern because on inspection they resemble the fascicular twitching that accompany motor neuron degeneration. The absence of weakness, atrophy, or denervation phenomena on electrophysiologic examination usually excludes ALS or other serious neurologic disease. Patients who have recovered from poliomyelitis may experience a delayed deterioration of motor neurons that presents clinically with progressive weakness, atrophy, and fasciculations. Its cause is unknown, but it is thought to reflect sublethal prior injury to motor neurons by poliovirus.

Rarely, ALS develops concurrently with features indicative of more widespread neurodegeneration. Thus, one infrequently encounters otherwise typical ALS patients with a parkinsonian movement disorder or dementia. It remains unclear whether this reflects the unlikely simultaneous occurrence of two disorders or a primary defect triggering two forms of neurodegeneration. The latter is suggested by the observation that multisystem neurodegenerative diseases may be inherited. For example, prominent amyotrophy has been described as a dominantly inherited disorder in individuals with bizarre behavior and a movement disorder suggestive of parkinsonism; many such cases have now been ascribed to mutations that alter the expression of tau protein in brain (Chap. 23). In other cases, ALS develops simultaneously with a striking frontotemporal dementia. These disorders may be dominantly co-inherited; in some families, this trait is linked to a locus on chromosome 9p, although the underlying genetic defect is not established.

Pathogenesis

The cause of sporadic ALS is not well defined. Several mechanisms that impair motor neuron viability have been elucidated in mice and rats induced to develop motor neuron disease by SOD1 transgenes with ALS-associated mutations. It is evident that excitotoxic neurotransmitters such as glutamate participate in the death of motor neurons in ALS. This may be a consequence of diminished uptake of synaptic glutamate by an astroglial glutamate transporter, EAAT2. It is striking that one cellular defense against such excitotoxicity is the enzyme SOD1, which detoxifies the free radical superoxide anion (Chap. 19). Precisely why the SOD1 mutations are toxic to motor nerves is not established, although it is clear the effect is not simply loss of normal scavenging of the superoxide anion. The mutant protein is conformationally unstable and prone to aberrant catalytic reactions. In turn, these features lead to aggregation of SOD1 protein, impairment of axonal transport, reduced production of ATP and other perturbations of mitochondrial function, activation of neuroinflammatory cascades within the ALS spinal cord, and ultimately induction of cell death via pathways that are at least partially dependent on caspases. Multiple recent studies have convincingly demonstrated that nonneuronal cells importantly influence the disease course, at least in ALS transgenic mice.

℞ Treatment: AMYOTROPHIC LATERAL SCLEROSIS

No treatment arrests the underlying pathologic process in ALS. The drug riluzole (100 mg/d) was approved for ALS because it produces a modest lengthening of

survival. In one trial, the survival rate at 18 months with riluzole was similar to placebo at 15 months. The mechanism of this effect is not known with certainty; riluzole may reduce excitotoxicity by diminishing glutamate release. Riluzole is generally well tolerated; nausea, dizziness, weight loss, and elevated liver enzymes occur occasionally. Pathophysiologic studies of mutant SOD1–related ALS in mice have disclosed diverse targets for therapy; consequently, multiple therapies are presently in clinical trails in ALS. These include studies of insulin-like growth factor I (IGF-I), which produced inconsistent results in ALS patients and is now undergoing further clinical trials and ceftriaxone, which may augment astroglial glutamate transport and thereby be anti-excitotoxic. Interventions such as antisense oligonucleotides (ASO) or inhibitory RNA that diminish expression of mutant SOD1 protein prolong survival in transgenic ALS mice and rats. Based on these data, a human trial of ASO is planned in SOD1-mediated ALS.

In the absence of a primary therapy for ALS, a variety of rehabilitative aids may substantially assist ALS patients. Foot-drop splints facilitate ambulation by obviating the need for excessive hip flexion and by preventing tripping on a floppy foot. Finger extension splints can potentiate grip. Respiratory support may be life-sustaining. For patients electing against long-term ventilation by tracheostomy, positive-pressure ventilation by mouth or nose provides transient (several weeks) relief from hypercarbia and hypoxia. Also extremely beneficial for some patients is a respiratory device (Cough Assist Device) that produces an artificial cough. This is highly effective in clearing airways and preventing aspiration pneumonia. When bulbar disease prevents normal chewing and swallowing, gastrostomy is uniformly helpful, restoring normal nutrition and hydration. Fortunately, an increasing variety of speech synthesizers are now available to augment speech when there is advanced bulbar palsy. These facilitate oral communication and may be effective for telephone use.

In contrast to ALS, several of the disorders (Tables 27-1 and 27-3) that bear some clinical resemblance to ALS are treatable. For this reason, a careful search for causes of secondary motor neuron disease is warranted.

OTHER MOTOR NEURON DISEASES

SELECTED LOWER MOTOR NEURON DISORDERS

In these motor neuron diseases, the peripheral motor neurons are affected without evidence of involvement of the corticospinal motor system (Tables 27-1 to 27-3).

X-Linked Spinobulbar Muscular Atrophy (Kennedy's Disease)

This is an X-linked lower motor neuron disorder in which progressive weakness and wasting of limb and bulbar muscles begins in males in mid-adult life and is conjoined with androgen insensitivity manifested by gynecomastia and reduced fertility. In addition to gynecomastia, which may be subtle, two findings distinguishing this disorder from ALS are the absence of signs of pyramidal tract disease (spasticity) and the presence of a subtle sensory neuropathy in some patients. The underlying molecular defect is an expanded trinucleotide repeat (-CAG-) in the first exon of the androgen receptor gene on the X chromosome. DNA testing is available. An inverse correlation appears to exist between the number of -CAG- repeats and the age of onset of the disease.

Adult Tay-Sach's Disease

Several reports have described adult-onset, predominantly lower motor neuropathies arising from deficiency of the enzyme β-hexosaminidase (hex A). These tend to be distinguishable from ALS because they are very slowly progressive; dysarthria and radiographically evident cerebellar atrophy may be prominent. In rare cases, spasticity may also be present, although it is generally absent.

Spinal Muscular Atrophy

The SMAs are a family of selective lower motor neuron diseases of early onset. Despite some phenotypic variability (largely in age of onset), the defect in the majority of families with SMA maps to a locus on chromosome 5 encoding a putative motor neuron survival protein (SMN, for survival motor neuron) that is important in the formation and trafficking of RNA complexes across the nuclear membrane. Neuropathologically these disorders are characterized by extensive loss of large motor neurons; muscle biopsy reveals evidence of denervation atrophy. Several clinical forms exist.

Infantile SMA (SMA I, Werdnig-Hoffmann disease) has the earliest onset and most rapidly fatal course. In some instances it is apparent even before birth, as indicated by decreased fetal movements late in the third trimester. Although alert, afflicted infants are weak and floppy (hypotonic) and lack muscle stretch reflexes. Death generally ensues within the first year of life. *Chronic childhood SMA* (SMA II) begins later in childhood and evolves with a more slowly progressive course. *Juvenile SMA* (SMA III, Kugelberg-Welander disease) manifests during late childhood and runs a slow, indolent course. Unlike most denervating diseases, in this chronic disorder weakness is greatest in the proximal muscles; indeed, the pattern of clinical weakness can suggest a primary myopathy such as limb-girdle dystrophy. Electrophysiologic and muscle biopsy evidence of denervation distinguish SMA III from the myopathic syndromes.

Multifocal Motor Neuropathy with Conduction Block

In this disorder lower motor neuron function is regionally and chronically disrupted by remarkably focal blocks in conduction. Many cases have elevated serum titers of mono- and polyclonal antibodies to ganglioside GM1; it is hypothesized that the antibodies produce selective, focal, paranodal demyelination of motor neurons. MMCB is not typically associated with corticospinal signs. In contrast with ALS, MMCB may respond dramatically to therapy such as IV immunoglobulin or chemotherapy; it is thus imperative that MMCB be excluded when considering a diagnosis of ALS.

Other Forms of Lower Motor Neuron Disease

In individual families, other syndromes characterized by selective lower motor neuron dysfunction in an SMA-like pattern have been described. There are rare X-linked and autosomal dominant forms of apparent SMA. There is an ALS variant of juvenile onset, the Fazio-Londe syndrome, that involves mainly the musculature innervated by the brainstem. A component of lower motor neuron dysfunction is also found in degenerative disorders such as Machado-Joseph disease and the related olivopontocerebellar degenerations (Chap. 26).

SELECTED DISORDERS OF THE UPPER MOTOR NEURON

Primary Lateral Sclerosis

This exceedingly rare disorder arises sporadically in adults in mid- to late life. Clinically PLS is characterized by progressive spastic weakness of the limbs, preceded or followed by spastic dysarthria and dysphagia, indicating combined involvement of the corticospinal and corticobulbar tracts. Fasciculations, amyotrophy, and sensory changes are absent; neither electromyography nor muscle biopsy shows denervation. On neuropathologic examination there is selective loss of the large pyramidal cells in the precentral gyrus and degeneration of the corticospinal and corticobulbar projections. The peripheral motor neurons and other neuronal systems are spared. The course of PLS is variable; while long-term survival is documented, the course may be as aggressive as in ALS, with ~3-year survival from onset to death. Early in its course, PLS raises the question of multiple sclerosis or other demyelinating diseases such as adrenoleukodystrophy as diagnostic considerations (Chap. 34). A myelopathy suggestive of PLS is infrequently seen with infection with the retrovirus human T cell lymphotropic virus (HTLV-I) (Chap. 30). The clinical course and laboratory testing will distinguish these possibilities.

Familial Spastic Paraplegia

In its pure form, FSP is usually transmitted as an autosomal trait; most adult-onset cases are dominantly inherited. Symptoms usually begin in the third or fourth decade, presenting as progressive spastic weakness beginning in the distal lower extremities; however, there are variants with onset so early that the differential diagnosis includes cerebral palsy. FSP typically has a long survival, presumably because respiratory function is spared. Late in the illness there may be urinary urgency and incontinence and sometimes fecal incontinence; sexual function tends to be preserved.

In pure forms of FSP, the spastic leg weakness is often accompanied by posterior column sensory loss and disturbance of bowel and bladder function. Some family members may have spasticity without clinical symptoms.

By contrast, particularly when recessively inherited, FSP may have complex or complicated forms in which altered corticospinal and dorsal column function is accompanied by significant involvement of other regions of the nervous system, including amyotrophy, mental retardation, optic atrophy, and sensory neuropathy.

Neuropathologically, in FSP there is degeneration of the corticospinal tracts, which appear nearly normal in the brainstem but show increasing atrophy at more caudal levels in the spinal cord; in effect, the pathologic picture is of a dying-back or distal axonopathy of long neuronal fibers within the CNS.

Defects at numerous loci underlie both dominantly and recessively inherited forms of FSP (Table 27-3). Eleven FSP genes have now been identified. The gene most commonly implicated in dominantly inherited FSP is *spastin,* which encodes a microtubule interacting protein. The most common childhood-onset dominant form arises from mutations in the *atlastin* gene. A kinesin heavy-chain protein implicated in microtubule motor function was found to be defective in a family with dominantly inherited FSP of variable onset age.

An infantile-onset form of X-linked, recessive FSP arises from mutations in the gene for myelin proteolipid protein (Chap. 19). This is an example of rather striking allelic variation, as most other mutations in the same gene cause not FSP but Pelizaeus-Merzbacher disease, a widespread disorder of CNS myelin. Another recessive variant is caused by defects in the *paraplegin* gene. Paraplegin has homology to metalloproteases that are important in mitochondrial function in yeast.

WEB SITES

Several web sites provide valuable information on ALS including those offered by the Muscular Dystrophy Association (*www.mdausa.org*), the Amyotrophic Lateral Sclerosis Association (*www.alsa.org*), and the World Federation of Neurology and the Neuromuscular Unit at

Washington University in St. Louis (*www.neuro.wustl. edu/neuromuscular*).

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CHAPTER 28
DISORDERS OF THE AUTONOMIC NERVOUS SYSTEM

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The autonomic nervous system (ANS) innervates the entire neuraxis and permeates all organ systems. It regulates blood pressure (BP), heart rate, sleep, and bladder and bowel function. It operates automatically; its full importance becomes recognized only when ANS function is compromised, resulting in dysautonomia. Hypothalamic disorders that cause disturbances in homeostasis are discussed in Chap. 33.

ANATOMIC ORGANIZATION

The activity of the ANS is regulated by central neurons responsive to diverse afferent inputs. After central integration of afferent information, autonomic outflow is adjusted to permit the functioning of the major organ systems in accordance with the needs of the organism as a whole. Connections between the cerebral cortex and the autonomic centers in the brainstem coordinate autonomic outflow with higher mental functions.

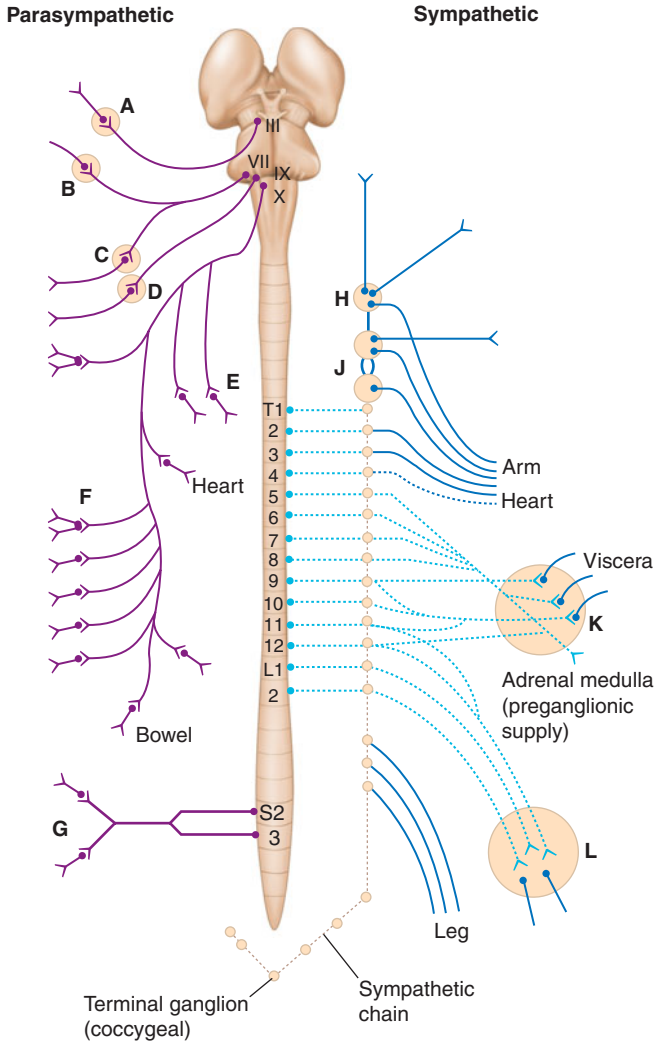
The preganglionic neurons of the parasympathetic nervous system leave the central nervous system (CNS) in the third, seventh, ninth, and tenth cranial nerves as well as the second and third sacral nerves, while the preganglionic neurons of the sympathetic nervous system exit the spinal cord between the first thoracic and the second lumbar segments (**Fig. 28-1**). The postganglionic neurons, located in ganglia outside the CNS, give rise to the postganglionic autonomic nerves that innervate organs and tissues throughout the body. Responses to sympathetic and parasympathetic stimulation are frequently antagonistic (**Table 28-1**), reflecting highly coordinated interactions within the CNS; the resultant changes in parasympathetic and sympathetic activity provide more precise control of autonomic responses than could be achieved by the modulation of a single system.

Acetylcholine (ACh) is the preganglionic neurotransmitter for both divisions of the ANS as well as the postganglionic neurotransmitter of the parasympathetic neurons. Norepinephrine (NE) is the neurotransmitter of the postganglionic sympathetic neurons, except for cholinergic neurons innervating the eccrine sweat glands.

CLINICAL EVALUATION

CLASSIFICATION

Disorders of the ANS may result from pathology of either the CNS or the peripheral nervous system (PNS) (**Table 28-2**). Signs and symptoms may result from interruption of the afferent limb, CNS processing centers, or efferent limb of reflex arcs controlling autonomic responses. For example, a lesion of the medulla produced by a posterior fossa tumor can impair BP responses to postural changes and result in orthostatic hypotension (OH). OH can also be caused by lesions of



Parasympathetic system
from cranial nerves III, VII, IX, X and from sacral nerves 2 and 3

Sympathetic system
from T1-L2
Preganglionic fibers
Postganglionic fibers

- **A** Ciliary ganglion
- **B** Sphenopalatine (pterygopalatine) ganglion
- **C** Submandibular ganglion
- **D** Otic ganglion
- **E** Vagal ganglion cells in the heart wall
- **F** Vagal ganglion cells in bowel wall
- **G** Pelvic ganglia
- **H** Superior cervical ganglion
- **J** Middle cervical ganglion and inferior cervical (stellate) ganglion including T1 ganglion
- **K** Coeliac and other abdominal ganglia
- **L** Lower abdominal sympathetic ganglia

FIGURE 28-1
Schematic representation of the autonomic nervous system. *(From M Moskowitz: Clin Endocrinol Metab 6:77, 1977.)*

the spinal cord or peripheral vasomotor nerve fibers (e.g., diabetic autonomic neuropathy). The site of reflex interruption is usually established by the clinical context in which the dysautonomia arises, combined with judicious use of ANS testing and neuroimaging studies. The presence or absence of CNS signs (pathophysiology and prognosis differ), association with sensory or motor

TABLE 28-1
FUNCTIONAL CONSEQUENCES OF NORMAL ANS ACTIVATION

	SYMPATHETIC	PARASYMPATHETIC
Heart rate	Increased	Decreased
Blood pressure	Increased	Mildly decreased
Bladder	Increased sphincter tone	Voiding (decreased tone)
Bowel motility	Decreased motility	Increased
Lung	Bronchodilation	Bronchoconstriction
Sweat glands	Sweating	—
Pupils	Dilation	Constriction
Adrenal glands	Catecholamine release	—
Sexual function	Ejaculation, orgasm	Erection
Lacrimal glands	—	Tearing
Parotid glands	—	Salivation

polyneuropathy, medical illnesses, medication use, and family history are often important considerations. Some syndromes do not fit easily into any classification scheme.

SYMPTOMS OF AUTONOMIC DYSFUNCTION

Clinical manifestations result from a loss of function (e.g., impaired baroreflexes leading to OH), overactivity (e.g., hyperhidrosis, hypertension, tachycardia), or loss of regulation (e.g., autonomic storms, autonomic dysreflexia) of autonomic circuits. Symptoms may be widespread or regional in distribution. An autonomic history focuses on systemic functions (BP, heart rate, sleep, thermoregulation) and involvement of individual organ systems (pupils, bowel, bladder, sexual function). More formal assessment is possible using a standardized instrument such as the autonomic symptom profile. It is also important to recognize the modulating effects of age and gender. For instance, OH commonly results in lightheadedness in the young, whereas cognitive slowing is more common in the elderly. Specific symptoms of orthostatic intolerance are diverse (Table 28-3). Autonomic symptoms may vary dramatically, reflecting the dynamic nature of autonomic control over homeostatic function. For example, OH might be manifest only in the early morning, following a meal, or with exercise, depending upon the regional vascular bed affected by dysautonomia.

Early symptoms may be overlooked. Impotence, although not specific for autonomic failure, often heralds autonomic failure in men and may precede other symptoms by years. A decrease in the frequency of spontaneous early morning erections may occur months before

TABLE 28-2

CLASSIFICATION OF CLINICAL AUTONOMIC DISORDERS

I. Autonomic disorders with brain involvement
  A. Associated with multisystem degeneration
    1. Multisystem degeneration: autonomic failure clinically prominent
      a. Multiple system atrophy (MSA)
      b. Parkinson's disease with autonomic failure
      c. Diffuse Lewy body disease (some cases)
    2. Multisystem degeneration: autonomic failure clinically not usually prominent
      a. Parkinson's disease
      b. Other extrapyramidal disorders (inherited spinocerebellar atrophies, progressive supranuclear palsy, corticobasal degeneration, Machado-Joseph disease)
  B. Unassociated with multisystem degeneration
    1. Disorders mainly due to cerebral cortex involvement
      a. Frontal cortex lesions causing urinary/bowel incontinence
      b. Partial complex seizures
    2. Disorders of the limbic and paralimbic circuits
      a. Shapiro's syndrome (agenesis of corpus callosum, hyperhidrosis, hypothermia)
      b. Autonomic seizures
    3. Disorders of the hypothalamus
      a. Wernicke-Korsakoff syndrome
      b. Diencephalic syndrome
      c. Neuroleptic malignant syndrome
      d. Serotonin syndrome
      e. Fatal familial insomnia
      f. Antidiuretic hormone (ADH) syndromes (diabetes insipidus, inappropriate ADH)
      g. Disturbances of temperature regulation (hyperthermia, hypothermia)
      h. Disturbances of sexual function
      i. Disturbances of appetite
      j. Disturbances of BP/HR and gastric function
      k. Horner's syndrome
    4. Disorders of the brainstem and cerebellum
      a. Posterior fossa tumors
      b. Syringobulbia and Arnold-Chiari malformation
      c. Disorders of BP control (hypertension, hypotension)
      d. Cardiac arrhythmias
      e. Central sleep apnea
      f. Baroreflex failure
      g. Horner's syndrome
II. Autonomic disorders with spinal cord involvement
  A. Traumatic quadriplegia
  B. Syringomyelia
  C. Subacute combined degeneration
  D. Multiple sclerosis
  E. Amyotrophic lateral sclerosis
  F. Tetanus
  G. Stiff-man syndrome
  H. Spinal cord tumors
III. Autonomic neuropathies
  A. Acute/subacute autonomic neuropathies
    1. Subacute autoimmune autonomic neuropathy (panautonomic neuropathy, pandysautonomia)
      a. Subacute paraneoplastic autonomic neuropathy
      b. Guillain-Barré syndrome
      c. Botulism
      d. Porphyria
      e. Drug induced autonomic neuropathies
      f. Toxic autonomic neuropathies
  B. Chronic peripheral autonomic neuropathies
    1. Distal small fiber neuropathy
    2. Combined sympathetic and parasympathetic failure
      a. Amyloid
      b. Diabetic autonomic neuropathy
      c. Autoimmune autonomic neuropathy (paraneoplastic and idiopathic)
      d. Sensory neuronopathy with autonomic failure
      e. Familial dysautonomia (Riley-Day syndrome)

Note: BP, blood pressure; HR, heart rate.

TABLE 28-3

SYMPTOMS OF ORTHOSTATIC INTOLERANCE	
Lightheadedness (dizziness)	88%
Weakness or tiredness	72%
Cognitive difficulty (thinking/concentrating)	47%
Blurred vision	47%
Tremulousness	38%
Vertigo	37%
Pallor	31%
Anxiety	29%
Palpitations	28%
Clammy feeling	19%
Nausea	18%

Source: From PA Low et al: Mayo Clin Proc 70:617,1995.

loss of nocturnal penile tumescence and development of total impotence. Bladder dysfunction may appear early in men and women, particularly in those with CNS involvement. Brain and spinal cord disease above the level of the lumbar spine results first in urinary frequency and small bladder volumes and eventually in incontinence (upper motor neuron or spastic bladder). Disease of PNS autonomic nerve fibers results in large bladder volumes, urinary frequency, and overflow incontinence (lower motor neuron flaccid bladder). Measurement of bladder volume (post-void residual) is a useful bedside test for distinguishing between upper and lower motor neuron bladder dysfunction in the early stages of dysautonomia. Gastrointestinal autonomic dysfunction typically presents as severe constipation. Diarrhea occurs occasionally (as in diabetes mellitus) due to rapid transit of contents or uncoordinated small-bowel motor activity, or on an osmotic basis from bacterial overgrowth associated with small-bowel stasis. Impaired glandular secretory function may cause difficulty with food intake due to decreased salivation or eye irritation due to decreased lacrimation. Occasionally, temperature elevation and vasodilation can result from anhidrosis because sweating is normally important for heat dissipation.

OH (also called *postural hypotension*) is perhaps the most disabling feature of autonomic dysfunction. The prevalence of OH is relatively high, especially when OH associated with aging and diabetes mellitus is included (Table 28-4). OH can cause a variety of symptoms, including dimming or loss of vision, lightheadedness, diaphoresis, diminished hearing, pallor, and weakness. Syncope results when the drop in BP impairs cerebral perfusion. Other manifestations of impaired baroreflexes are supine hypertension, a heart rate that is fixed regardless of posture, postprandial hypotension, and an excessively high nocturnal BP. Many patients with OH have a preceding diagnosis of hypertension or have concomitant supine hypertension, reflecting the great importance of baroreflexes in maintaining postural and supine normotension. The appearance of OH in patients receiving antihypertensive treatment may indicate overtreatment or the onset of an autonomic disorder. The most common causes of OH are not neurologic in origin; these must be distinguished from the neurogenic causes (Table 28-5). Neurocardiogenic and cardiac syncope are considered in Chap. 8.

TABLE 28-4

PREVALENCE OF ORTHOSTATIC HYPOTENSION IN DIFFERENT DISORDERS	
DISORDER	**PREVALENCE**
Aging	14–20%
Diabetic neuropathy	10%
Other autonomic neuropathies	10–50 per 100,000
Multiple system atrophy	5–15 per 100,000
Pure autonomic failure	10–30 per 100,000

Approach to the Patient: ORTHOSTATIC HYPOTENSION AND OTHER ANS DISORDERS

The first step in the evaluation of symptomatic OH is the exclusion of treatable causes. The history should include a review of medications that may affect the

TABLE 28-5

NONNEUROGENIC CAUSES OF ORTHOSTATIC HYPOTENSION	
Cardiac pump failure	Venous pooling
Myocardial infarction	Alcohol
Myocarditis	Postprandial dilation of splanchnic vessel beds
Constrictive pericarditis	Vigorous exercise with dilation of skeletal vessel beds
Aortic stenosis	Heat: hot environment, hot showers and baths, fever
Tachyarrhythmias	Prolonged recumbency or standing
Bradyarrhythmias	Sepsis
Salt-losing nephropathy	Medications
Adrenal insufficiency	Antihypertensives
Diabetes insipidus	Diuretics
Venous obstruction	Vasodilators: nitrates, hydralazine
Reduced intravascular volume	Alpha- and beta-blocking agents
Straining or heavy lifting, urination, defecation	CNS sedatives: barbiturates, opiates
Dehydration	Tricyclic antidepressants
Diarrhea, emesis	Phenothiazines
Hemorrhage	
Burns	
Metabolic	
Adrenocortical insufficiency	
Hypoaldosteronism	
Pheochromocytoma	
Severe potassium depletion	

TABLE 28-6

SOME DRUGS THAT AFFECT AUTONOMIC FUNCTION

SYMPTOM	DRUG CLASS	SPECIFIC EXAMPLES
Impotence	Opioids	Tylenol #3
	Anabolic steroids	—
	Some antiarrhythmics	Prazosin
	Some antihypertensives	Clonidine
	Some diuretics	Benazepril
	Some SSRIs	Venlafaxine
Urinary retention	Opioids	Fentanyl
	Decongestants	Brompheniramine
		Diphenhydramine
Diaphoresis	Some antihypertensives	Amlodipine
	Some SSRIs	Citalopram
	Opioids	Morphine
Hypotension	Tricyclics	Amitriptyline
	Beta blockers	Propranolol
	Diuretics	HCTZ
	CCBs	Verapamil

Note: SSRIs, selective serotonin reuptake inhibitors; HCTZ, hydrochlorothiazide; CCBs, calcium channel blockers.

autonomic system (Table 28-6). The main classes of drugs that may cause OH are diuretics, antihypertensives, antidepressants, phenothiazines, ethanol, narcotics, insulin, dopamine agonists, barbiturates, and calcium channel blocking agents. However, the precipitation of OH by medications may also be the first sign of an underlying autonomic disorder. The history may reveal an underlying cause for symptoms (e.g., diabetes, Parkinson's disease) or specific underlying mechanisms (e.g., cardiac pump failure, reduced intravascular volume). The relationship of symptoms to meals (splanchnic pooling), standing on awakening in the morning (intravascular volume depletion), ambient warming (vasodilatation), or exercise (muscle arteriolar vasodilatation) should be sought.

Physical examination includes measurement of supine and standing pulse and BP. OH is defined as a sustained drop in systolic (≥20 mmHg) or diastolic (≥10 mmHg) BP within 3 min of standing. In nonneurogenic causes of OH (such as hypovolemia), the BP drop is accompanied by a compensatory increase in heart rate of >15 beats/min. An important clinical clue that the patient has neurogenic OH is the aggravation or precipitation of OH by autonomic stressors (such as a meal, hot tub/hot bath, and exercise). Neurologic evaluation should include mental status (to exclude neurodegenerative disorders), cranial nerves (impaired downgaze with progressive supranuclear palsy; abnormal pupils with Horner's or Adie's syndrome), motor tone (Parkinson's disease and parkinsonian syndromes), reflexes, and sensation (polyneuropathies). In patients without a clear diagnosis initially, follow-up clinical and laboratory evaluations may reveal the underlying cause.

Disorders of autonomic function should be considered in patients with symptoms of altered sweating (hyperhidrosis or hypohidrosis), gastroparesis (bloating, nausea, vomiting of old food), constipation, impotence, or bladder dysfunction (urinary frequency, hesitancy, or incontinence).

AUTONOMIC TESTING Autonomic function tests (Table 28-7) are helpful when the history and examination findings are inconclusive, to detect subclinical involvement, or to follow the course of an autonomic disorder.

Heart Rate Variation with Deep Breathing This is a test of parasympathetic function on cardiovascular reflexes, via the vagus nerve. Results are influenced by the subject's posture, rate and depth of respiration [6 breaths per minute and a forced vital capacity (FVC) >1.5 L are optimal], age, medications, and degree of hypocapnia. Interpretation of results requires comparison of test data with results from normal individuals collected under the same test conditions. For example, the lower limit of normal heart rate variation with deep breathing in persons <20 years is >15–20 beats/min, but for persons >60 years it is 5–8 beats/min. Heart rate variation with deep breathing (respiratory sinus arrhythmia) is abolished by atropine but is unaffected by sympathetic blockade (e.g., propranolol).

TABLE 28-7

NEURAL PATHWAYS UNDERLYING SOME STANDARDIZED AUTONOMIC TESTS

TEST EVALUATED	PROCEDURE	AUTONOMIC FUNCTION
HRBD	6 deep breaths/min	Cardiovagal function
Valsalva ratio	Expiratory pressure, 40 mm Hg for 10–15 s	Cardiovagal function
QSART	Axon-reflex test 4 limb sites	Postganglionic sudomotor function
BP_{BB} to VM	BP_{BB} response to VM	Adrenergic function: baroreflex adrenergic control of vagal and vasomotor function
HUT	BP_{BB} and heart rate response to HUT	Adrenergic and cardiovagal responses to HUT

Note: HRDB, heart rate response to deep breathing; BP_{BB}, beat-to-beat blood pressure; QSART, quantitative sudomotor axon-reflex test; VM, Valsalva maneuver; HUT, head-up tilt.

Valsalva Response This response (Table 28-7) assesses the integrity of the baroreflex control of heart rate (parasympathetic) and BP (adrenergic). The response is obtained with the subject supine. A constant expiratory pressure of 40 mm Hg is maintained for 15 s while measuring changes in heart rate and beat-to-beat BP. There are four phases of BP and heart rate response to the Valsalva maneuver. Phases I and III are mechanical and related to changes in intrathoracic and intraabdominal pressure. In early phase II, reduced venous return results in a fall in stroke volume and BP, counteracted by a combination of reflex tachycardia and increased total peripheral resistance. Increased total peripheral resistance arrests the BP drop ~5–8 s after the onset of the maneuver. Late phase II begins with a progressive rise in BP toward or above baseline. Venous return and cardiac output return to normal in phase IV. Persistent peripheral arteriolar vasoconstriction and increased cardiac adrenergic tone results in a temporary BP overshoot and phase IV bradycardia (mediated by the baroreceptor reflex).

Autonomic function during the Valsalva maneuver can be measured using beat-to-beat blood pressure or heart rate changes. The *Valsalva ratio* is defined as the maximum phase II tachycardia divided by the minimum phase IV bradycardia. The ratio reflects cardiovagal function.

Sudomotor Function Sweating is induced by release of ACh from sympathetic postganglionic fibers. The quantitative sudomotor axon reflex test (QSART) is a measure of regional autonomic function mediated by ACh-induced sweating. A reduced or absent response indicates a lesion of the postganglionic sudomotor axon. For example, sweating may be reduced in the legs as a result of peripheral neuropathy (e.g., diabetes) before other signs of autonomic dysfunction emerge. The thermoregulatory sweat test (TST) is a qualitative measure of regional sweat production in response to an elevation of body temperature. An indicator powder placed on the anterior surface of the body changes color with sweat production during temperature elevation. The pattern of color changes is a measure of regional sweat secretion. Combining TST and QSART results will determine the site of the lesion. A postganglionic lesion is present if both QSART and TST show absent sweating. In a preganglionic lesion, QSART is intact but TST shows anhidrosis. Measurement of galvanic skin responses in the limbs after an induced electrical potential is a simple qualitative test for detecting the presence or absence of sweating.

Orthostatic BP Recordings Beat-to-beat BP measurements determined in supine, 70° tilt, and tilt-back positions are useful to quantitate orthostatic failure of BP control. It is important to allow a 20-min period of supine rest before assessing changes in BP during tilting. The BP change combined with heart rate monitoring can be useful for the evaluation of patients with suspected OH, unexplained syncope, or to detect vagally mediated syncope.

Tilt Table Testing for Syncope The great majority of patients with syncope do not have autonomic failure. Tilt-table testing can be used to make the diagnosis of vasovagal syncope with sensitivity, specificity, and reproducibility. A standardized protocol is used that specifies the tilt apparatus, angle and duration of tilt, and procedure for provocation of vasodilation (e.g., sublingual or spray nitroglycerin). A positive nitroglycerin-stimulated test predicts recurrence of syncope. Recommendations for the performance of tilt study for syncope have been incorporated in consensus guidelines.

Pharmacologic Tests Pharmacologic assessments can help localize an autonomic defect to the CNS or the PNS. A useful method to evaluate the systemic adrenergic response is the measurement of plasma NE, first with the patient supine and then after standing for at least 5 min. Supine values are reduced in postganglionic disorders (such as autonomic neuropathy or pure autonomic failure) and may fail to increase in preganglionic or postganglionic disorders (e.g., multiple system atrophy).

Administration of tyramine (releases NE from postganglionic terminals) and phenylephrine (denervation supersensitivity—directly acting α_1 agonist) is used to evaluate postganglionic adrenergic function. In a postganglionic lesion, the response to tyramine is reduced and there is an excessive response to subthreshold doses of phenylephrine. Other strategies include ganglionic blockade with trimethaphan (greater fall in resulting BP with a preganglionic lesion) or administration of arginine vasopressin (to evaluate afferent central pathways).

SPECIFIC SYNDROMES OF ANS DYSFUNCTION

MULTIPLE SYSTEM ATROPHY

Multiple system atrophy (MSA) is an uncommon entity that comprises autonomic failure (OH and/or a neurogenic bladder are required for diagnosis) combined with either striatonigral degeneration (Shy-Drager syndrome) or sporadic olivopontocerebellar atrophy (Chap. 26). The Parkinsonism is usually unassociated with rest tremor and is not responsive to levodopa. Levodopa-induced

dyskinesia is also uncommon. Autonomic function tests can usually differentiate MSA from Parkinson's disease; the severity and distribution of autonomic failure are more severe and generalized in MSA. Cardiac postganglionic adrenergic innervation, measured as labeled metaiodobenzylguanidine (MIBG) uptake on single photon emission computed tomography or fluorodopamine on positron emission tomography, is markedly impaired in the dysautonomia of Parkinson's disease but is normal in MSA.

MSA generally progresses relentlessly to death 7–10 years after onset. Neuropathologic changes include neuronal loss and gliosis in many CNS regions, including the brainstem, cerebellum, striatum, and intermediolateral cell column of the thoracolumbar spinal cord.

Autonomic dysfunction is a common feature in dementia with Lewy bodies (Chap. 23); the severity is usually less than that found in MSA or Parkinson's disease.

SPINAL CORD

Spinal cord lesions from any cause may result in focal autonomic deficits or autonomic hyperreflexia. Spinal cord transection or hemisection may be attended by autonomic hyperreflexia affecting bowel, bladder, sexual, temperature-regulation, or cardiovascular functions. Dangerous increases or decreases in body temperature may result from an inability to experience the sensory accompaniments of heat or cold exposure below the level of the injury. Quadriparetic patients exhibit both supine hypertension and OH after upward tilting. Markedly increased autonomic discharge can be elicited by stimulation of the bladder, skin, or muscles; suprapubic palpation of the bladder, a distended bladder, catheter insertion, catheter obstruction, or urinary infection are common and correctable precipitants. This phenomenon, termed *autonomic dysreflexia*, affects 85% of patients with a traumatic spinal cord lesion above the C6 level. In patients with supine hypertension, BP can be lowered by tilting the head upward. Vasodilator drugs may be used to treat acute elevations in BP. Clonidine is used prophylactically to reduce the hypertension resulting from bladder stimulation. Sudden, dramatic increases in BP can lead to intracranial hemorrhage and death.

PERIPHERAL NERVE AND NEUROMUSCULAR JUNCTION DISORDERS

Peripheral neuropathies (Chap. 40) are the most common cause of chronic autonomic insufficiency. Neuropathies that affect small myelinated and unmyelinated fibers of the sympathetic and parasympathetic nerves commonly occur in diabetes mellitus, amyloidosis, chronic alcoholism, porphyria, and Guillain-Barré syndrome. Neuromuscular junction disorders accompanied by autonomic involvement include botulism and Lambert-Eaton syndrome.

Diabetes Mellitus

Autonomic neuropathy typically begins ~10 years after the onset of diabetes and slowly progresses. The earliest autonomic abnormalities, typically asymptomatic, consist of vagal disturbances, which can be detected as reduced heart rate variation with deep breathing, and loss of distal sudomotor function, detected by QSART. Loss of small myelinated and unmyelinated nerve fibers in the splanchnic distribution, carotid sinus, and vagus nerves is characteristic. In advanced disease, widespread enteric neuropathy can cause profound disturbances in gut motility (*gastroparesis*), nausea and vomiting, malnutrition, achlorhydria, and bowel incontinence. Other symptoms can include impotence, urinary incontinence, pupillary abnormalities, and OH. Typical symptoms and signs of hypoglycemia may fail to appear because damage to the sympathetic innervation of the adrenal gland can result in a lack of epinephrine release. Insulin increases flow through arteriovenous shunts and may also aggravate OH. Autonomic dysfunction may lengthen the QT interval, increasing the risk of sudden death due to cardiac arrhythmia. Hyperglycemia appears to be a direct risk factor for autonomic involvement in diabetes. Biochemical and pharmacologic studies in diabetic neuropathy are compatible with autonomic failure localized to the PNS.

Amyloidosis

Autonomic neuropathy occurs in both sporadic and familial forms of amyloidosis. The AL (immunoglobulin light chain) type is associated with primary amyloidosis or amyloidosis secondary to multiple myeloma. The ATTR type, with transthyretin as the primary protein component, is responsible for the most common form of inherited amyloidosis. Although patients usually present with a distal painful neuropathy accompanied by sensory loss, autonomic insufficiency can precede the development of the polyneuropathy or occur in isolation. Diagnosis can be made by protein electrophoresis of blood and urine, tissue biopsy (abdominal fat pad, rectal mucosa, or sural nerve) to search for amyloid deposits, and genetic testing for transthyretin in familial cases. Treatment of familial cases with liver transplantation can be successful. The response of primary amyloidosis to melphalan and stem cell transplantation has been mixed. Death is usually due to cardiac or renal involvement. Postmortem studies reveal amyloid deposition in many organs, including two sites that contribute to autonomic failure: intraneural blood vessels and autonomic ganglia. Pathologic examination reveals a loss of unmyelinated and myelinated nerve fibers.

Alcoholic Neuropathy

Abnormalities in parasympathetic vagal and efferent sympathetic function are usually mild in individuals with alcoholic polyneuropathy. Pathologic changes can be demonstrated in the parasympathetic (vagus) and sympathetic fibers, and in ganglia. OH is usually due to brainstem involvement. Impotence is a major problem, but concurrent gonadal hormone abnormalities may obscure the parasympathetic component. Clinical symptoms of autonomic failure generally appear when the polyneuropathy is severe, and there is usually coexisting Wernicke's encephalopathy (Chap. 22). Autonomic involvement may contribute to the high mortality rates associated with alcoholism (Chap. 50).

Porphyria

Although each of the porphyrias can cause autonomic dysfunction, the condition is most extensively documented in the acute intermittent type. Autonomic symptoms include tachycardia, sweating, urinary retention, hypertension, or (less commonly) hypotension. Other prominent symptoms include anxiety, abdominal pain, nausea, and vomiting. Abnormal autonomic function can occur both during acute attacks and during remissions. Elevated catecholamine levels during acute attacks correlate with the degree of tachycardia and hypertension that is present.

Guillain-Barré Syndrome

(Chap. 41) BP fluctuations and arrhythmias can be severe. It is estimated that between 2 and 10% of patients with severe Guillain-Barré syndrome suffer fatal cardiovascular collapse. Gastrointestinal autonomic involvement, sphincter disturbances, abnormal sweating, and pupillary dysfunction also occur. Demyelination has been described in the vagus and glossopharyngeal nerves, the sympathetic chain, and the white rami communicantes. Interestingly, the degree of autonomic involvement appears to be independent of the severity of motor or sensory neuropathy.

Autoimmune Autonomic Neuropathy

This disorder presents with the subacute development of autonomic failure with OH, enteric neuropathy (gastroparesis, ileus, constipation/diarrhea), and cholinergic failure; the latter consists of loss of sweating, sicca complex, and a tonic pupil. Autoantibodies against the ganglionic ACh receptor (A_3 AChR) are present in the serum of many patients and are now considered to be diagnostic of this syndrome. In general, the antibody titer correlates with the severity of autonomic failure. Symptoms of cholinergic failure are also associated with a high antibody titer. Onset of the neuropathy follows a viral infection in approximately half of cases. Some patients appear to respond to immunotherapy. The spectrum of autoimmune autonomic neuropathy (AAN) is now broader than originally thought; some antibody-positive cases have an insidious onset and slow progression with a pure autonomic failure (see below) phenotype. A recent report describes a dramatic clinical response to repeated plasma exchange combined with immunosuppression in a patient with long-standing AAN.

AAN can have a paraneoplastic basis (Chap. 39). The clinical features of the autonomic neuropathy may be indistinguishable from the nonparaneoplastic form, or a coexisting paraneoplastic syndrome, such as cerebellar involvement or dementia, may be present (see Tables 39-2 and 39-3). The neoplasm may be truly occult and possibly suppressed by the autoantibody.

Botulism

Botulinum toxin binds presynaptically to cholinergic nerve terminals and, after uptake into the cytosol, blocks ACh release. Manifestations consist of motor paralysis and autonomic disturbances that include blurred vision, dry mouth, nausea, unreactive or sluggishly reactive pupils, constipation, and urinary retention.

PURE AUTONOMIC FAILURE (PAF)

This sporadic syndrome consists of postural hypotension, impotence, bladder dysfunction, and defective sweating. The disorder begins in the middle decades and occurs in women more often than men. The symptoms can be disabling, but the disease does not shorten life span. The clinical and pharmacologic characteristics suggest primary involvement of postganglionic sympathetic neurons. There is a severe reduction in the density of neurons within sympathetic ganglia that results in low supine plasma NE levels and noradrenergic supersensitivity. Some studies have questioned the specificity of PAF as a distinct clinical entity. Some cases are ganglionic antibody–positive and thus represent a type of AAN. Between 10 and 15% of cases evolve into MSA.

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME (POTS)

This syndrome is characterized by symptomatic orthostatic intolerance (not OH) and by either an increase in heart rate to >120 beats/min or an increase of 30 beats/min with standing that subsides on sitting or lying down. Women are affected approximately five times more often than men, and most develop the syndrome between the ages of 15 and 50. Approximately half of affected patients report an antecedent viral infection. Syncopal symptoms (lightheadedness, weakness, blurred vision) combined with symptoms of autonomic overactivity (palpitations, tremulousness, nausea) are common.

Recurrent unexplained episodes of dysautonomia and fatigue also occur. The pathogenesis is unclear in most cases; hypovolemia, venous pooling, impaired brainstem regulation, or β-receptor supersensitivity may play a role. In one affected individual, a mutation in the NE transporter, which resulted in impaired NE clearance from synapses, was responsible. Some cases are due to an underlying limited autonomic neuropathy. Although ~80% of patients improve, only one-quarter eventually resume their usual daily activities (including exercise and sports). Expansion of fluid volume and postural training (see Rx: Autonomic Failure) are initial approaches to treatment. If these approaches are inadequate, then midodrine, fludrocortisone, phenobarbital, beta blockers, or clonidine may be used with some success.

INHERITED DISORDERS

There are five known hereditary sensory and autonomic neuropathies (HSAN I–V). The most important ones are HSAN I and HSAN III (Riley-Day syndrome; familial dysautonomia). HSAN I is dominantly inherited and often presents as a distal small-fiber neuropathy (burning feet syndrome). The responsible gene, on chromosome 9q, is designated *SPTLC1*. SPTLC is an important enzyme in the regulation of ceramide. Cells from HSAN I patients affected by mutation of *SPTLC1* produce higher-than-normal levels of glucosyl ceramide, perhaps triggering apoptosis.

HSAN III, an autosomal recessive disorder of infants and children that occurs among Ashkenazi Jews, is much less prevalent than HSAN I. Decreased tearing, hyperhidrosis, reduced sensitivity to pain, areflexia, absent fungiform papillae on the tongue, and labile BP may be present. Episodic abdominal crises and fever are common. Pathologic examination of nerves reveals a loss of small myelinated and unmyelinated nerve fibers. The defective gene, named *IKBKAP*, is also located on the long arm of chromosome 9. Pathogenic mutations may prevent normal transcription of important molecules in neural development.

PRIMARY HYPERHIDROSIS

This syndrome presents with excess sweating of the palms of the hands and soles of the feet. The disorder affects 0.6–1.0% of the population; the etiology is unclear, but there may be a genetic component. While not dangerous, the condition can be socially embarrassing (e.g., shaking hands) or disabling (e.g., inability to write without soiling the paper). Onset of symptoms is usually in adolescence; the condition tends to improve with age. Topical antiperspirants are occasionally helpful. More useful are potent anticholinergic drugs such as glycopyrrolate (1–2 mg po tid). T2 ganglionectomy or sympathectomy is successful in >90% of patients with palmar hyperhidrosis. The advent of endoscopic transaxillary T2 sympathectomy has lowered the complication rate of the procedure. The most common postoperative complication is compensatory hyperhidrosis, which improves spontaneously over months; other potential complications include recurrent hyperhidrosis (16%), Horner's syndrome (<2%), gustatory sweating, wound infection, hemothorax, and intercostal neuralgia. Local injection of botulinum toxin has also been used to block cholinergic, postganglionic sympathetic fibers to sweat glands in patients with palmar hyperhidrosis. This approach is limited by the need for repetitive injections (the effect usually lasts 4 months before waning), pain with injection, the high cost of botulinum toxin, and the possibility of temporary intrinsic hand muscle weakness.

ACUTE AUTONOMIC SYNDROMES

The physician may be confronted occasionally with an acute autonomic syndrome, either acute autonomic failure (acute AAN syndrome) or a state of sympathetic overactivity. An *autonomic storm* is an acute state of sustained sympathetic surge that results in variable combinations of alterations in blood pressure and heart rate, body temperature, respiration and sweating. Causes of autonomic storm are brain and spinal cord injury, toxins and drugs, autonomic neuropathy, and chemodectomas (e.g., pheochromocytoma).

Brain injury is most commonly a cause of autonomic storm following severe head trauma (with diffuse axonal injury) and in postresuscitation encephalopathy following anoxic-ischemic brain insult. Autonomic storm can also occur with other acute intracranial lesions such as hemorrhage, cerebral infarction, rapidly expanding tumors, subarachnoid hemorrhage, hydrocephalus, or (less commonly) an acute spinal cord lesion. Lesions involving the diencephalon may be more prone to present with dysautonomia, but the most consistent setting is that of an acute intracranial catastrophe of sufficient size and rapidity to produce a massive catecholaminergic surge. The surge can cause seizures, neurogenic pulmonary edema, and myocardial injury. Manifestations include fever, tachycardia, hypertension, tachypnea, hyperhidrosis, pupillary dilatation, and flushing.

Drugs and toxins may also be responsible, including sympathomimetics such as phenylpropanolamine, cocaine, amphetamines, and tricyclic antidepressants; tetanus; and, less often, botulinum. Phenylpropanolamine, now off the market, was in the past a potent cause of this syndrome. Cocaine, including "crack," can cause a hypertensive state with CNS hyperstimulation. Tricyclic overdose, such as amitriptyline, can cause flushing, hypertension, tachycardia, fever, mydriasis, anhidrosis, and a toxic psychosis. *Neuroleptic malignant syndrome* refers to a syndrome of muscle rigidity, hyperthermia, and hypertension in psychotic patients treated with phenothiazines.

The hyperadrenergic state with Guillain-Barré syndrome can produce a moderate autonomic storm. Pheochromocytoma presents with a paroxysmal or sustained hyperadrenergic state, headache, hyperhidrosis, palpitations, anxiety, tremulousness, and hypertension.

Management of autonomic storm includes ruling out other causes of autonomic instability, including malignant hyperthermia, porphyria, and epilepsy. Sepsis and encephalitis need to be excluded with appropriate studies. EEG should be done to detect epileptiform activity; MRI of the brain and spine are often necessary. The patient should be managed in an intensive care unit. Management with morphine sulphate (10 mg every 4 h) and labetalol (100–200 mg twice daily) have worked relatively well. Treatment may need to be maintained for several weeks.

MISCELLANEOUS

Other conditions associated with autonomic failure include infections, poisoning (organophosphates), malignancy, and aging. Disorders of the hypothalamus can affect autonomic function and produce abnormalities in temperature control, satiety, sexual function, and circadian rhythms.

REFLEX SYMPATHETIC DYSTROPHY AND CAUSALGIA

The failure to identify a primary role of the ANS in the pathogenesis of these disorders has resulted in a change of nomenclature. Complex regional pain syndrome (CRPS) types I and II are now used in place of reflex sympathetic dystrophy (RSD) and causalgia, respectively.

CRPS type I is a regional pain syndrome that usually develops after tissue trauma. Examples of associated trauma include myocardial infarction, minor shoulder or limb injury, and stroke. *Allodynia* (the perception of a nonpainful stimulus as painful), *hyperpathia* (an exaggerated pain response to a painful stimulus), and spontaneous pain occur. The symptoms are unrelated to the severity of the initial trauma and are not confined to the distribution of a single peripheral nerve. CRPS type II is a regional pain syndrome that develops after injury to a peripheral nerve, usually a major nerve trunk. Spontaneous pain initially develops within the territory of the affected nerve but eventually may spread outside the nerve distribution.

Pain is the primary clinical feature of CRPS. Vasomotor dysfunction, sudomotor abnormalities, or focal edema may occur alone or in combination but must be present for diagnosis. Limb pain syndromes that do not meet these criteria are best classified as "limb pain—not otherwise specified." In CRPS, localized sweating (increased resting sweat output) and changes in blood flow may produce temperature differences between affected and unaffected limbs.

CRPS type I (RSD) has classically been divided into three clinical phases but is now considered to be more variable. Phase I consists of pain and swelling in the distal extremity occurring within weeks to 3 months after the precipitating event. The pain is diffuse, spontaneous, and either burning, throbbing, or aching in quality. The involved extremity is warm and edematous, and the joints are tender. Increased sweating and hair growth develop. In phase II (3–6 months after onset), thin, shiny, cool skin appears. After an additional 3–6 months (phase III), atrophy of the skin and subcutaneous tissue plus flexion contractures complete the clinical picture.

The natural history of typical CRPS may be more benign than reflected in the literature. A variety of surgical and medical treatments have been developed, with conflicting reports of efficacy. Clinical trials suggest that early mobilization with physical therapy or a brief course of glucocorticoids may be helpful for CRPS type I. Other medical treatments include the use of adrenergic blockers, nonsteroidal anti-inflammatory drugs, calcium channel blockers, phenytoin, opioids, and calcitonin. Stellate ganglion blockade is a commonly used invasive therapeutic technique that often provides temporary pain relief, but the efficacy of repetitive blocks is uncertain.

Rx Treatment: AUTONOMIC FAILURE

Management of autonomic failure is aimed at specific treatment of the cause and alleviation of symptoms. Of particular importance is the removal of drugs or amelioration of underlying conditions that cause or aggravate the autonomic symptoms, especially in the elderly. For instance, OH can be caused or aggravated by angiotensin-converting enzyme inhibitors, calcium channel blocking agents, tricyclic antidepressants, levodopa, alcohol, or insulin. A summary of drugs that can cause OH by class, putative mechanism, and magnitude of the BP drop, is given in Table 28-6.

PATIENT EDUCATION OH can be asymptomatic or symptomatic. Neurogenic OH requires treatment, but only a minority of patients require pharmacologic treatment. All patients should be taught the mechanisms of postural normotension (volume status, resistance and capacitance bed, autoregulation) and the nature of orthostatic stressors (time of day and the influence of meals, heat, standing, and exercise). Patients should learn to recognize orthostatic symptoms early in their evolution (especially subtle cognitive symptoms, weakness, and fatigue) and to modify activities that provoke episodes. Other helpful measures may include keeping a BP log, dietary education (salt/fluids), and recognizing medications and situations to avoid. Learning physical

TABLE 28-8

INITIAL TREATMENT OF ORTHOSTATIC HYPOTENSION (OH)

Patient education: mechanisms and stressors of OH
- High-salt diet (10–20 g/d)
- High-fluid intake (2 L/D)
- Elevate head of bed 10 cm (4 in.)
- Maintain postural stimuli
- Learn physical countermaneuvers
- Compression garments
- Correct anemia

countermaneuvers that reduce standing OH, practicing postural and resistance training, and learning to manage worsening OH in specific situations and at specific times are helpful measures.

SYMPTOMATIC TREATMENT Nonpharmacologic approaches are summarized in Table 28-8. Adequate intake of salt and fluids to produce a voiding volume between 1.5 and 2.5 L of urine (containing >170 meq of Na^+) each 24 h is essential. Sleeping with the head of the bed elevated will minimize the effects of supine nocturnal hypertension. Prolonged recumbency should be avoided when possible. Patients are advised to sit with legs dangling over the edge of the bed for several minutes before attempting to stand in the morning; other postural stresses should be similarly approached in a gradual manner. Physical countermaneuvers that can reduce OH include leg-crossing, with maintained contraction of leg muscles for 30 s. Such maneuvers compress leg veins and increase systemic resistance. Compressive garments, such as compression stockings and abdominal binders, are helpful on occasion but uncomfortable for some patients. Anemia should be corrected with erythropoietin, administered subcutaneously at doses of 25–75 U/kg three times per week. The hematocrit increases after 2–6 weeks. A weekly maintenance dose is usually necessary. The increased intravascular volume that accompanies the rise in hematocrit can exacerbate supine hypertension.

If these measures are not sufficient, drug treatment may be necessary. Midodrine is effective, but at higher doses it can aggravate supine hypertension. The drug is a directly acting α_1-agonist that does not cross the blood-brain barrier. It has a duration of action of 2–4 h. The usual dose is 5–10 mg orally tid, but some patients respond best to a decremental dose (e.g., 15 mg on awakening, 10 mg at noon, and 5 mg in the afternoon). Midodrine should not be taken after 6 P.M. Side effects include pruritus, uncomfortable piloerection, and supine hypertension. Pyridostigmine appears to improve OH without aggravating supine hypertension by enhancing ganglionic transmission (maximal when orthostatic, minimal supine). Fludrocortisone will reduce OH, but it aggravates supine hypertension. At doses between 0.1 mg/d and 0.3 mg bid orally, it enhances renal sodium conservation and increases the sensitivity of arterioles to NE. Susceptible patients may develop fluid overload, congestive heart failure, supine hypertension, or hypokalemia. Potassium supplements are often necessary with chronic administration of fludrocortisone. Sustained elevations of supine BP >180/110 mm Hg should be avoided.

Postprandial OH may respond to several measures. Frequent, small, low-carbohydrate meals may diminish splanchnic shunting of blood after meals and reduce postprandial OH. Prostaglandin inhibitors (ibuprofen or indomethacin) taken with meals or midodrine (10 mg with the meal) can be helpful. The somatostatin analogue octreotide can be useful in the treatment of postprandial syncope by inhibiting the release of gastrointestinal peptides that have vasodilator and hypotensive effects. The subcutaneous dose ranges from 25 µg bid to 100–200 µg tid.

The patient should be taught to self-treat transient worsening of OH. Drinking two 250-mL (8-oz) glasses of water can raise standing BP 20–30 mm Hg for about 2 h, beginning ~20 min after the fluid load. The patient can increase intake of salt and fluids (bouillon treatment), increase use of physical countermaneuvers, temporarily resort to a full-body stocking (compression pressure 30–40 mm Hg), or increase the dose of midodrine. Supine hypertension (>180/110 mm Hg) can be self-treated by avoiding the supine position and reducing fludrocortisone. A daily glass of wine, if requested by the patient, can be taken shortly before bedtime. If these simple measures are not adequate, drugs to be considered include oral hydralazine (25 mg qhs), oral procardia (10 mg qhs), or a nitroglycerin patch.

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CHAPTER 29

TRIGEMINAL NEURALGIA, BELL'S PALSY, AND OTHER CRANIAL NERVE DISORDERS

M. Flint Beal ■ Stephen L. Hauser

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Symptoms and signs of cranial nerve pathology are common in internal medicine. They often develop in the context of a widespread neurologic disturbance, and in such situations cranial nerve involvement may represent the initial manifestation of the illness. In other disorders, involvement is largely restricted to one or several cranial nerves; these distinctive disorders are reviewed in this chapter. Disorders of ocular movement are discussed in Chap. 17, disorders of hearing in Chap. 18, and vertigo and disorders of vestibular function in Chap. 9.

FACIAL PAIN OR NUMBNESS

ANATOMIC CONSIDERATIONS

The trigeminal (fifth cranial) nerve supplies sensation to the skin of the face and anterior half of the head (**Fig. 29-1**). Its motor part innervates the masseter and pterygoid masticatory muscles.

TRIGEMINAL NEURALGIA (TIC DOULOUREUX)

Clinical Manifestations

Trigeminal neuralgia is characterized by excruciating paroxysms of pain in the lips, gums, cheek, or chin and, very rarely, in the distribution of the ophthalmic division of the fifth nerve. The pain seldom lasts more than a few seconds or a minute or two but may be so intense that the patient winces, hence the term *tic*. The paroxysms, experienced as single jabs or clusters, tend to recur frequently, both day and night, for several weeks at a time. They may occur spontaneously or with movements of affected areas evoked by speaking, chewing, or smiling. Another characteristic feature is the presence of trigger zones, typically on the face, lips, or tongue, that provoke attacks; patients may report that tactile stimuli—e.g. washing the face, brushing the teeth, or exposure to a draft of air—generate excruciating pain. *An essential feature of trigeminal neuralgia is that objective signs of sensory loss cannot be demonstrated on examination.*

Trigeminal neuralgia is relatively common, with an estimated annual incidence of 4.5 per 100,000 individuals. Middle-aged and elderly persons are affected primarily, and ~60% of cases occur in women. Onset is typically sudden, and bouts tend to persist for weeks or months before remitting spontaneously. Remissions may be long-lasting, but in most patients the disorder ultimately recurs.

Pathophysiology

Symptoms result from ectopic generation of action potentials in pain-sensitive afferent fibers of the fifth cranial nerve root just before it enters the lateral surface of the pons. Compression or other pathology in the

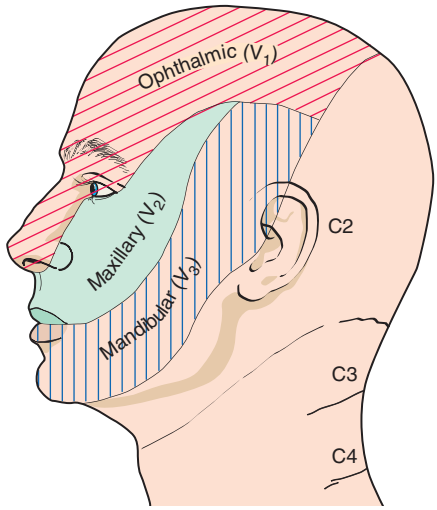


FIGURE 29-1
The three major sensory divisions of the trigeminal nerve consist of the ophthalmic, maxillary, and mandibular nerves.

nerve leads to demyelination of large myelinated fibers that do not themselves carry pain sensation but become hyperexcitable and electrically coupled with smaller unmyelinated or poorly myelinated pain fibers in close proximity; this may explain why tactile stimuli, conveyed via the large myelinated fibers, can stimulate paroxysms of pain. Compression of the trigeminal nerve root by a blood vessel, most often the superior cerebellar artery or on occasion a tortuous vein, is the source of trigeminal neuralgia in a substantial proportion of patients. In cases of vascular compression, age-related brain sagging and increased vascular thickness and tortuosity may explain the prevalence of trigeminal neuralgia in later life.

Differential Diagnosis

Trigeminal neuralgia must be discriminated from other causes of face and head pain (Chap. 6) and from pain arising from diseases of the jaw, teeth, or sinuses. Pain from migraine or cluster headache tends to be deep-seated and steady, unlike the superficial stabbing quality of trigeminal neuralgia; rarely, cluster headache is associated with trigeminal neuralgia, a syndrome known as *cluster-tic*. In temporal arteritis, superficial facial pain is present but is not typically shocklike, the patient frequently complains of myalgias and other systemic symptoms, and an elevated erythrocyte sedimentation rate (ESR) is usually present. When trigeminal neuralgia develops in a young adult or is bilateral, multiple sclerosis is a key consideration, and in such cases the cause is a demyelinating plaque at the root entry zone of the fifth nerve in the pons; often, evidence of facial sensory loss can be found on careful examination. Cases that are secondary to mass lesions—such as aneurysms, neurofibromas, acoustic schwannomas, or meningiomas—usually produce objective signs of sensory loss in the trigeminal nerve distribution (trigeminal neuropathy, see below).

Laboratory Evaluation

An ESR is indicated if temporal arteritis is suspected. In typical cases of trigeminal neuralgia, neuroimaging studies are usually unnecessary but may be valuable if multiple sclerosis is a consideration or in assessing overlying vascular lesions in order to plan for decompression surgery.

℞ Treatment: TRIGEMINAL NEURALGIA

Drug therapy with carbamazepine is effective in ~50–75% of patients. Carbamazepine should be started as a single daily dose of 100 mg taken with food and increased gradually (by 100 mg daily every 1–2 days) until substantial (>50%) pain relief is achieved. Most patients require a maintenance dose of 200 mg qid. Doses >1200 mg daily provide no additional benefit. Dizziness, imbalance, sedation, and rare cases of agranulocytosis are the most important side effects of carbamazepine. If treatment is effective, it is usually continued for 1 month and then tapered as tolerated. If carbamazepine is not well tolerated or is ineffective, phenytoin, 300–400 mg daily, can be tried; other anticonvulsants may also be effective. Baclofen may also be administered, either alone or in combination with carbamazepine or phenytoin. The initial dose is 5–10 mg tid, gradually increasing as needed to 20 mg qid.

If drug treatment fails, surgical therapy should be offered. The most widely applied procedure creates a heat lesion of the trigeminal (gasserian) ganglion or nerve, a method termed *radiofrequency thermal rhizotomy*. This procedure produces short-term relief in >95% of patients; however, long-term studies indicate that pain recurs in up to one-third of treated patients. These procedures result in partial numbness of the face, sometimes with unpleasant dysesthesias. Masseter (jaw) weakness is another potential complication, especially following bilateral procedures. When used for first-division trigeminal neuralgia, there is also a risk of corneal denervation with secondary keratitis.

Gamma knife radiosurgery is also utilized for treatment and results in complete pain relief in more than two-thirds of patients; the response is often long-lasting. Compared with thermal rhizotomy, gamma knife surgery appears to be somewhat less effective but has a lower risk of serious complications.

A third surgical treatment, microvascular decompression to relieve pressure on the trigeminal nerve as it exits the pons, requires a suboccipital craniotomy. This procedure has >70% efficacy rate and a low rate of pain

recurrence in responders; in a small number of cases, there is perioperative damage to the eighth or seventh cranial nerves or to the cerebellum. High-resolution magnetic resonance angiography is useful preoperatively to visualize the relationships between the fifth cranial nerve root and nearby blood vessels.

TRIGEMINAL NEUROPATHY

A variety of diseases may affect the trigeminal nerve (Table 29-1). Most present with sensory loss on the face or with weakness of the jaw muscles. Deviation of the jaw on opening indicates weakness of the pterygoids on the side to which the jaw deviates. Some cases are due to Sjögren's syndrome or a collagen-vascular disease such as systemic lupus erythematosus, scleroderma, or mixed connective tissue disease. Among infectious causes, herpes zoster and leprosy should be considered. Tumors of the middle cranial fossa (meningiomas), of the trigeminal nerve (schwannomas), or of the base of the skull (metastatic tumors) may cause a combination of motor and sensory signs. Lesions in the cavernous sinus can affect the first and second divisions of the trigeminal nerve, and lesions of the superior orbital fissure can affect the first (ophthalmic) division; the accompanying corneal anesthesia increases the risk of ulceration (neurokeratitis).

Loss of sensation over the chin (mental neuropathy) can be the only manifestation of systemic malignancy.

TABLE 29-1

TRIGEMINAL NERVE DISORDERS

Nuclear (brainstem) lesions	Peripheral nerve lesions
Multiple sclerosis	Nasopharyngeal carcinoma
Stroke	Trauma
Syringobulbia	Guillain-Barré syndrome
Glioma	Sjögren's syndrome
Lymphoma	Collagen-vascular diseases
Preganglionic lesions	Sarcoidosis
Acoustic neuroma	Leprosy
Meningioma	Drugs (stilbamidine, trichloroethylene)
Metastasis	Idiopathic trigeminal neuropathy
Chronic meningitis	
Cavernous carotid aneurysm	
Gasserian ganglion lesions	
Trigeminal neuroma	
Herpes zoster	
Infection (spread from otitis media or mastoiditis)	

Rarely, an idiopathic form of trigeminal neuropathy is observed. It is characterized by numbness and paresthesias, sometimes bilaterally, with loss of sensation in the territory of the trigeminal nerve but without weakness of the jaw. Gradual recovery is the rule. Tonic spasm of the masticatory muscles, known as *trismus*, is symptomatic of tetanus or may occur in patients treated with phenothiazine drugs.

FACIAL WEAKNESS

ANATOMIC CONSIDERATIONS

(Fig. 29-2) The seventh cranial nerve supplies all the muscles concerned with facial expression. The sensory component is small (the nervus intermedius); it conveys taste sensation from the anterior two-thirds of the tongue and probably cutaneous impulses from the anterior wall of the external auditory canal. The motor nucleus of the seventh nerve lies anterior and lateral to the abducens nucleus. After leaving the pons, the seventh nerve enters the internal auditory meatus with the acoustic nerve. The nerve continues its course in its own bony channel, the facial canal, and exits from the skull via the stylomastoid foramen. It then passes through the parotid gland and subdivides to supply the facial muscles.

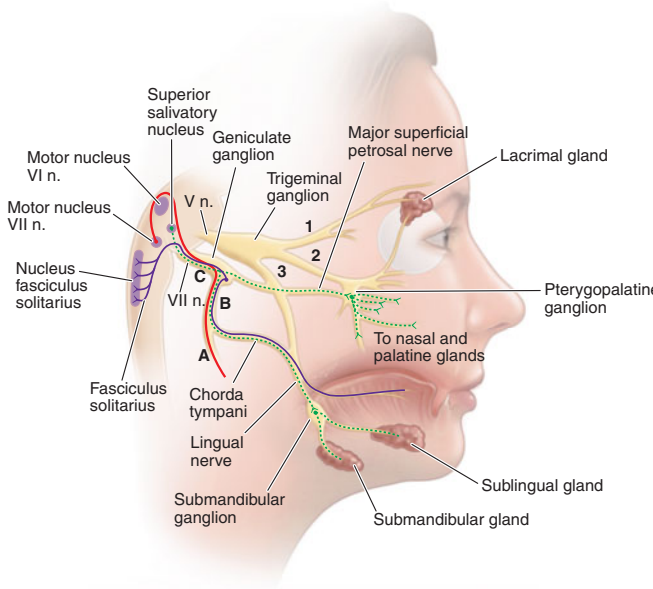


FIGURE 29-2

The facial nerve. A, B, and C denote lesions of the facial nerve at the stylomastoid foramen, distal and proximal to the geniculate ganglion, respectively. Green lines indicate the parasympathetic fibers, red line indicates motor fibers, and purple lines indicate visceral afferent fibers (taste). (*Adapted from Carpenter.*)

A complete interruption of the facial nerve at the stylomastoid foramen paralyzes all muscles of facial expression. The corner of the mouth droops, the creases and skinfolds are effaced, the forehead is unfurrowed, and the eyelids will not close. Upon attempted closure of the lids, the eye on the paralyzed side rolls upward (*Bell's phenomenon*). The lower lid sags and falls away from the conjunctiva, permitting tears to spill over the cheek. Food collects between the teeth and lips, and saliva may dribble from the corner of the mouth. The patient complains of a heaviness or numbness in the face, but sensory loss is rarely demonstrable and taste is intact.

If the lesion is in the middle-ear portion, taste is lost over the anterior two-thirds of the tongue on the same side. If the nerve to the stapedius is interrupted, there is hyperacusis (sensitivity to loud sounds). Lesions in the internal auditory meatus may affect the adjacent auditory and vestibular nerves, causing deafness, tinnitus, or dizziness. Intrapontine lesions that paralyze the face usually affect the abducens nucleus as well, and often the corticospinal and sensory tracts.

If the peripheral facial paralysis has existed for some time and recovery of motor function is incomplete, a continuous diffuse contraction of facial muscles may appear. The palpebral fissure becomes narrowed, and the nasolabial fold deepens. Attempts to move one group of facial muscles may result in contraction of all (associated movements, or *synkinesis*). Facial spasms, initiated by movements of the face, may develop (*hemifacial spasm*). Anomalous regeneration of seventh nerve fibers may result in other troublesome phenomena. If fibers originally connected with the orbicularis oculi come to innervate the orbicularis oris, closure of the lids may cause a retraction of the mouth, or if fibers originally connected with muscles of the face later innervate the lacrimal gland, anomalous tearing ("crocodile tears") may occur with any activity of the facial muscles, such as eating. Another facial synkinesia is triggered by jaw opening, causing closure of the eyelids on the side of the facial palsy (jaw-winking).

BELL'S PALSY

The most common form of facial paralysis is *Bell's palsy*. The annual incidence of this idiopathic disorder is ~25 per 100,000 annually, or about 1 in 60 persons in a lifetime.

Clinical Manifestations

The onset of Bell's palsy is fairly abrupt, maximal weakness being attained by 48 h as a general rule. Pain behind the ear may precede the paralysis for a day or two. Taste sensation may be lost unilaterally, and hyperacusis may be present. In some cases there is mild cerebrospinal fluid lymphocytosis. MRI may reveal swelling and uniform enhancement of the geniculate ganglion and facial nerve and, in some cases, entrapment of the swollen nerve in the temporal bone. Approximately 80% of patients recover within a few weeks or months. Electromyography may be of some prognostic value; evidence of denervation after 10 days indicates there has been axonal degeneration, that there will be a long delay (3 months as a rule) before regeneration occurs, and that it may be incomplete. The presence of incomplete paralysis in the first week is the most favorable prognostic sign.

Pathophysiology

Bell's palsy is associated with the presence of herpes simplex virus (HSV) type 1 DNA in endoneurial fluid and posterior auricular muscle, suggesting that a reactivation of this virus in the geniculate ganglion may be responsible. However, a causal role for HSV in Bell's palsy is unproven. An increased incidence of Bell's palsy was also reported among recipients of inactivated intranasal influenza vaccine, and it was hypothesized that this could have resulted from the *Escherichia coli* enterotoxin used as adjuvant or to reactivation of latent virus.

Differential Diagnosis

There are many other causes of acute facial palsy that must be considered in the differential diagnosis of Bell's palsy. Lyme disease can cause unilateral or bilateral facial palsies; in endemic areas, 10% or more of cases of facial palsy are likely due to infection with *Borrelia burgdorferi*. The *Ramsay Hunt syndrome*, caused by reactivation of herpes zoster in the geniculate ganglion, consists of a severe facial palsy associated with a vesicular eruption in the external auditory canal and sometimes in the pharynx and other parts of the cranial integument; often the eighth cranial nerve is affected as well. Facial palsy that is often bilateral occurs in sarcoidosis and in *Guillain-Barré syndrome* (Chap. 41). Leprosy frequently involves the facial nerve, and facial neuropathy may also occur in diabetes mellitus, connective tissue diseases including Sjögren's syndrome, and amyloidosis. The rare *Melkersson-Rosenthal syndrome* consists of recurrent facial paralysis; recurrent—and eventually permanent—facial (particularly labial) edema; and, less constantly, plication of the tongue. Its cause is unknown. *Acoustic neuromas* frequently involve the facial nerve by local compression. Infarcts, demyelinating lesions of multiple sclerosis, and tumors are the common pontine lesions that interrupt the facial nerve fibers; other signs of brainstem involvement are usually present. Tumors that invade the temporal bone (carotid body, cholesteatoma, dermoid) may

produce a facial palsy, but the onset is insidious and the course progressive.

All these forms of nuclear or peripheral facial palsy must be discriminated from the supranuclear type. In the latter, the frontalis and orbicularis oculi muscles are involved less than those of the lower part of the face, since the upper facial muscles are innervated by corticobulbar pathways from both motor cortices, whereas the lower facial muscles are innervated only by the opposite hemisphere. In supranuclear lesions there may be a dissociation of emotional and voluntary facial movements and often some degree of paralysis of the arm and leg, or an aphasia (in dominant hemisphere lesions) is present.

Laboratory Evaluation

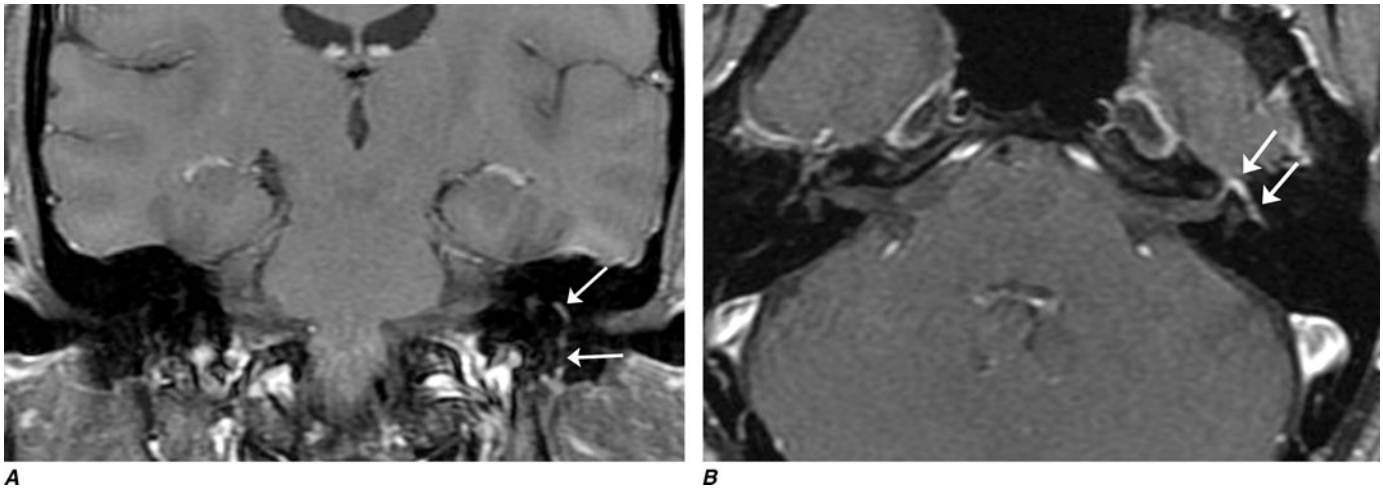
The diagnosis of Bell's palsy can usually be made clinically in patients with (1) a typical presentation, (2) no risk factors or preexisting symptoms for other causes of facial paralysis, (3) absence of cutaneous lesions of herpes zoster in the external ear canal, and (4) a normal neurologic examination with the exception of the facial nerve. Particular attention to the eighth cranial nerve, which courses near to the facial nerve in the pontomedullary junction and in the temporal bone, and to other cranial nerves is essential. In atypical or uncertain cases, an ESR, testing for diabetes mellitus, a Lyme titer, angiotensin-converting enzyme and chest imaging studies for possible sarcoidosis, a lumbar puncture for possible Guillain-Barré syndrome, or MRI scanning may be indicated. MRI often shows swelling and enhancement of the facial nerve in idiopathic Bell's palsy (**Fig. 29-3**).

℞ Treatment: BELL'S PALSY

Symptomatic measures include (1) the use of paper tape to depress the upper eyelid during sleep and prevent corneal drying, and (2) massage of the weakened muscles. A course of glucocorticoids, given as prednisone 60–80 mg daily during the first 5 days and then tapered over the next 5 days, appears to shorten the recovery period and modestly improve the functional outcome. A recently published randomized trial found no added benefit of acyclovir (400 mg five times daily for 10 days) in comparison with prednisolone alone for treatment of acute Bell's palsy; the value of valacyclovir (usual dose 1000 mg daily for 5–7 days) either alone or in combination with glucocorticoids is not known.

OTHER MOTOR DISORDERS OF THE FACE

Hemifacial spasm consists of painless irregular involuntary contractions on one side of the face. Symptoms may develop as a sequela to Bell's palsy but may also be due to an irritative lesion of the facial nerve (e.g., an acoustic neuroma, an aberrant artery that compresses the nerve, or a basilar artery aneurysm). However, in the most common form of hemifacial spasm, the cause and pathology are unknown. Mild cases can be treated with carbamazepine, gabapentin, or, if these drugs fail, with baclofen. Local injections of botulinum toxin into affected muscles can relieve spasms for 3–4 months, and the injections can be repeated. Refractory cases due to vascular compression



A *B*

FIGURE 29-3

Axial and coronal T1 weighted images post-Gadolinium with fat suppression demonstrate diffuse smooth linear enhancement of the left facial nerve, involving the genu, tympanic, and mastoid segments within the temporal bone (*arrows*), without evidence of mass lesion. Although highly suggestive of Bell's palsy, similar findings may be seen with other etiologies such as Lyme disease, sarcoidosis, and perineural malignant spread.

usually respond to surgical decompression of the facial nerve. *Blepharospasm* is an involuntary recurrent spasm of both eyelids that usually occurs in elderly persons as an isolated phenomenon or with varying degrees of spasm of other facial muscles. Severe, persistent cases of blepharospasm can be treated by local injection of botulinum toxin into the orbicularis oculi. *Facial myokymia* refers to a fine rippling activity of the facial muscles; it may be caused by multiple sclerosis or follow Guillain-Barré syndrome (Chap. 41).

Facial hemiatrophy occurs mainly in women and is characterized by a disappearance of fat in the dermal and subcutaneous tissues on one side of the face. It usually begins in adolescence or early adult years and is slowly progressive. In its advanced form, the affected side of the face is gaunt, and the skin is thin, wrinkled, and brown. The facial hair may turn white and fall out, and the sebaceous glands become atrophic. Bilateral involvement may occur. A limited form of systemic sclerosis (scleroderma) may be the cause of some cases. Treatment is cosmetic, consisting of transplantation of skin and subcutaneous fat.

OTHER CRANIAL NERVE DISORDERS

GLOSSOPHARYNGEAL NEURALGIA

This form of neuralgia involves the ninth (glossopharyngeal) and sometimes portions of the tenth (vagus) cranial nerves. It resembles trigeminal neuralgia in many respects but is much less common. The pain is intense and paroxysmal; it originates on one side of the throat, approximately in the tonsillar fossa. In some cases the pain is localized in the ear or may radiate from the throat to the ear because of involvement of the tympanic branch of the glossopharyngeal nerve. Spasms of pain may be initiated by swallowing or coughing. There is no demonstrable motor or sensory deficit; the glossopharyngeal nerve supplies taste sensation to the posterior third of the tongue and, together with the vagus nerve, sensation to the posterior pharynx. Cardiac symptoms—bradycardia or asystole, hypotension, and fainting—have been reported. Medical therapy is similar to that for trigeminal neuralgia, and carbamazepine is generally the first choice. If drug therapy is unsuccessful, surgical procedures—including microvascular decompression if vascular compression is evident—or rhizotomy of glossopharyngeal and vagal fibers in the jugular bulb is frequently successful.

Very rarely, herpes zoster involves the glossopharyngeal nerve. Glossopharyngeal neuropathy in conjunction with vagus and accessory nerve palsies may also occur with a tumor or aneurysm in the posterior fossa or in the jugular foramen. Hoarseness due to vocal cord paralysis, some difficulty in swallowing, deviation of the soft palate to the intact side, anesthesia of the posterior wall of the pharynx, and weakness of the upper part of the trapezius and sternocleidomastoid muscles make up the jugular foramen syndrome (**Table 29-2**).

DYSPHAGIA AND DYSPHONIA

When the intracranial portion of one vagus (tenth cranial) nerve is interrupted, the soft palate droops ipsilaterally and does not rise in phonation. There is loss of the gag reflex on the affected side, as well as of the "curtain movement" of the lateral wall of the pharynx, whereby the faucial pillars move medially as the palate rises in saying "ah." The voice is hoarse and slightly nasal, and the

TABLE 29-2

CRANIAL NERVE SYNDROMES

SITE	CRANIAL NERVES	USUAL CAUSE
Sphenoid fissure (superior orbital)	III, IV, first division V, VI	Invasive tumors of sphenoid bone; aneurysms
Lateral wall of cavernous sinus	III, IV, first division V, VI, often with proptosis	Infection, thrombosis, aneurysm, or fistula of cavernous sinus; invasive tumors from sinuses and sella turcica; benign granuloma responsive to glucocorticoids
Retrosphenoid space	II, III, IV, V, VI	Large tumors of middle cranial fossa
Apex of petrous bone	V, VI	Petrositis; tumors of petrous bone
Internal auditory meatus	VII, VIII	Tumors of petrous bone (dermoids, etc.); infectious processes; acoustic neuroma
Pontocerebellar angle	V, VII, VIII, and sometimes IX	Acoustic neuroma; meningioma
Jugular foramen	IX, X, XI	Tumors and aneurysms
Posterior laterocondylar space	IX, X, XI, XII	Tumors of parotid gland and carotid body and metastatic tumors
Posterior retroparotid space	IX, X, XI, XII and Horner syndrome	Tumors of parotid gland, carotid body, lymph nodes; metastatic tumor; tuberculous adenitis

vocal cord lies immobile midway between abduction and adduction. Loss of sensation at the external auditory meatus and the posterior pinna may also be present.

The pharyngeal branches of both vagal nerves may be affected in diphtheria; the voice has a nasal quality, and regurgitation of liquids through the nose occurs during the act of swallowing.

The vagus nerve may be involved at the meningeal level by neoplastic and infectious processes and within the medulla by tumors, vascular lesions (e.g., the lateral medullary syndrome), and motor neuron disease. This nerve may be involved by infection with herpes zoster virus. Polymyositis and dermatomyositis, which cause hoarseness and dysphagia by direct involvement of laryngeal and pharyngeal muscles, may be confused with diseases of the vagus nerves. Dysphagia is also a symptom in some patients with myotonic dystrophy.

The recurrent laryngeal nerves, especially the left, are most often damaged as a result of intrathoracic disease. Aneurysm of the aortic arch, an enlarged left atrium, and tumors of the mediastinum and bronchi are much more frequent causes of an isolated vocal cord palsy than are intracranial disorders. However, a substantial number of cases of recurrent laryngeal palsy remain idiopathic.

When confronted with a case of laryngeal palsy, the physician must attempt to determine the site of the lesion. If it is intramedullary, there are usually other signs, such as ipsilateral cerebellar dysfunction, loss of pain and temperature sensation over the ipsilateral face and contralateral arm and leg, and an ipsilateral Horner syndrome. If the lesion is extramedullary, the glossopharyngeal and spinal accessory nerves are frequently involved (jugular foramen syndrome). If it is extracranial in the posterior laterocondylar or retroparotid space, there may be a combination of ninth, tenth, eleventh, and twelfth cranial nerve palsies and a Horner syndrome (Table 29-2). If there is no sensory loss over the palate and pharynx and no palatal weakness or dysphagia, the lesion is below the origin of the pharyngeal branches, which leave the vagus nerve high in the cervical region; the usual site of disease is then the mediastinum.

NECK WEAKNESS

Isolated involvement of the accessory (eleventh cranial) nerve can occur anywhere along its route, resulting in partial or complete paralysis of the sternocleidomastoid and trapezius muscles. More commonly, involvement occurs in combination with deficits of the ninth and tenth cranial nerves in the jugular foramen or after exit from the skull (Table 29-2). An idiopathic form of accessory neuropathy, akin to Bell's palsy, has been described, and it may be recurrent in some cases. Most but not all patients recover.

TONGUE PARALYSIS

The hypoglossal (twelfth cranial) nerve supplies the ipsilateral muscles of the tongue. The nucleus of the nerve or its fibers of exit may be involved by intramedullary lesions such as tumor, poliomyelitis, or most often motor neuron disease. Lesions of the basal meninges and the occipital bones (platybasia, invagination of occipital condyles, Paget's disease) may compress the nerve in its extramedullary course or in the hypoglossal canal. Isolated lesions of unknown cause can occur. Atrophy and fasciculation of the tongue develop weeks to months after interruption of the nerve.

MULTIPLE CRANIAL NERVE PALSIES

Several cranial nerves may be affected by the same disease process. In this situation, the main clinical problem is to determine whether the lesion lies within the brainstem or outside it. Lesions that lie on the surface of the brainstem are characterized by involvement of adjacent cranial nerves (often occurring in succession) and late and rather slight involvement of the long sensory and motor pathways and segmental structures lying within the brainstem. The opposite is true of primary lesions within the brainstem. The extramedullary lesion is more likely to cause bone erosion or enlargement of the foramens of exit of cranial nerves. The intramedullary lesion involving cranial nerves often produces a crossed sensory or motor paralysis (cranial nerve signs on one side of the body and tract signs on the opposite side).

Involvement of multiple cranial nerves outside the brainstem is frequently the result of diabetes or trauma, localized infections such as herpes zoster, infectious and noninfectious (especially carcinomatous) causes of meningitis (Chaps. 35 and 36), granulomatous diseases such as Wegener's granulomatosis, Behçet's disease, enlarging saccular aneurysms, or tumors. Among the tumors, nasopharyngeal cancers, lymphomas, neurofibromas, meningiomas, chordomas, cholesteatomas, carcinomas, and sarcomas have all been observed to involve a succession of lower cranial nerves. Owing to their anatomic relationships, the multiple cranial nerve palsies form a number of distinctive syndromes, listed in Table 29-2. Sarcoidosis is the cause of some cases of multiple cranial neuropathy, and chronic glandular tuberculosis the cause of a few others. Platybasia, basilar invagination of the skull, and the adult Chiari malformation are additional causes. A purely motor disorder without atrophy always raises the question of myasthenia gravis (Chap. 42). As noted above, Guillain-Barré syndrome commonly affects the facial nerves bilaterally. In the Fisher variant of the Guillain-Barré syndrome, oculomotor paresis occurs with ataxia and areflexia in the limbs (Chap. 41). Wernicke encephalopathy can cause a severe ophthalmoplegia combined with other brainstem signs.

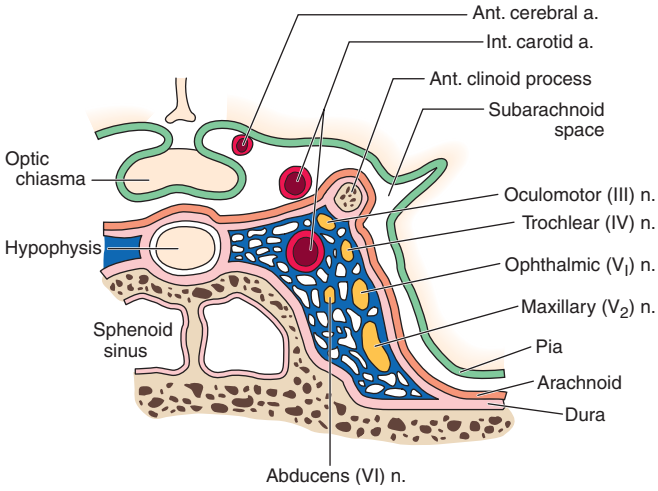


FIGURE 29-4

Anatomy of the cavernous sinus in coronal section, illustrating the location of the cranial nerves in relation to the vascular sinus, internal carotid artery (which loops anteriorly to the section), and surrounding structures.

The *cavernous sinus syndrome* (Fig. 29-4) is a distinctive and frequently life-threatening disorder. It often presents as orbital or facial pain; orbital swelling and chemosis due to occlusion of the ophthalmic veins; fever; oculomotor neuropathy affecting the third, fourth, and sixth cranial nerves; and trigeminal neuropathy affecting the ophthalmic (V_1) and occasionally the maxillary (V_2) divisions of the trigeminal nerve. Cavernous sinus thrombosis, often secondary to infection from orbital cellulitis (frequently *Staphylococcus aureus*), a cutaneous source on the face, or sinusitis (especially with mucormycosis in diabetic patients), is the most frequent cause; other etiologies include aneurysm of the carotid artery, a carotid-cavernous fistula (orbital bruit may be present), meningioma, nasopharyngeal carcinoma, other tumors, or an idiopathic granulomatous disorder (Tolosa-Hunt syndrome). The two cavernous sinuses directly communicate via intercavernous channels; thus, involvement on one side may extend to become bilateral. Early diagnosis is essential, especially when due to infection, and treatment depends on the underlying etiology.

In infectious cases, prompt administration of broad-spectrum antibiotics, drainage of any abscess cavities, and identification of the offending organism are essential. Anticoagulant therapy may benefit cases of primary thrombosis. Repair or occlusion of the carotid artery may be required for treatment of fistulas or aneurysms. The Tolosa-Hunt syndrome generally responds to glucocorticoids. A dramatic improvement in pain is usually evident within a few days; oral prednisone (60 mg daily) is usually continued for several weeks and then gradually tapered.

An idiopathic form of multiple cranial nerve involvement on one or both sides of the face is occasionally seen. The syndrome consists of a subacute onset of boring facial pain, followed by paralysis of motor cranial nerves. The clinical features overlap those of the Tolosa-Hunt syndrome and appear to be due to idiopathic inflammation of the dura mater, which may be visualized by MRI. The syndrome is frequently responsive to glucocorticoids.

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CHAPTER 30

DISEASES OF THE SPINAL CORD

Stephen L. Hauser ■ Allan H. Ropper

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Diseases of the spinal cord are frequently devastating. They produce quadriplegia, paraplegia, and sensory deficits far beyond the damage they would inflict elsewhere in the nervous system because the spinal cord contains, in a small cross-sectional area, almost the entire motor output and sensory input of the trunk and limbs. Many spinal cord diseases are reversible if recognized and treated at an early stage (**Table 30-1**); thus, they are among the most critical of neurologic emergencies. The efficient use of diagnostic procedures, guided by knowledge of the anatomy and the clinical features of spinal cord diseases, is required for a successful outcome.

Approach to the Patient: SPINAL CORD DISEASE

SPINAL CORD ANATOMY RELEVANT TO CLINICAL SIGNS The spinal cord is a thin, tubular extension of the central nervous system contained within the bony spinal canal. It originates at the medulla and continues caudally to the conus medullaris at the lumbar level; its fibrous extension, the filum terminale, terminates at the coccyx. The adult spinal cord is ~46 cm (18 in.) long, oval in shape, and enlarged in the cervical and lumbar regions, where neurons that innervate the upper and lower extremities, respectively, are located. The white matter tracts containing ascending sensory and descending motor pathways are located peripherally, whereas nerve cell bodies are clustered in an inner region shaped like a four-leaf clover that surrounds the central canal (anatomically an extension of the fourth ventricle). The membranes that cover the spinal cord—the pia, arachnoid, and dura—are continuous with those of the brain.

The spinal cord has 31 segments, each defined by an exiting ventral motor root and entering dorsal sensory root. During embryologic development, growth of the cord lags behind that of the vertebral column, and the mature spinal cord ends at approximately the first lumbar vertebral body. The lower spinal nerves take an increasingly downward course to exit via intervertebral foramina. The first seven pairs of cervical spinal nerves exit above the same-numbered vertebral bodies, whereas all the subsequent nerves exit below the same-numbered vertebral bodies because of the presence of eight cervical spinal cord segments but only seven cervical vertebrae. The relationship between spinal cord segments and the corresponding vertebral bodies is shown in **Table 30-2**. These relationships assume particular importance for localization of lesions that cause spinal cord

TABLE 30-1

TREATABLE SPINAL CORD DISORDERS

- Compressive
  - Epidural, intradural, or intramedullary neoplasm
  - Epidural abscess
  - Epidural hemorrhage
  - Cervical spondylosis
  - Herniated disc
  - Posttraumatic compression by fractured or displaced vertebra or hemorrhage
- Vascular
  - Arteriovenous malformation
  - Antiphospholipid syndrome and other hypercoagulable states
- Inflammatory
  - Multiple sclerosis
  - Neuromyelitis optica
  - Transverse myelitis
  - Sarcoidosis
  - Vasculitis
- Infectious
  - Viral: VZV, HSV-1 and -2, CMV, HIV, HTLV-I, others
  - Bacterial and mycobacterial: *Borrelia*, *Listeria*, syphilis, others
  - *Mycoplasma pneumoniae*
  - Parasitic: schistosomiasis, toxoplasmosis
- Developmental
  - Syringomyelia
  - Meningomyelocoele
  - Tethered cord syndrome
- Metabolic
  - Vitamin B_{12} deficiency (subacute combined degeneration)
  - Copper deficiency

Note: VZV, varicella-zoster virus; HSV, herpes simplex virus; CMV, cytomegalovirus; HTLV, human T cell lymphotropic virus.

compression. A T10 spinal cord sensory level, for example, indicates involvement of the cord adjacent to the seventh or eighth thoracic vertebral body (Figs. 12-2 and 12-3). In addition, at every level the main ascending and descending tracts are somatotopically organized with a laminated distribution that reflects the origin or destination of nerve fibers.

TABLE 30-2

SPINAL CORD LEVELS RELATIVE TO THE VERTEBRAL BODIES

SPINAL CORD LEVEL	CORRESPONDING VERTEBRAL BODY
Upper cervical	Same as cord level
Lower cervical	1 level higher
Upper thoracic	2 levels higher
Lower thoracic	2 to 3 levels higher
Lumbar	T10-T12
Sacral	T12-L1

Determining the Level of the Lesion The presence of a horizontally defined level below which sensory, motor, and autonomic function is impaired is a hallmark of spinal cord disease. This *sensory level* is sought by asking the patient to identify a pinprick or cold stimulus (e.g., a dry tuning fork after immersion in cold water) applied to the proximal legs and lower trunk and sequentially moved up toward the neck on each side. The sensory level indicates damage to the spinothalamic tract one to two segments above the perceived level of a unilateral spinal cord lesion and at the level of a bilateral lesion. That is the result of the ascent of second-order sensory fibers, which originate in the dorsal horn, proceed to cross anterior to the central canal while ascending to join the opposite spinothalamic tract. Lesions that transect the descending corticospinal and other motor tracts cause paraplegia or quadriplegia, with the evolution over time of increased muscle tone, heightened deep tendon reflexes, and Babinski signs (the upper motor neuron syndrome). Such lesions also typically produce autonomic disturbances consisting of absent sweating below the implicated cord level and bladder, bowel, and sexual dysfunction.

The uppermost level of a spinal cord lesion can also be localized by attention to the *segmental signs* corresponding to disturbed motor or sensory innervation by an individual cord segment. A band of altered sensation (hyperalgesia or hyperpathia) at the upper end of the sensory disturbance, fasciculations or atrophy in muscles innervated by one or several segments, or a muted or absent deep tendon reflex may be noted at this level. These signs also occur with focal root or peripheral nerve disorders; thus, segmental signs are most useful when they occur together with signs of long tract damage. With severe and acute transverse lesions, the limbs initially may be flaccid rather than spastic. This state of "spinal shock" lasts for several days, rarely for weeks, and should not be mistaken for extensive damage to many segments of the cord or for an acute polyneuropathy.

The main features of transverse damage at each level of the spinal cord are summarized below.

Cervical Cord Upper cervical cord lesions produce quadriplegia and weakness of the diaphragm. Lesions at C4-C5 produce quadriplegia; at C5-C6, there is loss of power and reflexes in the biceps; at C7 weakness is found only in finger and wrist extensors and triceps; and at C8, finger and wrist flexion are impaired. Horner's syndrome (miosis, ptosis, and facial hypohidrosis) may accompany a cervical cord lesion at any level.

Thoracic Cord Lesions here are localized by the sensory level on the trunk and by the site of midline

back pain if it accompanies the syndrome. Useful markers for localization are the nipples (T4) and umbilicus (T10). Leg weakness and disturbances of bladder and bowel function accompany the paralysis. Lesions at T9-T10 paralyze the lower—but not the upper—abdominal muscles, resulting in upward movement of the umbilicus when the abdominal wall contracts (*Beevor's sign*).

Lumbar Cord Lesions at the L2-L4 spinal cord levels paralyze flexion and adduction of the thigh, weaken leg extension at the knee, and abolish the patellar reflex. Lesions at L5-S1 paralyze only movements of the foot and ankle, flexion at the knee, and extension of the thigh, and abolish the ankle jerks (S1).

Sacral Cord/Conus Medullaris The conus medullaris is the tapered caudal termination of the spinal cord, comprising the lower sacral and single coccygeal segments. The conus syndrome is distinctive, consisting of bilateral saddle anesthesia (S3-S5), prominent bladder and bowel dysfunction (urinary retention and incontinence with lax anal tone), and impotence. The bulbocavernosus (S2-S4) and anal (S4-S5) reflexes are absent (Chap. 1). Muscle strength is largely preserved. By contrast, lesions of the cauda equina, the cluster of nerve roots derived from the lower cord, are characterized by low back and radicular pain, asymmetric leg weakness and sensory loss, variable areflexia in the lower extremities, and relative sparing of bowel and bladder function. Mass lesions in the lower spinal canal often produce a mixed clinical picture in which elements of both cauda equina and conus medullaris syndromes coexist. Cauda equina syndromes are also discussed in Chap. 7.

Special Patterns of Spinal Cord Disease

The location of the major ascending and descending pathways of the spinal cord are shown in **Fig. 30-1**. Most fiber tracts—including the posterior columns and the spinocerebellar and pyramidal tracts—are situated on the side of the body they innervate. However, afferent fibers mediating pain and temperature sensation ascend in the spinothalamic tract contralateral to the side they supply. The anatomic configurations of

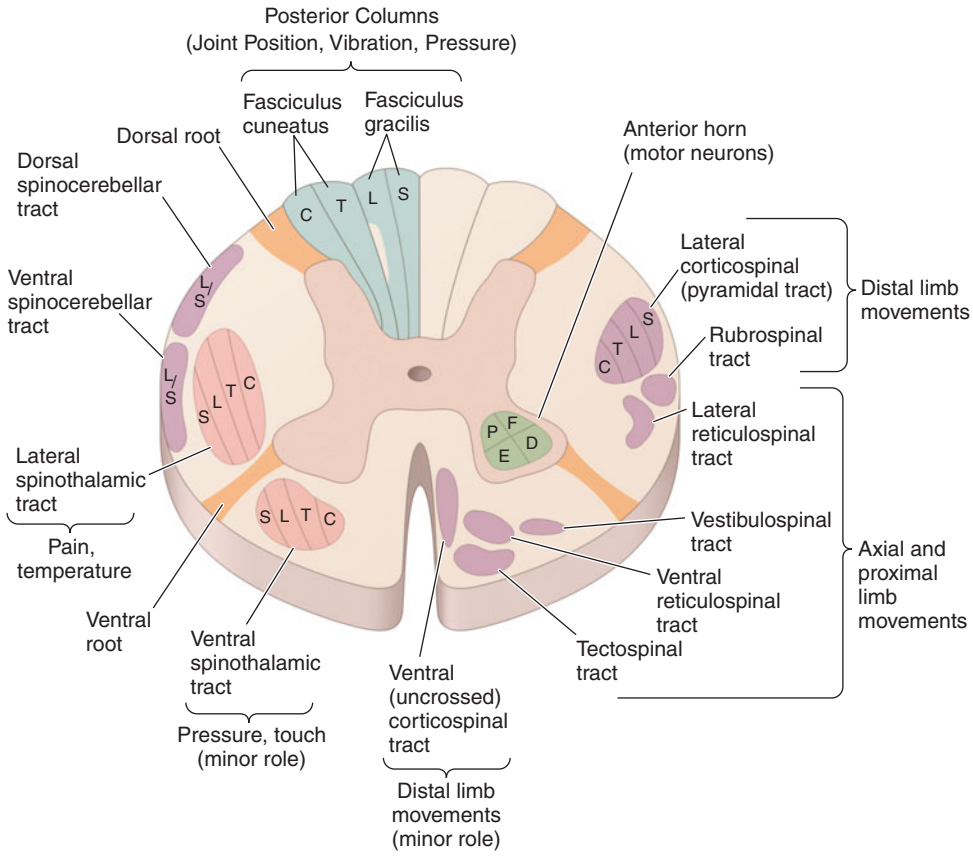


FIGURE 30-1

Transverse section through the spinal cord, composite representation, illustrating the principal ascending (*left*) and descending (*right*) pathways. The lateral and ventral spinothalamic tracts (*blue*) ascend contralateral to the side of the body that is innervated. C, cervical; T, thoracic; L, lumbar; S, sacral; P, proximal; D, distal; F, flexors, E, extensors.

these tracts produce characteristic syndromes that provide clues to the underlying disease process.

Brown-Sequard Hemicord Syndrome This consists of ipsilateral weakness (corticospinal tract) and loss of joint position and vibratory sense (posterior column), with contralateral loss of pain and temperature sense (spinothalamic tract) one or two levels below the lesion. Segmental signs, such as radicular pain, muscle atrophy, or loss of a deep tendon reflex, are unilateral. This classical pattern is rare, and partial forms are more commonly encountered.

Central Cord Syndrome The central cord syndrome results from damage to the gray matter nerve cells and crossing spinothalamic tracts near the central canal. In the cervical cord, the central cord syndrome produces arm weakness out of proportion to leg weakness and a "dissociated" sensory loss, signifying a loss of pain and temperature sense in a cape distribution over the shoulders, lower neck, and upper trunk in contrast to preservation of light touch, joint position, and vibration sense in these regions. Trauma, syringomyelia, tumors, and anterior spinal artery ischemia (including from aortic dissection) are the main causes.

Anterior Spinal Artery Syndrome Infarction of the cord is generally the result of occlusion or diminished flow in this artery. The result is extensive bilateral tissue destruction that spares the posterior columns. All spinal cord functions—motor, sensory, and autonomic—are lost below the level of the lesion, with the striking exception of retained vibration and position sensation.

Foramen Magnum Syndrome Lesions in this area interrupt decussating pyramidal tract fibers destined for the legs, which cross caudal to those of the arms, resulting in weakness of the legs (*crural paresis*). Compressive lesions near the foramen magnum may produce weakness of the ipsilateral shoulder and arm followed by weakness of the ipsilateral leg, then the contralateral leg, and finally the contralateral arm, an "around the clock" pattern that may begin in any of the four limbs. There is typically suboccipital pain spreading to the neck and shoulders.

Intramedullary and Extramedullary Syndromes It is useful to differentiate *intramedullary* processes, arising within the substance of the cord, from *extramedullary* ones that compress the spinal cord or its vascular supply. The differentiating features are only relative and serve as clinical guides. With extramedullary lesions, radicular pain is often prominent, and there is early sacral sensory loss (lateral spinothalamic tract) and spastic weakness in the legs (corticospinal tract) due to the superficial location of leg fibers in the corticospinal tract. Intramedullary lesions tend to produce poorly localized burning pain rather than radicular pain and spare sensation in the perineal and sacral areas ("sacral sparing"), reflecting the laminated configuration of the spinothalamic tract with sacral fibers outermost; corticospinal tract signs appear later. Regarding extramedullary lesions, a further distinction is made between extradural and intradural masses, as the former are generally malignant and the latter benign (neurofibroma being a common cause). Consequently, a long duration of symptoms favors an intradural origin.

ACUTE AND SUBACUTE SPINAL CORD DISEASES

The initial symptoms of disease that evolve over days or weeks are focal neck or back pain, followed by various combinations of paresthesias, sensory loss, motor weakness, and sphincter disturbance evolving over hours to several days. There may be only mild sensory symptoms or a devastating functional transection of the cord. Partial lesions selectively involve the posterior columns or anterior spinothalamic tracts or are limited to one side of the cord. Paresthesias or numbness typically begins in the feet and ascends symmetrically or asymmetrically. These symptoms initially simulate Guillain-Barré syndrome, but involvement of the trunk with a sharply demarcated spinal cord level indicates the myelopathic nature of the process. In severe and abrupt cases, areflexia reflecting spinal shock may be present, but hyperreflexia supervenes over days or weeks; persistent areflexic paralysis with a sensory level indicates necrosis over multiple segments of the spinal cord.

Approach to the Patient: COMPRESSIVE AND NONCOMPRESSIVE MYELOPATHY

DISTINGUISHING COMPRESSIVE FROM NONCOMPRESSIVE MYELOPATHY The first priority is to exclude a treatable compression of the cord by a mass. The common causes are tumor, epidural abscess or hematoma, herniated disc, or vertebral pathology. Epidural compression due to malignancy or abscess often causes warning signs of neck or back pain, bladder disturbances, and sensory symptoms that precede the development of paralysis. Spinal subluxation, hemorrhage, and noncompressive etiologies such as infarction are more likely to produce myelopathy without antecedent symptoms. MRI with gadolinium

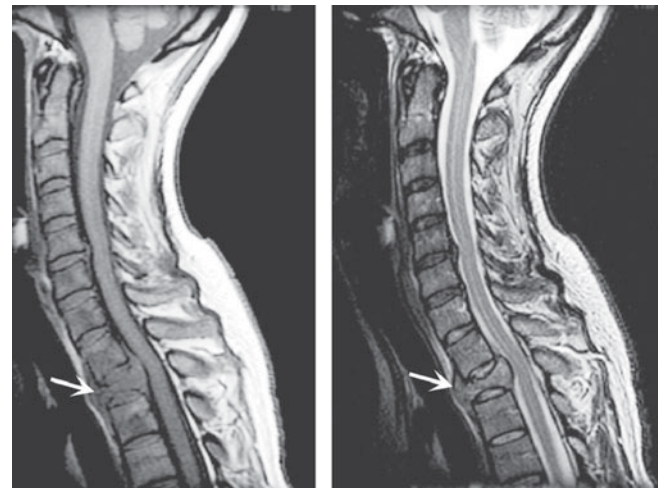
infusion, centered on the clinically suspected level, is the initial diagnostic procedure; in some cases it is appropriate to image the entire spine (cervical through sacral regions) to search for additional clinically silent lesions. Once compressive lesions have been excluded, noncompressive causes of acute myelopathy that are intrinsic to the cord are considered, primarily vascular, inflammatory, and infectious etiologies.

COMPRESSIVE MYELOPATHIES

Neoplastic Spinal Cord Compression

In adults, most neoplasms are epidural in origin, resulting from metastases to the adjacent spinal bones. The propensity of solid tumors to metastasize to the vertebral column probably reflects the high proportion of bone marrow located in the axial skeleton. Almost any malignant tumor can metastasize to the spinal column, with breast, lung, prostate, kidney, lymphoma, and plasma cell dyscrasia being particularly frequent. The thoracic cord is most commonly involved; exceptions are metastases from prostate and ovarian cancer, which occur disproportionately in the sacral and lumbar vertebrae, probably resulting from spread through Batson's plexus, a network of veins along the anterior epidural space. Retroperitoneal neoplasms (especially lymphomas or sarcomas) enter the spinal canal through the intervertebral foramina; they produce radicular pain and other signs of root involvement prior to cord compression.

Pain is usually the initial symptom; it may be aching and localized or sharp and radiating in quality. This spinal ache typically worsens with movement, coughing, or sneezing and characteristically awakens patients at night. A recent onset of persistent back pain, particularly if in the thoracic spine (which is uncommonly involved by spondylosis), should prompt consideration of vertebral metastasis. Rarely, pain is mild or absent. Plain radiographs of the spine and radionuclide bone scans have only a limited role in diagnosis because they do not identify 15–20% of metastatic vertebral lesions and fail to detect paravertebral masses that reach the epidural space through the intervertebral foramina. MRI provides excellent anatomic resolution of the extent of spinal tumors (**Fig. 30-2**) and is able to distinguish between malignant lesions and other masses—epidural abscess, tuberculoma, or epidural hemorrhage, among others—that present in a similar fashion. Vertebral metastases are usually hypointense relative to a normal bone marrow signal on T1-weighted MRI scans; after the administration of gadolinium, contrast enhancement may deceptively "normalize" the appearance of the tumor by increasing its intensity to that of normal bone marrow. Infections of the spinal column (osteomyelitis and related disorders) are distinctive in that, unlike tumor, they may cross the disk space to involve the adjacent vertebral body.



A *B*

FIGURE 30-2

Epidural spinal cord compression due to breast carcinoma. Sagittal T1-weighted (***A***) and T2-weighted (***B***) MRI scans through the cervicothoracic junction reveal an infiltrated and collapsed second thoracic vertebral body with posterior displacement and compression of the upper thoracic spinal cord. The low-intensity bone marrow signal in ***A*** signifies replacement by tumor.

If spinal cord compression is suspected, imaging should be obtained promptly. If there are radicular symptoms but no evidence of myelopathy, it is usually safe, if necessary, to defer imaging for 24–48 h. With back or neck pain only, imaging studies may be obtained within a few days. Up to 40% of patients who present with cord compression at one level are found to have asymptomatic epidural disease elsewhere; thus, the length of the spine should be imaged when epidural malignancy is in question.

Treatment:
NEOPLASTIC SPINAL CORD COMPRESSION

Management of cord compression includes glucocorticoids to reduce cord edema, local radiotherapy (initiated as early as possible) to the symptomatic lesion, and specific therapy for the underlying tumor type. Glucocorticoids (dexamethasone, up to 40 mg daily) can be administered before the imaging study if the clinical suspicion is strong and continued at a lower dose until radiotherapy (generally 3000 cGy administered in 15 daily fractions) is completed. Radiotherapy appears to be as effective as surgery, even for most classically radioresistant metastases. Biopsy of the epidural mass is

unnecessary in patients with known preexisting cancer but is indicated if a history of underlying cancer is lacking. Surgery, either decompression by laminectomy or vertebral body resection, should be considered when signs of cord compression worsen despite radiotherapy, when the maximum tolerated dose of radiotherapy has been delivered previously to the site, or when a vertebral compression fracture or spinal instability contributes to cord compression. A good response to radiotherapy can be expected in individuals who are ambulatory at presentation; new weakness is prevented, and some recovery of motor function occurs in approximately half of treated patients. Fixed motor deficits (paraplegia or quadriplegia), once established for >12 h, do not usually improve, and beyond 48 h the prognosis for substantial motor recovery is poor.

In contrast to tumors of the epidural space, most intradural mass lesions are slow-growing and benign. Meningiomas and neurofibromas account for most of these, with occasional cases caused by chordoma, lipoma, dermoid, or sarcoma. Meningiomas (Fig. 30–3) are often located posterior to the thoracic cord or near the foramen magnum, although they can arise from the meninges anywhere along the spinal canal. Neurofibromas are benign tumors of the nerve sheath that typically arise near the posterior root; when multiple, neurofibromatosis is the likely etiology. Symptoms usually begin with radicular sensory symptoms followed by an asymmetric, progressive spinal cord syndrome. Therapy is by surgical resection.

Primary intramedullary tumors of the spinal cord are uncommon. They present as central cord or hemicord syndromes, often in the cervical region; there may be poorly localized burning pain in the extremities and sparing of sacral sensation. In adults, these lesions are ependymomas, hemangioblastomas, or low-grade astrocytomas (Fig. 30–4). Complete resection of an intramedullary ependymoma is often possible with microsurgical techniques. Debulking of an intramedullary astrocytoma can also be helpful, as these are often slowly growing lesions; the value of adjunctive radiotherapy and chemotherapy is uncertain. Secondary (metastatic) intramedullary tumors are also common, especially in patients with advanced metastatic disease (Chap. 32).

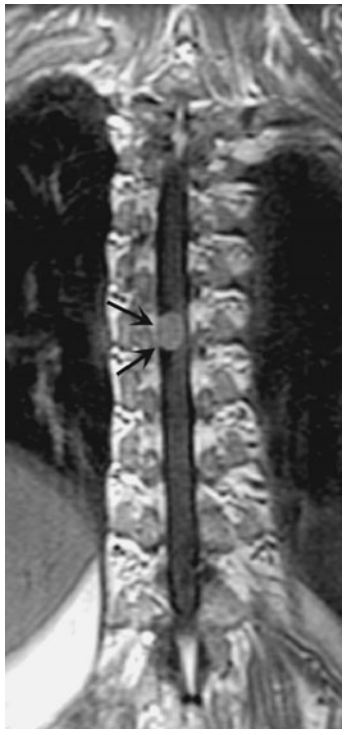


FIGURE 30-3
MRI of a thoracic meningioma. Coronal T1-weighted post-contrast image through the thoracic spinal cord demonstrates intense and uniform enhancement of a well-circumscribed extramedullary mass (*arrows*) which displaces the spinal cord to the left.

Spinal Epidural Abscess

Spinal epidural abscess presents as a clinical triad of midline dorsal pain, fever, and progressive limb weakness. Prompt recognition of this distinctive process will in most cases prevent permanent sequelae. Aching pain is almost always present, either over the spine or in a radicular

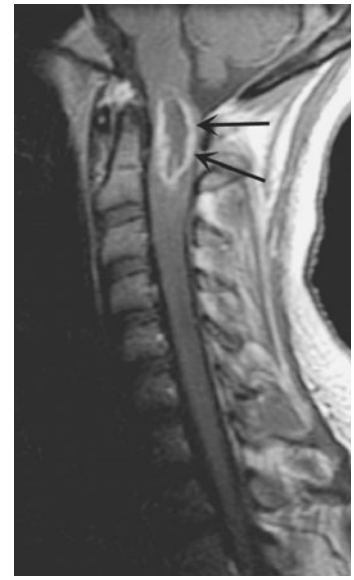
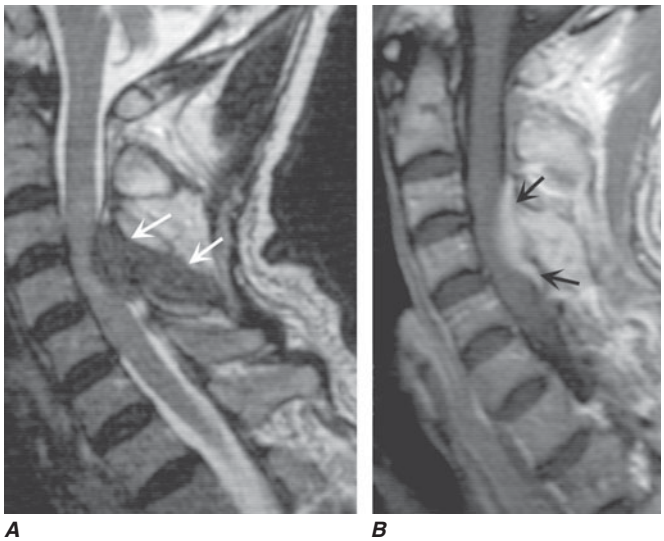


FIGURE 30-4
MRI of an intramedullary astrocytoma. Sagittal T1-weighted post-contrast image through the cervical spine demonstrates expansion of the upper cervical spine by a mass lesion emanating from within the spinal cord at the cervicomedullary junction. Irregular peripheral enhancement occurs within the mass (*arrows*).

pattern. The duration of pain prior to presentation is generally ≤2 weeks but may on occasion be several months or longer. Fever is usual, accompanied by elevated white blood cell count and sedimentation rate. As the abscess expands, further spinal cord damage results from venous congestion and thrombosis. Once weakness and other signs of myelopathy appear, progression may be rapid. A more chronic sterile granulomatous form of abscess is also known, usually after treatment of an acute epidural infection.

Risk factors include an impaired immune status (diabetes mellitus, renal failure, alcoholism, malignancy), intravenous drug abuse, and infections of the skin or other tissues. Two-thirds of epidural infections result from hematogenous spread of bacteria from the skin (furunculosis), soft tissue (pharyngeal or dental abscesses), or deep viscera (bacterial endocarditis). The remainder arise from direct extension of a local infection to the subdural space; examples of local predisposing conditions are vertebral osteomyelitis, decubitus ulcers, lumbar puncture, epidural anesthesia, or spinal surgery. Most cases are due to *Staphylococcus aureus*; gram-negative bacilli, *Streptococcus*, anaerobes, and fungi can also cause epidural abscesses. Tuberculosis from an adjacent vertebral source, Pott's disease, remains an important cause in the underdeveloped world.

MRI scans (Fig. 30–5) localize the abscess and exclude other causes of myelopathy. Lumbar puncture is only required if encephalopathy or other clinical signs raise the question of associated meningitis, a feature that is found in <25% of cases. The level of the puncture should be planned to minimize the risk of meningitis due to passage of the needle through infected tissue or herniation due to decompression below an area of obstruction to the flow of cerebrospinal fluid (CSF). A high cervical tap is often the safest approach. CSF abnormalities in subdural abscess consist of pleocytosis with a preponderance of polymorphonuclear cells, an elevated protein level, and a reduced glucose level, but the responsible organism is not cultured unless there is associated meningitis. Blood cultures are positive in <25% of cases.



A ***B***

FIGURE 30-5

MRI of a spinal epidural abscess due to tuberculosis. ***A.*** Sagittal T2-weighted free spin-echo MR sequence. A hypointense mass replaces the posterior elements of C3 and extends epidurally to compress the spinal cord (*arrows*). ***B.*** Sagittal T1-weighted image after contrast administration reveals a diffuse enhancement of the epidural process (*arrows*) with extension into the epidural space.

℞ Treatment: SPINAL EPIDURAL ABSCESS

Treatment is by decompressive laminectomy with debridement combined with long-term antibiotic treatment. Surgical evacuation prevents development of paralysis and may improve or reverse paralysis in evolution, but it is unlikely to improve deficits of more than several days duration. Antibiotics should be started empirically before surgery and then modified on the basis of culture results; medication is continued for at least 4 weeks. If surgery is contraindicated or if there is a fixed paraplegia or quadriplegia that is unlikely to improve following surgery, long-term administration of systemic and oral antibiotics can be used; in such cases, the choice of antibiotics may be guided by results of blood cultures. However, paralysis may develop or progress during antibiotic therapy; thus, initial surgical management remains the treatment of choice unless the abscess is limited in size and causes few or no neurologic signs.

Spinal Epidural Hematoma

Hemorrhage into the epidural (or subdural) space causes acute focal or radicular pain followed by variable signs of a spinal cord or conus medullaris disorder. Therapeutic anticoagulation, trauma, tumor, or blood dyscrasia are predisposing conditions. Rare cases complicate lumbar puncture or epidural anesthesia, sometimes in association with use of low-molecular-weight heparin. MRI and CT confirm the clinical suspicion and can delineate the extent of the bleeding. Treatment consists of prompt reversal of any underlying clotting disorder and surgical decompression. Surgery may be followed by substantial recovery, especially in patients with some preservation of motor function preoperatively. Because of the risk of hemorrhage, lumbar puncture should be avoided whenever possible in patients with severe thrombocytopenia or other coagulopathies.

Hematomyelia

Hemorrhage into the substance of the spinal cord is a rare result of trauma, intraparenchymal vascular malformation (see later), vasculitis due to polyarteritis nodosa or systemic lupus erythematosus (SLE), bleeding disorders, or a spinal cord neoplasm. Hematomyelia presents as an acute painful transverse myelopathy. With large lesions, extension into the subarachnoid space may occur, resulting in subarachnoid hemorrhage (Chap. 22). Diagnosis is by MRI or CT. Therapy is supportive, and surgical intervention is generally not useful. An exception is hematomyelia due to an underlying vascular malformation, for which selective spinal angiography may be indicated, followed by surgery to evacuate the clot and remove the underlying vascular lesion.

NONCOMPRESSIVE MYELOPATHIES

The most frequent causes of noncompressive acute transverse myelopathy (ATM) are spinal cord infarction; systemic inflammatory disorders, including SLE and sarcoidosis; demyelinating diseases, including multiple sclerosis (MS) and neuromyelitis optica; postinfectious or idiopathic transverse myelitis, which is presumed to be an immune condition related to acute disseminated encephalomyelitis (Chap. 34); and infectious (primarily viral) causes. After spinal cord compression is excluded, the evaluation generally requires a lumbar puncture and a search for underlying systemic disease (**Table 30-3**).

TABLE 30-3

EVALUATION OF ACUTE TRANSVERSE MYELOPATHY

1. MRI of spinal cord with and without contrast (exclude compressive causes).
2. CSF studies: Cell count, protein, glucose, IgG index/synthesis rate, oligoclonal bands, VDRL; Gram's stain, acid-fast bacilli, and India ink stains; PCR for VZV, HSV-2, HSV-1, EBV, CMV, HHV-6, enteroviruses, HIV; antibody for HTLV-I, *B. burgdorferi*, *M. pneumoniae*, and *Chlamydia pneumoniae*; viral, bacterial, mycobacterial, and fungal cultures.
3. Blood studies for infection: HIV; RPR; IgG and IgM enterovirus antibody; IgM mumps, measles, rubella, group B arbovirus, *Brucella melitensis*, *Chlamydia psittaci*, *Bartonella henselae*, schistosomal antibody; cultures for *B. melitensis*. Also consider nasal/pharyngeal/anal cultures for enteroviruses; stool O&P for *Schistosoma* ova.
4. Immune-mediated disorders: ESR; ANA; ENA; dsDNA; rheumatoid factor; anti-SSA; anti-SSB, complement levels; antiphospholipid and anticardiolipin antibodies; p-ANCA; antimicrosomal and antithyroglobulin antibodies; if Sjögren syndrome suspected, Schirmer test, salivary gland scintography, and salivary/lacrimal gland biopsy.
5. Sarcoidosis: Serum angiotensin-converting enzyme; serum Ca; 24-h urine Ca; chest x-ray; chest CT; total body gallium scan; lymph node biopsy.
6. Demyelinating disease: Brain MRI scan, evoked potentials, CSF oligoclonal bands, neuromyelitis optica antibody (aquaporin-4).
7. Vascular causes: CT myelogram; spinal angiogram.

Note: VDRL, Venereal Disease Research Laboratory; PCR, polymerase chain reaction; VZV, varicella-zoster virus; HHV, human herpes virus; RPR, rapid plasma reagin (test); O&P, ova and parasites; ESR, erythrocyte sedimentation rate; ANA, antinuclear antibodies; ENA, epithelial neutrophil-activating peptide.

Spinal Cord Infarction

The cord is supplied by three arteries that course vertically over its surface: a single anterior spinal artery and paired posterior spinal arteries. In addition to the vertebral arteries, the anterior spinal artery is fed by radicular vessels that arise at C6, at an upper thoracic level, and, most consistently, at T11-L2 (artery of Adamkiewicz). At each segment, paired penetrating vessels branch from the anterior spinal artery to supply the anterior two-thirds of the spinal cord; the posterior spinal arteries, which often become less distinct below the midthoracic level, supply the posterior columns.

Spinal cord ischemia can occur at any level; however, the presence of the artery of Adamkiewicz creates a watershed of marginal blood flow in the upper thoracic segments. With systemic hypotension, cord infarction occurs at the level of greatest ischemic risk, usually T3-T4, and also at boundary zones between the anterior and posterior spinal artery territories. The latter may result in a rapidly progressive syndrome over hours of weakness and spasticity with little sensory change.

Acute infarction in the territory of the *anterior spinal artery* produces paraplegia or quadriplegia, dissociated sensory loss affecting pain and temperature sense but sparing vibration and position sense, and loss of sphincter control ("anterior cord syndrome"). Onset may be sudden and dramatic but more typically is progressive over minutes or a few hours, quite unlike stroke in the cerebral hemispheres. Sharp midline or radiating back pain localized to the area of ischemia is frequent. Areflexia due to spinal shock is often present initially; with time, hyperreflexia and spasticity appear. Less common is infarction in the territory of the *posterior spinal arteries*, resulting in loss of posterior column function.

Spinal cord infarction results from aortic atherosclerosis, dissecting aortic aneurysm (manifest as chest or back pain with diminished pulses in legs), vertebral artery occlusion or dissection in the neck, or profound hypotension from any cause. Cardiogenic emboli, vasculitis related to collagen vascular disease [particularly SLE and the antiphospholipid antibody syndrome (see later in this chapter)], and surgical interruption of aortic aneurysms are other causative conditions. Occasional cases

develop from *embolism of nucleus pulposus* material into spinal vessels, usually from local spine trauma. In a substantial number of cases no cause can be found, and thromboembolism in arterial feeders is suspected. The MRI may fail to demonstrate limited infarctions of the cord, especially in the first day, but as often it is abnormal at the affected level.

In cord infarction due to presumed thromboembolism, acute anticoagulation is probably not indicated, with the exception of the unusual transient ischemic attack or incomplete infarction with a stuttering or progressive course. The antiphospholipid antibody syndrome is treated with anticoagulation. Drainage of spinal fluid has reportedly been successful in some cases of cord infarction but has not been studied systematically.

Inflammatory and Immune Myelopathies (Myelitis)

This broad category includes MS and postinfectious myelitis, both of which are demyelinating in nature (see later), as well as connective tissue disease. In approximately one-quarter of cases of myelitis, no underlying cause can be identified. Some will later manifest additional symptoms of a systemic immune-mediated disease such as SLE or, more often, MS. *Recurrent episodes of myelitis* are usually due to an immune-mediated disease such as a demyelinating disease, SLE, or sarcoid; or to infection with herpes simplex virus (HSV) type 2 (see later).

Systemic Inflammatory Disorders

Myelitis occurs in a small number of patients with SLE, many cases of which are associated with antiphospholipid antibodies. The CSF is usually normal or shows a mild lymphocytic pleocytosis; oligoclonal bands are a variable finding. Responses to glucocorticoids and/or cyclophosphamide have been reported, but there is no systematic evidence of their benefit. Other immune-mediated myelitides include cases associated with Sjögren's syndrome, mixed connective tissue disease, Behçet's syndrome, and vasculitis with perinuclear antineutrophilic cytoplasmic (p-ANCA) antibodies.

Another important consideration in this group is sarcoid myelopathy, in which an edematous swelling of the spinal cord may mimic tumor; there is almost always gadolinium enhancement of the lesion and of the adjacent surface of the cord. The CSF profile consists of variable lymphocytic pleocytosis; oligoclonal bands are present in one-third of cases. The diagnosis is particularly difficult when systemic manifestations of sarcoid are minor or absent (nearly 50% of cases) or when other classic neurologic manifestations of the disease—such as cranial neuropathy, hypothalamic involvement, or meningeal enhancement visualized by MRI—are lacking. A slit-lamp examination of the eye to search for uveitis, chest x-ray and CT to assess pulmonary involvement and mediastinal lymphadenopathy, serum angiotensin-converting enzyme [(ACE); positive in only one-quarter of cases], serum calcium, and a gallium scan may assist in the diagnosis. The usefulness of spinal fluid ACE is uncertain. Initial treatment is with oral glucocorticoids; immunosuppressant drugs are used for resistant cases.

Demyelinating Myelopathies

Multiple sclerosis (MS) (Chap. 34) may present with myelitis, particularly in individuals of Asian or African ancestry. In whites, MS rarely causes a complete transverse myelopathy (i.e., acute bilateral signs), but it is among the most common causes of a partial syndrome. Neuromyelitis optica (NMO) is a demyelinating syndrome consisting of a severe myelopathy associated with optic neuritis; the optic neuritis is often bilateral and may precede or follow myelitis by weeks or months (Chap. 34). A specific serum antibody test is available. NMO is also associated with SLE and antiphospholipid antibodies (see earlier) as well as with other connective tissue diseases.

MRI findings in MS-associated myelitis typically consist of mild swelling and edema of the cord and diffuse or multifocal areas of abnormal signal on T2-weighted sequences. Contrast enhancement, indicating disruption in the blood-brain barrier associated with inflammation, is present in many acute cases. A brain MRI is most helpful in gauging the likelihood that a case of myelitis represents an initial attack of MS. A normal scan indicates that the risk of evolution to MS is low, ~10–15% over 5 years; in contrast, the finding of multiple periventricular T2-bright lesions indicates a much higher risk, >50% over 5 years and >90% by 14 years. The CSF may be normal, but more often there is a mild pleocytosis, occasionally up to several hundred mononuclear cells per microliter, with normal or mildly elevated CSF protein levels; oligoclonal bands are variable, but when bands are present, a diagnosis of MS is more likely. These bands are generally absent in neuromyelitis optica.

There are no adequate trials of therapy for MS-associated transverse myelitis. Intravenous methylprednisolone (500 mg qd for 3 days) followed by oral prednisone (1 mg/kg per day for several weeks, then gradual taper) has been used as initial treatment. A course of plasma exchange is indicated for severe cases if glucocorticoids are ineffective. Preliminary data suggest that treatment with anti-CD20 (anti-B cell) monoclonal antibody may protect against relapses in patients with NMO.

Postinfectious Myelitis

Many cases of myelitis, termed *postinfectious* or *postvaccinal*, follow an infection or vaccination. Numerous organisms have been implicated, including Epstein-Barr virus (EBV), cytomegalovirus (CMV), mycoplasma, influenza, measles, varicella, rubeola, and mumps. As in the related

disorder acute disseminated encephalomyelitis (Chap. 34), postinfectious myelitis often begins as the patient appears to be recovering from an acute febrile infection, or in the subsequent days or weeks, but an infectious agent cannot be isolated from the nervous system or spinal fluid. The presumption is that the myelitis represents an autoimmune disorder triggered by infection and is not due to direct infection of the spinal cord. Treatment is usually with glucocorticoids or, in fulminant cases, plasma exchange. There are no trials by which to adequately judge these therapies.

Acute Infectious Myelitis

Many viruses have been associated with an acute myelitis that is infectious in nature rather than postinfectious. Nonetheless, the two processes are often difficult to distinguish. Herpes zoster is the best characterized viral myelitis, but HSV types 1 and 2, EBV, CMV, and rabies virus are other well-described causes. HSV-2 (and less commonly HSV-1) produces a distinctive syndrome of recurrent sacral myelitis in association with outbreaks of genital herpes mimicking MS. Poliomyelitis is the prototypic viral myelitis, but it is more or less restricted to the gray matter of the cord. Chronic viral myelitic infections, such as that due to HIV, are discussed below.

Bacterial and mycobacterial myelitis (most are essentially abscesses) are far less common than viral causes. Almost any pathogenic species may be responsible, including *Listeria monocytogenes*, *Borrelia burgdorferi* (Lyme disease), and *Treponema pallidum* (syphilis). *Mycoplasma pneumoniae* may be a cause of myelitis, but its status is uncertain since many cases are more properly classified as postinfectious.

Schistosomiasis is an important cause of parasitic myelitis in endemic areas. The process is intensely inflammatory and granulomatous, caused by a local response to tissue-digesting enzymes from the ova of the parasite. Toxoplasmosis can occasionally cause a focal myelopathy, and this diagnosis should be considered, particularly in patients with AIDS, Chap. 37).

In cases of suspected viral myelitis, it may be appropriate to begin specific therapy pending laboratory confirmation. Herpes zoster, HSV, and EBV myelitis are treated with intravenous acyclovir (10 mg/kg q8h) or oral valacyclovir (2 gm tid) for 10–14 days; CMV with ganciclovir (5 mg/kg IV bid) plus foscarnet (60 mg/kg IV tid), or cidofovir (5 mg/kg per week for 2 weeks).

CHRONIC MYELOPATHIES

SPONDYLITIC MYELOPATHY

Spondylitic myelopathy is one of the most common causes of gait difficulty in the elderly. Neck and shoulder pain with stiffness are early symptoms; impingement of bone and soft tissue overgrowth on nerve roots results in radicular arm pain, most often in a C5 or C6 distribution. Compression of the cervical cord, which occurs in fewer than one-third of cases, produces a slowly progressive spastic paraparesis, at times asymmetric and often accompanied by paresthesias in the feet and hands. Vibratory sense is diminished in the legs, there is a Romberg sign, and occasionally there is a sensory level for vibration on the upper thorax. In some cases, coughing or straining produces leg weakness or radiating arm or shoulder pain. Dermatomal sensory loss in the arms, atrophy of intrinsic hand muscles, increased deep-tendon reflexes in the legs, and extensor plantar responses are common. Urinary urgency or incontinence occurs in advanced cases, but there are many alternative causes of these problems in older individuals. A tendon reflex in the arms is often diminished at some level; the biceps is most often affected (C5-C6). In individual cases, radicular, myelopathic, or combined signs may predominate. The diagnosis should be considered in cases of progressive cervical myelopathy, paresthesias of the feet and hands, or wasting of the hands.

Diagnosis is made by MRI or myelography. Extrinsic cord compression and deformation is appreciated on axial MRI views, and T2-weighted sequences may reveal areas of high signal intensity within the cord adjacent to the site of compression. A cervical collar may be helpful in milder cases, but definitive therapy consists of surgical decompression. Posterior laminectomy or an anterior approach with resection of the protruded disc and bony material may be required. Cervical spondylosis and related degenerative diseases of the spine are discussed in Chap. 7.

VASCULAR MALFORMATIONS OF THE CORD AND DURA

Although uncommon, vascular malformations of the cord and overlying dura are treatable causes of progressive myelopathy. True arteriovenous malformations (AVMs) are located posteriorly along the surface of the cord or within the dura, where they are more properly classified as fistulas. Most are at or below the midthoracic level. The typical presentation is a middle-aged man with a progressive myelopathy that worsens slowly or intermittently and may have periods of apparent remission resembling MS. Acute deterioration due to hemorrhage into the spinal cord or subarachnoid space may also occur but is rare. A saltatory progression is most common and is the result of local ischemia and edema from venous congestion. Most patients have incomplete sensory, motor, and bladder disturbances. The motor disorder may predominate and produce a mixture of upper and restricted lower motor neuron signs, simulating amyotrophic lateral sclerosis (ALS). Pain over the dorsal spine, dysesthesias, or radicular pain may be present. Other symptoms suggestive of AVM include intermittent claudication, symptoms that change

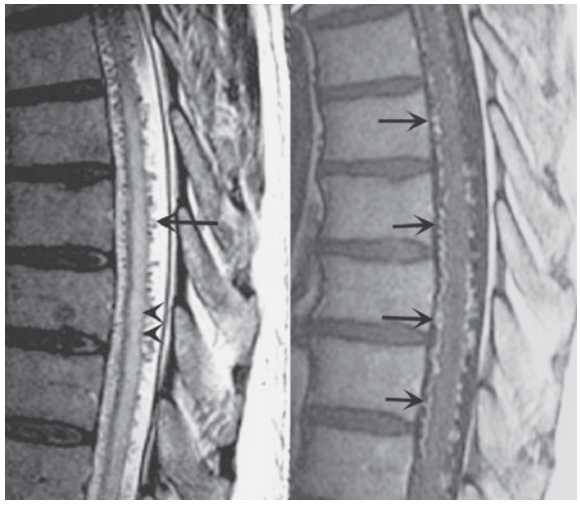
with posture, exertion such as singing, menses, or fever. A rare AVM process presents as a progressive thoracic myelopathy with paraparesis developing over weeks or several months, characterized pathologically by abnormally thick, hyalinized vessels within the cord (Foix-Alajouanine syndrome).

Spinal bruits are infrequent but should be sought at rest and after exercise in suspected cases. High-resolution MRI with contrast administration detects many but not all AVMs (**Fig. 30-6**). A small number not detected by MRI may be visualized by CT myelography as enlarged vessels along the surface of the cord. Definitive diagnosis requires selective spinal angiography, which defines the feeding vessels and the extent of the malformation. Endovascular embolization of the major feeding vessels may stabilize a progressive neurologic deficit or allow for gradual recovery.

RETROVIRUS-ASSOCIATED MYELOPATHIES

The myelopathy associated with the human T cell lymphotropic virus type I (HTLV-I), formerly called tropical spastic paraparesis, is a slowly progressive spastic syndrome with variable sensory and bladder disturbance. Approximately half of patients have mild back or leg pain. The neurologic signs may be asymmetric, often lacking a well-defined sensory level; the only sign in the arms may be hyperreflexia after several years of illness. The onset is insidious, and the illness is slowly progressive at a variable rate; most patients are unable to walk within 10 years of onset. This presentation may resemble primary progressive MS or a thoracic AVM. Diagnosis is made by demonstration of HTLV-I–specific antibody in serum by enzyme-linked immunosorbent assay (ELISA), confirmed by radioimmunoprecipitation or western blot analysis. There is no effective treatment, but symptomatic therapy for spasticity and bladder symptoms may be helpful.

A progressive myelopathy may also result from HIV infection (Chap. 37). It is characterized by vacuolar degeneration of the posterior and lateral tracts, resembling subacute combined degeneration (see later).



A B

FIGURE 30-6

Arteriovenous malformation. Sagittal MR scans of the thoracic spinal cord: T2 fast spin-echo technique (***A***) and T1 post-contrast image (***B***). On the T2-weighted image (*left*), abnormally high signal intensity is noted in the central aspect of the spinal cord (*arrowheads*). Numerous punctate flow voids indent the dorsal and ventral spinal cord (*arrow*). These represent the abnormally dilated venous plexus supplied by a dural arteriovenous fistula. After contrast administration (***B***), multiple, serpentine, enhancing veins (*arrows*) on the ventral and dorsal aspect of the thoracic spinal cord are visualized, diagnostic of arteriovenous malformation. This patient was a 54-year-old man with a 4-year history of progressive paraparesis.

SYRINGOMYELIA

Syringomyelia is a developmental cavitary expansion of the cervical cord that is prone to enlarge and produce progressive myelopathy. Symptoms begin insidiously in adolescence or early adulthood, progress irregularly, and may undergo spontaneous arrest for several years. Many young patients acquire a cervical-thoracic scoliosis. More than one-half of all cases are associated with Chiari type 1 malformations in which the cerebellar tonsils protrude through the foramen magnum and into the cervical spinal canal. The pathophysiology of syrinx expansion is controversial, but some interference with the normal flow of CSF seems likely, perhaps by the Chiari malformation. Acquired cavitations of the cord in areas of necrosis are also termed *syrinx cavities*; these follow trauma, myelitis, necrotic spinal cord tumors, and chronic arachnoiditis due to tuberculosis and other etiologies.

The classic presentation is a central cord syndrome consisting of a dissociated sensory loss and areflexic weakness in the upper limbs. The sensory deficit is recognizable by loss of pain and temperature sensation with sparing of touch and vibration in a distribution that is "suspended" over the nape of the neck, shoulders, and upper arms (cape distribution) or in the hands. Most cases begin asymmetrically with unilateral sensory loss in the hands that leads to injuries and burns that are not appreciated by the patient. Muscle wasting in the lower neck, shoulders, arms, and hands with asymmetric or absent reflexes in the arms reflects expansion of the cavity into the gray matter of the cord. As the cavity enlarges and further compresses the long tracts, spasticity and weakness of the legs, bladder and bowel dysfunction, and a Horner's syndrome appear. Some patients develop facial numbness and sensory loss from damage to the descending tract of the trigeminal nerve (C2 level

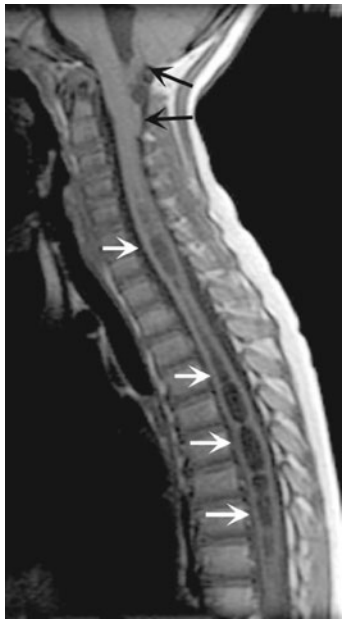


FIGURE 30-7

MRI of syringomyelia associated with a Chiari malformation. Sagittal T1-weighted image through the cervical and upper thoracic spine demonstrates descent of the cerebellar tonsils and vermis below the level of the foramen magnum (*black arrows*). Within the substance of the cervical and thoracic spinal cord, a CSF collection dilates the central canal (*white arrows*).

or above). In cases with Chiari malformations, cough-induced headache and neck, arm, or facial pain are reported. Extension of the syrinx into the medulla, syringobulbia, causes palatal or vocal cord paralysis, dysarthria, horizontal or vertical nystagmus, episodic dizziness, and tongue weakness.

MRI scans accurately identify developmental and acquired syrinx cavities and their associated spinal cord enlargement (Fig. 30-7). MRI scans of the brain and the entire spinal cord should be obtained to delineate the full longitudinal extent of the syrinx, assess posterior fossa structures for the Chiari malformation, and determine whether hydrocephalus is present.

Rx Treatment: SYRINGOMYELIA

Treatment of syringomyelia is generally unsatisfactory. The Chiari tonsillar herniation is usually decompressed, generally by suboccipital craniectomy, upper cervical laminectomy, and placement of a dural graft. Obstruction of fourth ventricular outflow is reestablished by this procedure. If the syrinx cavity is large, some surgeons recommend direct decompression or drainage by one of a number of methods, but the added benefit of this procedure is uncertain, and morbidity is common. With Chiari malformations, shunting of hydrocephalus should generally precede any attempt to correct the syrinx. Surgery may stabilize the neurologic deficit, and some patients improve.

Syringomyelia secondary to trauma or infection is treated with a decompression and drainage procedure in which a small shunt is inserted between the syrinx cavity and the subarachnoid space; alternatively, the cavity can be fenestrated. Cases due to intramedullary spinal cord tumor are generally managed by resection of the tumor.

CHRONIC MYELOPATHY OF MULTIPLE SCLEROSIS

A chronic progressive myelopathy is the most frequent cause of disability in both primary progressive and secondary progressive forms of MS. Involvement is typically bilateral but asymmetric and produces motor, sensory, and bladder/bowel disturbances. Fixed motor disability appears to result from extensive loss of axons in the corticospinal tracts; thus, the symptoms are not simply due to demyelination. Diagnosis is facilitated by identification of earlier attacks such as optic neuritis. MRI, CSF, and evoked response testing are confirmatory. Therapy with interferon β, glatiramer acetate, or natalizumab is indicated for patients with progressive myelopathy who also have coexisting MS relapses. These therapies are sometimes also offered to patients without relapses, despite the lack of evidence supporting their value in this setting. MS is discussed in Chap. 34.

SUBACUTE COMBINED DEGENERATION (VITAMIN B_{12} DEFICIENCY)

This treatable myelopathy presents with subacute paresthesias in the hands and feet, loss of vibration and position sensation, and a progressive spastic and ataxic weakness. Loss of reflexes due to an associated peripheral neuropathy in a patient who also has Babinski signs, is an important diagnostic clue. Optic atrophy and irritability or other mental changes may be prominent in advanced cases and are rarely the presenting symptoms. The myelopathy of subacute combined degeneration tends to be diffuse rather than focal; signs are generally symmetric and reflect predominant involvement of the posterior and lateral tracts, including Romberg's sign. The diagnosis is confirmed by the finding of macrocytic red blood cells, a low serum B_{12} concentration, elevated serum levels of homocysteine and methylmalonic acid, and in uncertain cases a positive Schilling test. Treatment is by replacement therapy, beginning

with 1000 μg of intramuscular vitamin B_{12} repeated at regular intervals or by subsequent oral treatment.

HYPOCUPRIC MYELOPATHY

This recently described myelopathy is virtually identical to subacute combined degeneration (described above) and probably explains many cases previously described with normal serum levels of B_{12}. Low levels of serum copper are found and often there is also a low level of serum ceruloplasmin. Some cases follow gastrointestinal procedures that result in impaired copper absorption, but many others are idiopathic. Improvement or at least stabilization may be expected with reconstitution of copper stores by oral supplementation. The pathophysiology and pathology are not known.

TABES DORSALIS

The classic syndromes of tabes dorsalis and meningovascular syphilis of the spinal cord are now less frequent than in the past but must be considered in the differential diagnosis of spinal cord disorders. The characteristic symptoms of tabes are fleeting and repetitive lancinating pains, primarily in the legs or less often in the back, thorax, abdomen, arms, and face. Ataxia of the legs and gait due to loss of position sense occurs in half of patients. Paresthesias, bladder disturbances, and acute abdominal pain with vomiting (visceral crisis) occur in 15–30% of patients. The cardinal signs of tabes are loss of reflexes in the legs; impaired position and vibratory sense; Romberg's sign; and, in almost all cases, bilateral Argyll Robertson pupils, which fail to constrict to light but accommodate. Diabetic polyradiculopathy may simulate tabes.

FAMILIAL SPASTIC PARAPLEGIA

Many cases of slowly progressive myelopathy are genetic in origin (Chap. 27). More than 20 different causative loci have been identified, including autosomal dominant, autosomal recessive, and X-linked forms. Most patients present with almost imperceptibly progressive spasticity and weakness in the legs, usually but not always symmetrical. Sensory symptoms and signs are absent or mild, but sphincter disturbances may be present. In some families additional neurologic signs are prominent, including nystagmus, ataxia, or optic atrophy. The onset may be as early as the first year of life or as late as middle adulthood. Only symptomatic therapies for the spasticity are currently available.

ADRENOMYELONEUROPATHY

This X-linked disorder is a variant of adrenoleukodystrophy. Affected males usually have a history of adrenal insufficiency beginning in childhood and then develop a progressive spastic (or ataxic) paraparesis beginning in early adulthood; some patients also have a mild peripheral neuropathy. Female heterozygotes may develop a slower, insidiously progressive spastic myelopathy beginning later in adulthood and without adrenal insufficiency. Diagnosis is usually made by demonstration of elevated levels of very long chain fatty acids in plasma and in cultured fibroblasts. The responsible gene encodes ADLP, a peroxisomal membrane transporter that is a member of the ATP-binding cassette (ABC) family. Steroid replacement is indicated if hypoadrenalism is present, and bone marrow transplantation and nutritional supplements have been attempted for this condition without clear evidence of efficacy.

OTHER CHRONIC MYELOPATHIES

Primary lateral sclerosis (Chap. 27) is a degenerative disorder characterized by progressive spasticity with weakness, eventually accompanied by dysarthria and dysphonia; bladder symptoms occur in approximately half of patients. Sensory function is spared. The disorder resembles ALS and is considered a variant of the motor neuron degenerations, but without the characteristic lower motor neuron disturbance. Some cases may represent familial spastic paraplegia, particularly autosomal recessive or X-linked varieties in which a family history may be absent.

There are a number of rare toxic causes of spastic myelopathy, including lathyrism due to ingestion of chick peas containing the excitotoxin β-*N*-oxalylaminoalanine (BOAA), seen primarily in the developing world, and nitrous oxide inhalation producing a myelopathy identical to subacute combined degeneration. SLE, Sjögren's syndrome, and sarcoidosis may each cause a myelopathy without overt evidence of systemic disease. Cancer-related causes of chronic myelopathy, besides the common neoplastic compressive myelopathy discussed earlier, include a rare paraneoplastic myelopathy (Chap. 39) or radiation injury (Chap. 32). It is notable that metastases to the cord are probably more common than either of these. In obscure cases, a cause can often be identified through periodic reassessment.

REHABILITATION OF SPINAL CORD DISORDERS

The prospects for recovery from an acute destructive spinal cord lesion fade after ~6 months. There are currently no effective means to promote repair of injured spinal cord tissue; promising experimental approaches include the use of factors that influence reinnervation by axons of the corticospinal tract, nerve and neural

TABLE 30-4

EXPECTED NEUROLOGIC FUNCTION FOLLOWING COMPLETE CORD LESIONS

LEVEL	SELF-CARE	TRANSFERS	MAXIMUM MOBILITY
High quadriplegia (C1-C4)	Dependent on others; requires respiratory support	Dependent on others	Motorized wheelchair
Low quadriplegia (C5-C8)	Partially independent with adaptive equipment	May be dependent or independent	May use manual wheelchair, drive an automobile with adaptive equipment
Paraplegia (below T1)	Independent	Independent	Ambulates short distances with aids

Source: Adapted from JF Ditunno, CS Formal: Chronic spinal cord injury. N Engl J Med 330:550, 1994; with permission.

sheath graft bridges, and the local introduction of stem cells. The disability associated with irreversible spinal cord damage is determined primarily by the level of the lesion and by whether the disturbance in function is complete or incomplete (Table 30-4). Even a complete high cervical cord lesion may be compatible with a productive life. The primary goals are development of a rehabilitation plan framed by realistic expectations and attention to the neurologic, medical, and psychological complications that commonly arise.

Many of the usual symptoms associated with medical illnesses, especially somatic and visceral pain, may be lacking because of the destruction of afferent pain pathways. Unexplained fever, worsening of spasticity, or deterioration in neurologic function should prompt a search for infection, thrombophlebitis, or an intraabdominal pathology. The loss of normal thermoregulation and inability to maintain normal body temperature can produce recurrent fever (*quadriplegic fever*), although most episodes of fever are due to infection of the urinary tract, lung, skin, or bone.

Bladder dysfunction generally results from loss of supraspinal innervation of the detrusor muscle of the bladder wall and the sphincter musculature. Detrusor spasticity is treated with anticholinergic drugs (oxybutinin, 2.5–5 mg qid) or tricyclic antidepressants with anticholinergic properties (imipramine, 25–200 mg/d). Failure of the sphincter muscle to relax during bladder emptying (urinary dyssynergia) may be managed with the α-adrenergic blocking agent terazosin hydrochloride (1–2 mg tid or qid), with intermittent catheterization, or, if that is not feasible, by use of a condom catheter in men or a permanent indwelling catheter. Surgical options include the creation of an artificial bladder by isolating a segment of intestine that can be catheterized intermittently (enterocystoplasty) or can drain continuously to an external appliance (urinary conduit). Bladder areflexia due to acute spinal shock or conus lesions is best treated by catheterization. Bowel regimens and disimpaction are necessary in most patients to ensure at least biweekly evacuation and avoid colonic distention or obstruction.

Patients with acute cord injury are at risk for venous thrombosis and pulmonary embolism. During the first 2 weeks, use of calf-compression devices and anticoagulation with heparin (5000 U subcutaneously every 12 h) or warfarin (INR, 2–3) are recommended. In cases of persistent paralysis, anticoagulation should probably be continued for 3 months.

Prophylaxis against decubitus ulcers should involve frequent changes in position in a chair or bed, the use of special mattresses, and cushioning of areas where pressure sores often develop, such as the sacral prominence and heels. Early treatment of ulcers with careful cleansing, surgical or enzyme debridement of necrotic tissue, and appropriate dressing and drainage may prevent infection of adjacent soft tissue or bone.

Spasticity is aided by stretching exercises to maintain mobility of joints. Drug treatment is effective but may result in reduced function, as some patients depend upon spasticity as an aid to stand, transfer, or walk. Baclofen (15–240 mg/d in divided doses) is effective; it acts by facilitating GABA-mediated inhibition of motor reflex arcs. Diazepam acts by a similar mechanism and is useful for leg spasms that interrupt sleep (2–4 mg at bedtime). Tizanidine (2–8 mg tid), an α_2 adrenergic agonist that increases presynaptic inhibition of motor neurons, is another option. For nonambulatory patients, the direct muscle inhibitor dantrolene (25–100 mg qid) may be used, but it is potentially hepatotoxic. In refractory cases, intrathecal baclofen administered via an implanted pump, botulinum toxin injections, or dorsal rhizotomy may be required to control spasticity.

A paroxysmal autonomic hyperreflexia may occur following lesions above the major splanchnic sympathetic outflow at T6. Headache, flushing, and diaphoresis above the level of the lesion, as well as hypertension with bradycardia or tachycardia, are the major symptoms. The trigger is typically a noxious stimulus—for example, bladder or bowel distention, a urinary tract infection, or a decubitus ulcer—below the level of the cord lesion. Treatment consists of removal of offending stimuli; ganglionic blocking agents (mecamylamine, 2.5–5 mg) or other short-acting antihypertensive drugs are useful in some patients.

Attention to these details allows longevity and a productive life for patients with complete transverse myelopathies.

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CHAPTER 31

CONCUSSION AND OTHER HEAD INJURIES

Allan H. Ropper

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Almost 10 million head injuries occur annually in the United States, about 20% of which are serious enough to cause brain damage. Among men <35 years, accidents, usually motor vehicle collisions, are the chief cause of death, and >70% of these involve head injury. Furthermore, minor head injuries are so common that almost all physicians will be called upon to provide immediate care or to see patients who are suffering from various sequelae.

Medical personnel caring for head injury patients should be aware that (1) spinal injury often accompanies head injury and care must be taken to prevent compression of the spinal cord due to instability of the spinal column; (2) intoxication is an important accompaniment of traumatic brain injury and, when appropriate, testing should be carried out for drugs and alcohol; and (3) accompanying systemic injuries, including rupture of abdominal organs, may produce vascular collapse or respiratory compromise requiring immediate attention.

TYPES OF HEAD INJURIES

CONCUSSION

This classically refers to an immediate but transient loss of consciousness that is associated with a short period of amnesia. Some patients do not lose consciousness after a minor head injury and instead may appear dazed, confused or report feeling "star struck." The mechanics of concussion involve a blunt forward impact that creates sudden deceleration of the head and an anterior-posterior movement of the brain within the skull. Severe concussion may precipitate a brief convulsion or autonomic signs such as facial pallor, bradycardia, faintness with mild hypotension, or sluggish pupillary reaction, but most patients are soon neurologically normal. The loss of consciousness in concussion is believed to be a transient electrophysiologic dysfunction of the reticular activating system in the upper midbrain caused by rotation of the cerebral hemispheres on the relatively fixed brainstem (Chap. 14).

Gross- and light-microscopic changes in the brain are usually absent following concussion, but biochemical and ultrastructural changes, such as mitochondrial ATP depletion and local disruption of the blood-brain barrier, suggest that transient abnormalities occur. CT and MRI scans are usually normal; however, a small number of patients will be found to have an intracranial hemorrhage or brain contusion.

A brief period of both retrograde and anterograde amnesia is typical of concussion and disappears rapidly in alert patients. The memory loss spans the moments before impact but with severe injuries loss of memory may encompass the previous days or weeks (rarely months). The extent of retrograde amnesia roughly correlates with the severity of injury. Memory is regained

in an orderly way from the most distant to recent memories, with islands of amnesia occasionally remaining. The mechanism of amnesia is not known. Hysterical posttraumatic amnesia is not uncommon after head injury and should be suspected when inexplicable abnormalities of behavior occur, such as recounting events that cannot be recalled on later testing, a bizarre affect, forgetting one's own name, or a persistent anterograde deficit that is excessive in comparison with the degree of injury. A further discussion of amnesia is provided in Chap. 15.

A single, uncomplicated concussion only infrequently produces permanent neurobehavioral changes in patients who are free of preexisting psychiatric problems and substance abuse. Nonetheless, residual minor problems in memory and concentration may have an anatomic correlate in microscopic cerebral lesions (see later).

CONTUSION, BRAIN HEMORRHAGE, AND AXONAL SHEARING LESIONS

A surface bruise of the brain, or *contusion*, consists of varying degrees of petechial hemorrhage, edema, and tissue destruction. Contusions and deeper hemorrhages result from mechanical forces that displace and compress the hemispheres forcefully and by deceleration of the brain against the inner skull, either under a point of impact (coup lesion) or, as the brain swings back, in the antipolar area (contrecoup lesion). Trauma sufficient to cause prolonged unconsciousness usually produces some degree of contusion. Blunt deceleration impact, as from an automobile dashboard or from falling forward while drunk, causes contusions on the orbital surfaces of the frontal lobes and the anterior and basal portions of the temporal lobes. With lateral forces, as from impact on an automobile door frame, the contusions are situated on the lateral convexity of the hemisphere. The clinical signs are determined by the location and size of the contusion; often, there are no focal neurologic abnormalities. A hemiparesis or gaze preference is fairly typical of moderately sized contusions. Large bilateral contusions produce coma with extensor posturing, while those limited to the frontal lobes cause a taciturn state. Contusions in the temporal lobe may cause delirium or an aggressive, combative syndrome.

Contusions are easily visible on CT and MRI scans, appearing as inhomogeneous hyperdensities on CT and as hyperintensities on MRI; the signal changes reflect small scattered areas of cortical and subcortical blood and localized brain edema (Fig. 31-1); there is usually some subarachnoid bleeding detected by scans or lumbar puncture. Blood in the cerebrospinal fluid (CSF) resulting from trauma may provoke a mild inflammatory reaction. Over a few days, contusions acquire a surrounding contrast enhancement and edema that may be mistaken for tumor or abscess. Glial and macrophage

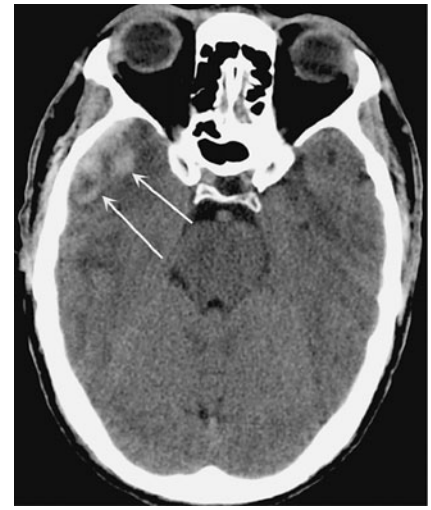

FIGURE 31-1
Traumatic cerebral contusion. Noncontrast CT scan demonstrating a hyperdense hemorrhagic region in the anterior temporal lobe.

reactions result in scarred, hemosiderin-stained depressions on the cortex (*plaques jaunes*) that are the main source of posttraumatic epilepsy.

Torsion or shearing forces within the brain cause hemorrhages of the basal ganglia and other deep regions. Large hemorrhages after minor trauma suggest that there is a bleeding diathesis or cerebrovascular amyloidosis. For unexplained reasons, deep cerebral hemorrhages may not develop until several days after injury. Sudden neurologic deterioration in a comatose patient or a sudden rise in intracranial pressure (ICP) should therefore prompt investigation with a CT scan.

Another type of deep white matter lesion consists of widespread acute disruption, or shearing, of axons at the time of impact. Most characteristic are small areas of tissue injury in the corpus callosum and dorsolateral pons. The presence of widespread axonal damage in both hemispheres, a state called *diffuse axonal injury*, is proposed to explain persistent coma and the vegetative state after closed head injury (Chap. 14), but small ischemic-hemorrhagic lesions in the midbrain and thalamus are as often the cause of this clinical state. Only severe shearing lesions that contain blood are visualized by CT, usually in the corpus callosum and centrum semiovale (Fig. 31-2); however, special imaging sequences of the MRI can demonstrate such lesions throughout the white matter.

SKULL FRACTURES

A blow to the skull causes fracture if the elastic tolerance of the bone is exceeded. Intracranial lesions accompany roughly two-thirds of skull fractures, and the presence of a skull fracture increases manyfold the chances of an

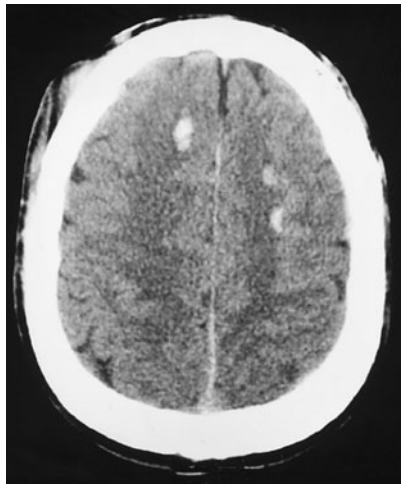

FIGURE 31-2
Multiple small areas of hemorrhage and tissue disruption in the white matter of the frontal lobes on noncontrast CT scan. These appear to reflect an extreme type of the diffuse axonal shearing lesions that occur with closed head injury.

underlying subdural or epidural hematoma. Consequently, fractures are primarily markers of the site and severity of injury. They also provide potential pathways for entry of bacteria (meningitis) or air (pneumocephalus) to the CSF and for leakage of CSF out through the dura.

Most fractures are linear and extend from the point of impact toward the base of the skull. Basilar skull fractures are often extensions of adjacent linear fractures over the convexity of the skull but may occur independently owing to stresses on the floor of the middle cranial fossa or occiput. Basilar fractures are usually parallel to the petrous bone or along the sphenoid bone and directed toward the sella turcica and ethmoidal groove. Although most basilar fractures are uncomplicated, they can cause CSF leakage, pneumocephalus, and cavernous-carotid fistulas. Hemotympanum (blood behind the tympanic membrane), delayed ecchymosis over the mastoid process (Battle sign), or periorbital ecchymosis ("raccoon sign") are associated signs. Because routine x-ray examination may fail to disclose basilar fractures, they should be suspected if these clinical signs are present.

CSF may leak through the cribriform plate or the adjacent sinus and allow a watery discharge from the nose (CSF rhinorrhea). Persistent rhinorrhea and recurrent meningitis are indications for surgical repair of torn dura underlying the fracture. The site of the leak is often difficult to determine, but useful diagnostic tests include the instillation of water-soluble contrast into the CSF followed by CT with the patient in various positions, or injection of radionuclide compounds or fluorescein into the CSF and the insertion of absorptive nasal pledgets. The site of an intermittent leak is rarely delineated, and many resolve spontaneously.

Sellar fractures, even those associated with serious neuroendocrine dysfunction, may be radiologically occult or are evident by an air-fluid level in the sphenoid sinus. Fractures of the dorsum sella cause sixth or seventh nerve palsies or optic nerve damage.

Petrous bone fractures, especially those oriented along the long axis of the bone, may be associated with facial palsy, disruption of ear ossicles, and CSF otorrhea. Transverse petrous fractures are less common; they almost always damage the cochlea or labyrinths and often the facial nerve as well. External bleeding from the ear is usually from local abrasion of the external canal but can also result from petrous fracture.

Fractures of the frontal bone are usually depressed, involving the frontal and paranasal sinuses and the orbits; permanent anosmia results if the olfactory filaments in the cribriform plate are disrupted. Depressed skull fractures are typically compound, but they are often asymptomatic because the impact energy is dissipated in breaking the bone; however, a few have underlying brain contusions. Debridement and exploration of compound fractures are required in order to avoid infection; simple fractures do not require surgery.

CRANIAL NERVE INJURIES

The cranial nerves most often injured with head trauma are the olfactory, optic, oculomotor, and trochlear; the first and second branches of the trigeminal nerve; and the facial and auditory nerves. Anosmia and an apparent loss of taste (actually a loss of perception of aromatic flavors, with elementary taste perception retained) occur in ~10% of persons with serious head injuries, particularly after falls on the back of the head. This is the result of displacement of the brain and shearing of the olfactory nerve filaments and may occur in the absence of a fracture. At least partial recovery of olfactory and gustatory function is the rule, but if bilateral anosmia persists for several months, the prognosis is poor. Partial optic nerve injuries from closed trauma result in blurring of vision, central or paracentral scotomas, or sector defects. Direct orbital injury may cause short-lived blurred vision for close objects due to reversible iridoplegia. Diplopia limited to downward gaze and corrected when the head is tilted away from the side of the affected eye indicates trochlear nerve damage. It occurs frequently as an isolated problem after minor head injury or may develop after a delay of several days without pathophysiologic explanation. Direct facial nerve injury caused by a basilar fracture is present immediately in up to 3% of severe injuries; it may also be delayed 5–7 days. Fractures through the petrous bone, particularly the less common transverse type, are liable to produce facial palsy. Delayed palsy, the mechanism of which is unknown, has a good prognosis. Injury to the eighth cranial nerve from a fracture of the petrous bone causes loss of hearing, vertigo,

and nystagmus immediately after injury. Deafness from eighth nerve injury must be distinguished from that due to rupture of the eardrum, blood in the middle ear, or disruption of the ossicles from fracture through the middle ear. Dizziness and high-tone hearing loss occur with direct cochlear concussion.

SEIZURES

Convulsions are surprisingly uncommon immediately after a head injury, but a brief period of tonic extensor posturing or a few clonic movements of the limbs just after the moment of impact can occur. However, the cortical scars that evolve from contusions are highly epileptogenic and may later manifest as seizures, even after many years (Chap. 20). The severity of injury roughly determines the risk of future seizures. It has been estimated that 17% of individuals with brain contusion, subdural hematoma, or prolonged loss of consciousness will develop a seizure disorder and that this risk extends for an indefinite period of time, whereas the risk is ≤2% after mild injury. The majority of convulsions in the latter group occurs within 5 years of injury but may be delayed for decades. Penetrating injuries have a much higher rate of subsequent epilepsy.

SUBDURAL AND EPIDURAL HEMATOMAS

Hemorrhages beneath the dura (subdural) or between the dura and skull (epidural) each have characteristic clinical and radiologic features. They are associated with underlying contusions and other injuries, often making it difficult to determine the relative contribution of each component to the clinical state. The mass effect and raised ICP caused by these hematomas may be life threatening, making it imperative to identify them rapidly by CT or MRI scan and to remove them when appropriate.

Acute Subdural Hematoma

(**Fig. 31-3**) Up to one-third of patients have a lucid interval lasting minutes to hours before coma supervenes, but most are drowsy or comatose from the moment of injury. Direct cranial trauma may be minor and is not required for acute subdural hemorrhage to occur, especially in the elderly and those taking anticoagulant medications. Acceleration forces alone, as from whiplash, are sometimes sufficient to produce subdural hemorrhage. A unilateral headache and slightly enlarged pupil on the same side are frequently but not invariably present. Stupor or coma, hemiparesis, and unilateral pupillary enlargement are signs of larger hematomas. In an acutely deteriorating patient, burr (drainage) holes or an emergency craniotomy are required. Small subdural hematomas may be asymptomatic and usually do not require evacuation.

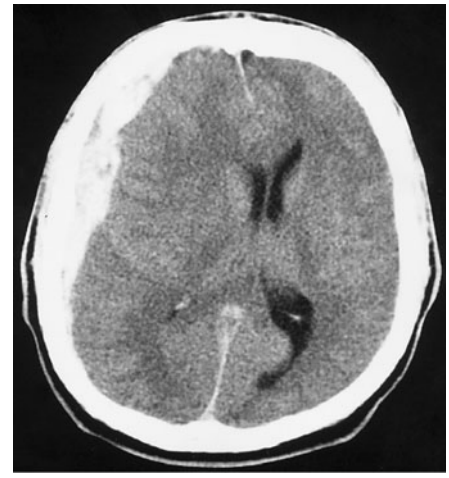

FIGURE 31-3

Acute subdural hematoma. Noncontrast CT scan reveals a hyperdense clot which has an irregular border with the brain and causes more horizontal displacement (mass effect) than might be expected from its thickness. The disproportionate mass effect is the result of the large rostral-caudal extent of these hematomas. Compare to Fig. 31-4.

A subacutely evolving syndrome due to subdural hematoma occurs days or weeks after injury with drowsiness, headache, confusion, or mild hemiparesis; it usually arises in alcoholics and in the elderly, often after only minor trauma.

On imaging studies subdural hematomas appear as crescentic collections over the convexity of one or both hemispheres, most commonly in the frontotemporal region, and less often in the inferior middle fossa or over the occipital poles (Fig. 31-3). Interhemispheric, posterior fossa, or bilateral convexity hematomas are less frequent and are difficult to diagnose clinically, although drowsiness and the signs expected for damage in each region can usually be detected. The bleeding that causes larger hematomas is primarily venous in origin, although additional arterial bleeding sites are sometimes found at operation and a few large hematomas have a purely arterial origin.

Epidural Hematoma

(**Fig. 31-4**) These evolve more rapidly than subdural hematomas and are correspondingly more treacherous. They occur in up to 10% of cases of severe head injury but are associated with underlying cortical damage less often than are subdural hematomas. Most patients are unconscious when first seen. A "lucid interval" of several minutes to hours before coma supervenes is most characteristic of epidural hemorrhage, but it is still uncommon, and epidural hemorrhage is by no means the only

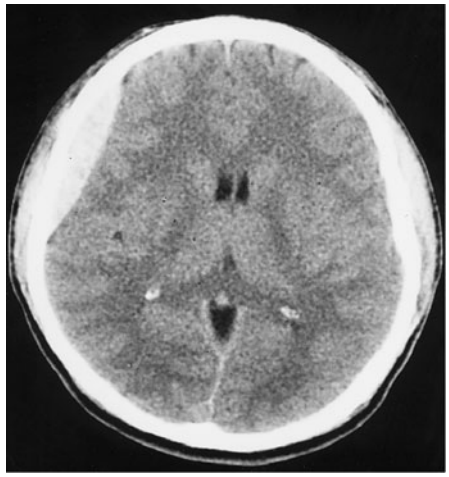

FIGURE 31-4
Acute epidural hematoma. The tightly attached dura is stripped from the inner table of the skull, producing a characteristic lenticular-shaped hemorrhage on noncontrast CT scan. Epidural hematomas are usually caused by tearing of the middle meningeal artery following fracture of the temporal bone.

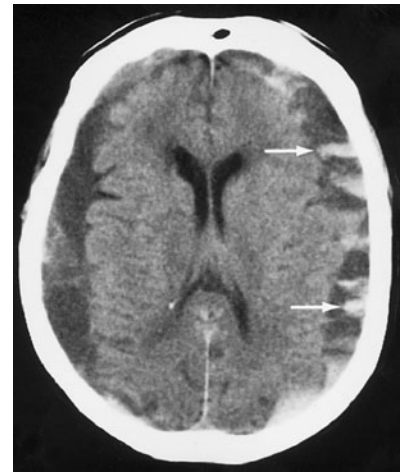

FIGURE 31-5
CT scan of chronic bilateral subdural hematomas of different ages. The collections began as acute hematomas and have become hypodense in comparison to the adjacent brain after a period during which they were isodense and difficult to appreciate. Some areas of resolving blood are contained on the more recently formed collection on the left (*arrows*).

cause of this temporal sequence. Rapid surgical evacuation and ligation or cautery of the damaged vessel that is the source of bleeding, usually the middle meningeal artery that has been lacerated by an overlying skull fracture, is indicated.

Chronic Subdural Hematoma

A history of trauma may or may not be elicited in relation to chronic subdural hematoma. The causative injury may have been trivial and forgotten; 20–30% of patients recall no head injury, particularly the elderly and those with clotting disorders. Headache is common but not invariable. Additional features may include slowed thinking, vague change in personality, seizure, or a mild hemiparesis. The headache may fluctuate in severity, sometimes with changes in head position. Bilateral chronic subdural hematomas produce perplexing clinical syndromes. Focal signs such as hemiparesis may be lacking, and the initial clinical impression may be of a stroke, brain tumor, drug intoxication, depression, or a dementing illness because drowsiness, inattentiveness, and incoherence of thought are more prominent than focal signs such as hemiparesis. Patients with undetected bilateral subdural hematomas have a low tolerance for surgery, anesthesia, and drugs that depress the nervous system, remaining drowsy or confused for long periods. Chronic hematomas rarely cause brief episodes of hemiparesis or aphasia that are indistinguishable from transient ischemic attacks; on occasion a chronic collection can expand over a period of days or weeks and clinically resemble a brain tumor.

Skull x-rays are usually normal except for a shift of the calcified pineal body to one side or an occasional unexpected fracture. In long-standing cases an irregular calcification of membranes that surround the hematoma may be appreciated. CT without contrast infusion shows a low-density mass over the convexity of the hemisphere (**Fig. 31-5**), but between 2 and 6 weeks after the initial bleeding the hemorrhage becomes isodense compared to adjacent brain and is then inapparent. Many subdural hematomas that are a week or more in age contain areas of blood adjacent to intermixed serous fluid. Bilateral chronic hematomas may fail to be detected because of the absence of lateral tissue shifts; this circumstance is suggested by a "hypernormal" CT scan with fullness of the cortical sulci and small ventricles in an older patient. The infusion of contrast material demonstrates enhancement of the vascular fibrous capsule surrounding the collection. MRI reliably identifies subacute and chronic hematomas.

Clinical observation coupled with serial imaging is a reasonable approach to patients with few symptoms and small chronic subdural collections. Treatment with glucocorticoids alone is sufficient for some hematomas, but surgical evacuation is more often successful. The fibrous membranes that grow from the dura and encapsulate the collection require removal to prevent recurrent fluid accumulation. Small hematomas are resorbed, leaving only the organizing membranes. On imaging studies very chronic subdural hematomas may be difficult to distinguish from hygromas, which are collections of CSF from a rent in the arachnoid membrane. As noted, cortical damage underlying a chronic hematoma may serve as the origin of seizures.

CLINICAL SYNDROMES AND TREATMENT OF HEAD INJURY

MINOR INJURY

The patient who is fully alert and attentive minutes after head injury but who has one or more symptoms of headache, dizziness, faintness, nausea, a single episode of emesis, difficulty with concentration, or slight blurring of vision has a good prognosis with little risk of subsequent deterioration. Such patients have usually sustained a concussion and are expected to have a brief amnestic period. Children are particularly prone to drowsiness, vomiting, and irritability, which are sometimes delayed for several hours after apparently minor injuries. Vasovagal syncope that follows injury may cause undue concern. Constant generalized or frontal headache is common in the following days. It may be migrainous (throbbing and hemicranial) in nature or aching and bilateral. After several hours of observation, patients with minor injury may be accompanied home and observed for a day by a family member or friend; written instructions to return if symptoms worsen should be provided.

Persistent severe headache and repeated vomiting in the context of normal alertness and no focal neurologic signs are usually benign, but radiologic studies should be obtained and a period of observation in the hospital is justified. The decision to perform imaging tests depends largely on clinical signs that indicate the impact was severe (e.g., prolonged concussion, periorbital or mastoid hematoma, repeated vomiting, palpable skull fracture), on the seriousness of other bodily injuries, and on the degree of surveillance that can be anticipated after discharge. Two prospective studies have suggested that older age, two or more episodes of vomiting, >30 min of retrograde or persistent anterograde amnesia, seizure, and concurrent drug or alcohol intoxication are sensitive (but not specific) indicators of intracranial hemorrhage that justify CT scanning. It is appropriate to be more liberal in obtaining CT scans in children since a small number, even without loss of consciousness, will display intracranial lesions.

Concussion in Sports

In the current absence of adequate data, a common sense approach has been taken to returning an athlete who has suffered a concussion to physical activities. It is generally advisable to avoid contact sports for several days at least, and for weeks after a severe concussion or after more than one minor concussion or if there are protracted neurologic symptoms (Table 31-1). These guidelines are designed to avoid cognitive decline and an extremely rare complication of recurrent head injury, termed the *second impact syndrome*, in which cerebral swelling follows a minor head injury. There is some

TABLE 31-1

GUIDELINES FOR MANAGEMENT OF CONCUSSION IN SPORTS

Severity of Concussion
Grade 1: Transient confusion, no loss of consciousness (LOC), all symptoms resolve within 15 min. Grade 2: Transient confusion, no LOC, but concussive symptoms or mental status abnormalities persist longer than 15 min. Grade 3: Any LOC, either brief (seconds) or prolonged (minutes).
On-site Evaluation
1. Mental status testing a. Orientation—time, place, person, circumstances of injury b. Concentration—digits backward, months of year in reverse order c. Memory—names of teams, details of contest, recent events, recall of three words and objects at 0 and 5 min 2. Finger-to-nose with eyes open and closed 3. Pupillary symmetry and reaction 4. Romberg and tandem gait 5. Provocative testing—40-yard sprint, 5 push ups, 5 sit ups, 5 knee bends (development of dizziness, headaches, or other symptoms is abnormal)
Management Guidelines
Grade 1: Remove from contest. Examine immediately and at 5 min intervals. May return to contest if exam clears within 15 min. A second grade 1 concussion eliminates player for 1 week, with return contingent upon normal neurologic assessment at rest and with exertion. Grade 2: Remove from contest, cannot return for at least 1 week. Examine at frequent intervals on sideline. Formal neurologic exam the next day. If headache or other symptoms persist for 1 week or longer, CT or MRI scan is indicated. After 1 full asymptomatic week, repeat neurologic assessment at rest and with exercise before cleared to resume play. A second grade 2 concussion eliminates player for at least 2 weeks following complete resolution of symptoms at rest or with exertion. If imaging shows abnormality, player is removed from play for the season. Grade 3: Transport by ambulance to emergency department if still unconscious or worrisome signs are present; cervical spine stabilization may be indicated. Neurologic exam and, when indicated, CT or MRI scan will guide subsequent management. Hospital admission indicated when signs of pathology are present or if mental status remains abnormal. If findings are normal at the time of the initial medical evaluation, the athlete may be sent home, but daily exams as an outpatient are indicated. A brief (LOC for seconds) grade 3 concussion eliminates player for 1 week, and a prolonged (LOC for minutes) grade 3 concussion for 2 weeks, following complete resolution of symptoms. A second grade 3 concussion should eliminate player from sports for at least 1 month following resolution of symptoms. Any abnormality on CT or MRI scans should result in termination of the season for the athlete, and return to play at any future time should be discouraged.

Source: Modified from Quality Standards Subcommittee of the American Academy of Neurology: *The American Academy of Neurology Practice Handbook.* The American Academy of Neurology, St. Paul, MN, 1997.

evidence that repeated concussions in football and soccer players are associated with mild but cumulative cognitive deficits, but this topic is controversial.

INJURY OF INTERMEDIATE SEVERITY

Patients who have persistent confusion, behavioral changes, subnormal alertness, extreme dizziness, or focal neurologic signs such as hemiparesis should be admitted to the hospital and soon thereafter have a CT scan. Usually a cerebral contusion or hematoma is found. The common clinical syndromes in this group include (1) delirium with a disinclination to be examined or moved, expletive speech, and resistance if disturbed (anterior temporal lobe contusions); (2) a quiet, disinterested, slowed mental state (abulia) with dull facial expression alternating with irascibility (inferior frontal and frontopolar contusions); (3) a focal deficit such as aphasia or mild hemiparesis (due to subdural hematoma or convexity contusion, or, less often but frequently missed, carotid artery dissection); (4) confusion and inattention, poor performance on simple mental tasks, and fluctuating or slightly erroneous orientation (associated with several types of injuries, including those described above as well as medial frontal contusions and interhemispheric subdural hematoma); (5) repetitive vomiting, nystagmus, drowsiness, and unsteadiness (usually from labyrinthine concussion, but occasionally due to a posterior fossa subdural hematoma or vertebral artery dissection); and (6) diabetes insipidus (damage to the median eminence or pituitary stalk). *Injuries of this degree are often complicated by drug or alcohol intoxication, and clinically inapparent cervical spine injury may be present.*

Most patients in this category, after appropriate surgical removal of hematomas, improve over several days or weeks. During the first week the state of alertness, memory, and other cognitive functions often fluctuates, and irascibility or agitation is common. Behavioral changes are worse at night, as with many other encephalopathies, and may be treated with small doses of antipsychotic medications. Subtle abnormalities of attention, intellect, spontaneity, and memory tend to return to normal weeks or months after the injury, sometimes surprisingly abruptly. Persistent problems in cognition are discussed below.

SEVERE INJURY

Patients who are comatose from the onset require immediate neurologic attention and resuscitation. After intubation, with care taken to immobilize the cervical spine, the depth of coma, pupillary size and reactivity, limb movements, and Babinski responses are assessed. As soon as vital functions permit and cervical spine x-rays and a CT scan have been obtained, the patient should be transported to a critical care unit where systemic complications that follow severe brain injury can be treated. Hypoxia should be reversed and normal saline used as the preferred resuscitation fluid. The finding of an epidural or subdural hematoma or large intracerebral hemorrhage is an indication for prompt surgery and intracranial decompression in an otherwise salvageable patient. The use of prophylactic anticonvulsants has been recommended by some neurosurgeons but there is little supportive data. Management of raised ICP, a frequent feature of severe head injury, is discussed in Chap. 22.

GRADING AND PROGNOSIS

In severe head injury, the clinical features of eye opening, motor responses of the limbs, and verbal output have been found to be generally predictive of outcome. These three features are summarized in the Glasgow Coma Scale; a score between 3 and 15 is assigned based on responses (Table 31-2). Over 85% of patients with aggregate scores of <5 die within 24 h. However, a number of patients with slightly higher scores and a poor initial prognosis, including a few without pupillary light responses, survive, suggesting that an initially aggressive approach is justified in most patients. Patients <20 years, particularly children, may make remarkable recoveries after having grave early neurologic signs. In one large study of severe head injury, 55% of children had a good outcome at 1 year, compared with 21% of adults. Older age, increased ICP, early hypoxia or hypotension, and evidence on imaging of compression of the cisterns surrounding the brainstem and shift of midline structures are all poor prognostic signs. A delay in the evacuation of large intracerebral hemorrhages is also associated with a poorer prognosis.

TABLE 31-2

GLASGOW COMA SCALE FOR HEAD INJURY

Eye opening (E)		Verbal response (V)	
Spontaneous	4	Oriented	5
To loud voice	3	Confused, disoriented	4
To pain	2	Inappropriate words	3
Nil	1	Incomprehensible sounds	2
Best motor response (M)		Nil	1
Obeys	6		
Localizes	5		
Withdraws (flexion)	4		
Abnormal flexion posturing	3		
Extension posturing	2		
Nil	1		

Note: Coma score = E + M + V. Patients scoring 3 or 4 have an 85% chance of dying or remaining vegetative, whereas scores >11 indicate only a 5–10% likelihood of death or vegetative state and 85% chance of moderate disability or good recovery. Intermediate scores correlate with proportional chances of recovery.

POSTCONCUSSION SYNDROME

The *postconcussion syndrome* refers to a state of nervous instability following mild or moderate head injury. The main features are fatigue, dizziness, headache, and difficulty in concentration. The syndrome is at times difficult to distinguish from asthenia and depression. Based largely on experimental models, it has been proposed that subtle axonal shearing lesions or as yet undefined biochemical alterations account for the cognitive symptoms. In moderate and severe trauma, neuropsychological changes such as difficulty with attention, memory, and other cognitive deficits are undoubtedly present, sometimes severe, but many deficits identified by formal testing do not impact daily functioning. Test scores tend to improve rapidly during the first 6 months after injury, then more slowly for years.

Rx Treatment: CONCUSSION

Management of the various symptoms of the postconcussive syndrome requires the identification and treatment of depression, sleeplessness, anxiety, persistent headache, and dizziness. A clear explanation of the problems that may follow concussion has been shown to reduce subsequent complaints. Care is taken to avoid prolonged use of drugs that produce dependence. Vestibular exercises (Chap. 9) and small doses of vestibular suppressants such as phenergan may be helpful when dizziness is the main problem. Patients who after minor or moderate injury report difficulty with memory or with complex cognitive tasks at work may also be reassured that these problems usually improve over 6–12 months. It is helpful to obtain serial and quantified neuropsychological testing in order to adjust the work environment to the patient's current abilities and to document improvement over time. Whether cognitive exercises are useful is uncertain, but patients certainly report them to be so. Previously energetic individuals usually have the best recoveries. In patients with persistent symptoms, the possibility exists of malingering or prolongation as a result of litigation.

FURTHER READINGS

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CHAPTER 32

PRIMARY AND METASTATIC TUMORS OF THE NERVOUS SYSTEM

Stephen M. Sagar ■ Mark A. Israel

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Malignant primary tumors of the central nervous system (CNS) occur in ~16,500 individuals and account for an estimated 13,000 deaths in the United States annually, a mortality rate of 6 per 100,000. The age-adjusted incidence appears to be about the same worldwide. An approximately equal number of benign tumors of the CNS are diagnosed, with a much lower mortality rate. Glial tumors account for 50–60% of primary brain tumors, meningiomas for 25%, schwannomas for 10%, and other CNS tumors for the remainder.

Brain and vertebral metastases from systemic cancer are far more prevalent than primary CNS tumors. About 15% of patients who die of cancer (80,000 individuals each year in the United States) have symptomatic brain metastases; an additional 5% suffer spinal cord involvement. Brain and spinal metastases therefore pose a major problem in the management of systemic cancer.

Approach to the Patient: BRAIN TUMORS

CLINICAL FEATURES Brain tumors usually present with one of three syndromes: (1) subacute progression of a focal neurologic deficit; (2) seizure; or (3) nonfocal neurologic disorder such as headache, dementia, personality change, or gait disorder. The presence of systemic symptoms such as malaise, weight loss, anorexia, or fever suggests a metastatic rather than a primary brain tumor.

Progressive focal neurologic deficits result from compression of neurons and white matter tracts by expanding tumor and surrounding edema. Less commonly, a brain tumor presents with a sudden stroke-like onset of a focal neurologic deficit. Although this presentation may be caused by hemorrhage into the tumor, often no hemorrhage can be demonstrated and the mechanism is obscure. Tumors frequently associated with hemorrhage include high-grade gliomas, metastatic melanoma, and choriocarcinoma.

Seizures may result from disruption of cortical circuits. Tumors that invade or compress the cerebral cortex, even small meningiomas, are more likely to be associated with seizures than subcortical neoplasms. Nonfocal neurologic dysfunction usually reflects increased intracranial pressure (ICP), hydrocephalus, or diffuse tumor spread. Tumors in some areas of the brain may produce behavioral disorders;

for example, frontal lobe tumors may present with personality change, dementia, or depression.

Headache may result from focal irritation or displacement of pain-sensitive structures (Chap. 6) or from a generalized increase in ICP. A headache that worsens rather than abates with recumbency is suggestive of a mass lesion. Headaches from increased ICP are usually holocephalic and episodic, occurring more than once a day. They typically develop rapidly over several minutes, persist for 20–40 min, and subside quickly. They may awaken the patient from a sound sleep, generally 60–90 min after retiring. Vomiting may occur with severe headaches. As elevated ICP becomes sustained, the headache becomes continuous but varying in intensity. Elevated ICP may cause papilledema (Chap. 17), although it is often not present in infants or patients >55 years.

The Karnofsky performance scale is useful in assessing patients with brain tumors (Table 32-1). A score ≥70 indicates that the patient is ambulatory and independent in self-care activities; it is often taken as a level of function justifying aggressive therapy.

NEUROIMAGING CT and MRI can reveal mass effect and contrast enhancement. Mass effect reflects the volume of neoplastic tissue as well as surrounding edema. Brain tumors typically produce a vasogenic pattern of edema, with accumulation of excess water in surrounding white matter. Contrast enhancement reflects a breakdown of the blood-brain barrier within the tumor, permitting leakage of contrast agent. Low-grade gliomas typically do not exhibit contrast enhancement.

Positron emission tomography (PET) and single-photon emission tomography (SPECT) have ancillary roles in the imaging of brain tumors, primarily in distinguishing tumor recurrence from tissue necrosis that can occur after irradiation (see below). Functional imaging with PET, MRI, or magnetoencephalography may be of use in surgical or radiosurgical planning to define the anatomic relationship of the tumor to critical brain regions such as the primary motor or language cortex.

LABORATORY EXAMINATION Primary brain tumors typically do not produce serologic abnormalities such as an elevated sedimentation rate or tumor-specific antigens. In contrast, metastases to the nervous system, depending on the type and extent of the primary tumor, may be associated with systemic signs of malignancy. Lumbar puncture is generally not useful in the diagnosis of brain tumors. The cerebrospinal fluid (CSF) rarely contains malignant cells, with the important exceptions of leptomeningeal metastases; primary CNS lymphoma; and primitive neuroectodermal tumors, including medulloblastoma. The primary use of lumbar puncture in the evaluation of a brain tumor is to exclude other diagnoses, such as infection or demyelinating disease. Moreover, lumbar puncture may precipitate brain herniation in patients with mass lesions and should be performed only in patients in whom imaging studies have demonstrated the basilar cisterns to be patent.

TABLE 32-1

KARNOFSKY PERFORMANCE INDEX

PERFORMANCE STATUS	FUNCTIONAL CAPABILITY OF THE PATIENT
100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance but is able to care for most needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated although death is not imminent
20	Very sick; hospitalization necessary; active supportive treatment is necessary
10	Moribund, fatal processes progressing rapidly
0	Dead

Rx Treatment: BRAIN TUMORS

SYMPTOMATIC Glucocorticoids decrease the volume of edema surrounding brain tumors and improve neurologic function; dexamethasone (initially 12–20 mg/d in divided doses PO or IV) is used because it has relatively little mineralocorticoid activity. Because of the toxicities of long-term glucocorticoid administration, the dexamethasone dose is rapidly tapered to the lowest dose that relieves symptoms.

The treatment of epilepsy associated with brain tumors is identical to the treatment of other forms of partial epilepsy. The first-line agents phenytoin, carbamazepine, and valproic acid are equally effective; levetiracetam and oxcarbazepine are also coming into wide use

(Chap. 20). It is common practice to administer antiepileptic drugs prophylactically to all patients with supratentorial brain tumors, although there are no good data supporting this practice.

Gliomas and primary CNS lymphomas are associated with an increased risk for deep vein thrombosis and pulmonary embolism, probably because these tumors secrete procoagulant factors into the systemic circulation. Even though hemorrhage within gliomas is a frequent histopathologic finding, patients are at no increased risk for symptomatic intracranial bleeding following treatment with an anticoagulant. Prophylaxis with low-dose SC heparin should be employed for patients with brain tumors who have lower limb immobility, which places them at risk for deep venous thrombosis.

PRIMARY BRAIN TUMORS

ETIOLOGY

Exposure to ionizing radiation is the only well-documented environmental risk factor for the development of gliomas. A number of hereditary syndromes are associated with an increased risk of brain tumors (Table 32-2). Genes that contribute to the development of brain tumors, as well as other malignancies, fall into two general classes, *tumor-suppressor genes* and *oncogenes*. Whereas germ-line mutations of such genes do occur in patients with hereditary predisposition syndromes (Table 32-2), most brain tumors do not occur in patients with such recognizable syndromes. As is the case in all other tumor types, somatic mutations are almost invariably present in malignant brain tumor tissue. Amplification of the *EGFR* gene occurs in approximately one-third of cases of glioblastoma multiforme (GBM), the highest grade astrocytoma. Moreover, cytogenetic analysis often reveals characteristic changes that can signal the alteration in cancer-related genes within these chromosomal regions. In astrocytic tumors, DNA is commonly lost on chromosomes 10p, 17p, 13q, and 9. Oligodendrogliomas frequently have deletions of 1p and 19q, resulting from a centromeric translocation and loss of one of the translocated chromosomes. In meningiomas portions of 22q, which contains the gene for neurofibromatosis (NF) type 2, are often lost.

The particular constellation of genetic alterations varies among individual gliomas, even those that are histologically indistinguishable. Moreover, gliomas are genetically unstable. Genetic abnormalities tend to accumulate with time, and these changes correspond with an increasingly malignant phenotype. There are at least two genetic routes for the development of GBM (Fig. 32-1). One route involves the progression, generally over years, from a low-grade astrocytoma with deletions of chromosome 17 and inactivation of the *p53* gene to a highly malignant glioma with additional chromosomal alterations. The second route is characterized by the de novo appearance of a malignant glioma with amplification of

TABLE 32-2

HEREDITARY SYNDROMES ASSOCIATED WITH BRAIN TUMORS

SYNDROME	GENE (LOCUS)	GENE PRODUCT (FUNCTION)	NERVOUS SYSTEM NEOPLASMS
Neurofibromatosis type 1 (von Recklinghausen's Disease)[a]	*NF1* (17q)	Neurofibromin (GTPase activating protein)	Neuroma, schwannoma, meningioma, optic glioma
Neurofibromatosis type 2[a]	*NF2* (22q)	Merlin (cytoskeletal protein)	Schwannoma, glioma, ependymoma, meningioma
Tuberous sclerosis	*TSC1* (9q) *TSC2* (16p)	Hamartin (unknown function) Tuberin (GTPase activating protein)	Astrocytoma Hemangioblastoma of retina,
von Hippel-Lindau[a]	*VHL* (3p)	pVHL (modulator of cellular hypoxic response)	cerebellum and spinal cord; pheochromocytoma
Li-Fraumeni[a]	*p53* (17p)	TP53 (cell cycle and transcriptional regulator)	Malignant glioma
Retinoblastoma[a]	*RB1* (13q)	RB (cell cycle regulator)	Retinoblastoma, pineoblastoma, malignant glioma
Turcot	*APC* (5q) (adenomatous polyposis coli)	APC (cell adhesion)	Medulloblastoma, malignant glioma
Gorlin (basal cell nevus syndrome)	*PTCH* (9q) (patched)	PTH (developmental regulator)	Medulloblastoma
Multiple endocrine neoplasia 1 (Werner syndrome)[a]	*MEN1* (11q13)	Menin (cofactor for transcription)	Pituitary adenoma, malignant schwannoma

[a]Genetic testing possible.

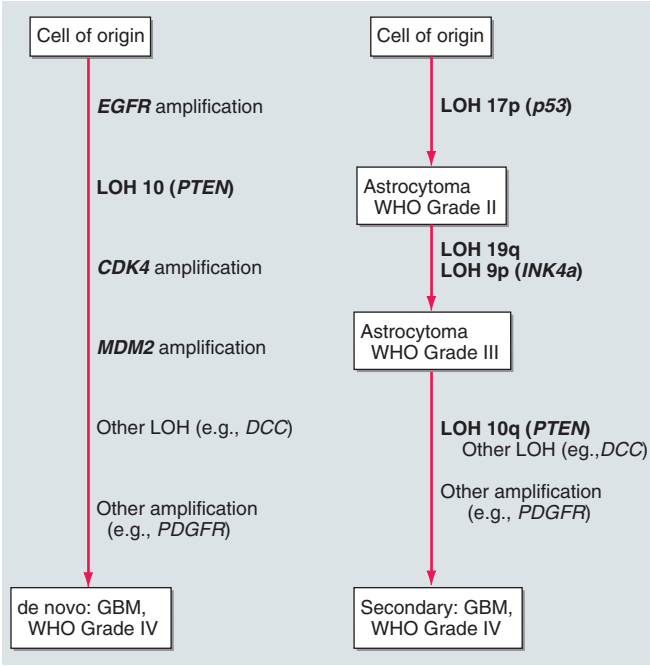


FIGURE 32-1

Model for the pathogenesis of human astrocytoma. Glioblastoma multiforme (GBM) typically presents without evidence of a precursor lesion, referred to as de novo GBM, frequently associated with amplification of the epidermal growth factor receptor (*EGFR*) gene. Less commonly, GBM arises in association with progressive genetic alterations after the diagnosis of a lower grade astrocytoma. These tumors are referred to as secondary GBM. The most widely described alterations are mutations of *p53* and *INK4a*. Other genes implicated in the development of these primary brain tumors include *CDK4*, *MDM2*, *DDC*, and *PDGFR*. LOH, loss of heterozygosity.

the *EGFR* gene and an intact *p53* gene in association with other genetic abnormalities.

ASTROCYTOMAS

Tumors with astrocytic cytologic features are the most common primary intracranial neoplasms (Fig. 32-2). The most widely used histologic grading system is the World Health Organization four-tiered grading system. Grade I is reserved for special histologic variants of astrocytoma that occur mainly in childhood and can have an excellent prognosis after surgical excision. These include *juvenile pilocytic astrocytoma*, *subependymal giant cell astrocytoma* (which most often occurs in patients with tuberous sclerosis), and *pleiomorphic xanthoastrocytoma*. At the other extreme is grade IV GBM, a clinically aggressive tumor. *Astrocytoma* (grade II) and *anaplastic astrocytoma* (grade III) are intermediate in their histologic and clinical manifestations. The histologic features associated with higher grade are hypercellularity, nuclear and

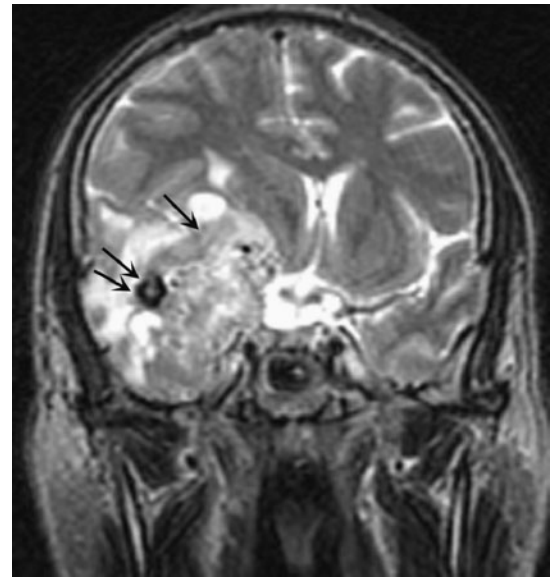


FIGURE 32-2

Malignant astrocytoma (glioblastoma). Coronal proton density–weighted MR scan through the temporal lobes demonstrates a heterogeneous right temporal lobe mass (*arrows*) compressing the third and lateral ventricles. The area of hypointense signal (*double arrows*) indicates either hemorrhage or calcification. Heterogeneous MR signal intensity is typical of glioblastoma.

cytoplasmic atypia, endothelial proliferation, mitotic activity, and necrosis. Endothelial proliferation and necrosis are strong predictors of aggressive behavior.

Quantitative measures of mitotic activity also correlate with prognosis. The proliferation index can be determined by immunohistochemical staining with antibodies to the proliferating cell nuclear antigen (PCNA) or with a monoclonal antibody termed *Ki-67*, which recognizes a histone protein expressed in proliferating but not quiescent cells.

The prognosis of brain tumor patients is closely associated with the histologic grade of the tumor. In a representative Finnish population, the median survival was 93.5 months for patients with grade I or II astrocytomas, 12.4 months for patients with grade III (anaplastic astrocytoma), and 5.1 months for patients with grade IV (GBM) tumors. Although these survival rates are somewhat lower than are generally reported, they represent a population-based experience and are not influenced by selection bias. Clinical features correlating with poor prognosis include age >65 years and a poor functional status, as defined by the Karnofsky performance scale.

Low-Grade Astrocytoma

Low-grade astrocytomas are more common in children than adults. Pilocytic astrocytoma, named for its characteristic spindle-shaped cells, is the most common childhood

brain tumor and is typically benign. It frequently occurs in the cerebellum and is well demarcated from adjacent brain. Complete surgical excision usually produces long-term, disease-free survival.

The median overall survival of grade II astrocytoma is 5–6 years. The optimum timing of surgery and radiation therapy for these patients is unknown. Since astrocytomas infiltrate surrounding brain, total surgical excision is impossible. Moreover, they are genetically unstable and accumulate mutations over time, leading to more aggressive behavior. For patients who are symptomatic from mass effect or poorly controlled epilepsy, surgical excision can relieve symptoms. For patients who are asymptomatic or minimally symptomatic at presentation, a diagnostic biopsy should be performed and, when surgically feasible, the tumor may be resected. Whether radiation therapy is administered immediately postoperatively or at the time of tumor progression is not thought to affect overall survival, but immediate radiation therapy does delay tumor progression. No role for chemotherapy in the management of low-grade astrocytoma has been defined.

High-Grade Astrocytoma

The large majority of astrocytomas arising in adults are high grade, supratentorial, and do not have a clearly defined margin between normal and malignant tissue. Neoplastic cells migrate away from the main tumor mass and infiltrate adjacent brain, often tracking along white matter pathways. Imaging studies do not indicate the full extent of the tumor. These tumors are almost all eventually fatal. Median survival of patients with grade III astrocytoma is <3 years and for those with a grade IV tumor, <1 year. Longer survival correlates with younger age, better performance status, and greater extent of surgical resection. Late in their course, astrocytomas, especially those located in the posterior fossa, can metastasize along CSF pathways to the spine. Metastases outside the CNS are rare.

High-grade astrocytomas are managed with glucocorticoids, surgery, radiation therapy, and chemotherapy. Dexamethasone is generally administered at the time of diagnosis and continued for the duration of radiation therapy. After completion of radiation therapy, dexamethasone is tapered to the lowest possible dose.

Because astrocytomas infiltrate adjacent normal brain, total surgical excision is not possible. Nevertheless, retrospective studies indicate that the extent of tumor resection correlates with survival in younger patients. Therefore, accessible astrocytomas are generally resected aggressively. Surgery is indicated to obtain tissue for pathologic diagnosis and to control mass effect.

Postoperative radiation therapy prolongs survival and improves quality of life. Treated with dexamethasone alone following surgery, the mean survival of patients <65 years with glioblastoma is 7–9 months. Survival is prolonged to 11–13 months with radiation therapy. For primary glial tumors, radiation is generally administered to the tumor mass, as defined by contrast enhancement on a CT or MRI scan, plus a 2-cm margin. A total dose of 5000–7000 cGy is administered in 25–35 equal fractions, 5 days per week.

The roles of stereotaxic radiosurgery and interstitial brachytherapy in glioma treatment are uncertain. *Stereotaxic radiosurgery* is the administration of a focused high dose of radiation to a precisely defined volume of tissue in a single treatment. Stereotaxic radiosurgery can potentially achieve tumor ablation within the treated volume. A major limitation of stereotaxic radiosurgery is that it can be used for only relatively small tumors, generally <4 cm in maximum diameter. *Interstitial brachytherapy*, the implantation of radioactive material into the tumor mass, is generally reserved for tumor recurrence because of its associated toxicity, necrosis of adjacent brain tissue.

Chemotherapy is marginally effective and is often used as an adjuvant therapy following surgery and radiation therapy. Temozolomide, an orally administered alkylating agent, has replaced nitrosureas, including carmustine (BCNU) and lomustine (CCNU), as the most widely used chemotherapeutic agent for high-grade gliomas. Temozolomide is generally better tolerated than nitrosoureas, notably producing less fatigue and pulmonary toxicity, and has the advantage of oral administration. Moreover, a randomized trial of radiation therapy plus temozolomide for the adjuvant treatment of GBM compared to radiation therapy alone was the first clinical trial to demonstrate a clear-cut advantage of adjuvant chemotherapy for that disease. The patients who received radiation therapy plus temozolomide had a median survival $2\frac{1}{2}$ months longer than those who received radiation therapy alone. The modest survival benefit appears to be restricted to a subgroup of patients with methylation and silencing of the promoter for the *MGMT* gene coding for O^6-methylguanine-DNA methyltransferase.

An alternative approach to the chemotherapy of high-grade gliomas that has shown survival benefit in controlled trials is the surgical implantation directly into the tumor resection cavity of polymer wafers that release BCNU locally into surrounding brain. The efficacy of this approach is similar to but probably slightly less than that of temozolomide, although without the attendant systemic toxicity of chemotherapy.

Experimental approaches to brain tumor chemotherapy include efforts to bypass the blood-brain barrier using local injection of chemotherapeutic agents into the tumor mass or the intraarterial injection of chemotherapy following osmotic disruption of the blood-brain barrier. Molecularly targeted therapies are also being tested in patients with GBM. In particular, since mutation or overexpression of EGFR is common in GBM, EGFR antagonists or inhibitors of its signaling pathways are being evaluated in patients with GBM in clinical trials.

Gliomatosis cerebri is a rare form of astrocytoma in which there is diffuse infiltration of the brain by malignant astrocytes without a focal enhancing mass. It generally presents as a multifocal CNS syndrome or a more generalized disorder including dementia, personality change, or seizures. Neuroimaging studies are often nonspecific, and biopsy is required to establish the diagnosis. Gliomatosis cerebri is treated with whole-brain radiation therapy or temozolomide; in selected patients, radiation to the entire neuroaxis is employed.

OLIGODENDROGLIOMAS

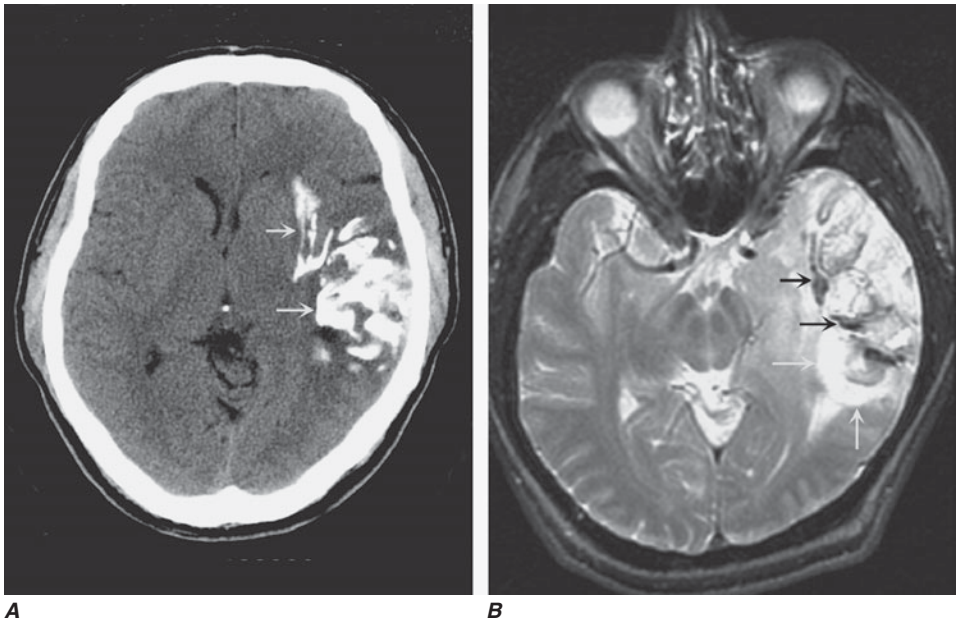
Oligodendrogliomas, which comprise about 15% of gliomas in adults, have a more benign course and are more responsive to cytotoxic treatment than astrocytomas. For grade II oligodendrogliomas, the median survival is 7–8 years, and there are a substantial number of patients with prolonged survival (>10 years). For grade III or anaplastic oligodendrogliomas, median survival is ~5 years. Oligodendrogliomas occur chiefly in supratentorial locations; in adults, ~30% contain areas of calcification (**Fig. 32-3**).

As a rule, oligodendrogliomas are less infiltrative than astrocytomas, permitting more complete surgical excision. Histologic features of mitoses, necrosis, and nuclear atypia are associated with a more aggressive clinical course. If these features are prominent, the tumor is termed an *anaplastic oligodendroglioma*. Some gliomas contain mixtures of cells with astrocytic and oligodendroglial features. If this mixed histology is prominent, the tumor is termed a *mixed glioma,* or an *oligoastrocytoma*. The greater the oligodendroglial component, the more benign the clinical course.

Surgery, at minimum a stereotaxic biopsy, is necessary to establish a diagnosis. Many oligodendrogliomas are amenable to gross total surgical resection. In addition, oligodendrogliomas may respond dramatically to systemic combination chemotherapy with procarbazine, lomustine, and vincristine (PCV), or to temozolomide, which, although not approved by the U.S. Food and Drug Administration (FDA) for this indication, is currently much more widely used than PCV. Oligodendrogliomas with deletions of chromosome 1p always respond to chemotherapy, but only ~25% of oligodendrogliomas lacking the 1p deletion respond. The simultaneous deletion of 1p and 19q, which results from a centromeric translocation of chromosomes 1 and 19, predicts a durable response to chemotherapy (>31 months on average) and a much longer survival. It appears that the chromosomal translocation identifies a subgroup of anaplastic oligodendrogliomas with a less aggressive natural course, and response to chemotherapy is another marker of that favorable phenotype.

EPENDYMOMAS

In adults, the most frequent histologic type is myxopapillary ependymoma, which typically arises from the filum terminale of the spinal cord and appears in the lumbosacral region. The term *myxopapillary* refers to the papillary arrangement of tumor cells, which produce mucin. Ependymomas in adults may also occur intracranially or at higher levels of the spinal cord. On CT or MRI, ependymomas typically appear as diffusely enhancing masses relatively well demarcated from adjacent neural tissue. Following gross total resection, the prognosis is good, with >80% 5-year disease-free survival.



A **B**

FIGURE 32-3
Oligodendroglioma. *A.* Noncontrast CT scan reveals a calcified mass involving the left temporal lobe (*arrows*) associated with mild mass effect but little edema. ***B.*** An MR T2-weighted image demonstrates a heterogeneous mass with hypointense signal (*black arrows*) surrounded by a zone of higher signal intensity (*white arrows*), consistent with a calcified temporal lobe mass. The tumor extends into the left medial temporal lobe and compresses the midbrain.

Ependymomas that cannot be totally resected are treated with stereotaxic radiosurgery or with a course of external beam radiation therapy.

MEDULLOBLASTOMAS AND PRIMITIVE NEUROECTODERMAL TUMORS (PNET)

These highly cellular malignant tumors are thought to arise from neural precursor cells. Medulloblastomas occur in the posterior fossa and, along with astrocytomas, are the most frequent malignant brain tumors of children. PNET is a term applied to tumors histologically indistinguishable from medulloblastoma but occurring either in adults or supratentorially in children. In adults, >50% present in the posterior fossa. These tumors frequently disseminate along CSF pathways.

If possible, these tumors should be surgically excised; the less residual tumor left behind, the better the prognosis. In adults, surgical excision of a PNET should be followed by irradiation of the entire neuraxis, with a boost in radiation dose to the primary tumor. If the tumor is not disseminated at presentation, the prognosis is generally favorable. Aggressive treatment can result in prolonged survival, although half of adult patients relapse within 5 years of treatment. Whereas chemotherapy is widely used in medulloblastoma and PNET in children, its role in adults is not yet defined.

CNS LYMPHOMA

Primary CNS Lymphoma

Primary CNS lymphoma is typically a high-grade B cell malignancy that presents within the neuraxis without evidence of systemic lymphoma. These occur most frequently in immunocompromised individuals, specifically organ transplant recipients and patients with AIDS (Chap. 37). In immunocompromised patients, CNS lymphomas are invariably associated with Epstein-Barr virus infection of the tumor cells.

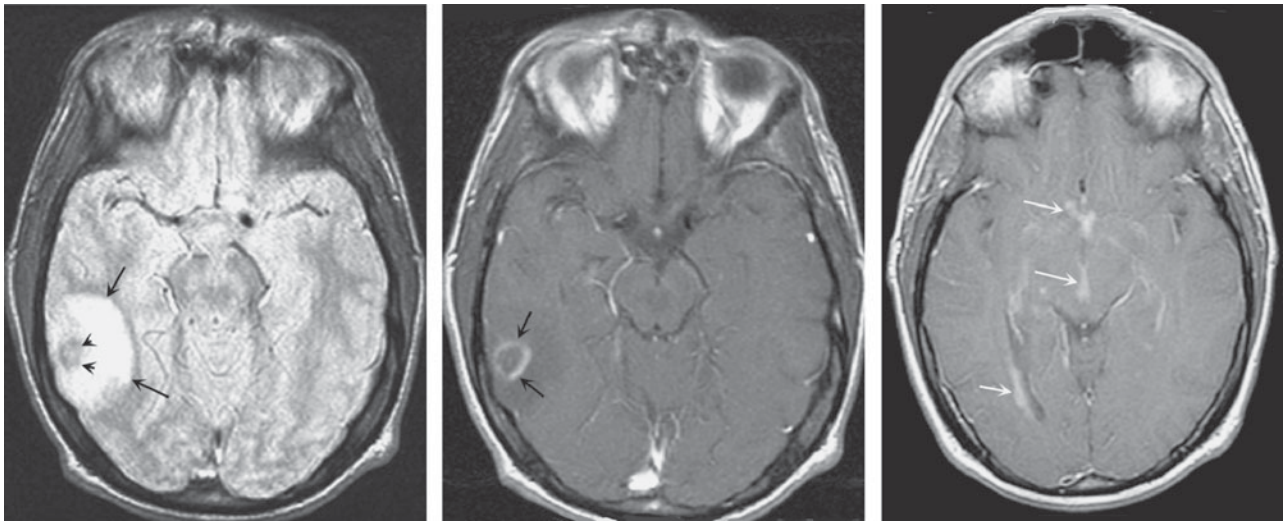
In immunocompetent patients, neuroimaging studies most often reveal a uniformly enhancing mass lesion. Stereotaxic needle biopsy can be used to establish the diagnosis. There is no benefit of surgical resection unless there is a need for immediate decompression of a life-threatening mass effect. Leptomeningeal involvement is present in ~15% of patients at presentation and in 50% at some time during the course of the illness. Moreover, the disease extends to the eyes in up to 15% of patients. Therefore, a slit-lamp examination and, if indicated, anterior chamber paracentesis or vitreous biopsy is necessary to define radiation ports.

The prognosis of primary CNS lymphoma is poor compared to histologically similar lymphoma occurring outside the CNS. Many patients experience a dramatic clinical and radiographic response to glucocorticoids; however, relapse almost invariably occurs within weeks. The mainstay of definitive therapy is chemotherapy. A single dose of rituximab is generally administered prior to cytotoxic chemotherapy as long as an enhancing mass lacking a blood-tumor barrier is present. Chemotherapy includes high-dose methotrexate, but multiagent chemotherapy, usually adding vincristine and procarbazine, appears to be more effective than methotrexate alone. Chemotherapy is followed in patients <60 years with whole-brain radiation therapy (WBRT). WBRT is postponed as long as possible or administered at reduced doses in patients >60 years because of the risk of dementia, gait disorder, and incontinence as manifestations of late-delayed radiation toxicity. Consolidation therapy is typically with high-dose cytarabine. Intraarterial chemotherapy with or without blood-brain barrier disruption is an alternative. Intrathecal chemotherapy with methotrexate can be added if leptomeningeal disease is present, but it has not proven to offer added benefit if high-dose methotrexate is used. Despite aggressive therapy, >90% of patients develop recurrent CNS disease. The median survival of patients who tolerate treatment with high-dose methotrexate is >3 years.

In immunodeficient patients, primary CNS lymphoma may be ring-enhancing rather than diffusely enhancing on CT or MRI (**Fig. 32-4**). It may therefore be impossible by imaging criteria to distinguish primary CNS lymphoma from metastatic malignancies or infections, particularly toxoplasmosis. The standard approach to this dilemma in a neurologically stable patient is to administer antibiotics to treat toxoplasmosis for 2–3 weeks and then repeat neuroimaging. If the imaging shows clear improvement, antibiotic treatment is continued. If not, a stereotaxic brain biopsy, which has substantially more risk in an immunodeficient than an immunocompetent patient, is performed. Alternatively, when the clinical situation permits a safe lumbar puncture, a CSF examination demonstrating Epstein-Barr virus DNA in CSF in an immunodeficient patient with neuroimaging findings consistent with lymphoma is diagnostic of primary CNS lymphoma. In organ transplant recipients, reversal of the immunosuppressed state can improve outcome. Survival with AIDS-related primary CNS lymphoma is very poor, generally ≤3 months; pretreatment performance status, the degree of immunosuppression, and the extent of CNS dissemination at diagnosis all appear to influence outcome.

Secondary CNS Lymphoma

Secondary CNS lymphoma is a manifestation of systemic disease and almost always occurs in adults with progressive B cell lymphoma or B cell leukemia who have tumor involvement of bone, bone marrow, testes, or the cranial sinuses. The leptomeninges are the most common site of CNS metastasis. Leptomeningeal lymphoma is usually detectable with contrast-enhanced CT or gadolinium-enhanced MRI of the brain and spine



A B C

FIGURE 32-4

CNS lymphoma. ***A.*** Proton density–weighted MR image through the temporal lobe demonstrates a low signal intensity nodule (*small arrows*) surrounded by a ring of high signal intensity edema (*larger arrows*). ***B.*** T1-weighted contrast-enhanced axial MRI demonstrates ring enhancement surrounded by a nonenhanced rim of edema. In this patient with AIDS, a solitary lesion of this type is consistent with either lymphoma or toxoplasmosis; the presence of multiple lesions favors toxoplasmosis. ***C.*** In a different patient with lymphomatous meningitis, an axial postcontrast T1-weighted MRI through the midbrain demonstrates multiple areas of abnormal enhancement in periventricular and subependymal regions (*arrows*). Lymphoma tends to spread subependymally at interfaces of CSF and brain parenchyma.

or by CSF examination. Treatment consists of systemic chemotherapy, intrathecal chemotherapy, and CNS irradiation. It is usually possible to suppress the leptomeningeal disease effectively, although the overall prognosis is determined by the course of the systemic lymphoma. Intraparenchymal lymphoma metastases may be treated with radiation therapy or systemic chemotherapy.

MENINGIOMAS

Meningiomas are derived from mesoderm, probably from cells giving rise to the arachnoid granulations. These tumors are usually benign and attached to the dura. They may invade the skull but only infrequently invade the brain. Meningiomas most often occur along the sagittal sinus, over the cerebral convexities, in the cerebellar-pontine angle, and along the dorsum of the spinal cord. They are more frequent in women than men, with a peak incidence in middle age.

Meningiomas may be found incidentally on a CT or MRI scan or may present with a focal seizure, a slowly progressive neurologic deficit, or symptoms of raised ICP. The radiologic image of a dural-based, extraaxial mass with dense, uniform contrast enhancement is essentially diagnostic, although a dural metastasis must also be considered (**Fig. 32-5**). A meningioma may have a "dural tail," a streak of dural enhancement flanking the main tumor mass; however, this finding may also be present with other dural tumors.

Total surgical resection of benign meningiomas is curative. If a total resection cannot be achieved, local external beam radiotherapy or stereotaxic radiosurgery reduces the recurrence rate to <10%. For meningiomas that are not surgically accessible, radiosurgery is the treatment of choice. Small asymptomatic meningiomas incidentally discovered in older patients can safely be followed radiologically; these tumors grow at an average rate of a few millimeters in diameter per year and only rarely become symptomatic.

Rare meningiomas invade the brain or have histologic evidence of malignancy such as nuclear pleomorphism and cellular atypia. A high mitotic index is also predictive of aggressive behavior. *Hemangiopericytoma*, although not strictly a meningioma, is a meningeal tumor with an especially aggressive behavior. Meningiomas with features of aggressiveness and hemangiopericytomas, even if totally excised by gross inspection, frequently recur and should receive postoperative radiotherapy. Chemotherapy has no proven benefit.

SCHWANNOMAS

These tumors are also called *neuromas*, *neurinomas*, or *neurolemmomas*. They arise from Schwann cells of nerve roots, most frequently in the eighth cranial nerve (*vestibular schwannoma*, formerly termed *acoustic schwannoma* or *acoustic neuroma*). The fifth cranial nerve is the second most frequent site; however, schwannomas may arise from any

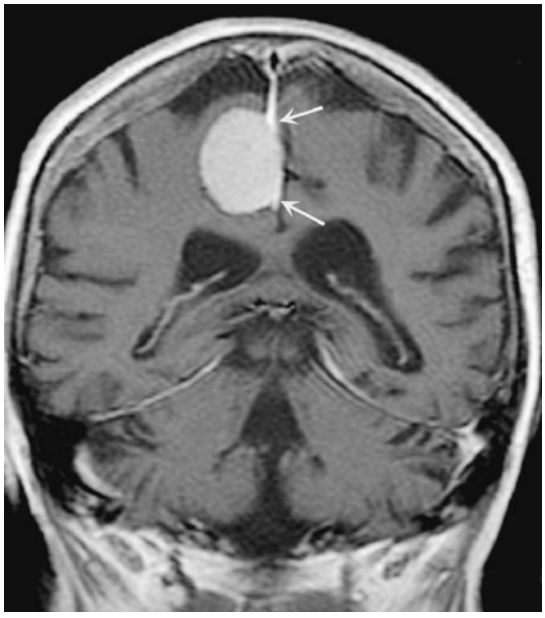


FIGURE 32-5
Meningioma. Coronal postcontrast T1-weighted MR image demonstrates an enhancing extraaxial mass arising from the falx cerebri (*arrows*). There is a "dural tail" of contrast enhancement extending superiorly along the intrahemispheric septum.

cranial or spinal root except the optic and olfactory nerves, which are myelinated by oligodendroglia rather than Schwann cells. Neurofibromatosis (NF) type 2 (see below) strongly predisposes to vestibular schwannoma. Schwannomas of spinal nerve roots also occur in patients with NF type 2 as well as patients with NF type 1.

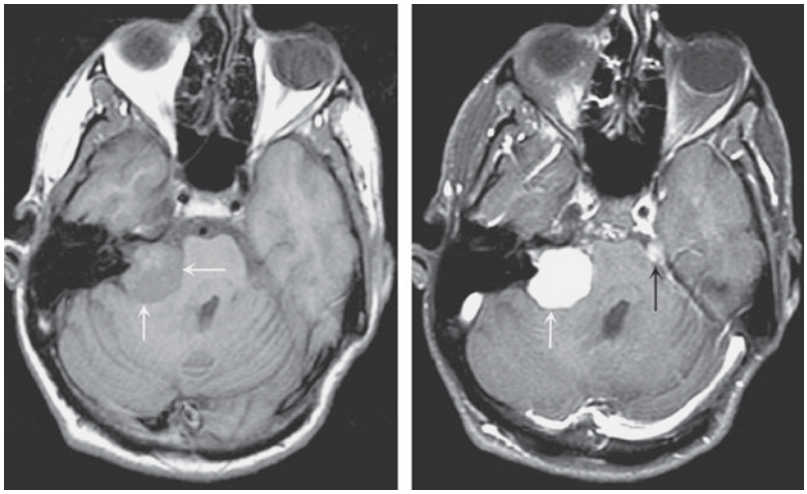
Eighth cranial nerve schwannomas typically arise from the vestibular division of the nerve. On MRI they are densely and uniformly enhancing neoplasms (**Fig. 32-6**). Vestibular schwannomas enlarge the internal auditory canal, an imaging feature that helps distinguish them from other cerebellopontine angle masses. Because the vestibular system adapts to slow destruction of the eighth nerve, patients with vestibular schwannomas characteristically present with progressive unilateral hearing loss rather than with dizziness or other vestibular symptoms. Unexplained unilateral hearing loss merits evaluation with audiometry and an MRI scan (Chap. 18). As a vestibular schwannoma grows, it can compress the cerebellum, pons, or facial nerve. With rare exceptions schwannomas are histologically and clinically benign.

Whenever possible, schwannomas should be surgically excised. When the tumors are small, it is usually possible to preserve hearing in the involved ear. In the case of large tumors, the patient is usually deaf at presentation; nonetheless, surgery is indicated to prevent further compression of posterior fossa structures. Stereotaxic radiosurgery is also effective treatment for schwannoma and has a complication rate equivalent to that of surgery.

OTHER BENIGN BRAIN TUMORS

Epidermoid tumors are cystic tumors with proliferative epidermal cells at the periphery and more mature epidermal cells towards the center of the cyst. The mature cells desquamate into the liquid center of the cyst. Epidermoid tumors are thought to arise from embryonic epidermal rests within the cranium. They occur extraaxially near the midline, in the middle cranial fossa, the suprasellar region, or the cerebellopontine angle. These well-demarcated lesions are amenable to complete surgical excision. Postoperative radiation therapy is unnecessary.

Dermoid cysts are thought to arise from embryonic rests of skin tissue trapped within the CNS during closure of the neural tube. The most frequent locations are in the midline supratentorially or at the cerebellopontine angle. Histologically, they are composed of multiple elements of the dermis including epidermis, hair follicles, and sweat glands; they frequently calcify. Treatment is surgical excision.



A ***B***

FIGURE 32-6
Vestibular schwannoma. ***A.*** Axial noncontrast MR scan through the cerebellopontine angle demonstrates an extraaxial mass that extends into a widened internal auditory canal, displacing the pons (*arrows*). ***B.*** Postcontrast T1-weighted image demonstrates intense enhancement of the vestibular schwannoma (*white arrow*). Abnormal enhancement of the left fifth nerve (*black arrow*) most likely represents another schwannoma in this patient with neurofibromatosis type 2.

Craniopharyngiomas are thought to arise from remnants of Rathke's pouch, the mesodermal structure from which the anterior pituitary gland is derived (Chap. 33). Craniopharyngiomas typically present as suprasellar masses. Because of their location, they may present as growth failure in children, endocrine dysfunction in adults, or visual loss in either age group. Histologically, craniopharyngiomas resemble epidermoid tumors; they are usually cystic, and in adults 80% are calcified. Treatment is surgical excision; postoperative external beam radiation or stereotaxic radiosurgery is added if total surgical removal cannot be achieved.

Colloid cysts are benign tumors of unknown cellular origin that occur within the third ventricle and can obstruct CSF flow. Other *rare benign primary brain tumors* include neurocytomas, subependymomas, and pleomorphic xanthoastrocytomas. Surgical excision of these neoplasms is the primary treatment and can be curative. Pituitary tumors are discussed in Chap. 33.

NEUROCUTANEOUS SYNDROMES

This group of genetic disorders, also known as the *phakomatoses*, produces a variety of developmental abnormalities of skin along with an increased risk of nervous system tumors (Table 32-2). These disorders are inherited as autosomal dominant conditions with variable penetrance.

NEUROFIBROMATOSIS TYPE 1 (VON RECKLINGHAUSEN'S DISEASE)

NF1 is characterized by cutaneous *neurofibromas*, pigmented lesions of the skin called *café au lait spots*, freckling in non-sun-exposed areas such as the axilla, hamartomas of the iris termed *Lisch nodules*, and pseudoarthrosis of the tibia. Neurofibromas are benign peripheral nerve tumors composed of proliferating Schwann cells and fibroblasts. They present as multiple, palpable, rubbery, cutaneous tumors. They are generally asymptomatic; however, if they grow in an enclosed space, e.g., the intervertebral foramen, they may produce a compressive radiculopathy or neuropathy. Aqueductal stenosis with hydrocephalus, scoliosis, short stature, hypertension, epilepsy, and mental retardation may also occur.

Patients with NF1 are at increased risk of developing nervous system neoplasms, including plexiform neurofibromas, optic pathway gliomas, ependymomas, meningiomas, astrocytomas, and pheochromocytomas. Neurofibromas may undergo secondary malignant degeneration and become sarcomatous.

Mutation of the *NF1* gene on chromosome 17 causes von Recklinghausen's disease. The *NF1* gene is a tumor-suppressor gene; it encodes a protein, *neurofibromin*, which modulates signal transduction through the *ras* GTPase pathway.

NEUROFIBROMATOSIS TYPE 2

NF2 is characterized by the development of bilateral vestibular schwannomas in >90% of individuals who inherit the gene. Patients with NF2 also have a predisposition for the development of meningiomas, gliomas, and schwannomas of cranial and spinal nerves. In addition, a characteristic type of cataract, juvenile posterior subcapsular lenticular opacity, occurs in NF2. Multiple café au lait spots and peripheral neurofibromas occur rarely.

In patients with NF2, vestibular schwannomas are usually associated with progressive unilateral deafness early in the third decade of life. Bilateral vestibular schwannomas are generally detectable by MRI at that time (Fig. 32-6). Surgical management is designed to treat the underlying tumor and preserve hearing as long as possible.

This syndrome is caused by mutation of the *NF2* gene on chromosome 22q. *NF2* encodes a protein called *neurofibromin 2*, *schwannomin*, or *merlin*, with homology to a family of cytoskeletal proteins that includes moesin, ezrin, and radixin.

TUBEROUS SCLEROSIS (BOURNEVILLE'S DISEASE)

Tuberous sclerosis is characterized by cutaneous lesions, seizures, and mental retardation. The cutaneous lesions include adenoma sebaceum (facial angiofibromas), ash leaf–shaped hypopigmented macules (best seen under ultraviolet illumination with a Wood's lamp), shagreen patches (yellowish thickenings of the skin over the lumbosacral region of the back), and depigmented nevi. Recognizable by neuroimaging studies, the presence of subependymal nodules, which may be calcified, is characteristic. Tuberous sclerosis patients are at increased risk of developing ependymomas and childhood astrocytomas, of which >90% are *subependymal giant cell astrocytomas*. These are benign neoplasms that may develop in the retina or along the border of the lateral ventricles. They may obstruct the foramen of Monro and produce hydrocephalus. Rhabdomyomas of the myocardium and angiomyomas of the kidney, liver, adrenals, and pancreas may also occur.

Treatment is symptomatic. Anticonvulsants for seizures, shunting for hydrocephalus, and behavioral and educational strategies for mental retardation are the mainstays of management. Severely affected individuals generally die before 30 years of age.

Mutations in either the *TSC-1* gene at 9q or the *TSC-2* gene at 16p are associated with tuberous sclerosis. These genes encode *tuberins*, proteins that modulate the GTPase activity of other cellular signaling proteins.

VON HIPPEL–LINDAU SYNDROME

This syndrome consists of retinal, cerebellar, and spinal hemangioblastomas, which are slowly growing cystic

tumors. Hypernephroma, renal cell carcinoma, pheochromocytoma, and benign cysts of the kidneys, pancreas, epididymis, or liver may also occur. Erythropoietin produced by hemangioblastomas may result in polycythemia. Mutation of the von Hippel–Lindau (*VHL*) gene on chromosome 3p, a tumor-suppressor gene, causes this disorder. *VHL* encodes a protein with multiple functions, including modulation of signal transduction in response to cellular hypoxia.

TUMORS METASTATIC TO BRAIN

MECHANISMS OF BRAIN METASTASES

Brain metastases arise from hematogenous spread. The anatomic distribution of brain metastases generally parallels regional cerebral blood flow, with a predilection for the gray matter–white matter junction and for the border zone between middle cerebral and posterior cerebral artery distributions. The lung is the most common origin of brain metastases; both primary lung cancer and cancers metastatic to the lung frequently metastasize to the brain. Breast cancer (especially ductal carcinoma) has a propensity to metastasize to the cerebellum and the posterior pituitary gland. Other common origins of brain metastases are gastrointestinal malignancies and melanoma (Table 32-3). Certain less common tumors have a special propensity to metastasize to brain, including germ cell tumors and thyroid cancer. By contrast, prostate cancer, ovarian cancer, and Hodgkin's disease rarely metastasize to the brain.

EVALUATION OF METASTASES FROM KNOWN CANCER

On MRI scans brain metastases typically appear as well-demarcated, approximately spherical lesions that are hypointense or isointense relative to brain on T1-weighted images and bright on T2-weighted images. They invariably enhance with gadolinium, reflecting extravasation of gadolinium through tumor vessels that lack a blood-tumor barrier (Fig. 32-7). Small metastases often enhance uniformly. Larger metastases typically produce ring enhancement surrounding a central mass of nonenhancing necrotic tissue that develops as the metastasis outgrows its blood supply. Metastases are surrounded by variable amounts of edema. Blood products may also be seen, reflecting hemorrhage of abnormal tumor vessels.

The radiologic appearance of a brain metastasis is not specific. The differential diagnosis of ring-enhancing lesions includes brain abscess, radiation necrosis, toxoplasmosis, granulomas, tuberculosis, sarcoidosis, demyelinating lesions, primary brain tumors, primary CNS lymphoma, stroke, hemorrhage, and trauma. Contrast-enhanced CT scanning is less sensitive than MRI for the detection of brain metastases. Cytologic examination of the CSF is not indicated, since intraparenchymal brain metastases almost never shed cells into the CSF.

BRAIN METASTASES WITHOUT A KNOWN PRIMARY TUMOR

In general hospital populations, up to one-third of patients presenting with brain metastases do not have a previously known underlying cancer. These patients generally present with either a seizure or a progressive neurologic deficit. Neuroimaging studies typically demonstrate one or multiple ring-enhancing lesions. In individuals who are not immunocompromised and not at risk for brain abscesses, this radiologic pattern is most likely due to brain metastasis.

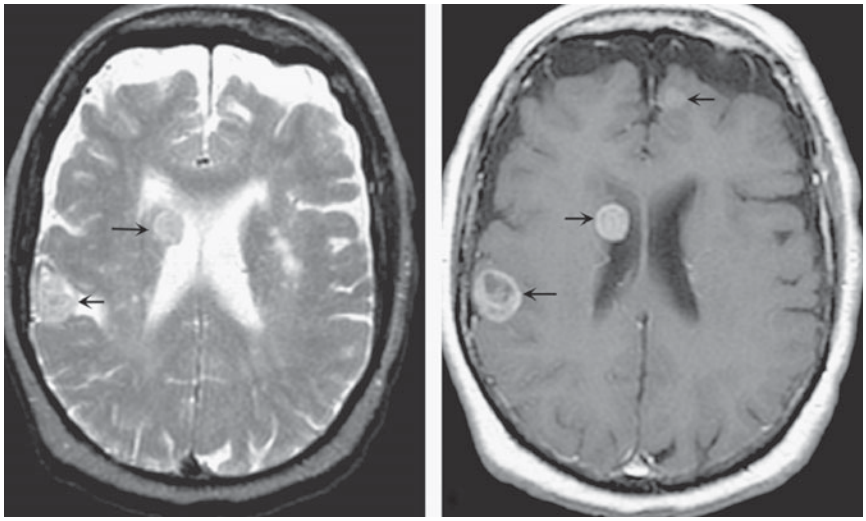
Diagnostic evaluation begins with a search for the primary tumor. Blood tests should include carcinoembryonic antigen and liver function tests. Examination of the skin for melanoma and the thyroid gland for masses should be carried out. The search for a primary cancer most often discloses lung cancer (particularly small cell lung cancer) or melanoma. In 30% of patients no primary tumor can be identified, even after extensive evaluation. A CT scan of the chest, abdomen, and pelvis should be obtained. If these are all negative, further imaging studies, including bone scan, other radionuclide scans, mammography, and upper and lower gastrointestinal barium studies, are unlikely to be productive.

A tissue diagnosis is essential. If a primary tumor is found, it will usually be more accessible to biopsy than a

TABLE 32-3

FREQUENCY OF NERVOUS SYSTEM METASTASES BY COMMON PRIMARY TUMORS

SITE OF PRIMARY TUMOR	BRAIN METASTASES, %	LEPTOMENINGEAL METASTASES, %	SPINAL CORD COMPRESSION, %
Lung	40	24	18
Breast	19	41	24
Melanoma	10	12	4
Gastrointestinal tract	7	13	6
Genitourinary tract	7		18
Other	17	10	30



A B

FIGURE 32-7
Brain metastasis. *A.* Axial T2-weighted MRI through the lateral ventricles reveals two isodense masses, one in the subependymal region and one near the cortex (*arrows*). ***B.*** T1-weighted postcontrast image at the same level as ***A*** reveals enhancement of the two masses seen on the T2-weighted image as well as a third mass in the left frontal lobe (*arrows*).

brain lesion. If a single brain lesion is found in a surgically accessible location, if a primary tumor is not found, or if the primary tumor is in a location difficult to biopsy, the brain metastasis should be biopsied or resected.

Rx Treatment: TUMORS METASTATIC TO BRAIN

Once a systemic cancer metastasizes to the brain it is, with rare exception, incurable. Therapy is therefore palliative, designed to prevent disability and suffering and, if possible, to prolong life. Published outcome studies have focused on survival as the primary endpoint, leaving questions regarding quality of life unanswered. There is, however, widespread agreement that glucocorticoids, anticonvulsants, radiation therapy, and surgery (see below) can contribute to the management of these patients.

GENERAL MEASURES Glucocorticoids frequently ameliorate symptoms of brain metastases. Improvement is often dramatic, occurring within 24 h, and is sustained with continued administration, although the toxicity of glucocorticoids is cumulative. Therefore, if possible, a more definitive therapy for metastases should be instituted to permit withdrawal of glucocorticoid therapy. One-third of patients with brain metastases have one or more seizures; anticonvulsants are used empirically for seizure prophylaxis.

SPECIFIC MEASURES

Radiation Therapy Radiation therapy is the primary treatment for brain metastases. Since multiple microscopic deposits of tumor cells throughout the brain are likely to be present in addition to metastases visualized by neuroimaging studies, WBRT is usually used. Its benefit has been established in controlled studies, but no clear dose response has been shown. Usually, 30–37.5 Gy is administered in 10–15 fractions; an additional dose ("boost") of focal irradiation to a single or large metastasis may also be administered. Stereotaxic radiosurgery is of benefit in patients with four or fewer metastases demonstrable by MRI. The addition of WBRT to stereotaxic radiosurgery delays tumor recurrence in the brain but does not prolong survival.

Surgery Up to 40% of patients with brain metastases have only a single tumor mass identified by CT. Accessible single metastases may be surgically excised as a palliative measure. If the systemic disease is under control, total resection of a single brain lesion has been demonstrated to improve survival and minimize disability. Survival is further improved if surgery is followed by WBRT.

Chemotherapy Brain metastases of certain tumors, including breast cancer, small cell lung cancer, and germ cell tumors, are often responsive to systemic chemotherapy. Although metastases frequently do not respond as well as the primary tumor, dramatic responses to systemic chemotherapy or hormonal therapy may occur in some cases. In patients who are neurologically asymptomatic, two to four cycles of systemic chemotherapy may be administered initially to reduce tumor mass and render the residual tumor more amenable to radiation therapy. Even if a complete radiologic remission is achieved from chemotherapy, WBRT should then be administered. Gene therapy, immunotherapy, intraarterial chemotherapy, and chemotherapy administered following osmotic disruption of the blood-brain barrier are currently under investigation.

LEPTOMENINGEAL METASTASES

Leptomeningeal metastases are also called *carcinomatous meningitis*, *meningeal carcinomatosis*, and, in the case of specific tumors, *leukemic meningitis* or *lymphomatous meningitis*. Clinical evidence of leptomeningeal metastases is present in 8% of patients with metastatic solid tumors; at necropsy, the prevalence is as high as 19%. Among solid tumors, adenocarcinomas of the breast, lung, and gastrointestinal tract and melanoma are the most common cause of leptomeningeal metastases (Table 32-3). In one-quarter of patients the systemic cancer is under control, and especially in these patients the effective control of leptomeningeal disease can improve the quality and duration of life.

Cancer usually metastasizes to the meninges via the bloodstream. Alternatively, cells may invade the subarachnoid space directly from a superficially located parenchymal brain metastasis. Some tumors, including squamous cell carcinoma of the skin and some non-Hodgkin's lymphomas, have a propensity to grow along peripheral nerves and may seed the meninges by that route.

CLINICAL FEATURES

Leptomeningeal metastases present with signs and symptoms at multiple levels of the nervous system, most often in a setting of known systemic malignancy. Encephalopathy is frequent, and cranial neuropathy or spinal radiculopathy from nodular nerve root compression is characteristic. Hydrocephalus can result from obstruction of CSF outflow. Focal neurologic deficits reflect coexisting intraparenchymal metastases.

LABORATORY AND IMAGING EVALUATION

Leptomeningeal metastases are diagnosed by cytologic demonstration of malignant cells in the CSF, by MRI demonstration of nodular tumor deposits or diffuse enhancement in the meninges (**Fig. 32-8**), and by meningeal biopsy. CSF findings are usually those of an inflammatory meningitis consisting of lymphocytic pleocytosis, elevated protein levels, and normal or low CSF glucose. A positive CSF cytology is unequivocal evidence of tumor spread to the subarachnoid space. CSF examination is more likely to be informative when larger volumes of CSF are submitted for cytology and when up to three CSF examinations are performed. A complete MRI examination of the neuraxis is indicated in all cases of suspected leptomeningeal metastases; in addition to nodular meningeal lesions, hydrocephalus due to obstruction of CSF pathways may be found.

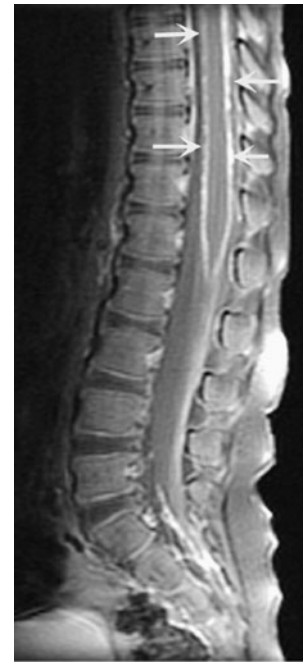


FIGURE 32-8
Carcinomatous meningitis. Sagittal postcontrast MRI through the lower thoracic region demonstrates diffuse pial enhancement along the surface of the spinal cord (*arrows*), typical of CSF spread of neoplasm.

℞ Treatment: LEPTOMENINGEAL METASTASES

Although the prognosis of patients with leptomeningeal metastases is poor, ~20% of patients treated aggressively can expect a response of ≥6 months. Intrathecal therapy exposes meningeal tumor implants to high concentrations of chemotherapy with minimal systemic toxicity. Methotrexate can be safely administered intrathecally and is effective against leptomeningeal metastases from a variety of solid tumors including lymphoma; cytarabine and thiotepa are alternative agents. Liposomal cytarabine provides prolonged cytotoxic levels of cytarabine in the CSF, requiring administration only every 2 weeks, in contrast to weekly or twice weekly administration of other agents. Intrathecal chemotherapy may be administered either by repeated lumbar puncture or through an indwelling Ommaya reservoir, which consists of a catheter in one lateral ventricle attached to a reservoir implanted under the scalp. If there is a question of patency of CSF pathways, a radionuclide flow study through the reservoir may be performed.

Large, nodular deposits of tumor on the meninges or along nerve roots are unlikely to respond to intrathecal chemotherapy, as the barrier to diffusion is too great.

Therefore, external beam radiation is employed, and these patients may also benefit from systemic chemotherapy. Hydrocephalus is treated with a ventriculoperitoneal shunt, although seeding of the peritoneum by tumor is a risk.

MALIGNANT SPINAL CORD COMPRESSION

Spinal cord compression from solid tumor metastases usually results from growth of a vertebral metastasis into the epidural space. Primary tumors that frequently metastasize to bone include lung, breast, and prostate cancer. Back pain is usually the first symptom and is prominent at presentation in 90% of patients. The pain is typically dull, aching, and may be associated with localized tenderness. If a nerve root is compressed, radicular pain is also present. The thoracic cord is most often affected. Weakness, sensory loss, and autonomic dysfunction (urinary urgency and incontinence, fecal incontinence, and sexual impotence in men) are hallmarks of spinal cord compression. Once signs of spinal cord compression appear, they tend to progress rapidly. It is thus essential to recognize and treat this serious complication of malignancy promptly to prevent irreversible neurologic deficits. Diagnosis and management are discussed in Chap. 30.

METASTASES TO THE PERIPHERAL NERVOUS SYSTEM

Systemic cancer may compress or invade peripheral nerves. Compression of the brachial plexus may occur by direct extension of Pancoast's tumors (cancer of the apex of the lung), by lymphoma, or by extension of local lymph node metastases in breast or lung cancer. The lumbosacral plexus may be compressed by retroperitoneal tumor invasion such as occurs in cases of prostate or ovarian cancer or lymphoma. Skull metastases may compress cranial nerve branches as they pass through the skull, and pituitary metastases may extend into the cavernous sinus.

The epineurium generally provides an effective barrier to invasion of the peripheral nerves by solid tumors, but certain tumors characteristically invade and spread along peripheral nerves. Squamous cell carcinoma of the skin may spread along the trigeminal nerve and extend intracranially. Non-Hodgkin's lymphoma may be neurotrophic and cause polyradiculopathy or a syndrome resembling mononeuropathy multiplex (Chap. 40). Focal external beam radiation may reduce pain, prevent irreversible loss of peripheral nerve function, and possibly restore function.

In patients with cancer who have brachial or lumbosacral plexopathy, it may be difficult to distinguish tumor invasion from radiation injury. High radiation dose or the presence of myokymia (rippling contractions of muscle) suggests radiation injury, whereas pain suggests tumor. Radiographic imaging studies may be equivocal, and surgical exploration is sometimes required.

COMPLICATIONS OF THERAPY

RADIATION TOXICITY

The nervous system is vulnerable to injury by therapeutic radiation. Histologically, there is demyelination, degeneration of small arterioles, and eventually brain infarction and necrosis.

Acute radiation injury to the brain occurs during or immediately after therapy. It is rarely seen with current protocols of external beam radiation but may occur after stereotaxic radiosurgery. Manifestations include headache, sleepiness, and worsening of preexisting neurologic deficits.

Early delayed radiation injury occurs within 4 months of therapy. It is associated with an increased white matter T2 signal on MRI scans. In children, the *somnolence syndrome* is a common form of early delayed radiation injury in which somnolence and ataxia develop after WBRT. Irradiation of the cervical spine may cause Lhermitte's phenomenon, an electricity-like sensation evoked by neck flexion. Symptoms resulting from acute and early delayed radiation injury often respond to glucocorticoid administration, are self-limited, and usually resolve without residual deficits. These injuries do not increase the risk of late radiation injury.

Late delayed radiation injury produces permanent damage to the nervous system. It occurs >4 months (generally 8–24 months) after completion of therapy; onset as late as 15 years after therapy has been described. Following focal brain irradiation, radiation necrosis can occur within the radiation field, producing a contrast-enhancing (frequently ring-enhancing) mass with surrounding white matter signal abnormalities (**Fig. 32-9**). MRI or CT scans are often unable to distinguish radiation necrosis from recurrent tumor, but PET or SPECT scans may demonstrate the increased glucose metabolism typical of tumor tissue or the decreased metabolism of necrotic tissue. Magnetic resonance spectroscopy may demonstrate a high lactate concentration with relatively low choline concentration in areas of necrosis. Biopsy is frequently required to establish the correct diagnosis. Peripheral nerves, including the brachial and lumbosacral plexuses, may also develop late delayed radiation injury.

If untreated, radiation necrosis of the CNS may act as an expanding mass lesion. Symptoms may resolve spontaneously or respond to treatment with glucocorticoids.

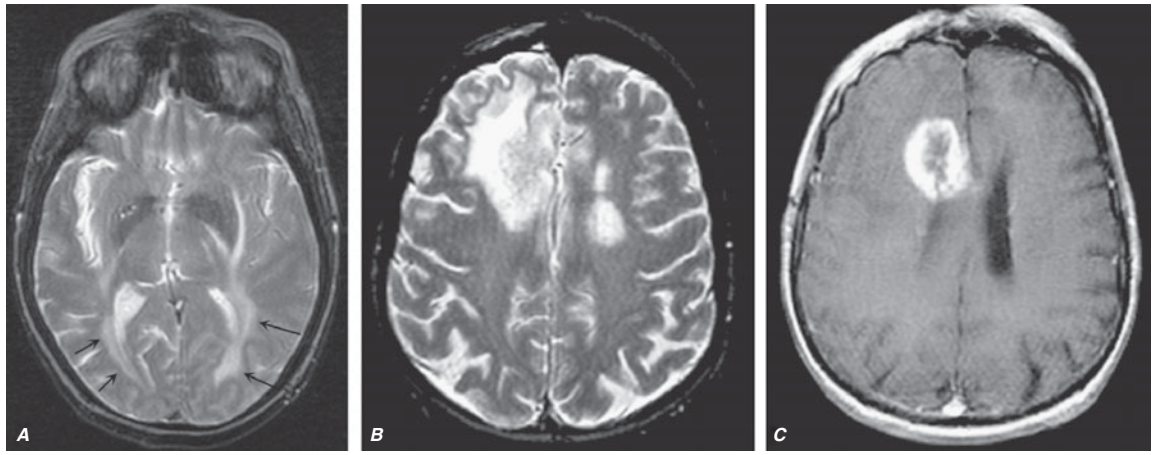


FIGURE 32-9

Radiation injury. ***A.*** Late delayed radiation injury 1 year after whole-brain radiation (5500 cGy). T2-weighted MR image at the level of the temporal lobes reveals high signal intensity abnormality in periventricular white matter (*arrows*). ***B*** and ***C.*** Focal radiation necrosis 3 years after radiotherapy (7000 cGy) for carcinoma of the nasopharynx. Axial T2-weighted MRI (***B***) demonstrates a mass in the right frontal lobe with surrounding vasogenic edema. Abnormal signal changes are also present on the left. T1-weighted postcontrast MRI (***C***) reveals a heterogeneously enhancing mass in the right cingulate gyrus.

Progressive radiation necrosis is best treated with surgical resection if the patient has a life expectancy of at least 6 months and a Karnofsky performance score >70. There are anecdotal reports that anticoagulation with heparin or warfarin may be beneficial. After WBRT, progressive dementia can occur, often accompanied by gait apraxia and urinary incontinence. Radiation injury of large arteries also accelerates the development of atherosclerosis, but an increase in the risk of stroke becomes significant only years after radiation treatment.

Endocrine dysfunction resulting in hypopituitarism frequently follows exposure of the hypothalamus or pituitary gland to therapeutic radiation. Growth hormone is the pituitary hormone most sensitive to radiation therapy, and thyroid-stimulating hormone is the least sensitive; ACTH, prolactin, and the gonadotropins have an intermediate sensitivity.

Development of a second neoplasm is another risk of therapeutic radiation that generally occurs many years after radiation exposure. Depending on the irradiated field, the risk of gliomas, meningiomas, sarcomas, and thyroid cancer is increased.

TOXICITIES OF CHEMOTHERAPY

Chemotherapy regimens used to treat primary brain tumors generally include alkylating agents, either temozolomide or nitrosoureas, and are relatively well tolerated. Infrequently, drugs used to treat CNS neoplasms are associated with the development of altered mental states (e.g., confusion, depression), ataxia, and seizures. Chemotherapy for systemic malignancy is a more frequent cause of nervous system toxicity and is more often toxic to the peripheral than the central nervous system. Cisplatin commonly produces tinnitus and high-frequency bilateral hearing loss, especially in younger patients. At cumulative doses >450 mg/m^2, cisplatin can produce a symmetric, large-fiber axonal neuropathy that is predominantly sensory; paclitaxel (Taxol) produces a similar picture. Fluorouracil and high-dose cytarabine can cause cerebellar dysfunction that resolves after discontinuation of therapy. Vincristine, which is commonly used to treat lymphoma, may cause an acute ileus and is frequently associated with development of a progressive distal, symmetric sensory motor neuropathy with foot drop and paresthesias.

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CHAPTER 33

NEUROLOGIC DISORDERS OF THE PITUITARY AND HYPOTHALAMUS

Shlomo Melmed ■ J. Larry Jameson ■ Gary L. Robertson

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The anterior pituitary is often referred to as the "master gland" because, together with the hypothalamus, it orchestrates the complex regulatory functions of multiple other endocrine glands. The anterior pituitary gland produces six major hormones: (1) prolactin (PRL), (2) growth hormone (GH), (3) adrenocorticotropin hormone (ACTH), (4) luteinizing hormone (LH), (5) follicle-stimulating hormone (FSH), and (6) thyroid-stimulating hormone (TSH).

Pituitary hormones are secreted in a pulsatile manner, reflecting stimulation by an array of specific hypothalamic releasing factors. Each of these pituitary hormones elicits specific responses in peripheral target tissues. The hormonal products of these peripheral glands, in turn, exert feedback control at the level of the hypothalamus and pituitary to modulate pituitary function (**Fig. 33-1**). Pituitary tumors cause characteristic hormone excess syndromes. Hormone deficiency may be inherited or acquired. Fortunately, efficacious treatments exist for the various pituitary hormone excess and deficiency syndromes. Nonetheless, these diagnoses are often elusive, emphasizing the importance of recognizing subtle clinical manifestations and performing the correct laboratory diagnostic tests.

ANATOMY AND DEVELOPMENT

ANATOMY

The pituitary gland weighs ~600 mg and is located within the sella turcica ventral to the diaphragma sella; it comprises anatomically and functionally distinct anterior and posterior lobes. The sella is contiguous to vascular and neurologic structures, including the cavernous sinuses, cranial nerves, and optic chiasm. Thus, expanding intrasellar pathologic processes may have significant central mass effects in addition to their endocrinologic impact.

Hypothalamic neural cells synthesize specific releasing and inhibiting hormones that are secreted directly into the portal vessels of the pituitary stalk. Blood supply of the pituitary gland is derived from the superior and inferior hypophyseal arteries (**Fig. 33-2**). The hypothalamic-pituitary portal plexus provides the major blood

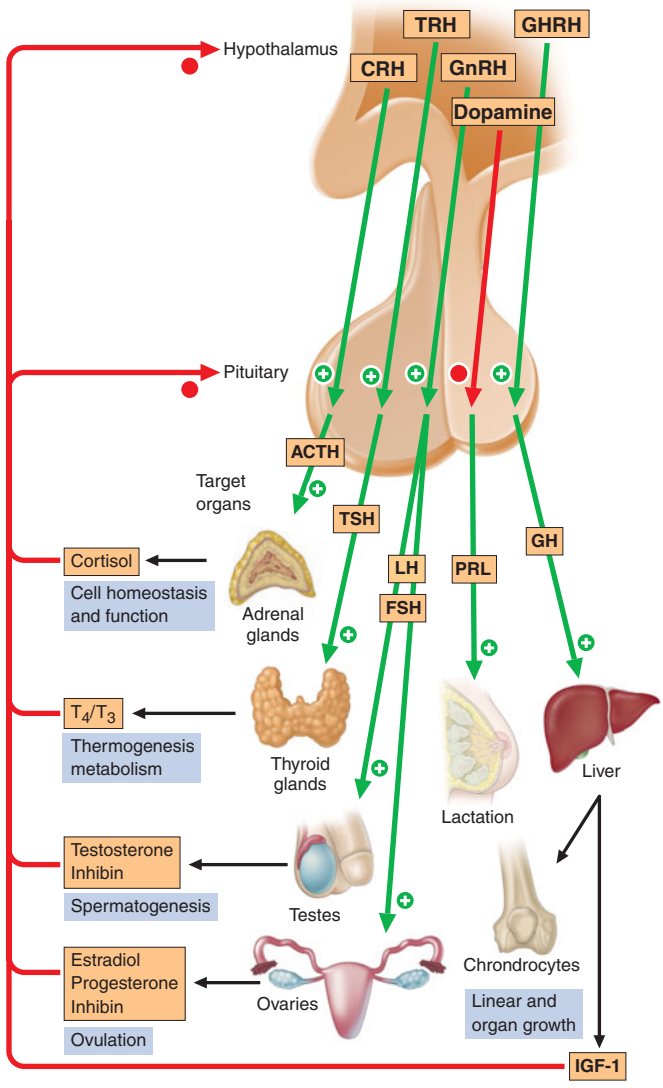

FIGURE 33-1

Diagram of pituitary axes. Hypothalamic hormones regulate anterior pituitary trophic hormones that, in turn, determine target gland secretion. Peripheral hormones feed back to regulate hypothalamic and pituitary hormones. For abbreviations, see text.

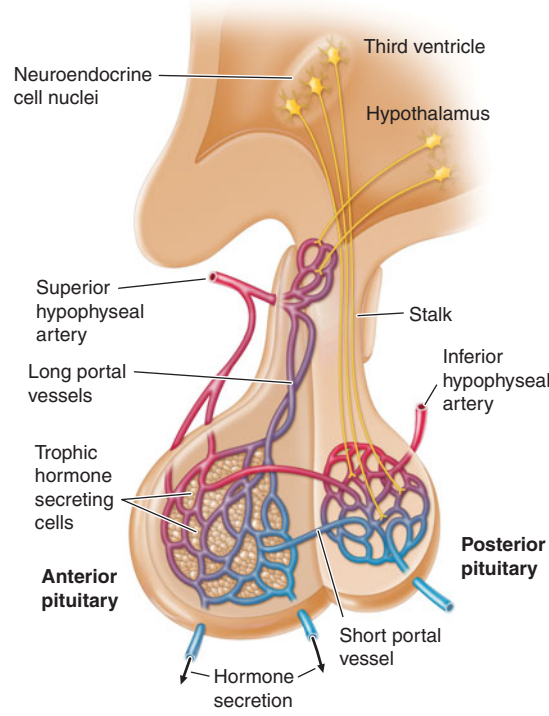

FIGURE 33-2

Diagram of hypothalamic-pituitary vasculature. The hypothalamic nuclei produce hormones that traverse the portal system and impinge on anterior pituitary cells to regulate pituitary hormone secretion. Posterior pituitary hormones are derived from direct neural extensions.

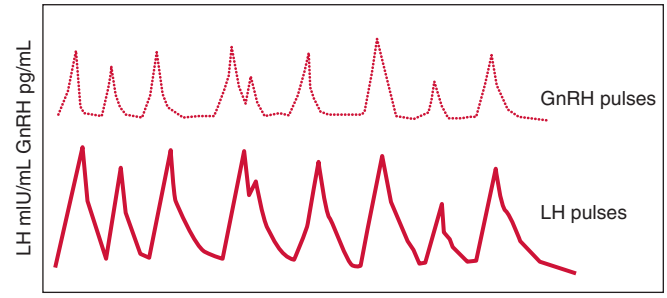

FIGURE 33-3

Hypothalamic gonadotropin-releasing hormone (GnRH) pulses induce secretory pulses of luteinizing hormone (LH).

source for the anterior pituitary, allowing reliable transmission of hypothalamic peptide pulses without significant systemic dilution; consequently, pituitary cells are exposed to releasing or inhibiting factors and in turn release their hormones as discrete pulses (Fig. 33-3).

The posterior pituitary is supplied by the inferior hypophyseal arteries. In contrast to the anterior pituitary, the posterior lobe is directly innervated by hypothalamic neurons (supraopticohypophyseal and tuberohypophyseal nerve tracts) via the pituitary stalk. Thus, posterior pituitary production of vasopressin [antidiuretic hormone (ADH)] and oxytocin is particularly sensitive to neuronal damage by lesions that affect the pituitary stalk or hypothalamus.

HYPOTHALAMIC AND ANTERIOR PITUITARY INSUFFICIENCY

Hypopituitarism results from impaired production of one or more of the anterior pituitary trophic hormones. Reduced pituitary function can result from inherited disorders; more commonly, it is acquired and reflects the mass effects of tumors or the consequences of inflammation or vascular damage. These processes may also impair synthesis or secretion of hypothalamic hormones, with resultant pituitary failure (Table 33-1).

TABLE 33-1

ETIOLOGY OF HYPOPITUITARISM[a]

Development/structural
- Transcription factor defect
- Pituitary dysplasia/aplasia
- Congenital CNS mass, encephalocele
- Primary empty sella
- Congenital hypothalamic disorders (septo-optic dysplasia, Prader-Willi syndrome, Laurence-Moon-Biedl syndrome, Kallmann syndrome)

Traumatic
- Surgical resection
- Radiation damage
- Head injuries

Neoplastic
- Pituitary adenoma
- Parasellar mass (meningioma, germinoma, ependymoma, glioma)
- Rathke's cyst
- Craniopharyngioma
- Hypothalamic hamartoma, gangliocytoma
- Pituitary metastases (breast, lung, colon carcinoma)
- Lymphoma and leukemia
- Meningioma

Infiltrative/inflammatory
- Lymphocytic hypophysitis
- Hemochromatosis
- Sarcoidosis
- Histiocytosis X
- Granulomatous hypophysitis

Vascular
- Pituitary apoplexy
- Pregnancy-related (infarction with diabetes; postpartum necrosis)
- Sickle cell disease
- Arteritis

Infections
- Fungal (histoplasmosis)
- Parasitic (toxoplasmosis)
- Tuberculosis
- *Pneumocystis carinii*

[a]Trophic hormone failure associated with pituitary compression or destruction usually occurs sequentially GH > FSH > LH > TSH > ACTH. During childhood, growth retardation is often the presenting feature, and in adults hypogonadism is the earliest symptom.

DEVELOPMENTAL AND GENETIC CAUSES OF HYPOPITUITARISM

ACQUIRED HYPOPITUITARISM

Hypopituitarism may be caused by accidental or neurosurgical trauma; vascular events such as apoplexy; pituitary or hypothalamic neoplasms such as pituitary adenomas, craniopharyngiomas, lymphoma, or metastatic tumors; inflammatory disease such as lymphocytic hypophysitis; infiltrative disorders such as sarcoidosis, hemochromatosis, and tuberculosis; or irradiation.

Increasing evidence suggests that patients with brain injury including trauma, subarachnoid hemorrhage, and irradiation have transient hypopituitarism and require intermittent long-term endocrine follow-up, as permanent hypothalamic or pituitary dysfunction will develop in 25–40% of these patients.

Hypothalamic Infiltration Disorders

These disorders—including sarcoidosis, histiocytosis X, amyloidosis, and hemochromatosis—frequently involve both hypothalamic and pituitary neuronal and neurochemical tracts. Consequently, diabetes insipidus occurs in one-half of patients with these disorders. Growth retardation is seen if attenuated GH secretion occurs before pubertal epiphyseal closure. Hypogonadotropic hypogonadism and hyperprolactinemia are also common.

Inflammatory Lesions

Pituitary damage and subsequent dysfunction can be seen with chronic infections such as tuberculosis, with opportunistic fungal infections associated with AIDS, and in tertiary syphilis. Other inflammatory processes, such as granulomas or sarcoidosis, may mimic the features of a pituitary adenoma. These lesions may cause extensive hypothalamic and pituitary damage, leading to trophic hormone deficiencies.

Cranial Irradiation

Cranial irradiation may result in long-term hypothalamic and pituitary dysfunction, especially in children and adolescents, as they are more susceptible to damage following whole-brain or head and neck therapeutic irradiation. The development of hormonal abnormalities correlates strongly with irradiation dosage and the time interval after completion of radiotherapy. Up to two-thirds of patients ultimately develop hormone insufficiency after a median dose of 50 Gy (5000 rad) directed at the skull base. The development of hypopituitarism occurs over 5–15 years and usually reflects hypothalamic damage rather than primary destruction of pituitary cells. Although the pattern of hormone loss is variable, GH deficiency is most common, followed by gonadotropin and ACTH deficiency. When deficiency of one or more hormones is documented, the possibility of diminished reserve of other hormones is likely. Accordingly, anterior pituitary function should be evaluated over the long term in previously irradiated patients, and replacement therapy instituted when appropriate (see later).

Lymphocytic Hypophysitis

This often occurs in postpartum women; it usually presents with hyperprolactinemia and MRI evidence of a prominent pituitary mass often resembling an adenoma,

with mildly elevated PRL levels. Pituitary failure caused by diffuse lymphocytic infiltration may be transient or permanent but requires immediate evaluation and treatment. Rarely, isolated pituitary hormone deficiencies have been described, suggesting a selective autoimmune process targeted to specific cell types. Most patients manifest symptoms of progressive mass effects with headache and visual disturbance. The erythrocyte sedimentation rate is often elevated. As the MRI image may be indistinguishable from that of a pituitary adenoma, hypophysitis should be considered in a postpartum woman with a newly diagnosed pituitary mass before embarking on unnecessary surgical intervention. The inflammatory process often resolves after several months of glucocorticoid treatment, and pituitary function may be restored, depending on the extent of damage.

Pituitary Apoplexy

Acute intrapituitary hemorrhagic vascular events can cause substantial damage to the pituitary and surrounding sellar structures. Pituitary apoplexy may occur spontaneously in a preexisting adenoma; post-partum (Sheehan's syndrome); or in association with diabetes, hypertension, sickle cell anemia, or acute shock. The hyperplastic enlargement of the pituitary during pregnancy increases the risk for hemorrhage and infarction. Apoplexy is an endocrine emergency that may result in severe hypoglycemia, hypotension, central nervous system (CNS) hemorrhage, and death. Acute symptoms may include severe headache with signs of meningeal irritation, bilateral visual changes, ophthalmoplegia, and, in severe cases, cardiovascular collapse and loss of consciousness. Pituitary computed tomography (CT) or MRI may reveal signs of intratumoral or sellar hemorrhage, with deviation of the pituitary stalk and compression of pituitary tissue.

Patients with no evident visual loss or impaired consciousness can be observed and managed conservatively with high-dose glucocorticoids. Those with significant or progressive visual loss or loss of consciousness require urgent surgical decompression. Visual recovery after surgery is inversely correlated with the length of time after the acute event. Therefore, severe ophthalmoplegia or visual deficits are indications for early surgery. Hypopituitarism is very common after apoplexy.

Empty Sella

A partial or apparently totally empty sella is often an incidental MRI finding. These patients usually have normal pituitary function, implying that the surrounding rim of pituitary tissue is fully functional. Hypopituitarism, however, may develop insidiously. Pituitary masses may undergo clinically silent infarction with development of a partial or totally empty sella by cerebrospinal fluid (CSF) filling the dural herniation. Rarely, small but functional pituitary adenomas may arise within the rim of pituitary tissue, and these are not always visible on MRI.

PRESENTATION AND DIAGNOSIS

The clinical manifestations of hypopituitarism depend on which hormones are lost and the extent of the hormone deficiency. GH deficiency causes growth disorders in children and leads to abnormal body composition in adults (see below). Gonadotropin deficiency causes menstrual disorders and infertility in women and decreased sexual function, infertility, and loss of secondary sexual characteristics in men. TSH and ACTH deficiency usually develop later in the course of pituitary failure. TSH deficiency causes growth retardation in children and features of hypothyroidism in children and in adults. The secondary form of adrenal insufficiency caused by ACTH deficiency leads to hypocortisolism with relative preservation of mineralocorticoid production. PRL deficiency causes failure of lactation. When lesions involve the posterior pituitary, polyuria and polydipsia reflect loss of vasopressin secretion. Epidemiologic studies have documented an increased mortality rate in patients with longstanding pituitary damage, primarily from increased cardiovascular and cerebrovascular disease.

LABORATORY INVESTIGATION

Biochemical diagnosis of pituitary insufficiency is made by demonstrating low levels of trophic hormones in the setting of low target hormone levels. For example, low free thyroxine in the setting of a low or inappropriately normal TSH level suggests secondary hypothyroidism. Similarly, a low testosterone level without elevation of gonadotropins suggests hypogonadotropic hypogonadism. Provocative tests may be required to assess pituitary reserve (**Table 33-2**). GH responses to insulin-induced hypoglycemia, arginine, l-dopa, growth hormone–releasing hormone (GHRH), or growth hormone–releasing peptides (GHRPs) can be used to assess GH reserve. Corticotropin-releasing hormone (CRH) administration induces ACTH release, and administration of synthetic ACTH (cortrosyn) evokes adrenal cortisol release as an indirect indicator of pituitary ACTH reserve. ACTH reserve is most reliably assessed during insulin-induced hypoglycemia. However, this test should be performed cautiously in patients with suspected adrenal insufficiency because

TABLE 33-2

TESTS OF PITUITARY SUFFICIENCY

HORMONE	TEST	BLOOD SAMPLES	INTERPRETATION
Growth hormone	Insulin tolerance test: Regular insulin (0.05–0.15 U/kg IV)	–30, 0, 30, 60, 120 min for glucose and GH	Glucose < 40 mg/dL; GH should be >3 μg/L
	GHRH test: 1 μg/kg IV	0, 15, 30, 45, 60, 120 min for GH	Normal response is GH >3 μg/L
	L-Arginine test: 30 g IV over 30 min	0, 30, 60, 120 min for GH	Normal response is GH >3 μg/L
	L-dopa test: 500 mg PO	0, 30, 60, 120 min for GH	Normal response is GH >3 μg/L
Prolactin	TRH test: 200–500 μg IV	0, 20, and 60 min for TSH and PRL	Normal prolactin is >2 μg/L and increase >200% of baseline
ACTH	Insulin tolerance test: Regular insulin (0.05–0.15 U/kg IV)	–30, 0, 30, 60, 90 min for glucose and cortisol	Glucose <40 mg/dL Cortisol should increase by >7 μg/dL or to >20 μg/dL
	CRH test: 1 μg/kg ovine CRH IV at 0800 h	0, 15, 30, 60, 90, 120 min for ACTH and cortisol	Basal ACTH increases 2- to 4-fold and peaks at 20–100 pg/mL Cortisol levels >20–25 μg/dL
	Metyrapone test: Metyrapone (30 mg/kg) at midnight	Plasma 11-deoxycortisol and cortisol at 8 A.M.; ACTH can also be measured	Plasma cortisol should be <4 μg/dL to assure an adequate response Normal response is 11-deoxycortisol >7.5 μg/dL or ACTH >75 pg/mL
	Standard ACTH stimulation test: ACTH 1-24 (Cosyntropin), 0.25 mg IM or IV	0, 30, 60 min for cortisol and aldosterone	Normal response is cortisol >21 μg/dL and aldosterone response of >4 ng/dL above baseline
	Low-dose ACTH test: ACTH 1-24 (Cosyntropin), 1 μg IV	0, 30, 60 min for cortisol	Cortisol should be >21 μg/dL
	3-day ACTH stimulation test consists of 0.25 mg ACTH 1-24 given IV over 8 h each day		Cortisol >21 μg/dL
TSH	Basal thyroid function tests: T_4, T_3, TSH	Basal tests	Low free thyroid hormone levels in the setting of TSH levels that are not appropriately increased
	TRH test: 200–500 μg IV	0, 20, 60 min for TSH and PRL[a]	TSH should increase by >5 mU/L unless thyroid hormone levels are increased
LH, FSH	LH, FSH, testosterone, estrogen	Basal tests	Basal LH and FSH should be increased in postmenopausal women Low testosterone levels in the setting of low LH and FSH
	GnRH test: GnRH (100 μg) IV	0, 30, 60 min for LH and FSH	In most adults, LH should increase by 10 IU/L and FSH by 2 IU/L Normal responses are variable
Multiple hormones	Combined anterior pituitary test: GHRH (1 μg/kg), CRH (1 μg/kg), GnRH (100 μg), TRH (200 μg) are given IV	–30, 0, 15, 30, 60, 90, 120 min for GH, ACTH, cortisol, LH, FSH, and TSH	Combined or individual releasing hormone responses must be elevated in the context of basal target gland hormone values and may not be uniformly diagnostic (see text)

[a]Evoked PRL response indicates lactotrope integrity.

Note: For abbreviations, see text.

of enhanced susceptibility to hypoglycemia and hypotension. Insulin-induced hypoglycemia is contraindicated in patients with active coronary artery disease or seizure disorders.

Rx Treatment: HYPOPITUITARISM

Hormone replacement therapy, including glucocorticoids, thyroid hormone, sex steroids, growth hormone, and vasopressin, is usually safe and free of complications. Treatment regimens that mimic physiologic hormone production allow for maintenance of satisfactory clinical homeostasis. Effective dosage schedules are outlined in Table 33-3. Patients in need of glucocorticoid replacement require careful dose adjustments during stressful events such as acute illness, dental procedures, trauma, and acute hospitalization.

TABLE 33-3

HORMONE REPLACEMENT THERAPY FOR ADULT HYPOPITUITARISM[a]

TROPHIC HORMONE DEFICIT	HORMONE REPLACEMENT
ACTH	Hydrocortisone (10–20 mg A.M.; 5–10 mg P.M.) Cortisone acetate (25 mg A.M.; 12.5 mg P.M.) Prednisone (5 mg A.M.; 2.5 mg P.M.)
TSH	L-Thyroxine (0.075–0.15 mg daily)
FSH/LH	Males Testosterone enanthate (200 mg IM every 2 weeks) Testosterone skin patch (5 mg/d) Females Conjugated estrogen (0.65–1.25 mg qd for 25 days) Progesterone (5–10 mg qd) on days 16–25 Estradiol skin patch (0.5 mg, every other day) For fertility: Menopausal gonadotropins, human chorionic gonadotropins
GH	Adults: Somatotropin (0.1–1.25 mg SC qd) Children: Somatotropin [0.02–0.05 (mg/kg per day)]
Vasopressin	Intranasal desmopressin (5–20 μg twice daily) Oral 300–600 μg qd

[a]All doses shown should be individualized for specific patients and should be reassessed during stress, surgery, or pregnancy. Male and female fertility requirements should be managed.
Note: For abbreviations, see text.

HYPOTHALAMIC, PITUITARY, AND OTHER SELLAR MASSES

PITUITARY TUMORS

Pituitary adenomas are the most common cause of pituitary hormone hypersecretion and hyposecretion syndromes in adults. They account for ~15% of all intracranial neoplasms. At autopsy, up to one-quarter of all pituitary glands harbor an unsuspected microadenoma (<10 mm diameter). Similarly, pituitary imaging detects small clinically inapparent pituitary lesions in at least 10% of individuals.

Pathogenesis

Pituitary adenomas are benign neoplasms that arise from one of the five anterior pituitary cell types. The clinical and biochemical phenotype of pituitary adenomas depend on the cell type from which they are derived. Thus, tumors arising from lactotrope (PRL), somatotrope (GH), corticotrope (ACTH), thyrotrope (TSH), or gonadotrope (LH, FSH) cells hypersecrete their respective hormones (Table 33-4). Plurihormonal tumors that express combinations of GH, PRL, TSH, ACTH, and the

TABLE 33-4

CLASSIFICATION OF PITUITARY ADENOMAS[a]

ADENOMA CELL ORIGIN	HORMONE PRODUCT	CLINICAL SYNDROME
Lactotrope	PRL	Hypogonadism, galactorrhea
Gonadotrope	FSH, LH, subunits	Silent or hypogonadism
Somatotrope	GH	Acromegaly/ gigantism
Corticotrope	ACTH	Cushing's disease
Mixed growth hormone and prolactin cell	GH, PRL	Acromegaly, hypogonadism, galactorrhea
Other plurihormonal cell	Any	Mixed
Acidophil stem cell	PRL, GH	Hypogonadism, galactorrhea, acromegaly
Mammosomatotrope	PRL, GH	Hypogonadism, galactorrhea, acromegaly
Thyrotrope	TSH	Thyrotoxicosis
Null cell	None	Pituitary failure
Oncocytoma	None	Pituitary failure

[a]Hormone-secreting tumors are listed in decreasing order of frequency. All tumors may cause local pressure effects, including visual disturbances, cranial nerve palsy, and headache.
Note: For abbreviations, see text.
Source: Adapted from S Melmed, in JL Jameson (ed): *Principles of Molecular Medicine*, Totowa, Humana Press, 1998.

glycoprotein hormone α subunit may be diagnosed by careful immunocytochemistry or may manifest as clinical syndromes that combine features of these hormonal hypersecretory syndromes. Morphologically, these tumors may arise from a single polysecreting cell type or comprise cells with mixed function within the same tumor.

Hormonally active tumors are characterized by autonomous hormone secretion with diminished responsiveness to physiologic inhibitory pathways. Hormone production does not always correlate with tumor size. Small hormone-secreting adenomas may cause significant clinical perturbations, whereas larger adenomas that produce less hormone may be clinically silent and remain undiagnosed (if no central compressive effects occur). About one-third of all adenomas are clinically nonfunctioning and produce no distinct clinical hypersecretory syndrome. Most of these arise from gonadotrope cells and may secrete small amounts of α- and β-glycoprotein hormone subunits or, very rarely, intact circulating gonadotropins. True pituitary carcinomas with documented extracranial metastases are exceedingly rare.

Almost all pituitary adenomas are monoclonal in origin, implying the acquisition of one or more somatic mutations that confer a selective growth advantage. In addition to direct studies of oncogene mutations, this model is supported by X-chromosomal inactivation analyses of tumors in female patients heterozygous for X-linked genes. Consistent with their clonal origin, complete surgical resection of small pituitary adenomas usually cures hormone hypersecretion. Nevertheless, hypothalamic hormones, such as GHRH or CRH, also enhance mitotic activity of their respective pituitary target cells, in addition to their role in pituitary hormone regulation. Thus, patients harboring rare abdominal or chest tumors elaborating ectopic GHRH or CRH may present with somatotrope or corticotrope hyperplasia.

Several etiologic genetic events have been implicated in the development of pituitary tumors. The pathogenesis of sporadic forms of acromegaly has been particularly informative as a model of tumorigenesis. GHRH, after binding to its G protein–coupled somatotrope receptor, utilizes cyclic AMP as a second messenger to stimulate GH secretion and somatotrope proliferation. A subset (~35%) of GH-secreting pituitary tumors contain sporadic mutations in Gsα (Arg 201 → Cys or His; Gln 227 →Arg). These mutations inhibit intrinsic GTPase activity, resulting in constitutive elevation of cyclic AMP, Pit-1 induction, and activation of cyclic AMP response element binding protein (CREB), thereby promoting somatotrope cell proliferation and GH secretion.

Characteristic loss of heterozygosity (LOH) in various chromosomes has been documented in large or invasive macroadenomas, suggesting the presence of putative tumor suppressor genes at these loci. LOH of chromosome regions on 11q13, 13, and 9 is present in up to 20% of sporadic pituitary tumors including GH-, PRL- and ACTH-producing adenomas and in some nonfunctioning tumors.

Compelling evidence also favors growth factor promotion of pituitary tumor proliferation. Basic fibroblast growth factor (bFGF) is abundant in the pituitary and has been shown to stimulate pituitary cell mitogenesis. Other factors involved in initiation and promotion of pituitary tumors include loss of negative-feedback inhibition (as seen with primary hypothyroidism or hypogonadism) and estrogen-mediated or paracrine angiogenesis. Growth characteristics and neoplastic behavior may also be influenced by several activated oncogenes, including *RAS* and pituitary tumor transforming gene (*PTTG*).

Genetic Syndromes Associated with Pituitary Tumors

Several familial syndromes are associated with pituitary tumors, and the genetic mechanisms for some of these have been unraveled.

Multiple endocrine neoplasia (MEN) 1 is an autosomal dominant syndrome characterized primarily by a genetic predisposition to parathyroid, pancreatic islet, and pituitary adenomas. MEN1 is caused by inactivating germline mutations in *MENIN*, a constitutively expressed tumor-suppressor gene located on chromosome 11q13. Loss of heterozygosity, or a somatic mutation of the remaining normal *MENIN* allele, leads to tumorigenesis. About half of affected patients develop prolactinomas; acromegaly and Cushing's syndrome are less commonly encountered.

Carney syndrome is characterized by spotty skin pigmentation, myxomas, and endocrine tumors including testicular, adrenal, and pituitary adenomas. Acromegaly occurs in about 20% of patients. A subset of patients have mutations in the R1α regulatory subunit of protein kinase A (*PRKAR1A*).

McCune-Albright syndrome consists of polyostotic fibrous dysplasia, pigmented skin patches, and a variety of endocrine disorders, including GH-secreting pituitary tumors, adrenal adenomas, and autonomous ovarian function. Hormonal hypersecretion is the result of constitutive cyclic AMP production caused by inactivation of the GTPase activity of Gsα. The Gsα mutations occur postzygotically, leading to a mosaic pattern of mutant expression.

Familial acromegaly is a rare disorder in which family members may manifest either acromegaly or gigantism. The disorder is associated with LOH at a chromosome 11q13 locus distinct from that of *MENIN*.

OTHER SELLAR MASSES

Craniopharyngiomas are benign, suprasellar cystic masses that present with headaches, visual field deficits, and variable degrees of hypopituitarism. They are derived from Rathke's pouch and arise near the pituitary stalk,

commonly extending into the suprasellar cistern. Craniopharyngiomas are often large, cystic, and locally invasive. Many are partially calcified, providing a characteristic appearance on skull x-ray and CT images. More than one-half of all patients present before 20 years of age, usually with signs of increased intracranial pressure, including headache, vomiting, papilledema, and hydrocephalus. Associated symptoms include visual field abnormalities, personality changes and cognitive deterioration, cranial nerve damage, sleep difficulties, and weight gain. Hypopituitarism can be documented in about 90% and diabetes insipidus occurs in about 10%. About one-half of affected children present with growth retardation. MRI is generally superior to CT to evaluate cystic structure and tissue components of craniopharyngiomas. CT is useful to define calcifications and to evaluate invasion into surrounding bony structures and sinuses.

Treatment usually involves transcranial or transsphenoidal surgical resection followed by postoperative radiation of residual tumor. Surgery alone is curative in less than half of patients because of adherence to vital structures or because of small tumor deposits in the hypothalamus or brain parenchyma. The goal of surgery is to remove as much tumor as possible without risking complications associated with efforts to remove firmly adherent or inaccessible tissue. In the absence of radiotherapy, about 75% of tumors recur, and 10-year survival is less than 50%. In patients with incomplete resection, radiotherapy improves 10-year survival to 70–90% but is associated with increased risk of secondary malignancies. Most patients require lifelong pituitary hormone replacement.

Developmental failure of Rathke's pouch obliteration may lead to *Rathke's cysts*, which are small (<5 mm) cysts entrapped by squamous epithelium, and are found in about 20% of individuals at autopsy. Although Rathke's cleft cysts do not usually grow and are often diagnosed incidentally, about a third present in adulthood with compressive symptoms, diabetes insipidus, and hyperprolactinemia due to stalk compression. Rarely, internal hydrocephalus develops. The diagnosis is suggested preoperatively by visualizing the cyst wall on MRI, which distinguishes these lesions from craniopharyngiomas. Cyst contents range from CSF-like fluid to mucoid material. *Arachnoid cysts* are rare and generate an MRI image isointense with cerebrospinal fluid.

Sella chordomas usually present with bony clival erosion, local invasiveness, and, on occasion, calcification. Normal pituitary tissue may be visible on MRI, distinguishing chordomas from aggressive pituitary adenomas. Mucinous material may be obtained by fine-needle aspiration.

Meningiomas arising in the sellar region may be difficult to distinguish from nonfunctioning pituitary adenomas. Meningiomas typically enhance on MRI and may show evidence of calcification or bony erosion. Meningiomas may cause compressive symptoms.

Histiocytosis X comprises a variety of syndromes associated with foci of eosinophilic granulomas. Diabetes insipidus, exophthalmos, and punched-out lytic bone lesions (*Hand-Schüller-Christian disease*) are associated with granulomatous lesions visible on MRI, as well as a characteristic axillary skin rash. Rarely, the pituitary stalk may be involved.

Pituitary metastases occur in ~3% of cancer patients. Blood-borne metastatic deposits are found almost exclusively in the posterior pituitary. Accordingly, diabetes insipidus can be a presenting feature of lung, gastrointestinal, breast, and other pituitary metastases. About one-half of pituitary metastases originate from breast cancer; about 25% of patients with metastatic breast cancer have such deposits. Rarely, pituitary stalk involvement results in anterior pituitary insufficiency. The MRI diagnosis of a metastatic lesion may be difficult to distinguish from an aggressive pituitary adenoma; the diagnosis may require histologic examination of excised tumor tissue. Primary or metastatic lymphoma, leukemias, and plasmacytomas also occur within the sella.

Hypothalamic hamartomas and *gangliocytomas* may arise from astrocytes, oligodendrocytes, and neurons with varying degrees of differentiation. These tumors may overexpress hypothalamic neuropeptides including GnRH, GHRH, or CRH. In GnRH-producing tumors, children present with precocious puberty, psychomotor delay, and laughing-associated seizures. Medical treatment of GnRH-producing hamartomas with long-acting GnRH analogues effectively suppresses gonadotropin secretion and controls premature pubertal development. Rarely, hamartomas are also associated with craniofacial abnormalities; imperforate anus; cardiac, renal, and lung disorders; and pituitary failure as features of *Pallister-Hall syndrome*, which is caused by mutations in the carboxyterminus of the *GLI3* gene. Hypothalamic hamartomas are often contiguous with the pituitary, and preoperative MRI diagnosis may not be possible. Histologic evidence of hypothalamic neurons in tissue resected at transsphenoidal surgery may be the first indication of a primary hypothalamic lesion.

Hypothalamic gliomas and *optic gliomas* occur mainly in childhood and usually present with visual loss. Adults have more aggressive tumors; about a third are associated with neurofibromatosis.

Brain germ-cell tumors may arise within the sellar region. These include *dysgerminomas*, which are frequently associated with diabetes insipidus and visual loss. They rarely metastasize. *Germinomas*, *embryonal carcinomas*, *teratomas*, and *choriocarcinomas* may arise in the parasellar region and produce hCG. These germ-cell tumors present with precocious puberty, diabetes insipidus, visual field defects, and thirst disorders. Many patients are GH-deficient with short stature.

METABOLIC EFFECTS OF HYPOTHALAMIC LESIONS

Lesions involving the anterior and preoptic hypothalamic regions cause paradoxical vasoconstriction, tachycardia, and hyperthermia. Acute hyperthermia is usually due to a hemorrhagic insult, but poikilothermia may also occur. Central disorders of thermoregulation result from posterior hypothalamic damage. The *periodic hypothermia syndrome* comprises episodic attacks of rectal temperatures <30°C, sweating, vasodilation, vomiting, and bradycardia. Damage to the ventromedial hypothalamic nuclei by craniopharyngiomas, hypothalamic trauma, or inflammatory disorders may be associated with *hyperphagia* and *obesity*. This region appears to contain an energy-satiety center where melanocortin receptors are influenced by leptin, insulin, POMC products, and gastrointestinal peptides. Polydipsia and hypodipsia are associated with damage to central osmoreceptors located in preoptic nuclei. Slow-growing hypothalamic lesions can cause increased somnolence and disturbed sleep cycles as well as obesity, hypothermia, and emotional outbursts. Lesions of the central hypothalamus may stimulate sympathetic neurons, leading to elevated serum catecholamine and cortisol levels. These patients are predisposed to cardiac arrhythmias, hypertension, and gastric erosions.

EVALUATION

Local Mass Effects

Clinical manifestations of sellar lesions vary, depending on the anatomic location of the mass and direction of its extension (Table 33-5). The dorsal sellar diaphragm presents the least resistance to soft tissue expansion from the sella; consequently, pituitary adenomas frequently extend in a suprasellar direction. Bony invasion may occur as well.

Headaches are common features of small intrasellar tumors, even with no demonstrable suprasellar extension. Because of the confined nature of the pituitary, small changes in intrasellar pressure stretch the dural plate; however, headache severity correlates poorly with adenoma size or extension.

Suprasellar extension can lead to visual loss by several mechanisms, the most common being compression of the optic chiasm, but direct invasion of the optic nerves or obstruction of CSF flow leading to secondary visual disturbances also occurs. Pituitary stalk compression by a hormonally active or inactive intrasellar mass may compress the portal vessels, disrupting pituitary access to hypothalamic hormones and dopamine; this results in hyperprolactinemia and concurrent loss of other pituitary hormones. This "stalk section" phenomenon may also be caused by trauma, whiplash injury with posterior clinoid stalk compression, or skull base fractures. Lateral mass invasion may impinge on the cavernous sinus and compress its neural contents, leading to cranial nerve III, IV, and VI palsies as well as effects on the ophthalmic and maxillary branches of the fifth cranial nerve (Chap. 29). Patients may present with diplopia, ptosis, ophthalmoplegia, and decreased facial sensation, depending on the extent of neural damage. Extension into the sphenoid sinus indicates that the pituitary mass has eroded through the sellar floor. Aggressive tumors rarely invade the palate roof and cause nasopharyngeal obstruction, infection, and CSF leakage. Temporal and frontal lobe involvement may lead to uncinate seizures, personality disorders, and anosmia. Direct hypothalamic encroachment by an invasive pituitary mass may cause important metabolic sequelae, including precocious puberty or hypogonadism, diabetes insipidus, sleep disturbances, dysthermia, and appetite disorders.

TABLE 33-5

FEATURES OF SELLAR MASS LESIONS[a]

IMPACTED STRUCTURE	CLINICAL IMPACT
Pituitary	Hypogonadism
	Hypothyroidism
	Growth failure and adult hyposomatotropism
	Hypoadrenalism
Optic chiasm	Loss of red perception
	Bitemporal hemianopia
	Superior or bitemporal field defect
	Scotoma
	Blindness
Hypothalamus	Temperature dysregulation
	Appetite and thirst disorders
	Obesity
	Diabetes insipidus
	Sleep disorders
	Behavioral dysfunction
	Autonomic dysfunction
Cavernous sinus	Ophthalmoplegia with or without ptosis or diplopia
	Facial numbness
Frontal lobe	Personality disorder
	Anosmia
Brain	Headache
	Hydrocephalus
	Psychosis
	Dementia
	Laughing seizures

[a]As the intrasellar mass expands, it first compresses intrasellar pituitary tissue, then usually invades dorsally through the dura to lift the optic chiasm or laterally to the cavernous sinuses. Bony erosion is rare, as is direct brain compression. Microadenomas may present with headache.

MRI

Sagittal and coronal T1-weighted MRI imaging, before and after administration of gadolinium, allow precise visualization of the pituitary gland with clear delineation of the hypothalamus, pituitary stalk, pituitary tissue and

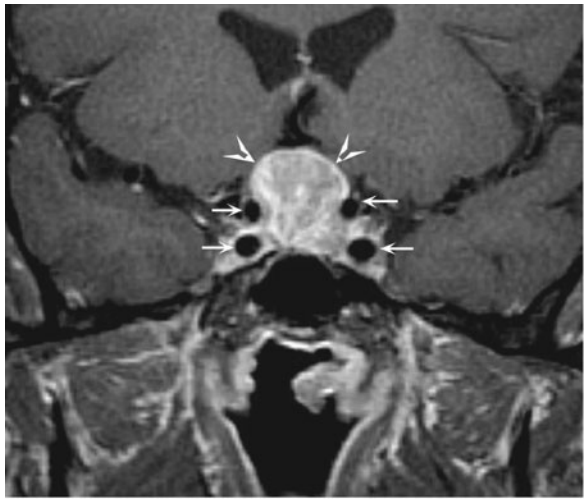

FIGURE 33-4
Pituitary adenoma. Coronal T1-weighted postcontrast MR image shows a homogeneously enhancing mass (*arrowheads*) in the sella turcica and suprasellar region compatible with a pituitary adenoma; the small arrows outline the carotid arteries.

surrounding suprasellar cisterns, cavernous sinuses, sphenoid sinus, and optic chiasm. Pituitary gland height ranges from 6 mm in children to 8 mm in adults; during pregnancy and puberty, the height may reach 10–12 mm. The upper aspect of the adult pituitary is flat or slightly concave, but in adolescent and pregnant individuals, this surface may be convex, reflecting physiologic pituitary enlargement. The stalk should be midline and vertical. CT scan is indicated to define the extent of bony erosion or the presence of calcification.

Anterior pituitary gland soft tissue consistency is slightly heterogeneous on MRI, and signal intensity resembles that of brain matter on T1-weighted imaging (Fig. 33-4). Adenoma density is usually lower than that of surrounding normal tissue on T1-weighted imaging, and the signal intensity increases with T2-weighted images. The high phospholipid content of the posterior pituitary results in a "pituitary bright spot."

Sellar masses are commonly encountered as incidental findings on MRI, and most of these are pituitary adenomas (incidentalomas). In the absence of hormone hypersecretion, these small lesions can be safely monitored by MRI, which is performed annually and then less often if there is no evidence of growth. Resection should be considered for incidentally discovered macroadenomas, as about one-third become invasive or cause local pressure effects. If hormone hypersecretion is evident, specific therapies are indicated. When larger masses (>1 cm) are encountered, they should also be distinguished from nonadenomatous lesions. Meningiomas are often associated with bony hyperostosis; craniopharyngiomas may be calcified and are usually hypodense, whereas gliomas are hyperdense on T2-weighted images.

Ophthalmologic Evaluation

Because optic tracts may be contiguous to an expanding pituitary mass, reproducible visual field assessment that uses perimetry techniques should be performed on all patients with sellar mass lesions that abut the optic chiasm (Chap. 17). Bitemporal hemianopia or superior bitemporal defects are classically observed, reflecting the location of these tracts within the inferior and posterior part of the chiasm. Homonymous cuts reflect postchiasmal and monocular field cuts prechiasmal lesions. Loss of red perception is an early sign of optic tract pressure. Early diagnosis reduces the risk of blindness, scotomas, or other visual disturbances.

Laboratory Investigation

The presenting clinical features of functional pituitary adenomas (e.g., acromegaly, prolactinomas, or Cushing's syndrome) should guide the laboratory studies (Table 33-6). However, for a sellar mass with no obvious clinical features

TABLE 33-6
SCREENING TESTS FOR FUNCTIONAL PITUITARY ADENOMAS

	TEST	COMMENTS
Acromegaly	Serum IGF-I	Interpret IGF-I relative to age- and gender-matched controls
	Oral glucose tolerance test with GH obtained at 0, 30, and 60 min	Normal subjects should suppress growth hormone to <1 μg/L
Prolactinoma	Serum PRL	Exclude medications MRI of the sella should be ordered if prolactin is elevated
Cushing's disease	24-h urinary free cortisol	Ensure urine collection is total and accurate
	Dexamethasone (1 mg) at 11 P.M. and fasting plasma cortisol measured at 8 A.M.	Normal subjects suppress to <5 μg/dL
	ACTH assay	Distinguishes adrenal adenoma (ACTH suppressed) from ectopic ACTH or Cushing's disease (ACTH normal or elevated)

Note: For abbreviations, see text.

of hormone excess, laboratory studies are geared towards determining the nature of the tumor and assessing the possible presence of hypopituitarism. When a pituitary adenoma is suspected based on MRI, initial hormonal evaluation usually includes (1) basal PRL; (2) insulin-like growth factor (IGF) I; (3) 24-h urinary free cortisol (UFC) and/or overnight oral dexamethasone (1 mg) suppression test; (4) α subunit, FSH, and LH; and (5) thyroid function tests. Additional hormonal evaluation may be indicated based on the results of these tests. Pending more detailed assessment of hypopituitarism, a menstrual history, testosterone and 8 A.M. cortisol levels, and thyroid function tests usually identify patients with pituitary hormone deficiencies that require hormone replacement before further testing or surgery.

Histologic Evaluation

Immunohistochemical staining of pituitary tumor specimens obtained at transsphenoidal surgery confirms clinical and laboratory studies and provides a histologic diagnosis when hormone studies are equivocal and in cases of clinically nonfunctioning tumors. Occasionally, ultrastructural assessment by electron microscopy is required for diagnosis.

Rx Treatment: HYPOTHALAMIC, PITUITARY, AND OTHER SELLAR MASSES

OVERVIEW Successful management of sellar masses requires accurate diagnosis as well as selection of optimal therapeutic modalities. Most pituitary tumors are benign and slow-growing. Clinical features result from local mass effects and hormonal hypo- or hypersecretion syndromes caused directly by the adenoma or as a consequence of treatment. Thus, lifelong management and follow-up are necessary for these patients.

MRI technology with gadolinium enhancement for pituitary visualization, new advances in transsphenoidal surgery and in stereotactic radiotherapy (including gamma-knife radiotherapy), and novel therapeutic agents have improved pituitary tumor management. The goals of pituitary tumor treatment include normalization of excess pituitary secretion, amelioration of symptoms and signs of hormonal hypersecretion syndromes, and shrinkage or ablation of large tumor masses with relief of adjacent structure compression. Residual anterior pituitary function should be preserved and can sometimes be restored by removing the tumor mass. Ideally, adenoma recurrence should be prevented.

TRANSSPHENOIDAL SURGERY Transsphenoidal rather than transfrontal resection is the desired surgical approach for pituitary tumors, except for the rare invasive suprasellar mass surrounding the frontal or middle fossa, the optic nerves, or invading posteriorly behind the clivus. Intraoperative microscopy facilitates visual distinction between adenomatous and normal pituitary tissue, as well as microdissection of small tumors that may not be visible by MRI (**Fig. 33-5**). Transsphenoidal surgery also avoids the cranial invasion and manipulation of brain tissue required by subfrontal surgical approaches. Endoscopic techniques with three-dimensional intraoperative localization have improved visualization and access to tumor tissue.

In addition to correction of hormonal hypersecretion, pituitary surgery is indicated for mass lesions that impinge on surrounding structures. Surgical decompression and resection are required for an expanding pituitary mass accompanied by persistent headache, progressive visual field defects, cranial nerve palsies, internal hydrocephalus, and, occasionally, intrapituitary hemorrhage and apoplexy. Transsphenoidal surgery is sometimes used for pituitary tissue biopsy to establish a histologic diagnosis.

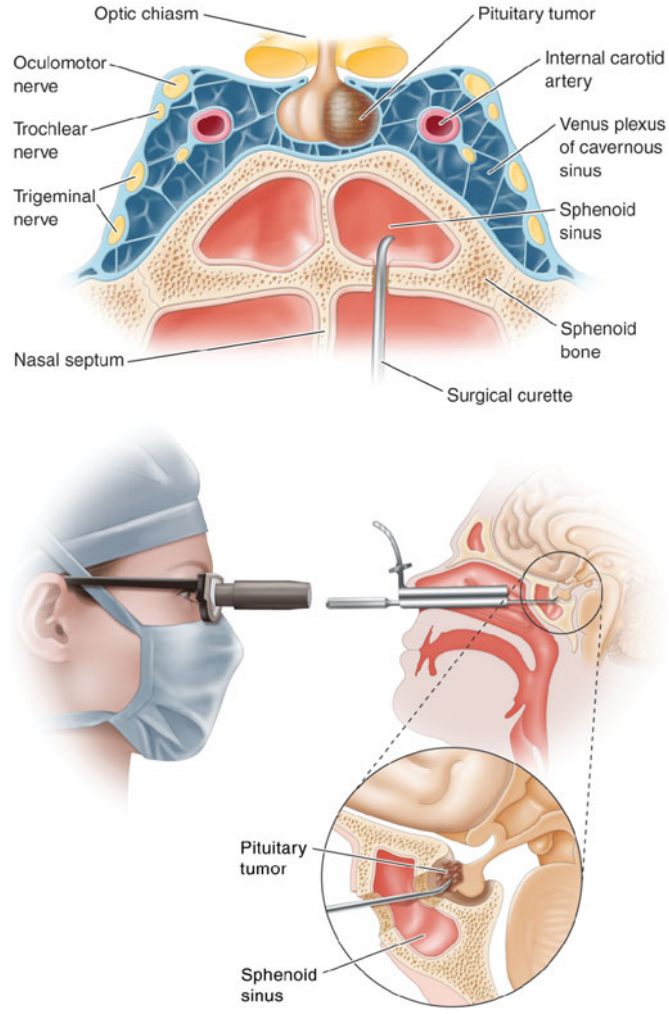

FIGURE 33-5
Transsphenoidal resection of pituitary mass via the endonasal approach. *(Adapted from Fahlbusch R: Endocrinol Metab Clin 21:669, 1992.)*

Whenever possible, the pituitary mass lesion should be selectively excised; normal tissue should be manipulated or resected only when critical for effective mass dissection. Nonselective hemihypophysectomy or total hypophysectomy may be indicated if no mass lesion is clearly discernible, multifocal lesions are present, or the remaining nontumorous pituitary tissue is obviously necrotic. This strategy, however, increases the likelihood of hypopituitarism and the need for lifelong hormonal replacement.

Preoperative mass effects, including visual field defects or compromised pituitary function, may be reversed by surgery, particularly when these deficits are not long-standing. For large and invasive tumors, it is necessary to determine the optimal balance between maximal tumor resection and preservation of anterior pituitary function, especially for preserving growth and reproductive function in younger patients. Similarly, tumor invasion outside of the sella is rarely amenable to surgical cure; the surgeon must judge the risk-benefit ratio of extensive tumor resection.

Side Effects Tumor size, the degree of invasiveness, and experience of the surgeon largely determine the incidence of surgical complications. Operative mortality is about 1%. Transient diabetes insipidus and hypopituitarism occur in up to 20% of patients. Permanent diabetes insipidus, cranial nerve damage, nasal septal perforation, or visual disturbances may be encountered in up to 10% of patients. CSF leaks occur in 4% of patients. Less common complications include carotid artery injury, loss of vision, hypothalamic damage, and meningitis. Permanent side effects are rare after surgery for microadenomas.

RADIATION Radiation is used either as a primary therapy for pituitary or parasellar masses or, more commonly, as an adjunct to surgery or medical therapy. Focused megavoltage irradiation is achieved by precise MRI localization, using a high-voltage linear accelerator and accurate isocentric rotational arcing. A major determinant of accurate irradiation is reproduction of the patient's head position during multiple visits and maintenance of absolute head immobility. A total of <50 Gy (5000 rad) is given as 180-cGy (180-rad) fractions split over about 6 weeks. Stereotactic radiosurgery delivers a large single high-energy dose from a cobalt 60 source (gamma knife), linear accelerator, or cyclotron. Long-term effects of gamma-knife surgery are as yet unknown.

The role of radiation therapy in pituitary tumor management depends on multiple factors including the nature of the tumor, age of the patient, and the availability of surgical and radiation expertise. Because of its relatively slow onset of action, radiation therapy is usually reserved for postsurgical management. As an adjuvant to surgery, radiation is used to treat residual tumor and in an attempt to prevent regrowth. Irradiation offers the only effective means for ablating significant postoperative residual nonfunctioning tumor tissue. In contrast, PRL-, GH-, and sometimes ACTH-secreting tumor tissues are amenable to medical therapy.

Side Effects In the short term, radiation may cause transient nausea and weakness. Alopecia and loss of taste and smell may be more long-lasting. Failure of pituitary hormone synthesis is common in patients who have undergone head and neck or pituitary-directed irradiation. More than 50% of patients develop loss of GH, ACTH, TSH, and/or gonadotropin secretion within 10 years, usually due to hypothalamic damage. Lifelong follow-up with testing of anterior pituitary hormone reserve is therefore necessary after radiation treatment. Optic nerve damage with impaired vision due to optic neuritis is reported in about 2% of patients who undergo pituitary irradiation. Cranial nerve damage is uncommon now that radiation doses are ≤2 Gy (200 rad) at any one treatment session and the maximum dose is <50 Gy (5000 rad). The use of stereotactic radiotherapy may reduce damage to adjacent structures. Radiotherapy of pituitary tumors has been associated with adverse mortality, mainly from cerebrovascular disease. The cumulative risk of developing a secondary tumor after conventional radiation is 1.3% after 10 years and 1.9% after 20 years.

MEDICAL Medical therapy for pituitary tumors is highly specific and depends on tumor type. For prolactinomas, dopamine agonists are the treatment of choice. For acromegaly and TSH-secreting tumors, somatostatin analogues and, occasionally, dopamine agonists are indicated. ACTH-secreting tumors and nonfunctioning tumors are generally not responsive to medications and require surgery and/or irradiation.

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CHAPTER 34

MULTIPLE SCLEROSIS AND OTHER DEMYELINATING DISEASES

Stephen L. Hauser ■ Douglas S. Goodin

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Demyelinating disorders are characterized by inflammation and selective destruction of central nervous system (CNS) myelin. The peripheral nervous system (PNS) is spared, and most patients have no evidence of an associated systemic illness.

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is characterized by a triad of inflammation, demyelination, and gliosis (scarring); the course can be relapsing-remitting or progressive. Lesions of MS typically occur at different times and in different CNS locations (i.e., disseminated in time and space). MS affects ~350,000 individuals in the United States and 2.5 million individuals worldwide. In Western societies, MS is second only to trauma as a cause of neurologic disability beginning in early to middle adulthood. Manifestations of MS vary from a benign illness to a rapidly evolving and incapacitating disease requiring profound lifestyle adjustments.

PATHOGENESIS

Anatomy

The lesions of MS (plaques) vary in size from 1 or 2 mm to several centimeters. Acute MS lesions are characterized by perivenular cuffing with inflammatory mononuclear cells, predominantly T cells and macrophages, which also infiltrate the surrounding white matter. At sites of inflammation, the blood-brain barrier (BBB) is disrupted, but unlike vasculitis, the vessel wall is preserved. In many lesions, myelin-specific autoantibodies are present, presumably promoting demyelination directly as well as stimulating macrophages and microglial cells (bone marrow–derived CNS phagocytes) that scavenge the myelin debris. As lesions evolve, there is prominent astrocytic proliferation (gliosis). Surviving oligodendrocytes or those that differentiate from precursor cells may partially remyelinate the surviving naked axons, producing so-called shadow plaques. In many lesions, oligodendrocyte precursors are present in large numbers but fail to remyelinate. Ultrastructural studies of MS lesions suggest that fundamentally different underlying pathologies may exist in different patients. Heterogeneity has been observed in terms of (1) whether the inflammatory cell infiltrate is associated with antibody deposition and activation of complement, and (2) whether the target of the immunopathologic process is the myelin sheath itself or the cell body of the oligodendrocyte. Although relative sparing of axons is typical of MS, partial or total axonal destruction can also occur, especially within highly

inflammatory lesions. Evidence also suggests that axonal loss is a major contributor to irreversible neurologic disability in MS (see Neurodegeneration, below).

Physiology

Nerve conduction in myelinated axons occurs in a saltatory manner, with the nerve impulse jumping from one node of Ranvier to the next without depolarization of the axonal membrane underlying the myelin sheath between nodes (Fig. 34-1). This produces considerably faster conduction velocities (~70 m/s) than the slow velocities (~1 m/s) produced by continuous propagation in unmyelinated nerves. Conduction block occurs when the nerve impulse is unable to traverse the demyelinated segment. This can happen when the resting axon membrane becomes hyperpolarized due to the exposure of voltage-dependent potassium channels that are normally buried underneath the myelin sheath. A temporary conduction block often follows a demyelinating event before sodium channels (originally concentrated at the nodes) redistribute along the naked axon (Fig. 34-1). This redistribution ultimately allows continuous propagation of nerve action potentials through the demyelinated segment. On occasion, conduction block is incomplete, affecting, for example, high- but not low-frequency volleys of impulses. Variable conduction block can occur with raised body temperature or metabolic alterations and may explain clinical fluctuations that vary from hour to hour or appear with fever or exercise. Conduction slowing occurs when the demyelinated segments support only (slow) continuous nerve impulse propagation.

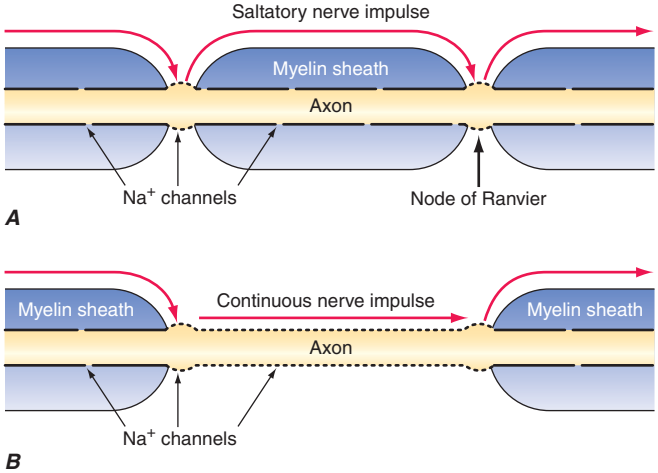


FIGURE 34-1

Nerve conduction in myelinated and demyelinated axons. ***A.*** Saltatory nerve conduction in myelinated axons occurs with the nerve impulse jumping from one node of Ranvier to the next. Sodium channels (shown as breaks in the solid black line) are concentrated at the nodes where axonal depolarization occurs. ***B.*** Following demyelination, additional sodium channels are redistributed along the axon itself, thereby allowing continuous propagation of the nerve action potential despite the absence of myelin.

Epidemiology

MS is approximately threefold more common in women than men. The age of onset is typically between 20 and 40 years (slightly later in men than in women), but the disease can present across the lifespan. Approximately 10% of cases begin before 18 years, and extremes with onset as early as 1–2 years or as late as the eighth decade have been described.

Geographical gradients have been repeatedly observed in MS, with prevalence rates increasing at higher latitudes. The highest known prevalence for MS (250 per 100,000) occurs in the Orkney Islands, located north of Scotland, and similarly high rates are found throughout northern Europe, the northern United States, and Canada. By contrast, the prevalence is low in Japan (6 per 100,000), in other parts of Asia, in equatorial Africa, and in the Middle East.

One proposed explanation for the latitude effect on MS is that there is a protective effect of sun exposure. Ultraviolet radiation from sun is the most important source of vitamin D in most individuals, and low levels of vitamin D are common at high latitudes where sun exposure may be low, particularly during winter months. Prospective studies have confirmed that vitamin D deficiency is associated with an increase in MS risk. Immunoregulatory effects of vitamin D could explain this possible relationship.

Migration studies and identification of possible point epidemics provide additional support for an environmental effect on MS risk. Migration studies suggest that some MS-related exposure occurs in childhood and years before MS is clinically evident. In some studies, migration early in life from a low- to high-risk area was found to increase MS risk, and conversely, migration from a high- to a low-risk area decreased risk. With respect to possible point epidemics, the most convincing example occurred in the Faeroe Islands north of Denmark after the British occupation during World War II.

The prevalence of MS appears to have steadily increased over the past century; furthermore, this increase has occurred primarily in women. Interestingly, recent epidemiologic data suggests that the latitude effect on MS may currently be decreasing, for unknown reasons.

MS risk also correlates with high socioeconomic status, which may reflect improved sanitation and delayed initial exposures to infectious agents. By analogy, some viral infections (e.g., poliomyelitis and measles viruses) produce neurologic sequelae more frequently when the age of initial infection is delayed. Occasional reports seem to implicate a specific infectious agent such as human herpes virus type 6 (HHV-6) or *Chlamydia pneumoniae*, although, in general, the available reports have been inconsistent.

Most intriguingly, the evidence of a remote Epstein-Barr virus (EBV) infection playing some role in MS is supported by a number of epidemiologic and laboratory studies. A higher risk of infectious mononucleosis (associated with relatively late EBV infection) and higher-antibody titers to latency-associated EBV nuclear antigen are associated with MS; conversely, individuals never infected with EBV are at low MS risk. At this time, however, a causal role for EBV or for any specific infectious agent in MS remains uncertain.

GENETIC CONSIDERATIONS

Evidence also supports an important genetic influence on MS. Whites are inherently at higher risk for MS than Africans or Asians, even when residing in a similar environment. MS also aggregates within some families, and adoption, half-sibling, twin, and spousal studies indicate that familial aggregation is due to genetic, and not environmental, factors (Table 34-1).

Susceptibility to MS is polygenic, with each gene contributing a relatively small amount to the overall risk. The major histocompatibility complex (MHC) on chromosome 6 is the strongest MS susceptibility region in the genome. Fine mapping studies implicate primarily the class II region of the MHC (encoding HLA molecules involved in presenting peptide antigens to T cells) and specifically the DR2 (molecular designation DRB1*1501) allele. Other recently identified MS susceptibility genes encode receptors for two proinflammatory cytokines, the IL-7 receptor alpha chain (CD127) and the IL-2 receptor alpha chain (CD25); the MS associated variant of the IL-7 receptor increases the amount of soluble compared to membrane bound receptor. It is also likely that genetic heterogeneity is present in MS, meaning that there are different causative genes in different individuals.

Immunology

An autoimmune cause for MS is supported by the laboratory model of experimental allergic encephalomyelitis (EAE) and by studies of the immune system in MS patients.

TABLE 34-1

RISK OF DEVELOPING MS	
1 in 3	If an identical twin has MS
1 in 15	If a fraternal twin has MS
1 in 25	If a sibling has MS
1 in 50	If a parent or half-sibling has MS
1 in 100	If a first cousin has MS
1 in 1000	If a spouse has MS
1 in 1000	If no one in the family has MS

Autoreactive T Lymphocytes

Myelin basic protein (MBP) is an important T cell antigen in EAE and probably also in human MS. Activated MBP-reactive T cells have been identified in the blood, in cerebrospinal fluid (CSF), and within MS lesions. Moreover, DR2 may influence the autoimmune response because it binds with high affinity to a fragment of MBP (spanning amino acids 89–96), stimulating T cell responses to this self-protein.

Humoral Autoimmunity

B cell activation and antibody responses also appear to be necessary for the full development of demyelinating lesions to occur, both in experimental models and in human MS. Increased numbers of clonally expanded B cells with properties of postgerminal center memory or antibody-producing lymphocytes are present in MS lesions and in CSF. Myelin-specific autoantibodies, some directed against myelin oligodendrocyte glycoprotein (MOG), have been detected bound to vesiculated myelin debris in MS plaques. In the CSF, elevated levels of locally synthesized immunoglobulins and oligoclonal antibodies derived from expansion of clonally restricted plasma cells are also characteristic of MS. The pattern of oligoclonal banding is unique to each individual, and attempts to identify the targets of these antibodies have been largely unsuccessful, although one recent report indicated that some bands recognized EBV antigens.

Cytokines

Cytokines and chemokines appear to regulate many of the cellular interactions that operate in MS. Proinflammatory T_H1 cytokines including interleukin (IL) 2, tumor necrosis factor (TNF) α, and interferon (IFN) γ play key roles in activating and maintaining autoimmune responses, and TNF-α and IFN-γ may directly injure oligodendrocytes or the myelin membrane.

Triggers

Studies reveal that in patients with early relapsing remitting MS, serial MRI has demonstrated bursts of focal inflammatory disease activity occurring far more frequently than would have been predicted by the frequency of relapses. Thus, early in MS, most disease activity is clinically silent. The triggers causing these bursts are unknown, although the fact that patients may experience relapses after nonspecific upper respiratory infections suggests that either molecular mimicry between viruses and myelin antigens or viral superantigens activating pathogenic T cells may play a role in MS pathogenesis.

Neurodegeneration

Axonal damage occurs in every newly formed MS lesion, and cumulative axonal loss is considered to be the major cause of progressive and irreversible neurological disability

in MS. As many as 70% of axons are lost from the lateral corticospinal tracts in patients with advanced paraparesis from MS, and longitudinal MRI studies suggest there is progressive axonal loss over time within established, inactive, lesions. Knowledge of the mechanisms responsible for axonal injury is incomplete, and it is even unclear whether demyelination is a prerequisite for axonal injury in MS. Demyelination can result in reduced trophic support for axons, redistribution of ion channels, and destabilization of action potential membrane potentials. Axons can initially adapt, but eventually distal and retrograde degeneration occurs. Therefore the early promotion of remyelination and preservation of oligodendrocytes remain important therapeutic goals in MS. Some evidence suggests that axonal damage is mediated directly by resident and invading inflammatory cells and their toxic products, in particular by microglia, macrophages, and CD8 T lymphocytes. Activated microglia are particularly likely to cause axonal injury through the release of NO and oxygen radicals and via glutamate, which is toxic to oligodendrocytes and neurons.

CLINICAL MANIFESTATIONS

The onset of MS may be abrupt or insidious. Symptoms may be severe or seem so trivial that a patient may not seek medical attention for months or years. Indeed, at autopsy some individuals who were asymptomatic during life will be found, unexpectedly, to have MS. In others, an MRI scan obtained for an unrelated reason may show evidence of asymptomatic MS. Symptoms of MS are extremely varied and depend on the location and severity of lesions within the CNS (Table 34-2). Examination generally reveals evidence of neurologic dysfunction, often in asymptomatic locations. For example, a patient may present with symptoms in one leg but signs in both.

Weakness of the limbs may manifest as loss of strength or dexterity, fatigue, or a disturbance of gait. Exercise-induced weakness is a characteristic symptom of MS.

TABLE 34-2

INITIAL SYMPTOMS OF MS

SYMPTOM	PERCENT OF CASES	SYMPTOM	PERCENT OF CASES
Sensory loss	37	Lhermitte	3
Optic neuritis	36	Pain	3
Weakness	35	Dementia	2
Paresthesias	24	Visual loss	2
Diplopia	15	Facial palsy	1
Ataxia	11	Impotence	1
Vertigo	6	Myokymia	1
Paroxysmal attacks	4	Epilepsy	1
Bladder	4	Falling	1

Source: After WB Matthews et al, *McAlpine's Multiple Sclerosis,* New York, Churchill Livingstone, 1991.

The weakness is of the upper motor neuron type (Chap. 10) and is usually accompanied by other pyramidal signs such as spasticity, hyperreflexia and Babinski signs. Occasionally a tendon reflex may be lost (simulating a lower motor neuron lesion) if an MS lesion disrupts the afferent reflex fibers in the spinal cord.

Spasticity (Chap. 10) is often associated with spontaneous and movement-induced muscle spasms. More than 30% of MS patients have moderate to severe spasticity, especially in the legs. This is often accompanied by painful spasms, interfering with ambulation, work, or self-care. Occasionally spasticity provides support for the body weight during ambulation, and in these cases treatment of spasticity may actually do more harm than good.

Optic neuritis (ON) presents as diminished visual acuity, dimness, or decreased color perception (desaturation) in the central field of vision. These symptoms may be mild or may progress to severe visual loss. Rarely, there is complete loss of light perception. Visual symptoms are generally monocular but may be bilateral. Periorbital pain (aggravated by eye movement) often precedes or accompanies the visual loss. An afferent pupillary defect (Chap. 17) is usually present. Funduscopic examination may be normal or reveal optic disc swelling (papillitis). Pallor of the optic disc (optic atrophy) commonly follows ON. Uveitis is rare and should raise the possibility of alternative diagnoses.

Visual blurring in MS may result from ON or diplopia; if the symptom resolves when either eye is covered, the cause is diplopia.

Diplopia may result from internuclear ophthalmoplegia (INO) or from palsy of the sixth cranial nerve (rarely the third or fourth). An INO consists of impaired adduction of one eye due to a lesion in the ipsilateral medial longitudinal fasciculus (Chap. 17). Prominent nystagmus is often observed in the abducting eye, along with a small skew deviation. A bilateral INO is particularly suggestive of MS. Other common gaze disturbances in MS include (1) a horizontal gaze palsy, (2) a "one and a half" syndrome (horizontal gaze palsy plus an INO), and (3) acquired pendular nystagmus.

Sensory symptoms are varied and include both paresthesias (e.g., tingling, prickling sensations, formications, "pins and needles," or painful burning) and hypesthesia (e.g., reduced sensation, numbness, or a "dead" feeling). Unpleasant sensations (e.g., feelings that body parts are swollen, wet, raw, or tightly wrapped) are also common. Sensory impairment of the trunk and legs below a horizontal line on the torso (a sensory level) indicates that the spinal cord is the origin of the sensory disturbance. It is often accompanied by a bandlike sensation of tightness around the torso. Pain is a common symptom of MS, experienced by >50% of patients. Pain can occur anywhere on the body and can change locations over time.

Ataxia usually manifests as cerebellar tremors (Chap. 26). Ataxia may also involve the head and trunk or the voice,

producing a characteristic cerebellar dysarthria (scanning speech).

Bladder dysfunction is present in >90% of MS patients, and in a third of patients, dysfunction results in weekly or more frequent episodes of incontinence. During normal reflex voiding, relaxation of the bladder sphincter (α-adrenergic innervation) is coordinated with contraction of the detrusor muscle in the bladder wall (muscarinic cholinergic innervation). *Detrusor hyperreflexia*, due to impairment of suprasegmental inhibition, causes urinary frequency, urgency, nocturia, and uncontrolled bladder emptying. *Detrusor sphincter dyssynergia*, due to loss of synchronization between detrusor and sphincter muscles, causes difficulty in initiating and/or stopping the urinary stream, producing hesitancy, urinary retention, overflow incontinence, and recurrent infection.

Constipation occurs in >30% of patients. Fecal urgency or *bowel incontinence* is less common (15%) but can be socially debilitating.

Cognitive dysfunction can include memory loss, impaired attention, difficulties in problem solving, slowed information processing, and problems shifting between cognitive tasks. Euphoria (elevated mood) was once thought to be characteristic of MS but is actually uncommon, occurring in <20% of patients. Cognitive dysfunction sufficient to impair activities of daily living is rare.

Depression, experienced by approximately half of patients, can be reactive, endogenous, or part of the illness itself and can contribute to fatigue. Suicide in MS patients is 7.5-fold more common than in age-matched controls.

Fatigue is experienced by 90% of patients; this symptom is the most common reason for work-related disability in MS. Fatigue can be exacerbated by elevated temperatures, by depression, by expending exceptional effort to accomplish basic activities of daily living, or by sleep disturbances (e.g., from frequent nocturnal awakenings to urinate).

Sexual dysfunction may manifest as decreased libido, impaired genital sensation, impotence in men, and diminished vaginal lubrication or adductor spasms in women.

Facial weakness due to a lesion in the pons may resemble idiopathic Bell's palsy (Chap. 29). Unlike Bell's palsy, facial weakness in MS is usually not associated with ipsilateral loss of taste sensation or retroauricular pain.

Vertigo may appear suddenly from a brainstem lesion, superficially resembling acute labyrinthitis (Chap. 9). *Hearing loss* may also occur in MS but is uncommon.

Ancillary Symptoms

Heat sensitivity refers to neurologic symptoms produced by an elevation of the body's core temperature. For example, unilateral visual blurring may occur during a hot shower or with physical exercise (*Uhthoff's symptom*). It is also common for MS symptoms to worsen transiently, sometimes dramatically, during febrile illnesses (see Acute Attacks or Initial Demyelinating Episodes, below). Such heat-related symptoms probably result from transient conduction block (see above).

Lhermitte's symptom is an electric shocklike sensation (typically induced by flexion or other movements of the neck) that radiates down the back into the legs. Rarely, it radiates into the arms. It is generally self-limited but may persist for years. Lhermitte's symptom can also occur with other disorders of the cervical spinal cord (e.g., cervical spondylosis).

Paroxysmal symptoms are distinguished by their brief duration (10 s to 2 min), high frequency (5–40 episodes per day), lack of any alteration of consciousness or change in background electroencephalogram during episodes, and a self-limited course (generally lasting weeks to months). They may be precipitated by hyperventilation or movement. These syndromes may include Lhermitte's symptom; tonic contractions of a limb, face, or trunk (tonic seizures); paroxysmal dysarthria and ataxia; paroxysmal sensory disturbances; and several other less well-characterized syndromes. Paroxysmal symptoms probably result from spontaneous discharges, arising at the edges of demyelinated plaques and spreading to adjacent white matter tracts.

Trigeminal neuralgia, hemifacial spasm, and *glossopharyngeal neuralgia* (Chap. 29) can occur when the demyelinating lesion involves the root entry (or exit) zone of the fifth, seventh, and ninth cranial nerve, respectively. Trigeminal neuralgia (tic douloureux) is a very brief lancinating facial pain often triggered by an afferent input from the face or teeth. Most cases of trigeminal neuralgia are not MS-related; however, atypical features such as onset before age 50 years, bilateral symptoms, objective sensory loss, or nonparoxysmal pain should raise concerns that MS could be responsible.

Facial myokymia consists of either persistent rapid flickering contractions of the facial musculature (especially the lower portion of the orbicularis oculus) or a contraction that slowly spreads across the face. It results from lesions of the corticobulbar tracts or brainstem course of the facial nerve.

DISEASE COURSE

Four clinical types of MS have been described (**Fig. 34-2**):

1. *Relapsing/remitting MS* (RRMS) accounts for 85% of MS cases at onset and is characterized by discrete attacks that generally evolve over days to weeks (rarely over hours). There is often complete recovery over the ensuing weeks to months (Fig. 34-2*A*). However, when ambulation is severely impaired during an attack, approximately half will fail to improve. Between attacks, patients are neurologically stable.
2. *Secondary progressive MS* (SPMS) always begins as RRMS (Fig. 34-2*B*). At some point, however, the

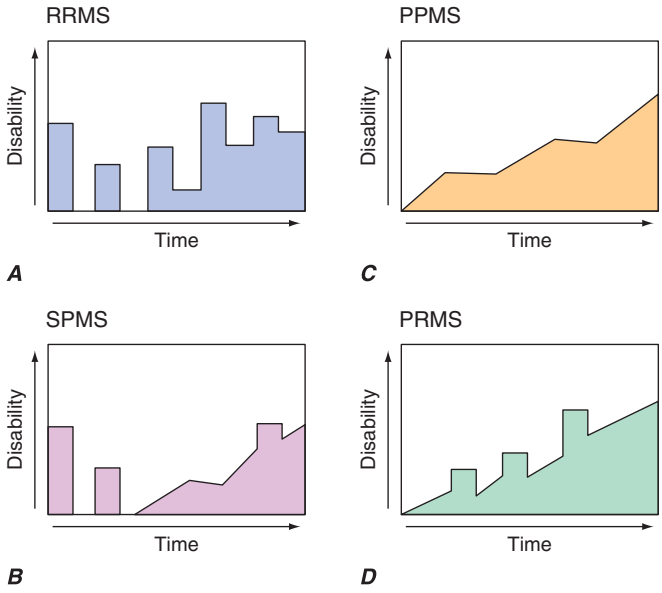


FIGURE 34-2
Clinical course of multiple sclerosis (MS). ***A.*** Relapsing/remitting MS. ***B.*** Secondary progressive MS. ***C.*** Primary progressive MS. ***D.*** Progressive/relapsing MS.

clinical course changes so that the patient experiences a steady deterioration in function unassociated with acute attacks (which may continue or cease during the progressive phase). SPMS produces a greater amount of fixed neurologic disability than RRMS. For a patient with RRMS, the risk of developing SPMS is ~2.5% each year, meaning that the great majority of RRMS ultimately evolves into SPMS. SPMS appears to represent a late stage of the same underlying illness as RRMS.

3. *Primary progressive MS* (PPMS) accounts for ~15% of cases. These patients do not experience attacks but only a steady functional decline from disease onset (Fig. 34-2*C*). Compared to RRMS, the sex distribution is more even, the disease begins later in life (mean age ~40 years), and disability develops faster (at least relative to the onset of the first clinical symptom). Whether PPMS is an uncommon form of the same underlying illness as RRMS or whether these are distinct illnesses is uncertain.
4. *Progressive/relapsing MS* (PRMS) overlaps PPMS and SPMS and accounts for ~5% of MS patients. Like patients with PPMS, these patients experience a steady deterioration in their condition from disease onset. However, like SPMS patients, they experience occasional attacks superimposed upon their progressive course (Fig. 34-2*D*).

DIAGNOSIS

There is no definitive diagnostic test for MS. Diagnostic criteria for clinically definite MS require documentation of two or more episodes of symptoms and two or more signs that reflect pathology in anatomically noncontiguous white matter tracts of the CNS (Table 34-3). Symptoms must last for >24 h and occur as distinct episodes that are separated by a month or more. At least one of the two required signs must be present on neurologic

TABLE 34-3

DIAGNOSTIC CRITERIA FOR MS
1. Examination must reveal *objective* abnormalities of the CNS.
2. Involvement must reflect predominantly disease of white matter long tracts, usually including (a) pyramidal pathways, (b) cerebellar pathways, (c) medial longitudinal fasciculus, (d) optic nerve, and (e) posterior columns.
3. Examination or history must implicate involvement of two or more areas of the CNS.
a. MRI may be used to document a second lesion when only one site of abnormality has been demonstrable on examination. A confirmatory MRI must have either four lesions involving the white matter or three lesions if one is periventricular in location. Acceptable lesions must be >3 mm in diameter. For patients older than 50 years, two of the following criteria must also be met: (a) lesion size >5 mm, (b) lesions adjacent to the bodies of the lateral ventricles, and (c) lesion(s) present in the posterior fossa.
b. Evoked response testing may be used to document a second lesion not evident on clinical examination.
4. The clinical pattern must consist of (a) two or more separate episodes of worsening involving different sites of the CNS, each lasting at least 24 h and occurring at least 1 month apart, or (b) gradual or stepwise progression over at least 6 months if accompanied by increased IgG synthesis or two or more oligoclonal bands. MRI may be used to document dissemination in time if a new T2 lesion or a Gd-enhancing lesion is seen 3 or more months after a clinically isolated syndrome.
5. The patient's neurologic condition could not better be attributed to another disease.
DIAGNOSTIC CATEGORIES
1. *Definite MS:* All five criteria fulfilled.
2. *Probable MS: All* five criteria fulfilled except (a) only one objective abnormality despite two symptomatic episodes or (b) only one symptomatic episode despite two or more objective abnormalities.
3. *At risk for MS:* Criteria 1, 2, 3, and 5 fulfilled; patient has only one symptomatic episode and one objective abnormality.

Note: CNS, central nervous system; MRI, magnetic resonance imaging; Gd, gadolinium.

examination. The second may be documented by abnormal paraclinical tests such as MRI or evoked potentials (EPs). Similarly, in the most recent diagnostic scheme, the second clinical event (in time) may be supported solely by paraclinical information, usually the development of new focal white matter lesions on MRI. In patients who experience gradual progression of disability for ≥6 months without superimposed relapses, documentation of intrathecal IgG may be used to support the diagnosis.

DIAGNOSTIC TESTS

Magnetic Resonance Imaging

MRI has revolutionized the diagnosis and management of MS (Fig. 34-3); characteristic abnormalities are found in >95% of patients. An increase in vascular permeability from a breakdown of the BBB is detected by leakage of intravenous gadolinium (Gd) into the parenchyma. Such leakage occurs early in the development of an MS lesion and serves as a useful marker of inflammation. Gd enhancement persists for approximately 1 month, and the residual MS plaque remains visible indefinitely as a focal area of hyperintensity (a lesion) on spin-echo (T2-weighted) and proton-density images. Lesions are frequently oriented perpendicular to the ventricular surface, corresponding to the pathologic pattern of perivenous demyelination (Dawson's fingers). Lesions are multifocal within the brain, brainstem, and spinal cord. Lesions larger than 6 mm located in the corpus callosum, periventricular white matter, brainstem,

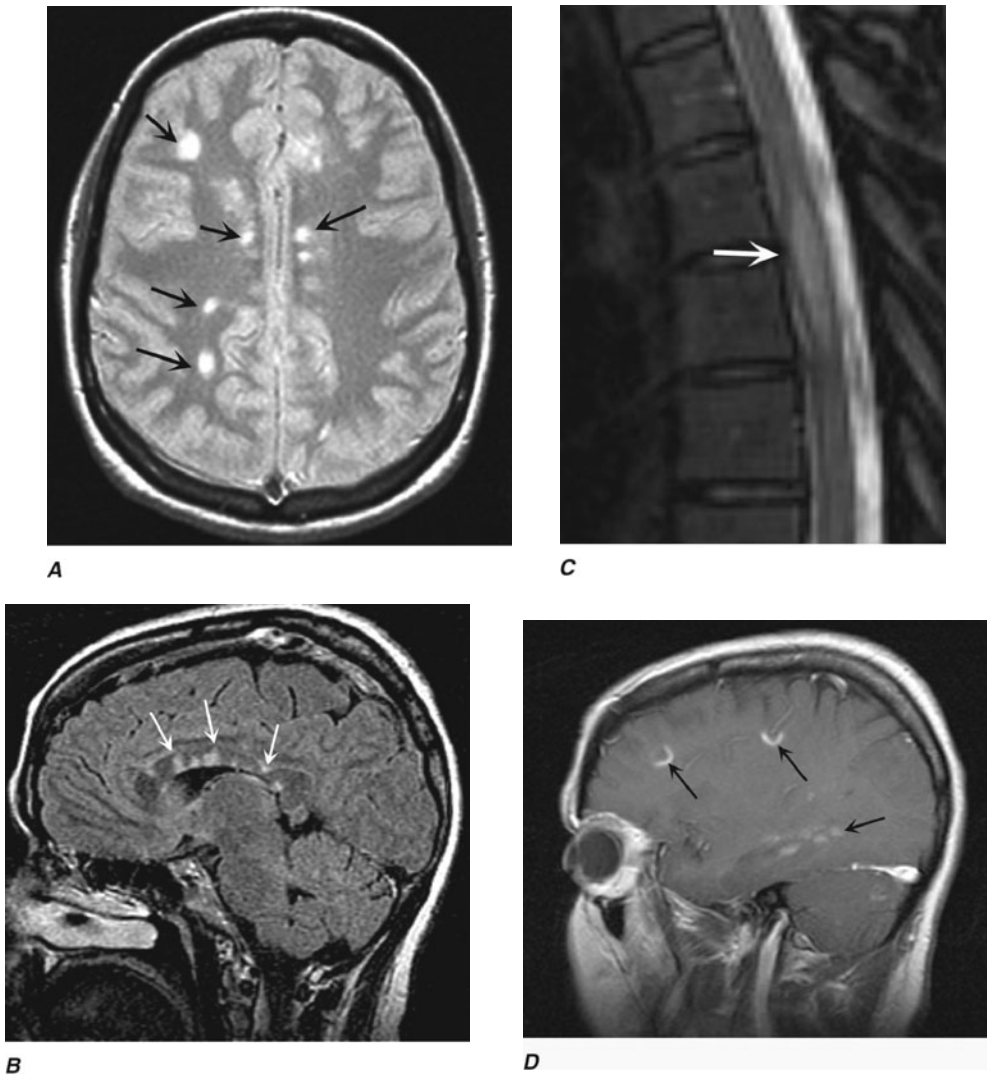


FIGURE 34-3

A. Axial first-echo image from T2-weighted sequence demonstrates multiple bright signal abnormalities in white matter, typical for MS. ***B.*** Sagittal T2-weighted FLAIR (fluid attenuated inversion recovery) image in which the high signal of CSF has been suppressed. CSF appears dark, while areas of brain edema or demyelination appear high in signal as shown here in the corpus callosum (*arrows*). Lesions in the anterior corpus callosum are frequent in MS and rare in vascular disease. ***C.*** Sagittal T2-weighted fast spin echo image of the thoracic spine demonstrates a fusiform high-signal-intensity lesion in the mid thoracic spinal cord. ***D.*** Sagittal T1-weighted image obtained after the intravenous administration of gadolinium DTPA reveals focal areas of blood-brain barrier disruption, identified as high-signal-intensity regions (*arrows*).

cerebellum, or spinal cord are particularly helpful diagnostically. Different criteria for the use of MRI in the diagnosis of MS have been proposed (Table 34-3).

The total volume of T2-weighted signal abnormality (the "burden of disease") shows a significant (albeit weak) correlation with clinical disability, as do measures of brain atrophy. Approximately one-third of T2-weighted lesions appear as hypointense lesions (black holes) on T1-weighted imaging. Black holes may be a marker of irreversible demyelination and axonal loss, although even this measure depends on the timing of the image acquisition (e.g., most acute Gd-enhancing T2 lesions are T1 dark).

Newer MRI measures such as magnetization transfer ratio (MTR) imaging and proton magnetic resonance spectroscopic imaging (MRSI) may ultimately serve as surrogate markers of clinical disability. For example, MRSI can quantitate molecules such as *N*-acetyl aspartate, which is a marker of axonal integrity, and MTR may be able to distinguish demyelination from edema.

Evoked Potentials

EP testing assesses function in afferent (visual, auditory, and somatosensory) or efferent (motor) CNS pathways. EPs use computer averaging to measure CNS electric potentials evoked by repetitive stimulation of selected peripheral nerves or of the brain. These tests provide the most information when the pathways studied are clinically uninvolved. For example, in a patient with a remitting and relapsing spinal cord syndrome with sensory deficits in the legs, an abnormal somatosensory EP following posterior tibial nerve stimulation provides little new information. By contrast, an abnormal visual EP in this circumstance would permit a diagnosis of clinically definite MS (Table 34-3). Abnormalities on one or more EP modalities occur in 80–90% of MS patients. EP abnormalities are not specific to MS, although a marked delay in the latency of a specific EP component (as opposed to a reduced amplitude or distorted waveshape) is suggestive of demyelination.

Cerebrospinal Fluid

CSF abnormalities found in MS include a mononuclear cell pleocytosis and an increased level of intrathecally synthesized IgG. The total CSF protein is usually normal or slightly elevated. Various formulas distinguish intrathecally synthesized IgG from IgG that may have entered the CNS passively from the serum. One formula, the CSF IgG index, expresses the ratio of IgG to albumin in the CSF divided by the same ratio in the serum. The IgG synthesis rate uses serum and CSF IgG and albumin measurements to calculate the rate of CNS IgG synthesis. The measurement of oligoclonal banding (OCB) in the CSF also assesses intrathecal production of IgG. OCBs are detected by agarose gel electrophoresis. Two or more OCBs are found in 75–90% of patients with MS. OCBs may be absent at the onset of MS, and in individual patients the number of bands may increase with time. It is important that paired serum samples be studied to exclude a peripheral (i.e., non-CNS) origin of any OCBs detected in the CSF.

A mild CSF pleocytosis (>5 cells/μL) is present in ~25% of cases, usually in young patients with RRMS. A pleocytosis of >75 cells/μL, the presence of polymorphonuclear leukocytes, or a protein concentration of >1.0 g/L (>100 mg/dL) in CSF should raise concern that the patient may not have MS.

DIFFERENTIAL DIAGNOSIS

No single clinical sign or test is diagnostic of MS. The diagnosis is readily made in a young adult with relapsing and remitting symptoms involving different areas of CNS white matter. The possibility of an alternative diagnosis should always be considered (**Table 34-4**), particularly when (1) symptoms are localized exclusively to the posterior fossa, craniocervical junction, or spinal cord; (2) the patient is <15 or >60 years of age; (3) the clinical course is progressive from onset; (4) the patient has never experienced visual, sensory, or bladder symptoms; or (5) laboratory findings (e.g., MRI, CSF, or EPs) are atypical. Similarly, uncommon or rare symptoms in MS (e.g., aphasia, parkinsonism, chorea, isolated dementia, severe

TABLE 34-4

DISORDERS THAT CAN MIMIC MS
Acute disseminated encephalomyelitis (ADEM)
Antiphospholipid antibody syndrome
Behçet's disease
Cerebral autosomal dominant arteriopathy, subcortical infarcts, and leukoencephalopathy (CADASIL)
Congenital leukodystrophies (e.g., adrenoleukodystrophy, metachromatic leukodystrophy)
Human immunodeficiency virus (HIV) infection
Ischemic optic neuropathy (arteritic and nonarteritic)
Lyme disease
Mitochondrial encephalopathy with lactic acidosis and stroke (MELAS)
Neoplasms (e.g., lymphoma, glioma, meningioma)
Sarcoid
Sjögren's syndrome
Stroke and ischemic cerebrovascular disease
Syphilis
Systemic lupus erythematosus and related collagen vascular disorders
Tropical spastic paraparesis (HTLV I/II infection)
Vascular malformations (especially spinal dural AV fistulas)
Vasculitis (primary CNS or other)
Vitamin B_{12} deficiency

Note: HTLV, human T cell lymphotropic virus; AV, arteriovenous; CNS, central nervous system.

muscular atrophy, peripheral neuropathy, episodic loss of consciousness, fever, headache, seizures, or coma) should increase concern about an alternative diagnosis. Diagnosis is also difficult in patients with a rapid or explosive (strokelike) onset or with mild symptoms and a normal neurologic examination. Rarely, intense inflammation and swelling may produce a mass lesion that mimics a primary or metastatic tumor. The specific tests required to exclude alternative diagnoses will vary with each clinical situation; however, an erythrocyte sedimentation rate, serum B_{12} level, ANA, and treponemal antibody should probably be obtained in all patients with suspected MS.

PROGNOSIS

Most patients with MS ultimately experience progressive neurologic disability. Fifteen years after onset, only 20% of patients have no functional limitation; between one-third and one-half will have progressed to SPMS and will require assistance with ambulation. Twenty-five years after onset, ~80% of MS patients will have reached this level of disability. In 1998, it was estimated that the total annual economic burden of MS in the United States exceeded $6.8 billion.

However, even if the prognosis for disability is grave for the average patient, the prognosis in an individual is difficult to establish. Certain clinical features suggest a more favorable prognosis, including ON or sensory symptoms at onset; fewer than two relapses in the first year of illness; and minimal impairment after 5 years. By contrast, patients with truncal ataxia, action tremor, pyramidal symptoms, or a progressive disease course are more likely to become disabled.

Importantly, some MS patients have a benign variant of MS and never develop neurologic disability. The likelihood of having benign MS is thought to be <20%. Patients with benign MS 15 years after onset who have entirely normal neurologic examinations are likely to maintain their benign course.

In patients with their first demyelinating event (i.e., a clinically isolated syndrome), the brain MRI provides prognostic information. With three or more typical T2-weighted lesions, the risk of developing MS after 10 years is 70–80%. Conversely, with a normal brain MRI, the likelihood of developing MS is <20%. Similarly, two or more Gd-enhancing lesions at baseline is highly predictive of future MS, as is the appearance of either new T2-weighted lesions or new Gd enhancement ≥3 months after the initial episode.

Mortality as a direct consequence of MS is uncommon, although it has been estimated that the 25-year survival is only 85% of expected. Death can occur during an acute MS attack, although this is distinctly rare. More commonly, death occurs as a complication of MS (e.g., pneumonia in a debilitated individual). Death also results from suicide.

Effect of Pregnancy

Pregnant MS patients experience fewer attacks than expected during gestation (especially in the last trimester), but more attacks than expected in the first 3 months postpartum. When considering the pregnancy year as a whole (i.e., 9 months pregnancy plus 3 months postpartum), the overall disease course is unaffected. Decisions about childbearing should thus be made based on (1) the mother's physical state, (2) her ability to care for the child, and (3) the availability of social support. Disease-modifying therapy is generally discontinued during pregnancy, although the actual risk from the interferons and glatiramer acetate (see below) appears to be low.

Rx Treatment: MULTIPLE SCLEROSIS

Therapy for MS can be divided into several categories: (1) treatment of acute attacks as they occur, (2) treatment with disease-modifying agents that reduce the biological activity of MS, and (3) symptomatic therapy. Treatments that promote remyelination or neural repair do not currently exist but would be highly desirable.

The Kurtzke Expanded Disability Status Score (EDSS) is a useful measure of neurologic impairment in MS (**Table 34-5**). Most patients with EDSS scores <3.5 have RRMS, walk normally, and are generally not disabled; by contrast, patients with EDSS scores >5.5 have progressive MS (SPMS or PPMS), are gait-impaired and, typically, are occupationally disabled.

ACUTE ATTACKS OR INITIAL DEMYELINATING EPISODES When patients experience acute deterioration, it is important to consider whether this change reflects new disease activity or a "pseudoexacerbation" resulting from an increase in ambient temperature, fever, or an infection. In such instances, glucocorticoid treatment is inappropriate. Glucocorticoids are used to manage either first attacks or acute exacerbations. They provide short-term clinical benefit by reducing the severity and shortening the duration of attacks. Whether treatment provides any long-term benefit on the course of the illness is less clear. Therefore, mild attacks are often not treated. Physical and occupational therapy can help with mobility and manual dexterity.

Glucocorticoid treatment is usually administered as intravenous methylprednisolone, 500–1000 mg/d for 3–5 days, either without a taper or followed by a course of oral prednisone beginning at a dose of 60–80 mg/d and gradually tapered over 2 weeks. Outpatient treatment is usually possible. If intravenous therapy is unavailable or inconvenient, oral glucocorticoids can be substituted.

TABLE 34-5

SCORING SYSTEMS FOR MS

KURTZKE EXPANDED DISABILITY STATUS SCORE (EDSS)

0.0 = Normal neurologic exam [all grade 0 in functional status (FS)]
1.0 = No disability, minimal signs in one FS (i.e., grade 1)
1.5 = No disability, minimal signs in more than one FS (more than one grade 1)
2.0 = Minimal disability in one FS (one FS grade 2, others 0 or 1)
2.5 = Minimal disability in two FS (two FS grade 2, others 0 or 1)
3.0 = Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory
3.5 = Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1)
4.0 = Ambulatory without aid or rest for ≥ 500 m
4.5 = Ambulatory without aid or rest for ≥ 300 m
5.0 = Ambulatory without aid or rest for ≥ 200 m
5.5 = Ambulatory without aid or rest for ≥ 100 m
6.0 = Unilateral assistance required to walk about 100 m with or without resting
6.5 = Constant bilateral assistance required to walk about 20 m without resting
7.0 = Unable to walk beyond about 5 m even with aid; essentially restricted to wheelchair; wheels self and transfers alone
7.5 = Unable to take more than a few steps; restricted to wheelchair; may need aid to transfer
8.0 = Essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms
8.5 = Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions
9.0 = Helpless bed patient; can communicate and eat
9.5 = Totally helpless bed patient; unable to communicate or eat
10.0 = Death due to MS

FUNCTIONAL STATUS (FS) SCORE

A. Pyramidal functions
- 0 = Normal
- 1 = Abnormal signs without disability
- 2 = Minimal disability
- 3 = Mild or moderate paraparesis or hemiparesis, or severe monoparesis
- 4 = Marked paraparesis or hemiparesis, moderate quadriparesis, or monoplegia
- 5 = Paraplegia, hemiplegia, or marked quadriparesis
- 6 = Quadriplegia

B. Cerebellar functions
- 0 = Normal
- 1 = Abnormal signs without disability
- 2 = Mild ataxia
- 3 = Moderate truncal or limb ataxia
- 4 = Severe ataxia all limbs
- 5 = Unable to perform coordinated movements due to ataxia

C. Brainstem functions
- 0 = Normal
- 1 = Signs only
- 2 = Moderate nystagmus or other mild disability
- 3 = Severe nystagmus, marked extraocular weakness, or moderate disability of other cranial nerves
- 4 = Marked dysarthria or other marked disability
- 5 = Inability to swallow or speak

D. Sensory functions
- 0 = Normal
- 1 = Vibration or figure-writing decrease only, in 1 or 2 limbs
- 2 = Mild decrease in touch or pain or position sense, and/or moderate decrease in vibration in 1 or 2 limbs, or vibratory decrease alone in 3 or 4 limbs
- 3 = Moderate decrease in touch or pain or position sense, and/or essentially lost vibration in 1 or 2 limbs, or mild decrease in touch or pain, and/or moderate decrease in all proprioceptive tests in 3 or 4 limbs
- 4 = Marked decrease in touch or pain or loss of proprioception, alone or combined, in 1 or 2 limbs or moderate decrease in touch or pain and/or severe proprioceptive decrease in more than 2 limbs
- 5 = Loss (essentially) of sensation in 1 or 2 limbs or moderate decrease in touch or pain and/or loss of proprioception for most of the body below the head
- 6 = Sensation essentially lost below the head

E. Bowel and bladder functions
- 0 = Normal
- 1 = Mild urinary hesitancy, urgency, or retention
- 2 = Moderate hesitancy, urgency, retention of bowel or bladder, or rare urinary incontinence
- 3 = Frequent urinary incontinence
- 4 = In need of almost constant catheterization
- 5 = Loss of bladder function
- 6 = Loss of bowel and bladder function

F. Visual (or optic) functions
- 0 = Normal
- 1 = Scotoma with visual acuity (corrected) better than 20/30
- 2 = Worse eye with scotoma with maximal visual acuity (corrected) of 20/30 to 20/59
- 3 = Worse eye with large scotoma, or moderate decrease in fields, but with maximal visual acuity (corrected) of 20/60 to 20/99
- 4 = Worse eye with marked decrease of fields and maximal acuity (corrected) of 20/100 to 20/200; grade 3 plus maximal acuity of better eye of 20/60 or less
- 5 = Worse eye with maximal visual acuity (corrected) less than 20/200; grade 4 plus maximal acuity of better eye of 20/60 or less
- 6 = Grade 5 plus maximal visual acuity of better eye of 20/60 or less

G. Cerebral (or mental) functions
- 0 = Normal
- 1 = Mood alteration only (does not affect EDSS score)
- 2 = Mild decrease in mentation
- 3 = Moderate decrease in mentation
- 4 = Marked decrease in mentation
- 5 = Chronic brain syndrome—severe or incompetent

Source: After JF Kurtzke: Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology 33:1444, 1983.

TABLE 34-6

TWO-YEAR OUTCOMES FOR FDA-APPROVED THERAPIES FOR MULTIPLE SCLEROSIS[a]

	OUTCOMES[b]		MRI OUTCOMES[c]	
DOSE, ROUTE, AND SCHEDULE	ATTACK RATE, MEAN	CHANGE IN DISEASE SEVERITY	NEW T2 LESIONS[d]	TOTAL BURDEN OF DISEASE
IFN-β-1b, 250 μg SC qod	–34%[e]	–29% (ns)	–83%[f]	–17%[e]
IFN-β-1a, 30 μg IM qw	–18%[g]	–37%[g]	–36%[f]	–4% (ns)
IFN-β-1a, 44 μg SC tiw	–32%[e]	–30%[g]	–78%[e]	–15%[e]
GA, 20 mg SC qd	–29%[f]	–12% (ns)	–38%[f]	–8%[f]
MTX, 12 mg/m^2 IV q3mo	–66%[e]	–75%[g]	–79%[g]	nr
NTZ, 300 mg IV qmo	–68%[e]	–42%[e]	–83%[e]	–18%[e]

[a]Percentage reductions (or increases) have been calculated by dividing the reported rates in the treated group by the comparable rates in the placebo group, except for MRI disease burden, which was calculated as the difference in the median % change between the treated and placebo groups.
[b]Severity = 1 point EDSS progression, sustained for 3 months (in the IFN-β-1a 30 μg qw trial, this change was sustained for 6 months; in the IFN-β-1b trial, this was over 3 years).
[c]Different studies measured these MRI measures differently, making comparisons difficult (numbers for new T2 represent the best case scenario for each trial).
[d]New lesions seen on T_2-weighted MRI.
[e]p = .001.
[f]p = .01.
[g]p = .05.
Note: IFN-β, interferon β; GA, glatiramer acetate; MTX, mitoxantrone; NTZ, natalizumab; IM, intramuscular; SC, subcutaneous; IV, intravenous; qod, every other day; qw, once per week; tiw, three times per week; qd, daily; q3mo, once every 3 months; qmo, once per month; ns, not significant; nr, not reported.

Side effects of short-term glucocorticoid therapy include fluid retention, potassium loss, weight gain, gastric disturbances, acne, and emotional lability. Concurrent use of a low-salt, potassium-rich diet and avoidance of potassium-wasting diuretics is advisable. Lithium carbonate (300 mg orally bid) may help to manage emotional lability and insomnia associated with glucocorticoid therapy. Patients with a history of peptic ulcer disease may require cimetidine (400 mg bid) or ranitidine (150 mg bid).

Plasma exchange (seven exchanges: 40–60 mL/kg per exchange, every other day for 14 days) may benefit patients with fulminant attacks of demyelination (not only MS) that are unresponsive to glucocorticoids. However, the cost is high, and the evidence of efficacy is only preliminary.

DISEASE-MODIFYING THERAPIES FOR RELAPSING FORMS OF MS (RRMS, SPMS WITH EXACERBATIONS) Five such agents are approved in the United States: (1) IFN-β-1a (Avonex), (2) IFN-β-1a (Rebif), (3) IFN-β-1b (Betaseron), (4) glatiramer acetate (Copaxone), and (5) natalizumab (Tysabri). Each of these treatments is also used in SPMS patients who continue to experience attacks, because SPMS can be difficult to distinguish from RRMS, and because clinical trials suggest that such patients also derive therapeutic benefit. In phase III clinical trials, recipients of IFN-β-1b, IFN-β-1a, glatiramer acetate, and natalizumab experienced fewer clinical exacerbations and fewer new MRI lesions compared to placebo recipients (Table 34-6). Mitoxantrone (Novantrone), an immune suppressant, has also been approved in the United States, although it is generally reserved for patients with progressive disability who have failed other treatments because of its potential toxicity.

Interferon β, Glatiramer Acetate, and Natalizumab IFN-β is a class I interferon originally identified by its antiviral properties. Efficacy in MS probably results from immunomodulatory properties including (1) downregulating expression of MHC molecules on antigen-presenting cells, (2) inhibiting proinflammatory and increasing regulatory cytokine levels, (3) inhibition of T cell proliferation, and (4) limiting the trafficking of inflammatory cells in the CNS. Glatiramer acetate is a synthetic, random polypeptide composed of four amino acids (l-glutamic acid, l-lysine, l-alanine, and l-tyrosine). Its mechanism of action may include (1) induction of antigen-specific suppressor T cells; (2) binding to MHC molecules, thereby displacing bound MBP; or (3) altering the balance between proinflammatory and regulatory cytokines. Natalizumab is a humanized monoclonal antibody directed against the α_4 subunit of $\alpha_4\beta_1$ integrin, a cellular adhesion molecule expressed on the surface of lymphocytes. It prevents lymphocytes from binding to endothelial cells, thereby preventing lymphocytes from penetrating the BBB and entering the CNS.

IFN-β reduces the attack rate and improves disease severity measures such as EDSS progression

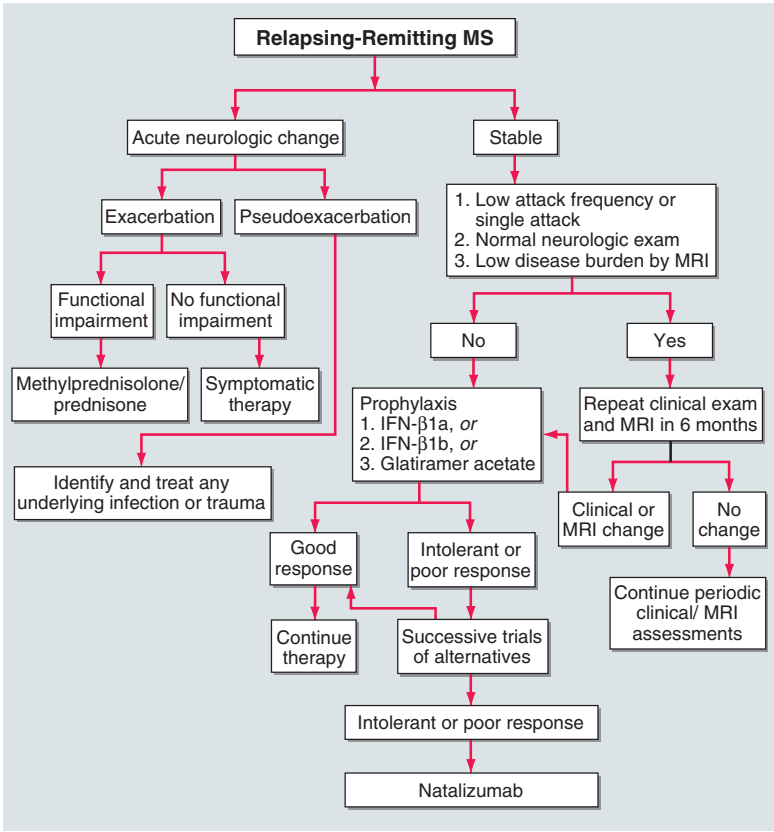
and MRI-documented disease burden. IFN-β should be considered in patients with either RRMS or SPMS with superimposed relapses. In patients with SPMS but without relapses, efficacy has not been established. Higher IFN-β doses appear to have slightly greater efficacy but are also more likely to induce neutralizing antibodies, which may reduce the clinical benefit (see below).

Glatiramer acetate also reduces the attack rate (whether measured clinically or by MRI) in RRMS. Glatiramer acetate may also benefit disease severity measures, although this is less well-established than for the relapse rate. Therefore, glatiramer acetate should be considered in RRMS patients. Its usefulness in progressive disease is entirely unknown.

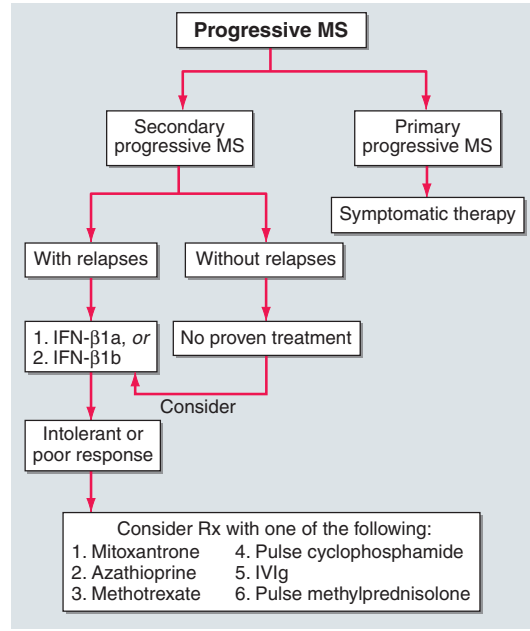
Natalizumab dramatically reduces the attack rate and significantly improves all measures of disease severity in MS. However, because of the development of progressive multifocal leukoencephalopathy (PML) in nearly two dozen patients treated with natalizumab, some in combination with other immunosuppressives, natalizumab is currently recommended only as monotherapy for patients who have failed treatment with beta interferon or glatiramer acetate, or who have particularly aggressive presentations. Its usefulness in the treatment of progressive disease has not been studied.

The long-term efficacy of these treatments remains uncertain, although several recent studies suggest that these agents can improve the long-term outcome of MS when administered in the RRMS stage of the illness. Beneficial effects seen in early MS include a reduction in the relapse rate and a reduction in CNS inflammation as measured by MRI. Unfortunately, already established progressive symptoms do not respond to treatment with these disease-modifying therapies. Because progressive symptoms are likely to result from delayed effects of earlier focal demyelinating episodes, many experts now believe that very early treatment with a disease-modifying drug is appropriate for most MS patients. It is reasonable to delay initiating treatment in patients with (1) normal neurologic exams, (2) a single attack or a low attack frequency, and (3) a low burden of disease as assessed by brain MRI. Untreated patients should be followed closely with periodic brain MRI scans; the need for therapy is reassessed if scans reveal evidence of ongoing, subclinical disease.

Most treated patients with relapsing forms of MS receive IFN-β or glatiramer acetate as first-line therapy. Regardless of which agent is chosen first, treatment should probably be changed in patents who continue to have frequent attacks or progressive disability (**Fig. 34-4**). The value of combination therapy is unknown.



A



B

FIGURE 34-4
Therapeutic decision-making for MS.

IFN-β-1a (Avonex), 30 μg, is administered by intramuscular injection once every week. IFN-β-1a (Rebif), 44 μg, is administered by subcutaneous injection three times per week. IFN-β-1b (Betaseron), 250 μg, is administered by subcutaneous injection every other day. Glatiramer acetate, 20 mg, is administered by subcutaneous injection every day. Natalizumab, 300 μg, is administered by IV infusion each month. Common side effects of IFN-β therapy include flulike symptoms (e.g., fevers, chills, and myalgias) and mild abnormalities on routine laboratory evaluation (e.g., elevated liver function tests or lymphopenia). Rarely, more severe hepatotoxicity may occur. Subcutaneous IFN-β also causes reactions at the injection site (e.g., pain, redness, induration, or, rarely, skin necrosis). Side effects can usually be managed with concomitant nonsteroidal anti-inflammatory medications and with the use of an autoinjector. Depression, increased spasticity, and cognitive changes have been reported, although these symptoms can also be due to the underlying disease. In any event, side effects to IFN-β therapy usually subside with time.

Approximately 2–10% of IFN-β-1a (Avonex) recipients, 15–25% of IFN-β-1a (Rebif) recipients, and 30–40% of IFN-β-1b (Betaseron) recipients develop neutralizing antibodies to IFN-β, which may disappear over time. Some evidence suggests that neutralizing antibodies reduce efficacy, especially for MRI outcomes. The current clinical data, however, are quite conflicted. Moreover, there are few situations where measurement of antibodies is necessary. Thus, for a patient doing well on therapy, the presence of antibodies should not affect treatment. Conversely, for a patient doing poorly on therapy, alternative treatment should be considered, even if there are no detectable antibodies.

Injection-site reactions also occur with glatiramer acetate but are less severe than with IFN-β-1b. Approximately 15% of patients experience one or more episodes of flushing, chest tightness, dyspnea, palpitations, and anxiety after injection. This systemic reaction is unpredictable, brief (duration <1 h), and tends not to recur.

Treatment with natalizumab is, in general, well tolerated. A small percentage (<10%) of patients experience hypersensitivity reactions (including anaphylaxis) and ~6% develop neutralizing antibodies to the molecule. As noted above, of greater potential concern is the risk of PML.

Mitoxantrone Hydrochloride Mitoxantrone (Novantrone), an anthracenedione, exerts its antineoplastic action by (1) intercalating into DNA and producing both strand breaks and interstrand cross-links, (2) interfering with RNA synthesis, and (3) inhibiting topoisomerase II (involved in DNA repair). The U.S. Food and Drug Administration (FDA) approved mitoxantrone on the basis of a single (relatively small) phase III clinical trial in Europe, in addition to an even smaller phase II study completed earlier. Mitoxantrone received (from the FDA) the broadest indication of any current treatment for MS. Thus, mitoxantrone is indicated for use in SPMS, in PRMS, and in patients with worsening RRMS (defined as patients whose neurologic status remains significantly abnormal between MS attacks). Despite this broad indication, however, the data supporting its efficacy are weaker than for other approved therapies.

Mitoxantrone can be cardiotoxic (e.g., cardiomyopathy, reduced left ventricular ejection fraction, and irreversible congestive heart failure). As a result, a cumulative dose >140 mg/m^2 is not recommended. At currently approved doses (12 mg/m^2 every 3 months), the maximum duration of therapy can be only 2–3 years. Furthermore, >40% of women will experience amenorrhea, which may be permanent. Finally, there is risk of acute leukemia, and this complication has already been reported in several mitoxantrone-treated MS patients.

Given these risks, mitoxantrone should not be used as a first-line agent in either RRMS or relapsing SPMS. It is reasonable to consider mitoxantrone in selected patients with a progressive course who have failed other approved therapies.

DISEASE-MODIFYING THERAPIES FOR SPMS

High-dose IFN-β probably has a beneficial effect in patients with SPMS who are still experiencing acute relapses. IFN-β is probably ineffective in patients with SPMS who are not having acute attacks. Glatiramer acetate and natalizumab have not been studied in this patient population.

Although mitoxantrone has been approved for patients with progressive MS, this is not the population studied in the pivotal trial. Therefore no evidence-based recommendation can be made with regard to its use in this setting.

PPMS No currently available therapies have shown any promise for treating PPMS at this time. A phase III clinical trial of glatiramer acetate in PPMS was recently stopped because of lack of efficacy. Trials of mitoxantrone and rituximab in PPMS are currently underway.

OFF-LABEL TREATMENT OPTIONS FOR RRMS AND SPMS *Azathioprine* (2–3 mg/kg per day) has been used primarily in SPMS. Meta-analysis of published trials suggests that azathioprine is marginally effective at lowering relapse rates, although a benefit on disability progression has not been demonstrated.

Methotrexate (7.5–20 mg/wk) was shown in one study to slow the progression of upper-extremity dysfunction in SPMS. Because of the possibility of developing irreversible liver damage, some experts recommend a blind liver biopsy after 2 years of therapy.

Cyclophosphamide (700 mg/m^2, every other month) may be helpful for treatment-refractory patients who are (1) otherwise in good health, (2) ambulatory, and (3) <40 years of age. Because cyclophosphamide can be used for periods in excess of 3 years, it may be preferable to mitoxantrone in these circumstances.

Intravenous immunoglobulin (IVIg), administered in monthly pulses (up to 1 g/kg) for up to 2 years, appears to reduce annual exacerbation rates. However, its use is limited because of its high cost, questions about optimal dose, and uncertainty about its effect on long-term disability outcome.

Methylprednisolone administered in one study as monthly high-dose intravenous pulses, reduced disability progression (see above).

OTHER THERAPEUTIC CLAIMS Many purported treatments for MS have never been subjected to scientific scrutiny. These include dietary therapies (e.g., the Swank diet in addition to others), megadose vitamins, low-dose naltrexone, calcium orotate, bee stings, cow colostrum, hyperbaric oxygen, procarin (a combination of histamine and caffeine), chelation, acupuncture, acupressure, various Chinese herbal remedies, and removal of mercury-amalgam tooth fillings, among many others. Patients should avoid costly or potentially hazardous unproven treatments. Many such treatments lack biologic plausibility. For example, no reliable case of mercury poisoning resembling typical MS has ever been described.

Although potential roles for EBV, HHV-6, or chlamydia have been suggested for MS, these reports are unconfirmed, and treatment with antiviral agents or antibiotics is not currently appropriate.

SYMPTOMATIC THERAPY Potassium channel blockers (e.g., 4-aminopyridine, 10–40 mg/d; and 3,4-di-aminopyridine, 40–80 mg/d) may be helpful for *weakness*, especially for heat-sensitive symptoms. At high doses they may cause seizures. These agents are not FDA-approved but can be obtained from compounding pharmacies around the United States.

Ataxia/tremor is often intractable. Clonazepam, 1.5–20 mg/d; mysoline, 50–250 mg/d; propranolol, 40–200 mg/d; or ondansetron, 8–16 mg/d may help. Wrist weights occasionally reduce tremor in the arm or hand. Thalamotomy or deep-brain stimulation has been tried with mixed success.

Spasticity and *spasms* may improve with physical therapy, regular exercise, and stretching. Avoidance of triggers (e.g., infections, fecal impactions, bed sores) is extremely important. Effective medications include lioresal (20–120 mg/d), diazepam (2–40 mg/d), tizanidine (8–32 mg/d), dantrolene (25–400 mg/d), and cyclobenzaprine hydrochloride (10–60 mg/d). For severe spasticity, a lioresal pump (delivering medication directly into the CSF) can provide substantial relief.

Pain is treated with anticonvulsants (carbamazepine, 100–1000 mg/d; phenytoin, 300–600 mg/d; gabapentin, 300–3600 mg/d; or pregabalin, 50–300 mg/d), antidepressants (amitriptyline, 25–150 mg/d; nortriptyline, 25–150 mg/d; desipramine, 100–300 mg/d; or venlafaxine, 75–225 mg/d), or antiarrhythmics (mexiletine, 300–900 mg/d). If these approaches fail, patients should be referred to a comprehensive pain management program.

Bladder dysfunction management is best guided by urodynamic testing. Evening fluid restriction or frequent voluntary voiding may help *detrusor hyperreflexia*. If these methods fail, propantheline bromide (10–15 mg/d), oxybutynin (5–15 mg/d), hyoscyamine sulfate (0.5–0.75 mg/d), tolterodine tartrate (2–4 mg/d), or solifenacin (5–10 mg/d) may help. Coadministration of pseudoephedrine (30–60 mg) is sometimes beneficial.

Detrusor/sphincter dyssynergia may respond to phenoxybenzamine (10–20 mg/d) or terazosin hydrochloride (1–20 mg/d). Loss of reflex bladder wall contraction may respond to bethanechol (30–150 mg/d). However, both conditions often require catheterization.

Urinary tract infections should be treated promptly. Patients with large post-void residual urine volumes are predisposed to infections. Prevention by urine acidification (with cranberry juice or vitamin C) inhibits some bacteria. Prophylactic administration of antibiotics is sometimes necessary but may lead to colonization by resistant organisms. Intermittent catheterization may help to prevent recurrent infections.

Treatment of *constipation* includes high-fiber diets and fluids. Natural or other laxatives may help. *Fecal incontinence* may respond to a reduction in dietary fiber.

Depression should be treated. Useful drugs include the selective serotonin reuptake inhibitors (fluoxetine, 20–80 mg/d, or sertraline, 50–200 mg/d); the tricyclic antidepressants (amitriptyline, 25–150 mg/d, nortriptyline, 25–150 mg/d, or desipramine, 100–300 mg/d); and the nontricyclic antidepressants (venlafaxine, 75–225 mg/d).

Fatigue may improve with assistive devices, help in the home, or successful management of spasticity. Patients with frequent nocturia may benefit from anticholinergic medication at bedtime. Primary MS fatigue may respond to amantadine (200 mg/d), methylphenidate (5–25 mg/d), or modafinil (100–400 mg/d).

Cognitive problems may respond to the cholinesterase inhibitor donepezil hydrochloride (10 mg/d).

Paroxysmal symptoms respond dramatically to low-dose anticonvulsants (acetazolamide, 200–600 mg/d; carbamazepine, 50–400 mg/d; phenytoin, 50–300 mg/d; or gabapentin, 600–1800 mg/d).

Heat sensitivity may respond to heat avoidance, air-conditioning, or cooling garments.

Sexual dysfunction may be helped by lubricants to aid in genital stimulation and sexual arousal. Management of pain, spasticity, fatigue, and bladder/bowel dysfunction may also help. Sildenafil (50–100 mg) taken 1–2 h before sex, is now the standard treatment for maintaining erections.

PROMISING EXPERIMENTAL THERAPIES Numerous clinical trials are currently underway. These include: (1) oral sphingosine-1-phosphate receptor modulators to sequester lymphocytes in the secondary lymphoid organs; (2) oral cladribine, a purine nucleoside agonist; (3) monoclonal antibodies against CD20 to deplete B cells, against the IL-2 receptor on activated T- cells, or against CD52 to induce global lymphocyte depletion; (4) use of MBP, or an altered peptide ligand resembling MBP, to induce antigen-specific tolerance; (5) use of statins as immunomodulators; (6) estriol to induce a pregnancy-like state; and (7) bone marrow transplantation.

CLINICAL VARIANTS OF MS

Neuromyelitis optica (NMO), or Devic's syndrome, consists of separate attacks of acute ON and myelitis. ON may be unilateral or bilateral and precede or follow an attack of myelitis by days, months, or years. In contrast to MS, patients with NMO do not experience brainstem, cerebellar, and cognitive involvement, and the brain MRI is typically normal. A focal enhancing region of swelling and cavitation, extending over three or more spinal cord segments, is typically seen on MRI. Histopathology of these lesions may reveal thickening of blood-vessel walls and deposition of antibody and complement. Occasional patients with apparent NMO also have brain MRI changes indicating involvement of the cerebral hemispheres.

NMO, which is uncommon in whites compared with Asians and Africans, is best understood as a syndrome with diverse causes. Some patients have a systemic autoimmune disorder, often systemic lupus erythematosus, Sjögren's syndrome, p-ANCA (perinuclear antineutrophil cytoplasmic antibody) associated vasculitis, or mixed connective tissue disease. In others, onset may be associated with acute infection with varicella-zoster virus, EBV, HIV, or tuberculosis. More frequently, however, NMO is idiopathic and probably represents an MS variant; in such cases the course can be monophasic but is more often recurrent.

A highly specific autoantibody directed against the water channel protein aquaporin-4 is present in the sera of more than one-half of patients who have a clinical diagnosis of NMO. Aquaporin-4 is localized to the foot processes of astrocytes in close apposition to endothelial surfaces. The role of aquaporin-4 antibodies in the pathogenesis of NMO, however, is unknown.

Disease-modifying therapies for MS have not been rigorously studied in NMO. Acute attacks are usually treated with high-dose glucocorticoids as for MS exacerbations (see above). Because of the possibility that NMO is antibody-mediated, plasma exchange has also been used empirically for acute episodes that fail to respond to glucocorticoids. Immunosuppressants (cyclophosphamide or azathioprine with glucocorticoids) are sometimes used in the hope that further relapses will be prevented. More recently, in a small open-case series, B cell depletion with anti-CD20 monoclonal antibody (rituxan) appeared to show promise in preventing relapses of NMO.

Acute MS (Marburg's variant) is a fulminant demyelinating process that in some cases progresses inexorably to death within 1–2 years. Typically, there are no remissions. When acute MS presents as a solitary, usually cavitary, lesion, a brain tumor is often suspected. In such cases a brain biopsy is usually required to establish the diagnosis. An antibody-mediated process appears to be responsible for most cases. Marburg's variant does not seem to follow infection or vaccination, and it is unclear whether this syndrome represents an extreme form of MS or another disease altogether. No controlled trials of therapy exist; high-dose glucocorticoids, plasma exchange, and cyclophosphamide have been tried, with uncertain benefit.

ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)

ADEM has a monophasic course and is frequently associated with antecedent immunization (postvaccinal encephalomyelitis) or infection (postinfectious encephalomyelitis). The hallmark of ADEM is the presence of widely scattered small foci of perivenular inflammation and demyelination. In its most explosive form, acute hemorrhagic leukoencephalitis, the lesions are vasculitic and hemorrhagic, and the clinical course is devastating.

Postvaccinal encephalomyelitis may follow the administration of smallpox and certain rabies vaccines. Postinfectious encephalomyelitis is most frequently associated with the viral exanthems of childhood. Infection with measles virus is the most common antecedent (1 in 1000 cases). Worldwide, measles encephalomyelitis is still common, although use of the live measles vaccine has dramatically reduced its incidence in developed countries. An ADEM-like illness rarely follows vaccination with live measles vaccine (1–2 in 10^6 immunizations). ADEM is now most frequently associated with varicella (chickenpox) infections (1 in 4000–10,000 cases). It may also follow infection with rubella, mumps, influenza, parainfluenza, infectious mononucleosis viruses, and *Mycoplasma*. Some patients may have a nonspecific upper respiratory infection or no known antecedent illness.

All forms of ADEM presumably result from a cross-reactive immune response to the infectious agent or vaccine that then triggers an inflammatory demyelinating response. Autoantibodies to MBP and to other myelin antigens have been detected in the CSF from many patients with ADEM. Attempts to demonstrate direct viral invasion of the CNS have been unsuccessful.

CLINICAL MANIFESTATIONS

In severe cases, onset is abrupt and progression rapid (hours to days). In postinfectious ADEM, the neurologic syndrome generally begins late in the course of the viral illness as the exanthem is fading. Fever reappears, and headache, meningismus, and lethargy progressing to coma may develop. Seizures are common. Signs of disseminated neurologic disease are consistently present (e.g., hemiparesis or quadriparesis, extensor plantar responses, lost or hyperactive tendon reflexes, sensory loss and brainstem involvement). In ADEM due to chickenpox, cerebellar involvement is often conspicuous. CSF protein is modestly elevated [0.5–1.5 g/L (50–150 mg/dL)]. Lymphocytic pleocytosis, generally 200 cells/μl, occurs in 80% of patients. Occasional patients have higher counts or a mixed polymorphonuclear-lymphocytic pattern during the initial days of the illness. Transient CSF oligoclonal banding has been reported. MRI may reveal extensive gadolinium enhancement of white matter in brain and spinal cord.

DIAGNOSIS

The diagnosis is easily established when there is a history of recent vaccination or exanthematous illness. In severe cases with predominantly cerebral involvement, acute encephalitis due to infection with herpes simplex or other viruses may be difficult to exclude. The simultaneous onset of disseminated symptoms and signs is common in ADEM and rare in MS. Similarly, meningismus, drowsiness, coma, or seizures suggest ADEM rather than MS. Unlike in MS, in ADEM optic nerve involvement is generally bilateral and transverse myelopathy complete. MRI findings that may support a diagnosis of ADEM include extensive and relatively symmetric white matter abnormalities and Gd enhancement of all abnormal areas, indicating active disease and a monophasic course.

Rx Treatment: ACUTE DISSEMINATED ENCEPHALOMYELITIS

Initial treatment is with high-dose glucocorticoids as for exacerbations of MS (see above); depending on the response, treatment may need to be continued for 4–8 weeks. Patients who fail to respond within a few days may benefit from a course of plasma exchange or intravenous immunoglobulin. The prognosis reflects the severity of the underlying acute illness. Measles encephalomyelitis is associated with a mortality rate of 5–20%, and most survivors have permanent neurologic sequelae. Children who recover may have persistent seizures and behavioral and learning disorders.

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CHAPTER 35

MENINGITIS, ENCEPHALITIS, BRAIN ABSCESS, AND EMPYEMA

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Acute infections of the nervous system are among the most important problems in medicine because early recognition, efficient decision-making, and rapid institution of therapy can be lifesaving. These distinct clinical syndromes include acute bacterial meningitis, viral meningitis, encephalitis, focal infections such as brain abscess and subdural empyema, and infectious thrombophlebitis. Each may present with a nonspecific prodrome of fever and headache, which in a previously healthy individual may initially be thought to be benign, until (with the exception of viral meningitis) altered consciousness, focal neurologic signs, or seizures appear. Key goals of early management are to emergently distinguish between these conditions, identify the responsible pathogen, and initiate appropriate antimicrobial therapy.

Approach to the Patient: CNS INFECTION

(Fig. 35-1) The first task is to identify whether an infection predominantly involves the subarachnoid space (*meningitis*) or whether there is evidence of either generalized or focal involvement of brain tissue in the cerebral hemispheres, cerebellum, or brainstem. When brain tissue is directly injured by a viral infection the disease is referred to as *encephalitis*, whereas

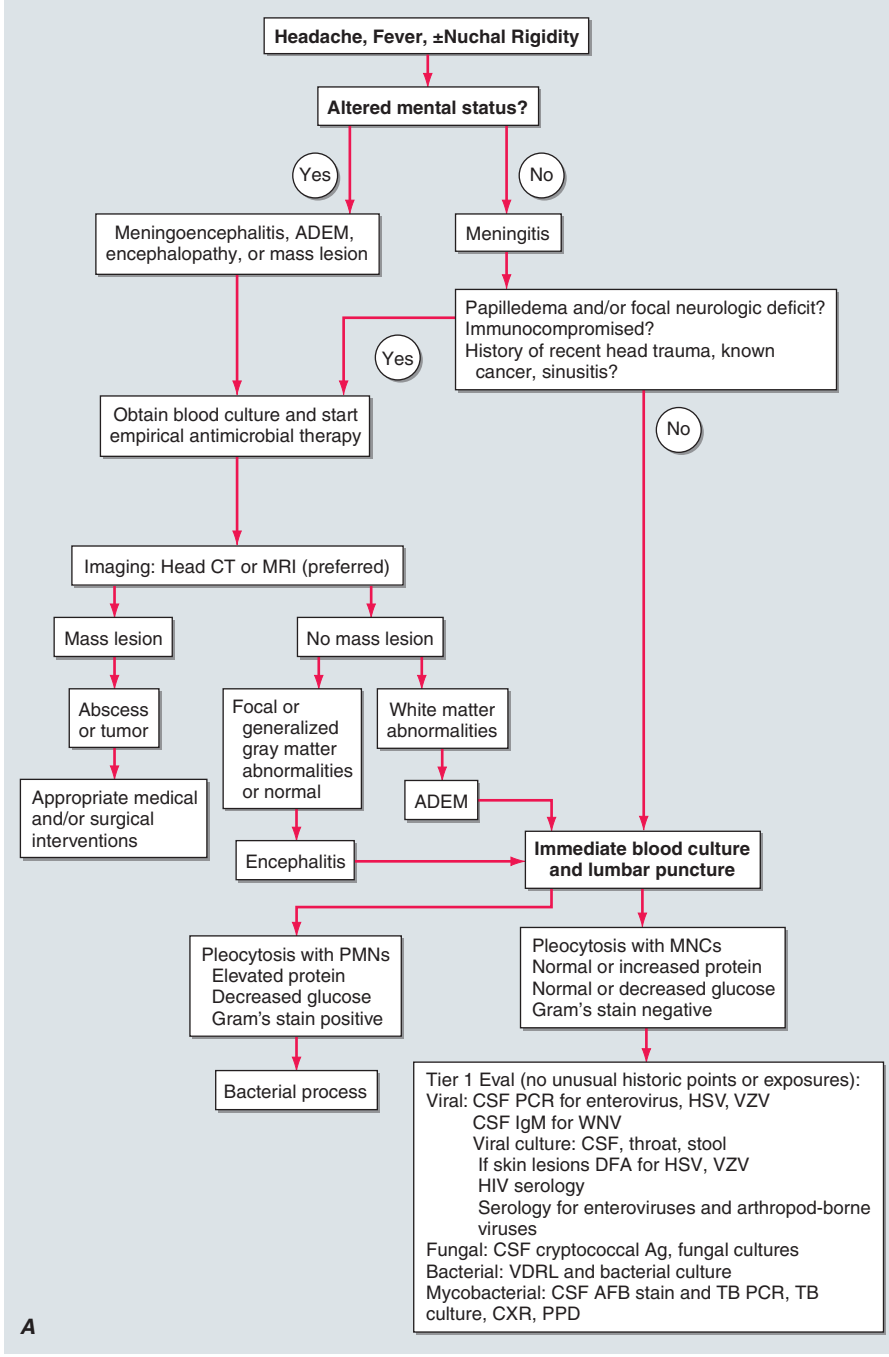


FIGURE 35-1

The management of patients with suspected CNS infection. ADEM, acute disseminated encephalomyelitis; CT, computed tomography; MRI, magnetic resonance imaging; PMNs, polymorphonuclear leukocytes; MNCs, mononuclear cells; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; HSV, herpes simplex virus; VZV, varicella-zoster virus; WNV, West Nile virus; DFA, direct fluorescent antibody; Ag, antigen; VDRL, Venereal Disease Research Laboratory; AFB, acid-fast bacillus; TB, tuberculosis; CXR, chest x-ray; PPD, purified protein derivative; EBV, Epstein-Barr virus; CTFV, Colorado tick fever virus; HHV, human herpesvirus; LCMV, lymphocytic choriomeningitis virus.

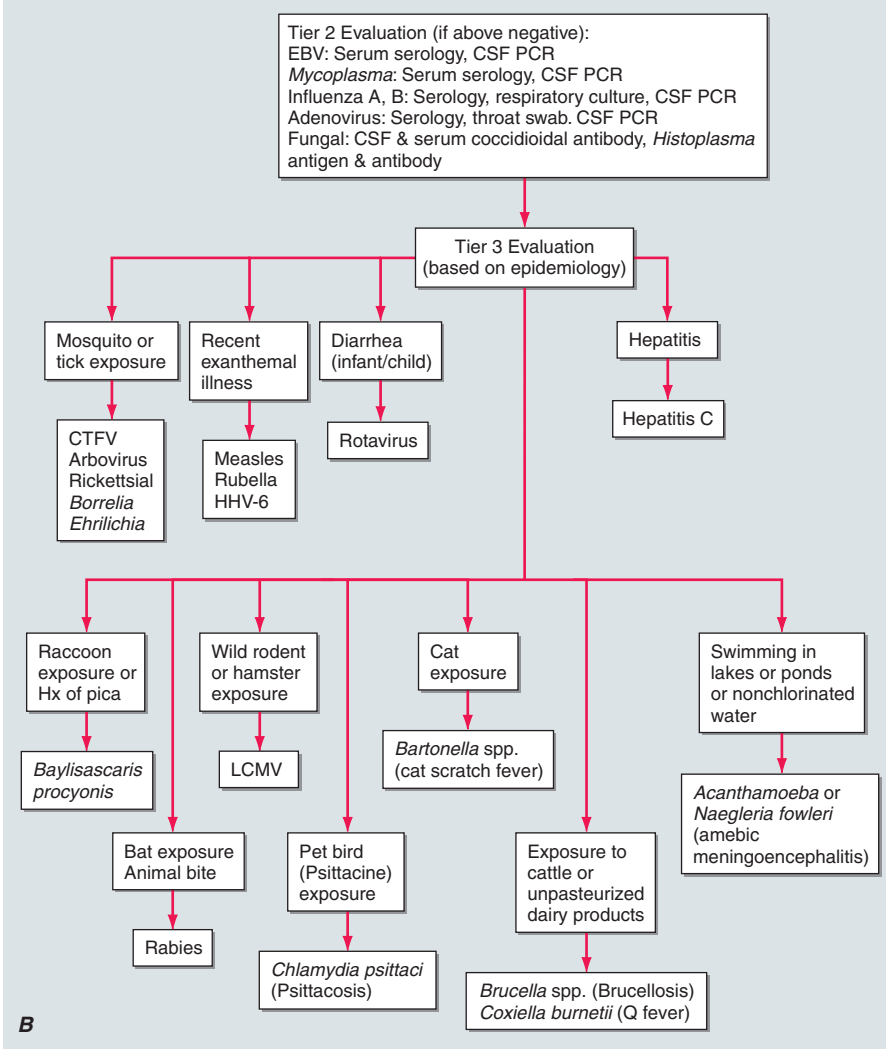


FIGURE 35-1
(*Continued*.)

focal bacterial, fungal, or parasitic infections involving brain tissue are classified as either *cerebritis* or *abscess*, depending on the presence or absence of a capsule.

Nuchal rigidity ("stiff neck") is the pathognomonic sign of meningeal irritation and is present when the neck resists passive flexion. Kernig's and Brudzinski's signs are also classic signs of meningeal irritation. *Kernig's sign* is elicited with the patient in the supine position. The thigh is flexed on the abdomen, with the knee flexed; attempts to passively extend the knee elicit pain when meningeal irritation is present. *Brudzinski's sign* is elicited with the patient in the supine position and is positive when passive flexion of the neck results in spontaneous flexion of the hips and knees. Although commonly tested on physical examinations, the sensitivity and specificity of Kernig's and Brudzinski's signs are uncertain. Both may be absent or reduced in very young or elderly patients, immunocompromised individuals, or patients with a severely depressed mental status. The high prevalence of cervical spine disease in older individuals may result in false-positive tests for nuchal rigidity.

Initial management can be guided by several considerations: (1) Empirical therapy should be initiated promptly whenever bacterial meningitis is a significant diagnostic consideration. (2) All patients who have had recent head trauma, are immunocompromised, have known malignant lesions or central nervous system (CNS) neoplasms, or have focal neurologic findings that include papilledema or a depressed level of consciousness should undergo CT or MRI of the brain prior to lumbar puncture (LP). In these cases empirical antibiotic therapy should not be delayed pending test results but should be administered prior to neuroimaging and LP. (3) A significantly depressed level of consciousness (e.g., somnolence, coma),

seizures, or focal neurologic deficits do not occur in viral (*aseptic*) meningitis; patients with these symptoms should be hospitalized for further evaluation and treated empirically for bacterial and viral meningoencephalitis. (4) Immunocompetent patients with a normal level of consciousness, no prior antimicrobial treatment, and a cerebrospinal fluid (CSF) profile consistent with viral meningitis (lymphocytic pleocytosis and a normal glucose concentration) can often be treated as outpatients if appropriate contact and monitoring can be ensured. Failure of a patient with suspected viral meningitis to improve within 48 h should prompt a reevaluation including follow-up neurologic and general medical examination and repeat imaging and laboratory studies, often including a second LP.

ACUTE BACTERIAL MENINGITIS

DEFINITION

Bacterial meningitis is an acute purulent infection within the subarachnoid space. It is associated with a CNS inflammatory reaction that may result in decreased consciousness, seizures, raised intracranial pressure (ICP), and stroke. The meninges, the subarachnoid space, and the brain parenchyma are all frequently involved in the inflammatory reaction (*meningoencephalitis*).

EPIDEMIOLOGY

Bacterial meningitis is the most common form of suppurative CNS infection, with an annual incidence in the United States of >2.5 cases/100,000 population. The epidemiology of bacterial meningitis has changed significantly in recent years, reflecting a dramatic decline in the incidence of meningitis due to *Haemophilus influenzae*, and a smaller decline in that due to *Neisseria meningitidis*, following the introduction and increasingly widespread use of vaccines for both these organisms. Currently, the organisms most commonly responsible for community-acquired bacterial meningitis are *Streptococcus pneumoniae* (~50%), *N. meningitidis* (~25%), group B streptococci (~15%), and *Listeria monocytogenes* (~10%). *H. influenzae* now accounts for <10% of cases of bacterial meningitis in most series.

ETIOLOGY

S. pneumoniae is the most common cause of meningitis in adults >20 years of age, accounting for nearly half the reported cases (1.1 per 100,000 persons per year). There are a number of predisposing conditions that increase the risk of pneumococcal meningitis, the most important of which is pneumococcal pneumonia. Additional risk factors include coexisting acute or chronic pneumococcal sinusitis or otitis media, alcoholism, diabetes, splenectomy, hypogammaglobulinemia, complement deficiency, and head trauma with basilar skull fracture and CSF rhinorrhea. Mortality remains ~20% despite antibiotic therapy. Recently, pneumococcal vaccination has been shown to decrease rates of meningitis.

N. meningitidis accounts for 25% of all cases of bacterial meningitis (0.6 cases per 100,000 persons per year) and for up to 60% of cases in children and young adults between 2 and 20 years of age. The presence of petechial or purpuric skin lesions can provide an important clue to the diagnosis of meningococcal infection. In some patients the disease is fulminant, progressing to death within hours of symptom onset. Infection may be initiated by nasopharyngeal colonization, which can result in either an asymptomatic carrier state or invasive meningococcal disease. The risk of invasive disease following nasopharyngeal colonization depends on both bacterial virulence factors and host immune defense mechanisms, including the host's capacity to produce antimeningococcal antibodies and to lyse meningococci by both classic and alternative complement pathways. Individuals with deficiencies of any of the complement components, including properdin, are highly susceptible to meningococcal infections.

Enteric gram-negative bacilli are an increasingly common cause of meningitis in individuals with chronic and debilitating diseases such as diabetes, cirrhosis, or alcoholism and in those with chronic urinary tract infections. Gram-negative meningitis can also complicate neurosurgical procedures, particularly craniotomy.

Group B streptococcus, or *S. agalactiae*, was previously responsible for meningitis predominantly in neonates, but it has been reported with increasing frequency in individuals >50 years, particularly those with underlying diseases.

L. monocytogenes has become an increasingly important cause of meningitis in neonates (<1 month), pregnant women, individuals >60 years, and immunocompromised individuals of all ages. Infection is acquired by ingesting foods contaminated by *Listeria*. Foodborne human listerial infection has been reported from contaminated coleslaw, milk, soft cheeses, and several types of "ready-to-eat" foods, including delicatessen meat and uncooked hotdogs.

The frequency of *H. influenzae* type b meningitis in children has declined dramatically since the introduction of the Hib conjugate vaccine, although rare cases of Hib meningitis in vaccinated children have been reported. More frequently, *H. influenzae* causes meningitis in unvaccinated children and adults.

Staphylococcus aureus and coagulase-negative staphylococci are important causes of meningitis that occurs following invasive neurosurgical procedures, particularly shunting procedures for hydrocephalus, or as a complication of the use of subcutaneous Ommaya reservoirs for administration of intrathecal chemotherapy.

PATHOPHYSIOLOGY

The most common bacteria that cause meningitis, *S. pneumoniae* and *N. meningitidis*, initially colonize the nasopharynx by attaching to nasopharyngeal epithelial cells. Bacteria are transported across epithelial cells in membrane-bound vacuoles to the intravascular space or invade the intravascular space by creating separations in the apical tight junctions of columnar epithelial cells. Once in the bloodstream, bacteria are able to avoid phagocytosis by neutrophils and classic complement–mediated bactericidal activity because of the presence of a polysaccharide capsule. Bloodborne bacteria can reach the intraventricular choroid plexus, directly infect choroid plexus epithelial cells, and gain access to the CSF. Some bacteria, such as *S. pneumoniae*, can adhere to cerebral capillary endothelial cells and subsequently migrate through or between these cells to reach the CSF. Bacteria are able to multiply rapidly within CSF because of the absence of effective host immune defenses. Normal CSF contains few white blood cells (WBCs) and relatively small amounts of complement proteins and immunoglobulins. The paucity of the latter two prevents effective opsonization of bacteria, an essential prerequisite for bacterial phagocytosis by neutrophils. Phagocytosis of bacteria is further impaired by the fluid nature of CSF, which is less conducive to phagocytosis than a solid tissue substrate.

A critical event in the pathogenesis of bacterial meningitis is the inflammatory reaction induced by the invading bacteria. Many of the neurologic manifestations and complications of bacterial meningitis result from the immune response to the invading pathogen rather than from direct bacteria-induced tissue injury. As a result, neurologic injury can progress even after the CSF has been sterilized by antibiotic therapy.

The lysis of bacteria with the subsequent release of cell-wall components into the subarachnoid space is the initial step in the induction of the inflammatory response and the formation of a purulent exudate in the subarachnoid space (Fig. 35-2). Bacterial cell-wall components,

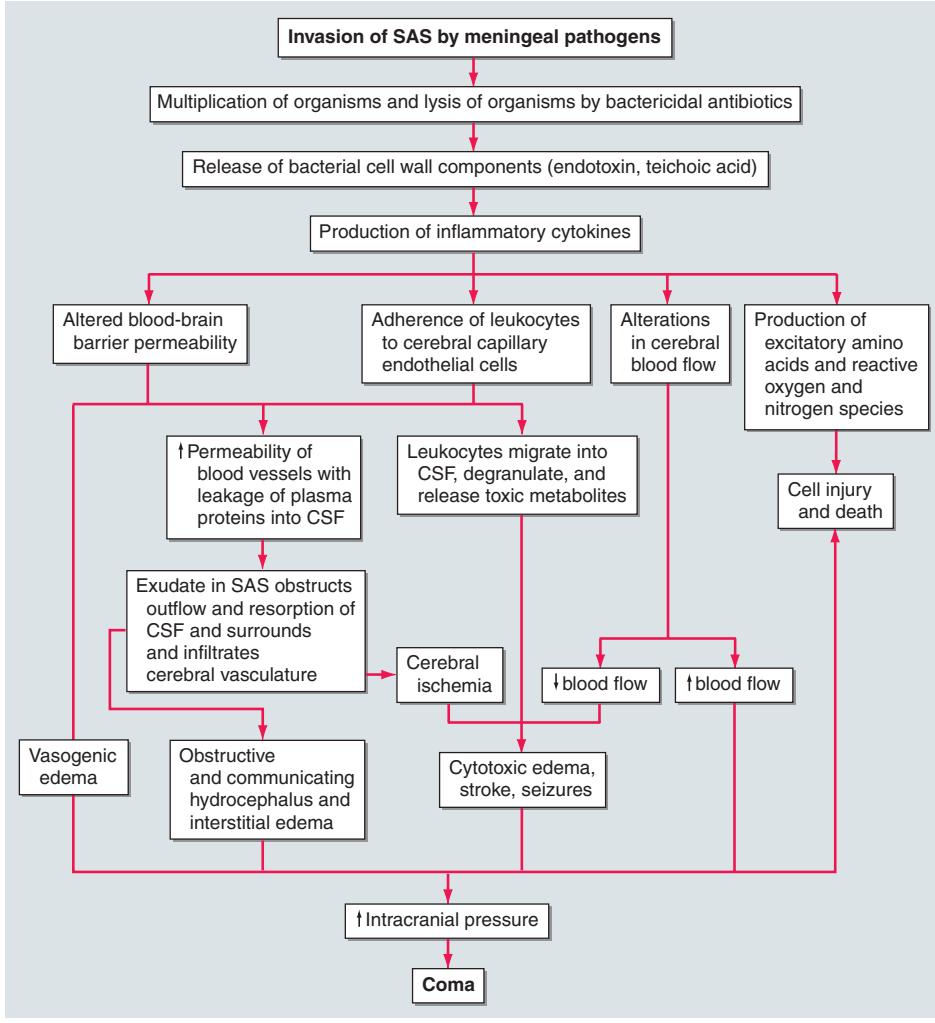


FIGURE 35-2

The pathophysiology of the neurologic complications of bacterial meningitis. SAS, subarachnoid space; CSF, cerebrospinal fluid.

such as the lipopolysaccharide (LPS) molecules of gram-negative bacteria and teichoic acid and peptidoglycans of *S. pneumoniae*, induce meningeal inflammation by stimulating the production of inflammatory cytokines and chemokines by microglia, astrocytes, monocytes, microvascular endothelial cells, and CSF leukocytes. In experimental models of meningitis, cytokines including tumor necrosis factor (TNF) and interleukin 1 (IL-1) are present in CSF within 1–2 h of intracisternal inoculation of LPS. This cytokine response is quickly followed by an increase in CSF protein concentration and leukocytosis. Chemokines (cytokines that induce chemotactic migration in leukocytes) and a variety of other proinflammatory cytokines are also produced and secreted by leukocytes and tissue cells that are stimulated by IL-1 and TNF. In addition, bacteremia and the inflammatory cytokines induce the production of excitatory amino acids, reactive oxygen and nitrogen species (free oxygen radicals, nitric oxide, and peroxynitrite), and other mediators that can induce death of brain cells.

Much of the pathophysiology of bacterial meningitis is a direct consequence of elevated levels of CSF cytokines and chemokines. TNF and IL-1 act synergistically to increase the permeability of the blood-brain barrier, resulting in induction of vasogenic edema and the leakage of serum proteins into the subarachnoid space (Fig. 35-2). The subarachnoid exudate of proteinaceous material and leukocytes obstructs the flow of CSF through the ventricular system and diminishes the resorptive capacity of the arachnoid granulations in the dural sinuses, leading to obstructive and communicating hydrocephalus and concomitant interstitial edema.

Inflammatory cytokines upregulate the expression of selectins on cerebral capillary endothelial cells and leukocytes, promoting leukocyte adherence to vascular endothelial cells and subsequent migration into the CSF. The adherence of leukocytes to capillary endothelial cells increases the permeability of blood vessels, allowing for the leakage of plasma proteins into the CSF, which adds to the inflammatory exudate. Neutrophil degranulation results in the release of toxic metabolites that contribute to cytotoxic edema, cell injury, and death. Contrary to previous beliefs, CSF leukocytes probably do little to contribute to the clearance of CSF bacterial infection.

During the very early stages of meningitis, there is an increase in cerebral blood flow, soon followed by a decrease in cerebral blood flow and a loss of cerebrovascular autoregulation (Chap. 22). Narrowing of the large arteries at the base of the brain due to encroachment by the purulent exudate in the subarachnoid space and infiltration of the arterial wall by inflammatory cells with intimal thickening (*vasculitis*) also occur and may result in ischemia and infarction, obstruction of branches of the middle cerebral artery by thrombosis, thrombosis of the major cerebral venous sinuses, and thrombophlebitis of the cerebral cortical veins. The combination of interstitial, vasogenic, and cytotoxic edema leads to raised ICP and coma. Cerebral herniation usually results from the effects of cerebral edema, either focal or generalized; hydrocephalus and dural sinus or cortical vein thrombosis may also play a role.

CLINICAL PRESENTATION

Meningitis can present as either an acute fulminant illness that progresses rapidly in a few hours or as a subacute infection that progressively worsens over several days. The classic clinical triad of meningitis is fever, headache, and nuchal rigidity. A decreased level of consciousness occurs in >75% of patients and can vary from lethargy to coma. Nausea, vomiting, and photophobia are also common complaints.

Seizures occur as part of the initial presentation of bacterial meningitis or during the course of the illness in 20–40% of patients. Focal seizures are usually due to focal arterial ischemia or infarction, cortical venous thrombosis with hemorrhage, or focal edema. Generalized seizure activity and status epilepticus may be due to hyponatremia, cerebral anoxia, or, less commonly, the toxic effects of antimicrobial agents such as high-dose penicillin.

Raised ICP is an expected complication of bacterial meningitis and the major cause of obtundation and coma in this disease. More than 90% of patients will have a CSF opening pressure >180 mm H_2O, and 20% have opening pressures >400 mm H_2O. Signs of increased ICP include a deteriorating or reduced level of consciousness, papilledema, dilated poorly reactive pupils, sixth nerve palsies, decerebrate posturing, and the Cushing reflex (bradycardia, hypertension, and irregular respirations). The most disastrous complication of increased ICP is cerebral herniation. The incidence of herniation in patients with bacterial meningitis has been reported to occur in as few as 1% to as many as 8% of cases.

Specific clinical features may provide clues to the diagnosis of individual organisms and are discussed in more detail in specific chapters devoted to individual pathogens. The most important of these clues is the rash of meningococcemia, which begins as a diffuse erythematous maculopapular rash resembling a viral exanthem; however, the skin lesions of meningococcemia rapidly become petechial. Petechiae are found on the trunk and lower extremities, in the mucous membranes and conjunctiva, and occasionally on the palms and soles.

DIAGNOSIS

When bacterial meningitis is suspected, blood cultures should be immediately obtained and empirical antimicrobial therapy is initiated without delay (**Table 35-1**). The diagnosis of bacterial meningitis is made by examination of the CSF (**Table 35-2**). The need to obtain

TABLE 35-1

ANTIBIOTICS USED IN EMPIRICAL THERAPY OF BACTERIAL MENINGITIS AND FOCAL CNS INFECTIONS[a]

INDICATION	ANTIBIOTIC
Preterm infants to infants <1 month	Ampicillin + cefotaxime
Infants 1–3 months	Ampicillin + cefotaxime or ceftriaxone
Immunocompetent children >3 months and adults <55 years	Cefotaxime or ceftriaxone + vancomycin
Adults >55 years and adults of any age with alcoholism or other debilitating illnesses	Ampicillin + cefotaxime or ceftriaxone + vancomycin
Hospital-acquired meningitis, posttraumatic or postneurosurgery meningitis, neutropenic patients, or patients with impaired cell-mediated immunity	Ampicillin + ceftazidime + vancomycin

ANTIMICROBIAL AGENT	TOTAL DAILY DOSE AND DOSING INTERVAL	
	CHILD (>1 MONTH)	ADULT
Ampicillin	200 (mg/kg)/d, q4h	12 g/d, q4h
Cefepime	150 (mg/kg)/d, q8h	6 g/d, q8h
Cefotaxime	200 (mg/kg)/d, q6h	12 g/d, q4h
Ceftriaxone	100 (mg/kg)/d, q12h	4 g/d, q12h
Ceftazidime	150 (mg/kg)/d, q8h	6 g/d, q8h
Gentamicin	7.5 (mg/kg)/d, q8h[b]	7.5 (mg/kg)/d, q8h
Meropenem	120 (mg/kg)/d, q8h	3 g/d, q8h
Metronidazole	30 (mg/kg)/d, q6h	1500–2000 mg/d, q6h
Nafcillin	100–200 (mg/kg)/d, q6h	9–12 g/d, q4h
Penicillin G	400,000 (U/kg)/d, q4h	20–24 million U/d, q4h
Vancomycin	60 (mg/kg)/d, q6h	2 g/d, q12h[b]

[a]All antibiotics are administered intravenously; doses indicated assume normal renal and hepatic function.
[b]Doses should be adjusted based on serum peak and trough levels: gentamicin therapeutic level: peak: 5–8 μg/mL; trough: <2 μg/mL; vancomycin therapeutic level: peak: 25–40 μg/mL; trough: 5–15 μg/mL.

TABLE 35-2

CEREBROSPINAL FLUID (CSF) ABNORMALITIES IN BACTERIAL MENINGITIS

Opening pressure	>180 mm H_2O
White blood cells	10/μL to 10,000/μL; neutrophils predominate
Red blood cells	Absent in nontraumatic tap
Glucose	<2.2 mmol/L (<40 mg/dL)
CSF/serum glucose	<0.4
Protein	>0.45 g/L (>45 mg/dL)
Gram's stain	Positive in >60%
Culture	Positive in >80%
Latex agglutination	May be positive in patients with meningitis due to *S. pneumoniae, N. meningitidis, H. influenzae* type b, *E. coli,* group B streptococci
Limulus lysate	Positive in cases of gram-negative meningitis
PCR	Detects bacterial DNA

Note: PCR, polymerase chain reaction.

neuroimaging studies (CT or MRI) prior to LP requires clinical judgment. In an immunocompetent patient with no known history of recent head trauma, a normal level of consciousness, and no evidence of papilledema or focal neurologic deficits, it is considered safe to perform LP without prior neuroimaging studies. If LP is delayed in order to obtain neuroimaging studies, empirical antibiotic therapy should be initiated after blood cultures are obtained. Antibiotic therapy initiated a few hours prior to LP will not significantly alter the CSF WBC count or glucose concentration, nor is it likely to prevent visualization of organisms by Gram's stain or detection of bacterial nucleic acid by polymerase chain reaction (PCR) assay.

The classic CSF abnormalities in bacterial meningitis (Table 35-2) are (1) polymorphonuclear (PMN) leukocytosis (>100 cells/μL in 90%), (2) decreased glucose concentration [<2.2 mmol/L (<40 mg/dL) and/or CSF/serum glucose ratio of <0.4 in ~60%], (3) increased protein concentration [>0.45 g/L (>45 mg/dL) in 90%], and (4) increased opening pressure (>180 mm H_2O in 90%). CSF bacterial cultures are positive in >80% of patients, and CSF Gram's stain demonstrates organisms in >60%.

CSF glucose concentrations <2.2 mmol/L (<40 mg/dL) are abnormal, and a CSF glucose concentration of zero can be seen in bacterial meningitis. Use of the CSF/serum glucose ratio corrects for hyperglycemia that may mask a relative decrease in the CSF glucose concentration. The CSF glucose concentration is low when the CSF/serum glucose ratio is <0.6. A CSF/ serum glucose ratio <0.4 is highly suggestive of bacterial meningitis but may also be seen in other conditions, including fungal, tuberculous, and carcinomatous meningitis. It takes from 30 min to several hours for the concentration of CSF glucose to reach equilibrium with blood glucose levels; therefore, administration of 50 mL of 50% glucose (D50) prior to LP, as commonly occurs in emergency department settings, is unlikely to alter CSF glucose concentration significantly unless more than a few hours have elapsed between glucose administration and LP.

A broad-range PCR can detect small numbers of viable and nonviable organisms in CSF and is expected

to be useful for making a diagnosis of bacterial meningitis in patients who have been pretreated with oral or parenteral antibiotics and in whom Gram's stain and CSF culture are negative. When the broad-range PCR is positive, a PCR that uses specific bacterial primers to detect the nucleic acid of *S. pneumoniae, N. meningitidis, Escherichia coli, L. monocytogenes, H. influenzae*, and *S. agalactiae* can be obtained based on the clinical suspicion of the meningeal pathogen. The latex agglutination (LA) test for the detection of bacterial antigens of *S. pneumoniae*, *N. meningitidis*, *H. influenzae* type b, group B streptococcus, and *E. coli* K1 strains in the CSF has been useful for making a diagnosis of bacterial meningitis but is being replaced by the CSF bacterial PCR assay. The CSF LA test has a *specificity* of 95–100% for *S. pneumoniae* and *N. meningitidis*, so a positive test is virtually diagnostic of bacterial meningitis caused by these organisms. However, the *sensitivity* of the CSF <LA test is only 70–100% for detection of *S. pneumoniae* and 33–70% for detection of *N. meningitidis* antigens, so a negative test does not exclude infection by these organisms. The Limulus amebocyte lysate assay is a rapid diagnostic test for the detection of gram-negative endotoxin in CSF and thus for making a diagnosis of gram-negative bacterial meningitis. The test has a specificity of 85–100% and a sensitivity approaching 100%. Thus, a positive Limulus amebocyte lysate assay occurs in virtually all patients with gram-negative bacterial meningitis, but false positives may occur.

Almost all patients with bacterial meningitis will have neuroimaging studies performed during the course of their illness. MRI is preferred over CT because of its superiority in demonstrating areas of cerebral edema and ischemia. In patients with bacterial meningitis, diffuse meningeal enhancement is often seen after the administration of gadolinium. Meningeal enhancement is not diagnostic of meningitis but occurs in any CNS disease associated with increased blood-brain barrier permeability.

Petechial skin lesions, if present, should be biopsied. The rash of meningococcemia results from the dermal seeding of organisms with vascular endothelial damage, and biopsy may reveal the organism on Gram's stain.

DIFFERENTIAL DIAGNOSIS

Viral meningoencephalitis, and particularly herpes simplex virus (HSV) encephalitis, can mimic the clinical presentation of bacterial meningitis (see Encephalitis, below). HSV encephalitis typically presents with headache, fever, altered consciousness, focal neurologic deficits (e.g., dysphasia, hemiparesis), and focal or generalized seizures. The findings on CSF studies, neuroimaging, and electroencephalogram (EEG) distinguish HSV encephalitis from bacterial meningitis. The typical CSF profile with viral CNS infections is a lymphocytic pleocytosis with a normal glucose concentration, in contrast to PMN pleocytosis and hypoglycorrhachia characteristic of bacterial meningitis. MRI abnormalities (other than meningeal enhancement) are not seen in uncomplicated bacterial meningitis. By contrast, in HSV encephalitis, on T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI images, high signal intensity lesions are seen in the orbitofrontal, anterior, and medial temporal lobes in the majority of patients within 48 h of symptom onset. Some patients with HSV encephalitis have a distinctive periodic pattern on EEG (see later).

Rickettsial disease can resemble bacterial meningitis. Rocky Mountain spotted fever (RMSF) is transmitted by a tick bite and caused by the bacteria *Rickettsia rickettsii*. The disease may present acutely with high fever, prostration, myalgia, headache, nausea, and vomiting. Most patients develop a characteristic rash within 96 h of the onset of symptoms. The rash is initially a diffuse erythematous maculopapular rash that may be difficult to distinguish from that of meningococcemia. It progresses to a petechial rash, then to a purpuric rash and, if untreated, to skin necrosis or gangrene. The color of the lesions changes from bright red to very dark red, then yellowish-green to black. The rash typically begins in the wrist and ankles and then spreads distally and proximally within a matter of a few hours, involving the palms and soles. Diagnosis is made by immunofluorescent staining of skin biopsy specimens. Ehrlichioses are also transmitted by a tick bite. These are small gram-negative coccobacilli of which two species cause human disease. *Anaplasma phagocytophilum* causes human granulocytic ehrlichiosis (anaplasmosis), and *Ehrlichia chaffeensis* causes human monocytic ehrlichiosis. The clinical and laboratory manifestations of the infections are similar. Patients present with fever, headache, nausea, and vomiting. Twenty percent of patients have a maculopapular or petechial rash. There is laboratory evidence of leukopenia, thrombocytopenia and anemia, and mild to moderate elevations in alanine aminotransferases, alkaline phosphatase, and lactate dehydrogenase. Patients with RMSF and those with ehrlichial infections may have an altered level of consciousness ranging from mild lethargy to coma, confusion, focal neurologic signs, cranial nerve palsies, hyperreflexia, and seizures.

Focal suppurative CNS infections (see later), including subdural and epidural empyema and brain abscess, should also be considered, especially when focal neurologic findings are present. MRI should be performed promptly in all patients with suspected meningitis who have focal features, both to detect the intracranial infection and to search for associated areas of infection in the sinuses or mastoid bones.

A number of noninfectious CNS disorders can mimic bacterial meningitis. Subarachnoid hemorrhage (SAH; Chap. 22) is generally the major consideration. Other

possibilities include chemical meningitis due to rupture of tumor contents into the CSF (e.g., from a cystic glioma or craniopharyngioma epidermoid or dermoid cyst); drug-induced hypersensitivity meningitis; carcinomatous or lymphomatous meningitis; meningitis associated with inflammatory disorders such as sarcoid, systemic lupus erythematosus (SLE), and Behçet's syndrome; pituitary apoplexy; and uveomeningitic syndromes (Vogt-Koyanagi-Harada syndrome).

On occasion, subacutely evolving meningitis may be considered in the differential diagnosis of acute meningitis. The principal causes include *Mycobacterium tuberculosis*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Coccidioides immitis*, and *Treponema pallidum*.

Rx Treatment: ACUTE BACTERIAL MENINGITIS

EMPIRICAL ANTIMICROBIAL THERAPY

(Table 35-1) Bacterial meningitis is a medical emergency. The goal is to begin antibiotic therapy within 60 min of a patient's arrival in the emergency department. Empirical antimicrobial therapy is initiated in patients with suspected bacterial meningitis before the results of CSF Gram's stain and culture are known. *S. pneumoniae* and *N. meningitidis* are the most common etiologic organisms of community-acquired bacterial meningitis. Due to the emergence of penicillin- and cephalosporin-resistant *S. pneumoniae*, empirical therapy of community-acquired suspected bacterial meningitis in children and adults should include a combination of dexamethasone, a third-generation cephalosporin (e.g., ceftriaxone or cefotaxime) and vancomycin, plus acyclovir, as HSV encephalitis is the leading disease in the differential diagnosis, and doxycycline during tick season to treat tick-borne bacterial infections. Ceftriaxone or cefotaxime provide good coverage for susceptible *S. pneumoniae*, group B streptococci, and *H. influenzae* and adequate coverage for *N. meningitidis*. Cefepime is a broad-spectrum fourth-generation cephalosporin with in vitro activity similar to that of cefotaxime or ceftriaxone against *S. pneumoniae* and *N. meningitidis* and greater activity against *Enterobacter* species and *Pseudomonas aeruginosa*. In clinical trials, cefepime has been demonstrated to be equivalent to cefotaxime in the treatment of penicillin-sensitive pneumococcal and meningococcal meningitis, and it has been used successfully in some patients with meningitis due to *Enterobacter* species and *P. aeruginosa*. Ampicillin should be added to the empirical regimen for coverage of *L. monocytogenes* in individuals <3 months, those >55 years, or those with suspected impaired cell-mediated immunity because of chronic illness, organ transplantation, pregnancy, malignancy, or immunosuppressive therapy. In hospital-acquired meningitis, and particularly meningitis following neurosurgical procedures, staphylococci and gram-negative organisms including *P. aeruginosa* are the most common etiologic organisms. In these patients, empirical therapy should include a combination of vancomycin and ceftazidime, cefepime, or meropenem. Ceftazidime, cefepime, or meropenem should be substituted for ceftriaxone or cefotaxime in neurosurgical patients and in neutropenic patients, as ceftriaxone and cefotaxime do not provide adequate activity against CNS infection with *P. aeruginosa*. Meropenem is a carbapenem antibiotic that is highly active in vitro against *L. monocytogenes*, has been demonstrated to be effective in cases of meningitis caused by *P. aeruginosa*, and shows good activity against penicillin-resistant pneumococci. In experimental pneumococcal meningitis, meropenem was comparable to ceftriaxone and inferior to vancomycin in sterilizing CSF cultures. The number of patients with bacterial meningitis enrolled in clinical trials of meropenem has not been sufficient to definitively assess the efficacy of this antibiotic.

SPECIFIC ANTIMICROBIAL THERAPY

Meningococcal Meningitis (Table 35-3) Although ceftriaxone and cefotaxime provide adequate empirical coverage for *N. meningitidis*, penicillin G remains the antibiotic of choice for meningococcal meningitis caused by susceptible strains. Isolates of *N. meningitidis* with moderate resistance to penicillin have been identified, but patients infected with these strains have still

TABLE 35-3

ANTIMICROBIAL THERAPY OF CNS BACTERIAL INFECTIONS BASED ON PATHOGEN[a]

ORGANISM	ANTIBIOTIC
Neisseria meningitides	
Penicillin-sensitive	Penicillin G or ampicillin
Penicillin-resistant	Ceftriaxone or cefotaxime
Streptococcus pneumoniae	
Penicillin-sensitive	Penicillin G
Penicillin-intermediate	Ceftriaxone or cefotaxime
Penicillin-resistant	(Ceftriaxone or cefotaxime) + vancomycin
Gram-negative bacilli (except *Pseudomonas* spp.)	Ceftriaxone or cefotaxime
Pseudomonas aeruginosa	Ceftazidime or cefepime or meropenem
Staphylococci spp.	
Methicillin-sensitive	Nafcillin
Methicillin-resistant	Vancomycin
Listeria monocytogenes	Ampicillin + gentamicin
Haemophilus influenzae	Ceftriaxone or cefotaxime
Streptococcus agalactiae	Penicillin G or ampicillin
Bacteroides fragilis	Metronidazole
Fusobacterium spp.	Metronidazole

[a]Doses are as indicated in Table 35-1.

been successfully treated with penicillin. CSF isolates of *N. meningitidis* should be tested for penicillin and ampicillin susceptibility, and if resistance is found, cefotaxime or ceftriaxone should be substituted for penicillin. A 7-day course of intravenous antibiotic therapy is adequate for uncomplicated meningococcal meningitis. The index case and all close contacts should receive chemoprophylaxis with a 2-day regimen of rifampin (600 mg every 12 h for 2 days in adults and 10 mg/kg every 12 h for 2 days in children >1 year). Rifampin is not recommended in pregnant women. Alternatively, adults can be treated with one dose of ciprofloxacin (750 mg), one dose of azithromycin (500 mg), or one intramuscular dose of ceftriaxone (250 mg). Close contacts are defined as those individuals who have had contact with oropharyngeal secretions, either through kissing or by sharing toys, beverages, or cigarettes.

Pneumococcal Meningitis Antimicrobial therapy of pneumococcal meningitis is initiated with a cephalosporin (ceftriaxone, cefotaxime, or cefepime) and vancomycin. All CSF isolates of *S. pneumoniae* should be tested for sensitivity to penicillin and the cephalosporins. Once the results of antimicrobial susceptibility tests are known, therapy can be modified accordingly (Table 35-3). For *S. pneumoniae* meningitis, an isolate of *S. pneumoniae* is considered to be susceptible to penicillin with a minimal inhibitory concentration (MIC) <0.06 μg/mL, to have intermediate resistance when the MIC is 0.1–1.0 μg/mL, and to be highly resistant when the MIC >1.0 μg/mL. Isolates of *S. pneumoniae* that have cephalosporin MICs ≤0.5 μg/mL are considered sensitive to the cephalosporins (cefotaxime, ceftriaxone, cefepime). Those with MICs of 1 μg/mL are considered to have intermediate resistance, and those with MICs ≥2 μg/mL are considered resistant. For meningitis due to pneumococci with cefotaxime or ceftriaxone MICs ≤0.5 μg/mL, treatment with cefotaxime or ceftriaxone is usually adequate. If the MIC >1 μg/mL, vancomycin is the antibiotic of choice. Rifampin can be added to vancomycin for its synergistic effect but is inadequate as monotherapy because resistance develops rapidly when it is used alone. A 2-week course of intravenous antimicrobial therapy is recommended for pneumococcal meningitis.

Patients with *S. pneumoniae* meningitis should have a repeat LP performed 24–36 h after the initiation of antimicrobial therapy to document sterilization of the CSF. Failure to sterilize the CSF after 24–36 h of antibiotic therapy should be considered presumptive evidence of antibiotic resistance. Patients with penicillin- and cephalosporin-resistant strains of *S. pneumoniae* who do not respond to intravenous vancomycin alone may benefit from the addition of intraventricular vancomycin. The intraventricular route of administration is preferred over the intrathecal route because adequate concentrations of vancomycin in the cerebral ventricles are not always achieved with intrathecal administration.

Listeria Meningitis Meningitis due to *L. monocytogenes* is treated with ampicillin for at least 3 weeks (Table 35-3). Gentamicin is often added (2 mg/kg loading dose, then 7.5 mg/kg per day given every 8 h and adjusted for serum levels and renal function). The combination of trimethoprim [10–20 (mg/kg)/d] and sulfamethoxazole [50–100 (mg/kg)/d] given every 6 h may provide an alternative in penicillin-allergic patients.

Staphylococcal Meningitis Meningitis due to susceptible strains of *S. aureus* or coagulase-negative staphylococci is treated with nafcillin (Table 35-3). Vancomycin is the drug of choice for methicillin-resistant staphylococci and for patients allergic to penicillin. In these patients, the CSF should be monitored during therapy. If the CSF is not sterilized after 48 h of intravenous vancomycin therapy, then either intraventricular or intrathecal vancomycin, 20 mg once daily, can be added.

Gram-Negative Bacillary Meningitis The third-generation cephalosporins (cefotaxime, ceftriaxone, and ceftazidime) are equally efficacious for the treatment of gram-negative bacillary meningitis, with the exception of meningitis due to *P. aeruginosa*, which should be treated with ceftazidime, cefepime, or meropenem (Table 35-3). A 3-week course of intravenous antibiotic therapy is recommended for meningitis due to gram-negative bacilli.

Adjunctive Therapy The release of bacterial cell-wall components by bactericidal antibiotics leads to the production of the inflammatory cytokines IL-1 and TNF in the subarachnoid space. Dexamethasone exerts its beneficial effect by inhibiting the synthesis of IL-1 and TNF at the level of mRNA, decreasing CSF outflow resistance, and stabilizing the blood-brain barrier. The rationale for giving dexamethasone 20 min before antibiotic therapy is that dexamethasone inhibits the production of TNF by macrophages and microglia only if it is administered before these cells are activated by endotoxin. Dexamethasone does not alter TNF production once it has been induced. The results of clinical trials of dexamethasone therapy in children, predominantly with meningitis due to *H. influenzae* and *S. pneumoniae*, have demonstrated its efficacy in decreasing meningeal inflammation and neurologic sequelae such as the incidence of sensorineural hearing loss.

A prospective European trial of adjunctive therapy for acute bacterial meningitis in 301 adults found that dexamethasone reduced the number of unfavorable outcomes (15% vs. 25%, $p = .03$) including death (7% vs. 15%, $p = .04$). The benefits were most striking in patients with

pneumococcal meningitis. Dexamethasone (10 mg intravenously) was administered 15–20 min before the first dose of an antimicrobial agent, and the same dose was repeated every 6 h for 4 days. These results were confirmed in a second trial of dexamethasone in adults with pneumococcal meningitis. Therapy with dexamethasone should ideally be started 20 min before, or not later than concurrent with, the first dose of antibiotics. It is unlikely to be of significant benefit if started >6 h after antimicrobial therapy has been initiated. Dexamethasone may decrease the penetration of vancomycin into CSF, and it delays the sterilization of CSF in experimental models of *S. pneumoniae* meningitis. As a result, its potential benefit should be carefully weighed when vancomycin is the antibiotic of choice. Alternatively, vancomycin can be administered by the intraventricular route.

INCREASED INTRACRANIAL PRESSURE Emergency treatment of increased ICP includes elevation of the patient's head to 30°–45°, intubation and hyperventilation (Pa_{CO2} 25–30 mm Hg), and mannitol. Patients with increased ICP should be managed in an intensive care unit; accurate ICP measurements are best obtained with an ICP monitoring device. Treatment of increased intracranial pressure is discussed in detail in Chap. 22.

PROGNOSIS

Mortality is 3–7% for meningitis caused by *H. influenzae*, *N. meningitidis*, or group B streptococci; 15% for that due to *L. monocytogenes*; and 20% for *S. pneumoniae*. In general, the risk of death from bacterial meningitis increases with (1) decreased level of consciousness on admission, (2) onset of seizures within 24 h of admission, (3) signs of increased ICP, (4) young age (infancy) and >50 years, (5) the presence of comorbid conditions including shock and/or the need for mechanical ventilation, and (6) delay in the initiation of treatment. Decreased CSF glucose concentration [<2.2 mmol/L (<40 mg/dL)] and markedly increased CSF protein concentration [>3 g/L (>300 mg/dL)] have been predictive of increased mortality and poorer outcomes in some series. Moderate or severe sequelae occur in ~25% of survivors, although the exact incidence varies with the infecting organism. Common sequelae include decreased intellectual function, memory impairment, seizures, hearing loss and dizziness, and gait disturbances.

ACUTE VIRAL MENINGITIS

CLINICAL MANIFESTATIONS

Patients with viral meningitis usually present with headache, fever, and signs of meningeal irritation coupled with an inflammatory CSF profile (see later). The headache of viral meningitis is usually frontal or retroorbital and is often associated with photophobia and pain on moving the eyes. Nuchal rigidity is present in most cases but may be mild and present only near the limit of neck anteflexion. Constitutional signs can include malaise, myalgia, anorexia, nausea and vomiting, abdominal pain, and/or diarrhea. Patients often have mild lethargy or drowsiness; however, profound alterations in consciousness, such as stupor, coma, or marked confusion, are unusual in viral meningitis and suggest the presence of encephalitis or other alternative diagnoses. Similarly, seizures or focal neurologic signs or symptoms or neuroimaging abnormalities indicative of brain parenchymal involvement are not typical of viral meningitis and suggest the presence of encephalitis or another CNS infectious or inflammatory process.

ETIOLOGY

Using a variety of diagnostic techniques, including CSF PCR, culture, and serology, a specific viral cause can be found in 75–90% of cases of viral meningitis. The most important agents are enteroviruses, HSV type 2 (HSV-2), and arboviruses (Table 35-4). CSF cultures are positive in 30–70% of patients, the frequency of isolation depending on the specific viral agent. Approximately two-thirds of culture-negative

TABLE 35-4

VIRUSES CAUSING ACUTE MENINGITIS AND ENCEPHALITIS IN NORTH AMERICA[a]

ACUTE MENINGITIS	
COMMON	**LESS COMMON**
Enteroviruses (coxsackieviruses, echoviruses, and human enteroviruses 68–71)	Varicella zoster virus
Herpes simplex virus 2	Epstein-Barr virus
Arthropod-borne viruses	Lymphocytic choriomeningitis virus
HIV	
ACUTE ENCEPHALITIS	
COMMON	**LESS COMMON**
Herpesviruses	Rabies
Herpes simplex virus 1	Eastern equine encephalitis virus
Varicella zoster virus	Western equine encephalitis virus
Epstein-Barr virus	Powassan virus
Arthropod-borne viruses	Cytomegalovirus[a]
La Crosse virus	Enteroviruses[a]
West Nile virus	Colorado tick fever
St. Louis encephalitis virus	Mumps

[a]Immunocompromised host.

cases of aseptic meningitis have a specific viral etiology identified by CSF PCR testing (see later).

EPIDEMIOLOGY

Viral meningitis is not a nationally reportable disease; however, it has been estimated that the incidence is ~75,000 cases per year. In temperate climates, there is a substantial increase in cases during the summer and early fall months, reflecting the seasonal predominance of enterovirus and arthropod-borne virus (arbovirus) infections, with a peak monthly incidence of about 1 reported case per 100,000 population.

LABORATORY DIAGNOSIS

CSF Examination

The most important laboratory test in the diagnosis of viral meningitis is examination of the CSF. The typical profile is a lymphocytic pleocytosis (25–500 cells/μL), a normal or slightly elevated protein concentration [0.2–0.8 g/L (20–80 mg/dL)], a normal glucose concentration, and a normal or mildly elevated opening pressure (100–350 mm H_2O). Organisms are *not* seen on Gram's or acid-fast stained smears or India ink preparations of CSF. Rarely, PMNs may predominate in the first 48 h of illness, especially with infections due to echovirus 9, eastern equine encephalitis (EEE) virus, or mumps. A pleocytosis of polymorphonuclear neutrophils also occurs in 45% of patients with West Nile virus (WNV) meningitis and can persist for a week or longer before shifting to a lymphocytic pleocytosis. Despite these exceptions, the presence of a CSF PMN pleocytosis in a patient with suspected viral meningitis should always prompt consideration of alternative diagnoses, including bacterial meningitis or parameningeal infections. The total CSF cell count in viral meningitis is typically 25–500/μL, although cell counts of several thousand/μL are occasionally seen, especially with infections due to lymphocytic choriomeningitis virus (LCMV) and mumps virus. The CSF glucose concentration is typically normal in viral infections, although it may be decreased in 10–30% of cases due to mumps or LCMV. Rare instances of decreased CSF glucose concentration occur in cases of meningitis due to echoviruses and other enteroviruses, HSV-2, and varicella-zoster virus (VZV). As a rule, a lymphocytic pleocytosis with a low glucose concentration should suggest fungal or tuberculous meningitis, *Listeria* meningoencephalitis, or noninfectious disorders (e.g., sarcoid, neoplastic meningitis).

A number of tests measuring levels of various CSF proteins, enzymes, and mediators—including C-reactive protein, lactic acid, lactate dehydrogenase, neopterin, quinolinate, IL-1β, IL-6, soluble IL-2 receptor, β_2-microglobulin, and TNF—have been proposed as potential discriminators between viral and bacterial meningitis or as markers of specific types of viral infection (e.g., infection with HIV), but they remain of uncertain sensitivity and specificity and are not widely used for diagnostic purposes.

Polymerase Chain Reaction Amplification of Viral Nucleic Acid

Amplification of viral-specific DNA or RNA from CSF using PCR amplification has become the single most important method for diagnosing CNS viral infections. In both enteroviral and HSV infections of the CNS, PCR has become the diagnostic procedure of choice and is substantially more sensitive than viral cultures. HSV PCR is also an important diagnostic test in patients with recurrent episodes of "aseptic" meningitis, many of whom have amplifiable HSV DNA in CSF despite negative viral cultures. CSF PCR is also used routinely to diagnose CNS viral infections caused by cytomegalovirus (CMV), Epstein-Barr virus (EBV), VZV, and human herpesvirus 6 (HHV-6). CSF PCR tests are available for WNV but are not as sensitive as CSF IgM. PCR is also useful in the diagnosis of CNS infection caused by *Mycoplasma pneumoniae,* which can mimic viral meningitis and encephalitis.

Viral Culture

The sensitivity of CSF cultures for the diagnosis of viral meningitis and encephalitis, in contrast to its utility in bacterial infections, is generally poor. In addition to CSF, specific viruses may also be isolated from throat swabs, stool, blood, and urine. Enteroviruses and adenoviruses may be found in feces; arboviruses, some enteroviruses, and LCMV in blood; mumps and CMV in urine; and enteroviruses, mumps, and adenoviruses in throat washings. During enteroviral infections, viral shedding in stool may persist for several weeks. The presence of enterovirus in stool is not diagnostic and may result from residual shedding from a previous enteroviral infection; it also occurs in some asymptomatic individuals during enteroviral epidemics.

Serologic Studies

For some viruses, including many arboviruses such as WNV, serologic studies remain a crucial diagnostic tool. Serum antibody determination is less useful for viruses with high seroprevalence rates in the general population such as HSV, VZV, CMV, and EBV. For viruses with low seroprevalence rates, diagnosis of acute viral infection can be made by documenting seroconversion between acute-phase and convalescent sera (typically obtained after 2–4 weeks) or by demonstrating the presence of virus-specific IgM antibodies. Documentation of synthesis of virus-specific antibodies in CSF, as shown by an

increased IgG index or the presence of CSF IgM antibodies, is more useful than serum serology alone and can provide presumptive evidence of CNS infection. Although serum and CSF IgM antibodies generally persist for only a few months after acute infection, there are exceptions to this rule. For example, WNV IgM has been shown to persist in some patients for >1 year following acute infection. Unfortunately, the delay between onset of infection and the host's generation of a virus-specific antibody response often means that serologic data are useful mainly for the retrospective establishment of a specific diagnosis, rather than in aiding acute diagnosis or management.

CSF oligoclonal gamma globulin bands occur in association with a number of viral infections. The associated antibodies are often directed against viral proteins. Oligoclonal bands occur commonly in certain noninfectious neurologic diseases (e.g., multiple sclerosis) and may be found in nonviral infections (e.g., neurosyphilis, Lyme neuroborreliosis).

Other Laboratory Studies

All patients with suspected viral meningitis should have a complete blood count and differential, liver and renal function tests, erythrocyte sedimentation rate (ESR) and C-reactive protein, electrolytes, glucose, creatine kinase, aldolase, amylase, and lipase. Neuroimaging studies (MRI, CT) are not necessary in patients with uncomplicated viral meningitis but should be performed in patients with altered consciousness, seizures, focal neurologic signs or symptoms, or atypical CSF profiles.

DIFFERENTIAL DIAGNOSIS

The most important issue in the differential diagnosis of viral meningitis is to consider diseases that can mimic viral meningitis, including (1) untreated or partially treated bacterial meningitis; (2) early stages of meningitis caused by fungi, mycobacteria, or *Treponema pallidum* (neurosyphilis), in which a lymphocytic pleocytosis is common, cultures may be slow growing or negative, and hypoglycorrhachia may not be present early; (3) meningitis caused by agents such as *Mycoplasma*, *Listeria* spp., *Brucella* spp., *Coxiella* spp., *Leptospira* spp., and *Rickettsia* spp.; (4) parameningeal infections; (5) neoplastic meningitis; and (6) meningitis secondary to noninfectious inflammatory diseases, including hypersensitivity meningitis, SLE and other rheumatologic diseases, sarcoidosis, Behçet's syndrome, and the uveomeningitic syndromes.

SPECIFIC VIRAL ETIOLOGIES

Enteroviruses are the most common cause of viral meningitis, accounting for >75% of cases in which a specific etiology can be identified. CSF reverse transcriptase PCR (RT-PCR) is the diagnostic procedure of choice and is both sensitive (>95%) and specific (>100%). Enteroviruses are the most likely cause of viral meningitis in the summer months, especially in children (<15 years), although cases occur at reduced frequency year round. Although the incidence of enteroviral meningitis declines with increasing age, some outbreaks have preferentially affected older children and adults. Meningitis outside the neonatal period is usually benign. Patients present with sudden onset of fever; headache; nuchal rigidity; and often constitutional signs, including vomiting, anorexia, diarrhea, cough, pharyngitis, and myalgias. The physical examination should include a careful search for stigmata of enterovirus infection, including exanthemata, hand-foot-mouth disease, herpangina, pleurodynia, myopericarditis, and hemorrhagic conjunctivitis. The CSF profile is typically a lymphocytic pleocytosis (100–1000 cells/μL) with normal glucose and normal or mildly elevated protein concentration. In rare cases, PMNs may predominate during the first 48 h of illness. Treatment is supportive, and patients usually recover without sequelae. Chronic and severe infections can occur in neonates and in individuals with hypo- or agammaglobulinemia.

Arbovirus infections occur predominantly in the summer and early fall. Arboviral meningitis should be considered when clusters of meningitis and encephalitis cases occur in a restricted geographic region during the summer or early fall. In WNV epidemics, avian deaths may serve as sentinel infections for subsequent human disease. A history of tick exposure or travel or residence in the appropriate geographic area should suggest the possibility of Colorado tick fever virus or Powassan virus infection, although nonviral tick-borne diseases, including RMSF and Lyme neuroborreliosis, may present similarly. Arbovirus meningoencephalitis is typically associated with a CSF lymphocytic pleocytosis, normal glucose concentration, and normal or mildly elevated protein concentration. However, 40–45% of patients with WNV meningoencephalitis have CSF neutrophilia, which can persist for a week or more. The rarity of hypoglycorrhachia in WNV infection as well as the absence of positive Gram's stains and the negative cultures helps distinguish these patients from those with bacterial meningitis. The presence of increased numbers of plasmacytoid cells or Mollaret-like large mononuclear cells in the CSF may be a clue to the diagnosis of WNV infection. Definitive diagnosis of arboviral meningoencephalitis is based on demonstration of viral-specific IgM in CSF or seroconversion. CSF PCR tests are available for some viruses in selected diagnostic laboratories and at the Centers for Disease Control and Prevention (CDC), but in the case of WNV, sensitivity (~70%) of CSF PCR is less than that of CSF serology.

HSV-2 meningitis occurs in ~25% of women and 11% of men at the time of an initial (primary) episode of

genital herpes. Of these patients, 20% go on to have recurrent attacks of meningitis. HSV-2 has been increasingly recognized as a major cause of viral meningitis in adults, and overall it is probably second in importance to enteroviruses as a cause of viral meningitis. Diagnosis of HSV meningitis is usually by HSV CSF PCR as cultures may be negative, especially in patients with recurrent meningitis. Demonstration of intrathecal synthesis of HSV-specific antibody may also be useful in diagnosis, although antibody tests are less sensitive and less specific than PCR and may not become positive until after the first week of infection. In contrast to HSV encephalitis in adults in which >90% of cases are due to HSV-1, the overwhelming majority of HSV meningitis is due to HSV-2. Although a history of or the presence of HSV genital lesions is an important diagnostic clue, many patients with HSV meningitis give no history and have no evidence of active genital herpes at the time of presentation. Most cases of recurrent viral or "aseptic" meningitis, including cases previously diagnosed as Mollaret's meningitis, are likely due to HSV.

VZV meningitis should be suspected in the presence of concurrent chickenpox or shingles. However, it is important to recognize that in some series, up to 40% of VZV meningitis cases have been reported to occur in the absence of rash. The frequency of VZV as a cause of meningitis is extremely variable, ranging from as low as 3% to as high as 20% in different series. Diagnosis is usually based on CSF PCR, although the sensitivity of this test may not be as high as for the other herpesviruses. In patients with negative CSF PCR results, the diagnosis of VZV CNS infection can be made by the demonstration of VZV-specific intrathecal antibody synthesis and/or the presence of VZV CSF IgM antibodies, or by positive CSF cultures.

EBV infections may also produce aseptic meningitis, with or without associated infectious mononucleosis. The presence of atypical lymphocytes in the CSF or peripheral blood is suggestive of EBV infection but may occasionally be seen with other viral infections. EBV is almost never cultured from CSF. Serum and CSF serology can help establish the presence of acute infection, which is characterized by IgM viral capsid antibodies (VCAs), antibodies to early antigens (EA), and the absence of antibodies to EBV-associated nuclear antigen (EBNA). CSF PCR is another important diagnostic test, although positive results may reflect viral reactivation associated with other infectious or inflammatory processes.

HIV meningitis should be suspected in any patient presenting with a viral meningitis with known or suspected risk factors for HIV infection. Meningitis may occur following primary infection with HIV in 5–10% of patients and less commonly at later stages of illness. Cranial nerve palsies, most commonly involving cranial nerves V, VII, or VIII, are more common in HIV meningitis than in other viral infections. Diagnosis can be confirmed by detection of HIV genome in blood or CSF. Seroconversion may be delayed, and patients with negative HIV serologies who are suspected of having HIV meningitis should be monitored for delayed seroconversion. For further discussion of HIV infection, see Chap. 37.

Mumps should be considered when meningitis occurs in the late winter or early spring, especially in males (male:female ratio 3:1). With the widespread use of the live attenuated mumps vaccine in the United States since 1967, the incidence of mumps meningitis has fallen by >95%. The presence of parotitis, orchitis, oophoritis, pancreatitis, or elevations in serum lipase and amylase are suggestive of mumps meningitis; however, their absence does not exclude the diagnosis. Clinical meningitis occurs in up to 30% of patients with mumps parotitis, and CSF pleocytosis occurs in >50%. Mumps infection confers lifelong immunity, so a documented history of previous infection excludes this diagnosis. Patients with meningitis have a CSF pleocytosis that can exceed 1000 cells/μL in 25%. Lymphocytes predominate in 75%, although CSF neutrophilia occurs in 25%. Hypoglycorrhachia, occurs in 10–30% of patients and may be a clue to the diagnosis when present. Diagnosis is typically made by culture of virus from CSF or by detecting IgM antibodies or seroconversion. CSF PCR is available in some diagnostic and research laboratories. The frequency of mumps meningitis has declined dramatically with the widespread use of the live-attenuated mumps vaccine. Rare cases of vaccine-associated meningitis occur, with a frequency of 10–100/100,000 doses typically 2–4 weeks after vaccination.

LCMV infection should be considered when aseptic meningitis occurs in the late fall or winter and in individuals with a history of exposure to house mice (*Mus musculus*), pet or laboratory rodents (e.g., hamsters, rats, mice), or their excreta. Some patients have an associated rash, pulmonary infiltrates, alopecia, parotitis, orchitis, or myopericarditis. Laboratory clues to the diagnosis of LCMV, in addition to the clinical findings noted above, may include the presence of leukopenia, thrombocytopenia, or abnormal liver function tests. Some cases present with a marked CSF pleocytosis (>1000 cells/μL) and hypoglycorrachia (<30%). Diagnosis is based on serology and/or culture of virus from CSF.

℞ Treatment: ACUTE VIRAL MENINGITIS

Treatment of almost all cases of viral meningitis is primarily symptomatic and includes use of analgesics, antipyretics, and antiemetics. Fluid and electrolyte status

should be monitored. Patients with suspected bacterial meningitis should receive appropriate empirical therapy pending culture results (see earlier). Hospitalization may not be required in immunocompetent patients with presumed viral meningitis and no focal signs or symptoms, no significant alteration in consciousness, and a classic CSF profile (lymphocytic pleocytosis, normal glucose, negative Gram's stain) if adequate provision for monitoring at home and medical follow-up can be ensured. Immunocompromised patients; patients with significant alteration in consciousness, seizures, or the presence of focal signs and symptoms suggesting the possibility of encephalitis or parenchymal brain involvement; and those patients who have an atypical CSF profile should be hospitalized. Oral or intravenous acyclovir may be of benefit in patients with meningitis caused by HSV-1 or -2 and in cases of severe EBV or VZV infection. Data concerning treatment of HSV, EBV, and VZV meningitis are extremely limited. Seriously ill patients should probably receive intravenous acyclovir (15–30 mg/kg per day in three divided doses), which can be followed by an oral drug such as acyclovir (800 mg, five times daily), famciclovir (500 mg tid), or valacyclovir (1000 mg tid) for a total course of 7–14 days. Patients who are less ill can be treated with oral drugs alone. Patients with HIV meningitis should receive highly active antiretroviral therapy (Chap. 37).

Patients with viral meningitis who are known to have deficient humoral immunity (e.g., X-linked agammaglobulinemia) and who are not already receiving either intramuscular gamma globulin or intravenous immunoglobulin (IVIg), should be treated with these agents. Intraventricular administration of immunoglobulin through an Ommaya reservoir has been tried in some patients with chronic enteroviral meningitis who have not responded to intramuscular or intravenous immunoglobulin.

An investigational drug, pleconaril, has shown efficacy against a variety of enteroviral infections and has good oral bioavailability and excellent CNS penetration. Clinical trials in patients with enteroviral meningitis indicated that pleconaril decreased the duration of symptoms compared to placebo. Most cases of enteroviral CNS infection are benign and self-limited and do not require specific antiviral therapy. However, pleconaril treatment might benefit patients with chronic CNS enteroviral infections in the setting of agammaglobulinemia or those who develop poliomyelitis as a complication of polio vaccine administration. Unfortunately, the availability of pleconaril for compassionate-use purposes is currently uncertain.

Vaccination is an effective method of preventing the development of meningitis and other neurologic complications associated with poliovirus, mumps, and measles infection. A live attenuated VZV vaccine (Varivax) is available in the United States. Clinical studies indicate an effectiveness rate of 70–90% for this vaccine, but a booster may be required to maintain immunity. An inactivated varicella vaccine is available for transplant recipients.

PROGNOSIS

In adults, the prognosis for full recovery from viral meningitis is excellent. Rare patients complain of persisting headache, mild mental impairment, incoordination, or generalized asthenia for weeks to months. The outcome in infants and neonates (<1 year) is less certain; intellectual impairment, learning disabilities, hearing loss, and other lasting sequelae have been reported in some studies.

VIRAL ENCEPHALITIS

DEFINITION

In contrast to viral meningitis, where the infectious process and associated inflammatory response are limited largely to the meninges, in encephalitis the brain parenchyma is also involved. Many patients with encephalitis also have evidence of associated meningitis (meningoencephalitis) and, in some cases, involvement of the spinal cord or nerve roots (encephalomyelitis, encephalomyeloradiculitis).

CLINICAL MANIFESTATIONS

In addition to the acute febrile illness with evidence of meningeal involvement characteristic of meningitis, the patient with encephalitis commonly has an altered level of consciousness (confusion, behavioral abnormalities), or a depressed level of consciousness, ranging from mild lethargy to coma, and evidence of either focal or diffuse neurologic signs and symptoms. Patients with encephalitis may have hallucinations, agitation, personality change, behavioral disorders, and, at times, a frankly psychotic state. Focal or generalized seizures occur in many patients with encephalitis. Virtually every possible type of focal neurologic disturbance has been reported in viral encephalitis; the signs and symptoms reflect the sites of infection and inflammation. The most commonly encountered focal findings are aphasia, ataxia, upper or lower motor neuron patterns of weakness, involuntary movements (e.g., myoclonic jerks, tremor), and cranial nerve deficits (e.g., ocular palsies, facial weakness). Involvement of the hypothalamic-pituitary axis may result in temperature dysregulation, diabetes insipidus, or the development of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

Despite the clear neuropathologic evidence that viruses differ in the regions of the CNS they injure, it is often impossible to distinguish reliably on clinical grounds alone one type of viral encephalitis (e.g., that caused by HSV) from others (see Differential Diagnosis, below).

ETIOLOGY

In the United States, there are ~20,000 reported cases of encephalitis per year, although the actual number of cases is likely to be significantly larger. Hundreds of viruses are capable of causing encephalitis, although only a limited subset is responsible for most cases in which a specific cause is identified (Table 35-4). The same organisms responsible for aseptic meningitis are also responsible for encephalitis, although the relative frequencies with which specific organisms cause these two patterns of infection often differ. The most important viruses causing sporadic cases of encephalitis in immunocompetent adults are herpesviruses (HSV, VZV, EBV). Epidemics of encephalitis are caused by arboviruses, which belong to several different viral taxonomic groups including *Alphaviruses* (e.g., EEE virus, western equine encephalitis virus), *Flaviviruses* (e.g., WNV, St. Louis encephalitis virus, Japanese encephalitis virus, Powassan virus), and *Bunyaviruses* (e.g., California encephalitis virus serogroup, LaCrosse virus). Historically, the largest number of cases of arbovirus encephalitis in the United States has been due to St. Louis encephalitis virus and the California encephalitis virus serogroup. However, since 2002, WNV has been responsible for the majority of arbovirus meningitis and encephalitis cases in the United States. The 2003 epidemic was the largest epidemic of arboviral neuroinvasive disease (encephalitis + meningitis) ever recorded in the United States, with 2860 cases and 264 deaths. Since 2003, WNV has accounted for ~1100–1300 cases of neuroinvasive disease per year and 100–120 deaths in the United States. New causes of viral CNS infections are constantly appearing, as evidenced by the recent outbreak of cases of encephalitis in Southeast Asia caused by Nipah virus, a newly identified member of the Paramyxovirus family, and of meningitis in Europe caused by Toscana virus, an arbovirus belonging to the Bunyavirus family.

LABORATORY DIAGNOSIS

CSF Examination

CSF examination should be performed in all patients with suspected viral encephalitis unless contraindicated by the presence of severely increased ICP. The characteristic CSF profile is indistinguishable from that of viral meningitis and typically consists of a lymphocytic pleocytosis, a mildly elevated protein concentration, and a normal glucose concentration. A CSF pleocytosis (>5 cells/μL) occurs in >95% of patients with documented viral encephalitis. In rare cases, a pleocytosis may be absent on the initial LP but present on subsequent LPs. Patients who are severely immunocompromised by HIV infection, glucocorticoid or other immunosuppressant drugs, chemotherapy, or lymphoreticular malignancies may fail to mount a CSF inflammatory response. CSF cell counts exceed 500/μL in only about 10% of patients with encephalitis. Infections with certain arboviruses (e.g., EEE virus or California encephalitis virus), mumps, and LCMV may occasionally result in cell counts >1000/μL, but this degree of pleocytosis should suggest the possibility of nonviral infections or other inflammatory processes. Atypical lymphocytes in the CSF may be seen in EBV infection and less commonly with other viruses, including CMV, HSV, and enteroviruses. Increased numbers of plasmacytoid or Mollaret-like large mononuclear cells have been reported in WNV encephalitis. Polymorphonuclear pleocytosis occurs in ~40% of patients with WNV encephalitis. Large numbers of CSF PMNs may be present in patients with encephalitis due to EEE virus, echovirus 9, and, more rarely, other enteroviruses. However, persisting CSF neutrophilia should prompt consideration of bacterial infection, leptospirosis, amebic infection, and noninfectious processes such as acute hemorrhagic leukoencephalitis. About 20% of patients with encephalitis will have a significant number of red blood cells (>500/μL) in the CSF in a nontraumatic tap. The pathologic correlate of this finding may be a hemorrhagic encephalitis of the type seen with HSV; however, CSF red blood cells occur with similar frequency and in similar numbers in patients with nonherpetic focal encephalitides. A decreased CSF glucose concentration is distinctly unusual in viral encephalitis and should suggest the possibility of bacterial, fungal, tuberculous, parasitic, leptospiral, syphilitic, sarcoid, or neoplastic meningitis. Rare patients with mumps, LCMV, or advanced HSV encephalitis may have low CSF glucose concentrations.

CSF PCR

CSF PCR has become the primary diagnostic test for CNS infections caused by CMV, EBV, VZV, HHV-6, and enteroviruses (see Viral Meningitis, above). The sensitivity and specificity of CSF PCRs varies with the virus being tested. The sensitivity (~96%) and specificity (~99%) of HSV CSF PCR is equivalent to or exceeds that of brain biopsy. It is important to recognize that HSV CSF PCR results need to be interpreted after considering the likelihood of disease in the patient being tested, the timing of the test in relationship to onset of symptoms, and the prior use of antiviral therapy. A negative HSV CSF PCR test performed by a qualified laboratory at the appropriate time during illness in a patient with a high likelihood of HSV encephalitis based on clinical and laboratory abnormalities significantly

reduces the likelihood of HSV encephalitis but does not exclude it. For example, in a patient with a pretest probability of 35% of having HSV encephalitis, a negative HSV CSF PCR reduces the posttest probability to ~2%, and for a patient with a pretest probability of 60%, a negative test reduces the posttest probability to ~6%. In both situations a positive test makes the diagnosis almost certain (98–99%). There have been several recent reports of initially negative HSV CSF PCR tests that were obtained early (≤72 h) following symptom onset, and that became positive when repeated 1–3 days later. The frequency of positive HSV CSF PCRs in patients with herpes encephalitis also decreases as a function of the duration of illness, with only ~20% of cases remaining positive after ≥14 days. PCR results are generally not affected by ≤1 week of antiviral therapy. In one study, 98% of CSF specimens remained PCR-positive during the first week of initiation of antiviral therapy, but the numbers fell to ~50% by 8–14 days and to ~21% by >15 days after initiation of antiviral therapy.

The sensitivity and specificity of CSF PCR tests for viruses other than herpes simplex have not been definitively characterized. Enteroviral CSF PCR appears to have a sensitivity and specificity of >95%. The specificity of EBV CSF PCR has not been established. Positive EBV CSF PCRs associated with positive tests for other pathogens have been reported and may reflect reactivation of EBV latent in lymphocytes that enter the CNS as a result of an unrelated infectious or inflammatory process. In patients with CNS infection due to VZV, CSF antibody and PCR studies should be considered complementary, as patients may have evidence of intrathecal synthesis of VZV-specific antibodies and negative CSF PCRs. In the case of WNV infection, CSF PCR appears to be less sensitive (~70% sensitivity) than detection of WNV-specific CSF IgM, although PCR testing remains useful in immunocompromised patients who may not mount an effective anti-WNV antibody response.

CSF Culture

Attempts to culture viruses from the CSF in cases of encephalitis are often disappointing. Cultures are negative in >95% of cases of HSV-1 encephalitis.

Serologic Studies and Antigen Detection

The basic approach to the serodiagnosis of viral encephalitis is identical to that discussed earlier for viral meningitis. In patients with HSV encephalitis, both antibodies to HSV-1 glycoproteins and glycoprotein antigens have been detected in the CSF. Optimal detection of both HSV antibodies and antigen typically occurs after the first week of illness, limiting the utility of these tests in acute diagnosis. Nonetheless, HSV CSF antibody testing is of value in selected patients whose illness is >1 week in duration and who are CSF PCR–negative for HSV. Demonstration of WNV IgM antibodies is diagnostic of WNV encephalitis as IgM antibodies do not cross the blood-brain barrier, and their presence in CSF is therefore indicative of intrathecal synthesis. Timing of antibody collection may be important as the rate of CSF WNV IgM seropositivity increases by ~10% per day during the first week after illness onset.

MRI, CT, EEG

Patients with suspected encephalitis almost invariably undergo neuroimaging studies and often EEG. These tests help identify or exclude alternative diagnoses and assist in the differentiation between a focal, as opposed to a diffuse, encephalitic process. Focal findings in a patient with encephalitis should always raise the possibility of HSV encephalitis. Examples of focal findings include: (1) areas of increased signal intensity in the frontotemporal, cingulate, or insular regions of the brain on T2-weighted, FLAIR, or diffusion-weighted MRI images (**Fig. 35-3**); (2) focal areas of low absorption, mass effect, and contrast enhancement on CT; or (3) periodic focal temporal lobe spikes on a background of slow or low-amplitude ("flattened") activity on EEG. Approximately 10% of patients with PCR-documented HSV encephalitis will have a normal MRI, although nearly 80% will have abnormalities in

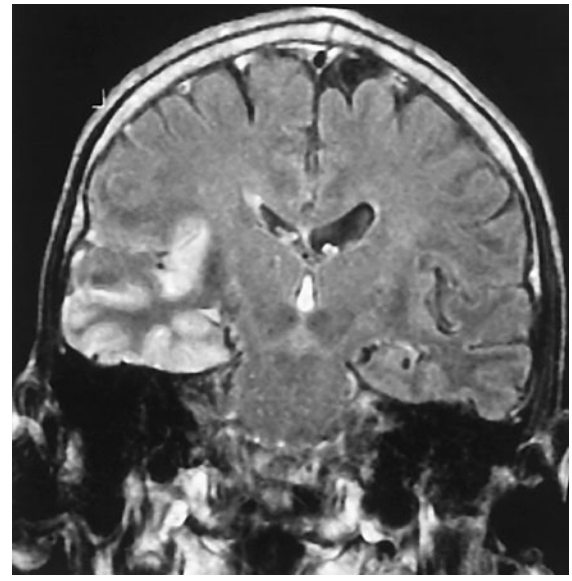


FIGURE 35-3

Coronal FLAIR magnetic resonance image from a patient with herpes simplex encephalitis. Note the area of increased signal in the right temporal lobe (left side of image) confined predominantly to the gray matter. This patient had predominantly unilateral disease; bilateral lesions are more common but may be quite asymmetric in their intensity.

the temporal lobe, and an additional 10% in extratemporal regions. The lesions are typically hyperintense on T2-weighted images. CT is less sensitive than MRI and is normal in up to 33% of patients. The addition of FLAIR and diffusion-weighted images to the standard MRI sequences enhances sensitivity. EEG abnormalities occur in >90% of PCR-documented cases of HSV encephalitis; they typically involve the temporal lobes but are often nonspecific. Some patients with HSV encephalitis have a distinctive EEG pattern consisting of periodic, stereotyped, sharp-and-slow complexes originating in one or both temporal lobes and repeating at regular intervals of 2–3 s. The periodic complexes are typically noted between the 2nd and 15th day of the illness and are present in two-thirds of pathologically proven cases of HSV encephalitis.

Significant MRI abnormalities are found in only ~50% of patients with WNV encephalitis, a frequency less than that with HSV encephalitis. When present, abnormalities often involve deep brain structures, including the thalamus, basal ganglia, and brainstem, rather than the cortex and may only be apparent on FLAIR images. EEGs typically show generalized slowing that may be more anteriorly prominent rather than the temporally predominant pattern of sharp or periodic discharges more characteristic of HSV encephalitis. Patients with VZV encephalitis may show multifocal areas of hemorrhagic and ischemic infarction reflecting the tendency of this virus to produce a CNS vasculopathy rather than a true encephalitis. Immunocompromised adult patients with CMV often have enlarged ventricles with areas of increased T2 signal on MRI outlining the ventricles and sub-ependymal enhancement on T1-weighted post-contrast images. **Table 35-5** highlights specific diagnostic test results in encephalitis that can be useful in clinical decision-making.

Brain Biopsy

Brain biopsy is now generally reserved for patients in whom CSF PCR studies fail to lead to a specific diagnosis, who have focal abnormalities on MRI, and who continue to show progressive clinical deterioration despite treatment with acyclovir and supportive therapy.

DIFFERENTIAL DIAGNOSIS

Infection by a variety of other organisms can mimic viral encephalitis. In studies of biopsy-proven HSV encephalitis, common infectious mimics of focal viral encephalitis included mycobacteria, fungi, rickettsia, *Listeria* and other bacteria (including *Bartonella* sp.), and *Mycoplasma*.

Infection caused by the ameba *Naegleria fowleri* can also cause acute meningoencephalitis (primary amebic

TABLE 35-5

USE OF DIAGNOSTIC TESTS IN ENCEPHALITIS

The best test for WNV encephalitis is the *CSF IgM antibody test*. The prevalence of positive CSF IgM tests increases by about 10%/day after illness onset and reaches 70–80% by the end of the first week. Serum WNV IgM can provide evidence for recent WNV infection, but in the absence of other findings does not establish the diagnosis of neuroinvasive disease (meningitis, encephalitis, acute flaccid paralysis).

Approximately 80% of patients with proven HSV encephalitis have *MRI* abnormalities involving the temporal lobes. This percentage likely increases to >90% when FLAIR and DWI MR sequences are also utilized. The absence of temporal lobe lesions on MR reduces the likelihood of HSV encephalitis and should prompt consideration of other diagnostic possibilities.

The *CSF HSV PCR* test may be negative in the first 72 h of symptoms of HSV encephalitis. A repeat study should be considered in patients with an initial early negative PCR in whom diagnostic suspicion of HSV encephalitis remains high and no alternative diagnosis has yet been established.

Detection of *intrathecal synthesis* (increased CSF/serum HSV antibody ratio corrected for breakdown of the blood-brain barrier) of *HSV-specific antibody* may be useful in diagnosis of HSV encephalitis in patients in whom only late (>1 week post-onset) CSF specimens are available and PCR studies are negative. Serum serology alone is of no value in diagnosis of HSV encephalitis due to the high seroprevalence rate in the general population.

Negative *CSF viral cultures* are of no value in excluding the diagnosis of HSV or EBV encephalitis.

VZV CSF IgM antibodies may be present in patients with a negative VZV CSF PCR. Both tests should be performed in patients with suspected VZV CNS disease.

The specificity of *EBV CSF PCR* for diagnosis of CNS infection is unknown. Positive tests may occur in patients with a CSF pleocytosis due to other causes. Detection of EBV CSF IgM or intrathecal synthesis of antibody to VCA supports the diagnosis of EBV encephalitis. Serological studies consistent with acute EBV infection (e.g., IgM VCA, presence of antibodies against EA but not against EBNA) can help support the diagnosis.

Note: CSF, cerebrospinal fluid; IgM, immunoglobulin M; WNV, West Nile virus; HSV, herpes simplex virus; MRI, magnetic resonance imaging; FLAIR, fluid attenuated inversion recovery; DWI, diffusion-weighted imaging; PCR, polymerase chain reaction; EBV, Epstein-Barr virus; VZV, varicella-zoster virus; CNS, central nervous system; VCA, viral capsid antibody; EA, early antigen; EBNA, EBV-associated nuclear antigen.

meningoencephalitis), whereas that caused by *Acanthamoeba* and *Balamuthia* more typically produces subacute or chronic granulomatous amebic meningoencephalitis. *Naegleria* thrive in warm, iron-rich pools of water, including those found in drains, canals, and both natural and human-made outdoor pools. Infection has typically occurred in immunocompetent children with a history of swimming in potentially infected water. The CSF, in contrast to the typical profile seen in viral encephalitis, often resembles that of bacterial meningitis with a neutrophilic pleocytosis and hypoglycorrhachia. Motile trophozoites can be seen in a wet mount of warm, fresh CSF. No effective treatment has been identified, and mortality approaches 100%.

Encephalitis can be caused by the raccoon pinworm *Baylisascaris procyonis*. Clues to the diagnosis include a history of raccoon exposure, and especially of playing in or eating dirt potentially contaminated with raccoon feces. Most patients are children, and many have an associated eosinophilia.

Once nonviral causes of encephalitis have been excluded, the major diagnostic challenge is to distinguish HSV from other viruses that cause encephalitis. This distinction is particularly important because in virtually every other instance the therapy is supportive, whereas specific and effective antiviral therapy is available for HSV, and its efficacy is enhanced when it is instituted early in the course of infection. HSV encephalitis should be considered when clinical features suggesting involvement of the inferomedial frontotemporal regions of the brain are present, including prominent olfactory or gustatory hallucinations, anosmia, unusual or bizarre behavior or personality alterations, or memory disturbance. HSV encephalitis should always be suspected in patients with focal findings on clinical examination, neuroimaging studies, or EEG. The diagnostic procedure of choice in these patients is CSF PCR analysis for HSV. A positive CSF PCR establishes the diagnosis, and a negative test dramatically reduces the likelihood of HSV encephalitis (see earlier).

The anatomic distribution of lesions may provide an additional clue to diagnosis. Patients with rapidly progressive encephalitis and prominent brainstem signs, symptoms, or neuroimaging abnormalities may be infected by flaviviruses (WNV, St. Louis encephalitis virus, Japanese encephalitis virus), HSV, rabies, or *L. monocytogenes*. Significant involvement of deep gray matter structures, including the basal ganglia and thalamus, should also suggest possible flavivirus infection. These patients may present clinically with prominent movement disorders (tremor, myoclonus) or parkinsonian features. Patients with WNV infection can also present with a poliomyelitis-like acute flaccid paralysis, as can patients infected with enterovirus 71 and, less commonly, other enteroviruses. Acute flaccid paralysis is characterized by the acute onset of a lower motor neuron type of weakness with flaccid tone, reduced or absent reflexes, and relatively preserved sensation. Despite an aggressive World Health Organization poliovirus eradication initiative, >1200 cases of wild-type poliovirus-induced poliomyelitis have been reported worldwide in 2006, with 88% occurring in Nigeria and India and >20 cases each from Somalia, Afghanistan, and Namibia. There have been recent small outbreaks of poliomyelitis associated with vaccine strains of virus that have reverted to virulence through mutation or recombination with circulating wild-type enteroviruses in Hispaniola, China, the Philippines, and Madagascar.

Epidemiologic factors may provide important clues to the diagnosis of viral meningitis or encephalitis. Particular attention should be paid to the season of the year; the geographic location and travel history; and possible exposure to animal bites or scratches, rodents, and ticks. Although transmission from the bite of an infected dog remains the most common cause of rabies worldwide, in the United States very few cases of dog rabies occur, and the most common risk factor is exposure to bats—although a clear history of a bite or scratch is often lacking. The classic clinical presentation of encephalitic (furious) rabies is of fever, fluctuating consciousness, and autonomic hyperactivity. Phobic spasms of the larynx, pharynx, neck muscles, and diaphragm can be triggered by attempts to swallow water (*hydrophobia*) or by inspiration (*aerophobia*). Patients may also present with paralytic (dumb) rabies characterized by acute ascending paralysis. Rabies due to the bite of a bat has a different clinical presentation than classic rabies. Patients present with focal neurologic deficits, myoclonus, seizures, and hallucinations; phobic spasms are not a typical feature. Patients with rabies have a CSF lymphocytic pleocytosis and may show areas of increased T2 signal abnormality in the brainstem, hippocampus, and hypothalamus. Diagnosis can be made by finding rabies virus antigen in brain tissue or in the neural innervation of hair follicles at the nape of the neck. PCR amplification of viral nucleic acid from CSF and saliva or tears may also enable diagnosis. Serology is frequently negative in both serum and CSF in the first week after onset of infection, which limits its acute diagnostic utility. No specific therapy is available, and cases are almost invariably fatal, with isolated survivors having devastating neurologic sequelae.

State public health authorities provide a valuable resource concerning isolation of particular agents in individual regions. Regular updates concerning the number, type and distribution of cases of arboviral encephalitis can be found on the CDC and U.S. Geological Survey (USGS) web sites (*http://www.cdc.gov* and *http://diseasemaps.usgs.gov*).

The major noninfectious etiologies that should be included in the differential diagnosis of acute encephalitis are nonvasculitic autoimmune meningoencephalitis, which may or may not be associated with serum

antithyroid microsomal and antithyroglobulin antibodies; limbic encephalitis associated with antineuronal antibodies; limbic encephalopathy not associated with cancer; acute disseminated encephalomyelitis and related fulminant demyelinating disorders (Chap. 34); and lymphoma. Finally, Creutzfeldt-Jakob disease (Chap. 38) can rarely present in an explosive fashion mimicking viral encephalitis.

℞ Treatment: VIRAL ENCEPHALITIS

Specific antiviral therapy should be initiated when appropriate. Vital functions, including respiration and blood pressure, should be monitored continuously and supported as required. In the initial stages of encephalitis, many patients will require care in an intensive care unit. Basic management and supportive therapy should include careful monitoring of ICP, fluid restriction, avoidance of hypotonic intravenous solutions, and suppression of fever. Seizures should be treated with standard anticonvulsant regimens, and prophylactic therapy should be considered in view of the high frequency of seizures in severe cases of encephalitis. As with all seriously ill, immobilized patients with altered levels of consciousness, encephalitis patients are at risk for aspiration pneumonia, stasis ulcers and decubiti, contractures, deep venous thrombosis and its complications, and infections of indwelling lines and catheters.

Acyclovir is of benefit in the treatment of HSV and should be started empirically in patients with suspected viral encephalitis, especially if focal features are present, while awaiting viral diagnostic studies. Treatment should be discontinued in patients found not to have HSV encephalitis, with the possible exception of patients with severe encephalitis due to VZV or EBV. HSV, VZV, and EBV all encode an enzyme, deoxypyrimidine (thymidine) kinase, that phosphorylates acyclovir to produce acyclovir-5μ-monophosphate. Host cell enzymes then phosphorylate this compound to form a triphosphate derivative. It is the triphosphate that acts as an antiviral agent by inhibiting viral DNA polymerase and by causing premature termination of nascent viral DNA chains. The specificity of action depends on the fact that uninfected cells do not phosphorylate significant amounts of acyclovir to acyclovir-5μ-monophosphate. A second level of specificity is provided by the fact that the acyclovir triphosphate is a more potent inhibitor of viral DNA polymerase than of the analogous host cell enzymes.

Adults should receive a dose of 10 mg/kg of acyclovir intravenously every 8 h (30 mg/kg per day total dose) for a minimum of 14 days. CSF PCR can be repeated at the completion of the 14-day course, with PCR-positive patients receiving an additional 7 days of treatment, followed by a repeat CSF PCR test. Neonatal HSV CNS infection is less responsive to acyclovir therapy than HSV encephalitis in adults; it is recommended that neonates with HSV encephalitis receive 20 mg/kg of acyclovir every 8 h (60 mg/kg per day total dose) for a minimum of 21 days.

Prior to intravenous administration, acyclovir should be diluted to a concentration ≤7 mg/mL. (A 70-kg person would receive a dose of 700 mg, which would be diluted in a volume of 100 mL.) Each dose should be infused slowly over 1 h rather than by rapid or bolus infusion, to minimize the risk of renal dysfunction. Care should be taken to avoid extravasation or intramuscular or subcutaneous administration. The alkaline pH of acyclovir can cause local inflammation and phlebitis (9%). Dose adjustment is required in patients with impaired renal glomerular filtration. Penetration into CSF is excellent, with average drug levels ~50% of serum levels. Complications of therapy include elevations in blood urea nitrogen and creatinine levels (5%), thrombocytopenia (6%), gastrointestinal toxicity (nausea, vomiting, diarrhea) (7%), and neurotoxicity (lethargy or obtundation, disorientation, confusion, agitation, hallucinations, tremors, seizures) (1%). Acyclovir resistance may be mediated by changes in either the viral deoxypyrimidine kinase or DNA polymerase. To date, acyclovir-resistant isolates have not been a significant clinical problem in immunocompetent individuals. However, there have been reports of clinically virulent acyclovir-resistant HSV isolates from sites outside the CNS in immunocompromised individuals, including those with AIDS.

Oral antiviral drugs with efficacy against HSV, VZV, and EBV, including acyclovir, famciclovir, and valacyclovir, have not been evaluated in the treatment of encephalitis either as primary therapy or as supplemental therapy following completion of a course of parenteral acyclovir. A National Institute of Allergy and Infectious Disease (NIAID)/National Institute of Neurological Disorders and Stroke–sponsored phase III trial of supplemental oral valacyclovir therapy (2 g tid for 3 months) following the initial 14- to 21-day course of therapy with parenteral acyclovir is ongoing in patients with HSV encephalitis; this may help clarify the role of extended oral antiviral therapy.

Ganciclovir and foscarnet, either alone or in combination, are often utilized in the treatment of CMV-related CNS infections, although their efficacy remains unproven. Cidofovir (see later) may provide an alternative in patients who fail to respond to ganciclovir and foscarnet, although data concerning its use in CMV CNS infections is extremely limited.

Ganciclovir is a synthetic nucleoside analogue of 2μ-deoxyguanosine. The drug is preferentially phosphorylated by virus-induced cellular kinases. Ganciclovir

triphosphate acts as a competitive inhibitor of the CMV DNA polymerase, and its incorporation into nascent viral DNA results in premature chain termination. Following intravenous administration, CSF concentrations of ganciclovir are 25–70% of coincident plasma levels. The usual dose for treatment of severe neurologic illnesses is 5 mg/kg every 12 h given intravenously at a constant rate over 1 h. Induction therapy is followed by maintenance therapy of 5 mg/kg every day for an indefinite period. Induction therapy should be continued until patients show a decline in CSF pleocytosis and a reduction in CSF CMV DNA copy number on quantitative PCR testing (where available). Doses should be adjusted in patients with renal insufficiency. Treatment is often limited by the development of granulocytopenia and thrombocytopenia (20–25%), which may require reduction in or discontinuation of therapy. Gastrointestinal side effects, including nausea, vomiting, diarrhea, and abdominal pain, occur in ~20% of patients. Some patients treated with ganciclovir for CMV retinitis have developed retinal detachment, but the causal relationship to ganciclovir treatment is unclear. Valganciclovir is an orally bioavailable prodrug that can generate high serum levels of ganciclovir, although studies of its efficacy in treating CMV CNS infections are limited.

Foscarnet is a pyrophosphate analogue that inhibits viral DNA polymerases by binding to the pyrophosphate-binding site. Following intravenous infusion, CSF concentrations range from 15 to 100% of coincident plasma levels. The usual dose for serious CMV-related neurologic illness is 60 mg/kg every 8 h administered by constant infusion over 1 h. Induction therapy for 14–21 days is followed by maintenance therapy (60–120 mg/kg per day). Induction therapy may need to be extended in patients who fail to show a decline in CSF pleocytosis and a reduction in CSF CMV DNA copy number on quantitative PCR tests (where available). Approximately one-third of patients develop renal impairment during treatment, which is reversible following discontinuation of therapy in most, but not all, cases. This is often associated with elevations in serum creatinine and proteinuria and is less frequent in patients who are adequately hydrated. Many patients experience fatigue and nausea. Reduction in serum calcium, magnesium, and potassium occur in ~15% of patients and may be associated with tetany, cardiac rhythm disturbances, or seizures.

Cidofovir is a nucleotide analogue that is effective in treating CMV retinitis and equivalent or better than ganciclovir in some experimental models of murine CMV encephalitis, although data concerning its efficacy in human CMV CNS disease are limited. The usual dose is 5 mg/kg intravenously once weekly for 2 weeks, then biweekly for two or more additional doses, depending on clinical response. Patients must be prehydrated with normal saline (e.g., 1 L over 1–2 h) prior to each dose and treated with probenecid (e.g., 1 g 3 h before cidofovir and 1 g 2 and 8 h after cidofovir). Nephrotoxicity is common; the dose should be reduced if renal function deteriorates.

Intravenous ribavirin (15–25 mg/kg per day in divided doses given every 8 h) has been reported to be of benefit in isolated cases of severe encephalitis due to California encephalitis (LaCrosse) virus. Ribavirin might be of benefit for the rare patients, typically infants or young children, with severe adenovirus or rotavirus encephalitis and in patients with encephalitis due to LCMV or other arenaviruses. However, clinical trials are lacking. Hemolysis, with resulting anemia, has been the major side effect limiting therapy.

No specific antiviral therapy of proven efficacy is currently available for treatment of WNV encephalitis. Patients have been treated with μ-interferon, ribavirin, WNV-specific antisense oligonucleotides, and an Israeli IVIg preparation that contains high-titer anti-WNV antibody (Omr-IgG-am). WNV chimeric vaccines, in which WNV envelope and premembrane proteins are inserted into the background of another flavivirus, are already undergoing human clinical testing for safety and immunogenicity. Both chimeric and killed inactivated WNV vaccines have been found to be safe and effective in preventing equine WNV infection, and several effective flavivirus vaccines are already in human use, creating optimism that a safe and effective human WNV vaccine can also be developed.

SEQUELAE

There is considerable variation in the incidence and severity of sequelae in patients surviving viral encephalitis. In the case of EEE virus infection, nearly 80% of survivors have severe neurologic sequelae. At the other extreme are infections due to EBV, California encephalitis virus, and Venezuelan equine encephalitis virus, where severe sequelae are unusual. For example, approximately 5–15% of children infected with LaCrosse virus have a residual seizure disorder, and 1% have persistent hemiparesis. Detailed information about sequelae in patients with HSV encephalitis treated with acyclovir is available from the NIAID-CASG trials. Of 32 acyclovir-treated patients, 26 survived (81%). Of the 26 survivors, 12 (46%) had no or only minor sequelae, 3 (12%) were moderately impaired (gainfully employed but not functioning at their previous level), and 11 (42%) were severely impaired (requiring continuous supportive care). The incidence and severity of sequelae were directly related to the age of the patient and the level of consciousness at the time of initiation of therapy. Patients with severe neurologic impairment

(Glasgow coma score 6) at initiation of therapy either died or survived with severe sequelae. Young patients (<30 years) with good neurologic function at initiation of therapy did substantially better (100% survival, 62% with no or mild sequelae) compared with their older counterparts (>30 years; 64% survival, 57% no or mild sequelae). Some recent studies using quantitative HSV CSF PCR tests indicate that clinical outcome following treatment also correlates with the amount of HSV DNA present in CSF at the time of presentation. Many patients with WNV infection have acute sequelae, including cognitive impairment; weakness; and hyper- or hypokinetic movement disorders, including tremor, myoclonus, and parkinsonism. Improvement in these symptoms may occur over the subsequent 6–12 months, although detailed clinical studies of the duration and severity of WNV sequelae are not yet available.

SUBACUTE MENINGITIS

CLINICAL MANIFESTATIONS

Patients with subacute meningitis typically have an unrelenting headache, stiff neck, low-grade fever, and lethargy for days to several weeks before they present for evaluation. Cranial nerve abnormalities and night sweats may be present. This syndrome overlaps that of chronic meningitis, discussed in detail in Chap. 36.

ETIOLOGY

Common causative organisms include *M. tuberculosis*, *C. neoformans*, *H. capsulatum*, *C. immitis*, and *T. pallidum*. Initial infection with *M. tuberculosis* is acquired by inhalation of aerosolized droplet nuclei. Tuberculous meningitis in adults does not develop acutely from hematogenous spread of tubercle bacilli to the meninges. Rather, millet seed–size (miliary) tubercles form in the parenchyma of the brain during hematogenous dissemination of tubercle bacilli in the course of primary infection. These tubercles enlarge and are usually caseating. The propensity for a caseous lesion to produce meningitis is determined by its proximity to the subarachnoid space (SAS) and the rate at which fibrous encapsulation develops. Subependymal caseous foci cause meningitis via discharge of bacilli and tuberculous antigens into the SAS. Mycobacterial antigens produce an intense inflammatory reaction that leads to the production of a thick exudate that fills the basilar cisterns and surrounds the cranial nerves and major blood vessels at the base of the brain.

Fungal infections are typically acquired by the inhalation of airborne fungal spores. The initial pulmonary infection may be asymptomatic or present with fever, cough, sputum production, and chest pain. The pulmonary infection is often self-limited. A localized pulmonary fungal infection can then remain dormant in the lungs until there is an abnormality in cell-mediated immunity that allows the fungus to reactivate and disseminate to the CNS. The most common pathogen causing fungal meningitis is *C. neoformans*. This fungus is found worldwide in soil and bird excreta. *H. capsulatum* is endemic to the Ohio and Mississippi River valleys of the central United States and to parts of Central and South America. *C. immitis* is endemic to the desert areas of the southwest United States, northern Mexico, and Argentina.

Syphilis is a sexually transmitted disease that is manifest by the appearance of a painless chancre at the site of inoculation. *T. pallidum* invades the CNS early in the course of syphilis. Cranial nerves VII and VIII are most frequently involved.

LABORATORY DIAGNOSIS

The classic CSF abnormalities in tuberculous meningitis are as follows: (1) elevated opening pressure, (2) lymphocytic pleocytosis (10–500 cells/μL), (3) elevated protein concentration in the range of 1–5 g/L (10–500 mg/dL), and (4) decreased glucose concentration in the range of 1.1–2.2 mmol/L (20–40 mg/dL). *The combination of unrelenting headache, stiff neck, fatigue, night sweats, and fever with a CSF lymphocytic pleocytosis and a mildly decreased glucose concentration is highly suspicious for tuberculous meningitis.* The last tube of fluid collected at LP is the best tube to send for a smear for acid-fast bacilli (AFB). If there is a pellicle in the CSF or a cobweb-like clot on the surface of the fluid, AFB can best be demonstrated in a smear of the clot or pellicle. Positive smears are typically reported in only 10–40% of cases of tuberculous meningitis in adults. Cultures of CSF take 4–8 weeks to identify the organism and are positive in ~50% of adults. Culture remains the "gold standard" to make the diagnosis of tuberculous meningitis. PCR for the detection of *M. tuberculosis* DNA has a sensitivity of 70–80% but is limited at the present time by a high rate of false-positive results.

The characteristic CSF abnormalities in fungal meningitis are a mononuclear or lymphocytic pleocytosis, an increased protein concentration, and a decreased glucose concentration. There may be eosinophils in the CSF in *C. immitis* meningitis. Large volumes of CSF are often required to demonstrate the organism on India ink smear or grow the organism in culture. If spinal fluid examined by LP on two separate occasions fails to yield an organism, CSF should be obtained by high-cervical or cisternal puncture.

The cryptococcal polysaccharide antigen test is a highly sensitive and specific test for cryptococcal meningitis. A reactive CSF cryptococcal antigen test establishes the diagnosis. The detection of the histoplasma polysaccharide antigen in CSF establishes the diagnosis of a

fungal meningitis but is not specific for meningitis due to *H. capsulatum*. It may be falsely positive in coccidioidal meningitis. The CSF complement fixation antibody test is reported to have a specificity of 100% and a sensitivity of 75% for coccidioidal meningitis.

The diagnosis of syphilitic meningitis is made when a reactive serum treponemal test [fluorescent treponemal antibody absorption test (FTA-ABS) or microhemagglutination-*T. pallidum* (MHA-TP)] is associated with a CSF lymphocytic or mononuclear pleocytosis and an elevated protein concentration, or when the CSF VDRL (Venereal Disease Research Laboratory) is positive. A reactive CSF FTA-ABS is not definitive evidence of neurosyphilis. The CSF FTA-ABS can be falsely positive from blood contamination. A negative CSF VDRL does not rule out neurosyphilis. A negative CSF FTA-ABS or MHA-TP rules out neurosyphilis.

℞ Treatment: SUBACUTE MENINGITIS

Empirical therapy of tuberculous meningitis is often initiated on the basis of a high index of suspicion without adequate laboratory support. Initial therapy is a combination of isoniazid (300 mg/d), rifampin (10 mg/kg per day), pyrazinamide (30 mg/kg per day in divided doses), ethambutol (15–25 mg/kg per day in divided doses), and pyridoxine (50 mg/d). If the clinical response is good, pyrazinamide and ethambutol can be discontinued after 8 weeks and isoniazid and rifampin continued alone for the next 6–12 months. A 6-month course of therapy is acceptable, but therapy should be prolonged for 9–12 months in patients who have an inadequate resolution of symptoms of meningitis or who have positive mycobacterial cultures of CSF during the course of therapy. Dexamethasone therapy is recommended for patients who develop hydrocephalus.

Meningitis due to *C. neoformans* is treated with amphotericin B (0.7 mg/kg IV per day) or AmBisome (5 mg/kg per day), plus flucytosine (100 mg/kg per day in four divided doses) for 2 weeks or until CSF culture is sterile. This treatment is followed by an 8–10-week course of fluconazole (400–800 mg/d PO). If the CSF culture is sterile after 10 weeks of acute therapy, the dose of fluconazole is decreased to 200 mg/d for 6 months to a year. Patients with HIV infection may require indefinite maintenance therapy. Meningitis due to *H. capsulatum* is treated with amphotericin B (0.7–1.0 mg/kg per day) for 4–12 weeks. A total dose of 30 mg/kg is recommended. Therapy with amphotericin B is not discontinued until fungal cultures are sterile. After completing a course of amphotericin B, maintenance therapy with itraconazole 200 mg twice daily is initiated and continued for at least 6 months to a year. *C. immitis* meningitis is treated with either high-dose fluconazole (1000 mg daily) as monotherapy or intravenous amphotericin B (0.5–0.7 mg/kg per day) for >4 weeks. Intrathecal amphotericin B (0.25–0.75 mg/d three times weekly) may be required to eradicate the infection. Lifelong therapy with fluconazole (200–400 mg daily) is recommended to prevent relapse. AmBisome (5 mg/kg per day) or amphotericin B lipid complex (5 mg/kg per day) can be substituted for amphotericin B in patients who have or who develop significant renal dysfunction. The most common complication of fungal meningitis is hydrocephalus. Patients who develop hydrocephalus should receive a CSF diversion device. A ventriculostomy can be used until CSF fungal cultures are sterile, at which time the ventriculostomy is replaced by a ventriculoperitoneal shunt.

Syphilitic meningitis is treated with aqueous penicillin G in a dose of 3–4 million units intravenously every 4 h for 10–14 days. An alternative regimen is 2.4 million units of procaine penicillin G intramuscularly daily with 500 mg of oral probenecid four times daily for 10–14 days. Either regimen is followed with 2.4 million units of benzathine penicillin G intramuscularly once a week for 3 weeks. The standard criterion for treatment success is reexamination of the CSF. The CSF should be reexamined at 6-month intervals for 2 years. The cell count is expected to normalize within 12 months, and the VDRL titer to decrease by two dilutions or revert to nonreactive within 2 years of completion of therapy. Failure of the CSF pleocytosis to resolve or an increase in the CSF VDRL titer by two or more dilutions requires retreatment.

CHRONIC ENCEPHALITIS

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Clinical Features and Pathology

Progressive multifocal leukoencephalopathy (PML) is a progressive disorder characterized pathologically by multifocal areas of demyelination of varying size distributed throughout the brain but sparing the spinal cord and optic nerves. In addition to demyelination, there are characteristic cytologic alterations in both astrocytes and oligodendrocytes. Astrocytes are enlarged and contain hyperchromatic, deformed, and bizarre nuclei and frequent mitotic figures. Oligodendrocytes have enlarged, densely staining nuclei that contain viral inclusions formed by crystalline arrays of JC virus (JCV) particles. Patients often present with visual deficits (45%), typically a homonymous hemianopia; mental impairment (38%) (dementia, confusion, personality change); weakness, including hemi- or monoparesis; and ataxia. Seizures occur in ~20% of patients, predominantly in those with lesions abutting the cortex.

Almost all patients have an underlying immunosuppressive disorder. In recent series, the most common associated conditions were AIDS (80%), hematologic malignancies (13%), transplant recipients (5%), and chronic inflammatory diseases (2%). It has been estimated that up to 5% of AIDS patients will develop PML. There have been nearly 2 dozen cases of PML occurring in patients being treated for multiple sclerosis and inflammatory bowel disease with natalizumab, a humanized monoclonal antibody that inhibits lymphocyte trafficking into CNS and bowel mucosa by binding to α_4 integrins. Risk in these patients has been estimated at 1 PML case per 1000 treated patients after a mean of 18 months of therapy. The basic clinical and diagnostic features are similar in AIDS and non-AIDS–associated PML.

Diagnostic Studies

The diagnosis of PML is frequently suggested by MRI. MRI reveals multifocal asymmetric, coalescing white matter lesions located periventricularly, in the centrum semiovale, in the parietal-occipital region, and in the cerebellum. These lesions have increased signal on T2 and FLAIR images and decreased signal on T1-weighted images. PML lesions are classically nonenhancing (90%) but may rarely show ring enhancement, especially in more immunocompetent patients. PML lesions are not typically associated with edema or mass effect. CT scans, which are less sensitive than MRI for the diagnosis of PML, often show hypodense nonenhancing white matter lesions.

The CSF is typically normal, although mild elevation in protein and/or IgG may be found. Pleocytosis occurs in <25% of cases, is predominantly mononuclear, and rarely exceeds 25 cells/μL. PCR amplification of JCV DNA from CSF has become an important diagnostic tool. The presence of a positive CSF PCR for JCV DNA in association with typical MRI lesions in the appropriate clinical setting is diagnostic of PML, reflecting the assay's relatively high specificity (92–100%); however, sensitivity is variable. In HIV-negative patients and HIV-positive patients not receiving highly active antiviral therapy (HAART), sensitivity is likely 70–90%. In HAART-treated patients, sensitivity may be closer to 60%, reflecting the lower JCV CSF viral load in this relatively more immunocompetent group. Studies with quantitative JCV CSF PCR indicate that patients with low JCV loads (<100 copies/μL) have a generally better prognosis than those with higher viral loads. Patients with negative CSF PCR studies may require brain biopsy for definitive diagnosis. In biopsy or necropsy specimens of brain, JCV antigen and nucleic acid can be detected by immunocytochemistry, in situ hybridization, or PCR amplification. Detection of JCV antigen or genomic material should only be considered diagnostic of PML if accompanied by characteristic pathologic changes, since both antigen and genomic material have been found in the brains of normal patients.

Serologic studies are of no utility in diagnosis due to high basal seroprevalence level (>80%).

℞ Treatment: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

No effective therapy for PML is available. Intravenous and/or intrathecal cytarabine were not shown to be of benefit in a randomized controlled trial in HIV-associated PML. Another randomized controlled trial of cidofovir in HIV-associated PML also failed to show significant benefit. Some patients with HIV-associated PML have shown disease stabilization and, in rare cases, improvement associated with improvement in their immune status following institution of HAART. In HIV-positive patients treated with HAART, 1-year survival is ~50%, although up to 80% of survivors may have significant neurologic sequelae. HIV-positive patients with higher CD4 counts (>300 mm^3) and low or nondetectable HIV viral loads have a better prognosis than those with lower CD4 counts and higher viral loads.

SUBACUTE SCLEROSING PANENCEPHALITIS (SSPE)

SSPE is a rare chronic, progressive demyelinating disease of the CNS associated with a chronic nonpermissive infection of brain tissue with measles virus. The frequency has been estimated at 1 in 100,000–500,000 measles cases. An average of five cases per year are reported in the United States. The incidence has declined dramatically since the introduction of a measles vaccine. Most patients give a history of primary measles infection at an early age (2 years), which is followed after a latent interval of 6–8 years by the development of progressive neurologic disorder. Some 85% of patients are between 5 and 15 years of age at diagnosis. Initial manifestations include poor school performance and mood and personality changes. Typical signs of a CNS viral infection, including fever and headache, do not occur. As the disease progresses, patients develop progressive intellectual deterioration, focal and/or generalized seizures, myoclonus, ataxia, and visual disturbances. In the late stage of the illness, patients are unresponsive, quadriparetic, and spastic, with hyperactive tendon reflexes and extensor plantar responses.

Diagnostic Studies

MRI is often normal early, although areas of increased T2 signal develop in the white matter of the brain and brainstem as disease progresses. The EEG may initially show

only nonspecific slowing, but with disease progression, patients develop a characteristic periodic pattern with bursts of high-voltage, sharp, slow waves every 3–8 s, followed by periods of attenuated ("flat") background. The CSF is acellular with a normal or mildly elevated protein concentration and a markedly elevated gamma globulin level (>20% of total CSF protein). CSF antimeasles antibody levels are invariably elevated, and oligoclonal antimeasles antibodies are often present. Measles virus can be cultured from brain tissue using special cocultivation techniques. Viral antigen can be identified immunocytochemically, and viral genome can be detected by in situ hybridization or PCR amplification.

℞ Treatment: SUBACUTE SCLEROSING PANENCEPHALITIS

No definitive therapy for SSPE is available. Treatment with isoprinosine (Inosiplex, 100 mg/kg per day), alone or in combination with intrathecal or intraventricular alpha interferon, has been reported to prolong survival and produce clinical improvement in some patients but has never been subjected to a controlled clinical trial.

PROGRESSIVE RUBELLA PANENCEPHALITIS

This is an extremely rare disorder that primarily affects males with congenital rubella syndrome, although isolated cases have been reported following childhood rubella. After a latent period of 8–19 years, patients develop progressive neurologic deterioration. The manifestations are similar to those seen in SSPE. CSF shows a mild lymphocytic pleocytosis, slightly elevated protein concentration, markedly increased gamma globulin, and rubella virus–specific oligoclonal bands. No therapy is available. Universal prevention of both congenital and childhood rubella through the use of the available live attenuated rubella vaccine would be expected to eliminate the disease.

BRAIN ABSCESS

DEFINITION

A brain abscess is a focal, suppurative infection within the brain parenchyma, typically surrounded by a vascularized capsule. The term *cerebritis* is often employed to describe a nonencapsulated brain abscess.

EPIDEMIOLOGY

A bacterial brain abscess is a relatively uncommon intracranial infection, with an incidence of ~0.3–1.3/100,000 persons per year. Predisposing conditions include otitis media and mastoiditis, paranasal sinusitis, pyogenic infections in the chest or other body sites, penetrating head trauma or neurosurgical procedures, and dental infections. In immunocompetent individuals the most important pathogens are *Streptococcus* spp. [anaerobic, aerobic, and viridans (40%)], Enterobacteriaceae [*Proteus* spp., *E. coli* sp., *Klebsiella* spp. (25%)], anaerobes [e.g., *Bacteroides* spp., *Fusobacterium* spp. (30%)], and staphylococci (10%). In immunocompromised hosts with underlying HIV infection, organ transplantation, cancer, or immunosuppressive therapy, most brain abscesses are caused by *Nocardia* spp., *Toxoplasma gondii*, *Aspergillus* spp., *Candida* spp., and *C. neoformans*. In Latin America and in immigrants from Latin America, the most common cause of brain abscess is *Taenia solium* (neurocysticercosis). In India and the Far East, mycobacterial infection (tuberculoma) remains a major cause of focal CNS mass lesions.

ETIOLOGY

A brain abscess may develop (1) by direct spread from a contiguous cranial site of infection, such as paranasal sinusitis, otitis media, mastoiditis, or dental infection; (2) following head trauma or a neurosurgical procedure; or (3) as a result of hematogenous spread from a remote site of infection. In up to 25% of cases, no obvious primary source of infection is apparent (cryptogenic brain abscess).

Approximately one-third of brain abscesses are associated with otitis media and mastoiditis, often with an associated cholesteatoma. Otogenic abscesses occur predominantly in the temporal lobe (55–75%) and cerebellum (20–30%). In some series, up to 90% of cerebellar abscesses are otogenic. Common organisms include streptococci, *Bacteroides* spp., *Pseudomonas* spp., *Haemophilus* spp., and Enterobacteriaceae. Abscesses that develop as a result of direct spread of infection from the frontal, ethmoidal, or sphenoidal sinuses and those that occur due to dental infections are usually located in the frontal lobes. Approximately 10% of brain abscesses are associated with paranasal sinusitis, and this association is particularly strong in young males in their second and third decades of life. The most common pathogens in brain abscesses associated with paranasal sinusitis are streptococci (especially *S. milleri*), *Haemophilus* spp., *Bacteroides* spp., *Pseudomonas* spp., and *S. aureus*. Dental infections are associated with ~2% of brain abscesses, although it is often suggested that many "cryptogenic" abscesses are in fact due to dental infections. The most common pathogens in this setting are streptococci, staphylococci, *Bacteroides* spp., and *Fusobacterium* spp.

Hematogenous abscesses account for ~25% of brain abscesses. Hematogenous abscesses are often multiple, and multiple abscesses often (50%) have a hematogenous

origin. These abscesses show a predilection for the territory of the middle cerebral artery (i.e., posterior frontal or parietal lobes). Hematogenous abscesses are often located at the junction of the gray and white matter and are often poorly encapsulated. The microbiology of hematogenous abscesses is dependent on the primary source of infection. For example, brain abscesses that develop as a complication of infective endocarditis are often due to viridans streptococci or *S. aureus*. Abscesses associated with pyogenic lung infections such as lung abscess or bronchiectasis are often due to streptococci, staphylococci, *Bacteroides* spp., *Fusobacterium* spp., or Enterobacteriaceae. Abscesses that follow penetrating head trauma or neurosurgical procedures are frequently due to methicillin-resistant *S. aureus* (MRSA), *S. epidermidis*, Enterobacteriaceae, *Pseudomonas* spp., and *Clostridium* spp. Enterobacteriaceae and *P. aeruginosa* are important causes of abscesses associated with urinary sepsis. Congenital cardiac malformations that produce a right-to-left shunt, such as tetralogy of Fallot, patent ductus arteriosus, and atrial and ventricular septal defects, allow bloodborne bacteria to bypass the pulmonary capillary bed and reach the brain. Similar phenomena can occur with pulmonary arteriovenous malformations. The decreased arterial oxygenation and saturation from the right-to-left shunt and polycythemia may cause focal areas of cerebral ischemia, thus providing a nidus for microorganisms that bypassed the pulmonary circulation to multiply and form an abscess. Streptococci are the most common pathogens in this setting.

PATHOGENESIS AND HISTOPATHOLOGY

Results of experimental models of brain abscess formation suggest that for bacterial invasion of brain parenchyma to occur, there must be preexisting or concomitant areas of ischemia, necrosis, or hypoxia in brain tissue. The intact brain parenchyma is relatively resistant to infection. Once bacteria have established infection, brain abscess frequently evolves through a series of stages, influenced by the nature of the infecting organism and by the immunocompetence of the host. The early cerebritis stage (days 1–3) is characterized by a perivascular infiltration of inflammatory cells, which surround a central core of coagulative necrosis. Marked edema surrounds the lesion at this stage. In the late cerebritis stage (days 4–9), pus formation leads to enlargement of the necrotic center, which is surrounded at its border by an inflammatory infiltrate of macrophages and fibroblasts. A thin capsule of fibroblasts and reticular fibers gradually develops, and the surrounding area of cerebral edema becomes more distinct than in the previous stage. The third stage, early capsule formation (days 10–13), is characterized by the formation of a capsule that is better developed on the cortical than on the ventricular side of the lesion. This stage correlates with the appearance of a ring-enhancing capsule on neuroimaging studies. The final stage, late capsule formation (day 14 and beyond), is defined by a well-formed necrotic center surrounded by a dense collagenous capsule. The surrounding area of cerebral edema has regressed, but marked gliosis with large numbers of reactive astrocytes has developed outside the capsule. This gliotic process may contribute to the development of seizures as a sequelae of brain abscess.

CLINICAL PRESENTATION

A brain abscess typically presents as an expanding intracranial mass lesion rather than as an infectious process. Although the evolution of signs and symptoms is extremely variable, ranging from hours to weeks or even months, most patients present to the hospital 11–12 days following onset of symptoms. The classic clinical triad of headache, fever, and a focal neurologic deficit is present in <50% of cases. The most common symptom in patients with a brain abscess is headache, occurring in >75% of patients. The headache is often characterized as a constant, dull, aching sensation, either hemicranial or generalized, and it becomes progressively more severe and refractory to therapy. Fever is present in only 50% of patients at the time of diagnosis, and its absence should not exclude the diagnosis. The new onset of focal or generalized seizure activity is a presenting sign in 15–35% of patients. Focal neurologic deficits including hemiparesis, aphasia, or visual field defects are part of the initial presentation in >60% of patients.

The clinical presentation of a brain abscess depends on its location, the nature of the primary infection if present, and the level of the ICP. Hemiparesis is the most common localizing sign of a frontal lobe abscess. A temporal lobe abscess may present with a disturbance of language (dysphasia) or an upper homonymous quadrantanopia. Nystagmus and ataxia are signs of a cerebellar abscess. Signs of raised ICP—papilledema, nausea and vomiting, and drowsiness or confusion—can be the dominant presentation of some abscesses, particularly those in the cerebellum. Meningismus is not present unless the abscess has ruptured into the ventricle or the infection has spread to the subarachnoid space.

DIAGNOSIS

Diagnosis is made by neuroimaging studies. MRI (**Fig. 35-4**) is better than CT for demonstrating abscesses in the early (cerebritis) stages and is superior to CT for identifying abscesses in the posterior fossa. Cerebritis appears on MRI as an area of low-signal intensity on T1-weighted images with irregular postgadolinium enhancement and as an area of increased signal intensity on T2-weighted images. Cerebritis is

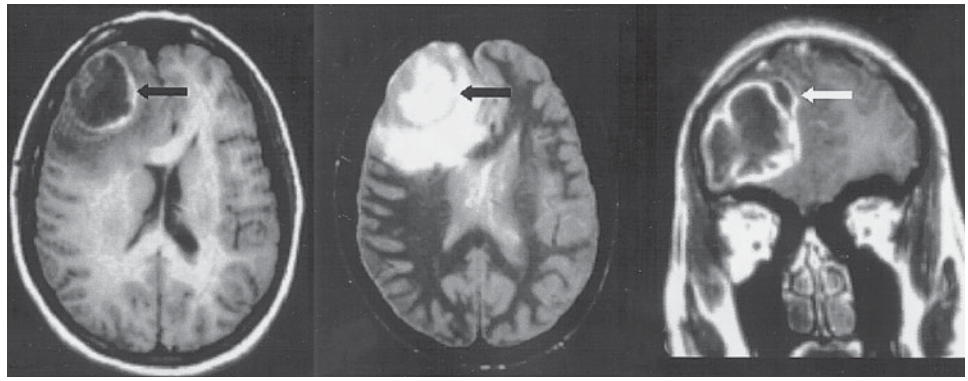


FIGURE 35-4

Pneumococcal brain abscess. Note that the abscess wall has hyperintense signal on the axial T1-weighted MRI (***A**, black arrow*), hypointense signal on the axial proton density images (***B**, black arrow*), and enhances prominently after gadolinium administration on the coronal T1-weighted image (*C*). The abscess is surrounded by a large amount of vasogenic edema and has a small "daughter" abscess (***C**, white arrow*). (*Courtesy of Joseph Lurito, MD; with permission.*)

often not visualized by CT scan but, when present, appears as an area of hypodensity. On a contrast-enhanced CT scan, a mature brain abscess appears as a focal area of hypodensity surrounded by ring enhancement with surrounding edema (hypodensity). On contrast-enhanced T1-weighted MRI, a mature brain abscess has a capsule that enhances surrounding a hypodense center and surrounded by a hypodense area of edema. On T2-weighted MRI, there is a hyperintense central area of pus surrounded by a well-defined hypointense capsule and a hyperintense surrounding area of edema. It is important to recognize that the CT and MR appearance, particularly of the capsule, may be altered by treatment with glucocorticoids. The distinction between a brain abscess and other focal CNS lesions such as primary or metastatic tumors may be facilitated by the use of diffusion-weighted imaging sequences on which brain abscesses typically show increased signal and low apparent diffusion coefficient.

Microbiologic diagnosis of the etiologic agent is most accurately determined by Gram's stain and culture of abscess material obtained by stereotactic needle aspiration. Aerobic and anaerobic bacterial cultures and mycobacterial and fungal cultures should be obtained. Up to 10% of patients will also have positive blood cultures. LP should not be performed in patients with known or suspected focal intracranial infections such as abscess or empyema; CSF analysis contributes nothing to diagnosis or therapy, and LP increases the risk of herniation.

Additional laboratory studies may provide clues to the diagnosis of brain abscess in patients with a CNS mass lesion. About 50% of patients have a peripheral leukocytosis, 60% an elevated ESR, and 80% an elevated C-reactive protein. Blood cultures are positive in ~10% of cases overall but may be positive in >85% of patients with abscesses due to *Listeria*.

DIFFERENTIAL DIAGNOSIS

Conditions that can cause headache, fever, focal neurologic signs, and seizure activity include brain abscess, subdural empyema, bacterial meningitis, viral meningoencephalitis, superior sagittal sinus thrombosis, and acute disseminated encephalomyelitis. When fever is absent, primary and metastatic brain tumors become the major differential diagnosis. Less commonly, cerebral infarction or hematoma can have an MRI or CT appearance resembling brain abscess.

℞ Treatment: BRAIN ABSCESS

Optimal therapy of brain abscesses involves a combination of high-dose parenteral antibiotics and neurosurgical drainage. Empirical therapy of community-acquired brain abscess in an immunocompetent patient typically includes a third-generation cephalosporin (e.g., cefotaxime or ceftriaxone) and metronidazole (see Table 35-1 for antibiotic dosages). In patients with penetrating head trauma or recent neurosurgical procedures, treatment should include ceftazidime as the third-generation cephalosporin to enhance coverage of *Pseudomonas* spp. and vancomycin for coverage of staphylococci. Meropenem plus vancomycin also provides good coverage in this setting.

Aspiration and drainage of the abscess under stereotactic guidance are beneficial for both diagnosis and

therapy. Empirical antibiotic coverage should be modified based on the results of Gram's stain and culture of the abscess contents. Complete excision of a bacterial abscess via craniotomy or craniectomy is generally reserved for multiloculated abscesses or those in which stereotactic aspiration is unsuccessful.

Medical therapy alone is not optimal for treatment of brain abscess and should be reserved for patients whose abscesses are neurosurgically inaccessible, for patients with small (<2–3 cm) or nonencapsulated abscesses (cerebritis), and patients whose condition is too tenuous to allow performance of a neurosurgical procedure. All patients should receive a minimum of 6–8 weeks of parenteral antibiotic therapy. The role, if any, of supplemental oral antibiotic therapy following completion of a standard course of parenteral therapy has never been adequately studied.

In addition to surgical drainage and antibiotic therapy, patients should receive prophylactic anticonvulsant therapy because of the high risk (~35%) of focal or generalized seizures. Anticonvulsant therapy is continued for at least 3 months after resolution of the abscess, and decisions regarding withdrawal are then based on the EEG. If the EEG is abnormal, anticonvulsant therapy should be continued. If the EEG is normal, anticonvulsant therapy can be slowly withdrawn, with close follow-up and repeat EEG after the medication has been discontinued.

Glucocorticoids should not be given routinely to patients with brain abscesses. Intravenous dexamethasone therapy (10 mg every 6 h) is usually reserved for patients with substantial periabscess edema and associated mass effect and increased ICP. Dexamethasone should be tapered as rapidly as possible to avoid delaying the natural process of encapsulation of the abscess.

Serial MRI or CT scans should be obtained on a monthly or twice-monthly basis to document resolution of the abscess. More frequent studies (e.g., weekly) are probably warranted in the subset of patients who are receiving antibiotic therapy alone. A small amount of enhancement may remain for months after the abscess has been successfully treated.

PROGNOSIS

The mortality of brain abscess has declined in parallel with the development of enhanced neuroimaging techniques, improved neurosurgical procedures for stereotactic aspiration, and improved antibiotics. In modern series, the mortality is typically <15%. Significant sequelae, including seizures, persisting weakness, aphasia, or mental impairment, occur in ≥20% of survivors.

NONBACTERIAL CAUSES OF INFECTIOUS FOCAL CNS LESIONS

ETIOLOGY

Neurocysticercosis is the most common parasitic disease of the CNS worldwide. Humans acquire cysticercosis by the ingestion of food contaminated with the eggs of the parasite *T. solium*. Toxoplasmosis is a parasitic disease caused by *T. gondii* and acquired from the ingestion of undercooked meat and from handling cat feces.

CLINICAL PRESENTATION

The most common manifestation of neurocysticercosis is new-onset partial seizures with or without secondary generalization. Cysticerci may develop in the brain parenchyma and cause seizures or focal neurologic deficits. When present in the subarachnoid or ventricular spaces, cysticerci can produce increased ICP by interference with CSF flow. Spinal cysticerci can mimic the presentation of intraspinal tumors. When the cysticerci first lodge in the brain, they frequently cause little in the way of an inflammatory response. As the cysticercal cyst degenerates, it elicits an inflammatory response that may present clinically as a seizure. Eventually the cyst dies, a process that may take several years and is typically associated with resolution of the inflammatory response and, often, abatement of seizures.

Primary *toxoplasma* infection is often asymptomatic. However, during this phase parasites may spread to the CNS, where they become latent. Reactivation of CNS infection is almost exclusively associated with immunocompromised hosts, particularly those with HIV infection. During this phase patients present with headache, fever, seizures, and focal neurologic deficits.

DIAGNOSIS

The lesions of neurocysticercosis are readily visualized by MRI or CT scans. Lesions with viable parasites appear as cystic lesions. The scolex can often be visualized on MRI. Lesions may appear as contrast-enhancing lesions surrounded by edema. A very early sign of cyst death is hypointensity of the vesicular fluid on T2-weighted images when compared with CSF. Parenchymal brain calcifications are the most common finding and evidence that the parasite is no longer viable. MRI findings of toxoplasmosis consist of multiple lesions in the deep white matter, the thalamus, and basal ganglia and at the gray-white junction in the cerebral hemispheres. With contrast administration, the majority of the lesions enhance in a ringed, nodular, or homogeneous pattern and are surrounded by edema. In the presence of the characteristic

neuroimaging abnormalities of *T. gondii* infection, serum IgG antibody to *T. gondii* should be obtained and, when positive, the patient should be treated.

Rx Treatment: INFECTIOUS FOCAL CNS LESIONS

Anticonvulsant therapy is initiated when the patient with neurocysticercosis presents with a seizure. There is controversy about whether or not antihelminthic therapy should be given to all patients. Such therapy does not necessarily reduce the risk of seizure recurrence. Cysticerci appearing as cystic lesions or as enhancing lesions in the brain parenchyma or in the subarachnoid space at the convexity of the cerebral hemispheres should be treated with anticysticidal therapy. Cysticidal drugs accelerate the destruction of the parasites, resulting in a faster resolution of the infection. Albendazole and praziquantel are used in the treatment of neurocysticercosis. Approximately 85% of parenchymal cysts are destroyed by a single course of albendazole, and ~75% are destroyed by a single course of praziquantel. The dose of albendazole is 15 mg/kg per day in two doses for 8 days. The dose of praziquantel is 50 mg/kg per day for 15 days, although a number of other dosage regimens are also frequently cited. Antiepileptic therapy can be stopped once the follow-up CT scan shows resolution of the lesion. Long-term antiepileptic therapy is recommended when seizures occur after resolution of edema and resorption or calcification of the degenerating cyst.

CNS toxoplasmosis is treated with a combination of sulfadiazine, 1.5–2.0 g orally qid, plus pyrimethamine, 100 mg orally to load then 75–100 mg orally qd, plus folinic acid, 10–15 mg orally qd. Folinic acid is added to the regimen to prevent megaloblastic anemia. Therapy is continued until there is no evidence of active disease on neuroimaging studies, which typically takes at least 6 weeks, and then the dose of sulfadiazine is reduced to 2–4 g/d and pyrimethamine to 50 mg/d. Clindamycin plus pyrimethamine is an alternative therapy for patients who cannot tolerate sulfadiazine, but the combination of pyrimethamine and sulfadiazine is more effective.

SUBDURAL EMPYEMA

A subdural empyema (SDE) is a collection of pus between the dura and arachnoid membranes (Fig. 35-5).

EPIDEMIOLOGY

SDE is a rare disorder that accounts for 15–25% of focal suppurative CNS infections. Sinusitis is the most common

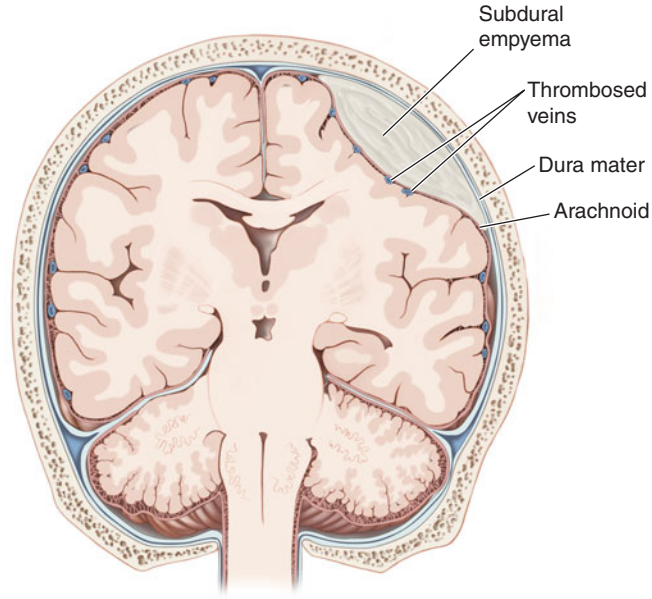


FIGURE 35-5
Subdural empyema.

predisposing condition and typically involves the frontal sinuses, either alone or in combination with the ethmoid and maxillary sinuses. Sinusitis-associated empyema has a striking predilection for young men, possibly reflecting sex-related differences in sinus anatomy and development. It has been suggested that SDE may complicate 1–2% of cases of frontal sinusitis severe enough to require hospitalization. As a consequence of this epidemiology, SDE shows an ~3:1 male:female predominance, with 70% of cases occurring in the second and third decades of life. SDE may also develop as a complication of head trauma or neurosurgery. Secondary infection of a subdural effusion may also result in empyema, although secondary infection of hematomas, in the absence of a prior neurosurgical procedure, is rare.

ETIOLOGY

Aerobic and anaerobic streptococci, staphylococci, Enterobacteriaceae, and anaerobic bacteria are the most common causative organisms of sinusitis-associated SDE. Staphylococci and gram-negative bacilli are often the etiologic organisms when SDE follows neurosurgical procedures or head trauma. Up to one-third of cases are culture-negative, possibly reflecting difficulty in obtaining adequate anaerobic cultures.

PATHOPHYSIOLOGY

Sinusitis-associated SDE develops as a result of either retrograde spread of infection from septic thrombophlebitis of

the mucosal veins draining the sinuses or contiguous spread of infection to the brain from osteomyelitis in the posterior wall of the frontal or other sinuses. SDE may also develop from direct introduction of bacteria into the subdural space as a complication of a neurosurgical procedure. The evolution of SDE can be extremely rapid because the subdural space is a large compartment that offers few mechanical barriers to the spread of infection. In patients with sinusitis-associated SDE, suppuration typically begins in the upper and anterior portions of one cerebral hemisphere and then extends posteriorly. SDE is often associated with other intracranial infections, including epidural empyema (40%), cortical thrombophlebitis (35%), and intracranial abscess or cerebritis (>25%). Cortical venous infarction produces necrosis of underlying cerebral cortex and subcortical white matter, with focal neurologic deficits and seizures (see later).

CLINICAL PRESENTATION

A patient with SDE typically presents with fever and a progressively worsening headache. The diagnosis of SDE should always be suspected in a patient with known sinusitis who presents with new CNS signs or symptoms. Patients with underlying sinusitis frequently have symptoms related to this infection. As the infection progresses, focal neurologic deficits, seizures, nuchal rigidity, and signs of increased ICP commonly occur. Headache is the most common complaint at the time of presentation; initially it is localized to the side of the subdural infection, but then it becomes more severe and generalized. Contralateral hemiparesis or hemiplegia is the most common focal neurologic deficit and can occur from the direct effects of the SDE on the cortex or as a consequence of venous infarction. Seizures begin as partial motor seizures that then become secondarily generalized. Seizures may be due to the direct irritative effect of the SDE on the underlying cortex or result from cortical venous infarction (see earlier). In untreated SDE, the increasing mass effect and increase in ICP cause progressive deterioration in consciousness, leading ultimately to coma.

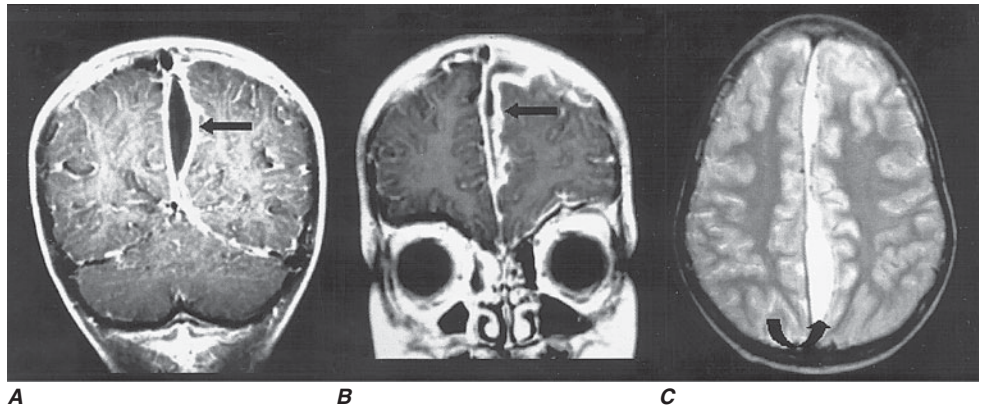
DIAGNOSIS

MRI (Fig. 35-6) is superior to CT in identifying SDE and any associated intracranial infections. The administration of gadolinium greatly improves diagnosis by enhancing the rim of the empyema and allowing the empyema to be clearly delineated from the underlying brain parenchyma. Cranial MRI is also extremely valuable in identifying sinusitis, other focal CNS infections, cortical venous infarction, cerebral edema, and cerebritis. CT may show a crescent-shaped hypodense lesion over one or both hemispheres or in the interhemispheric fissure. Frequently the degree of mass effect, exemplified by midline shift, ventricular compression, and sulcal effacement, is far out of proportion to the mass of the SDE.

CSF examination should be avoided in patients with known or suspected SDE as it adds no useful information and is associated with the risk of cerebral herniation.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the combination of headache, fever, focal neurologic signs, and seizure activity that progresses rapidly to an altered level of consciousness includes subdural hematoma, bacterial meningitis, viral encephalitis, brain abscess, superior sagittal sinus thrombosis, and acute disseminated encephalomyelitis. The presence of nuchal rigidity is unusual with brain abscess or epidural empyema and should suggest the possibility of SDE when associated with significant focal neurologic signs and fever. Patients with bacterial meningitis also have nuchal rigidity but do not typically have focal deficits of the severity seen with SDE.



A B C

FIGURE 35-6

Subdural empyema. There is marked enhancement of the dura and leptomeninges (***A***, ***B***, *straight arrows*) along the left medial hemisphere. The pus is hypointense on T1-weighted images (***A***, ***B***) but markedly hyperintense on the proton density–weighted (***C***, *curved arrow*) image. (*Courtesy of Joseph Lurito, MD; with permission.*)

℞ Treatment: SUBDURAL EMPYEMA

SDE is a medical emergency. Emergent neurosurgical evacuation of the empyema, either through burr-hole drainage or craniotomy, is the definitive step in the management of this infection. Empirical antimicrobial therapy should include a combination of a third-generation cephalosporin (e.g., cefotaxime or ceftriaxone), vancomycin, and metronidazole (Table 35-1 for dosages). Parenteral antibiotic therapy should be continued for a minimum of 4 weeks. Specific diagnosis of the etiologic organisms is made based on Gram's stain and culture of fluid obtained via either burr holes or craniotomy; the initial empirical antibiotic coverage can be modified accordingly.

PROGNOSIS

Prognosis is influenced by the level of consciousness of the patient at the time of hospital presentation, the size of the empyema, and the speed with which therapy is instituted. Long-term neurologic sequelae, which include seizures and hemiparesis, occur in up to 50% of cases.

EPIDURAL ABSCESS

Cranial epidural abscess is a suppurative infection occurring in the potential space between the inner skull table and dura (Fig. 35-7).

ETIOLOGY AND PATHOPHYSIOLOGY

Epidural abscess is less common than either brain abscess or SDE and accounts for <2% of focal suppurative CNS infections. A cranial epidural abscess develops as a complication of a craniotomy or compound skull fracture or as a result of spread of infection from the frontal sinuses, middle ear, mastoid, or orbit. An epidural abscess may develop contiguous to an area of osteomyelitis, when craniotomy is complicated by infection of the wound or bone flap, or as a result of direct infection of the epidural space. Infection in the frontal sinus, middle ear, mastoid, or orbit can reach the epidural space through retrograde spread of infection from septic thrombophlebitis in the emissary veins that drain these areas or by way of direct spread of infection through areas of osteomyelitis. Unlike the subdural space, the epidural space is really a potential rather than an actual compartment. The dura is normally tightly adherent to the inner skull table, and infection must dissect the dura away from the skull table as it spreads. As a result, epidural abscesses are often smaller than SDEs. Cranial epidural abscesses, unlike brain abscesses, only rarely result from hematogenous spread of infection from extracranial primary sites. The bacteriology of a cranial epidural abscess is similar to that of SDE (see earlier). The etiologic organisms of an epidural abscess that arises from frontal sinusitis, middle ear infections, or mastoiditis are usually streptococci or anaerobic organisms. Staphylococci or gram-negative organisms are the usual cause of an epidural abscess that develops as a complication of craniotomy or compound skull fracture.

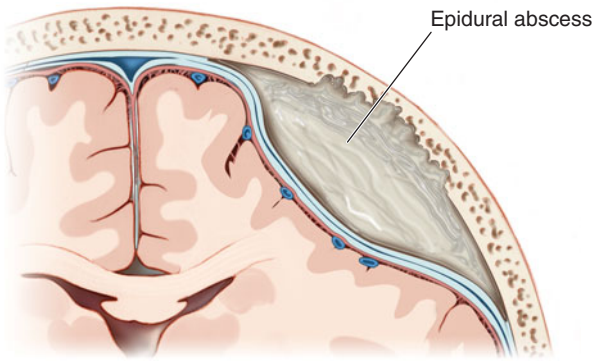


FIGURE 35-7
Cranial epidural abscess is a collection of pus between the dura and the inner table of the skull. altered mental status (45%), fever (35%), and headache (20%). The diagnosis should also be considered when fever and headache follow recent head trauma or occur in the setting of frontal sinusitis, mastoiditis, or otitis media.

CLINICAL PRESENTATION

Patients present with fever (60%), headache (40%), nuchal rigidity (35%), seizures (10%), and focal deficits (5%). Periorbital edema and Potts puffy tumor, reflecting underlying associated frontal bone osteomyelitis, are present in ~40%. In patients with a recent neurosurgical procedure, wound infection is invariably present, but other symptoms may be subtle and can include

DIAGNOSIS

Cranial MRI is the procedure of choice to demonstrate a cranial epidural abscess. The sensitivity of CT is limited by the presence of signal artifacts arising from the bone of the inner skull table. The CT appearance of an epidural empyema is that of a lens or crescent-shaped hypodense extraaxial lesion. On MRI, an epidural empyema appears as a lentiform or crescent-shaped fluid collection that is hyperintense compared to CSF on T2-weighted images. On T1-weighted images, the fluid collection has a signal intensity that is intermediate between that of brain tissue and CSF. Following the administration of gadolinium, a significant enhancement of the dura is seen on T1-weighted images. In distinction to subdural empyema, signs of mass effect or other parenchymal abnormalities are uncommon.

Rx Treatment: EPIDURAL ABSCESS

Immediate neurosurgical drainage is indicated. Empirical antimicrobial therapy, pending the results of Gram's stain and culture of the purulent material obtained at surgery, should include a combination of a third-generation cephalosporin, vancomycin, and metronidazole (Table 35-1). Ceftazidime or meropenem should be substituted for ceftriaxone or cefotaxime in neurosurgical patients. When the organism has been identified, antimicrobial therapy can be modified accordingly. Antibiotics should be continued for at least 3 weeks after surgical drainage.

PROGNOSIS

Mortality is <5% in modern series, and full recovery is the rule in most survivors.

SUPPURATIVE THROMBOPHLEBITIS

DEFINITION

Suppurative intracranial thrombophlebitis is septic venous thrombosis of cortical veins and sinuses. This may occur as a complication of bacterial meningitis; SDE; epidural abscess; or infection in the skin of the face, paranasal sinuses, middle ear, or mastoid.

ANATOMY AND PATHOPHYSIOLOGY

The cerebral veins and venous sinuses have no valves; therefore, blood within them can flow in either direction. The superior sagittal sinus is the largest of the venous sinuses (Fig. 35-8). It receives blood from the frontal, parietal, and occipital superior cerebral veins and the diploic veins, which communicate with the meningeal veins. Bacterial meningitis is a common predisposing condition for septic thrombosis of the superior sagittal sinus. The diploic veins, which drain into the superior sagittal sinus, provide a route for the spread of infection from the meninges, especially in cases where there is purulent exudate near areas of the superior sagittal sinus. Infection can also spread to the superior sagittal sinus from nearby SDE or epidural abscess. Dehydration from vomiting, hypercoagulable states, and immunologic abnormalities, including the presence of circulating antiphospholipid antibodies, also contribute to cerebral venous sinus thrombosis. Thrombosis may extend from one sinus to another, and at autopsy thrombi of different histologic ages can often be detected in several sinuses. Thrombosis of the superior sagittal sinus is often associated with thrombosis of superior cortical veins and small parenchymal hemorrhages.

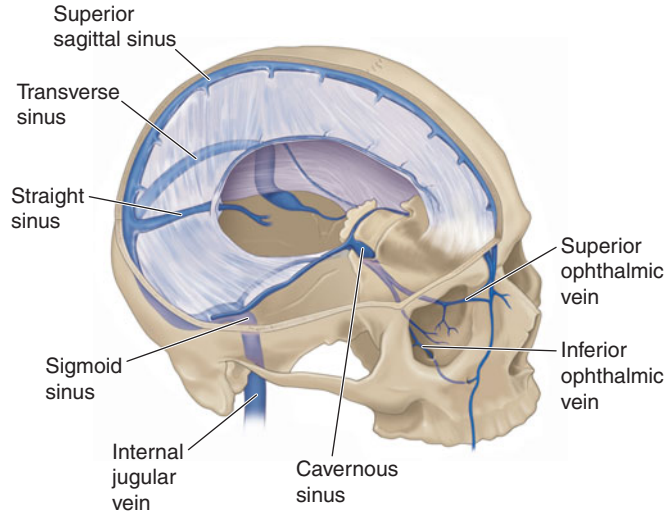


FIGURE 35-8
Anatomy of the cerebral venous sinuses.

The superior sagittal sinus drains into the transverse sinuses (Fig. 35-8). The transverse sinuses also receive venous drainage from small veins from both the middle ear and mastoid cells. The transverse sinus becomes the sigmoid sinus before draining into the internal jugular vein. Septic transverse/sigmoid sinus thrombosis can be a complication of acute and chronic otitis media or mastoiditis. Infection spreads from the mastoid air cells to the transverse sinus via the emissary veins or by direct invasion. The cavernous sinuses are inferior to the superior sagittal sinus at the base of the skull. The cavernous sinuses receive blood from the facial veins via the superior and inferior ophthalmic veins. Bacteria in the facial veins enter the cavernous sinus via these veins. Bacteria in the sphenoid and ethmoid sinuses can spread to the cavernous sinuses via the small emissary veins. The sphenoid and ethmoid sinuses are the most common sites of primary infection resulting in septic cavernous sinus thrombosis.

CLINICAL MANIFESTATIONS

Septic thrombosis of the superior sagittal sinus presents with headache, fever, nausea and vomiting, confusion, and focal or generalized seizures. There may be a rapid development of stupor and coma. Weakness of the lower extremities with bilateral Babinski signs or hemiparesis is often present. When superior sagittal sinus thrombosis occurs as a complication of bacterial meningitis, nuchal rigidity and Kernig's and Brudzinski's signs may be present.

The oculomotor nerve, the trochlear nerve, the abducens nerve, the ophthalmic and maxillary branches of the trigeminal nerve, and the internal carotid artery all pass through the cavernous sinus (Fig. 29-4). The

symptoms of *septic cavernous sinus thrombosis* are fever, headache, frontal and retroorbital pain, and diplopia. The classic signs are ptosis, proptosis, chemosis, and extraocular dysmotility due to deficits of cranial nerves III, IV, and VI; hyperesthesia of the ophthalmic and maxillary divisions of the fifth cranial nerve and a decreased corneal reflex may be detected. There may be evidence of dilated, tortuous retinal veins and papilledema.

Headache and earache are the most frequent symptoms of *transverse sinus thrombosis*. A transverse sinus thrombosis may also present with otitis media, sixth nerve palsy, and retroorbital or facial pain (*Gradinego's syndrome*). Sigmoid sinus and internal jugular vein thrombosis may present with neck pain.

DIAGNOSIS

The diagnosis of septic venous sinus thrombosis is suggested by an absent flow void within the affected venous sinus on MRI and confirmed by magnetic resonance venography, CT angiogram, or the venous phase of cerebral angiography. The diagnosis of thrombophlebitis of intracerebral and meningeal veins is suggested by the presence of intracerebral hemorrhage but requires cerebral angiography for definitive diagnosis.

℞ Treatment: SUPPURATIVE THROMBOPHLEBITIS

Septic venous sinus thrombosis is treated with antibiotics, hydration, and removal of infected tissue and thrombus in septic lateral or cavernous sinus thrombosis. The choice of antimicrobial therapy is based on the bacteria responsible for the predisposing or associated condition. Optimal duration of therapy is unknown, but antibiotics are usually continued for 6 weeks or until there is radiographic evidence of resolution of thrombosis. Anticoagulation with dose-adjusted heparin has been reported to be beneficial in patients with aseptic venous sinus thrombosis; it is also used in the treatment of septic venous sinus thrombosis complicating bacterial meningitis in patients who are worsening despite antimicrobial therapy and intravenous fluids. The presence of a small intracerebral hemorrhage from septic thrombophlebitis is not an absolute contraindication to heparin therapy. Successful management of aseptic venous sinus thrombosis has been reported with catheter-directed urokinase therapy and with a combination of intrathrombus recombinant tissue plasminogen activator (rtPA) and intravenous heparin, but there has not been enough experience with these therapies in septic venous sinus thrombosis to make recommendations regarding their use.

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CHAPTER 36

CHRONIC AND RECURRENT MENINGITIS

Walter J. Koroshetz ■ Morton N. Swartz

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Chronic inflammation of the meninges (pia, arachnoid, and dura) can produce profound neurologic disability and may be fatal if not successfully treated. The condition is most commonly diagnosed when a characteristic neurologic syndrome exists for >4 weeks and is associated with a persistent inflammatory response in the cerebrospinal fluid (CSF) (white blood cell count >5/μL). The causes are varied, and appropriate treatment depends on identification of the etiology. Five categories of disease account for most cases of chronic meningitis: (1) meningeal infections, (2) malignancy, (3) noninfectious inflammatory disorders, (4) chemical meningitis, and (5) parameningeal infections.

CLINICAL PATHOPHYSIOLOGY

Neurologic manifestations of chronic meningitis (**Table 36-1**) are determined by the anatomic location of the inflammation and its consequences. Persistent headache with or without stiff neck, hydrocephalus, cranial neuropathies, radiculopathies, and cognitive or personality changes are the cardinal features. These can occur alone or in combination. When they appear in combination, widespread dissemination of the inflammatory process along CSF pathways has occurred. In some cases, the presence of an underlying systemic illness points to a specific agent or class of agents as the probable cause. The diagnosis of chronic meningitis is usually made when the clinical presentation prompts the astute physician to examine the CSF for signs of inflammation. CSF is produced by the choroid plexus of the cerebral ventricles, exits through narrow foramina into the subarachnoid space surrounding the brain and spinal cord, circulates around the base of the brain and over the cerebral hemispheres, and is resorbed by arachnoid villi projecting into the superior sagittal sinus. CSF flow provides a pathway for rapid spread of infectious and other infiltrative processes over the brain, spinal cord, and cranial and spinal nerve roots. Spread from the subarachnoid space into brain parenchyma may occur via the arachnoid cuffs that surround blood vessels that penetrate brain tissue (Virchow-Robin spaces).

Intracranial Meningitis

Nociceptive fibers of the meninges are stimulated by the inflammatory process, resulting in headache or neck or back pain. Obstruction of CSF pathways at the foramina or arachnoid villi may produce *hydrocephalus* and symptoms of raised intracranial pressure (ICP), including headache, vomiting, apathy or drowsiness, gait instability, papilledema, visual loss, impaired upgaze, or palsy of the sixth cranial nerve (CN) (Chap. 29). Cognitive and behavioral changes during the course of chronic meningitis may also result from vascular damage, which may similarly produce seizures, stroke, or myelopathy. Inflammatory deposits seeded via the CSF circulation are often prominent around the brainstem and cranial nerves and along the undersurface of the frontal and temporal lobes. Such cases, termed *basal meningitis*, often present as multiple cranial neuropathies, with visual loss (CN II), facial weakness (CN VII), hearing loss (CN VIII),

TABLE 36-1

SYMPTOMS AND SIGNS OF CHRONIC MENINGITIS

SYMPTOM	SIGN
Chronic headache	+/– Papilledema
Neck or back pain	Brudzinski's or Kernig's sign of meningeal irritation
Change in personality	Altered mental status—drowsiness, inattention, disorientation, memory loss, frontal release signs (grasp, suck, snout), perseveration
Facial weakness	Peripheral seventh CN palsy
Double vision	Palsy of CN III, IV, VI
Visual loss	Papilledema, optic atrophy
Hearing loss	Eighth CN palsy
Arm or leg weakness	Myelopathy or radiculopathy
Numbness in arms or legs	Myelopathy or radiculopathy
Sphincter dysfunction	Myelopathy or radiculopathy Frontal lobe dysfunction (hydrocephalus)
Clumsiness	Ataxia

Note: CN, cranial nerve.

diplopia (CNs III, IV, and VI), sensory or motor abnormalities of the oropharynx (CNs IX, X, and XII), decreased olfaction (CN I), or facial sensory loss and masseter weakness (CN V).

Spinal Meningitis

Injury may occur to motor and sensory roots as they traverse the subarachnoid space and penetrate the meninges. These cases present as multiple radiculopathies with combinations of radicular pain, sensory loss, motor weakness, and sphincter dysfunction. Meningeal inflammation can encircle the cord, resulting in myelopathy. Patients with slowly progressive involvement of multiple cranial nerves and/or spinal nerve roots are likely to have chronic meningitis. Electrophysiologic testing (electromyography, nerve conduction studies, and evoked response testing) may be helpful in determining whether there is involvement of cranial and spinal nerve roots.

Systemic Manifestations

In some patients, evidence of systemic disease provides clues to the underlying cause of chronic meningitis. A careful history and physical examination are essential before embarking on a diagnostic workup, which may be costly, prolonged, and associated with risk from invasive procedures. A complete history of travel, sexual practice, and exposure to infectious agents should be sought. Infectious causes are often associated with fever, malaise, anorexia, and signs of localized or disseminated infection outside the nervous system. Infectious causes are of major concern in the immunosuppressed patient, especially in patients with AIDS, in whom chronic meningitis may present without headache or fever. Noninfectious inflammatory disorders often produce systemic manifestations, but meningitis may be the initial manifestation. Carcinomatous meningitis may or may not be accompanied by clinical evidence of the primary neoplasm.

Approach to the Patient:
CHRONIC MENINGITIS

The occurrence of chronic headache, hydrocephalus, cranial neuropathy, radiculopathy, and/or cognitive decline in a patient should prompt consideration of a lumbar puncture for evidence of meningeal inflammation. On occasion the diagnosis is made when an imaging study (CT or MRI) shows contrast enhancement of the meninges, which is always abnormal with the exception of dural enhancement after lumbar puncture, neurosurgical procedures, or spontaneous CSF leakage. Once chronic meningitis is confirmed by CSF examination, effort is focused on identifying the cause (**Tables 36-2** and **36-3**) by (1) further analysis of the CSF, (2) diagnosis of an underlying systemic infection or noninfectious inflammatory condition, or (3) pathologic examination of meningeal biopsy specimens.

Two clinical forms of chronic meningitis exist. In the first, the symptoms are chronic and persistent, whereas in the second there are recurrent, discrete episodes of illness. In the latter group, all symptoms, signs, and CSF parameters of meningeal inflammation resolve completely between episodes without specific therapy. In such patients, the likely etiologies include herpes simplex virus (HSV) type 2; chemical meningitis due to leakage into CSF of contents from an epidermoid tumor, craniopharyngioma, or cholesteatoma; primary inflammatory conditions, including Vogt-Koyanagi-Harada syndrome, Behçet's syndrome, systemic lupus erythematosus; and drug hypersensitivity with repeated administration of the offending agent.

The epidemiologic history is of considerable importance and may provide direction for selection of laboratory studies. Pertinent features include a history of tuberculosis or exposure to a likely case; past travel to areas endemic for fungal infections (the San Joaquin Valley in California and southwestern states for coccidioidomycosis, midwestern states for histoplasmosis, southeastern states for blastomycosis); travel to the Mediterranean region or ingestion of imported unpasteurized dairy products (*Brucella*); time spent in wooded areas endemic for Lyme disease;

TABLE 36-2

INFECTIOUS CAUSES OF CHRONIC MENINGITIS

CAUSATIVE AGENT	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Common Bacterial Causes			
Partially treated suppurative meningitis	Mononuclear or mixed mononuclear-polymorphonuclear cells	CSF culture and Gram stain	History consistent with acute bacterial meningitis and incomplete treatment
Parameningeal infection	Mononuclear or mixed polymorphonuclear-mononuclear cells	Contrast-enhanced CT or MRI to detect parenchymal, subdural, epidural, or sinus infection	Otitis media, pleuropulmonary infection, right-to-left cardiopulmonary shunt for brain abscess; focal neurologic signs; neck, back, ear, or sinus tenderness
Mycobacterium tuberculosis	Mononuclear cells except polymorphonuclear cells in early infection (commonly <500 WBC/μL); low CSF glucose, high protein	Tuberculin skin test may be negative; AFB culture of CSF (sputum, urine, gastric contents if indicated); tuberculostearic acid detection in CSF; identify tubercle bacillus on acid-fast stain CSF or protein pellicle; of PCR	Exposure history; previous tuberculous illness; immunosuppressed or AIDS; young children; fever, meningismus, night sweats, miliary TB on x-ray or liver biopsy; stroke due to arteritis
Lyme disease (Bannwarth's syndrome) *Borrelia burgdorferi*	Mononuclear cells; elevated protein	Serum Lyme antibody titer; Western blot confirmation; (patients with syphilis may have false-positive Lyme titer)	History of tick bite or appropriate exposure history; erythema chronicum migrans skin rash; arthritis, radiculopathy, Bell's palsy, meningoencephalitis–multiple sclerosis-like syndrome
Syphilis (secondary, tertiary) *Treponema pallidum*	Mononuclear cells; elevated protein	CSF VDRL; serum VDRL (or RPR); fluorescent treponemal antibody-absorbed (FTA) or MHA-TP; serum VDRL may be negative in tertiary syphilis	Appropriate exposure history; HIV seropositive individuals at increased risk of aggressive infection; "dementia"; cerebral infarction due to endarteritis
Uncommon Bacterial Causes			
Actinomyces	Polymorphonuclear cells	Anaerobic culture	Parameningeal abscess or sinus tract (oral or dental focus); pneumonitis
Nocardia	Polymorphonuclear; occasionally mononuclear cells; often low glucose	Isolation may require weeks; weakly acid fast	Associated brain abscess may be present
Brucella	Mononuclear cells (rarely polymorphonuclear); elevated protein; often low glucose	CSF antibody detection; serum antibody detection	Intake of unpasteurized dairy products; exposure to goats, sheep, cows; fever, arthralgia, myalgia, vertebral osteomyelitis
Whipple's disease *Tropherema whippelii*	Mononuclear cells	Biopsy of small bowel or lymph node; CSF PCR for *T. whippelii*; brain and meningeal biopsy (with PAS stain and EM examination)	Diarrhea, weight loss, arthralgias, fever; dementia, ataxia, paresis, ophthalmoplegia, oculomasticatory myoclonus
Rare Bacterial Causes			
Leptospirosis (occasionally if left untreated may last 3–4 weeks)			

TABLE 36-2 (*CONTINUED*)

INFECTIOUS CAUSES OF CHRONIC MENINGITIS

CAUSATIVE AGENT	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Fungal Causes			
Cryptococcus neoformans	Mononuclear cells; count not elevated in some patients with AIDS	India ink or fungal wet mount of CSF (budding yeast); blood and urine cultures; antigen detection in CSF	AIDS and immune suppression; pigeon exposure; skin and other organ involvement due to disseminated infection
Coccidioides immitis	Mononuclear cells (sometimes 10–20% eosinophils); often low glucose	Antibody detection in CSF and serum	Exposure history—southwestern US; increased virulence in dark-skinned races
Candida sp.	Polymorphonuclear or mononuclear	Fungal stain and culture of CSF	IV drug abuse; post surgery; prolonged intravenous therapy; disseminated candidiasis
Histoplasma capsulatum	Mononuclear cells; low glucose	Fungal stain and culture of large volumes of CSF; antigen detection in CSF, serum, and urine; antibody detection in serum, CSF	Exposure history—Ohio and central Mississippi River Valley; AIDS; mucosal lesions
Blastomyces dermatitidis	Mononuclear cells	Fungal stain and culture of CSF; biopsy and culture of skin, lung lesions; antibody detection in serum	Midwestern and southeastern USA; usually systemic infection; abscesses, draining sinus, ulcers
Aspergillus sp.	Mononuclear or polymorphonuclear	CSF culture	Sinusitis; granulocytopenia or immunosuppression
Sporothrix schenckii	Mononuclear cells	Antibody detection in CSF and serum; CSF culture	Traumatic inoculation; IV drug use; ulcerated skin lesion
Rare Fungal Causes			
Xylohypha (formerly *Cladosporium*) trichoides and other dark-walled (dematiaceous) fungi such as *Curvularia*, *Drechslera*; *Mucor*, *Pseudoallescheria boydii*			
Protozoal Causes			
Toxoplasma gondii	Mononuclear cells	Biopsy or response to empirical therapy in clinically appropriate context (including presence of antibody in serum)	Usually with intracerebral abscesses; common in HIV seropositive patients
Trypanosomiasis *Trypanosoma gambiense*, *T. rhodesiense*	Mononuclear cells, elevated protein	Elevated CSF IgM; identification of trypanosomes in CSF and blood smear	Endemic in Africa; chancre, lymphadenopathy; prominent sleep disorder
Rare Protozoal Causes			
Acanthamoeba sp. causing granulomatous amebic encephalitis and meningoencephalitis in immunocompromised and debilitated individuals			
Helminthic Causes			
Cysticercosis (infection with cysts of *Taenia solium*)	Mononuclear cells; may have eosinophils; glucose level may be low	Indirect hemagglutination assay in CSF; ELISA immunoblotting in serum	Usually with multiple cysts in basal meninges and hydrocephalus; cerebral cysts, muscle calcification

(Continued)

TABLE 36-2 (*CONTINUED*)

INFECTIOUS CAUSES OF CHRONIC MENINGITIS

CAUSATIVE AGENT	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Helminthic Causes			
Gnathostoma spinigerum	Eosinophils, mononuclear cells	Peripheral eosinophilia	History of eating raw fish; common in Thailand and Japan; subarachnoid hemorrhage; painful radiculopathy
Angiostrongylus cantonensis	Eosinophils, mononuclear cells	Recovery of worms from CSF	History of eating raw shellfish; common in tropical Pacific regions; often benign
Baylisascaris procyonis (raccoon ascarid)	Eosinophils, mononuclear cells		Infection follows accidental ingestion of *B. procyonis* eggs from raccoon feces; fatal meningoencephalitis
Rare Helminthic Causes			
Trichinella spiralis (trichinosis); *Echinococcus* cysts; *Schistosoma* sp. The former may produce a lymphocytic pleocytosis whereas the latter two may produce an eosinophilic response in CSF associated with cerebral cysts (*Echinococcus*) or granulomatous lesions of brain or spinal cord			
Viral Causes			
Mumps	Mononuclear cells	Antibody in serum	No prior mumps or immunization; may produce meningoencephalitis; may persist for 3–4 weeks
Lymphocytic choriomeningitis	Mononuclear cells	Antibody in serum	Contact with rodents or their excreta; may persist for 3–4 weeks
Echovirus	Mononuclear cells; may have low glucose	Virus isolation from CSF	Congenital hypogammaglobulinemia; history of recurrent meningitis
HIV (acute retroviral syndrome)	Mononuclear cells	p24 antigen in serum and CSF; high level of HIV viremia	HIV risk factors; rash, fever, lymphadenopathy; lymphopenia in peripheral blood; syndrome may persist long enough to be considered as "chronic meningitis"; or chronic meningitis may develop in later stages (AIDS) due to HIV
Herpes simplex (HSV)	Mononuclear cells	PCR for HSV, CMV DNA; CSF antibody for HSV, EBV	Recurrent meningitis due to HSV-2 (rarely HSV-1) often associated with genital recurrences; EBV associated with myeloradiculopathy, CMV with polyradiculopathy

Note: AFB, acid-fast bacillus; CMV, cytomegalovirus; CSF, cerebrospinal fluid; CT, computed tomography; EBV, Epstein-Barr virus; ELISA, enzyme-linked immunosorbent assay; EM, electron microscopy; FTA, fluorescent treponemal antibody absorption test; HSV, herpes simplex virus; MHA-TP, microhemagglutination assay–*T. pallidum;* MRI, magnetic resonance imaging; PAS, periodic acid–Schiff; PCR, polymerase chain reaction; RPR, rapid plasma reagin test; TB, tuberculosis; VDRL, Venereal Disease Research Laboratories test.

exposure to sexually transmitted disease (syphilis); exposure of an immunocompromised host to pigeons and their droppings (*Cryptococcus*); gardening (*Sporothrix schenkii*); ingestion of poorly cooked meat or contact with a household cat (*Toxoplasma gondii*); residence in Thailand or Japan (*Gnathostoma spinigerum*), Latin America (*Paracoccidioides brasiliiensis*), or the South Pacific (*Angiostrongylus cantonensis*); rural residence and raccoon exposure (*Baylisascaris procyonis*); and residence in Latin America, the Philippines,

TABLE 36-3

NONINFECTIOUS CAUSES OF CHRONIC MENINGITIS

CAUSATIVE AGENT	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Malignancy	Mononuclear cells, elevated protein, low glucose	Repeated cytologic examination of large volumes of CSF; CSF exam by polarizing microscopy; clonal lymphocyte markers; deposits on nerve roots or meninges seen on myelogram or contrast-enhanced MRI; meningeal biopsy	Metastatic cancer of breast, lung, stomach, or pancreas; melanoma, lymphoma, leukemia; meningeal gliomatosis; meningeal sarcoma; cerebral dysgerminoma; meningeal melanoma or B cell lymphoma
Chemical compounds (may cause recurrent meningitis)	Mononuclear or PMNs, low glucose, elevated protein; xanthochromia from subarachnoid hemorrhage in week prior to presentation with "meningitis"	Contrast-enhanced CT scan or MRI Cerebral angiogram to detect aneurysm	History of recent injection into the subarachnoid space; history of sudden onset of headache; recent resection of acoustic neuroma or craniopharyngioma; epidermoid tumor of brain or spine, sometimes with dermoid sinus tract; pituitary apoplexy
Primary inflammation			
CNS sarcoidosis	Mononuclear cells; elevated protein; often low glucose	Serum and CSF angiotensin-converting enzyme levels; biopsy of extraneural affected tissues or brain lesion/ meningeal biopsy	CN palsy, especially of CN VII; hypothalamic dysfunction, especially diabetes insipidus; abnormal chest radiograph; peripheral neuropathy or myopathy
Vogt-Koyanagi-Harada syndrome (recurrent meningitis)	Mononuclear cells		Recurrent meningoencephalitis with uveitis, retinal detachment, alopecia, lightening of eyebrows and lashes, dysacousia, cataracts, glaucoma
Isolated granulomatous angiitis of the nervous system	Mononuclear cells, elevated protein	Angiography or meningeal biopsy	Subacute dementia; multiple cerebral infarctions; recent zoster ophthalmicus
Systemic lupus erythematosus	Mononuclear or PMNs	Anti-DNA antibody, antinuclear antibodies	Encephalopathy; seizures; stroke; transverse myelopathy; rash; arthritis
Behçet's syndrome (recurrent meningitis)	Mononuclear or PMNs, elevated protein		Oral and genital aphthous ulcers; iridocyclitis; retinal hemorrhages; pathergic lesions at site of skin puncture
Chronic benign lymphocytic meningitis	Mononuclear cells		Recovery in 2–6 months, diagnosis by exclusion
Mollaret's meningitis (recurrent meningitis)	Large endothelial cells and PMNs in first hours, followed by mononuclear cells	PCR for herpes; MRI/CT to rule out epidermoid tumor or dural cyst	Recurrent meningitis; exclude HSV-2; rare cases due to HSV-1; occasional case associated with dural cyst
Drug hypersensitivity	PMNs; occasionally mononuclear cells or eosinophils		Exposure to ibuprofen, sulfonamides, isoniazid, tolmetin, ciprofloxacin, phenazopyridine; improvement after discontinuation of drug; recurrent episodes with recurrent exposure

(Continued)

TABLE 36-3 (*CONTINUED*)

NONINFECTIOUS CAUSES OF CHRONIC MENINGITIS

CAUSATIVE AGENT	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Wegener's granulomatosis	Mononuclear cells	Chest and sinus radiographs; urinalysis; ANCA antibodies in serum	Associated sinus, pulmonary, or renal lesions; CN palsies; skin lesions; peripheral neuropathy
Other: multiple sclerosis, Sjögren's syndrome, neonatal onset multisystemic inflammatory disease (NOMID), and rarer forms of vasculitis (e.g., Cogan's syndrome)			

Note: ANCA, anti-neutrophil cytoplasmic antibodies; CN, cranial nerve; CSF, cerebrospinal fluid; CT, computed tomography; HSV, herpes simplex virus; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PMNs, polymorphonuclear cells.

or Southeast Asia when eosinophilic meningitis is present (*Taenia solium*).

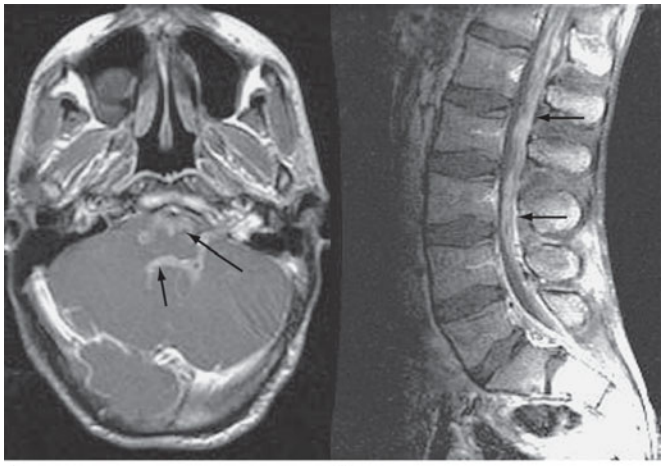
The presence of focal cerebral signs in a patient with chronic meningitis suggests the possibility of a brain abscess or other parameningeal infection; identification of a potential source of infection (chronic draining ear, sinusitis, right-to-left cardiac or pulmonary shunt, chronic pleuropulmonary infection) supports this diagnosis. In some cases, diagnosis may be established by recognition and biopsy of unusual skin lesions (Behçet's syndrome, cryptococcosis, blastomycosis, SLE, Lyme disease, IV drug use, sporotrichosis, trypanosomiasis) or enlarged lymph nodes (lymphoma, tuberculosis, sarcoid, infection with HIV, secondary syphilis, or Whipple's disease). A careful ophthalmologic examination may reveal uveitis [Vogt-Koyanagi-Harada syndrome, sarcoid, or central nervous system (CNS) lymphoma], keratoconjunctivitis sicca (Sjögren's syndrome), or iridocyclitis (Behçet's syndrome) and is essential to assess visual loss from papilledema. Aphthous oral lesions, genital ulcers, and hypopyon suggest Behçet's syndrome. Hepatosplenomegaly suggests lymphoma, sarcoid, tuberculosis, or brucellosis. Herpetic lesions in the genital area or on the thighs suggest HSV-2 infection. A breast nodule, a suspicious pigmented skin lesion, focal bone pain, or an abdominal mass directs attention to possible carcinomatous meningitis.

IMAGING Once the clinical syndrome is recognized as a potential manifestation of chronic meningitis, proper analysis of the CSF is essential. However, if the possibility of raised ICP exists, a brain imaging study should be performed before lumbar puncture. If ICP is elevated because of a mass lesion, brain swelling, or a block in ventricular CSF outflow (obstructive hydrocephalus), then lumbar puncture carries the potential risk of brain herniation. Obstructive hydrocephalus usually requires direct ventricular drainage of CSF. In patients with open CSF flow pathways, elevated ICP can still occur due to impaired resorption of CSF by arachnoid villi. In such patients, lumbar puncture is usually safe, but repetitive or continuous lumbar drainage may be necessary to prevent relatively sudden death from raised ICP. In some patients, especially those with cryptococcal meningitis, fatal levels of raised ICP can occur without enlarged ventricles.

Contrast-enhanced MRI or CT studies of the brain and spinal cord can identify meningeal enhancement, parameningeal infections (including brain abscess), encasement of the spinal cord (malignancy or inflammation and infection), or nodular deposits on the meninges or nerve roots (malignancy or sarcoidosis) (**Fig. 36-1**). Imaging studies are also useful to localize areas of meningeal disease prior to meningeal biopsy.

Cerebral angiography may be indicated in patients with chronic meningitis and stroke to identify cerebral arteritis (granulomatous angiitis, other inflammatory arteritides, or infectious arteritis).

CEREBROSPINAL FLUID ANALYSIS The CSF pressure should be measured and samples sent for bacterial, fungal, and tuberculous culture; Venereal Disease Research Laboratories (VDRL) test; cell count and differential; Gram's stain; and measurement of glucose and protein. Wet mount for fungus and parasites, India ink preparation and culture, culture for fastidious bacteria and fungi, assays for cryptococcal antigen and oligoclonal immunoglobulin bands, and cytology should be performed. Other specific CSF tests (Tables 36-2 and 36-3) or blood tests and cultures should be ordered as indicated on the basis of the history, physical examination, or preliminary CSF results (i.e., eosinophilic, mononuclear, or polymorphonuclear meningitis). Rapid diagnosis may be facilitated by serologic tests and polymerase chain reaction (PCR) testing to identify DNA sequences in the CSF that are specific for the suspected pathogen.



A B

FIGURE 36-1

Primary central nervous system lymphoma. A 24-year-old man, immunosuppressed due to intestinal lymphangiectasia, developed multiple cranial neuropathies. CSF findings consisted of 100 lymphocytes/μL and a protein of 2.5 g/L (250 mg/dL); cytology and cultures were negative. Gadolinium-enhanced T1 MRI revealed diffuse, multifocal meningeal enhancement surrounding the brainstem (***A***), spinal cord and cauda equina (***B***).

In most categories of chronic (not recurrent) meningitis, mononuclear cells predominate in the CSF. When neutrophils predominate after 3 weeks of illness, the principal etiologic considerations are *Nocardia asteroides*, *Actinomyces israelii*, *Brucella*, *Mycobacterium tuberculosis* (5–10% of early cases only), various fungi (*Blastomyces dermatitidis*, *Candida albicans*, *Histoplasma capsulatum*, *Aspergillus* spp., *Pseudallescheria boydii*, *Cladophialophora bantiana*), and noninfectious causes (SLE, exogenous chemical meningitis). When eosinophils predominate or are present in limited numbers in a primarily mononuclear cell response in the CSF, the differential diagnosis includes parasitic diseases (*A. cantonensis*, *G. spinigerum*, *B. procyonis*, or *Toxocara canis* infection, cysticercosis, schistosomiasis, echinococcal disease, *T. gondii* infection), fungal infections (6–20% eosinophils along with a predominantly lymphocyte pleocytosis, particularly with coccidioidal meningitis), neoplastic disease (lymphoma, leukemia, metastatic carcinoma), or other inflammatory processes (sarcoidosis, hypereosinophilic syndrome).

It is often necessary to broaden the number of diagnostic tests if the initial workup does not reveal the cause. In addition, repeated samples of large volumes of CSF may be required to diagnose certain infectious and malignant causes of chronic meningitis. For instance, lymphomatous or carcinomatous meningitis may be diagnosed by examination of sections cut from a cell block formed by spinning down the sediment from a large volume of CSF. The diagnosis of fungal meningitis may require large volumes of CSF for culture of sediment. If standard lumbar puncture is unrewarding, a cervical cisternal tap to sample CSF near to the basal meninges may be fruitful.

LABORATORY INVESTIGATION In addition to the CSF examination, an attempt should be made to uncover pertinent underlying illnesses. Tuberculin skin test, chest radiograph, urine analysis and culture, blood count and differential, renal and liver function tests, alkaline phosphatase, sedimentation rate, antinuclear antibody, anti-Ro, anti-La antibody and serum angiotensin-converting enzyme level are often indicated. Liver or bone marrow biopsy may be diagnostic in some cases of miliary tuberculosis, disseminated fungal infection, sarcoidosis, or metastatic malignancy. Abnormalities discovered on chest radiograph or chest CT can be pursued by bronchoscopy or transthoracic needle biopsy.

MENINGEAL BIOPSY A meningeal biopsy should be strongly considered in patients who are severely disabled, who need chronic ventricular decompression, or whose illness is progressing rapidly. The activities of the surgeon, pathologist, microbiologist, and cytologist should be coordinated so that a large enough sample is obtained and the appropriate cultures and histologic and molecular studies, including electron-microscopic and PCR studies, are performed. The diagnostic yield of meningeal biopsy can be increased by targeting regions that enhance with contrast on MRI or CT. With current microsurgical techniques, most areas of the basal meninges can be accessed for biopsy via a limited craniotomy. In a series from the Mayo Clinic reported by Cheng et al., MRI demonstrated meningeal enhancement in 47% of patients undergoing meningeal biopsy. Biopsy of an enhancing region was diagnostic in 80% of patients; biopsy of nonenhancing regions was diagnostic in only 9%; sarcoid (31%) and metastatic adenocarcinoma (25%) were the most common conditions identified. Tuberculosis is the most common condition identified in many reports from outside the United States.

APPROACH TO THE ENIGMATIC CASE In approximately one-third of patients, the diagnosis is not known despite careful evaluation of CSF and potential extraneural sites of disease. A number of the organisms that cause chronic meningitis may take weeks to be identified by cultures. In enigmatic cases several options are available, determined by the extent of the clinical deficits and rate of progression. It is prudent to wait until cultures are finalized if the patient is asymptomatic or symptoms are mild and not progressive. Unfortunately, in many patients progressive neurologic

deterioration occurs, and rapid treatment is required. Ventricular-peritoneal shunts may be placed to relieve hydrocephalus, but the risk of disseminating the undiagnosed inflammatory process into the abdomen must be considered.

EMPIRICAL TREATMENT Diagnosis of the causative agent is essential because effective therapies exist for many etiologies of chronic meningitis, but if the condition is left untreated, progressive damage to the CNS and cranial nerves and roots is likely to occur. Occasionally, empirical therapy must be initiated when all attempts at diagnosis fail. In general, empirical therapy in the United States consists of antimycobacterial agents, amphotericin for fungal infection, or glucocorticoids for noninfectious inflammatory causes. It is important to direct empirical therapy of lymphocytic meningitis at tuberculosis, particularly if the condition is associated with hypoglycorrhachia and sixth and other CN palsies, since untreated disease is fatal in 4–8 weeks. In the Mayo Clinic series, the most useful empirical therapy was administration of glucocorticoids rather than antituberculous therapy. Carcinomatous or lymphomatous meningitis may be difficult to diagnose initially, but the diagnosis becomes evident with time.

THE IMMUNOSUPPRESSED PATIENT

Chronic meningitis is not uncommon in the course of HIV infection. Pleocytosis and mild meningeal signs often occur at the onset of HIV infection, and occasionally low-grade meningitis persists. Toxoplasmosis commonly presents as intracranial abscesses and may also be associated with meningitis. Other important causes of chronic meningitis in AIDS include infection with *Cryptococcus*, *Nocardia*, *Candida*, or other fungi; syphilis; and lymphoma (Fig. 36-1). Toxoplasmosis, cryptococcosis, nocardiosis, and other fungal infections are important etiologic considerations in individuals with immunodeficiency states other than AIDS, including those due to immunosuppressive medications. Because of the increased risk of chronic meningitis and the attenuation of clinical signs of meningeal irritation in immunosuppressed individuals, CSF examination should be performed for any persistent headache or unexplained change in mental state.

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CHAPTER 37

HIV NEUROLOGY

Anthony S. Fauci ■ H. Clifford Lane

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Clinical disease of the nervous system accounts for a significant degree of morbidity in a high percentage of patients with HIV infection. Neurologic problems occur throughout the course of infection and may be inflammatory, demyelinating, or degenerative in nature. The problems fall into four basic categories: neurologic disease caused by HIV itself, HIV-related neoplasms, opportunistic infections of the nervous system, and adverse effects of medical therapy (**Table 37-1**).

AIDS CLASSIFICATION

The current U.S. Centers for Disease Control and Prevention (CDC) classification system for HIV-infected adolescents and adults categorizes persons on the basis of clinical conditions associated with HIV infection and CD4+ T lymphocyte counts. The system is based on three ranges of CD4+ T lymphocyte counts and three clinical categories and is represented by a matrix of nine mutually exclusive categories (**Tables 37-2** and **37-3**). Using this system, any HIV-infected individual with a CD4+ T cell count of <200/μL has AIDS by definition, regardless of the presence of symptoms or opportunistic diseases (Table 37-2). Once individuals have had a clinical condition in category B, their disease classification cannot be reverted back to category A, even if the condition resolves; the same holds true for category C in relation to category B.

The definition of AIDS is indeed complex and comprehensive and was established not for the practical care of patients, but for surveillance purposes. Thus, the clinician should not focus on whether or not the patient fulfills the strict definition of AIDS, but should view HIV disease as a spectrum ranging from primary infection, with or without the acute syndrome, to the asymptomatic stage, to advanced disease.

ETIOLOGIC AGENT

The etiologic agent of AIDS is HIV, which belongs to the family of human retroviruses (Retroviridae) and the subfamily of lentiviruses. Nononcogenic lentiviruses cause disease in other animal species, including sheep, horses, goats, cattle, cats, and monkeys. The four recognized human retroviruses belong to two distinct groups: the human T lymphotropic viruses (HTLV)-I and HTLV-II, which are transforming retroviruses; and the human immunodeficiency viruses, HIV-1 and HIV-2, which cause cytopathic effects either directly or indirectly. The most common cause of HIV disease throughout the world, and certainly in the United States, is HIV-1, which comprises several subtypes with different

TABLE 37-1

NEUROLOGIC DISEASES IN PATIENTS WITH HIV INFECTION

Opportunistic infections	**Myelopathy**
Toxoplasmosis	Vacuolar myelopathy
Cryptococcosis	Pure sensory ataxia
Progressive multifocal leukoencephalopathy	Paresthesia/dysesthesia
Cytomegalovirus	**Peripheral neuropathy**
Syphilis	Acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome)
Mycobacterium tuberculosis	Chronic inflammatory demyelinating polyneuropathy (CIDP)
HTLV-I infection	Mononeuritis multiplex
Neoplasms	Distal symmetric polyneuropathy
Primary CNS lymphoma	**Myopathy**
Kaposi's sarcoma	
Result of HIV-1 infection	
Aseptic meningitis	
HIV-associated neurocognitive impairment, including HIV encephalopathy/ AIDS dementia complex	

geographic distributions. HIV-2 was first identified in 1986 in West African patients and was originally confined to West Africa. However, a number of cases that can be traced to West Africa or to sexual contacts with West Africans have been identified throughout the world. Both HIV-1 and HIV-2 are zoonotic infections. The *Pan troglodytes troglodytes* species of chimpanzees has been established as the natural reservoir of HIV-1 and the most likely source of original human infection. HIV-2 is more closely related phylogenetically to the simian immunodeficiency virus (SIV) found in sooty mangabeys than it is to HIV-1.

MORPHOLOGY OF HIV

Electron microscopy shows that the HIV virion is an icosahedral structure (Fig. 37-1*A*) containing numerous external spikes formed by the two major envelope proteins, the external gp120 and the transmembrane gp41. The virion buds form the surface of the infected cell and incorporates a variety of host proteins, including major histocompatibility complex (MHC) class I and II antigens, into its lipid bilayer. The structure of HIV-1 is schematically diagrammed in Fig. 37-1*B*.

REPLICATION CYCLE OF HIV

HIV is an RNA virus whose hallmark is the reverse transcription of its genomic RNA to DNA by the enzyme *reverse transcriptase*. The replication cycle of HIV begins with the high-affinity binding of the gp120 protein via a portion of its V1 region near the N terminus to its receptor on the host cell surface, the CD4 molecule (Fig. 37-2). The CD4 molecule is a 55-kDa protein found predominantly on a subset of T lymphocytes that are responsible for helper function in the immune system. It is also expressed on the surface of monocytes/macrophages and dendritic/Langerhans cells. Once gp120 binds to CD4, the gp120 undergoes a conformational change that facilitates binding to one of a group of co-receptors. The two major co-receptors for HIV-1 are CCR5 and CXCR4. Both receptors belong to the family of seven-transmembrane-domain G protein–coupled cellular receptors, and the use of one or the other or both receptors by the virus for entry into the cell is an important determinant of the cellular tropism of the virus. Certain dendritic cells express a diversity of C-type lectin receptors on their surface, one of which is called *DC-SIGN*, that also bind with high affinity to the HIV gp120 envelope protein, allowing the dendritic cell to facilitate the binding of virus to the CD4+ T cell upon engagement of dendritic cells with CD4+ T cells. Following binding of the envelope protein to the CD4 molecule associated with the above-mentioned conformational change in the viral envelope gp120, fusion with the host cell membrane occurs via the newly exposed

TABLE 37-2

1993 REVISED CLASSIFICATION SYSTEM FOR HIV INFECTION AND EXPANDED AIDS SURVEILLANCE CASE DEFINITION FOR ADOLESCENTS AND ADULTS

	CLINICAL CATEGORIES		
CD4+ T CELL CATEGORIES	**A ASYMPTOMATIC, ACUTE (PRIMARY) HIV OR PGL[a]**	**B SYMPTOMATIC, NOT A OR C CONDITIONS**	**C AIDS-INDICATOR CONDITIONS**
>500/μL	A1	B1	C1
200–499/μL	A2	B2	C2
<200/μL	A3	B3	C3

[a]PGL, progressive generalized lymphadenopathy.
Source: MMWR 42(No. RR-17), December 18, 1992.

TABLE 37-3

CLINICAL CATEGORIES OF HIV INFECTION

Category A: Consists of one or more of the conditions listed below in an adolescent or adult (>13 years) with documented HIV infection. Conditions listed in categories B and C must not have occurred.
- Asymptomatic HIV infection
- Persistent generalized lymphadenopathy
- Acute (primary) HIV infection with accompanying illness or history of acute HIV infection

Category B: Consists of symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in clinical category C and that meet at least one of the following criteria: (1) The conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or (2) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection. Examples include, but are not limited to, the following:
- Bacillary angiomatosis
- Candidiasis, oropharyngeal (thrush)
- Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy
- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- Constitutional symptoms, such as fever (38.5°C) or diarrhea lasting >1 month
- Hairy leukoplakia, oral
- Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome
- Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease, particularly if complicated by tuboovarian abscess
- Peripheral neuropathy

Category C: Conditions listed in the AIDS surveillance case definition.
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive[a]
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (>1 month's duration); or bronchitis, pneumonia, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis, any site (pulmonarya or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis jiroveci pneumonia
- Pneumonia, recurrenta
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV

[a]Added in the 1993 expansion of the AIDS surveillance case definition.
Source: MMWR 42(No. RR-17), December 18, 1992.

gp41 molecule penetrating the plasma membrane of the target cell and then coiling upon itself to bring the virion and target cell together. Following fusion, the preintegration complex, composed of viral RNA and viral enzymes and surrounded by a capsid protein coat, is released into the cytoplasm of the target cell. As the preintegration complex traverses the cytoplasm to reach the nucleus, the viral reverse transcriptase enzyme catalyzes the reverse transcription of the genomic RNA into DNA, and the protein coat opens to release the resulting double-stranded HIV-DNA. At this point in the replication cycle, the viral genome is vulnerable to cellular factors that can block the progression of infection. In particular, the cytoplasmic TRIM5-α protein in rhesus macaque cells blocks SIV replication at a point shortly after the virus fuses with the host cell. Although the exact mechanisms of action of

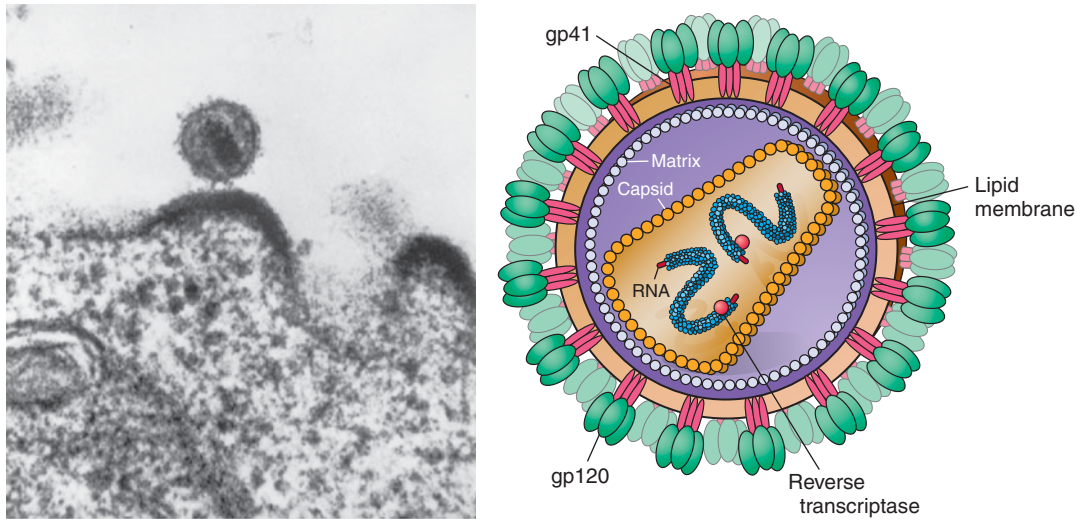

FIGURE 37-1

***A*. Electron micrograph of HIV.** Figure illustrates a typical virion following budding from the surface of a CD4+ T lymphocyte, together with two additional incomplete virions in the process of budding from the cell membrane. ***B*.** Structure of HIV-1, including the gp120 outer membrane, gp41 transmembrane components of the envelope, genomic RNA, enzyme reverse transcriptase, p18(17) inner membrane (matrix), and p24 core protein (capsid) (copyright by George V. Kelvin). *(Adapted from RC Gallo: Sci Am 256:46, 1987.)*

TRIM5-α remain unclear, the human form is inhibited by cyclophilin A and is not effective in restricting HIV replication in human cells. The recently described APOBEC family of cellular proteins also inhibits progression of virus infection after virus has entered the cell. APOBEC proteins bind to nascent reverse transcripts and deaminate viral cytidine, causing hypermutation of HIV genomes. It is still not clear whether (1) viral replication is inhibited by the binding of APOBEC to the virus genome with subsequent accumulation of reverse transcripts, or (2) by the hypermutations caused by the enzymatic deaminase activity of APOBEC proteins. HIV has evolved a powerful strategy to protect itself from APOBEC. The viral protein Vif targets APOBEC for proteasomal degradation.

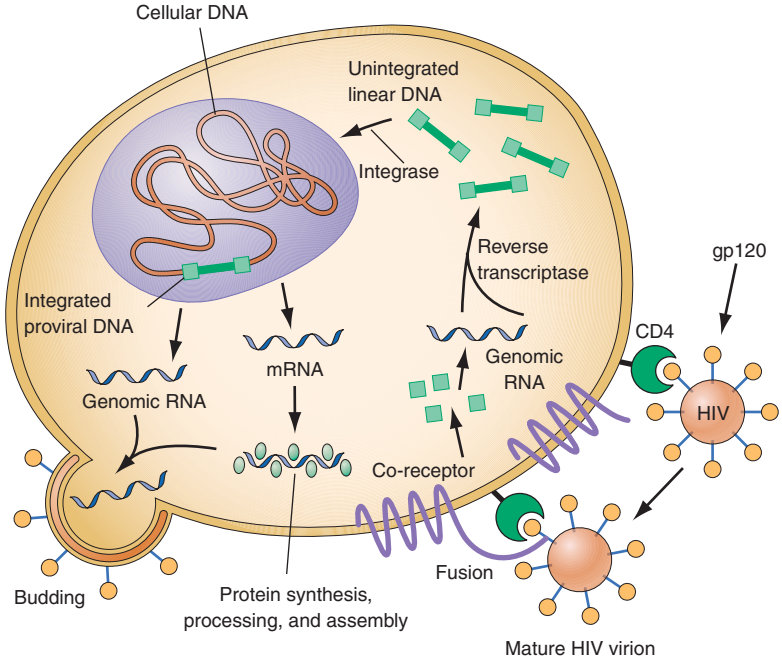

FIGURE 37-2

The replication cycle of HIV. See text for description. *(Adapted from Fauci, 1996.)*

With activation of the cell, the viral DNA accesses the nuclear pore and is exported from the cytoplasm to the nucleus, where it is integrated into the host cell chromosomes through the action of another virally encoded enzyme, *integrase*. HIV provirus (DNA) selectively integrates into the nuclear DNA preferentially within introns of active genes and regional hotspots. This provirus may remain transcriptionally inactive (latent) or it may manifest varying levels of gene expression, up to active production of virus.

Cellular activation plays an important role in the replication cycle of HIV and is critical to the pathogenesis of HIV disease. Following initial binding and internalization of virions into the target cell, incompletely reverse-transcribed DNA intermediates are labile in quiescent cells and do not integrate efficiently into the host cell genome unless cellular activation occurs shortly after infection. Furthermore, some degree of activation of the host cell is required for the initiation of transcription of the integrated proviral DNA into either genomic RNA or mRNA. This latter process may not necessarily be associated with the detectable expression of the classic cell surface markers of activation. In this regard, activation of HIV expression from the latent state depends on the interaction of a number of cellular and viral factors. Following transcription, HIV mRNA is translated into proteins that undergo modification through glycosylation, myristylation, phosphorylation, and cleavage. The viral particle is formed by the assembly of HIV proteins, enzymes, and genomic RNA at the plasma membrane of the cells. Budding of the progeny virion occurs through specialized regions in the lipid bilayer of the host cell membrane known as *lipid rafts*, where the core acquires its external envelope. The virally encoded protease then catalyzes the cleavage of the gag-pol precursor to yield the mature virion. Progression through the virus replication cycle is profoundly influenced by a variety of viral regulatory gene products. Likewise, each point in the replication cycle of HIV is a real or potential target for therapeutic intervention. Thus far, the reverse transcriptase, protease, and integrase enzymes as well as the process of virus–target cell binding and fusion have proven clinically to be susceptible to pharmacologic disruption. Inhibitors of the maturation process of virions during the latter phase of the replication cycle are currently being evaluated in clinical trials.

PATHOPHYSIOLOGY AND PATHOGENESIS

The hallmark of HIV disease is a profound immunodeficiency resulting primarily from a progressive quantitative and qualitative deficiency of the subset of T lymphocytes referred to as *helper T cells*. This subset of T cells is defined phenotypically by the presence on its surface of the CD4 molecule, which serves as the primary cellular receptor for HIV. When the number of CD4+ T cells declines below a certain level, the patient is at high risk for developing a variety of opportunistic diseases, particularly the infections and neoplasms that are AIDS-defining illnesses. Some features of AIDS, such as Kaposi sarcoma and neurologic abnormalities, cannot be explained completely by the immunosuppressive effects of HIV, since these complications may occur prior to the development of severe immunologic impairment.

NEUROPATHOGENESIS

Although there has been a remarkable decrease in the incidence of HIV encephalopathy among those with access to treatment in the era of effective ARV therapy, HIV-infected individuals can still experience a variety of neurologic abnormalities due either to opportunistic infections and neoplasms or to direct effects of HIV or its products. With regard to the latter, HIV has been demonstrated in the brain and CSF of infected individuals with and without neuropsychiatric abnormalities. The main cell types that are infected in the brain in vivo are the perivascular macrophages and the microglial cells; monocytes that have already been infected in the blood can migrate into the brain, where they then reside as macrophages, or macrophages can be directly infected within the brain. The precise mechanisms whereby HIV enters the brain are unclear; however, they are thought to relate, at least in part, to the ability of virus-infected and immune-activated macrophages to induce adhesion molecules such as E-selectin and vascular cell adhesion molecule-1 (VCAM-1) on brain endothelium. Other studies have demonstrated that HIV gp120 enhances the expression of intercellular adhesion molecule-1 (ICAM-1) in glial cells; this effect may facilitate entry of HIV-infected cells into the CNS and may promote syncytia formation. Virus isolates from the brain are preferentially R5 strains as opposed to X4 strains; in this regard, HIV-infected individuals who are heterozygous for *CCR5-Δ32* appear to be relatively protected against the development of HIV encephalopathy compared to wild-type individuals. Distinct HIV envelope sequences are associated with the clinical expression of the AIDS dementia complex. There is no convincing evidence that brain cells other than those of monocyte/macrophage lineage can be productively infected in vivo. Astrocytes have been reported to be susceptible to HIV infection in vitro despite the fact that they do not express detectable levels of cell-surface CD4 or the main HIV co-receptors. Nonetheless, they do not support active virus replication. There is no convincing evidence that oligodendrocytes or neurons can be infected with HIV (see below).

HIV-infected individuals may manifest white matter lesions as well as neuronal loss. Given the absence of evidence of HIV infection of neurons either in vivo or in vitro, it is highly unlikely that direct infection of these

cells accounts for their loss. Rather, the HIV-mediated effects on neurons and oligodendrocytes are thought to involve indirect pathways whereby viral proteins, particularly gp120 and Tat, trigger the release of endogenous neurotoxins from macrophages and to a lesser extent from astrocytes. In addition, it has been demonstrated that both HIV-1 Nef and Tat can induce chemotaxis of leukocytes, including monocytes, into the CNS. Neurotoxins can be released from monocytes as a consequence of infection and/or immune activation. Monocyte-derived neurotoxic factors have been reported to kill neurons via the *N*-methyl-d-aspartate (NMDA) receptor. In addition, HIV gp120 shed by virus-infected monocytes could cause neurotoxicity by antagonizing the function of vasoactive intestinal peptide (VIP), by elevating intracellular calcium levels, and by decreasing nerve growth factor levels in the cerebral cortex. A variety of monocyte-derived cytokines can contribute directly or indirectly to the neurotoxic effects in HIV infection; these include TNF-α, IL-1, IL-6, TGF-β, IFN-γ, platelet-activating factor, and endothelin. Furthermore, among the CC-chemokines, elevated levels of monocyte chemotactic protein (MCP)1 in the brain and CSF have been shown to correlate best with the presence and degree of HIV encephalopathy. In addition, infection and/or activation of monocyte-lineage cells can result in increased production of eicosanoids, nitric oxide, and quinolinic acid, which may contribute to neurotoxicity. Astrocytes may play diverse roles in HIV neuropathogenesis. Reactive gliosis or astrocytosis has been demonstrated in the brains of HIV-infected individuals, and TNF-α and IL-6 have been shown to induce astrocyte proliferation. In addition, astrocyte-derived IL-6 can induce HIV expression in infected cells in vitro. Furthermore, it has been suggested that astrocytes may downregulate macrophage-produced neurotoxins. It has been reported that HIV-infected individuals with the E4 allele for apolipoprotein E (apo E) are at increased risk for AIDS encephalopathy and peripheral neuropathy. The likelihood that HIV or its products are involved in neuropathogenesis is supported by the observation that neuropsychiatric abnormalities may undergo remarkable and rapid improvement upon the initiation of ARV therapy.

It has also been suggested that the CNS may serve as a relatively sequestered site for a reservoir of latently infected cells and for the slow, continual replication of HIV that might be a barrier for the eradication of virus by ARV therapy.

CLINICAL MANIFESTATIONS

The neurologic problems that occur in HIV-infected individuals may be either primary to the pathogenic processes of HIV infection or secondary to opportunistic infections or neoplasms. Among the more frequent opportunistic diseases that involve the CNS are toxoplasmosis, cryptococcosis, progressive multifocal leukoencephalopathy, and primary CNS lymphoma. Other less common problems include mycobacterial infections; syphilis; and infection with CMV, HTLV-I, *T. cruzi*, or *Acanthamoeba*. Overall, secondary diseases of the CNS occur in approximately one-third of patients with AIDS. These data antedate the widespread use of combination ARV therapy, and this frequency is considerably less in patients receiving effective ARV drugs.

NEUROLOGIC DISEASE CAUSED BY HIV

HIV-Associated Cognitve Impairment

The term *HIV-associated neurocognitive impairment* (HNCI) is used to describe a spectrum of disorders that range from asymptomatic to apparent only through extensive neuropsychiatric testing to clinically severe. The most severe form, the *AIDS dementia complex*, or *HIV encephalopathy*, is considered an AIDS-defining illness. Most HIV-infected patients have some neurologic problem during the course of their disease. As noted in the section on pathogenesis, damage to the CNS may be a direct result of viral infection of the CNS macrophages or glial cells or may be secondary to the release of neurotoxins and potentially toxic cytokines such as IL-1β, TNF-α, IL-6, and TGF-β. It has been reported that HIV-infected individuals with the E4 allele for apo E are at increased risk for AIDS encephalopathy and peripheral neuropathy. Virtually all patients with HIV infection have some degree of nervous system involvement with the virus. This is evidenced by the fact that CSF findings are abnormal in ~90% of patients, even during the asymptomatic phase of HIV infection. CSF abnormalities include pleocytosis (50–65% of patients), detection of viral RNA (~75%), elevated CSF protein (35%), and evidence of intrathecal synthesis of anti-HIV antibodies (90%). It is important to point out that evidence of infection of the CNS with HIV does not imply impairment of cognitive function. The neurologic function of an HIV-infected individual should be considered normal unless clinical signs and symptoms suggest otherwise.

HIV encephalopathy, also called HIV-associated dementia or AIDS dementia complex, consists of a constellation of signs and symptoms of CNS disease. Although this is generally a late complication of HIV infection that progresses slowly over months, it can be seen in patients with CD4+ T cell counts >350 cells/μL. A major feature of this entity is the development of dementia, defined as a decline in cognitive ability from a previous level. It may present as impaired ability to concentrate, increased forgetfulness, difficulty reading, or increased difficulty performing complex tasks. Initially these symptoms may be indistinguishable from findings of situational depression or fatigue. In contrast to "cortical" dementia (such

TABLE 37-4

CLINICAL STAGING OF HIV ENCEPHALOPATHY (AIDS DEMENTIA COMPLEX)

STAGE	DEFINITION
Stage 0 (normal)	Normal mental and motor function
Stage 0.5 (equivocal/ subclinical)	Absent, minimal, or equivocal symptoms without impairment of work or capacity to perform activities of daily living. Mild signs (snout response, slowed ocular or extremity movements) may be present. Gait and strength are normal.
Stage 1 (mild)	Able to perform all but the more demanding aspects of work or activities of daily living but with unequivocal evidence (signs or symptoms that may include performance on neuropsychological testing) of functional, intellectual, or motor impairment. Can walk without assistance.
Stage 2 (moderate)	Able to perform basic activities of self-care but cannot work or maintain the more demanding aspects of daily life. Ambulatory, but may require a single prop.
Stage 3 (severe)	Major intellectual incapacity (cannot follow news or personal events, cannot sustain complex conversation, considerable slowing of all output) or motor disability (cannot walk unassisted, usually with slowing and clumsiness of arms as well).
Stage 4 (end-stage)	Nearly vegetative. Intellectual and social comprehension and output are at a rudimentary level. Nearly or absolutely mute. Paraparetic or paraplegic with urinary and fecal incontinence.

Source: Adapted from JJ Sidtis, RW Price, Neurology 40:197, 1990.

as Alzheimer's disease), aphasia, apraxia, and agnosia are uncommon, leading some investigators to classify HIV encephalopathy as a "subcortical dementia." In addition to dementia, patients with HIV encephalopathy may also have motor and behavioral abnormalities. Among the motor problems are unsteady gait, poor balance, tremor, and difficulty with rapid alternating movements. Increased tone and deep tendon reflexes may be found in patients with spinal cord involvement. Late stages may be complicated by bowel and/or bladder incontinence. Behavioral problems include apathy and lack of initiative, with progression to a vegetative state in some instances. Some patients develop a state of agitation or mild mania. These changes usually occur without significant changes in level of alertness. This is in contrast to the finding of somnolence in patients with dementia due to toxic/metabolic encephalopathies.

HIV encephalopathy is the initial AIDS-defining illness in ~3% of patients with HIV infection and thus only rarely precedes clinical evidence of immunodeficiency. Clinically significant encephalopathy eventually develops in ~25% of patients with AIDS. As immunologic function declines, the risk and severity of HIV encephalopathy increase. Autopsy series suggest that 80–90% of patients with HIV infection have histologic evidence of CNS involvement. Several classification schemes have been developed for grading HIV encephalopathy; a commonly used clinical staging system is outlined in **Table 37-4**.

The precise cause of HIV encephalopathy remains unclear, although the condition is thought to be a result of a combination of direct effects of HIV on the CNS and associated immune activation. HIV has been found in the brains of patients with HIV encephalopathy by Southern blot, in situ hybridization, PCR, and electron microscopy. Multinucleated giant cells, macrophages, and microglial cells appear to be the main cell types harboring virus in the CNS. Histologically, the major changes are seen in the subcortical areas of the brain and include pallor and gliosis, multinucleated giant cell encephalitis, and vacuolar myelopathy. Less commonly, diffuse or focal spongiform changes occur in the white matter. Areas of the brain involved in motor, language, and judgment are most severely affected.

There are no specific criteria for a diagnosis of HIV encephalopathy, and this syndrome must be differentiated from a number of other diseases that affect the CNS of HIV-infected patients. The diagnosis of dementia depends upon demonstrating a decline in cognitive function. This can be accomplished objectively with the use of a Mini-Mental Status Examination (MMSE) in patients for whom prior scores are available. For this reason, it is advisable for all patients with a diagnosis of HIV infection to have a baseline MMSE. However,

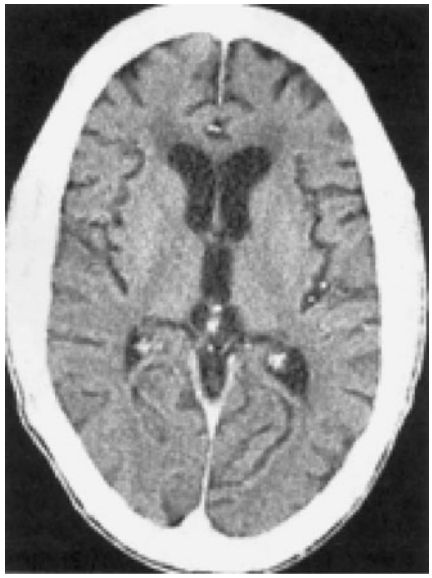

FIGURE 37-3
AIDS dementia complex. Postcontrast CT scan through the lateral ventricles of a 47-year-old man with AIDS, altered mental status, and dementia. The lateral and third ventricles and the cerebral sulci are abnormally prominent. Mild white matter hypodensity is also seen adjacent to the frontal horns of the lateral ventricles.

changes in MMSE scores may be absent in patients with mild HIV encephalopathy. Imaging studies of the CNS, by either MRI or CT, often demonstrate evidence of cerebral atrophy (Fig. 37-3). MRI may also reveal small areas of increased density on T2-weighted images. Lumbar puncture is an important element of the evaluation of patients with HIV infection and neurologic abnormalities. It is generally most helpful in ruling out or making a diagnosis of opportunistic infections. In HIV encephalopathy, patients may have the nonspecific findings of an increase in CSF cells and protein level. Although HIV RNA can often be detected in the spinal fluid and HIV can be cultured from the CSF, this finding is not specific for HIV encephalopathy. There appears to be no correlation between the presence of HIV in the CSF and the presence of HIV encephalopathy. Elevated levels of macrophage chemoattractant protein (MCP-1), β_2-microglobulin, neopterin, and quinolinic acid (a metabolite of tryptophan reported to cause CNS injury) have been noted in the CSF of patients with HIV encephalopathy. These findings suggest that these factors as well as inflammatory cytokines may be involved in the pathogenesis of this syndrome.

Combination ARV therapy is of benefit in patients with HIV encephalopathy. Improvement in neuropsychiatric test scores has been noted for both adult and pediatric patients treated with ARVs. The rapid improvement in cognitive function noted with the initiation of ARV therapy suggests that at least some component of this problem is quickly reversible, again supporting at least a partial role of soluble mediators in the pathogenesis. It should also be noted that these patients have an increased sensitivity to the side effects of neuroleptic drugs. The use of these drugs for symptomatic treatment is associated with an increased risk of extrapyramidal side effects; therefore, patients with HIV encephalopathy who receive these agents must be monitored carefully.

TABLE 37-5
CLINICAL FINDINGS IN THE ACUTE HIV SYNDROME

General	Neurologic
Fever	Meningitis
Pharyngitis	Encephalitis
Lymphadenopathy	Peripheral neuropathy
Headache/retroorbital pain	Myelopathy
Arthralgias/myalgias	**Dermatologic**
Lethargy/malaise	Erythematous maculopapular rash
Anorexia/weight loss	Mucocutaneous ulceration
Nausea/vomiting/diarrhea	

Source: From B Tindall, DA Cooper: AIDS 5:1, 1991.

Aseptic Meningitis and Encephalitis

Aseptic meningitis may be seen in any but the very late stages of HIV infection. In the setting of acute primary infection patients may experience a syndrome of headache, photophobia, and meningismus (Table 37-5). Rarely, an acute encephalopathy due to encephalitis may occur. Cranial nerve involvement may be seen, predominantly cranial nerve VII but occasionally V and/or VIII. CSF findings include a lymphocytic pleocytosis, elevated protein level, and normal glucose level. This syndrome, which cannot be clinically differentiated from other viral meningitides (Chap. 35), usually resolves spontaneously within 2–4 weeks; however, in some patients, signs and symptoms may become chronic. Aseptic meningitis may occur any time in the course of HIV infection; however, it is rare following the development of AIDS. This fact suggests that clinical aseptic meningitis in the context of HIV infection is an immune-mediated disease.

HIV Myelopathy

Spinal cord disease, or myelopathy, is present in ~20% of patients with AIDS, often as part of HIV encephalopathy. In fact, 90% of the patients with HIV-associated myelopathy have some evidence of dementia, suggesting that similar pathologic processes may be responsible for both conditions. Three main types of spinal cord disease are seen in patients with AIDS. The first of these is a vacuolar myelopathy, as discussed above under HIV encephalopathy. This condition is pathologically similar to subacute combined degeneration of the cord such as

occurs with pernicious anemia. Although vitamin B_{12} deficiency can be seen in patients with AIDS as a primary complication of HIV infection, it does not appear to be responsible for the myelopathy seen in the majority of patients. Vacuolar myelopathy is characterized by a subacute onset and often presents with gait disturbances, predominantly ataxia and spasticity; it may progress to include bladder and bowel dysfunction. Physical findings include evidence of increased deep tendon reflexes and extensor plantar responses. The second form of spinal cord disease involves the dorsal columns and presents as a pure sensory ataxia. The third form is also sensory in nature and presents with paresthesias and dysesthesias of the lower extremities. In contrast to the cognitive problems seen in patients with HIV encephalopathy, these spinal cord syndromes do not respond well to ARV drugs, and therapy is mainly supportive.

One important disease of the spinal cord that also involves the peripheral nerves is a *myelopathy* and *polyradiculopathy* seen in association with CMV infection. This entity is generally seen late in the course of HIV infection and is fulminant in onset, with lower extremity and sacral paresthesias, difficulty in walking, areflexia, ascending sensory loss, and urinary retention. The clinical course is rapidly progressive over a period of weeks. CSF examination reveals a predominantly neutrophilic pleocytosis, and CMV DNA can be detected by CSF PCR. Therapy with ganciclovir or foscarnet can lead to rapid improvement, and prompt initiation of foscarnet or ganciclovir therapy is important in minimizing the degree of permanent neurologic damage. Combination therapy with both drugs should be considered in patients who have been previously treated for CMV disease. Other diseases involving the spinal cord in patients with HIV infection include HTLV-I-associated myelopathy (HAM), neurosyphilis, infection with herpes simplex or varicella-zoster, TB, and lymphoma.

HIV Neuropathy

Peripheral neuropathies are common in patients with HIV infection. They occur at all stages of illness and take a variety of forms. Early in the course of HIV infection, an acute inflammatory demyelinating polyneuropathy resembling Guillain-Barré syndrome may occur (Chap. 41). In other patients, a progressive or relapsing-remitting inflammatory neuropathy resembling chronic inflammatory demyelinating polyneuropathy (CIDP) has been noted. Patients commonly present with progressive weakness, areflexia, and minimal sensory changes. CSF examination often reveals a mononuclear pleocytosis, and peripheral nerve biopsy demonstrates a perivascular infiltrate suggesting an autoimmune etiology. Plasma exchange or IVIg has been tried with variable success. Because of the immunosuppressive effects of glucocorticoids, they should be reserved for severe cases of CIDP refractory to other measures. Another autoimmune peripheral neuropathy seen in patients with AIDS is mononeuritis multiplex (Chap. 40) due to a necrotizing arteritis of peripheral nerves. The most common peripheral neuropathy in patients with HIV infection is a *distal sensory polyneuropathy* that may be a direct consequence of HIV infection or a side effect of dideoxynucleoside therapy. Two-thirds of patients with AIDS may be shown by electrophysiologic studies to have some evidence of peripheral nerve disease. Presenting symptoms are usually painful burning sensations in the feet and lower extremities. Findings on examination include a stocking-type sensory loss to pinprick, temperature, and touch sensation and a loss of ankle reflexes. Motor changes are mild and are usually limited to weakness of the intrinsic foot muscles. Response of this condition to ARVs has been variable, perhaps because ARVs are responsible for the problem in some instances. When due to dideoxynucleoside therapy, patients with lower extremity peripheral neuropathy may complain of a sensation that they are walking on ice. Other entities in the differential diagnosis of peripheral neuropathy include diabetes mellitus, vitamin B_{12} deficiency, and side effects from metronidazole or dapsone. For distal symmetric polyneuropathy that fails to resolve following the discontinuation of dideoxynucleosides, therapy is symptomatic; gabapentin, carbamazepine, tricyclics, or analgesics may be effective for dysesthesias. Treatment-naive patients may respond to combination ARV therapy.

HIV Myopathy

Myopathy may complicate the course of HIV infection; causes include HIV infection itself, zidovudine, and the generalized wasting syndrome. HIV-associated myopathy may range in severity from an asymptomatic elevation in creatine kinase levels to a subacute syndrome characterized by proximal muscle weakness and myalgias. Quite pronounced elevations in creatine kinase may occur in asymptomatic patients, particularly after exercise. The clinical significance of this as an isolated laboratory finding is unclear. A variety of both inflammatory and noninflammatory pathologic processes have been noted in patients with more severe myopathy, including myofiber necrosis with inflammatory cells, nemaline rod bodies, cytoplasmic bodies, and mitochondrial abnormalities. Profound muscle wasting, often with muscle pain, may be seen after prolonged zidovudine therapy. This toxic side effect of the drug is dose-dependent and is related to its ability to interfere with the function of mitochondrial polymerases. It is reversible following discontinuation of the drug. Red ragged fibers are a histologic hallmark of zidovudine-induced myopathy.

Systemic Lymphoma

Lymphomas occur with an increased frequency in patients with congenital or acquired T cell immunodeficiencies. AIDS is no exception; at least 6% of all patients with AIDS develop lymphoma at some time during the course of their illness. This is a 120-fold increase in incidence compared to the general population. In contrast to the situation with KS, primary CNS lymphoma, and most opportunistic infections, the incidence of AIDS-associated systemic lymphomas has not experienced as dramatic a decrease as a consequence of the widespread use of effective ARV therapy. Lymphoma occurs in all risk groups, with the highest incidence in patients with hemophilia and the lowest incidence in patients from the Caribbean or Africa with heterosexually acquired infection. Lymphoma is a late manifestation of HIV infection, generally occurring in patients with CD4+ T cell counts <200/μL. As HIV disease progresses, the risk of lymphoma increases. In contrast to KS, which occurs at a relatively constant rate throughout the course of HIV disease, the attack rate for lymphoma increases exponentially with increasing duration of HIV infection and decreasing level of immunologic function. At 3 years following a diagnosis of HIV infection, the risk of lymphoma is 0.8% per year; by 8 years after infection, it is 2.6% per year. As individuals with HIV infection live longer as a consequence of improved ARV therapy and better treatment and prophylaxis of opportunistic infections, it is anticipated that the incidence of lymphomas may increase.

The clinical presentation of lymphoma in patients with HIV infection is quite varied, ranging from focal seizures to rapidly growing mass lesions in the oral mucosa to persistent unexplained fever. At least 80% of patients present with extranodal disease, and a similar percentage have B-type symptoms of fever, night sweats, or weight loss. Virtually any site in the body may be involved. The most common extranodal site is the CNS, which is involved in approximately one-third of all patients with lymphoma. Approximately 60% of these cases are primary CNS lymphoma.

CNS lymphoma

Primary CNS lymphoma accounts for ~20% of the cases of lymphoma in patients with HIV infection. In contrast to HIV-associated Burkitt's lymphoma, primary CNS lymphomas are usually positive for EBV. In one study, the incidence of Epstein-Barr positivity was 100%. This malignancy does not have a predilection for any particular age group. The median CD4+ T cell count at the time of diagnosis is ~50/μL. Thus, CNS lymphoma generally presents at a later stage of HIV infection than systemic lymphoma. This fact may at least in part explain the poorer prognosis for this subset of patients.

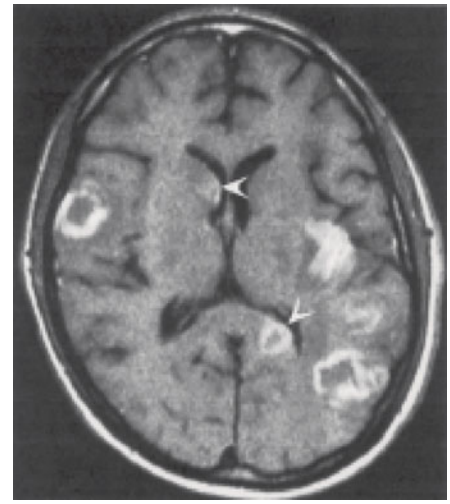

FIGURE 37-4
Central nervous system lymphoma. Postcontrast T1-weighted MR scan in a patient with AIDS, an altered mental status, and hemiparesis. Multiple enhancing lesions, some ring-enhancing, are present. The left Sylvian lesion shows gyral and subcortical enhancement, and the lesions in the caudate and splenium (*arrowheads*) show enhancement of adjacent ependymal surfaces.

Primary CNS lymphoma generally presents with focal neurologic deficits, including cranial nerve findings, headaches, and/or seizures. MRI or CT generally reveals a limited number (one to three) of 3- to 5-cm lesions (Fig. 37-4). The lesions often show ring enhancement on contrast administration and may occur in any location. Locations that are most commonly involved with CNS lymphoma are deep in the white matter. Contrast enhancement is usually less pronounced than that seen with toxoplasmosis. The main diseases in the differential diagnosis are cerebral toxoplasmosis and cerebral Chagas' disease. In addition to the 20% of lymphomas in HIV-infected individuals that are primary CNS lymphomas, CNS disease is also seen in HIV-infected patients with systemic lymphoma. Approximately 20% of patients with systemic lymphoma have CNS disease in the form of leptomeningeal involvement. This fact underscores the importance of lumbar puncture in the staging evaluation of patients with systemic lymphoma.

Systemic lymphoma is seen at earlier stages of HIV infection than primary CNS lymphoma. In one series the mean CD4+ T cell count was 189/μL. In addition to lymph node involvement, systemic lymphoma may commonly involve the gastrointestinal tract, bone marrow, liver, and lung. Gastrointestinal tract involvement is seen in ~25% of patients. Any site in the gastrointestinal tract may be involved, and patients may complain of difficulty swallowing or abdominal pain. The diagnosis is usually suspected on the basis of CT or MRI of the abdomen. Bone marrow involvement is seen in ~20% of

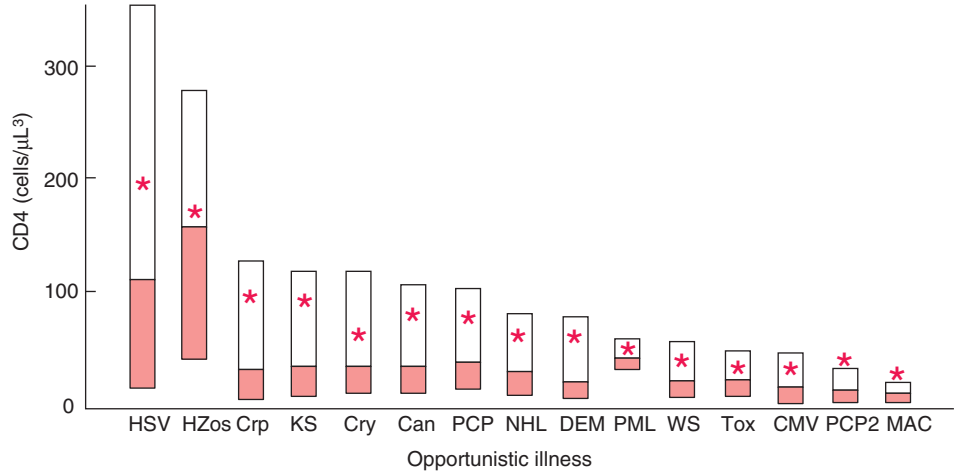

FIGURE 37-5

Relationship between CD4+ T cell counts and the development of opportunistic diseases. Boxplot of the median (line inside the box), first quartile (bottom of the box), third quartile (top of the box), and mean (asterisk) CD4+ lymphocyte count at the time of the development of opportunistic disease. Can, candidal esophagitis; CMV, cytomegalovirus infection; Crp, cryptosporidiosis; Cry, cryptococcal meningitis; DEM, AIDS dementia complex; HSV, herpes simplex virus infection; HZos, herpes zoster; KS, Kaposi's sarcoma; MAC, *Mycobacterium avium* complex bacteremia; NHL, non-Hodgkin's lymphoma; PCP, primary *Pneumocystis jiroveci* pneumonia; PCP2, secondary *P. jiroveci* pneumonia; PML, progressive multifocal leukoencephalopathy; Tox, *Toxoplasma gondii* encephalitis; WS, wasting syndrome. *(From RD Moore, RE Chaisson: Ann Intern Med 124:633, 1996.)*

patients and may lead to pancytopenia. Liver and lung involvement are each seen in ~10% of patients. Pulmonary disease may present as either a mass lesion, multiple nodules, or an interstitial infiltrate.

Both conventional and unconventional approaches have been employed in an attempt to treat HIV-related lymphomas. Systemic lymphoma is generally treated by the oncologist with combination chemotherapy. Earlier disappointing figures are being replaced with more optimistic results for the treatment of systemic lymphoma following the availability of more effective combination ARV therapy. As in most situations in patients with HIV disease, those with the higher CD4+ T cell counts tend to do better. Response rates as high as 72% with a median survival of 33 months and disease-free intervals up to 9 years have been reported. Treatment of primary CNS lymphoma remains a significant challenge. Treatment is complicated by the fact that this illness usually occurs in patients with advanced HIV disease. Palliative measures such as radiation therapy provide some relief. The prognosis remains poor in this group, with a 2-year survival of 29%.

HIV-Related Opportunistic Infections

Patients with HIV infection may present with focal neurologic deficits from a variety of causes. The most common causes are toxoplasmosis, progressive multifocal leukoencephalopathy, and CNS lymphoma. Other causes include cryptococcal infections, stroke, and reactivation Chagas' disease. A broad spectrum of opportunistic infections has been described in AIDS patients. The risk of many such infections correlates well with the CD4+ T cell count (**Figure 37-5**). A selected group of common and important opportunistic infections of the nervous system in patients with HIV is discussed below.

Cryptococcosis

C. neoformans is the leading infectious cause of meningitis in patients with AIDS. It is the initial AIDS-defining illness in ~2% of patients and generally occurs in patients with CD4+ T cell counts <100/μL. Cryptococcal meningitis is particularly common in patients with AIDS in Africa, occurring in ~20% of patients. Most patients present with a picture of subacute meningoencephalitis with fever, nausea, vomiting, altered mental status, headache, and meningeal signs. The incidence of seizures and focal neurologic deficits is low. The CSF profile may be normal or may show only modest elevations in WBC or protein levels and decreases in glucose. In addition to meningitis, patients may develop cryptococcomas and cranial nerve involvement. Approximately one-third of patients also have pulmonary disease. Uncommon manifestations of cryptococcal infection include skin lesions that resemble *molluscum contagiosum*, lymphadenopathy, palatal and glossal ulcers, arthritis, gastroenteritis, myocarditis, and prostatitis. The prostate gland may serve as a reservoir for smoldering cryptococcal infection. The diagnosis of cryptococcal meningitis is made by identification of organisms in spinal fluid with India ink examination or by the detection of cryptococcal antigen. A biopsy may be needed to make a diagnosis of CNS cryptococcoma. Treatment is with IV amphotericin B, at a dose of 0.7 mg/kg daily, with flucytosine,

25 mg/kg qid for 2 weeks, followed by fluconazole, 400 mg/d PO for 10 weeks, and then fluconazole, 200 mg/d until the CD4+ T cell count has increased to >200 cells/μL for 6 months in response to HAART. Repeated lumbar puncture may be required to manage increased intracranial pressure. Symptoms may recur with initiation of HAART as an immune reconstitution syndrome. Other fungi that may cause meningitis in patients with HIV infection are *C. immitis* and *H. capsulatum*. Meningoencephalitis has also been reported due to *Acanthamoeba* or *Naegleria*.

Toxoplasmosis

Toxoplasmosis has been one of the most common causes of secondary CNS infections in patients with AIDS, but its incidence is decreasing in the era of HAART. It is most common in patients from the Caribbean and from France. Toxoplasmosis is generally a late complication of HIV infection and usually occurs in patients with CD4+ T cell counts <200/μL. Cerebral toxoplasmosis is thought to represent a reactivation syndrome. It is 10 times more common in patients with antibodies to the organism than in patients who are seronegative. Patients diagnosed with HIV infection should be screened for IgG antibodies to *T. gondii* during the time of their initial workup. Those who are seronegative should be counseled about ways to minimize the risk of primary infection including avoiding the consumption of undercooked meat and careful hand washing after contact with soil or changing the cat litter box. The most common clinical presentation of cerebral toxoplasmosis in patients with HIV infection is fever, headache, and focal neurologic deficits. Patients may present with seizure, hemiparesis, or aphasia as a manifestation of these focal deficits or with a picture more influenced by the accompanying cerebral edema and characterized by confusion, dementia, and lethargy, which can progress to coma. The diagnosis is usually suspected on the basis of MRI findings of multiple lesions in multiple locations, although in some cases only a single lesion is seen. Pathologically, these lesions generally exhibit inflammation and central necrosis and, as a result, demonstrate ring enhancement on contrast MRI (**Fig. 37-6**) or, if MRI is unavailable or contraindicated, on double-dose contrast CT. There is usually evidence of surrounding edema. In addition to toxoplasmosis, the differential diagnosis of single or multiple enhancing mass lesions in the HIV-infected patient includes primary CNS lymphoma (see below) and, less commonly, TB or fungal or bacterial abscesses. The definitive diagnostic procedure is brain biopsy. However, given the morbidity than can accompany this procedure, it is usually reserved for the patient who has failed 2–4 weeks of empirical therapy. If the patient is seronegative for *T. gondii*, the likelihood that a mass lesion is due to toxoplasmosis is <10%. In that setting, one may choose to be more aggressive and perform a brain biopsy sooner. Standard treatment is

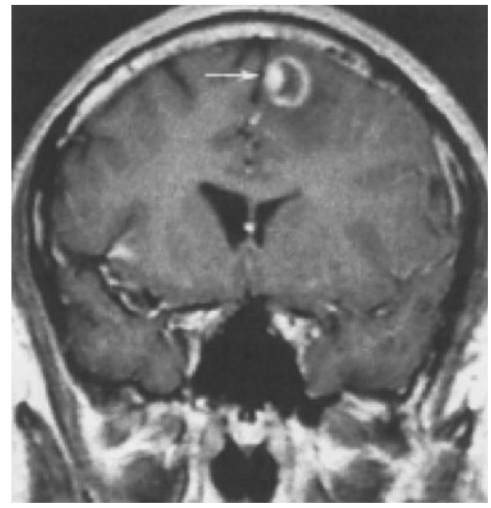

FIGURE 37-6

Central nervous system toxoplasmosis. A coronal post-contrast T1-weighted MR scan demonstrates a peripheral enhancing lesion in the left frontal lobe, associated with an eccentric nodular area of enhancement (*arrow*); this so-called eccentric target sign is typical of toxoplasmosis.

sulfadiazine and pyrimethamine with leucovorin as needed for a minimum of 4–6 weeks. Alternative therapeutic regimens include clindamycin in combination with pyrimethamine; atovaquone plus pyrimethamine; and azithromycin plus pyrimethamine plus rifabutin. Relapses are common, and it is recommended that patients with a history of prior toxoplasmic encephalitis receive maintenance therapy with sulfadiazine, pyrimethamine, and leucovorin as long as their CD4+ T cell counts remain <200 cells/μL. Patients with CD4+ T cell counts <100/μL and IgG antibody to *Toxoplasma* should receive primary prophylaxis for toxoplasmosis. Fortunately, the same daily regimen of a single double-strength tablet of TMP/SMX used for *P. jiroveci* prophylaxis provides adequate primary protection against toxoplasmosis. Secondary prophylaxis/maintenance therapy for toxoplasmosis may be discontinued in the setting of effective ARV therapy and increases in CD4+ T cell counts to >200/μL for 6 months.

Progressive Multifocal Leukoencephalopathy (PML)

JC virus, a human polyomavirus that is the etiologic agent of *progressive multifocal leukoencephalopathy* (PML), is an important opportunistic pathogen in patients with AIDS. Although ~70% of the general adult population have antibodies to JC virus, indicative of prior infection, <10% of healthy adults show any evidence of ongoing viral replication. PML is the only known clinical manifestation of JC virus infection. It is a late manifestation of AIDS and is seen in ~4% of patients with AIDS. The lesions of PML begin as small foci of demyelination in

subcortical white matter that eventually coalesce. The cerebral hemispheres, cerebellum, and brainstem may all be involved. Patients typically have a protracted course with multifocal neurologic deficits, with or without changes in mental status. Approximately 20% of patients experience seizures. Ataxia, hemiparesis, visual field defects, aphasia, and sensory defects may occur. MRI typically reveals multiple, nonenhancing white matter lesions that may coalesce and have a predilection for the occipital and parietal lobes. The lesions show signal hyperintensity on T2-weighted images and diminished signal on T1-weighted images. The measurement of JC virus DNA levels in CSF has a diagnostic sensitivity of 76% and a specificity of close to 100%. Prior to the availability of potent ARV combination therapy, the majority of patients with PML died within 3–6 months of the onset of symptoms. Paradoxical worsening of PML has been seen with initiation of HAART as an immune reconstitution syndrome. There is no specific treatment for PML; however, a minimal median survival of 18 months and survival of >7 years have been reported in patients with PML treated with HAART for their HIV disease. Unfortunately only ~50% of patients with HIV infection and PML show neurologic improvement with HAART. Studies with other antiviral agents such as cidofovir have failed to show clear benefit. Factors influencing a favorable prognosis for PML in the setting of HIV infection include a CD4+ T cell count >100/μL at baseline and the ability to maintain an HIV viral load of <500 copies per mL. Baseline HIV-1 viral load does not have independent predictive value of survival. PML is one of the few opportunistic infections that continues to occur with some frequency despite the widespread use of HAART.

Chagas' Disease

Reactivation American trypanosomiasis may present as acute meningoencephalitis with focal neurologic signs, fever, headache, vomiting, and seizures. In South America, reactivation of *Chagas' disease* is considered to be an AIDS-defining condition and may be the initial AIDS-defining condition. Lesions appear radiographically as single or multiple hypodense areas, typically with ring enhancement and edema. They are found predominantly in the subcortical areas, a feature that differentiates them from the deeper lesions of toxoplasmosis. *Trypanosoma cruzi* amastigotes, or trypanosomes, can be identified from biopsy specimens or CSF. Other CSF findings include elevated protein and a mild (<100 cells/μL) lymphocytic pleocytosis. Organisms can also be identified by direct examination of the blood. Treatment consists of benzimidazole (2.5 mg/kg bid) or nifurtimox (2 mg/kg qid) for at least 60 days, followed by maintenance therapy for the duration of immunodeficiency with either drug at a dose of 5 mg/kg three times a week. As is the case with cerebral toxoplasmosis, successful therapy with ARVs may allow discontinuation of therapy for Chagas' disease.

SPECIFIC NEUROLOGIC PRESENTATIONS

Stroke

Stroke may occur in patients with HIV infection. In contrast to the other causes of focal neurologic deficits in patients with HIV infection, the symptoms of a stroke are sudden in onset. Among the secondary infectious diseases in patients with HIV infection that may be associated with stroke are vasculitis due to cerebral varicella zoster or neurosyphilis and septic embolism in association with fungal infection. Other elements of the differential diagnosis of stroke in the patient with HIV infection include atherosclerotic cerebral vascular disease, thrombotic thrombocytopenic purpura, and cocaine or amphetamine use.

Seizures

Seizures may be a consequence of opportunistic infections, neoplasms, or HIV encephalopathy (Table 37-6). The seizure threshold is often lower than normal in

TABLE 37-6

CAUSES OF SEIZURES IN PATIENTS WITH HIV INFECTION

DISEASE	OVERALL CONTRIBUTION TO FIRST SEIZURE, %	FRACTION OF PATIENTS WHO HAVE SEIZURES, %
HIV encephalopathy	24–47	7–50
Cerebral toxoplasmosis	28	15–40
Cryptococcal meningitis	13	8
Primary central nervous system lymphoma	4	15–30
Progressive multifocal leukoencephalopathy	1	

Source: From DM Holtzman et al: Am J Med 87:173, 1989.

patients with advanced HIV infection due to the frequent presence of electrolyte abnormalities. Seizures are seen in 15–40% of patients with cerebral toxoplasmosis, 15–35% of patients with primary CNS lymphoma, 8% of patients with cryptococcal meningitis, and 7–50% of patients with HIV encephalopathy. Seizures may also be seen in patients with CNS tuberculosis, aseptic meningitis, and progressive multifocal leukoencephalopathy. Seizures may be the presenting clinical symptom of HIV disease. In one study of 100 patients with HIV infection presenting with a first seizure, cerebral mass lesions were the most common cause, responsible for 32 of the 100 new-onset seizures. Of these 32 cases, 28 were due to toxoplasmosis and 4 to lymphoma. HIV encephalopathy accounted for an additional 24 new-onset seizures. Cryptococcal meningitis was the third most common diagnosis, responsible for 13 of the 100 seizures. In 23 cases, no cause could be found, and it is possible that these cases represent a subcategory of HIV encephalopathy. Of these 23 cases, 16 (70%) had two or more seizures, suggesting that anticonvulsant therapy is indicated in all patients with HIV infection and seizures unless a rapidly correctable cause is found. While phenytoin remains the initial treatment of choice, hypersensitivity reactions to this drug have been reported in >10% of patients with AIDS, and therefore the use of phenobarbital or valproic acid must be considered as alternatives.

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CHAPTER 38

PRION DISEASES

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Prions are infectious proteins that cause degeneration of the central nervous system (CNS). Prion diseases are disorders of protein conformation, the most common of which in humans is called Creutzfeldt-Jakob disease (CJD). CJD typically presents with dementia and myoclonus, is relentlessly progressive, and generally causes death within a year of onset. Most CJD patients are between 50 and 75 years of age; however, patients as young as 17 and as old as 83 have been recorded.

In mammals, prions reproduce by binding to the normal, cellular isoform of the *pr*ion protein (PrP^C) and stimulating conversion of PrP^C into the disease-causing isoform (PrP^{Sc}). PrP^C is rich in α-helix and has little β-structure, while PrP^{Sc} has less α-helix and a high amount of β-structure (**Fig. 38-1**). This α-to-β structural transition in the prion protein (PrP) is the fundamental event underlying prion diseases (**Table 38-1**).

Four new concepts have emerged from studies of prions: (1) Prions are the only known infectious pathogens that are devoid of nucleic acid; all other infectious agents possess genomes composed of either RNA or DNA that direct the synthesis of their progeny. (2) Prion diseases may be manifest as infectious, genetic, and sporadic disorders; no other group of illnesses with a single etiology presents with such a wide spectrum of clinical manifestations. (3) Prion diseases result from the accumulation of PrP^{Sc}, the conformation of which differs substantially from that of its precursor, PrP^C. (4) PrP^{Sc} can exist in a variety of different conformations, each of which seems to specify a particular disease phenotype. How a specific conformation of a PrP^{Sc} molecule is imparted to PrP^C during prion replication to produce nascent PrP^{Sc} with the same conformation is unknown. Additionally, it is unclear what factors determine where in the CNS a particular PrP^{Sc} molecule will be deposited.

SPECTRUM OF PRION DISEASES

The sporadic form of CJD is the most common prion disorder in humans. Sporadic CJD (sCJD) accounts for ~85% of all cases of human prion disease, while inherited prion diseases account for 10–15% of all cases (**Table 38-2**). Familial CJD (fCJD), Gerstmann-Sträussler-Scheinker (GSS) disease, and fatal familial insomnia (FFI) are all dominantly inherited prion diseases that are caused by mutations in the PrP gene. Although infectious prion diseases account for <1% of all cases and infection does not seem to play an important role in the natural history of these illnesses, the transmissibility of prions is an important biologic feature. *Kuru* of the Fore people of New Guinea is thought to have resulted from the consumption of brains from dead relatives during ritualistic cannibalism. With the cessation of ritualistic cannibalism in the late 1950s, kuru has nearly disappeared, with the

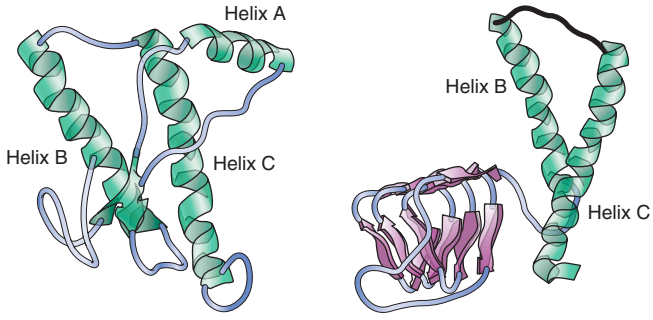

FIGURE 38-1

Structures of prion proteins. *A*. NMR structure of Syrian hamster recombinant (rec) PrP(90–231). Presumably, the structure of the α-helical form of recPrP(90–231) resembles that of PrP^C. recPrP(90–231) is viewed from the interface where PrP^{Sc} is thought to bind to PrP^C. Shown are: α-helices A (residues 144–157), B (172–193), and C (200–227). Flat ribbons depict β-strands S1 (129–131) and S2 (161–163). (***A***, *from SB Prusiner: N Engl J Med 344:1516, 2006; with permission*.) ***B***. Structural model of PrP^{Sc}. The 90–160 region has been modeled onto a β-helical architecture while the COOH terminal helices B and C are preserved as in PrP^C. (*Image prepared by C. Govaerts*.)

TABLE 38-1

GLOSSARY OF PRION TERMINOLOGY	
Prion	*Pro*teinaceous *in*fectious particle that lacks nucleic acid. Prions are composed largely, if not entirely, of PrP^{Sc} molecules. They can cause scrapie in sheep and goats, and related neurodegenerative diseases of humans such as Creutzfeldt-Jakob disease (CJD).
PrP^{Sc}	Disease-causing isoform of the prion protein. This protein is the only identifiable macromolecule in purified preparations of scrapie prions.
PrP^C	Cellular isoform of the prion protein. PrP^C is the precursor of PrP^{Sc}.
PrP 27-30	A fragment of PrP^{Sc}, generated by truncation of the NH_2-terminus by limited digestion with proteinase K. PrP 27-30 retains prion infectivity and polymerizes into amyloid.
PRNP	PrP gene located on human chromosome 20.
Prion rod	An aggregate of prions composed largely of PrP 27-30 molecules. Created by detergent extraction and limited proteolysis of PrP^{Sc}. Morphologically and histochemically indistinguishable from many amyloids.
PrP amyloid	Amyloid containing PrP in the brains of animals or humans with prion disease; often accumulates as plaques.

exception of a few recent patients exhibiting incubation periods of >40 years. Iatrogenic CJD (iCJD) seems to be the result of the accidental inoculation of patients with prions. Variant CJD (vCJD) in teenagers and young adults in Europe is the result of exposure to tainted beef from cattle with bovine spongiform encephalopathy (BSE).

Six diseases of animals are caused by prions (Table 38-2). Scrapie of sheep and goats is the prototypic prion disease. Mink encephalopathy, BSE, feline spongiform encephalopathy, and exotic ungulate encephalopathy are all thought to occur after the consumption of prion-infected foodstuffs. The BSE epidemic emerged in Britain in the late 1980s and was shown to be due to industrial cannibalism. Whether BSE began as a sporadic case of BSE in a cow or started with scrapie in sheep is unknown. The origin of chronic wasting disease (CWD), a prion disease endemic in deer and elk in regions of North America, is uncertain.

EPIDEMIOLOGY

CJD is found throughout the world. The incidence of sCJD is approximately one case per million population, and thus it accounts for about one in every 10,000 deaths. Because sCJD is an age-dependent neurodegenerative disease, its incidence is expected to increase steadily as older segments of populations in developed and developing countries continue to expand. Although many geographic clusters of CJD have been reported, each has been shown to segregate with a PrP gene mutation. Attempts to identify common exposure to some etiologic agent have been unsuccessful for both the sporadic and familial cases. Ingestion of scrapie-infected sheep or goat meat as a cause of CJD in humans has not been demonstrated by epidemiologic studies, although speculation about this potential route of inoculation continues. Of particular interest are deer hunters who develop CJD, because up to 90% of culled deer in some game herds have been shown to harbor CWD prions. Whether prion disease in deer or elk can be passed to cows, sheep, or directly to humans remains unknown. Studies with Syrian hamsters demonstrate that oral infection with prions can occur, but the process is inefficient compared to intracerebral inoculation.

PATHOGENESIS

The human prion diseases were initially classified as neurodegenerative disorders of unknown etiology on the basis of pathologic changes being confined to the CNS. With the transmission of kuru and CJD to apes, investigators began to view these diseases as infectious CNS illnesses caused by slow viruses. Even though the familial nature of a subset of CJD cases was well described, the significance of this observation became more obscure with the transmission of CJD to animals. Eventually the meaning of heritable CJD became clear

TABLE 38-2

THE PRION DISEASES

DISEASE	HOST	MECHANISM OF PATHOGENESIS
Human		
Kuru	Fore people	Infection through ritualistic cannibalism
iCJD	Humans	Infection from prion-contaminated hGH, dura mater grafts, etc.
vCJD	Humans	Infection from bovine prions
fCJD	Humans	Germ-line mutations in *PRNP*
GSS	Humans	Germ-line mutations in *PRNP*
FFI	Humans	Germ-line mutation in *PRNP* (D178N, M129)
sCJD	Humans	Somatic mutation or spontaneous conversion of PrP^{C} into PrP^{Sc}?
sFI	Humans	Somatic mutation or spontaneous conversion of PrP^{C} into PrP^{Sc}?
Animal		
Scrapie	Sheep, goats	Infection in genetically susceptible sheep
BSE	Cattle	Infection with prion-contaminated MBM
TME	Mink	Infection with prions from sheep or cattle
CWD	Mule deer, elk	Unknown
FSE	Cats	Infection with prion-contaminated beef
Exotic ungulate encephalopathy	Greater kudu, nyala, or oryx	Infection with prion-contaminated MBM

Note: BSE, bovine spongiform encephalopathy; CJD, Creutzfeldt-Jakob disease; fCJD, familial Creutzfeldt-Jakob disease; iCJD, iatrogenic Creutzfeldt-Jakob disease; sCJD, sporadic Creutzfeldt-Jakob disease; vCJD, variant Creutzfeldt-Jakob disease; CWD, chronic wasting disease; FFI, fatal familial insomnia; sFI, sporadic fatal insomnia; FSE, feline spongiform encephalopathy; GSS, Gerstmann-Sträussler-Scheinker disease; hGH, human growth hormone; MBM, meat and bone meal; TME, transmissible mink encephalopathy.

with the discovery of mutations in the PRNP gene of these patients. The prion concept explains how a disease can manifest as a heritable as well as an infectious illness. Moreover, the hallmark of all prion diseases, whether sporadic, dominantly inherited, or acquired by infection, is that they involve the aberrant metabolism of PrP.

A major feature that distinguishes prions from viruses is the finding that both PrP isoforms are encoded by a chromosomal gene. In humans, the PrP gene is designated *PRNP* and is located on the short arm of chromosome 20. Limited proteolysis of PrP^{Sc} produces a smaller, protease-resistant molecule of ~142 amino acids designated PrP 27-30; PrP^{C} is completely hydrolyzed under the same conditions (Fig. 38-2). In the presence of detergent, PrP 27-30 polymerizes into amyloid. Prion rods formed by limited proteolysis and detergent extraction are indistinguishable from the filaments that aggregate to form PrP amyloid plaques in the CNS. Both the rods and the PrP amyloid filaments found in brain tissue exhibit similar ultrastructural morphology and green-gold birefringence after staining with Congo red dye.

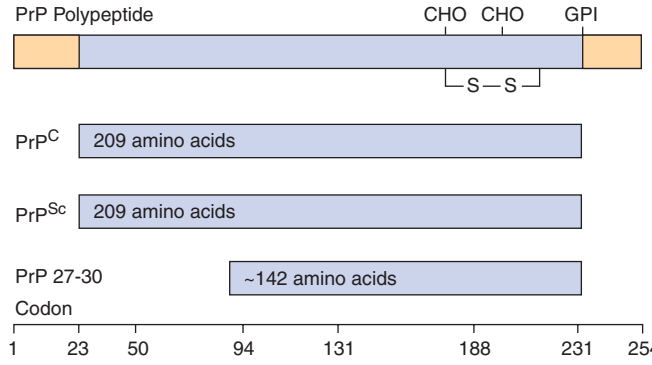

FIGURE 38-2

Prion protein isoforms. Bar diagram of Syrian hamster PrP, which consists of 254 amino acids. After processing of the NH_2 and COOH termini, both PrP^{C} and PrP^{Sc} consist of 209 residues. After limited proteolysis, the NH_2 terminus of PrP^{Sc} is truncated to form PrP 27–30 composed of ~142 amino acids.

Prion Strains

The existence of prion strains raised the question of how heritable biologic information can be enciphered in a molecule other than nucleic acid. Various strains of prions have been defined by incubation times and the distribution of neuronal vacuolation. Subsequently, the patterns of PrP^{Sc} deposition were found to correlate with vacuolation profiles, and these patterns were also used to characterize prion strains.

TABLE 38-3

DISTINCT PRION STRAINS GENERATED IN HUMANS WITH INHERITED PRION DISEASES AND TRANSMITTED TO TRANSGENIC MICE[a]

INOCULUM	HOST SPECIES	HOST PrP GENOTYPE	INCUBATION TIME [DAYS ± SEM] (n/n_0)	PrP^{Sc} (kDa)
None	Human	FFI(D178N, M129)		19
FFI	Mouse	Tg(MHu2M)	206 ± 7 (7/7)	19
FFI → Tg(MHu2M)	Mouse	Tg(MHu2M)	136 ± 1 (6/6)	19
None	Human	fCJD(E200K)		21
fCJD	Mouse	Tg(MHu2M)	170 ± 2 (10/10)	21
fCJD → Tg(MHu2M)	Mouse	Tg(MHu2M)	167 ± 3 (15/15)	21

[a]Tg(MHu2M) mice express a chimeric mouse-human PrP gene.
Note: Clinicopathologic phenotype is determined by the conformation of PrP^{Sc} in accord with the results of the transmission of human prions from patients with FFI to transgenic mice. FFI, fatal familial insomnia; fCJD, familial Creutzfeldt-Jakob disease.

Persuasive evidence that strain-specific information is enciphered in the tertiary structure of PrP^{Sc} comes from transmission of two different inherited human prion diseases to mice expressing a chimeric human-mouse PrP transgene. In FFI, the protease-resistant fragment of PrP^{Sc} after deglycosylation has a molecular mass of 19 kDa, whereas in fCJD and most sporadic prion diseases, it is 21 kDa (Table 38-3). This difference in molecular mass was shown to be due to different sites of proteolytic cleavage at the NH_2 termini of the two human PrP^{Sc} molecules, reflecting different tertiary structures. These distinct conformations were not unexpected because the amino acid sequences of the PrPs differ.

Extracts from the brains of patients with FFI transmitted disease into mice expressing a chimeric human-mouse PrP transgene and induced formation of the 19-kDa PrP^{Sc}, whereas brain extracts from fCJD and sCJD patients produced the 21-kDa PrP^{Sc} in mice expressing the same transgene. On second passage, these differences were maintained, demonstrating that chimeric PrP^{Sc} can exist in two different conformations based on the sizes of the protease-resistant fragments, even though the amino acid sequence of PrP^{Sc} is invariant.

This analysis was extended when patients with sporadic fatal insomnia (sFI) were identified. Although they did not carry a *PRNP* gene mutation, the patients demonstrated a clinical and pathologic phenotype that was indistinguishable from that of patients with FFI. Furthermore, 19-kDa PrP^{Sc} was found in their brains, and on passage of prion disease to mice expressing a chimeric human-mouse PrP transgene, 19-kDa PrP^{Sc} was also found. These findings indicate that the disease phenotype is dictated by the conformation of PrP^{Sc} and not the amino acid sequence. PrP^{Sc} acts as a template for the conversion of PrP^{C} into nascent PrP^{Sc}. On the passage of prions into mice expressing a chimeric hamster-mouse PrP transgene, a change in the conformation of PrP^{Sc} was accompanied by the emergence of a new strain of prions.

New strains of prions were also generated from recombinant (rec) PrP produced in bacteria. In these studies, recPrP was polymerized into amyloid fibrils and inoculated into transgenic mice expressing very high levels of truncated mouse PrP^{C}; about 500 days later, the mice died of prion disease. These "synthetic prions" were found to be much more stable than any prions previously isolated from animals or humans with naturally occurring prion diseases. Surprisingly, studies of synthetic and naturally occurring prions indicate that the incubation time is directly proportional to the stability of the prion. As the stability increases, the incubation time lengthens; thus, less-stable prions replicate more rapidly. These studies also showed that PrP^{Sc} can adopt a continuum of conformational states, each of which enciphers a distinct incubation-time phenotype.

Species Barrier

Studies on the role of the primary and tertiary structures of PrP in the transmission of prion disease have given new insights into the pathogenesis of these maladies. The amino acid sequence of PrP encodes the species of the prion, and the prion derives its PrP^{Sc} sequence from the last mammal in which it was passaged. While the primary structure of PrP is likely to be the most important or even sole determinant of the tertiary structure of PrP^{C}, PrP^{Sc} seems to function as a template in determining the tertiary structure of nascent PrP^{Sc} molecules as they are formed from PrP^{C}. In turn, prion diversity appears to be enciphered in the conformation of PrP^{Sc}, and thus prion strains seem to represent different conformers of PrP^{Sc}.

In general, transmission of prion disease from one species to another is inefficient, in that not all intracerebrally inoculated animals develop disease, and those that fall ill do so only after long incubation times that can approach the natural life span of the animal. This "species barrier" to transmission is correlated with the degree of

similarity between the amino acid sequences of PrP^{C} in the inoculated host and of PrP^{Sc} in the prion inoculum. The importance of sequence similarity between the host and donor PrP argues that PrP^{C} directly interacts with PrP^{Sc} in the prion conversion process.

SPORADIC AND INHERITED PRION DISEASES

Several different scenarios might explain the initiation of sporadic prion disease: (1) A somatic mutation may be the cause and thus follow a path similar to that for germ-line mutations in inherited disease. In this situation, the mutant PrP^{Sc} must be capable of targeting wild-type PrP^{C}, a process known to be possible for some mutations but less likely for others. (2) The activation barrier separating wild-type PrP^{C} from PrP^{Sc} could be crossed on rare occasions when viewed in the context of a population. Most individuals would be spared while presentations in the elderly with an incidence of ~1 per million would be seen. (3) PrP^{Sc} may be present at very low levels in some normal cells, where it performs some important, as yet unknown, function. The level of PrP^{Sc} in such cells is hypothesized to be sufficiently low as to be not detected by bioassay. In some altered metabolic states, the cellular mechanisms for clearing PrP^{Sc} might become compromised and the rate of PrP^{Sc} formation would then begin to exceed the capacity of the cell to clear it. The third possible mechanism is attractive since it suggests PrP^{Sc} is not simply a misfolded protein, as proposed for the first and second mechanisms, but that it is an alternatively folded molecule with a function. Moreover, the multitude of conformational states that PrP^{Sc} can adopt, as described above, raises the possibility that PrP^{Sc} or another prion-like protein might function in a process like short-term memory where information storage occurs in the absence of new protein synthesis.

More than 30 different mutations resulting in nonconservative substitutions in the human *PRNP* gene have been found to segregate with inherited human prion diseases. Missense mutations and expansions in the octapeptide repeat region of the gene are responsible for familial forms of prion disease. Five different mutations of the *PRNP* gene have been linked genetically to heritable prion disease.

Although phenotypes may vary dramatically within families, specific phenotypes tend to be observed with certain mutations. A clinical phenotype indistinguishable from typical sCJD is usually seen with substitutions at codons 180, 183, 200, 208, 210, and 232. Substitutions at codons 102, 105, 117, 198, and 217 are associated with the GSS variant of prion disease. The normal human PrP sequence contains five repeats of an eight-amino-acid sequence. Insertions from two to nine extra octarepeats frequently cause variable phenotypes ranging from a condition indistinguishable from sCJD to a slowly progressive dementing illness of many years' duration to an early-age-of-onset disorder that is similar to Alzheimer's disease. A mutation at codon 178 resulting in substitution of asparagine for aspartic acid produces FFI if a methionine is encoded at the polymorphic 129 residue on the same allele. Typical CJD is seen if a valine is encoded at position 129 of the same allele.

HUMAN PRNP GENE POLYMORPHISMS

Polymorphisms influence the susceptibility to sporadic, inherited, and infectious forms of prion disease. The methionine/valine polymorphism at position 129 not only modulates the age of onset of some inherited prion diseases but can also determine the clinical phenotype. The finding that homozygosity at codon 129 predisposes to sCJD supports a model of prion production that favors PrP interactions between homologous proteins.

Substitution of the basic residue lysine at position 218 in mouse PrP produced dominant-negative inhibition of prion replication in transgenic mice. This same lysine at position 219 in human PrP has been found in 12% of the Japanese population, and this group appears to be resistant to prion disease. Dominant-negative inhibition of prion replication was also found with substitution of the basic residue arginine at position 171; sheep with arginine are resistant to scrapie prions but are susceptible to BSE prions that were inoculated intracerebrally.

INFECTIOUS PRION DISEASES

IATROGENIC CJD

Accidental transmission of CJD to humans appears to have occurred with corneal transplantation, contaminated electroencephalogram (EEG) electrode implantation, and surgical procedures. Corneas from donors with inapparent CJD have been transplanted to apparently healthy recipients who developed CJD after prolonged incubation periods. The same improperly decontaminated EEG electrodes that caused CJD in two young patients with intractable epilepsy caused CJD in a chimpanzee 18 months after their experimental implantation.

Surgical procedures may have resulted in accidental inoculation of patients with prions, presumably because some instrument or apparatus in the operating theater became contaminated when a CJD patient underwent surgery. Although the epidemiology of these studies is highly suggestive, no proof for such episodes exists.

Dura Mater Grafts

More than 160 cases of CJD after implantation of dura mater grafts have been recorded. All of the grafts were

thought to have been acquired from a single manufacturer whose preparative procedures were inadequate to inactivate human prions. One case of CJD occurred after repair of an eardrum perforation with a pericardium graft.

Human Growth Hormone and Pituitary Gonadotropin Therapy

The possibility of transmission of CJD from contaminated human growth hormone (hGH) preparations derived from human pituitaries has been raised by the occurrence of fatal cerebellar disorders with dementia in >180 patients ranging from 10 to 41 years of age. These patients received injections of hGH every 2–4 days for 4–12 years. If it is assumed that these patients developed CJD from injections of prion-contaminated hGH preparations, the possible incubation periods range from 4 to 30 years. Even though several investigations argue for the efficacy of inactivating prions in hGH fractions prepared from human pituitaries with 6 *M* urea, it seems doubtful that such protocols will be used for purifying hGH because recombinant hGH is available. Four cases of CJD have occurred in women receiving human pituitary gonadotropin.

VARIANT CJD

The restricted geographic occurrence and chronology of vCJD raised the possibility that BSE prions have been transmitted to humans through the consumption of tainted beef. More than 190 cases of vCJD have occurred, with >90% of these in Britain. vCJD has also been reported in people either living in or originating from France, Ireland, Italy, Netherlands, Portugal, Spain, Saudi Arabia, United States, Canada, and Japan.

Because the number of vCJD cases is still small, it not possible to decide if we are at the beginning of a prion disease epidemic in Europe, similar to those seen for BSE and kuru, or if the number of vCJD cases will remain small. What is certain is that prion-tainted meat should be prevented from entering the human food supply.

The most compelling evidence that vCJD is caused by BSE prions was obtained from experiments in mice expressing the bovine PrP transgene. Both BSE and vCJD prions were efficiently transmitted to these transgenic mice and with similar incubation periods. In contrast to sCJD prions, vCJD prions did not transmit disease efficiently to mice expressing a chimeric human-mouse PrP transgene. Earlier studies with nontransgenic mice suggested that vCJD and BSE might be derived from the same source because both inocula transmitted disease with similar but very long incubation periods.

Attempts to determine the origin of BSE and vCJD prions have relied on passaging studies in mice, some of which are described above, as well as studies of the conformation and glycosylation of PrP^{Sc}. One scenario suggests that a particular conformation of bovine PrP^{Sc} was selected for heat resistance during the rendering process and was then reselected multiple times as cattle infected by ingesting prion-contaminated meat and bone meal (MBM) were slaughtered and their offal rendered into more MBM.

NEUROPATHOLOGY

Frequently the brains of patients with CJD have no recognizable abnormalities on gross examination. Patients who survive for several years have variable degrees of cerebral atrophy.

On light microscopy, the pathologic hallmarks of CJD are spongiform degeneration and astrocytic gliosis. The lack of an inflammatory response in CJD and other prion diseases is an important pathologic feature of these degenerative disorders. Spongiform degeneration is characterized by many 1- to 5-μm vacuoles in the neuropil between nerve cell bodies. Generally the spongiform changes occur in the cerebral cortex, putamen, caudate nucleus, thalamus, and molecular layer of the cerebellum. Astrocytic gliosis is a constant but nonspecific feature of prion diseases. Widespread proliferation of fibrous astrocytes is found throughout the gray matter of brains infected with CJD prions. Astrocytic processes filled with glial filaments form extensive networks.

Amyloid plaques have been found in ~10% of CJD cases. Purified CJD prions from humans and animals exhibit the ultrastructural and histochemical characteristics of amyloid when treated with detergents during limited proteolysis. In first passage from some human Japanese CJD cases, amyloid plaques have been found in mouse brains. These plaques stain with antibodies raised against PrP.

The amyloid plaques of GSS disease are morphologically distinct from those seen in kuru or scrapie. GSS plaques consist of a central dense core of amyloid surrounded by smaller globules of amyloid. Ultrastructurally, they consist of a radiating fibrillar network of amyloid fibrils, with scant or no neuritic degeneration. The plaques can be distributed throughout the brain but are most frequently found in the cerebellum. They are often located adjacent to blood vessels. Congophilic angiopathy has been noted in some cases of GSS disease.

In vCJD, a characteristic feature is the presence of "florid plaques." These are composed of a central core of PrP amyloid, surrounded by vacuoles in a pattern suggesting petals on a flower.

CLINICAL FEATURES

Nonspecific prodromal symptoms occur in about a third of patients with CJD and may include fatigue, sleep

disturbance, weight loss, headache, malaise, and ill-defined pain. Most patients with CJD present with deficits in higher cortical function. These deficits almost always progress over weeks or months to a state of profound dementia characterized by memory loss, impaired judgment, and a decline in virtually all aspects of intellectual function. A few patients present with either visual impairment or cerebellar gait and coordination deficits. Frequently the cerebellar deficits are rapidly followed by progressive dementia. Visual problems often begin with blurred vision and diminished acuity, rapidly followed by dementia.

Other symptoms and signs include extrapyramidal dysfunction manifested as rigidity, masklike facies, or choreoathetoid movements; pyramidal signs (usually mild); seizures (usually major motor) and, less commonly, hypoesthesia; supranuclear gaze palsy; optic atrophy; and vegetative signs such as changes in weight, temperature, sweating, or menstruation.

Myoclonus

Most patients (~90%) with CJD exhibit myoclonus that appears at various times throughout the illness. Unlike other involuntary movements, myoclonus persists during sleep. Startle myoclonus elicited by loud sounds or bright lights is frequent. It is important to stress that myoclonus is neither specific nor confined to CJD. Dementia with myoclonus can also be due to Alzheimer's disease (AD) (Chap. 23), dementia with Lewy bodies (Chap. 23), cryptococcal encephalitis, or the myoclonic epilepsy disorder Unverricht-Lundborg disease (Chap. 20).

Clinical Course

In documented cases of accidental transmission of CJD to humans, an incubation period of 1.5–2.0 years preceded the development of clinical disease. In other cases, incubation periods of up to 30 years have been suggested. Most patients with CJD live 6–12 months after the onset of clinical signs and symptoms, whereas some live for up to 5 years.

DIAGNOSIS

The constellation of dementia, myoclonus, and periodic electrical bursts in an afebrile 60-year-old patient generally indicates CJD. Clinical abnormalities in CJD are confined to the CNS. Fever, elevated sedimentation rate, leukocytosis in blood, or a pleocytosis in cerebrospinal fluid (CSF) should alert the physician to another etiology to explain the patient's CNS dysfunction.

Variations in the typical course appear in inherited and transmitted forms of the disease. fCJD has an earlier mean age of onset than sCJD. In GSS disease, ataxia is usually a prominent and presenting feature, with dementia occurring late in the disease course. GSS disease typically presents earlier than CJD (mean age 43 years) and is typically more slowly progressive than CJD; death usually occurs within 5 years of onset. FFI is characterized by insomnia and dysautonomia; dementia occurs only in the terminal phase of the illness. Rare sporadic cases have been identified. vCJD has an unusual clinical course, with a prominent psychiatric prodrome that may include visual hallucinations and early ataxia, while frank dementia is usually a late sign of vCJD.

DIFFERENTIAL DIAGNOSIS

Many conditions may mimic CJD superficially. Dementia with Lewy bodies (Chap. 23) is the most common disorder to be mistaken for CJD. It can present in a subacute fashion with delirium, myoclonus, and extrapyramidal features. Other neurodegenerative disorders to consider include AD, frontotemporal dementia, progressive supranuclear palsy, ceroid lipofuscinosis (Chap. 23), and myoclonic epilepsy with Lafora bodies (Chap. 20). The absence of abnormalities on diffusion-weighted and FLAIR MRI will usually distinguish these dementing conditions from CJD.

Hashimoto's encephalopathy, which presents as a subacute progressive encephalopathy with myoclonus and periodic triphasic complexes on the EEG, should be excluded in every case of suspected CJD. It is diagnosed by the finding of high titers of antithyroglobulin or antithyroid peroxidase (antimicrosomal) antibodies in the blood and improves with glucocorticoid therapy. Unlike CJD, fluctuations in severity typically occur in Hashimoto's encephalopathy.

Intracranial vasculitides may produce nearly all of the symptoms and signs associated with CJD, sometimes without systemic abnormalities. Myoclonus is exceptional with cerebral vasculitis, but focal seizures may confuse the picture. Prominent headache, absence of myoclonus, stepwise change in deficits, abnormal CSF, and focal white matter changes on MRI or angiographic abnormalities all favor vasculitis.

Paraneoplastic conditions, particularly limbic encephalitis and cortical encephalitis, can also mimic CJD. In many of these patients, dementia appears prior to the diagnosis of a tumor, and in some, no tumor is ever found. Detection of the paraneoplastic antibodies is often the only way to distinguish these cases from CJD.

Other diseases that can simulate CJD include neurosyphilis, AIDS dementia complex (Chap. 37), progressive multifocal leukoencephalopathy (Chap. 35), subacute sclerosing panencephalitis, progressive rubella panencephalitis, herpes simplex encephalitis, diffuse intracranial tumor (gliomatosis cerebri; Chap. 32), anoxic encephalopathy, dialysis dementia, uremia, hepatic encephalopathy, and lithium or bismuth intoxication.

LABORATORY TESTS

The only specific diagnostic tests for CJD and other human prion diseases measure PrP^{Sc}. The most widely used method involves limited proteolysis that generates PrP 27-30, which is detected by immunoassay after denaturation. The conformation-dependent immunoassay (CDI) is based on immunoreactive epitopes that are exposed in PrP^{C} but buried in PrP^{Sc}. The CDI is extremely sensitive and quantitative and is likely to find wide application in both the post- and antemortem detection of prions. In humans, the diagnosis of CJD can be established by brain biopsy if PrP^{Sc} is detected. If no attempt is made to measure PrP^{Sc}, but the constellation of pathologic changes frequently found in CJD is seen in a brain biopsy, then the diagnosis is reasonably secure (see "Neuropathology," above). Because PrP^{Sc} is not uniformly distributed throughout the CNS, the apparent absence of PrP^{Sc} in a limited sample such as a biopsy does not rule out prion disease. At autopsy, sufficient brain samples should be taken for both PrP^{Sc} immunoassay, preferably by CDI, and immunohistochemistry of tissue sections.

To establish the diagnosis of either sCJD or familial prion disease, sequencing the *PRNP* gene must be performed. Finding the wild-type *PRNP* gene sequence permits the diagnosis of sCJD if there is no history to suggest infection from an exogenous source of prions. The identification of a mutation in the *PRNP* gene sequence that encodes a nonconservative amino acid substitution argues for familial prion disease.

CT may be normal or show cortical atrophy. MRI is valuable for distinguishing sCJD from most other conditions. On FLAIR sequences and diffusion-weighted imaging, ~90% of patients show increased intensity in the basal ganglia and cortical ribboning (**Fig. 38-3**). This pattern is not seen with other neurodegenerative disorders but has been seen infrequently with viral encephalitis, paraneoplastic syndromes, or seizures. When the typical MRI pattern is present, in the proper clinical setting, diagnosis is facilitated. However, some cases of sCJD do not show this typical pattern, and other early diagnostic approaches are still needed.

CSF is nearly always normal but may show protein elevation and, rarely, mild pleocytosis. Although the stress protein 14-3-3 is elevated in the CSF of some patients with CJD, similar elevations of 14-3-3 are found in patients with other disorders; thus this elevation is not specific.

The EEG is often useful in the diagnosis of CJD, although only about 60% of individuals show the typical pattern. During the early phase of CJD, the EEG is usually normal or shows only scattered theta activity. In most advanced cases, repetitive, high-voltage, triphasic, and polyphasic sharp discharges are seen, but in many cases their presence is transient. The presence of these stereotyped periodic bursts of <200 ms duration, occurring every 1–2 s, makes the diagnosis of CJD very likely. These discharges are frequently but not always symmetric; there may be a one-sided predominance in amplitude. As CJD progresses, normal background rhythms become fragmentary and slower.

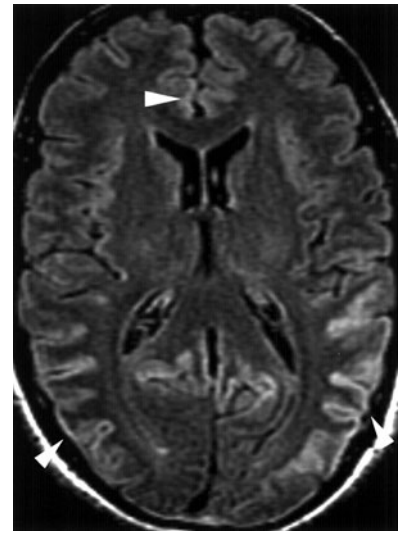

FIGURE 38-3
T2-weighted (FLAIR) MRI showing hyperintensity in the cortex in a patient with sporadic CJD. This so-called "cortical ribboning" along with increased intensity in the basal ganglia on T2 or diffusion-weighted imaging can aid in the diagnosis of CJD.

CARE OF CJD PATIENTS

Although CJD should not be considered either contagious or communicable, it is transmissible. The risk of accidental inoculation by aerosols is very small; nonetheless, procedures producing aerosols should be performed in certified biosafety cabinets. Biosafety level 2 practices, containment equipment, and facilities are recommended by the Centers for Disease Control and Prevention and the National Institutes of Health. The primary problem in caring for patients with CJD is the inadvertent infection of health care workers by needle and stab wounds. The transmission of prions through the air has never been documented. Electroencephalographic and electromyographic needles should not be reused after studies on patients with CJD have been performed.

There is no reason for pathologists or other morgue employees to resist performing autopsies on patients whose clinical diagnosis was CJD. Standard microbiologic practices outlined here, along with specific recommendations for decontamination, seem to be adequate precautions for the care of patients with CJD and the handling of infected specimens.

DECONTAMINATION OF CJD PRIONS

Prions are extremely resistant to common inactivation procedures, and there is some disagreement about the optimal conditions for sterilization. Some investigators recommend treating CJD-contaminated materials once with 1 *N* NaOH at room temperature, but we believe this procedure may be inadequate for sterilization. Autoclaving at 134°C for 5 h or treatment with 2 *N* NaOH for several hours is recommended for sterilization of prions. The term *sterilization* implies complete destruction of prions; any residual infectivity can be hazardous. Recent studies show that sCJD prions bound to stainless steel surfaces are resistant to inactivation by autoclaving at 134°C for 2 h; exposure of bound prions to an acidic detergent solution prior to autoclaving rendered prions susceptible to inactivation.

PREVENTION AND THERAPEUTICS

There is no known effective therapy for preventing or treating CJD. The finding that phenothiazines and acridines inhibit PrP^{Sc} formation in cultured cells led to clinical studies of quinacrine in CJD patients. Although quinacrine seems to slow the rate of decline in some CJD patients, no cure of the disease has been observed. In wild-type mice, quinacrine treatment has been ineffective. Recent studies indicate that inhibition of the P-glycoprotein (Pgp) transport system results in substantially increased quinacrine levels in the brains of mice. Whether such an approach can be used to treat CJD remains to be established.

Like the acridines, anti-PrP antibodies have been shown to eliminate PrP^{Sc} from cultured cells. Additionally, such antibodies in mice, either administered by injection or produced from a transgene, have been shown to prevent prion disease when prions are introduced by a peripheral route, such as intraperitoneal inoculation. Unfortunately, the antibodies were ineffective in mice inoculated intracerebrally with prions. Several drugs, including pentosan polysulfate and porphyrin derivatives, delay the onset of disease in animals inoculated intracerebrally with prions if the drugs are given intracerebrally beginning soon after inoculation.

Structure-based drug design predicated on dominant-negative inhibition of prion formation has produced several promising compounds. Modified quinacrine compounds that are more potent than the parent drug have been found. Whether improving the efficacy of such small molecules will provide general methods for developing novel therapeutics for other neurodegenerative disorders, including AD and Parkinson's disease as well as amyotrophic lateral sclerosis (ALS), remains to be established.

Disclosure: SBP has a financial interest in InPro Biotechnology, Inc.

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CHAPTER 39

PARANEOPLASTIC NEUROLOGIC SYNDROMES

Josep Dalmau ■ Myrna R. Rosenfeld

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Paraneoplastic neurologic disorders (PNDs) are cancer-related syndromes that can affect any part of the nervous system (**Table 39-1**). They are remote effects of cancer, caused by mechanisms other than metastasis or by any of the complications of cancer such as coagulopathy, stroke, metabolic and nutritional conditions, infections, and side effects of cancer therapy. In 60% of patients the neurologic symptoms precede the cancer diagnosis. Overall, clinically disabling PNDs occur in 0.5–1% of all cancer patients, but they occur in 2–3% of patients with neuroblastoma or small cell lung cancer (SCLC), and in 30–50% of patients with thymoma or sclerotic myeloma.

PATHOGENESIS

Most PNDs are mediated by immune responses triggered by neuronal proteins (onconeuronal antigens) expressed by tumors. In PNDs of the central nervous system (CNS), many antibody-associated immune responses have been identified (**Table 39-2**). These antibodies usually react with the patient's tumor, and their detection in serum or cerebrospinal fluid (CSF) strongly predicts the presence of cancer. The target antigens are usually intracellular proteins with roles in neuronal development and function. Some of the antibodies react with epitopes located in critical protein domains, disrupting protein function and leading to neuronal apoptosis. In addition to onconeuronal antibodies, most PNDs of the CNS are associated with infiltrates of CD4+ and CD8+ T cells, microglial activation, gliosis, and variable neuronal loss. The infiltrating T cells are often in close contact with neurons undergoing degeneration, suggesting a primary pathogenic role. T cell–mediated cytotoxicity may contribute directly to cell death in these PNDs. Thus both humoral and cellular immune mechanisms participate in the pathogenesis of many PNDs. This complex immunopathogenesis may underlie the resistance of many of these conditions to therapy.

Neuronal cell-surface antigens can be the target of antibodies in some patients with paraneoplastic encephalitis. A few of these antigens have been identified, including the NR1/NR2 subunits of NMDA receptors (**Fig. 39-1**) and voltage-gated potassium channels (VGKC). These disorders are more responsive to immunotherapy than those associated with immune responses to intracellular antigens.

Only four of the antibodies listed in Table 39-2 have been shown to play a direct pathogenic role in PNDs; all produce distinctive disorders of the peripheral nervous system. These are: antibodies to P/Q-type voltage-gated calcium channels (VGCC) in patients with the Lambert-Eaton myasthenic syndrome (LEMS); antibodies to acetylcholine receptors in patients with myasthenia

TABLE 39-1

PARANEOPLASTIC SYNDROMES OF THE NERVOUS SYSTEM

- Syndromes of the brain, brainstem, and cerebellum
  - Focal encephalitis
    - Cortical encephalitis
    - Limbic encephalitis
    - Brainstem encephalitis
    - Cerebellar dysfunction
    - Autonomic dysfunction
  - Paraneoplastic cerebellar degeneration
  - Opsoclonus-myoclonus
- Syndromes of the spinal cord
  - Subacute necrotizing myelopathy
  - Motor neuron dysfunction
  - Myelitis
  - Stiff-person syndrome
- Syndromes of dorsal root ganglia
  - Sensory neuronopathy
- Multiple levels of involvement
  - Encephalomyelitis[a], sensory neuronopathy, autonomic dysfunction
- Syndromes of peripheral nerve
  - Chronic and subacute sensorimotor peripheral neuropathy
  - Vasculitis of nerve and muscle
  - Neuropathy associated with malignant monoclonal gammopathies
  - Peripheral nerve hyperexcitability
  - Autonomic neuropathy
- Syndromes of the neuromuscular junction
  - Lambert-Eaton myasthenic syndrome
  - Myasthenia gravis
- Syndromes of the muscle
  - Polymyositis/dermatomyositis
  - Acute necrotizing myopathy
- Syndromes affecting the visual system
  - Cancer-associated retinopathy (CAR)
  - Melanoma-associated retinopathy (MAR)
  - Uveitis (usually in association with encephalomyelitis)

[a]Includes cortical, limbic, or brainstem encephalitis, cerebellar dysfunction, myelitis.

gravis; antibodies to VGKC in some patients with peripheral nerve hyperexcitability (neuromyotonia); and antibodies to ganglionic acetylcholine receptors in some patients with autonomic neuropathy. Common features of these four antibodies are that they target cell-surface molecules and that their passive transfer to animals reproduces the disorders. Plasma exchange or immunomodulation with intravenous immunoglobulin (IVIg) usually produces neurologic improvement. Each of these disorders can occur without cancer, and therefore detection of these antibodies does not predict the presence of cancer.

Other PNDs are likely immune-mediated, although their antigens are unknown. These include several syndromes of inflammatory neuropathies and myopathies. In addition, many patients with typical PND syndromes are antibody-negative.

For still other PNDs, the cause remains quite obscure. These include, among others, several neuropathies that occur in the terminal stages of cancer and a number of neuropathies associated with plasma cell dyscrasias or lymphoma without evidence of inflammatory infiltrates or deposits of immunoglobulin, cryoglobulin, or amyloid.

Approach to the Patient: PARANEOPLASTIC NEUROLOGIC DISORDERS

The diagnosis and management of PNDs may be difficult for several reasons. First, it is common for symptoms to appear before the presence of a tumor is known. Second, the neurologic syndrome can evolve in a rapidly progressive fashion, producing a severe and usually irreversible neurologic deficit in a short period of time. There is evidence that prompt tumor control improves the course of PNDs. Therefore, the major concern of the physician is to recognize a disorder promptly as paraneoplastic in order to identify and treat the tumor.

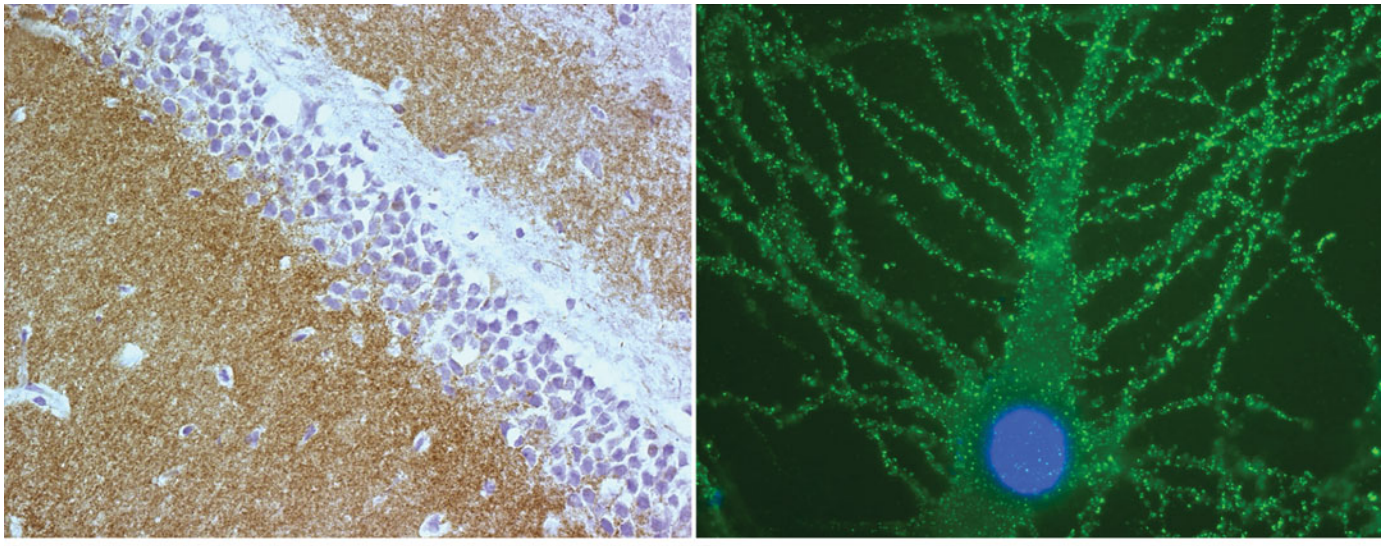
PND OF THE CENTRAL NERVOUS SYSTEM AND DORSAL ROOT GANGLIA When symptoms involve brain, spinal cord, or dorsal root ganglia, the suspicion of PND is usually based on a combination of clinical, radiologic, and CSF findings. In these cases, a biopsy of the affected tissue is often difficult to obtain, and although useful to rule out other disorders (e.g., metastasis, infection), neuropathologic findings are not specific for PND. Furthermore, there are no specific radiologic or electrophysiologic tests that are diagnostic of PND. The presence of antineuronal antibodies (Table 39-2) may help in the diagnosis with the following caveats: (1) antibodies are detected in only 60–70% of PNDs of the CNS; (2) antibodies may be present in both the serum and CSF, but in some patients only the CSF is positive (especially with antibodies to Tr and Ma proteins); (3) antibodies (usually at low titer) are present in a variable proportion of cancer patients without PND; (4) there is an imperfect correlation between antibody titers and the course of the neurologic disorder; (5) several antibodies may associate with a similar syndrome, with the antibody specificity often correlating with the tumor type (e.g., cerebellar degeneration is associated with anti-Tr antibodies if the tumor is Hodgkin's disease but with anti-Yo antibodies if the tumor is ovarian or breast cancer); and (6) several antibodies may be present in the serum or CSF of the same patient (e.g., anti-Hu and anti-CV_2/CRMP5).

TABLE 39-2

PARANEOPLASTIC ANTINEURONAL ANTIBODIES, ASSOCIATED SYNDROMES AND CANCERS

ANTIBODY	SYNDROME	ASSOCIATED CANCERS
Anti-Hu (ANNA-1)	PEM (including cortical, limbic, brainstem encephalitis, cerebellar dysfunction, myelitis), PSN, autonomic dysfunction	SCLC, other neuroendocrine tumors
Anti-Yo (PCA-1)	PCD	Ovary and other gynecologic cancers, breast
Anti-Ri (ANNA-2)	PCD, brainstem encephalitis, opsoclonus-myoclonus	Breast, gynecological, SCLC
Anti-Tr	PCD	Hodgkin's lymphoma
Anti-Zic	PCD, encephalomyelitis	SCLC and other neuroendocrine tumors
Anti-CV_2/CRMP5	PEM, PCD, chorea, peripheral neuropathy, uveitis	SCLC, thymoma, other
Anti-Ma proteins[a]	Limbic, hypothalamic, brainstem encephalitis (infrequently PCD)	Germ-cell tumors of testis, lung cancer, other solid tumors
Anti-NR1/NR2 subunits of NMDA receptor	Encephalitis with prominent psychiatric symptoms, seizures, hypoventilation	Ovarian teratoma
Anti-amphiphysin	Stiff-person syndrome, PEM	Breast, SCLC
Anti-VGCC[b]	LEMS, PCD	SCLC, lymphoma
Anti-AChR[b]	MG	Thymoma
Anti-VGKC[b]	Peripheral nerve hyperexcitability (neuromyotonia), limbic encephalitis	Thymoma, SCLC, others
Anti-recoverin	Cancer-associated retinopathy (CAR)	SCLC and other
Anti-bipolar cells of the retina	Melanoma-associated retinopathy (MAR)	Melanoma

[a]Patients with antibodies to Ma2 are usually men with testicular cancer. Patients with additional antibodies to other Ma proteins are men or women with a variety of solid tumors.
[b]These antibodies can occur with or without a cancer association.
Note: PEM: paraneoplastic encephalomyelitis; PCD, paraneoplastic cerebellar degeneration; PSN, paraneoplastic sensory neuronopathy; LEMS, Lambert-Eaton myasthenic syndrome; MG, myasthenia gravis; VGCC, voltage-gated calcium channel; AChR, acetylcholine receptor; VGKC, voltage-gated potassium channel; SCLC, small-cell lung cancer; NMDA, *N*-methyl-D-aspartate.



A ***B***

FIGURE 39-1

Antibodies to NR1/NR2 subunits of the NMDA receptor in a patient with paraneoplastic encephalitis and ovarian teratoma. ***Panel A*** is a section of dentate gyrus of rat hippocampus immunolabeled (brown staining) with the patient's antibodies. The reactivity predominates in the molecular layer, which is highly enriched in dendritic processes. ***Panel B*** shows the antibody reactivity with cultures of rat hippocampal neurons; the intense green immunolabeling is due to the antibodies against the NR1/NR2 subunits of NMDA receptors.

MRI and CSF studies are important to rule out neurologic complications due to the direct spread of cancer, particularly metastatic and leptomeningeal disease. In most PNDs the MRI findings are nonspecific. Paraneoplastic limbic encephalitis is usually associated with characteristic MRI abnormalities in the mesial temporal lobes (see later), but similar findings can occur with other disorders [e.g., nonparaneoplastic limbic encephalitis with antibodies to VGKC, human herpesvirus (HHV) 6 encephalitis] (**Fig. 39-2**). The CSF profile of patients with PND of the CNS or dorsal root ganglia typically consists of mild to moderate pleocytosis (<200 mononuclear cells, predominantly lymphocytes), an increase in the protein concentration, intrathecal synthesis of IgG, and a variable presence of oligoclonal bands.

PND OF NERVE AND MUSCLE If symptoms involve peripheral nerve, neuromuscular junction, or muscle, the diagnosis of a specific PND is usually established on clinical, electrophysiologic, and pathologic grounds. The clinical history, accompanying symptoms (e.g., anorexia, weight loss), and type of syndrome dictate the studies and degree of effort needed to demonstrate a neoplasm. For example, the frequent association of LEMS with SCLC should lead to a chest and abdomen CT or body positron emission tomography (PET) scan and, if negative, periodic tumor screening for at least 3 years after the neurologic diagnosis. In contrast, the weak association of polymyositis with cancer calls into question the need for repeated cancer screenings in this situation. Serum and urine immunofixation studies should be considered in patients with peripheral neuropathy of unknown cause; detection of a monoclonal gammopathy suggests the need for additional studies to uncover a B cell or plasma cell malignancy. In paraneoplastic neuropathies, diagnostically useful antineuronal antibodies are limited to anti-CV_2/CRMP5 and anti-Hu.

For any type of PND, if antineuronal antibodies are negative, the diagnosis relies on the demonstration of cancer and the exclusion of other cancer-related or independent neurologic disorders. Body PET scans often uncover tumors undetected by other tests.

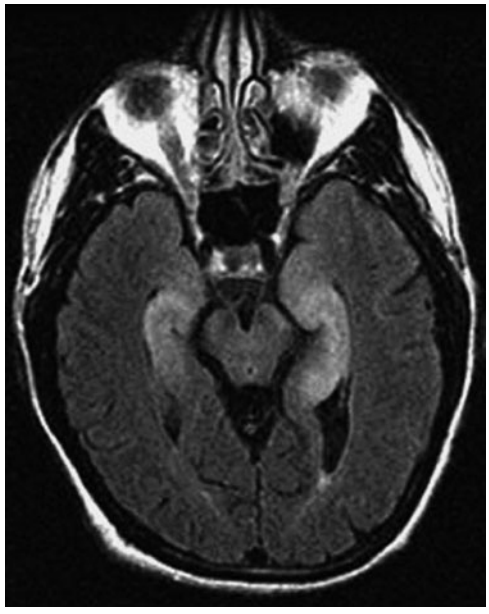


FIGURE 39-2
Fluid-attenuated inversion recovery sequence MRI of a patient with limbic encephalitis and voltage-gated potassium channel antibodies. Note the abnormal hyperintensity involving the medial aspect of the temporal lobes.

SPECIFIC PARANEOPLASTIC NEUROLOGIC SYNDROMES (Table 39-3)

PARANEOPLASTIC ENCEPHALOMYELITIS AND FOCAL ENCEPHALITIS

The term *encephalomyelitis* describes an inflammatory process with multifocal involvement of the nervous system, including brain, brainstem, cerebellum, and spinal cord. It is often associated with dorsal root ganglia and autonomic dysfunction. For any given patient, the clinical manifestations are determined by the area or areas predominantly involved, but pathology almost always reveals abnormalities (inflammatory infiltrates, neuronal loss, gliosis) beyond the symptomatic regions. Several clinicopathologic syndromes may occur alone or in combination: (1) *cortical encephalitis*, which may present as "epilepsia partialis continua"; (2) *limbic encephalitis*, characterized by confusion, depression, agitation, anxiety, severe short-term memory deficits, partial complex seizures, and dementia; the MRI usually shows unilateral or bilateral medial temporal lobe abnormalities, best seen with T2 and fluid-attenuated inversion recovery sequences, and occasionally enhancing with gadolinium; (3) *brainstem encephalitis,* resulting in eye movement disorders (nystagmus, opsoclonus, supranuclear or nuclear paresis), cranial nerve paresis, dysarthria, dysphagia, and central autonomic dysfunction; (4) *cerebellar gait and limb ataxia*; (5) *myelitis*, which may cause lower or upper motor neuron symptoms, myoclonus, muscle rigidity, and spasms; and (6) *autonomic dysfunction* as a result of involvement of the neuraxis at multiple levels, including hypothalamus, brainstem, and autonomic nerves (see autonomic neuropathy). Cardiac arrhythmias, postural hypotension, or central hypoventilation are frequent causes of death in patients with encephalomyelitis.

Paraneoplastic encephalomyelitis and focal encephalitis are usually associated with SCLC, but many other cancers have also been reported. Patients with SCLC and these syndromes usually have anti-Hu antibodies in

TABLE 39-3

ANTIBODY-ASSOCIATED PARANEOPLASTIC AND NONPARANEOPLASTIC SYNDROMES[a]

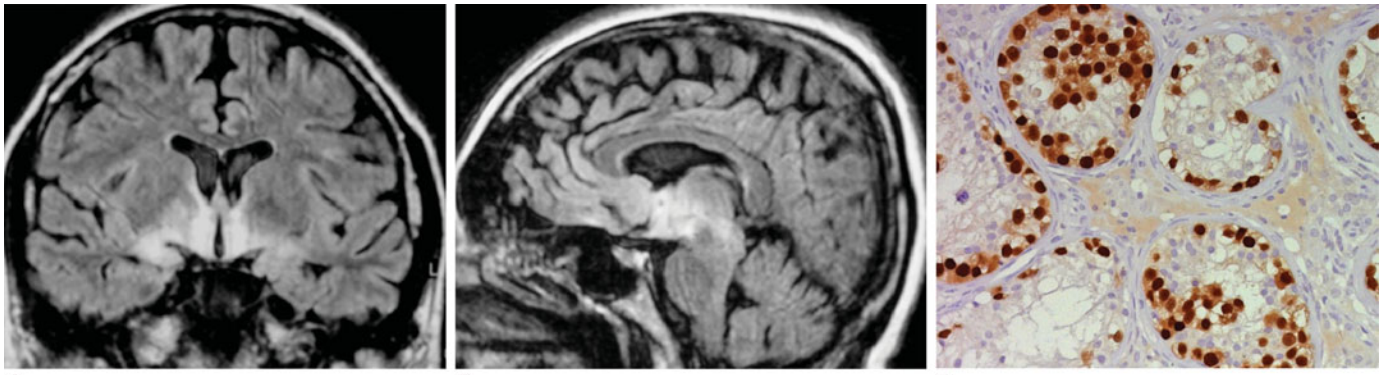
	ANTIBODIES		
	PARANEOPLASTIC		
SYNDROME	FREQUENT	INFREQUENT	NONPARANEOPLASTIC
Limbic encephalitis	Ma2, Hu, CV_2/CRMP5, *anti-NR1/NR2 of NMDA receptor*	Tr, VGKC	VGKC
Cerebellar degeneration	Yo, Tr, P/Q VGCC, Hu, Zic, Ri, CV_2/CRMP5, Ma1-2	*mGluR1*, *MAZ*	Gliadin, GAD
Hypothalamic, brainstem encephalitis	Ma2, Hu	CV_2/CRMP5	
Encephalomyelitis	Hu, Zic	CV_2/CRMP5, Ri, amphiphysin	
Chorea	CV_2/CRMP5		
Opsoclonus-myoclonus	Ri	Hu, Ma2, Yo,	
Stiff-person syndrome	Amphiphysin	*Gephyrin*, Ri	GAD
PNH (neuromyotonia)	VGKC		VGKC
Myasthenia gravis	AChR		AChR, MuSK
LEMS	P/Q-type VGCC	*MysB*	P/Q-type VGCC
Sensory neuronopathy	Hu		
Axonal sensorimotor neuropathy	Hu, CV_2/CRMP5		Monoclonal gammopathy (M protein)[b]
Autonomic neuropathy	Hu	CV_2/CRMP5, ganglionic AChR	Ganglionic AChR
Predominant sensory demyelinating neuropathy		MAG, ganglioside antibodies: often present with Waldenström's macroglobulinemia	MAG, ganglioside antibodies, often present with MGUS
Paraneoplastic retinopathy	Recoverin (CAR), anti-bipolar cell antibodies (*MAR*), *anti-enolase*	*Tubby-like protein 1*, *PNR*	*Anti-enolase*

[a]Antibodies have been validated by more than one laboratory and/or the protein sequence of the target antigen is known.
[b]The M protein usually does not have specific antibody activity.
Note: *Italics* indicate that commercial testing for these antibodies is not available. PNH, peripheral nerve hyperexcitability; CAR, cancer-associated retinopathy; MAR, melanoma-associated retinopathy; PNR, photoreceptor-specific nuclear receptor; MGUS, monoclonal gammopathy of uncertain significance; VGKC, voltage-gated potassium channel; GAD, glutamic acid decarboxylase; AChR, acetylcholine receptor; LEMS, Lambert-Eaton myasthenic syndrome; VGCC, voltage-gated calcium channel; MAG, myelin-associated glycoprotein; NMDA, N-methyl-D-aspartate.

serum and CSF. Anti-CV_2/CRMP5 antibodies occur less frequently; some of these patients may develop chorea or uveitis. Antibodies to Ma proteins are associated with limbic, hypothalamic and brainstem encephalitis and occasionally with cerebellar symptoms (Fig. 39-3); some patients develop hypersomnia, cataplexy, and severe hypokinesia. MRI abnormalities are frequent, including those described with limbic encephalitis and variable involvement of the hypothalamus, basal ganglia, or upper brainstem. Antibodies to NR1/NR2 subunits of the NMDA receptor associate with a severe, potentially lethal, but treatment-responsive encephalitis. The affected patients are young women who develop combinations of psychiatric symptoms, seizures, dyskinesias, stupor and hypoventilation. The oncologic associations of these antibodies are shown in Table 39-2.

Rx Treatment: ENCEPHALITIS AND ENCEPHALOMYELITIS

Most types of paraneoplastic encephalitis and encephalomyelitis respond poorly to treatment. Stabilization of symptoms or partial neurologic improvement may occasionally occur, particularly if there is a satisfactory response of the tumor to treatment. The roles of plasma exchange, IVIg, and immunosuppression have not been established. Approximately 30% of patients with anti-Ma2-associated encephalitis respond to treatment of the tumor (usually a germ-cell neoplasm of the testis) and immunotherapy. Two other syndromes that are responsive to treatment of the tumor and immunotherapy are



A B C

FIGURE 39-3

MRI and tumor of a patient with anti-Ma2-associated encephalitis. ***Panels A*** and ***B*** are fluid-attenuated inversion recovery MRI sequences showing abnormal hyperintensities in the medial temporal lobes, hypothalamus and upper brainstem. ***Panel C*** corresponds to a section of the patient's orchiectomy incubated with a specific marker (Oct4) of germ-cell tumors. The positive (brown) cells correspond to an intratubular germ-cell neoplasm.

the encephalitis that associates with antibodies to the NR1/NR2 subunits of NMDA receptors in patients with teratoma of the ovary, and the encephalitis that associates with VGKC antibodies in some patients with thymoma or SCLC.

PARANEOPLASTIC CEREBELLAR DEGENERATION

This disorder is often preceded by a prodrome that may include dizziness, oscillopsia, blurry or double vision, nausea, and vomiting. A few days or weeks later, dysarthria, gait and limb ataxia, and variable dysphagia can appear. The examination usually shows downbeating nystagmus and, rarely, opsoclonus. Brainstem dysfunction, upgoing toes, or a mild neuropathy may occur, but more often the symptoms and signs are restricted to the cerebellum. Early in the course, MRI studies are usually normal; later, the MRI typically reveals cerebellar atrophy. The disorder results from extensive degeneration of Purkinje cells, with variable involvement of other cerebellar cortical neurons, deep cerebellar nuclei, and spinocerebellar tracts. The tumors more frequently involved are SCLC, cancer of the breast and ovary, and Hodgkin's lymphoma.

Anti-Yo antibodies in patients with breast and gynecologic cancers and anti-Tr antibodies in patients with Hodgkin's lymphoma are the two paraneoplastic antibodies typically associated with prominent or pure cerebellar degeneration. Antibodies to P/Q-type VGCC occur in some patients with SCLC and cerebellar dysfunction; only some of these patients develop LEMS. Of note, a variable degree of cerebellar dysfunction can be associated with virtually any type of antibody-related PND of the CNS (Table 39-2).

℞ Treatment: CEREBELLAR DEGENERATION

A number of single case reports have described neurologic improvement after tumor removal, plasma exchange, IVIg, cyclophosphamide, rituximab, or glucocorticoids. However, large series of patients with antibody-positive paraneoplastic cerebellar degeneration show that this disorder rarely improves with any treatment.

PARANEOPLASTIC OPSOCLONUS-MYOCLONUS SYNDROME

Opsoclonus is a disorder of eye movement characterized by involuntary, chaotic saccades that occur in all directions of gaze; it is frequently associated with myoclonus and ataxia. Opsoclonus-myoclonus may be cancer-related or idiopathic. When the cause is paraneoplastic, the tumors involved are usually cancer of the lung and breast in adults and neuroblastoma in children. The pathologic substrate of opsoclonus-myoclonus is unclear. Most SCLC patients do not have detectable antineuronal antibodies. A small subset of patients with ataxia, opsoclonus, and other eye movement disorders develop anti-Ri antibodies; in rare instances muscle rigidity, autonomic dysfunction, and dementia also occur. The tumor most frequently involved in anti-Ri-associated syndromes is breast cancer.

If the tumor is not successfully treated, the paraneoplastic opsoclonus-myoclonus syndrome in adults often progresses to encephalopathy, coma, and death. In addition to treating the tumor, symptoms may respond to immunotherapy (glucocorticoids, plasma exchange, and/or IVIg).

At least 50% of children with opsoclonus-myoclonus have an underlying neuroblastoma. Hypotonia, ataxia, behavioral changes, and irritability are frequent accompanying symptoms. Many patients harbor antibodies to neuronal cell surface antigens of unknown identity. Neurologic symptoms often improve with treatment of the tumor (including chemotherapy) and with glucocorticoids, adrenocorticotropic hormone (ACTH), plasma exchange, IVIg, and rituximab. Many patients are left with psychomotor retardation and behavioral and sleep problems.

PARANEOPLASTIC SYNDROMES OF THE SPINAL CORD

The number of reports of paraneoplastic spinal cord syndromes, such as *subacute motor neuronopathy* and *acute necrotizing myelopathy*, has decreased in recent years. This may represent a true decrease in incidence, due to improved and prompt oncologic interventions, or may be because of the identification of nonparaneoplastic etiologies.

Some patients with cancer develop *upper* or *lower motor neuron dysfunction* or both, resembling amyotrophic lateral sclerosis. It is unclear whether these disorders have a paraneoplastic etiology or simply coincide with the presence of cancer. There are isolated case reports of cancer patients with motor neuron dysfunction who had neurologic improvement after tumor treatment. A more than coincidental association occurs between lymphoma and motor neuron dysfunction. A search for lymphoma should be undertaken in patients with a motor neuron syndrome who are found to have a monoclonal protein in serum or CSF.

Paraneoplastic myelitis may present with upper or lower motor neuron symptoms, segmental myoclonus, and rigidity. This syndrome can appear as the presenting manifestation of encephalomyelitis and may be associated with SCLC and serum anti-Hu, anti-CV_2/CRMP5, or anti-amphiphysin antibodies.

Paraneoplastic myelopathy can also produce several syndromes characterized by prominent muscle stiffness and rigidity. The spectrum ranges from focal symptoms in one or several extremities (*stiff-limb syndrome* or *stiff-person syndrome*) to a disorder that also affects the brainstem (known as *encephalomyelitis with rigidity*) and likely has a different pathogenesis.

PARANEOPLASTIC STIFF-PERSON SYNDROME

This disorder is characterized by progressive muscle rigidity, stiffness, and painful spasms triggered by auditory, sensory, or emotional stimuli. Rigidity mainly involves the lower trunk and legs, but it can affect the upper extremities and neck. Symptoms improve with sleep and general anesthetics. Electrophysiologic studies demonstrate continuous motor unit activity. Antibodies associated with the stiff-person syndrome target proteins [glutamic acid decarboxylase (GAD), amphiphysin] involved in the function of inhibitory synapses utilizing γ-aminobutyric acid (GABA) or glycine as neurotransmitters. Paraneoplastic stiff-person syndrome and amphiphysin antibodies are often related to breast cancer. By contrast, antibodies to GAD may occur in some cancer patients but are much more frequently present in the nonparaneoplastic disorder.

℞ Treatment: STIFF-PERSON SYNDROME

Optimal treatment of stiff-person syndrome requires therapy of the underlying tumor, glucocorticoids, and symptomatic use of drugs that enhance GABA-ergic transmission (diazepam, baclofen, sodium valproate, tiagabine, vigabatrin). A benefit of IVIg has been demonstrated for the nonparaneoplastic disorder but remains to be established for the paraneoplastic syndrome.

PARANEOPLASTIC SENSORY NEURONOPATHY OR DORSAL ROOT GANGLIONOPATHY

This syndrome is characterized by sensory deficits that may be symmetric or asymmetric, painful dysesthesias, radicular pain, and decreased or absent reflexes. All modalities of sensation and any part of the body including face and trunk can be involved. Specialized sensations such as taste and hearing can also be affected. Electrophysiologic studies show decreased or absent sensory nerve potentials with normal or near-normal motor conduction velocities. Symptoms result from an inflammatory, likely immune-mediated, process that targets the dorsal root ganglia, causing neuronal loss, proliferation of satellite cells, and secondary degeneration of the posterior columns of the spinal cord. The dorsal nerve roots, and less frequently the anterior nerve roots and peripheral nerves, may also be involved.

℞ Treatment: SENSORY NEUROPATHY

This disorder often precedes or is associated with encephalomyelitis and autonomic dysfunction and has the same immunologic and oncologic associations, e.g., anti-Hu antibodies and SCLC. As with anti-Hu-associated encephalomyelitis, the therapeutic approach focuses on prompt treatment of the tumor. Glucocorticoids occasionally produce clinical stabilization or improvement. The benefit of IVIg and plasma exchange is not proved.

PARANEOPLASTIC PERIPHERAL NEUROPATHIES

These disorders may develop any time during the course of the neoplastic disease. Neuropathies occurring at late stages of cancer or lymphoma usually cause mild to moderate sensorimotor deficits due to axonal degeneration of unclear etiology. These neuropathies are often masked by concurrent neurotoxicity from chemotherapy and other cancer therapies. In contrast, the neuropathies that develop in the early stages of cancer often show a rapid progression, sometimes with a relapsing and remitting course, and evidence of inflammatory infiltrates and axonal loss or demyelination in biopsy studies. If demyelinating features predominate (Chap. 34), IVIg or glucocorticoids may improve symptoms. Occasionally anti-CV_2/CRMP5 antibodies are present; detection of anti-Hu suggests concurrent dorsal root ganglionitis.

Guillain-Barré syndrome and *brachial plexitis* have occasionally been reported in patients with lymphoma, but there is no clear evidence of a paraneoplastic association.

Malignant monoclonal gammopathies include: (1) multiple myeloma and sclerotic myeloma associated with IgG or IgA monoclonal proteins; and (2) Waldenström's macroglobulinemia, B cell lymphoma, and chronic B cell lymphocytic leukemia associated with IgM monoclonal proteins. These disorders may cause neuropathy by a variety of mechanisms, including compression of roots and plexuses by metastasis to vertebral bodies and pelvis, deposits of amyloid in peripheral nerves, and paraneoplastic mechanisms. The paraneoplastic variety has several distinctive features. Approximately half of patients with sclerotic myeloma develop a sensorimotor neuropathy with predominantly motor deficits, resembling a chronic inflammatory demyelinating neuropathy (Chap. 41); some patients develop elements of the POEMS syndrome (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M* protein, *s*kin changes). Treatment of the plasmacytoma or sclerotic lesions usually improves the neuropathy. In contrast, the sensorimotor or sensory neuropathy associated with multiple myeloma rarely responds to treatment. Between 5 and 10% of patients with Waldenström's macroglobulinemia develop a distal symmetric sensorimotor neuropathy with predominant involvement of large sensory fibers. These patients may have IgM antibodies in their serum against myelin-associated glycoprotein and various gangliosides (Chap. 41). In addition to treating the Waldenström's macroglobulinemia, other therapies may improve the neuropathy, including plasma exchange, IVIg, chlorambucil, cyclophosphamide, fludarabine, or rituximab.

Vasculitis of the nerve and muscle causes a painful symmetric or asymmetric distal sensorimotor neuropathy with variable proximal weakness. It predominantly affects elderly men and is associated with an elevated erythrocyte sedimentation rate and increased CSF protein concentration. SCLC and lymphoma are the primary tumors involved. Pathology demonstrates axonal degeneration and T cell infiltrates involving the small vessels of the nerve and muscle. Immunosuppressants (glucocorticoids and cyclophosphamide) often result in neurologic improvement.

Peripheral nerve hyperexcitability (*neuromyotonia,* or *Isaacs' syndrome*) is characterized by spontaneous and continuous muscle fiber activity of peripheral nerve origin. Clinical features include cramps, muscle twitching (fasciculations or myokymia), stiffness, delayed muscle relaxation (pseudomyotonia), and spontaneous or evoked carpal or pedal spasms. The involved muscles may be hypertrophic, and some patients develop paresthesias and hyperhydrosis. CNS dysfunction, including mood changes, sleep disorder, or hallucinations, may occur. The electromyogram (EMG) shows fibrillations; fasciculations; and doublet, triplet, or multiplet single unit (myokymic) discharges that have a high intraburst frequency. An immune pathogenesis is suggested by the frequent presence of serum antibodies to VGKC. The disorder often occurs without cancer; if paraneoplastic, benign and malignant thymomas and SCLC are the usual tumors. Phenytoin, carbamazepine, and plasma exchange improve symptoms.

Paraneoplastic autonomic neuropathy usually develops as a component of other disorders, such as LEMS and encephalomyelitis. It may rarely occur as a pure or predominantly autonomic neuropathy with adrenergic or cholinergic dysfunction at the pre- or postganglionic levels. Patients can develop several life-threatening complications, such as gastrointestinal paresis with pseudoobstruction, cardiac dysrhythmias, and postural hypotension. Other symptoms include dry mouth, erectile dysfunction, anhidrosis, and sphincter dysfunction; abnormal pupillary responses may be found. The disorder has been reported to occur in association with several tumors, including SCLC, cancer of the pancreas or testis, carcinoid tumors, and lymphoma. Because autonomic symptoms can also be the presenting feature of encephalomyelitis, serum anti-Hu and anti-CV_2/CRMP5 antibodies should also be sought. Serum antibodies to ganglionic acetylcholine receptors have been reported in this syndrome, but they also occur without a cancer association. (See Chap. 28.)

LAMBERT-EATON MYASTHENIC SYNDROME

LEMS is discussed in Chap. 42.

MYASTHENIA GRAVIS

Myasthenia gravis is discussed in Chap. 42.

POLYMYOSITIS-DERMATOMYOSITIS

Polymyositis and dermatomyositis are discussed in detail in Chap. 44.

ACUTE NECROTIZING MYOPATHY

Patients with this syndrome develop myalgias and rapid progression of weakness involving the extremities and the pharyngeal and respiratory muscles, often resulting in death. Serum muscle enzymes are elevated, and muscle biopsy shows extensive necrosis with minimal or absent inflammation and sometimes deposits of complement. The disorder occurs as a paraneoplastic manifestation of a variety of cancers including SCLC and cancer of the gastrointestinal tract, breast, kidney, and prostate, among others. Glucocorticoids or treatment of the underlying tumor rarely control the disorder.

PARANEOPLASTIC VISUAL SYNDROMES

This group of disorders involves the retina and, less frequently, the uvea and optic nerves. The term *cancer-associated retinopathy* is used to describe paraneoplastic cone and rod dysfunction characterized by photosensitivity, progressive loss of vision and color perception, central or ring scotomas, night blindness, and attenuation of photopic and scotopic responses in the electroretinogram (ERG). The most commonly associated tumor is SCLC. Melanoma-associated retinopathy affects patients with metastatic cutaneous melanoma. Patients develop the acute onset of night blindness and shimmering, flickering, or pulsating photopsias that often progress to visual loss. The ERG demonstrates reduction in the b-wave amplitude. Paraneoplastic optic neuritis and uveitis are very uncommon and can develop in association with encephalomyelitis. Some patients with paraneoplastic uveitis harbor anti-CV_2/CRMP5 antibodies.

Some paraneoplastic retinopathies are associated with serum antibodies that specifically react with the subset of retinal cells undergoing degeneration, supporting an immune-mediated pathogenesis (Tables 39-2 and 39-3). Paraneoplastic retinopathies usually fail to improve with treatment, although rare responses to glucocorticoids, plasma exchange, and IVIg have been reported.

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CHAPTER 40

PERIPHERAL NEUROPATHY

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Peripheral neuropathy describes disorders of peripheral nerves, including the dorsal or ventral nerve roots; dorsal root ganglia; brachial or lumbosacral plexus; cranial nerves (except I and II); and other sensory, motor, autonomic, or mixed nerves; the term *peripheral* indicates that the disorder is outside the central nervous system (brain and spinal cord). Peripheral neuropathy affects ~2–8% of adults; the incidence increases with age. Evaluation begins with a history focusing on the time course of the illness, symptoms, medical conditions that predispose to neuropathy (e.g., diabetes mellitus, connective tissue disease, nutritional deficiency), toxic exposures (drug or environmental), and family history. Physical examination assesses the function of small sensory fibers (pain and temperature), large sensory fibers (vibration, proprioception, reflex changes), and/or motor nerves (weakness). The distribution of sensory, motor, and reflex changes determines whether the neuropathy is asymmetric or symmetric. Electrodiagnostic studies (EDx) help to classify the neuropathy into one of three major categories: axonal, demyelinating, or neuronal. Focused laboratory tests are then performed based on the history, examination, and EDx. An underlying cause can be identified in ~75% of neuropathies.

Approach to the Patient: PERIPHERAL NEUROPATHY

A stepwise approach to diagnosis is presented in Fig. 40-1. The following questions should be addressed initially:

1. *Is this a peripheral neuropathy?* The initial symptoms of peripheral neuropathy are often intermittent, and examination can be normal. Patients may present with positive and/or negative symptoms (Table 40-1). In most situations, sensory symptoms precede motor symptoms. Small-fiber neuropathies often present with dysesthesias and paresthesias, terms used interchangeably to describe unpleasant, unusual, or abnormal sensations such as burning or cutting pain, electric shock–like sensations, tingling, pins and needles, formication, prickly feelings such as a limb falling asleep, or cramp-like sensations (Chap. 12). Large-fiber neuropathies can present as numbness, tingling, or a gait disturbance (sensory ataxia). In most cases, the abnormal sensation originates in the toes and feet and ascends proximally to the legs in a stocking

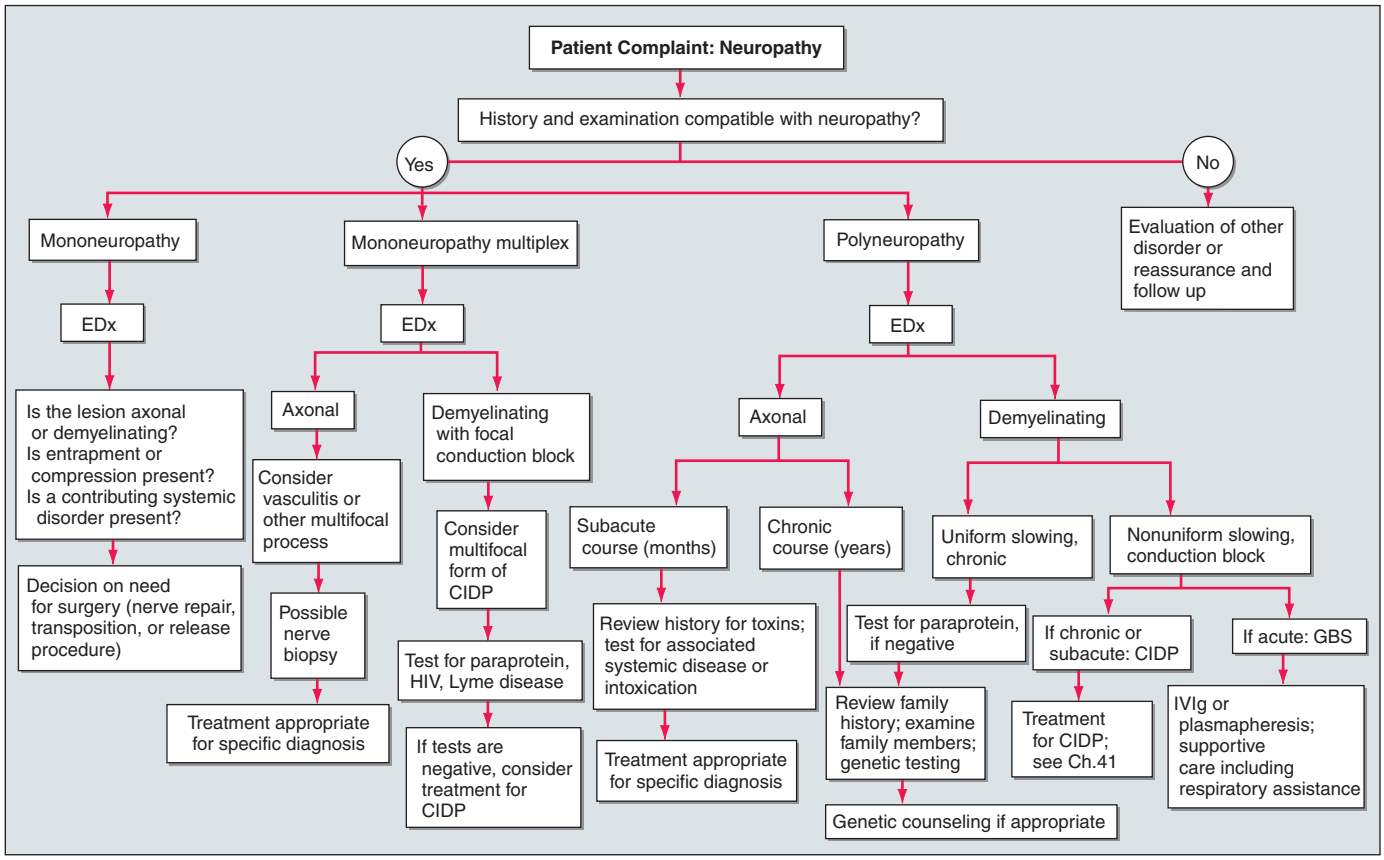

FIGURE 40-1

Approach to the evaluation of peripheral neuropathies. CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; GBS, Guillain-Barré syndrome.

TABLE 40-1

SYMPTOMS, SIGNS, AND TESTS IN PERIPHERAL NEUROPATHY

LARGE FIBER	SMALL FIBER	MOTOR	AUTONOMIC
Symptoms			
Numbness "Pins and needles" Tingling Poor balance	Pain: burning, shock-like, stabbing, prickling, shooting, lancinating Allodynia	Cramps Weak grip Footdrop Twitching	Decreased or increased sweating Dry eyes, mouth, Erectile dysfunction Gastroparesis/diarrhea Faintness, light-headedness
Signs			
Decreased Vibration Joint-position sense Reflexes	Decreased Pin prick Temperature sensation	Reduced Strength Reflexes	Orthostasis Unequal pupil size
Tests			
NCS-EMG Nerve biopsy LP	Skin biopsy QST Nerve biopsy	NCS-EMG	QSART Tilt table R-R interval Valsalva

Note: NCS-EMG, nerve conduction studies/electromyography; QSART, quantitative sudomotor axon reflex testing; QST, quantitative sensory test; LP, lumbar puncture.

distribution. Only when the sensation reaches the level of the knee or thigh do symptoms appear in the hands, producing a length-dependent, or stocking-glove, pattern. Paresthesias that begin in one hand suggest an entrapment neuropathy such as carpal tunnel syndrome.

Motor symptoms usually have a later onset than sensory symptoms. In long-standing inherited neuropathies, patients may present with isolated weakness of the feet without sensory symptoms; the ankle jerk, the most distal deep tendon reflex, is invariably absent. When confronted with a length-dependent pattern of sensory symptoms, the diagnosis of a peripheral neuropathy is not difficult. However, in cases with pure motor weakness or wasting, localization may be difficult, and in such cases the presence of distal weakness is helpful in differentiating a peripheral neuropathy from muscle or neuromuscular junction disorders, which typically present with proximal weakness. Motor neuron disease can also present with distal weakness and wasting; however, the findings are not in the distribution of an individual nerve.

2. *What is its distribution?* Polyneuropathy involves widespread and symmetric dysfunction of the peripheral nerves; mononeuropathy involves a single peripheral nerve; multiple mononeuropathy involves multiple individual peripheral nerves (Table 40-2 and Fig. 40-1). Mononeuropathies are usually due to compression, trauma, or vascular causes. Multiple mononeuropathies (also referred to as mononeuropathy multiplex) can be a result of multiple entrapments, infiltration, or vasculitis. Plexopathies (brachial or lumbosacral) also involve multiple peripheral nerves, in an asymmetric fashion.

TABLE 40-2

CLASSIFICATION OF NEUROPATHY BY LOCATION

Polyneuropathy	**Multiple Mononeuropathy**
Fairly symmetric	In distribution of single nerve(s)
Distal stocking-glove	Setting: diabetes, pressure, vasculitis
May or may not be painful	May or may not be painful
Sensorimotor	Isolated reflex loss
Symmetrically decreased reflexes	**Not a Neuropathy**
Plexopathy	Upper motor neuron signs (brisk reflexes)
Asymmetric	Prominent bladder and bowel involvement
Painful onset	Unilateral (arm, leg, face) symptoms
Multiple nerves in a single limb	Sensory level
Rapid onset of weakness, atrophy	Hyperventilation
Isolated reflex loss	

3. *Which fibers are affected?* In a polyneuropathy, manifestations can be classified as small-fiber sensory, large-fiber sensory, motor, and/or autonomic (Table 40-3). Often there is overlap, but if there is predominant involvement of one fiber group, the differential diagnosis and evaluation can be narrowed. For example, if a patient has burning pain in the feet, a small-fiber neuropathy is likely and diabetes mellitus is a possible etiology. If a patient has sensory ataxia, large fibers are likely affected and Sjögren's syndrome or a paraneoplastic process should be considered.
4. *What is the anatomic pattern?* Clinical evaluation is often helpful in categorizing a neuropathy as axonal,

TABLE 40-3

CLASSIFICATION OF NEUROPATHY BY FIBER TYPE

Small-fiber sensory (painful neuropathies and dissociated sensory loss)
- Hereditary sensory neuropathies (early)
- Lepromatous leprosy
- Diabetic (includes glucose intolerance) small-fiber neuropathy
- Amyloidosis
- Analphalipoproteinemia (Tangier disease)
- Fabry's disease (pain predominates)
- Dysautonomia (Riley-Day syndrome)
- HIV and antiretroviral therapy neuropathy

Large-fiber sensory (ataxic-neuropathies)
- Sjögren's syndrome
- Vitamin B_{12} neuropathy (from dorsal column involvement)
- Cisplatin neuropathy
- Pyridoxine toxicity
- Friedreich's ataxia

Small- and large-fiber: Global sensory loss
- Carcinomatous sensory neuropathy
- Hereditary sensory neuropathies (recessive and dominant)
- Diabetic sensory neuropathy
- Vacor intoxication
- Xanthomatous neuropathy of primary biliary cirrhosis (tabes dorsalis)

Motor-predominant neuropathies
- Immune neuropathies: acute (Guillain-Barré syndrome); relapsing
- Heritable motor-sensory neuropathies
- Acute intermittent porphyria
- Diphtheritic neuropathy
- Lead neuropathy
- Brachial neuritis
- Diabetic lumbosacralplexus neuropathy (diabetic amyotrophy)

Autonomic
- Acute: Acute pandysautonomic neuropathy, botulism, porphyria, GBS, vacore, amiodarone, vincristine
- Chronic: Amyloid, diabetes, Sjögren's, HSAN I and III (Riley-Day), Chagas, paraneoplastic

Note: GBS, Guillain-Barré syndrome; HSAN, hereditary sensory and autonomic neuropathy.

TABLE 40-4

CLASSIFICATION OF NEUROPATHY BY HISTOPATHOLOGY

	DEMYELINATING	AXONAL	NEURONAL
Pattern	Proximal = distal	Distal > proximal; length-dependent	Non-length-dependent; UE, LE, face
Onset	Acute/subacute	Slow evolution	Rapid
Symptoms	Paresthesia and weakness	Dysesthesias and distal weakness	Paresthesias, gait ataxia
Sensory signs	Vibration and proprioception > pain and temperature	Pain and temperature affected > vibration and proprioception	Vibration and proprioception > pain and temperature
Motor	Distal and proximal weakness	Distal weakness	Proprioceptive weakness
DTRs	Areflexia	Distal areflexia	Areflexia
NCS	Velocity affected > amplitude	Amplitudes affected > velocity	Sensory amplitudes affected; radial > sural
Nerve biopsy	Demyelination and remyelination	Axonal degeneration and regeneration	Axonal degeneration but no regeneration
Prognosis	Rapid recovery	Slow recovery	Poor recovery
Causes	GBS, diphtheria, CIDP, DM, MMN	Toxic, metabolic, HIV, CMT2, DM	Sjögren's, cisplatin, pyridoxine

Note: UE, LE, upper, lower extremities; DTRs, deep tendon reflexes; NCS, nerve conduction studies; GBS, Guillain-Barré syndrome; CIDP, chronic inflammatory demyelinating neuropathy; DM, diabetes mellitus; MMN, multifocal motor neuropathy; CMT, Charcot-Marie-Tooth.

demyelinating, or neuronal [dorsal root ganglion (DRG)] (Table 40-4). Most axonal neuropathies follow a length-dependent (stocking-glove) pattern with sensory (small fiber more than large fiber) symptoms and signs predominating over motor manifestations; distal reflexes are absent. In contrast, most demyelinating neuropathies affect motor fibers and sensory fibers (large fiber more than small fiber) equally, and areflexia or hyporeflexia is more generalized. DRG lesions involve purely sensory fibers in a non-length-dependent fashion; sensory ataxia and generalized loss of reflexes are usually found. EDx studies are also important in defining the anatomy of a neuropathy.

5. *What is the time course?* Rapidly evolving peripheral neuropathies are usually inflammatory [Guillain-Barré syndrome (GBS)] or toxic in origin. Subacute evolution suggests an inflammatory, toxic, or nutritional cause (Table 40-5). Chronic neuropathies, especially those that are long-standing over many years, are usually hereditary, such as Charcot-Marie-Tooth (CMT) disease.
6. *What is the likely etiology?* It is helpful to consider potential etiologies by category: metabolic (diabetes mellitus, renal failure, amyloid, porphyria); infectious [HIV, Lyme disease, cytomegalovirus (CMV), syphilis, leprosy, diphtheria]; immune-mediated [GBS, chronic inflammatory demyelinating neuropathy (CIDP), multifocal motor neuropathy, anti-myelin-associated glycoprotein (MAG) neuropathy]; hereditary (CMT); toxic (HIV drugs, anticancer drugs, alcohol, heavy metals, tick bite); vasculitic (polyarteritis nodosa, Churg-Strauss syndrome, cryoglobulinemia, isolated vasculitis of the peripheral nervous system); paraneoplastic (especially lung); nutritional (vitamin B_{12}, B_1, B_6 deficiencies); and

TABLE 40-5

CLASSIFICATION OF NEUROPATHY BY TIME COURSE

Acute
GBS, porphyria, toxic (triorthocresyl phosphate, vacor, thallium), diphtheria, brachial neuritis

Subacute
Toxic (hexacarbon, acrylamid), angiopathic, nutritional, alcoholic

Chronic
Diabetic, CIDP, paraneoplastic, paraprotein

Longstanding heritable
CMT, Friedreich's ataxia

Recurrent
Relapsing CIDP, porphyria, Refsum's disease, HNPP

Note: GBS, Guillain-Barré syndrome; CIDP, chronic inflammatory demyelinating neuropathy; CMT, Charcot-Marie-Tooth (disease); HNPP, hereditary neuropathy with pressure palsies.

miscellaneous causes (celiac disease, Fabry disease, hypothyroidism).

7. *What tests are indicated?* These may include fasting blood glucose and hemoglobin A_{1C} (HbA_{1C}); serum vitamin B_{12}; tests for systemic vasculitis or collagen vascular disease; measurement of neuropathy-associated autoantibodies; urine screen for heavy metals; spinal fluid analysis; autonomic function testing (Chap. 28); and genetic tests for hereditary neuropathies. An impaired glucose tolerance test is found in more than half of patients with idiopathic sensory neuropathy and is more sensitive than tests of fasting glucose or HbA_{1C}. Diagnostic tests to further characterize the neuropathy include quantitative sensory testing, EDx studies, sural nerve biopsy, and muscle biopsy. Diagnostic tests and procedures are more likely to be informative in patients with asymmetric, motor-predominant, rapid-onset or demyelinating neuropathies than in patients with slowly evolving length-dependent sensory > motor types.
8. *What treatment is appropriate?* Treatment of the underlying disorder, pain management, and supportive care to protect and rehabilitate damaged tissue all need to be considered. Examples of therapies directed at the underlying etiology include glycemic control for diabetic neuropathy, vitamin replacement for B_{12} deficiency, immunosuppression for vasculitis, surgery for entrapment neuropathy, enzyme replacement for Fabry disease, liver or bone marrow transplant for amyloid neuropathy, and treatment for immune-mediated neuropathies (Chap. 41).

   Pain management usually begins with tricyclic antidepressants (TCAs) such as amitriptyline, imipramine, and desipramine, which can reduce burning, aching, sharp, throbbing, and stinging (**Table 40-6**; see also Table 5-1). Duloxetine hydrochloride, a dual reuptake inhibitor of serotonin and norepinephrine, is approved for the management of neuropathic pain from diabetes. Tramadol is also effective for painful diabetic neuropathy. Anticonvulsants such as phenytoin, carbamazepine, clonazepam, gabapentin, topiramate, lamotrigine, and pregabalin are effective for lancinating pains. Topical anesthetic agents including lidocaine, mexiletine, and capsaicin creams provide transient relief for focal neuropathic pain. Narcotics may be required for severe cases of refractory neuropathic pain. Treatment of pain is discussed in detail in Chap. 5.

   The role of physical therapy, occupational therapy, and assistive devices (such as a foot brace) should not be overlooked. Trophic changes in a denervated/immobile extremity, combined with recurrent, unnoticed, painless trauma, predisposes to skin ulceration, poor healing, tissue resorption, neurogenic arthropathy, and mutilation; amputation may be required. This unfortunate sequence of events is avoidable with proper care of the denervated areas.

TABLE 40-6

TREATMENT OF PAINFUL NEUROPATHY

FIRST-LINE THERAPY
Antidepressants
Tricyclic
Amitriptyline, nortriptyline, imipramine, desimipramine, doxepin (10–150 mg qd)
Serotonin-noradrenaline reuptake inhibitors (SNRI)
Duloxetine (60–120 mg qd)
Venlafaxine (150–225 mg qd)
Antiepileptics
Carbamazepine 100–800 mg qd
Oxcarabazepine 1200–2400 mg qd
Lamotrigine 200–400 mg qd
Topiramate 300–400 mg qd
Gabapentin 900–3600 mg qd
Pregabalin 150–600 mg qd
Valproic acid 1000–1200 mg qd
SECOND-LINE THERAPY
Opioids
Oxycodone 40–160 mg qd
Morphine 90–360 mg qd PO
Tramadol 50–400 mg qd
Fentanyl patch 25–75 µg/h q 3 days
Antiarrhythmics
Mexilitine 600–1200 mg qd
Topical
Capsaicin 0.075% topical tid or qid
Lidocaine 5% patch bid
Isosorbide dinitrate spray 30 mg qhs
Others
Clonidine 0.1–2.4 mg qd
Memantine 55 mg qd
Dextromethorphan 400 mg
Levodopa 100 mg tid
Alpha-lipoic acid (thioctic acid) 600 mg
Spinal cord stimulator
Transcutaneous electrical nerve stimulation (TENS)
Alternative
Acupuncture
Pain psychologist/counselor

ELECTROPHYSIOLOGIC STUDIES (SEE CHAP. 3)

Electrophysiologic studies serve as an extension of the neurologic examination and thus play an important role in the evaluation of peripheral neuropathies. The following

information should be obtained from nerve conduction studies and electromyography (NCS-EMG):

1. Is the process axonal or demyelinating? This determination is one of the main goals of an NCS-EMG study since approaches to management and prognosis hinge largely on this distinction. In general, axonal processes affect sensory fibers more than motor fibers, whereas equal involvement is characteristic of most demyelinating processes.
2. Are the findings focal or generalized and are they symmetric or asymmetric?
3. Is this a length-dependent neuropathy? A distal axonopathy generally gives rise to length-dependent findings. The order of nerves affected, as measured by sensory NCS, for example, is sural, followed by ulnar, median, and radial. By contrast, a neuronopathy (or ganglionopathy) may affect the radial nerve before the sural or ulnar nerve.
4. How severe is the lesion? The complete absence of a response may reflect complete loss of fibers or complete conduction block.
5. What is the approximate age of the lesion? In axonal processes, the compound muscle action potential amplitudes are lost early (7 days) compared with sensory amplitudes (10 days). In demyelinating lesions it is often useful to follow progression of findings with serial studies (Chap. 41).
6. Is this a hereditary or acquired neuropathy? A uniform slowing of NCS suggests a hereditary neuropathy, although exceptions exist, such as x-linked CMT and hereditary neuropathy with liability to pressure palsies (HNPP).
7. Is there a subclinical neuropathy? In patients receiving chemotherapy or other potentially neurotoxic drugs, directed examination and limited NCS may help the physician adjust therapy before a significant neuropathy develops.
8. What is the prognosis? For both demyelinating and axonal neuropathies, the degree of axonal loss serves as a guide to prognosis.

It is important to recognize that EDx studies have limitations, and that not all patients with neuropathic symptoms will have informative findings.

MONONEUROPATHIES

Mononeuropathy (**Table 40-7**) refers to disease or damage of a single nerve. The most common causes are compression, entrapment, and trauma. Extrinsic compression usually occurs when a limb is maintained in a fixed position that produces sustained pressure on the nerve. The neuropathy is often reversible if the position is changed. However, if the patient is unable to move (e.g., during anesthesia or with intoxication), permanent injury can result. Intrinsic factors such as arthritis, fluid retention (pregnancy), amyloid, tumors, and diabetes mellitus may make nerves at entrapment sites more susceptible to injury. Often both extrinsic and intrinsic factors contribute to neuropathy, e.g., an anatomically narrowed region coupled with repetitive activity, poor posture or position. Common entrapment neuropathies include the median nerve at the wrist (carpal tunnel), ulnar nerve at the cubital tunnel or in the ulnar groove, lower trunk of the brachial plexus at the thoracic outlet, common peroneal nerve at the fibular head, posterior tibial nerve at the tarsal tunnel, and lateral femoral cutaneous nerve at the inguinal ligament. Symptoms and signs of various entrapment neuropathies are listed in Table 40-7. Histologic changes of subacute compression consist of a mixture of segmental demyelination and Wallerian degeneration reflecting retrograde axonal injury.

Since most entrapped nerves contain both motor and sensory fibers, both types of symptoms occur, usually in the distribution of the affected nerve. Sensory symptoms may include numbness, pins and needles, tingling, prickling, burning, or electric shock sensations. Light touch is often more affected than pinprick, and subtle sensory abnormalities may be revealed by measuring two-point discrimination. Aching and nondescript pain can also occur proximal to the site of nerve compression. In mild cases, no motor symptoms are evident, but in more affected patients, weakness, wasting, or fasciculations may occur. Knowledge of the anatomy of individual nerves is important to be able to localize the site of the lesion to the root, plexus, or nerves or their branches. Sensory testing may occasionally provoke paresthesias. Reflexes are generally unaffected since most entrapped nerves are distal to the deep tendon reflexes typically examined. Percussion of the nerve at the affected site may induce paresthesias (Tinel's sign); however, this may also occur in normal individuals and is not a reliable sign. Placing the limb in a posture known to aggravate the compression may accentuate symptoms (e.g., Phalen's sign evoked by flexing the wrist for carpal tunnel syndrome).

EDx studies confirm the clinical diagnosis and provide information about location, severity, and prognosis. Focal demyelination is detected as a focally reduced nerve conduction velocity along the length of the sensory and/or motor fibers. Wallerian degeneration is reflected in a reduction of distal amplitudes and as denervation potentials. The latter is associated with a relatively poor prognosis for recovery. Bone or joint abnormalities and soft tissue masses can be revealed by appropriate imaging techniques. MR neurography and ultrasonography are useful in identifying thickening of nerves at sites of compression; these studies are useful for proximal entrapments (brachial plexus, lumbosacral plexus, or sciatic or gluteal nerve lesions).

TABLE 40-7

MONONEUROPATHIES

	SYMPTOMS	PRECIPITATING ACTIVITIES	EXAMINATION	ELECTRO-DIAGNOSIS	DIFFERENTIAL DIAGNOSIS	TREATMENT
Carpal tunnel syndrome	Numbness, pain or paresthesias in fingers	Sleep or repetitive hand activity	Sensory loss in thumb, second, and third fingers Weakness in thenar muscles; inability to make a circle with thumb and index finger Tinel and Phalen signs	Slowing of sensory and motor conduction across carpal tunnel	C6 radiculopathy	Splint Surgery definitive treatment
Ulnar nerve entrapment at the elbow (UNE)	Numbness or paresthesias in ulnar aspect of hand	Elbow flexion during sleep; elbow resting on desk	Sensory loss in the little finger and ulnar half of ring finger Weakness of the interossei and thumb adductor; claw-hand	Focal slowing of nerve conduction velocity at the elbow	Thoracic outlet syndrome C8-T1 radiculopathy	Elbow pads Avoid further injury Surgery when conservative treatment fails
Ulnar nerve entrapment at the wrist	Numbness or weakness in the ulnar distribution in the hand	Unusual hand activities with tools, bicycling	Like UNE but sensory examination spares dorsum of the hand, and selected hand muscles affected	Prolongation of distal motor latency in the hand	UNE	Avoid precipitating activities
Radial neuropathy at the spiral groove	Wrist drop	Sleeping on arm after inebriation with alcohol—"Saturday night palsy"	Wrist drop with sparing of elbow extension (triceps sparing); finger and thumb extensors paralyzed; sensory loss in radial region of wrist	Early—conduction block along the spiral groove Late—denervation in radial muscles; reduced radial SNAP	Posterior cord lesion; deltoid also weak Posterior interosseous nerve (PIN); isolated finger drop C7 radiculopathy	Splint Spontaneous recovery provided no ongoing injury
Thoracic outlet syndrome	Numbness, paresthesias in medial arm, forearm, hand, and fingers	Lifting heavy objects with the hand	Sensory loss resembles ulnar nerve and motor loss resembles median nerve	Absent ulnar sensory response and reduced median motor response	UNE	Surgery if correctable lesion present
Femoral neuropathy	Buckling of knee, numbness or tingling in thigh/medial leg	Abdominal hysterectomy; lithotomy position; hematoma, diabetes	Wasting and weakness of quadriceps; absent knee jerk; sensory loss in medial thigh and lower leg	EMG of quadriceps, iliopsoas, paraspinal muscles, adductor muscles	L2-4 radiculopathy Lumbar plexopathy	Physiotherapy to strengthen quadriceps and mobilize hip joint Surgery if needed
Obturator neuropathy	Weakness of the leg, thigh numbness	Stretch during hip surgery; pelvic fracture; childbirth	Weakness of hip adductors; sensory loss in upper medial thigh	EMG—denervation limited to hip adductors sparing the quadriceps	L3-4 radiculopathy Lumbar plexopathy	Conservative management Surgery if needed
Meralgia paresthetica	Pain or numbness in the anterior lateral thigh	Standing or walking Recent weight gain	Sensory loss in the pocket of the pant distribution	Sometimes slowing of sensory response can be demonstrated across the inguinal ligament	L2 radiculopathy	Usually resolves spontaneously
Peroneal nerve entrapment at the fibular head	Footdrop	Usually an acute compressive episode identifiable; weight loss	Weak dorsiflexion, eversion of the foot Sensory loss in the anterolateral leg and dorsum of the foot	Focal slowing of nerve conduction across fibular head Denervation in tibialis anterior and peroneus longus muscles	L5 radiculopathy	Foot brace; remove external source of compression
Sciatic neuropathy	Flail foot and numbness in foot	Injection injury; fracture/dislocation of hip; prolonged pressure on hip (comatose patient)	Weakness of hamstring, plantar and dorsiflexion of foot; sensory loss in tibial and peroneal nerve distribution	NCS—abnormal sural, peroneal, and tibial amplitudes EMG—denervation in sciatic nerve distribution sparing glutei and paraspinal	L5-S1 radiculopathies Common peroneal neuropathy (partial sciatic nerve injury) LS plexopathies	Conservative follow up for partial sciatic nerve injuries Brace and physiotherapy Surgical exploration if needed
Tarsal tunnel syndrome	Pain and paresthesias in the sole of the foot but not in the heel	At the end of the day after standing or walking; nocturnal	Sensory loss in the sole of the foot Tinel's sign at tarsal tunnel	Reduced amplitude in sensory or motor components of medial and planter nerves	Polyneuropathy, foot deformity, poor circulation	Surgery if no external cause identified

Note: UE, LE, upper, lower extremities; DTRs, deep tendon reflexes; NCS, nerve conduction studies; GBS, Guillain-Barré syndrome; CIDP, chronic inflammatory demyelinating neuropathy; DM, diabetes mellitus; MMN, multifocal motor neuropathy; CMT, Charcot-Marie-Tooth.

Rx Treatment: MONONEUROPATHIES

Treatment for acute and subacute compressive neuropathies consists of identifying and removing extrinsic contributors and the use of splints to avoid further compression. In patients with chronic compressive neuropathies, exacerbating factors should be identified and treated before surgical correction is considered. The use of splints, a change of work habits to avoid activities or movements that precipitate the neuropathy, or anti-inflammatory medication for tenosynovitis may be helpful (see later).

Surgical treatment may be required for management of chronic compressive neuropathies when conservative measures have failed and the site of entrapment is clearly delineated. Studies of surgery in carpal tunnel syndrome have been encouraging.

MONONEUROPATHY MULTIPLEX

Mononeuropathy multiplex refers to the multifocal involvement of individual peripheral nerves. Although multiple compressive neuropathies can present in this manner, more often an inflammatory cause is responsible, and in such cases the disorder is referred to as *mononeuritis multiplex*. Both systemic (67%) and nonsystemic (33%) vasculitis may present as mononeuritis multiplex; less commonly, vasculitic neuropathy can present as an asymmetric or distal symmetric neuropathy. Among the systemic vasculitides, polyarteritis nodosa, rheumatoid arthritis, systemic lupus erythematosus (SLE), Churg-Strauss syndrome, Wegener's granulomatosis, and hypersensitivity vasculitis should be considered; these are often associated with constitutional symptoms such as fever and weight loss. The common fibular nerve (previously called the common peroneal nerve) is affected in ~75% of patients with vasculitic neuropathy; symptoms consist of a painful foot drop. The ulnar, median, and radial nerves may also be involved.

Rx Treatment: MONONEURITIS MULTIPLEX

Therapy of the necrotizing systemic vasculitides can stabilize and in some cases improve the neuropathy. Glucocorticoids [prednisone (1.5 mg/kg per day)] plus a cytotoxic agent (usually oral cyclophosphamide at 2 mg/kg per day) is the treatment of choice. Aggressive therapy is warranted since the prognosis for survival of untreated patients is poor. Prednisone can be changed to an alternate-day regimen after 1 month to minimize side effects. Once a clinical response is documented, prednisone may be tapered by 5 mg every 2–4 weeks. The cytotoxic agent is usually continued for 1 year. Therapy of hypersensitivity vasculitis is focused primarily upon removal of the offending antigen trigger. Treatment of localized vasculitis restricted to the peripheral nervous system can be less aggressive than for systemic vasculitis because the risk of death from untreated disease is very low. Monotherapy with either oral glucocorticoids or a brief course of cyclophosphamide (3–6 months) may be sufficient. A tissue diagnosis of vasculitis should be obtained before initiating therapy; a positive nerve biopsy helps to justify long-term immunosuppressive treatment, and pathologic confirmation of the diagnosis is often difficult after treatment has commenced.

POLYNEUROPATHIES

DIABETIC NEUROPATHY

Diabetes mellitus is associated with various neuropathy syndromes that differ in their etiology, natural history, and treatment. The overall prevalence of neuropathy is 66% for type 1 and 59% for type 2 diabetes. Neuropathy can be broadly divided into symmetric and asymmetric types, although a great deal of overlap exists between these categories. Symmetric neuropathies may present as small-fiber involvement (e.g., dysesthesias in the feet) or autonomic dysfunction (e.g., sexual impotence), but often both occur together; examination usually reveals additional evidence of large-fiber involvement and of an underlying generalized neuropathy.

The asymmetric neuropathies are divided into those with acute onset and those with gradual onset. Asymmetric abrupt-onset neuropathies include diabetic truncal radiculoneuropathy (DTRN), diabetic lumbosacral radiculoplexus neuropathy (DLSRPN), and oculomotor (third or sixth nerve) neuropathy. These monophasic conditions are thought to be due to vascular causes such as infarction. Neuropathies of more gradual onset are usually caused by entrapment or compression and include median neuropathy at the wrist, ulnar neuropathy at the elbow, peroneal neuropathy at the fibular head, and lateral cutaneous neuropathy at the thigh at the inguinal ligament (meralgia paresthetica).

Symmetric Diabetic Neuropathy

By far the most common form of diabetic neuropathy is a length-dependent diabetic sensorimotor polyneuropathy (DSPN). The lifetime prevalence is ~55% for type 1 and 45% for type 2 diabetes. DSPN is a mixed neuropathy with small- and large-fiber sensory, autonomic, and motor nerve involvement in various combinations, although sensory and autonomic symptoms are more

prominent than motor ones (Table 40-1). Proposed criteria for the diagnosis of DSPN are two or more of the following: symptoms or signs of neuropathy, abnormal EDx studies, quantitative sensation test abnormalities, heart rate decrease with deep breathing or Valsalva maneuver.

DSPN has an insidious, progressive course. Initial symptoms may consist of numbness, tingling, buzzing, burning, or prickling sensation affecting the toes and feet. Paresthesias ascend up to the legs and then hands in a stocking-glove distribution. Over time, gait disturbance and distal weakness may occur. Painful or insensitive extremities predispose to foot ulcers; amputation is sometimes required. Examination shows a distal sensory loss to pin, temperature, touch, and vibration sense. Ankle reflexes are invariably reduced or absent. Weakness, if present, is mild and involves toe flexors and extensors. The length-dependent pattern of neuropathy is evident in the stocking-glove sensory loss, and some patients also show sensory loss in the anterior abdominal region in a wedge-shaped distribution. Autonomic symptoms including impotence, nocturnal diarrhea, difficulty voiding, abnormalities of sweating, and abnormal fullness after eating and orthostatic hypotension may be present.

The diagnosis of DSPN is usually straightforward, although other contributors to the neuropathy should be excluded, including nutritional (vitamins B_1 and B_{12} and folate deficiencies), toxic (alcohol, vitamin B_6 toxicity), immune-mediated (paraprotein), and inherited causes. An alternative diagnosis should be sought in patients with rapidly progressive or asymmetric weakness, a family history of neuropathy, exposure to toxins, or prior malignancy. A glucose tolerance test is indicated in all patients presenting with neuropathy. EDx studies show mixed findings of axonal loss and demyelination in a length-dependent pattern. Nerve biopsy and lumbar puncture are not necessary unless alternative diagnoses are being considered.

Various hypotheses have been invoked to account for DSPN. Increased neuronal concentrations of glucose induce the conversion of glucose to sorbitol by aldose reductase using NADPH as a coenzyme. Sorbitol decreases levels of *myo*-inositol and phosphoinositides, leading to a decrease in diacylglycerol, protein kinase C, and Na^+, K^+, ATPase activity. This sequence of events leads to axonal loss and demyelination and is the basis of trials using aldose reductase inhibitors and high *myo*-inositol diets. A second hypothesis proposes insufficient blood flow: increased aldose reductase activity results in competitive inhibition of nitric oxide synthetase for NADPH, resulting in decreased nitric oxide and reduced blood flow in the vasa nervorum. Altered metabolism of fatty acids, reduced concentrations of nerve growth factor, and oxidative stress are possible additional contributing factors.

℞ Treatment: DIABETIC SENSORIMOTOR POLYNEUROPATHY

Treatment consists of strict glucose control, which prevents the neuropathy from worsening; established neuropathy does not usually reverse. Aldose reductase inhibitors to treat and prevent diabetic neuropathy have been studied in >30 trials. Although controlled trials of the aldose reductase inhibitors sorbinol and tolrestat were found to improve electrophysiologic or morphometric markers of DSPN, any clinically meaningful improvement in pain or sensation has been inconsistent. Treatment with recombinant nerve growth factor was ineffective. Alpha lipoic acid (thioctic acid), an antioxidant, has been shown to improve experimental diabetic neuropathy, and a meta-analysis of clinical trials suggested that the treatment (600 mg/d IV for 3 weeks) is safe and improves symptoms and signs of neuropathy. Pancreatic transplantation can halt progression of DSPN but is a realistic therapy only for patients who have renal failure and are undergoing combined kidney and pancreas transplantation.

Glycemic control is essential for the prevention of diabetic autonomic neuropathy. Once neuropathy is established, few effective treatments exist.

Asymmetric Diabetic Neuropathy

Cranial Neuropathies

The oculomotor nerves (in decreasing order of frequency the sixth, third, and rarely fourth nerves) are most often affected. In general, cranial neuropathy occurs in patients older than 50 years who already have evidence of DSPN. Abducens (sixth) nerve palsy manifests as the sudden onset of painless double vision, and examination shows paralysis of abduction on the affected side (Chap. 17). In a patient with diabetes who has no other clinical findings the diagnosis is straightforward. Spontaneous recovery typically occurs within 3–5 months and no treatment except an eye patch or prism is necessary. Diabetic third nerve palsy is also abrupt in onset but is often heralded by intense retroorbital pain that may be present for several days. Symptoms include double vision, unilateral ptosis, and restriction of medial gaze and upgaze. Unlike compressive etiologies (e.g., aneurysms of the superior cerebellar or posterior communicating arteries), which present with an enlarged ("blown") pupil, the pupil is nearly always spared in diabetic third nerve palsy. This is due to the fact that pupillomotor fibers are present on the outer layers of the third nerve fascicle, and an ischemic lesion tends to involve the center of the fascicle. In atypical cases, such as those with pupillary involvement or without pain, a neuroimaging study, usually MRI or

MR angiography (MRA), is indicated to exclude an aneurysm. Most patients improve spontaneously in 3–6 months without any treatment. Symptomatic treatment with eye prisms is often helpful. Idiopathic neuropathy of the facial nerve (seventh; Bell's palsy) is also more common in older diabetics than in nondiabetics. The clinical features and prognosis are similar to the nondiabetic form (Chap. 29).

Limb Mononeuropathies

Diabetics are also susceptible to entrapment neuropathies, including median neuropathy at the wrist (carpal tunnel syndrome), ulnar neuropathy at the elbow, fibular (peroneal) neuropathy at the fibular head, and lateral cutaneous neuropathy at the inguinal ligament (meralgia paresthetica). The special susceptibility of diabetic nerves may be related to endoneurial edema and vascular factors. Patients typically present with several weeks or months of pain, numbness, or weakness in the distribution of the affected nerve. The approach to these entrapments is similar to that in individuals without diabetes. Decompressive surgery may be needed if there is associated weakness, numbness, or pain in the distribution of the affected nerves and if no reversible extrinsic source of compression (position/habits) can be identified.

Radiculopathies and Plexopathies

Diabetic truncal radiculoneuropathy occurs in diabetics in middle or later life, usually in association with underlying DSPN. Patients present with an abrupt onset, typically over days to weeks, of severe pain in the thoracic spine, flank, rib cage, or upper abdomen. The pain is described as burning, stabbing, or belt-like. Contact hyperesthesia is present in the area of pain. Associated, sometimes profound, weight loss is often described; this can also be seen in diabetic amyotrophy (see later). Examination may be normal or may reveal variable sensory loss in the distribution of one or several intercostal nerves and their branches. Anterior abdominal wall weakness may be noted as focal bulging of the weakened region when the patient attempts to sit up. A needle EMG of the affected muscles may confirm denervation in the abdominal or intercostal muscles; the paraspinal muscles may be spared. This finding, and a reduced fiber density measured by skin biopsy from symptomatic regions, suggests that the injury in diabetic truncal radiculoneuropathy is at, or distal to, the sensory ganglion. The differential diagnosis in this elderly population should include herpes zoster infection (without rash) and an abdominal malignancy. Most patients improve spontaneously, although the pain may persist for weeks to months. Pain management may be difficult and includes topical capsaicin and narcotics. The abrupt onset and spontaneous recovery suggest a vascular cause to this syndrome, although an inflammatory etiology can not be excluded.

Diabetic amyotrophy (femoral neuropathy; proximal diabetic neuropathy) occurs in older patients, usually with type 2 diabetes. Patients present with the abrupt onset of severe pain affecting the anterior thigh. Buttock and lower back pain may also be present. The pain is worse at night and is described as burning. Weakness and wasting in the thigh muscles leads to difficulty climbing stairs and walking. Males are more likely to be affected, and weight loss, at times dramatic, is invariably present. Although symptoms may be bilateral, one side is more severely affected than the other. Examination shows prominent wasting of the quadriceps muscle unilaterally with weakness of the knee extensor and hip flexor and, variably, ankle dorsiflexor, accompanied by sensory loss in the thigh and leg in the distribution of the femoral nerve, and a reduced knee jerk on the affected side. The syndrome progresses over weeks to months, then stabilizes and gradually improves. EDx studies show findings of radiculopathy (L2-4), lumbar plexopathy, or femoral neuropathy along with a distal sensorimotor neuropathy. An MRI of the lumbosacral spine and plexus is indicated to exclude a compressive cause. Cerebrospinal fluid (CSF) examination and nerve biopsy should be considered whenever the diagnosis is uncertain. The level of CSF protein is often elevated, and biopsy of the intermediate femoral cutaneous nerve may show microvasculitis. The condition may be quite painful and require opiates for pain control. Treatment with high-dose glucocorticoids or intravenous immunoglobulin (IVIg) has been effective in case reports, although controlled trials have not shown clear benefit. Physiotherapy and orthotic devices are helpful. The prognosis is generally favorable; improvement occurs over several months in most patients treated with symptomatic measures only. A similar condition may also occur in nondiabetic patients.

Uncommon Diabetic Neuropathies

Diabetic neuropathic cachexia (acute painful neuropathy of diabetes) is an uncommon painful sensory neuropathy occurring in type 1 diabetics in the setting of poor glucose control and weight loss. Manifestations include severe pain in the feet ascending up to the legs and trunk with associated allodynia. Examination may reveal distal sensory loss to pinprick and vibration and reduced or absent ankle jerks. Strength is preserved. EDx studies may show a distal neuropathy. Unlike DSPN, the prognosis is favorable with glucose control. The painful symptoms reverse over months to a year.

Insulin neuritis describes a painful neuropathy seen with initiation of insulin treatment for diabetes. The clinical presentation is similar to the acute painful neuropathy of diabetes, and most patients improve.

A reversible sensory and motor polyneuropathy has been reported in association with diabetic ketoacidosis.

Most patients also have upper and lower motor neuron signs, as well as a preexisting neuropathy. The etiology is not clear; critical illness neuropathy may be the underlying cause. Finally, chronic inflammatory demyelinating neuropathy (CIDP) occurs in diabetics; the disease resembles that seen in nondiabetics.

TOXIC INCLUDING CHEMOTHERAPY-INDUCED NEUROPATHIES

Most toxic neuropathies are distal axonal degenerations that develop gradually over time. The causes are varied, including drugs, heavy metals, and industrial and environmental substances (**Table 40-8**). Novel anticancer drugs and antiretroviral agents are the most common drugs implicated, although over-the-counter medications (especially pyridoxine) can also cause neuropathy. A temporal relationship between introduction of the toxic substance and the onset of neuropathy is usually noted, as is a dose-response relationship. In general, a lower dose over a longer period of time is less toxic than a higher dose for a short period, even if the eventual cumulative doses are similar. Onset following introduction of the agent and reversal or at least arrest following its removal provide the best evidence of a toxic neuropathy, along with the symptoms and signs typically caused by the suspected agent. The neuropathy may first manifest or may continue to progress after discontinuing the substance; this phenomenon, known as *coasting*, is seen with the platinum cancer drugs, hexacarbons, nucleoside analogue reverse transcriptase inhibitors, and pyridoxine.

Clinical evaluation includes a history focusing on the temporal relationship between exposure and onset of sensory or motor symptoms, comorbid diseases that may cause neuropathy, and symptoms of systemic toxicity. Nerve biopsy occasionally demonstrates pathognomonic features such as osmiophillic Schwann cell inclusions in amiodarone, perhexiline and chloroquine neuropathies, and paranodal giant axonal swellings in hexacarbon neuropathies. Levels of some toxins can be measured in certain tissues: heavy metals such as lead, arsenic, and thallium can be measured in urine; arsenic can be measured in hair or nails. Blood levels of drugs are also useful.

Table 40-8 lists some of the better-documented neurotoxic substances. Awareness of the types of industries in which toxic exposure can occur is important in identifying occupational exposure. Lower dosages and shorter durations of exposure may produce neuropathy in susceptible individuals such as those with underlying inherited neuropathy. An acute onset of neuropathy occurs with drugs such as paclitaxel, suramin, and vacor, and with biologic agents such as ciguatera, puffer fish (tetrodotoxin), and buckthorn. Some toxic agents that otherwise require long-term exposure to produce chronic neuropathy may do so acutely when used at higher doses; examples include arsenic, thallium, and pyridoxine. The combination of two toxic drugs, commonly seen with anticancer therapy (e.g., paclitaxel and cisplatin), may produce greater nerve toxicity than either one alone. Patients with underlying conditions may be predisposed to neuropathy when exposed to some compounds, e.g., vitamin B_{12}–deficient patients who receive nitrous oxide anesthesia, or patients with porphyria who receive barbiturates. Usually, however, toxic neuropathy is subacute in onset, developing over a period of months. Vincristine, amiodarone, nitrofurantoin, isoniazid, dimethylaminopropionitrile (DMAPN), inorganic mercury, and thallium all cause a subacute neuropathy. The insidious onset of a chronic neuropathy occurs with exposure to industrial toxins at low dosages over a prolonged period of time. Examples include acrylamide, allyl chloride, hexacarbons, carbon disulfide, ethylene oxide, lead, and arsenic. In addition to preexisting neuropathy, other host factors, including diabetes, hepatic or renal impairment, and alcohol abuse, may reduce the threshold for neurotoxicity. The neuropathy may be predominantly motor with lead, inorganic mercury, organophosphates, buckthorn, dapsone, and vincristine; small-fiber sensory with DMAPN, thallium, nucleoside analogue reverse transcriptase inhibitors (dideoxycytidine ddC, dideoxyinosine ddI, stavudine d4T), ethionamide, metronidazole, and taxane; or large-fiber sensory with cisplatin, high doses of taxol, pyridoxine, or acrylamide. Autonomic dysfunction can occur with vincristine, vacor, perhexiline, high dose-pyridoxine, and platinum. Other toxins that may involve autonomic nerves include acrylamide (acral and pedal hyperhidrosis), DMAPN (urologic and sexual dysfunction), and hexacarbons (hyperhidrosis and impotence). Some toxic neuropathies also involve the cranial nerves. These include trichloroethylene, which causes acute dysfunction of the cranial nerves V, VII, III, and II; thallium and acute fulminant vacor poisonings, which cause facial diplegia with generalized neuropathy resembling Guillain-Barré syndrome; perhexiline, which causes facial diplegia and perioral numbness; vincristine and paclitaxel, which may be associated with numbness in the trigeminal nerve distribution; and chloramphenicol, ethambutol, and nitrous oxide, all of which may cause optic neuropathy. Asymmetric neuropathy or mononeuritis multiplex is rare but may be seen with lead, which may cause unilateral wrist drop; or with DMAPN, which causes sacral dermatomal sensory loss. Signs of toxicity to kidney, liver, or other organs can in some cases alert the clinician to the possibility that a neuropathy could be toxic in origin.

Cisplatin

Cisplatin (*cis*-diaminodichloroplatinum) is a heavy metal used to treat a variety of solid tumors. Cisplatin is toxic

TABLE 40-8

TOXIC NEUROPATHIES

	CIRCUMSTANCES OF TOXICITY	NEUROPATHY	COMMENTS
AXONOPATHY			
Nonpharmaceutical toxins			
Acrylamide monomer	Flocculators, grouting agents	Sensory ataxia; large fiber	Numbness, excessive sweating, exfoliative dermatitis
Allyl chloride	Epoxy resin, glycerin	Dysesthesia and distal weakness	
Arsenic (inorganic)	Copper/lead smelting, contaminant in recreational drugs, suicide/homicide (herbicide/insecticide)	S > M; painful; usually subacute or chronic; may be acute following large doses	Skin: hyperkeratosis, "rain-drop" pigmentation of skin, Mees' line in nails
Carbon disulphide	Viscose rayon, cellophane; airborne industrial exposure	SM	Slow NCS
Dimethylaminopropionitrile (DMAPN)	Polyurethane foam	SM	Small-fiber neuropathy with prominent bladder symptoms and impotence
Ethylene oxide	Sterilization of biomedicals		
Hexacarbons (paranodal giant axonal)	Solvents, adhesives Substance abuse (glues and thinners)	SM	Neurofilament swelling of axons; CNS
Lead	Batteries, smelting metal ores, paints	M > S; wrist drop	Burton's line, anemia, basophilic stippling
Mercury (inorganic)	Environmental/workplace	CNS > PNS; neuropathy uncommon	Tremor, insomnia, behavioral change
Methyl bromide	Fumigant, insecticide, refrigerant, fire extinguisher	Variable recovery	Encephalitis, ataxia
Organophosphorus esters	Insecticide, petroleum, plastics	SM	Acute toxicity presents as cholinergic crisis
Thallium (rat poison)	Rodenticides, insecticides	Painful SM	Thallium (alopecia, Mees' line, hyperkeratosis)
Vacor	Rodenticide, suicide	Rapid onset of severe axonopathy and autonomic dysfunction	Diabetic ketoacidosis a feature of acute toxicity
Pharmaceutical agents			
Chloramphenicol	Mean cumulative dose 255 g, duration	S > M	Also optic neuropathy
Colchicine	Chronic dosing at 1.2 mg/d especially in the presence of renal dysfunction	Distal paresthesias and proximal weakness	Also myopathy with elevated serum CK
Dapsone	200–400 mg/d over many months	Pure motor, especially upper limbs	May look like motor neuron disease
Disulfiram	250–500 mg/d after several months used for alcoholism	SM	Difficult to distinguish from alcohol neuropathy
Ethambutol	>20 mg/kg per day over many months	Sensory neuropathy	Also optic neuropathy
Ethionamide	>15 mg/kg	Sensory neuropathy	Limited by GI, dermatologic and CNS side effects
Gold	Controversial, as rheumatoid arthritis can cause neuropathy Not dose dependent	S > M with myokymia	Rash, pruritus
Isoniazid	>5 mg/kg over weeks or about 6 months, depending on acetylator status	Dose-dependent SM neuropathy	Add pyridoxine 50 mg/d when using INH
Metronidazole	Cumulative dose > 30 g	Sensory (small and large fiber)	
Misonidazole	Cumulative dose > 18 g/m^2	Sensory axonopathy	Dose-limiting side effect
Nitrofurantoin	Standard dose of 200 mg/day over a few weeks	Mild SM neuropathy	
Nitrous oxide	Dental surgery, anesthesia, substance abuse	S >> M	Toxic myeloneuropathy resembles cobalamine deficiency
Nucleoside analogues (ddC, ddI, 4dT)	>12.5 mg/kg per day for ddI, 0.02 mg/kg per day for ddC, and 0.5 mg/kg per day for 4dT	Painful sensory neuropathy	Difficult to distinguish from HIV neuropathy
Pyridoxine	>200 mg a day over several months	Length-dependent axonopathy	Neuronopathy at higher doses
Suramin	Peak serum concentration of 350 µg/mL	S > M; may be demyelinating	
Taxol	Cumulative dose of >1500 mg/m^2	S > M	Higher single doses may cause neuronopathy
Thalidomide	100 mg/d for 6 months.	S > M	Thalidomide (brittle nails, palmar erythema)
Vincristine and other vinca alkaloids	Almost all patients	S > M but autonomic fibers also affected	Vacuolar myopathy

TABLE 40-8 (*CONTINUED*)

TOXIC NEUROPATHIES

	CIRCUMSTANCES OF TOXICITY	NEUROPATHY	COMMENTS
Myelinopathy			
Amiodarone	400 mg/day for 6–36 months, serum concentration of 2.4 mg/L	SM; dose-dependent	Tremor
Perhexiline	Not dose-related	S (large fiber) and M, facial, autonomic	Hepatic toxicity
Polychlorinated biphenyls	Plasticizers, electrical insulators	SM	Acne, brown nails
Suramin	Not dose-related	Demyelinating like subacute GBS	
Trichloroethylene	Dry-cleaning, rubber, degreasing agent	Mainly cranial nerves: trigeminal, facial, oculomotor, optic	Limbs rarely affected
Sensory Neuronopathy			
Platinum compounds, e.g., cisplatin	Cumulative dose more than 900 mg/m^2	Large-fiber sensory	Irreversible
High-dose pyridoxine	Massive parenteral doses in grams over days	Sensory neuronopathy; gait ataxia, pseudoathetosis	May be irreversible
Taxol	Single dose of ≥250 mg/m^2	Sensory ataxia	May be irreversible

Note: S, sensory; M, motor; SM, sensorimotor; NCS, nerve conduction studies; CNS/PNS, central/peripheral nervous system; CK, creatine kinase; GI, gastrointestinal; GBS, Guillain-Barré syndrome; EDx, electrodiagnosis; CSF, cerebrospinal fluid; CMV, cytomegalovirus; DSPN, diabetic sensory polyneuropathy.

to dorsal root ganglia neurons, producing a dose-related large-fiber sensory neuropathy (*neuronopathy*). It also injures hair cells of the cochlea, causing hearing loss. Peripheral neuropathy is the dose-limiting toxicity of cisplatin. A cumulative cisplatin dose of at least 300 mg/m^2 may lead to paresthesias in the extremities and numbness. Lhermitte's sign, an electric shock–like sensation evoked by flexion of the neck, may occur due to retrograde degeneration of axons in the posterior columns of the spinal cord. Patients with preexisting neuropathy and those who receive combination chemotherapy may develop symptoms after lower cumulative doses. Sensory ataxia may be disabling in patients who have severe neuropathy. Small-fiber sensation (e.g., pain and temperature) and strength are generally spared.

Oxaliplatin

Oxaliplatin can cause an early acute and a late chronic neuropathy. The acute neuropathy begins during the infusion, within minutes to hours, or within 1–2 days of administration. Patients complain of paresthesias in the hands or feet, mouth, or throat along with myalgias, cramps, or stiffness. Shortness of breath or difficulty swallowing may occur. Symptoms are often triggered by exposure to cold. Neuromyotonia may be seen on EMG. Although this acute toxicity occurs in >90% of patients, it is often self-limited and resolves within days. A channelopathy is thought to be the underlying mechanism. A chronic large-fiber ataxic neuropathy, similar to that caused by cisplatin, occurs with cumulative doses ≥780 mg/m^2, generally after eight or nine treatment cycles. Even though the signs and symptoms (paresthesias, distal sensory loss, and loss of reflexes) are similar to those caused by cisplatin, oxaliplatin neuropathy is more likely to be reversible.

Paclitaxel

Paclitaxel, a diterpene alkaloid drug, is widely used as a chemotherapeutic agent. Peripheral neuropathy, which can be severe, is the dose-limiting toxicity. A symmetric, length-dependent neuropathy with prominent sensory (large more than small fiber) and minor motor manifestations, is typically present. Preexisting neuropathy is a risk factor. The neuropathy is dose-dependent, and both single and cumulative doses are important. The drug affects microtubule assembly, causing disruption of axonal transport and a "dying back" axonal neuropathy.

Vincristine

Vincristine, an alkaloid derived from the pericuwinkle plant, vinca rosea, causes a dose-dependent sensorimotor neuropathy. Lower cumulative doses (4–19 mg) cause only reflex changes, while higher doses progressively cause paresthesias, sensory loss (upper extremity more than lower), weakness with footdrop, and hand weakness and clumsiness. Autonomic neuropathy can manifest as cardiac arrhythmias, orthostasis, urinary bladder dysfunction, constipation, or paralytic ileus. Cranial neuropathies have also been described.

Suramin

Suramin is a polysulfonated naphthylurea that has been used as an antineoplastic agent and as a treatment for

certain parasitic diseases. Suramin causes a length-dependent distal axonal neuropathy in over half of patients and a subacute inflammatory demyelinating neuropathy in ~15% of patients. Neuropathy occurs with peak plasma concentrations >300 μg/mL.

Thalidomide

Peripheral neuropathy remains the dose-limiting toxicity of thalidomide, which causes a length-dependent painful sensory axonal neuropathy; a sensory neuronopathy has also been reported. Peripheral neuropathy occurs in up to 75% of patients and is dose-dependent, rarely occurring with cumulative doses <20 g, but invariably noted at cumulative doses >100 g. The risk of neuropathy is minimized at doses ≤150 mg/d. Serial sensory action potential measurements are important in the early detection of the neuropathy. Symptoms often, though not always, improve with cessation or dose reduction. The neuropathy develops at a lower dose and is typically more severe in patients with a preexisting diabetic neuropathy.

Bortezomib

Bortezomib (Velcade), a novel proteosome inhibitor used in the treatment of multiple myeloma, induces a length-dependent, sensory more than motor, axonal polyneuropathy that is dose-dependent, increasing with increasing cycles of treatment. Both small- and large-fiber sensory symptoms occur. In a few patients the symptoms stabilize or improve after stopping treatment. A toxic acquired demyelinating neuropathy has also been reported.

℞ Treatment: TOXIC NEUROPATHIES

Removal of the toxic substance is the most important step. Specific treatments are available for some toxic neuropathies. Treatment for heavy metal toxicity includes chelation therapy: penicillamine or calcium-EDTA for lead toxicity; penicillamine or British anti-Lewisite (BAL) for arsenic toxicity; and potassium chloride or Prussian blue for thallium toxicity. Pyridoxine (10–50 mg/d) can be used to prevent and treat isoniazid neurotoxicity. Niacin and pyridoxine are recommended for ethionamide neurotoxicity. There may be some benefit from the use of neuroprotective agents. Vitamin E (tocopherol) was reported to be neuroprotective in one small, unblinded study, but these results have not been confirmed. Org 2766, glutathione, diethyldithiocarbamate, and amifostine have also been tried without conclusive outcomes. Studies are under way to evaluate the possible efficacy of nerve growth factor.

Prognosis for recovery depends on both the site of pathology and the severity of the neuropathy. Involvement of the dorsal root ganglion is associated with a poor prognosis. Severe axonopathy requires years for recovery. Demyelinating disorders, if detected early, generally are associated with a relatively rapid recovery. Most toxic neuropathies, even if advanced, will at least stabilize, and some will improve, when exposure to the toxic agent is stopped.

NUTRITIONAL NEUROPATHIES

Thiamine (Vitamin B_1) (Dry Beriberi)

Thiamine deficiency can be a result of inadequate intake, as may occur in alcoholism, anorexia, intentional dieting, starvation, or bulimia. Protracted vomiting, e.g., in patients receiving chemotherapy or in pregnant women with hyperemesis gravidarum, may also cause thiamine deficiency. Neuropathy from thiamine deficiency presents as the acute or subacute onset of paresthesias, dysesthesias, and mild weakness in the legs. On examination a stocking-glove sensory loss, distal weakness in the legs, and loss of ankle jerks is typical. Nerve conduction tests and sural nerve biopsies show axonal degeneration. Erythrocyte transketolase activity is reduced in the blood. Treatment consists of oral thiamine replacement, 100 mg/d. Alcohol-induced neuropathy develops in some patients without any identifiable nutritional deficiencies, suggesting that alcohol itself may cause sensory neuropathy. It predominantly affects small fibers and is painful, but there is considerable overlap with thiamine deficiency neuropathy.

Pyridoxine (Vitamin B_6)

A subacute length-dependent axonal neuropathy occurs as a result of pyridoxine deficiency. Causes include dietary deficiency and drugs such as isoniazid, cycloserine, and penicillamine, which act as pyridoxine antagonists by combining to the aldehyde moiety of the vitamin. Dietary deficiency of pyridoxine is uncommon, although the requirement is increased in pregnancy. Measurement of xanthurenic acid after tryptophan loading can help confirm the diagnosis. Treatment consists of oral pyridoxine, 30 mg/d. Pyridoxine supplements are recommended for prophylaxis during pregnancy and for patients taking isoniazid. Overzealous treatment with pyridoxine should be avoided, as high doses of pyridoxine cause a toxic sensory neuronopathy.

Vitamin B_{12} (Cobalamin)

Peripheral neuropathy is a minor part of the vitamin B_{12} deficiency syndrome; subacute combined degeneration of the spinal cord is more prominent. Distal sensory loss

predominantly involving large-fiber modalities, dysequilibrium, Lhermitte's sign, and the combination of an absent ankle jerk and upgoing toe may be present. Pancytopenia, megaloblastic anemia, and glossitis are other signs. The principal dietary sources of vitamin B_{12} are meat and dairy products; enteric processing and absorption typically occur in the terminal ileum. Common causes of vitamin B_{12} deficiency include inadequate intake, malabsorption (including post-gastrectomy), and pernicious anemia. Borderline vitamin B_{12} deficiency may develop after exposure to nitrous oxide during anesthesia or with chronic recreational use. Diagnosis of vitamin B_{12} deficiency is made by low serum cobalamin levels and raised levels of methylmalonic acid and homocysteine. Autoantibodies to intrinsic factor and gastric parietal cells are present in pernicious anemia. Treatment is with parenteral administration of cobalamin (vitamin B_{12}) .

Riboflavin, Nicotinic Acid and Other B-Group Vitamins

Riboflavin and nicotinic acid deficiencies have been incriminated in neuropathies, usually in association with deficiencies of other water-soluble vitamins. Peripheral neuropathy may be accompanied by dermatitis, diarrhea, and dementia (pellagra). The diagnosis is made on clinical grounds, and treatment consists of administration of 40–250 mg niacin daily. *Strachan's syndrome* is characterized by a painful sensory neuropathy associated with orogenital dermatitis, amblyopia, and deafness. This syndrome was first reported in Jamaica and later in malnourished field workers and prisoners of war. Distal sensory loss with hyporeflexia at the ankles (peripheral nerve lesion), combined with hyperreflexia at the knees and an ataxic gait (spinal cord involvement), indicate the combined peripheral and central axonal loss that is characteristic of this deficiency state. Treatment with vitamin B complex frequently improves the symptoms.

Vitamin E Deficiency

Vitamin E deficiency can occur from fat malabsorption or from abetalipoproteinemia. The clinical features of vitamin E deficiency resemble those of Friedreich's ataxia (Chap. 26), with severe large-fiber loss and a non-length-dependent reduction of sensory nerve action potentials suggestive of dorsal root ganglionopathy. The diagnosis is confirmed by measurement of serum α tocopherol and the ratio of vitamin E to total serum lipids. Treatment consists of administration of α tocopherol (400 mg bid), which may reverse or prevent progression of the sensory neuronopathy.

INFECTIONS AND PERIPHERAL NEUROPATHY

HIV Infection

(See also Chap. 37) HIV infection is associated with polyradiculopathies, distal symmetric polyneuropathies, inflammatory demyelinating polyneuropathies, multifocal mononeuropathies, cranial neuropathies, and neuropathies induced by antiretroviral drugs (Table 40-9).

TABLE 40-9

NEUROPATHIES ASSOCIATED WITH HIV INFECTION

HIV NEUROPATHY	SYMPTOMS AND SIGNS	TYPICAL CD4 COUNTS, CELLS/μL	DIAGNOSTIC TESTS
Distal symmetric polyneuropathy	Painful paresthesias, distal sensory loss, absent ankle jerk	<200	EDx studies Skin biopsy
GBS, CIDP	Progressive weakness, areflexia, numbness	<500; >50	EDx studies CSF studies: elevated protein, variable pleocytosis
Mononeuropathy multiplex (cryoglobulinemia, hepatitis C)	Footdrop, wrist drop, facial weakness	<500; >50	EDx studies, nerve biopsy
CMV polyradiculopathy	Flaccid paraparesis, saddle anesthesia, urinary retention	<50	EDx, CSF studies
Herpes zoster, tuberculosis, lymphoma	Depends on specific etiology	<50	EDx, CSF studies Nerve biopsy
Toxic neuropathy	Similar to DSPN	<500	Eliminate drug: stavudine (d4T), didanosine (ddI), zalcidabine (ddC)

Note: GBS, Guillain-Barré syndrome; CIDP, chronic inflammatory demyelinating polyneuropathy; EDx, electrodiagnosis; CSF, cerebrospinal fluid; CMV, cytomegalovirus; DSPN, diabetic sensory polyneuropathy.

Lumbosacral polyradiculopathies are usually due to CMV infection and occur with advanced HIV/AIDS. These present with pain, incontinence, and rapidly progressive asymmetric lower extremity weakness leading to paraplegia. Saddle anesthesia is always present. Deep tendon reflexes are often preserved. EMG reveals findings of both peripheral neuropathy and lumbosacral radiculopathy. CSF analysis shows pleocytosis with polymorphonuclear cells; polymerase chain reaction for CMV is positive. The differential diagnosis includes GBS; other infections including herpes viruses, treponema, or tuberculosis; and carcinomatous meningoradiculitis from lymphoma. Aggressive and rapid treatment with ganciclovir, foscanet, or cidofovir should be considered.

Distal Symmetric Polyneuropathy Associated with HIV

HIV distal sensory symmetric polyneuropathy presents as a painful, predominantly small-fiber neuropathy. This syndrome cannot be distinguished reliably from neuropathy caused by antiretroviral drugs (nucleoside reverse transcriptase inhibitors); its onset with respect to exposure to the offending drugs may be the only clue. It is estimated that ~30% of hospitalized patients with AIDS and 100% of individuals dying with AIDS have evidence of neuropathy. The prevalence is lower in less advanced HIV infection, occurring in only 3% of those with CD4 cell counts >200/μL. Older age, associated nutritional deficiencies, and toxic exposures are additional risk factors for AIDS-related neuropathy. Most patients present with painful burning, tingling, and numbness in the feet. Symptoms are typically bilateral, gradual in onset, and worse at night (features common to all painful neuropathies). Examination usually shows distal loss to pin and temperature sensation and absent or decreased ankle jerk. Weakness is either not detected or is confined to the intrinsic foot muscles. Asymmetric presentations suggest the possibility of vasculitis (nerve biopsy indicated) or an entrapment neuropathy. The possibility of a confounding neuropathy from diabetes, alcohol, nutritional causes, or toxin exposure should always be considered.

Nerve biopsy shows a length-dependent axonal degeneration of sensory fibers, with little evidence of nerve-fiber regeneration. Both large myelinated and unmyelinated nerve fibers are lost. Inflammatory infiltrates of lymphocytes and activated macrophages and reduced numbers of DRG neurons may be seen.

Toxic Neuropathy from Antiretroviral Drugs

A toxic neuropathy follows exposure to specific dideoxynucleosides (d4T, ddI, and especially ddC), particularly in advanced HIV disease. Sural nerve biopsy shows severe axonal destruction, most prominently in unmyelinated fibers, along with mitochondrial abnormalities. Serum lactate concentrations are elevated and acetylcarnitine levels are reduced as a result of mitochondrial dysfunction. Dideoxynucleosides have also been shown in vitro to inhibit gamma DNA polymerase, whereas zidovudine, lamivudine, and abacavir (drugs that are not associated with neuropathy) have only limited effects on this enzyme.

℞ Treatment: TOXIC NEUROPATHY FROM ANTIRETROVIRAL DRUGS

Treatment consists of discontinuing the offending dideoxynucleoside and changing the highly active antiretroviral therapy (HAART) regimen, provided that there is another regimen to offer. Failing this, a patient may need to continue the regimen with the addition of pain-modifying drugs. Prescribing patterns have changed in the developed world to limit the use of specific dideoxynucleosides. However, in resource-limited countries, generic antiretroviral combinations typically contain d4T. After discontinuation of a toxic dideoxynucleoside, symptomatic improvement can be expected in most individuals within ~3 months.

Various pain-modifying drugs have been tried without success, including tricyclic antidepressants and anticonvulsants. Lamotrigine was reported to be efficacious in a subgroup of patients in one class I trial, but results of a smaller class II trial were contradictory. Some positive results have been achieved with topical capsaicin or topical lidocaine, especially in patients with symptoms confined to the feet. Patients with severe neuropathies may require narcotic analgesics for pain relief, and long-acting narcotics such as transdermal fentanyl, morphine, or oxycodone preparations are particularly useful. Specific prescribing guidelines should be used, particularly if there is any history of substance abuse. Regenerative strategies, including trials of recombinant human nerve growth factor, have been attempted.

Neuropathies with Lyme Disease

A focal or multifocal radiculoneuropathy may occur with *Borrelia burgdorferi* infection. Subacute cranial neuropathy (especially VII) or painful radiculopathy may occur in the acute phase of Lyme disease, with or without associated meningitis. The radiculitis is dysesthetic or painful and is variable in distribution. CSF pleocytosis with intrathecal production of *B. burgdorferi* antibodies is typical. Most patients improve either spontaneously or after IV ceftriaxone treatment. In the chronic phase, a mild, chronic distal polyneuropathy (sensory more than motor) has been described; however,

the CSF is normal and the association may be coincidental.

Herpes Zoster

Reactivation of varicella zoster virus (VZV) in dorsal root ganglia produces lancinating pain and hyperalgesia in a dermatomal distribution. The pain is followed 3–4 days later by the appearance of a blistering skin rash. The inflammation may at times involve the adjacent motor nerve roots, causing weakness and wasting. Ophthalmoplegic zoster causes weakness in the division of one or more oculomotor nerves; facial zoster causes facial palsy (Ramsay Hunt syndrome); thoracolumbar zoster causes rash and sensory loss in a thoracic or lumbar nerve root. Although pain usually subsides after a few days to a week, it sometimes persists (postherpetic neuralgia). Herpes zoster and postherpetic neuralgia both occur more commonly in the elderly and in immunosuppressed individuals. In the acute setting acyclovir, famciclovir, or valacyclovir are equally effective, although acyclovir must be given five times a day as opposed to three times a day for the other two drugs. Glucocorticoids are of unproven benefit. Treatment of postherpetic neuralgia includes tricyclic antidepressants, duloxetin, gabapentin, pregabalin, oxycodone, morphine sulfate, tramodol, lidocaine patch, and topical capsaicin. A zoster vaccine (Zostavax) has been approved to prevent VZV in elderly patients; the incidence of shingles is reduced by 50% and postherpetic neuralgia by 67%.

Leprous Neuritis

Mycobacterium leprae causes mononeuropathy multiplex affecting peripheral nerves in cooler regions of the body, reflecting the predilection for this bacterium to thrive at cooler temperatures. The deformities caused by untreated leprous neuritis have led to the fear and stigma attached to this disease. Although the incidence of leprous neuritis has declined, it remains a leading cause of neuropathy worldwide. Leprosy is classified into tuberculoid, lepromatous, and borderline types; peripheral nerves may be affected in all three types, and involved nerves are often palpably thickened. In tuberculoid leprosy, a single patch of hypesthetic or anesthetic skin may occur in any location. The area is generally hypopigmented, thickened, or red. A mononeuropathy involving a nearby superficial nerve may occur. Lepromatous leprosy produces more widespread skin thickening, hypesthesia, and anhidrosis affecting the pinnae of ears, dorsum of hands or feet, dorsomedial surfaces of the forearm, and anteromedial aspects of the legs. The sensory loss spares the midline of the trunk anteriorly, the groin, axilla, and scalp; these are the warmer regions of the body. The fifth and seventh cranial nerves, greater auricular nerve in the neck, median and ulnar nerves, and peroneal nerves can all be involved. Over the long term, untreated leprosy leads to claw hand deformity (from ulnar and median nerve weakness), footdrop, and inability to close the eyelids due to orbicularis oculi weakness.

INHERITED NEUROPATHIES

CHARCOT-MARIE-TOOTH DISEASE

Clinical Features

CMT neuropathy is the most common heritable neuromuscular disorder with an estimated incidence of 17–40 cases per 100,000 (**Table 40-10**). It is a chronic distal sensory and motor neuropathy presenting as longstanding gait difficulty with frequent tripping, followed by difficulty with buttoning, handling keys, turning door knobs, and opening jars. There is often a history of clumsiness, frequent ankle injuries, inability to jump well or to keep up with other children in races, and being unathletic. In some patients the history suggests a more recent onset. If carefully sought, a family history can often be obtained. Wasting and weakness of the distal muscles of the legs (inverted champagne bottle appearance) with hammer toes and high arched feet (pes cavus) are commonly present, along with steppage gait, distal sensory loss, and distal loss of reflexes. Pes cavus and hammer toes indicate that the neuropathy dates from early life. An inability to walk on the heels or perform tandem gait is often present. The differential diagnosis is limited if there is an early age of onset, a positive family history, and longstanding symptoms. If the EDx findings indicate a demyelinating process, the diagnosis of CMT can be made with confidence, although genetic testing may be needed to confirm the precise genotype. If the EDx findings are axonal, or if the family history is uncertain or negative, CMT becomes a diagnosis of exclusion. Diabetes, as well as nutritional, toxic, endocrine, inflammatory, paraprotein-associated, and infectious causes, may all need to be excluded. Physical examination and EDx studies of at-risk family members can be more useful diagnostically than additional laboratory testing of the patient. Treatment is supportive; patients often need foot braces but rarely, if ever, become wheelchair dependent. CMT does not reduce the life span and only rarely involves respiratory muscles.

Classification

Demyelinating forms of CMT are classified as CMT1, and axonal forms as CMT2. Patients with nerve conduction velocities (NCVs) intermediate between CMT1 and CMT2 are classified as having "intermediate CMT," and most of these cases are X-linked. CMT is usually

TABLE 40-10

FORMS OF CHARCOT-MARIE-TOOTH DISEASE (HEREDITARY MOTOR AND SENSORY NEUROPATHY) AND RELATED DISORDERS

DISORDER	LOCUS	GENE	INHERITANCE
Charcot-Marie-Tooth Type 1			
(HMSNI)			
CMT1A	17p11.2-p12	*PMP22*	AD
CMT1B	1q22-q23	P_0	AD
CMT1C	16p12-p13	*SIMPLE*	AD
CMT1D	10q21-q22	*EGR2*	AD/AR
CMT1X	Xq13.1	*GJB1*	X-linked
CMT5X	Xq21.32-24	*PRPS1*	X-linked
CMT4A	8q13-q21	*GDAP1*	AR
CMT4B1	11q22	*MTMR2*	AR
CMT4B2	11p15	*SBF2*	AR
CMT4D (HMSN-Lom)	8q24	*NDRG1*	AR
CMT4E	10q21.1-q22.1	*EGR2*	AR
CMT4F	19q13	*PRX*	AR
CMT4J	6q21	*FIG4*	AR
Charcot-Marie-Tooth Type 2			
(HMSNII)			
CMT2A	1p35-p36	*KIF1B*	AD
CMT2B	3q13-q22	*RAB7*	AD
CMT2C	12q23-q24	Unknown	AD
CMT2D	7p14	*GARS*	AD
CMT2E	8p21	*NEF-L*	AD
CMT2B1	11q21	*LMNA*	AR
Déjerine-Sottas			
(HMSNIII)			
DSS	17p11.2-p12	*PMP22*	AD
	1q22-p23	P_0	AD
	10q21-q22	*EGR2*	AD/AR
	19q13	*PRX*	AD
Congenital Hypomyelination			
CHN	1q22-23	P_0	AD
	10q21-q22	*EGR2*	AR/AD
Hereditary Neuropathy with Pressure Palsies			
HNPP	17p11.2-p12	*PMP22*	AD

Note: HMSN, hereditary motor and sensory neuropathies; *PMP22*, peripheral myelin protein 22; P_0, myelin protein zero; *SIMPLE*, small integral membrane protein of late endosome; *Cx32*, connexin32; *EGR2* (Krox-20) early growth response 2 gene; *GDAP1*, ganglioside-induced differentiation-associated protein-1; *MTMR2*, myotubularin-related protein-2; *SBF2*, SET binding factor 2; *NDRG1*, N-myc downstream regulated gene1; *PRX*, periaxin; *KIF1B*, kinesin family member 1B; *RAB7*, *ras*-associated protein 7; *GARS*, Glycyl-tRNA synthetase; *NEFL*, neurofilament, light polypeptide; *LMNA*, lamin A.

transmitted as an autosomal dominant trait, but X-linked-dominant CMT is responsible for ~10% of CMT cases. Rare autosomal recessive forms, designated CMT4, tend to have an early onset and are more severe than the dominant types. In total, ~35 different loci and >24 genes have been identified in CMT.

Charcot-Marie-Tooth 1 (CMT1) Demyelinating Neuropathies

CMT1 is the most common of the heritable neuropathies; inheritance is autosomal dominant. Distal weakness, wasting, and sensory loss with distal reduction of tendon reflexes and foot deformities occur as with other forms of CMT. The onset is in the first or second decade of life, although patients may not come to attention until much later in life. EDx studies show a pattern of generalized demyelination with NCVs that are uniformly and proportionately slowed in distal, intermediate, and proximal segments of the same nerve on the opposite side, and in adjacent nerves. Findings suggestive of heterogeneous demyelination, such as conduction block or dispersion, are not seen. Electrophysiologic evidence of demyelination may be prominent even in patients who are clinically asymptomatic. Nerve biopsies show evidence of repeated bouts of demyelination and remyelination. Proliferation of Schwann cells occurs in an attempt to remyelinate; the supernumerary Schwann cells are concentrically arranged around demyelinated and remyelinated axons, giving a characteristic "onion bulb" appearance. There is also increased collagen between the layers of Schwann cells leading to palpably thickened nerves.

CMT1 is classified into several genetically distinct subtypes (Table 40-10), all of which are clinically similar. In addition, distinct phenotypes with overlapping genotypes are identified. These include HNPP; infantile-onset or severe childhood forms, which include Déjerine-Sottas syndrome (DSS) and congenital hypomyelinating neuropathies (CHN); and Roussy-Lévy syndrome.

CMT1A

This is the most common form; it is associated with the 17p11.2-p12 duplication in the *PMP22* gene expressed by Schwann cells. The duplication involves a large segment of DNA (~1.4 Mb) encoding a 160-amino-acid protein localized to compact myelin in peripheral nerves. CMT1A accounts for up to 90% of CMT1 and 50% of all CMT. Deletion of the *PMP22* gene produces a different phenotype—HNPP (see later). Commercial testing for *PMP22* duplication/deletion is widely available. *PMP22* appears to be important in the initiation of myelin spirals; regulation and growth of Schwann cells; and control of thickness, stability, and maintenance of myelin sheaths.

CMT1B

CMT1B accounts for <5% of CMT1 cases. It is due to a mutation in the myelin protein zero (*MPZ*, or P_0) gene. Different mutations in the same gene can produce a wide spectrum of phenotypes including DSS, CHN, or CMT2. P_0 is quantitatively the major structural

protein of peripheral nerve myelin and is important in myelin compaction. CMT1B is clinically indistinguishable from CMT1A; a late adult-onset form with footdrop can occur. Genetic testing is available.

CMT1X

This is an X-linked dominant form of CMT that can also affect heterozygote females. It is responsible for up to 10% of CMT. Males are more often affected, and female carriers are usually mildly affected or asymptomatic. Male-to-male transmission does not occur. Onset in males is between 5 and 20 years of age; symptoms include difficulty running, sprained ankles, footdrop, distal wasting, weakness, sensory loss, and reduced reflexes. These features do not distinguish CMT1X from other forms of CMT1. Signs of central nervous system (CNS) involvement, including ataxia, dysarthria, weakness, aphasia, disorientation, and hearing loss, may be present, especially in males. Spontaneously resolving confluent white matter changes may be seen on MRI. NCVs are in an intermediate range, although males have slower conduction velocities (25–45 m/s), which may be nonuniform with conduction block and dispersion. This nonuniform pattern may mimic findings of an acquired disorder such as CIDP. The mutated gene, *GJB1*, encodes the gap junction protein connexin-32, which is expressed at the paranodal regions and at the Schmidt-Lanterman incisures of noncompact myelin.

Hereditary Neuropathy with Liability to Pressure Palsies

This is also called *tomaculous neuropathy*. It is an autosomal dominant disorder that presents as recurrent episodes of focal entrapment neuropathy with attacks of numbness and weakness in peroneal, ulnar, radial, and median nerves (in descending order) or in a brachial plexus distribution. Malposition of a limb or trauma may provoke episodes of neuropathy. Some patients present with a progressive length-dependent polyneuropathy rather than with recurrent mononeuropathies, and others remain entirely asymptomatic. Increased distal latencies in median and peroneal nerves and reduced velocities across the elbow of the ulnar and fibular head segment of the peroneal nerves may be found. Tomaculae are sausage-shaped bodies that indicate segmental demyelination. CMT1A and HNPP are both associated with copy number changes in the *PMP22* gene—a duplication causing CMT1A and deletion causing HNPP. Hence, CMT1A and HNPP are the reciprocal products of unequal crossing-over during meiosis. When HNPP presents as a painless brachial plexus neuropathy, it should be distinguished from brachial plexus neuritis and from hereditary neuralgic amyotrophy, a familial disorder with painful weakness and sensory loss in the brachial plexus distribution. Treatment for HNPP is supportive. Avoiding further compression or trauma to the entrapment sites is preferred over surgical release or transposition.

Déjerine-Sottas Syndrome and Congenital Hypomyelinating Neuropathy

These are severe childhood forms of CMT1. DSS and CHN both present with muscle weakness at birth or infancy, with absent or very slow NCVs. Delayed motor milestones are noted in early childhood. Patients either never ambulate or lose their ability to ambulate in infancy or childhood. NCVs are markedly slow (typically 10 m/s); CSF protein is elevated. Clinically DSS and CHN are indistinguishable. DSS can be either autosomal dominant or recessive; CHN is autosomal recessive. Nerve biopsy can distinguish the two, with DSS showing a thin myelin sheath surrounded by onion bulbs composed of concentric layers of basal lamina (Schwann cells are degenerated leaving the basal lamina), while CHN shows lack of onion bulbs and absent myelin sheaths. DSS may be caused by mutations of *PMP22*, myelin protein zero (*MPZ*), or early growth response gene (*ERG2*); *EGR2* or *MPZ* mutations underlie CHN.

Roussy-Lévy Syndrome

This describes a combination of demyelinating CMT with postural and action tremor. The original family members had the *MPZ* mutation, but mutations in *PMP22* (CMT1A), *MPZ* (CMT1B), or *GJB1* (CMT1X) genes may also cause this syndrome.

Charcot-Marie-Tooth 2 (CMT2) Axonal Neuropathies

CMT2, an autosomal dominant neuropathy, is responsible for one-third of CMT disease, although the number of patients is increasing as more genetic abnormalities are being identified. CMT2 has a later age of onset than CMT1; family members may be affected subclinically. Although typical length-dependent sensory and motor loss develops over the years, intrinsic hand weakness and atrophy, present in CMT1, do not develop.

CMT2A (classic CMT2) is caused by mutations in *MFN2* and represents 10% of dominant CMT2; CMT2B is caused by mutations in *RAB7*, a member of the Rab family of *ras*-related GTPases that function in intracellular membrane trafficking; it presents with severe sensory involvement and limb ulcerations. CMT2B overlaps with hereditary sensory neuropathy (HSN) type I with prominent sensory loss and severe sensory loss to touch and pain (see later). CMT2C is associated with vocal cord and respiratory (diaphragm) involvement; the genetic defects have not been identified. CMT2D is an axonal CMT with upper limb predominance associated with mutations in the glycyl-tRNA synthetase gene; predominant hand involvement with

atrophy of distal hand muscles in a patient with a positive family history suggests CMT2D.

Autosomal Recessive Forms of CMT

Autosomal recessive CMTs account for <10% of inherited neuropathy cases in the Western world but may be more common in regions of the world where consanguinity is common. Several genes have been identified, especially in inbred families. Demyelinating autosomal recessive forms, designated CMT4, are usually characterized by early onset and more severe involvement, with congenital or delayed motor milestones, facial weakness, bulbar weakness, sensorineural deafness, diaphragm weakness, and vocal cord paralysis.

Molecular Testing

The phenotype, the inheritance pattern, and electrophysiologic data guide the approach to the diagnosis of an inherited neuropathy. **Figure 40-2** summarizes an approach to genetic testing for CMT. If the proband has CMT1, a single nerve study (median motor forearm conduction velocity) in family members is a quick screening tool. However, if the proband has axonal CMT (CMT2), more detailed evaluation of family members may be required. Evaluation for HNPP employs the same molecular test as for the CMT1A duplication. Most CMT1 and CMT2 pedigrees are autosomal dominant. X-linked inheritance should be suspected if males are more often affected, there is no male-to-male transmission, and EDx studies show heterogeneous findings. Sporadic cases are difficult to evaluate since family members may not be available. Testing for the CMT1A duplication/deletion and for *GJB1* mutation can diagnose ~80% of all cases of CMT.

OTHER INHERITED NEUROPATHIES

Hereditary Motor Neuropathies (HMN)

The distal HMNs present with distal motor weakness with sparing of sensory fibers. Seven subtypes have been described based on the age of onset and mode of inheritance, which is usually autosomal dominant or recessive. The common HMNs present as footdrop with severe wasting and weakness distally. Some variants may manifest with predominantly upper limb involvement, vocal cord paralysis, or with upper motor neuron signs mimicking amyotrophic lateral sclerosis (Chap. 27); the prognosis is relatively good.

Hereditary Sensory Neuropathies (HSN)

HSNs, also called *hereditary sensory and autonomic neuropathies* (HSANs), are a heterogeneous group of disorders affecting the sensory and/or autonomic neurons.

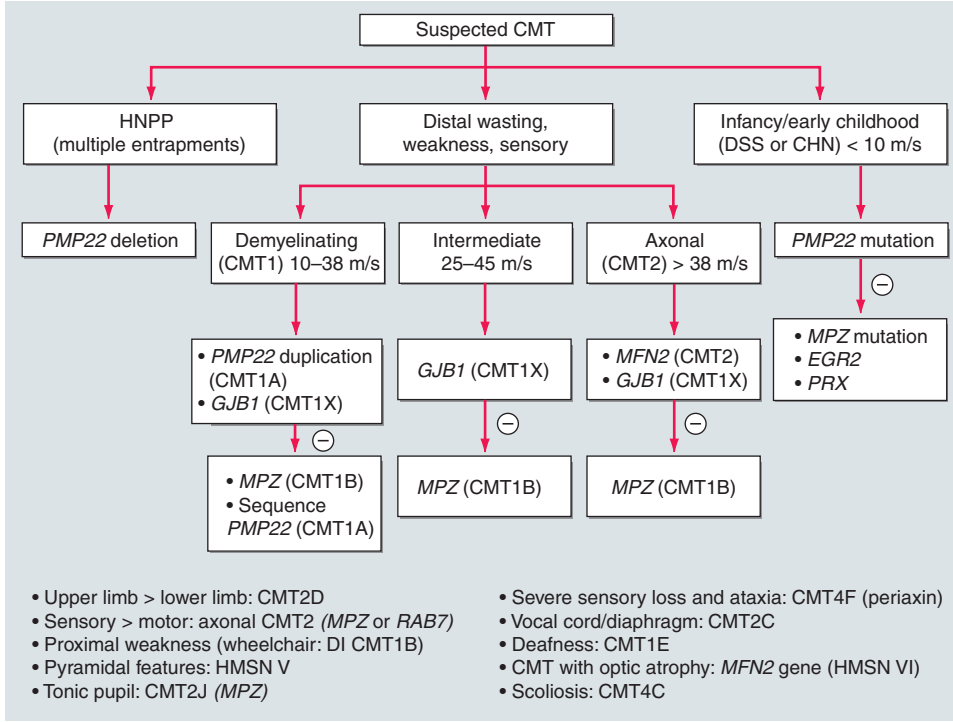

FIGURE 40-2

Diagnostic approach to Charcot-Marie-Tooth disease (CMT). HNPP, hereditary neuropathy with pressure palsies; DSS, Déjerine-Sottas syndrome; CHN, congenital hypomyelinating neuropathy; HMSN, hereditary motor and sensory neuropathy.

The predominant clinical presentation is of progressive distal sensory loss, although some weakness and wasting is also observed. The classification of HSN and HSAN is based on the age of onset and mode of inheritance. Five subtypes are described. The most common is HSN 1 (also called HSAN 1), an autosomal dominant neuropathy presenting with predominant small-fiber sensory involvement with lancinating pain, loss of pain and temperature sensation, and foot ulceration. Of note, CMT2B (see earlier) also presents with predominantly sensory loss to all modalities and foot ulcerations. HSN 2–5 are all autosomal recessive. HSN 2 presents in the first two decades of life with prominent sensory loss and mutilation in hands and feet. HSN 3 (HSAN 3), also called *Riley-Day syndrome*, has prominent dysautonomia. HSN 4 (HSAN 4) presents with episodic fever, anhidrosis, and reduced response to painful stimuli. HSAN 5 presents with congenital insensitivity to pain; mutations in a sodium channel (SCN1.7) are causative.

Refsum Disease

This is an autosomal recessive hypertrophic neuropathy caused by defective oxidation of phytanic acid, a branched-chain fatty acid found in dairy products, beef, lamb, and fish. The onset is in late childhood or adolescence, with a slowly progressive course of a sensorimotor demyelinating neuropathy with sensorineural deafness, cerebellar ataxia, and anosmia. Retinitis pigmentosa presenting as night blindness often precedes the onset of neuropathy. Thickened skin (ichthyosis), syndactyly and shortening of the fourth toe, cardiomyopathy, and cataracts are other features. CSF protein is typically elevated. Abnormally high plasma and urinary levels of phytanic acid are diagnostic. Although a diet low in phytanic acid may prevent the onset of some of the complications, compliance with this diet is usually poor. Plasma exchange and dialysis may be helpful for episodes of worsening.

Familial Amyloid Neuropathy

This is an autosomal dominant disorder in which there is extracellular deposition of amyloid in peripheral nerves and other organs. A painful sensory neuropathy with early involvement of autonomic nerves and cardiomyopathy is typically present. Age of onset can vary from 18–83 years. Small fibers (pain and temperature) are more affected than large fibers (vibration and proprioception); anhidrosis, gastrointestinal disturbances (diarrhea alternating with constipation), impotence, orthostatic intolerance, visual changes, and arrhythmias are additional features. Mutations in transthyretin (FAP 1 and 2), apolipoprotein A1 (FAP 3) or gelosin (FAP 4) are responsible. Transthyretin is most often implicated in peripheral neuropathy. Nearly 100 different mutations have been identified in the *TTR* gene, the most common being the *Val30Met* mutation. Liver transplantation halts disease progression.

Tangier Disease (TD)

This is a rare syndrome caused by a severe deficiency of high-density lipoproteins (HDL) in plasma. Peripheral neuropathy is the most disabling feature of TD and affects ~50% of patients. Three patterns are recognized: a transient or relapsing, often asymmetric neuropathy (including isolated cranial nerve deficits); a slowly progressive symmetric neuropathy most marked in the distal upper limbs (syringomyelia-like); and a slowly progressive symmetric sensory motor neuropathy most marked in the lower limbs. Mononeuropathies involving the oculomotor nerve, long thoracic nerve, or any of the limb nerves may occur. The syringomyelic presentation includes wasting of hand muscles, loss of pain and temperature sensation, and facial diplegia. The length-dependent sensorimotor neuropathy pattern is the least common variant. Deposits of cholesterol esters in tonsils, liver, spleen, rectal mucosa, and cornea lead to the other non-neurologic manifestations of TD. There is no treatment available; a low-cholesterol diet or other dietary changes do not modify the natural history. Gene therapy may be possible in the future.

Porphyric Neuropathy

Peripheral neuropathy accompanies the inherited hepatic porphyrias. The triad of acute neuropathy, psychiatric symptoms, and abdominal involvement are similar in all hepatic porphyrias. Variegate porphyria and hereditary coproporphyria are characterized by additional skin lesions (blisters and bullae) in ~50% of patients. Most patients with porphyria are asymptomatic between attacks. Attacks can occur spontaneously or be precipitated by certain drugs, stress, hormonal factors, and reduced caloric intake. Abdominal pain, constipation, vomiting, and mental changes frequently herald the attacks. Peripheral neuropathy has an acute onset and may be preceded or accompanied by autonomic manifestations such as tachycardia, hypertension, and postural hypotension. The neuropathy is usually subacutely progressive (over 2–4 weeks) with diffuse weakness (often proximal more than distal) and areflexia. Sensory loss is generally mild and may be more prominent proximally in a "bathing trunk" distribution. Porphyric neuropathy should be considered in the differential diagnosis of GBS, the most common cause of rapidly progressive ascending paralysis.

CSF is acellular but the protein level is elevated, similar to that in GBS. Acute attacks are invariably

associated with increased urinary excretion of aminolevulinic acid and/or porphobilinogen. Measuring 24-h urinary excretion of porphobilinogen and aminolevulinic acid and 24-h fecal excretion of protoporphyrin and coproporphyrin during a symptomatic period is the most helpful method of determining whether symptoms are due to acute porphyria. Since porphyrins are light sensitive, specimens must be stored in the dark and tested as soon as possible.

Treatment is largely supportive during the acute crisis and includes fluid management, ventilatory support, management of heart rate and blood pressure (autonomic dysfunction), and avoidance of medications that are known to precipitate an acute attack. Oral and IV glucose and heme arginate are the mainstays of treatment. Recovery from an acute attack may take several months.

Critical Illness Neuropathy

See Chap. 22.

SPECIAL PERIPHERAL NEUROPATHY PRESENTATIONS

AUTONOMIC NEUROPATHY

Symptoms may include orthostatic hypotension (syncope, light headedness, dizziness, fatigue, and lethargy), heat intolerance, abnormal (reduced or increased) sweating, constipation, diarrhea, incontinence, sexual dysfunction, dry eyes, dry mouth, or visual blurriness. Autonomic neuropathy is usually a manifestation of a more generalized polyneuropathy, as in diabetes, GBS, and alcoholic polyneuropathy, but occasionally syndromes of pure pandysautonomia are encountered. Other causes include amyloidosis and multiple drugs and toxins. Autonomic neuropathies are discussed in detail in Chap. 28.

PURE MOTOR NEUROPATHY

Examples of predominantly motor neuropathies include acute inflammatory neuropathies such as GBS; chronic neuropathies such as CIDP and multifocal motor neuropathy (MMN) (Chap. 41); some inherited neuropathies; brachial neuropathy; diabetic lumbosacral radiculoplexus neuropathy (diabetic amyotrophy); and neuropathy due to spinal muscular atrophy, acute intermittent porphyria, diphtheria, lead, and dapsone. Motor neuronopathies include the lower-motor form of amyotrophic lateral sclerosis, poliomyelitis, hereditary spinal muscular atrophies, and an adult variant of hexosaminidase A deficiency (Chap. 27). Neuromuscular junction disorders (e.g., Lambert-Eaton myasthenic syndrome, tick bite paralysis, and other types of toxic neuromuscular blockade) are purely motor and can be recognized and localized electrodiagnostically (Chap. 42).

PURE SENSORY NEUROPATHY

Causes include Friedreich's ataxia, idiopathic sensory neuropathy, sensory neuropathy associated with Sjögren syndrome, vitamin B_{12} neuropathy (dorsal column involvement is the major factor), pyridoxine toxicity, and cisplatin neuropathy. The most severe and widespread of these pure sensory syndromes exhibit poor or no recovery, suggesting irreversible lesions of nerve cell bodies in dorsal root and trigeminal ganglia (neuronopathy). A painful sensory neuropathy is an early feature of hereditary sensory neuropathies, lepromatous leprosy, diabetic small-fiber neuropathy, amyloidosis, TD, Fabry's disease, and dysautonomia. Global sensory loss can occur with carcinomatous sensory neuropathy, hereditary sensory neuropathies, diabetic sensory neuropathy, vacor intoxication, and xanthomatous neuropathy of primary biliary cirrhosis.

PLEXOPATHY

This refers to disorders of either the brachial or the lumbosacral plexus. *Brachial plexopathy* is a broad term used to define any injury, traumatic or otherwise, to the brachial plexus. Causes include birth injury, trauma, neoplasm, radiation, and familial and immune-mediated processes (**Fig. 40-3**; **Table 40-11**). Trauma to the plexus is responsible for up to 70% of brachial plexus lesions; the upper plexus is the most vulnerable. Brachial neuritis (neuralgic amyotrophy; Chap. 7), characterized by sudden onset of pain in the shoulder region followed by weakness and atrophy, is the second most common cause. In this disorder, the shoulder girdle muscles are most frequently affected, and individual peripheral nerves tend to be more commonly involved. Other causes include a cervical rib or band, infiltration by malignant tumor, or prior radiation therapy.

Brachial plexus lesions demonstrate characteristic motor and sensory signs. When the upper parts of the brachial plexus (cervical roots 5–7) are affected, weakness and atrophy of shoulder girdle and upper arm muscles occurs. Injuries to the lower brachial plexus (C8-T1 roots) produce distal arm weakness, atrophy, and focal sensory deficits in the forearm and hand. In general, idiopathic brachial neuritis, irradiation with >60 Gy (6000 rad), and specific types of trauma (arm jerked downward) result in damage to the upper portions of the brachial plexus. In contrast, infiltration by malignant tumor, a cervical rib or band, and specific types of trauma (arm jerked upward) cause damage to the lower brachial plexus.

The *lumbosacral plexus* is formed by the ventral primary rami of L1-S4. Although often considered as a

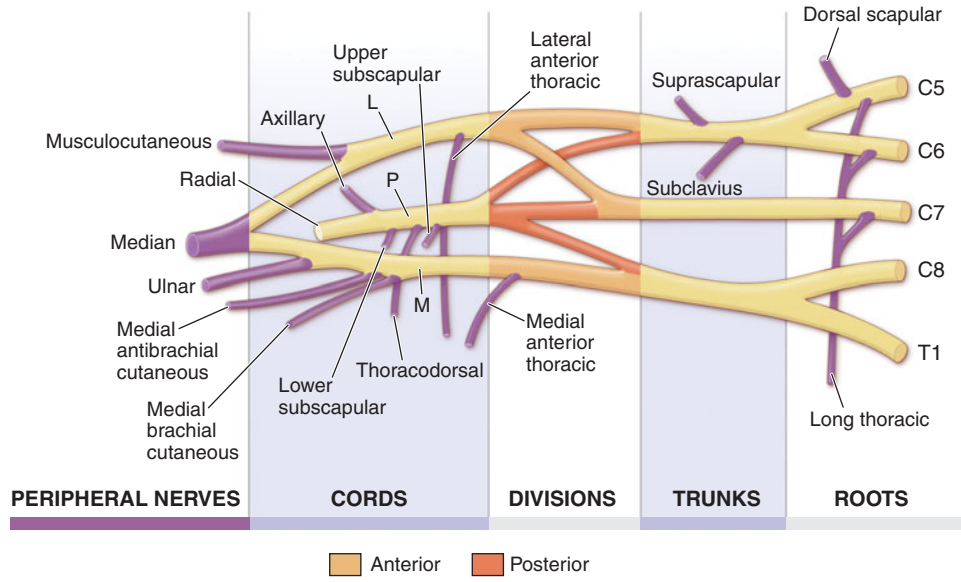

FIGURE 40-3

Brachial plexus anatomy. L, lateral; M, medial; P, posterior. *(From J Goodgold: Anatomical Correlates of Clinical Electromyography. Baltimore, Williams and Wilkins, 1974, p. 126; with permission.)*

TABLE 40-11

BRACHIAL PLEXUS LESIONS

SITE OF INJURY	NERVES/NERVE ROOTS	MUSCLES AFFECTED	SENSORY LOSS	COMMON CAUSES
Upper trunk	C-5 and C-6	Weakness of shoulder abduction (supraspinatus & deltoid), external rotation (infraspinatus) and elbow flexion (biceps)	Small patch of skin overlying the deltoid	Birth injury during difficult delivery (Erb-Duchenne palsy); brachial neuritis, also called neuralgica myotrophy (Parsonage-Turner syndrome)
Lower trunk	C-8 and T-1	Weakness and wasting of small muscles of the hand (claw-hand deformity)	Ulnar border of the hand and inner forearm	Birth injury, especially breech delivery (Déjerine-Klumpke paralysis), compression by cervical rib or band (thoracic outlet syndrome), tumor infiltration
Lateral cord	Musculocutaneous nerve and lateral part of median nerve	Weakness of flexion and pronation of forearm	Radial border of forearm and hand	Trauma, stretch
Medial cord	Medial part of median nerve and ulnar nerve	Weakness and wasting of small muscles of the hand (claw hand deformity)	Ulnar border of the hand and inner forearm	Trauma
Posterior cord	Axillary and radial nerves	Deltoid, extensors of elbow, wrist, and fingers	Outer aspect of upper arm	Trauma, shoulder dislocation

single entity, it can be divided into a lumbar plexus (ventral rami of L1–L4) and a sacral plexus (lumbosacral trunk L4 and L5 and ventral rami of S1–S4) (**Figs. 40-4** and **40-5**). The femoral and obturator nerves are the main nerves formed from the lumbar plexus, and the sciatic, gluteal, and pudendal nerves are the main nerves formed by the sacral plexus. The lumbosacral plexus courses near the paravertebral psoas muscle and the sacroiliac notch and sacral ala, where it is relatively well protected from injury, unlike its upper extremity counterpart. Disorders affecting the lumbosacral plexus include: trauma, intraoperative damage,

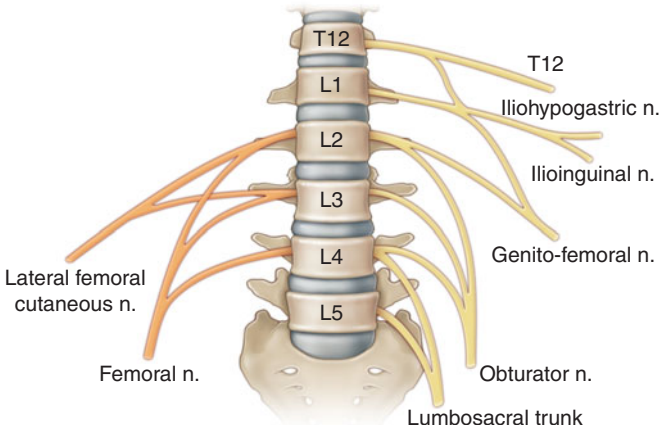

FIGURE 40-4

Lumbar plexus. Posterior divisions are in orange, anterior divisions are in yellow. *(From J Goodgold: Anatomical Correlates of Clinical Electromyography. Baltimore, Williams and Wilkins, 1974, p. 126; with permission.)*

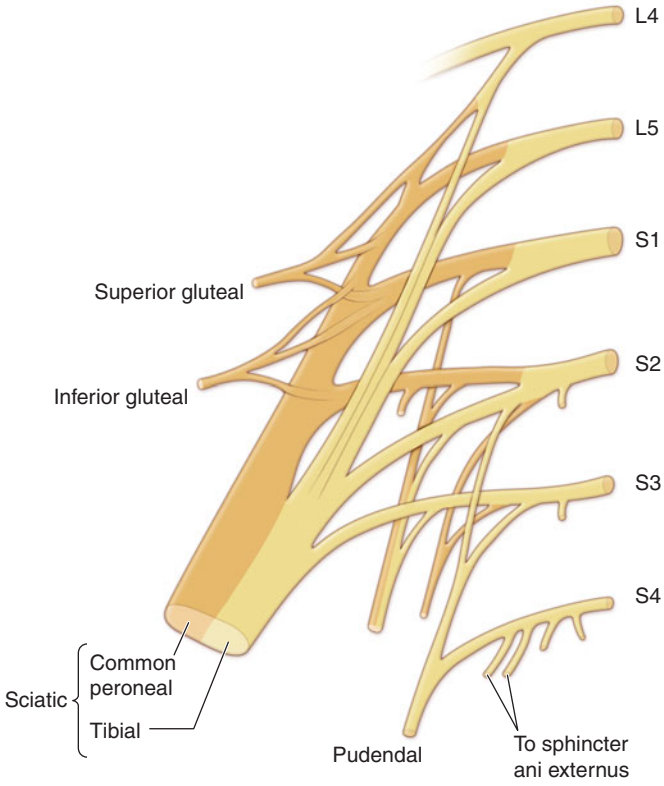

FIGURE 40-5

Lumbosacral plexus. Posterior divisions are in orange, anterior divisions are in yellow. *(From J Goodgold: Anatomical Correlates of Clinical Electromyography. Baltimore, Williams and Wilkins, 1974, p. 126; with permission.)*

retroperitoneal hemorrhage, radiotherapy, neoplastic invasion, diabetes mellitus, pregnancy and labor, retroperitoneal abscess or hemorrhage, abdominal aortic aneurysm, and idiopathic lumbosacral plexopathy (Table 40-12). Most patients present with varying degrees of pain, sensory deficits, and weakness in the lower limbs, generally in an asymmetric distribution. The onset may be acute, subacute, or insidious depending on the etiology; the course may vary from being monophasic, stepwise, or progressive. EDx studies are invaluable aids for diagnosis and localization.

PERIPHERAL NERVE INJURY

Physical damage to peripheral nerves may result from sudden compression, crush, transection, or stretching of a nerve. The mildest form of nerve injury results when a stretch or pressure injury distorts the myelin overlying the nodes of Ranvier and produces focal conduction block. This type of injury, with conduction block but without Wallerian degeneration, is referred to as *neurapraxia,* or *class 1 injury*. This results in a transient sensation of numbness in an extremity, as occurs after lying or sitting in a certain position. Nerve injury that interrupts the axon's continuity and results in Wallerian degeneration of the nerve distal to the lesion is considered moderate or severe. If the endoneurium is preserved, the lesion is considered moderate and is called *axonotmesis*, or *class 2 injury*. If the endoneurium is destroyed, the lesion is considered severe and is called *neurotmesis*. Peripheral nerve lesions are often mixed; neurapraxia and axonotmesis may coexist. Similarly, one fascicle may be completely disrupted while another is only partially affected. If the clinical and electrophysiologic examinations show that the lesion is complete, and if the mechanism of injury is known to be a clean laceration, then surgical repair should be considered within 24 h of the injury. If the mechanism of injury is contusion, stretch, traction, or compression, nerve conduction studies to determine whether the lesion is neurapraxic or axonotmesic should be delayed for 3 weeks. If neurapraxic, a return of function can be expected, provided care is taken to ensure that there is no ongoing compressive injury. If clinical and electrophysiologic examinations (no motor units seen by EMG) fail to reveal evidence of return of function after 3 months, the lesion was most likely neurotmesic, and exploration and surgical repair may need to be undertaken. If the lesion is incomplete, follow-up evaluations should be performed monthly; if no improvement is seen, then surgery may be required. Approximately 80% of closed injuries resolve spontaneously, because these lesions are in continuity. The appearance of an advancing Tinel's sign in the distribution of the injured nerve indicates that the nerve is in continuity and justifies postponement of surgery. The growth rate of regenerating axons is about 2.5 cm/month. The time required for regeneration is dependent on the distance from the site of injury to the first muscle innervated below the lesion. Since this distance is greater for proximal nerve lesions, severe proximal injuries are

TABLE 40-12

LUMBOSACRAL PLEXUS LESIONS

SITE	NERVE ROOTS	MUSCLES	SENSORY LOSS	COMMON CAUSES
Upper plexus	L-2, L-3, L4	Weakness of thigh flexion (psoas), thigh adduction, and knee extension (quadriceps)	Anterior thigh and medial leg; absent knee jerk	Diabetic amyotrophy; abdominal surgery—either directly/retraction, or due to positioning; lumbosacral plexitis
Lower plexus	L-4, L-5, S-1, and S-2	Weakness of thigh extension (glutei), knee flexion (hamstrings), foot dorsiflexion and plantar flexion	Posterior thigh, lateral leg, and entire foot; absent ankle jerk	Lumbosacral plexitis, perioperative, cancer infiltration, radiation

associated with poor recovery. Brachial plexus injuries during birth carry a better prognosis for spontaneous recovery than do those in adults.

PERIPHERAL NERVE TUMORS

Peripheral nerve tumors, which can present as peripheral neuropathy, are mostly benign and can arise in any nerve trunk or nerve twig. Although peripheral nerve tumors can occur anywhere in the body, including the spinal roots and cauda equina, many are subcutaneous in location and present as a soft swelling, sometimes with a purplish discoloration of the skin. Symptoms can include tingling or pain when the lesion is touched. Diagnostic studies may include imaging (CT/MRI), EMG and nerve conduction studies, and tumor biopsy. Two major categories of peripheral nerve tumors are recognized: neurilemmoma (schwannoma) and neurofibroma. Neurilemmomas are usually solitary and grow in the nerve sheath, rendering the tumor relatively easy to dissect free. In contrast, neurofibromas tend to be multiple and grow in the endoneurial substance, which renders them difficult to dissect. They may undergo malignant changes. Neurofibromas are the hallmark of von Recklinghausen's neurofibromatosis (NF1) (Chap. 32).

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CHAPTER 41

GUILLAIN-BARRÉ SYNDROME AND OTHER IMMUNE-MEDIATED NEUROPATHIES

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GUILLAIN-BARRÉ SYNDROME

Guillain-Barré syndrome (GBS) is an acute, frequently severe, and fulminant polyradiculoneuropathy that is autoimmune in nature. It occurs year-round at a rate of about one case per million per month, or ~3500 cases per year in the United States and Canada. Men are at 1.5-fold higher risk for GBS than women, and in western countries adults are more frequently affected than children.

Clinical Manifestations

GBS manifests as rapidly evolving areflexic motor paralysis with or without sensory disturbance. The usual pattern is an ascending paralysis that may be first noticed as rubbery legs. Weakness typically evolves over hours to a few days and is frequently accompanied by tingling dysesthesias in the extremities. The legs are usually more affected than the arms, and facial diparesis is present in 50% of affected individuals. The lower cranial nerves are also frequently involved, causing bulbar weakness with difficulty handling secretions and maintaining an airway; the diagnosis in these patients may initially be mistaken for brainstem ischemia. Pain in the neck, shoulder, back, or diffusely over the spine is also common in the early stages of GBS, occurring in ~50% of patients. Most patients require hospitalization, and almost 30% require ventilatory assistance at some time during the illness. Fever and constitutional symptoms are absent at the onset and, if present, cast doubt on the diagnosis. Deep tendon reflexes attenuate or disappear within the first few days of onset. Cutaneous sensory deficits (e.g., loss of pain and temperature sensation) are usually relatively mild, but functions subserved by large sensory fibers, such as deep tendon reflexes and proprioception, are more severely affected. Bladder dysfunction may occur in severe cases but is usually transient. If bladder dysfunction is a prominent feature and comes early in the course, diagnostic possibilities other than GBS should be considered, particularly spinal cord disease. Once clinical worsening stops and the patient reaches a plateau (almost always within 4 weeks of onset), further progression is unlikely.

Autonomic involvement is common and may occur even in patients whose GBS is otherwise mild. The usual manifestations are loss of vasomotor control with wide fluctuation in blood pressure, postural hypotension, and cardiac dysrhythmias. These features require close monitoring and management and can be fatal. Pain is another common feature of GBS; in addition to the acute pain described above, a deep aching pain may be present in weakened muscles that patients liken to having overexercised the previous day.

TABLE 41-1

SUBTYPES OF GUILLAIN-BARRÉ SYNDROME (GBS)

SUBTYPE	FEATURES	ELECTRODIAGNOSIS	PATHOLOGY
Acute inflammatory demyelinating polyneuropathy (AIDP)	Adults affected more than children; 90% of cases in western world; recovery rapid; anti-GM1 antibodies (<50%)	Demyelinating	First attack on Schwann myelin cell surface; widespread damage, macrophage activation, and lymphocytic infiltration; variable secondary axonal damage
Acute motor axonal neuropathy (AMAN)	Children and young adults; prevalent in China and Mexico; may be seasonal; recovery rapid; anti-GD1a antibodies	Axonal	First attack at motor nodes of Ranvier; macrophage activation, few lymphocytes, frequent periaxonal macrophages; extent of axonal damage highly variable
Acute motor sensory axonal neuropathy (AMSAN)	Mostly adults; uncommon; recovery slow, often incomplete; closely related to AMAN	Axonal	Same as AMAN, but also affects sensory nerves and roots; axonal damage usually severe
M. Fisher syndrome (MFS)	Adults and children; uncommon; ophthalmoplegia, ataxia, and areflexia; anti-GQ1b antibodies (90%)	Demyelinating	Few cases examined; resembles AIDP

Other pains in GBS include dysesthetic pain in the extremities as a manifestation of sensory nerve fiber involvement. These pains are self-limited and often respond to standard analgesics (Chap. 5).

Several subtypes of GBS are recognized, as determined primarily by electrodiagnostic and pathologic distinctions (**Table 41-1**). These include the axonal variants, which are often clinically severe—either acute motor axonal neuropathy (AMAN) or acute motor sensory axonal neuropathy (AMSAN). In addition, a range of limited or regional GBS syndromes are also encountered. Notable among these is the Miller Fisher syndrome (MFS; Table 41-1), which presents as rapidly evolving ataxia and areflexia of limbs without weakness, and ophthalmoplegia, often with pupillary paralysis. The MFS variant accounts for ~5% of all cases and is strongly associated with antibodies to the ganglioside GQ1b (see Immunopathogenesis, below). Other regional variants of GBS include (1) pure sensory forms; (2) ophthalmoplegia with anti-GQ1b antibodies as part of severe motor-sensory GBS; (3) GBS with severe bulbar and facial paralysis, sometimes associated with antecedent cytomegalovirus (CMV) infection and anti-GM2 antibodies; and (4) acute pandysautonomia (Chap. 28).

Antecedent Events

Approximately 70% of cases of GBS occur 1–3 weeks after an acute infectious process, usually respiratory or gastrointestinal. Culture and seroepidemiologic techniques show that 20–30% of all cases occurring in North America, Europe, and Australia are preceded by infection or reinfection with *Campylobacter jejuni*. A similar proportion is preceded by a human herpes virus infection, often CMV or Epstein-Barr virus. Other viruses and also *Mycoplasma pneumoniae* have been identified as agents involved in antecedent infections, as have recent immunizations. The swine influenza vaccine, administered widely in the United States in 1976, is the most notable example; influenza vaccines in use from 1992–1994, however, resulted in only one additional case of GBS per million persons vaccinated. Older-type rabies vaccine, prepared in nervous system tissue, is implicated as a trigger of GBS in developing countries where it is still used; the mechanism is presumably immunization against neural antigens. GBS also occurs more frequently than can be attributed to chance alone in patients with lymphoma (including Hodgkin's disease), in HIV-seropositive individuals, and in patients with systemic lupus erythematosus (SLE). *C. jejuni* has also been implicated in summer outbreaks of AMAN among children and young adults exposed to chickens in rural China.

Immunopathogenesis

Several lines of evidence support an autoimmune basis for acute inflammatory demyelinating polyneuropathy (AIDP), the most common and best-studied type of GBS; the concept extends to all of the subtypes of GBS (Table 41-1).

It is likely that both cellular and humoral immune mechanisms contribute to tissue damage in AIDP. T cell activation is suggested by the finding that elevated levels of cytokines and cytokine receptors are present in serum [interleukin (IL) 2, soluble IL-2 receptor] and in cerebrospinal fluid (CSF) (IL-6, tumor necrosis factor α, interferon-γ). AIDP is also closely analogous to an experimental T cell–mediated immunopathy designated *experimental allergic neuritis* (EAN); EAN is induced in laboratory animals by immune sensitization against protein fragments derived from peripheral nerve proteins, and in particular against the P2 protein. Based on analogy to EAN, it was initially thought that AIDP was likely to be primarily a T cell–mediated disorder; however, abundant data now suggest that autoantibodies directed against nonprotein determinants may be central to many cases.

Circumstantial evidence suggests that all GBS results from immune responses to nonself antigens (infectious agents, vaccines) that misdirect to host nerve tissue through a resemblance-of-epitope (molecular mimicry) mechanism (**Fig. 41-1**). The neural targets are likely to be glycoconjugates, specifically gangliosides (**Table 41-2**; **Fig. 41-2**). Gangliosides are complex glycosphingolipids that contain one or more sialic acid residues; various gangliosides participate in cell-cell interactions (including those between axons and glia), modulation of receptors, and regulation of growth. They are typically exposed on the plasma membrane of cells, rendering them susceptible to an antibody-mediated attack. Gangliosides and other glycoconjugates are present in large quantity in human nervous tissues and in key sites, such as nodes of Ranvier. Antiganglioside antibodies, most frequently to GM1, are common in GBS (20–50% of cases), particularly in those preceded by *C. jejuni* infection. Furthermore, isolates of *C. jejuni* from stool cultures of patients with GBS have surface glycolipid structures that antigenically cross

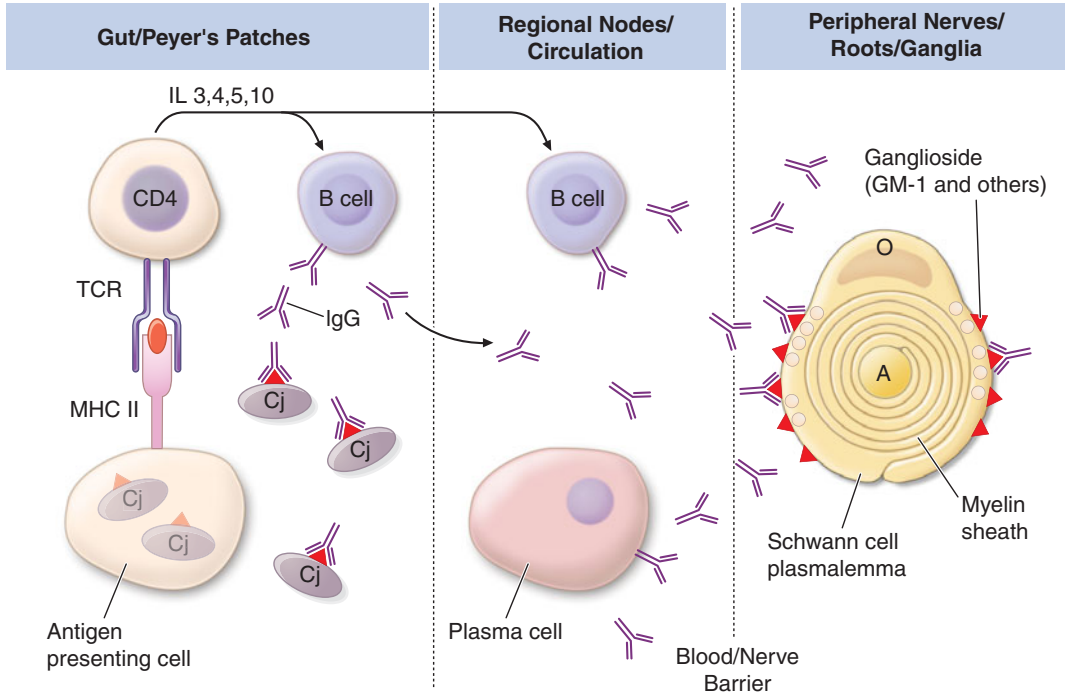

FIGURE 41-1

Postulated immunopathogenesis of GBS associated with *C. jejuni* infection. B cells recognize glycoconjugates on *C. jejuni* (Cj) (triangles) that cross-react with ganglioside present on Schwann cell surface and subjacent peripheral nerve myelin. Some B cells, activated via a T cell–independent mechanism, secrete primarily IgM (not shown). Other B cells (upper left side) are activated via a partially T cell–dependent route and secrete primarily IgG; T cell help is provided by CD4 cells activated locally by fragments of Cj proteins that are presented on the surface of antigen-presenting cells (APC). A critical event in the development of GBS is the escape of activated B cells from Peyer's patches into regional lymph nodes. Activated T cells probably also function to assist in opening of the blood-nerve barrier, facilitating penetration of pathogenic autoantibodies. The earliest changes in myelin (right) consist of edema between myelin lamellae and vesicular disruption (shown as circular blebs) of the outermost myelin layers. These effects are associated with activation of the C5b-C9 membrane attack complex and probably mediated by calcium entry; it is possible that the macrophage cytokine tumor necrosis factor (TNF) also participates in myelin damage. B, B cell; MHC II, class II major histocompatibility complex molecule; TCR, T cell receptor; A, axon; O, oligodendrocyte.

TABLE 41-2

PRINCIPAL ANTI-GLYCOLIPID ANTIBODIES IMPLICATED IN IMMUNE NEUROPATHIES

CLINICAL PRESENTATION	ANTIBODY TARGET	USUAL ISOTYPE
Acute Immune Neuropathies (Guillain-Barré Syndrome)		
Acute inflammatory demyelinating polyneuropathy (AIDP)	No clear patterns GM1 most common	IgG (polyclonal)
Acute motor axonal neuropathy (AMAN)	GD1a, GM1, GM1b, GalNAc–GD1a (<50% for any)	IgG (polyclonal)
Miller Fisher syndrome (MFS)	GQ1b (>90%)	IgG (polyclonal)
Acute pharyngeal cervicobrachial neuropathy (APCBN)	GT1a (Most)	IgG (polyclonal)
Chronic Immune Neuropathies		
Chronic inflammatory demyelinating polyneuropathy (CIDP) (75%)	Po in some	No clear pattern
CIDPa (MGUS associated) (25%)	Neural binding sites	IgG, IgA (monoclonal)
Chronic sensory > motor neuropathy	SPGP, SGLPG (on MAG) (50%)	IgM (monoclonal)
	Uncertain (50%)	IgM (monoclonal)
Multifocal motor neuropathy (MMN)	GM1, GalNAc–GD1a, others (25–50%)	IgM (polyclonal, monoclonal)
Chronic sensory ataxic neuropathy	GD1b, GQ1b, and other b-series gangliosides	IgM (monoclonal)

Note: MGUS, monoclonal gammopathy of undetermined significance; MAG, myelin-associated glycoprotein.
Source: Modified from HJ Willison, N Yuki: Brain 125:2591, 2002.

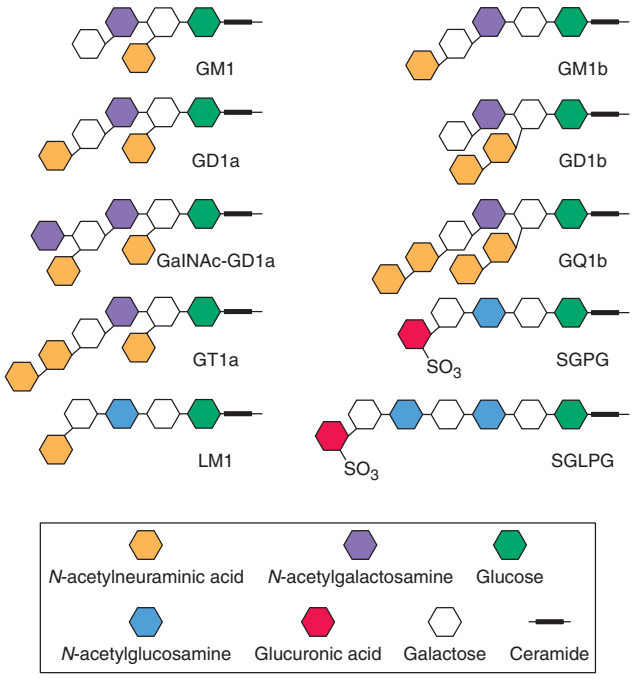

FIGURE 41-2
Glycolipids implicated as antigens in immune-mediated neuropathies. (*Modified from HJ Willison, N Yuki: Brain 125: 2591, 2002.*)

react with gangliosides, including GM1, concentrated in human nerves. Another line of evidence is derived from experience in Europe with parenteral use of purified bovine brain gangliosides for treatment of various neuropathic disorders. Between 5 and 15 days after injection some recipients developed acute motor axonal GBS with high titers of anti-GM1 antibodies that recognized epitopes at nodes of Ranvier and motor endplates. Experimentally, anti-GM1 antibodies can trigger complement-mediated injury at paranodal axon-glial junctions, disrupting the clustering of sodium channels and likely contributing to conduction block (see Pathophysiology, below).

Anti-GQ1b IgG antibodies are found in >90% of patients with MFS (Table 41-2; Fig. 41-2), and titers of IgG are highest early in the course. Anti-GQ1b antibodies are not found in other forms of GBS unless there is extraocular motor nerve involvement. A possible explanation for this association is that extraocular motor nerves are enriched in GQ1b gangliosides in comparison to limb nerves. In addition, a monoclonal anti-GQ1b antibody raised against *C. jejuni* isolated from a patient with MFS blocked neuromuscular transmission experimentally.

Taken together, these observations provide strong but still inconclusive evidence that autoantibodies play an important pathogenic role in GBS. Although anti-ganglioside antibodies have been studied most intensively, other antigenic targets may also be important. One report identified IgG antibodies against Schwann cells and neurons (nerve growth cone region) in some GBS cases. Proof that these antibodies are pathogenic requires that they be capable of mediating disease following direct passive transfer to naïve hosts; this has not yet

been demonstrated, although one case of apparent maternal-fetal transplacental transfer of GBS has been described.

In ADEM, an early step in the induction of tissue damage appears to be complement deposition along the outer surface of the Schwann cell. Activation of complement initiates a characteristic vesicular disintegration of the myelin sheath, and also leads to recruitment of activated macrophages, which participate in damage to myelin and axons. In AMAN, the pattern is different in that complement is deposited along with IgG at the nodes of Ranvier along large motor axons.

Pathophysiology

In the demyelinating forms of GBS, the basis for flaccid paralysis and sensory disturbance is conduction block. This finding, demonstrable electrophysiologically, implies that the axonal connections remain intact. Hence, recovery can take place rapidly as remyelination occurs. In severe cases of demyelinating GBS, secondary axonal degeneration usually occurs; its extent can be estimated electrophysiologically. More secondary axonal degeneration correlates with a slower rate of recovery and a greater degree of residual disability. When a severe primary axonal pattern is encountered electrophysiologically, the implication is that axons have degenerated and become disconnected from their targets, specifically the neuromuscular junctions, and must therefore regenerate for recovery to take place. In motor axonal cases in which recovery is rapid, the lesion is thought to be localized to preterminal motor branches, allowing regeneration and reinnervation to take place quickly. Alternatively, in mild cases, collateral sprouting and reinnervation from surviving motor axons near the neuromuscular junction may begin to reestablish physiologic continuity with muscle cells over a period of several months.

Laboratory Features

CSF findings are distinctive, consisting of an elevated CSF protein level [1–10 g/L (100–1000 mg/dL)] without accompanying pleocytosis. The CSF is often normal when symptoms have been present for ≤48 h; by the end of the first week the level of protein is usually elevated. A transient increase in the CSF white cell count (10–100/μL) occurs on occasion in otherwise typical GBS; however, a sustained CSF pleocytosis suggests an alternative diagnosis (viral myelitis) or a concurrent diagnosis such as unrecognized HIV infection. Electrodiagnostic features are mild or absent in the early stages of GBS and lag behind the clinical evolution. In cases with demyelination (Table 41-1), prolonged distal latencies, conduction velocity slowing, evidence of conduction block, and temporal dispersion of compound action potential are the usual features. In cases with primary axonal pathology, the principal electrodiagnostic finding is reduced amplitude of compound action potentials without conduction slowing or prolongation of distal latencies.

Diagnosis

GBS is a descriptive entity. The diagnosis is made by recognizing the pattern of rapidly evolving paralysis with areflexia, absence of fever or other systemic symptoms, and characteristic antecedent events (Table 41-3). Other disorders that may enter into the differential diagnosis include acute myelopathies (especially with prolonged back pain and sphincter disturbances); botulism (pupillary reactivity lost early); diphtheria (early oropharyngeal disturbances); Lyme polyradiculitis and other tick-borne paralyses; porphyria (abdominal pain, seizures, psychosis); vasculitic neuropathy (check erythrocyte sedimentation rate, described below); poliomyelitis (fever and meningismus common); CMV polyradiculitis (in immunocompromised patients); critical illness neuropathy; neuromuscular disorders such as myasthenia gravis; poisonings with organophosphates, thallium, or arsenic; tick paralysis; paralytic shellfish poisoning; or severe hypophosphatemia (rare). Laboratory tests are helpful primarily to exclude mimics of GBS. Electrodiagnostic features may be minimal, and the CSF protein level may not rise until the end of the first week. If the diagnosis is strongly suspected, treatment should be initiated without waiting for evolution of the characteristic electrodiagnostic and CSF findings to occur. Both tau and 14-3-3 protein levels

TABLE 41-3

DIAGNOSTIC CRITERIA FOR GUILLAIN-BARRÉ SYNDROME

Required
1. Progressive weakness of 2 or more limbs due to neuropathy[a]
2. Areflexia
3. Disease course <4 weeks
4. Exclusion of other causes [e.g., vasculitis (polyarteritis nodosa, systemic lupus erythematosus, Churg-Strauss syndrome), toxins (organophosphates, lead), botulism, diphtheria, porphyria, localized spinal cord or cauda equina syndrome]
Supportive
1. Relatively symmetric weakness
2. Mild sensory involvement
3. Facial nerve or other cranial nerve involvement
4. Absence of fever
5. Typical CSF profile (acellular, increase in protein level)
6. Electrophysiologic evidence of demyelination

[a]Excluding M. Fisher and other variant syndromes.

Source: Modified from AK Asbury, DR Cornblath: Ann Neurol 27:S21, 1990.

are reported to be elevated early (during the first few days of symptoms) in some cases of GBS. Tau increases in CSF may reflect axonal damage and predict a residual deficit. GBS patients with risk factors for HIV or with CSF pleocytosis should have a serologic test for HIV.

Rx Treatment: GUILLAIN-BARRÉ SYNDROME

In the vast majority of patients with GBS, treatment should be initiated as soon after diagnosis as possible. Each day counts; ~2 weeks after the first motor symptoms, immunotherapy is no longer effective. Either high-dose intravenous immune globulin (IVIg) or plasmapheresis can be initiated, as they are equally effective. A combination of the two therapies is not significantly better than either alone. IVIg is often the initial therapy chosen because of its ease of administration and good safety record. IVIg is administered as five daily infusions for a total dose of 2 g/kg body weight. There is some evidence that GBS autoantibodies are neutralized by anti-idiotypic antibodies present in IVIg preparations, perhaps accounting for the therapeutic effect. A course of plasmapheresis usually consists of ~40–50 mL/kg plasma exchange (PE) four times over a week. Meta-analysis of randomized clinical trials indicates that treatment reduces the need for mechanical ventilation by nearly half (from 27% to 14% with PE), and increases the likelihood of full recovery at 1 year (from 55% to 68%). In patients who are treated early in the course of GBS and improve, relapse may occur in the second or third week. Brief retreatment with the original therapy is usually effective. Glucocorticoids have not been found to be effective in GBS. Occasional patients with very mild forms of GBS, especially those who appear to have already reached a plateau when initially seen, may be managed conservatively without IVIg or PE.

In the worsening phase of GBS, most patients require monitoring in a critical care setting, with particular attention to vital capacity, heart rhythm, blood pressure, nutrition, deep vein thrombosis prophylaxis, cardiovascular status, early consideration (after 2 weeks of intubation) of tracheotomy, and chest physiotherapy. As noted, ~30% of patients with GBS require ventilatory assistance, sometimes for prolonged periods of time (several weeks or longer). Frequent turning and assiduous skin care are important, as are daily range-of-motion exercises to avoid joint contractures and daily reassurance as to the generally good outlook for recovery.

Prognosis and Recovery

Approximately 85% of patients with GBS achieve a full functional recovery within several months to a year, although minor findings on examination (such as areflexia) may persist. The mortality rate is <5% in optimal settings; death usually results from secondary pulmonary complications. The outlook is worst in patients with severe proximal motor and sensory axonal damage. Such axonal damage may be either primary or secondary in nature (see Pathophysiology, above), but in either case successful regeneration cannot occur. Other factors that worsen the outlook for recovery are advanced age, a fulminant or severe attack, and a delay in the onset of treatment. Between 5 and 10% of patients with typical GBS have one or more late relapses; such cases are then classified as chronic inflammatory demyelinating polyneuropathy (CIDP).

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

CIDP is distinguished from GBS by its chronic course. In other respects, this neuropathy shares many features with the common demyelinating form of GBS, including elevated CSF protein levels and the electrodiagnostic findings of acquired demyelination. Most cases occur in adults, and men are affected slightly more often than women. The incidence of CIDP is lower than that of GBS, but due to the protracted course the prevalence is greater.

Clinical Manifestations

Onset is usually gradual, sometimes subacute; in a few, the initial attack is indistinguishable from that of GBS. An acute-onset form of CIDP should be considered when GBS deteriorates >9 weeks after onset or relapses at least three times. Symptoms are both motor and sensory in most cases. Weakness of the limbs is usually symmetric but can be strikingly asymmetric. There is considerable variability from case to case. Some patients experience a chronic progressive course, whereas others, usually younger patients, have a relapsing and remitting course. Some have only motor findings, and a small proportion present with a relatively pure syndrome of sensory ataxia. Tremor occurs in ~10% and may become more prominent during periods of subacute worsening or improvement. A small proportion have cranial nerve findings, including external ophthalmoplegia. CIDP tends to ameliorate over time with treatment; the result is that many years after onset nearly 75% of patients have reasonable functional status. Death from CIDP is uncommon.

Diagnosis

The diagnosis rests on characteristic clinical, CSF, and electrophysiologic findings. The CSF is usually acellular with an elevated protein level, sometimes several times normal. Electrodiagnostically, variable degrees of conduction slowing,

prolonged distal latencies, temporal dispersion of compound action potentials, and conduction block are the principal features. In particular, the presence of conduction block is a certain sign of an acquired demyelinating process. Evidence of axonal loss, presumably secondary to demyelination, is present in >50% of patients. Serum protein electrophoresis with immunofixation is indicated to search for monoclonal gammopathy and associated conditions (see Monoclonal Gammopathy of Undetermined Significance, below). In all patients with presumptive CIDP, it is also reasonable to exclude vasculitis, collagen vascular disease (especially SLE), chronic hepatitis, HIV infection, and diabetes mellitus. Other associated conditions include inflammatory bowel disease and Hodgkin's lymphoma.

Pathogenesis

Although there is evidence of immune activation in CIDP, the precise mechanisms of pathogenesis are unknown. Biopsy typically reveals little inflammation and onion-bulb changes (imbricated layers of attenuated Schwann cell processes surrounding an axon) that result from recurrent demyelination and remyelination (Fig. 41-1). The response to therapy suggests that CIDP is immune-mediated; CIDP responds to glucocorticoids, whereas GBS does not. Passive transfer of demyelination into experimental animals has been accomplished using IgG purified from the serum of some patients with CIDP, lending support for a humoral autoimmune pathogenesis. Although the target antigen or antigens in CIDP have not yet been identified, the myelin protein Po has been implicated as a potential autoantigen in some patients. It is also of interest that a CIDP-like illness developed spontaneously in the nonobese diabetic (NOD) mouse when the immune costimulatory molecule B7-2 (CD86) was genetically deleted; this suggests that CIDP can result from altered triggering of T cells by antigen-presenting cells.

Approximately 25% of patients with clinical features of CIDP also have a monoclonal gammopathy of undetermined significance (MGUS). Cases associated with monoclonal IgA or IgG usually respond to treatment as favorably as cases without a monoclonal gammopathy. Patients with IgM monoclonal gammopathy tend to have more sensory findings, a more protracted course, and may have a less satisfactory response to treatment, although this is an area of controversy.

℞ Treatment: CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

Most authorities initiate treatment for CIDP when progression is rapid or walking is compromised. If the disorder is mild, management can be expectant, awaiting spontaneous remission. Controlled studies have shown that high-dose IVIg, PE, and glucocorticoids are all more effective than placebo. Initial therapy is usually with IVIg, administered as 0.4 g/kg body weight daily for 5 days; most patients require periodic re-treatment at ~6-week intervals. PE, which appears to be as effective as IVIg, is initiated at two to three treatments per week for 6 weeks; periodic re-treatment may also be required. Treatment with glucocorticoids is another option (60–80 mg prednisone PO daily for 1–2 months, followed by a gradual dose reduction of 10 mg per month as tolerated), but long-term adverse effects including bone demineralization, gastrointestinal bleeding, and cushingoid changes are problematic. Anecdotal experience suggested that glucocorticoids might be harmful to some patients with a purely motor form of CIDP, thus glucocorticoids should probably be avoided when sensory findings are absent. Approximately one-half of patients with CIDP fail to respond adequately to the initial therapy chosen; a different treatment should then be tried. Patients who fail therapy with IVIg, PE, and glucocorticoids may benefit from treatment with immunosuppressive agents such as azathioprine, methotrexate, cyclosporine, and cyclophosphamide, either alone or as adjunctive therapy. Early experience with anti-CD20 (rituximab) has also shown promise. Use of these therapies requires periodic reassessment of their risks and benefits.

MULTIFOCAL MOTOR NEUROPATHY

Multifocal motor neuropathy (MMN) is a distinctive but uncommon neuropathy that presents as slowly progressive motor weakness and atrophy evolving over years in the distribution of selected nerve trunks, associated with sites of persistent focal motor conduction block in the same nerve trunks. Sensory fibers are relatively spared. The arms are affected more frequently than the legs, and >75% of all patients are men. Some cases have been confused with lower motor neuron forms of amyotrophic lateral sclerosis (Chap. 27). Approximately 50% of patients present with high titers of polyclonal IgM antibody to the ganglioside GM1. It is uncertain how this finding relates to the discrete foci of persistent motor conduction block, but high concentrations of GM1 gangliosides are normal constituents of nodes of Ranvier in peripheral nerve fibers. Pathology reveals demyelination and mild inflammatory changes at the sites of conduction block.

Most patients with MMN respond to high-dose IVIg (dosages as for CIDP, above); periodic re-treatment is required in more than half of responders to maintain the benefit. Some refractory patients have responded to cyclophosphamide. Glucocorticoids and PE are not effective.

NEUROPATHIES WITH MONOCLONAL GAMMOPATHY

MULTIPLE MYELOMA

Clinically overt polyneuropathy occurs in ~5% of patients with the commonly encountered type of multiple myeloma, which exhibits either lytic or diffuse osteoporotic bone lesions. These neuropathies are sensorimotor, are usually mild and slowly progressive but may be severe, and generally do not reverse with successful suppression of the myeloma. In most cases, electrodiagnostic and pathologic features are consistent with a process of axonal degeneration.

In contrast, myeloma with osteosclerotic features, although representing only 3% of all myelomas, is associated with polyneuropathy in one-half of cases. These neuropathies, which may also occur with solitary plasmacytoma, are distinct because they (1) are usually demyelinating in nature; (2) often respond to radiation therapy or removal of the primary lesion; (3) are associated with different monoclonal proteins and light chains (almost always lambda as opposed to primarily kappa in the lytic type of multiple myeloma); and (4) may occur in association with other systemic findings including thickening of the skin, hyperpigmentation, hypertrichosis, organomegaly, endocrinopathy, anasarca, and clubbing of fingers. These are features of the POEMS syndrome (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M* protein, and *s*kin changes). The pathogenesis of this uncommon syndrome and the explanation for its association with lambda light chains are unknown. Treatment of the neuropathy is best directed at the osteosclerotic myeloma using surgery, radiotherapy, or chemotherapy, as indicated.

Neuropathies are also encountered in other systemic conditions with gammopathy including Waldenström's macroglobulinemia, primary systemic amyloidosis, and cryoglobulinemic states (mixed essential cryoglobulinemia, some cases of hepatitis C).

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

Chronic polyneuropathies occurring in association with MGUS are usually associated with the immunoglobulin isotypes IgG, IgA, and IgM. From a clinical standpoint, many of these patients are indistinguishable from patients with CIDP without monoclonal gammopathy (see Chronic Inflammatory Demyelinating Polyneuropathy, above), and their response to immunosuppressive agents is also similar. An exception is the syndrome of IgM kappa monoclonal gammopathy associated with an indolent, longstanding, sometimes static sensory neuropathy, frequently with tremor and sensory ataxia. Most patients are men and older than 50 years. In the majority, the monoclonal IgM immunoglobulin binds to a normal peripheral nerve constituent, myelin-associated glycoprotein (MAG), found in the paranodal regions of Schwann cells. Binding appears to be specific for a polysaccharide epitope that is also found in other normal peripheral nerve myelin glycoproteins, P0 and PMP22, and also in other normal nerve-related glycosphingolipids (Fig. 41-1). In the MAG-positive cases, IgM paraprotein is incorporated into the myelin sheaths of affected patients and widens the spacing of the myelin lamellae, thus producing a distinctive ultrastructural pattern. Demyelination and remyelination are the hallmarks of the lesions. The chronic demyelinating neuropathy appears to result from a destabilization of myelin metabolism rather than activation of an immune response. Therapy with chlorambucil, or cyclophosphamide combined with glucocorticoids or PE, often results in improvement of the neuropathy associated with a prolonged reduction in the levels in the circulating paraprotein; chronic use of these alkylating agents is associated with significant risks. Recent preliminary data also suggest that anti-CD20 (rituximab) therapy may be effective. In a small proportion of patients (30% at 10 years), MGUS will in time evolve into frankly malignant conditions such as multiple myeloma or lymphoma.

VASCULITIC NEUROPATHY

Peripheral nerve involvement is common in polyarteritis nodosa (PAN), appearing in half of all cases clinically and in 100% of cases at postmortem studies. The most common pattern is multifocal (asymmetric) motor-sensory neuropathy (mononeuropathy multiplex) due to ischemic lesions of nerve trunks and roots; however, some cases of vasculitic neuropathy present as a distal, symmetric sensorimotor polyneuropathy. Symptoms of neuropathy are a common presenting complaint in patients with PAN. The electrodiagnostic findings are those of an axonal process. Small- to medium-sized arteries of the vasa nervorum, particularly the epineural vessels, are affected in PAN, resulting in a widespread ischemic neuropathy. A high frequency of neuropathy occurs in allergic angiitis and granulomatosis (Churg-Strauss syndrome).

Systemic vasculitis should always be considered when a subacute or chronically evolving mononeuropathy multiplex occurs in conjunction with constitutional symptoms (fever, anorexia, weight loss, loss of energy, malaise, and nonspecific pains). Diagnosis of suspected vasculitic neuropathy is made by a combined nerve and muscle biopsy, with serial section or skip-serial techniques.

Approximately one-third of biopsy-proven cases of vasculitic neuropathy are "nonsystemic" in that the vasculitis appears to affect only peripheral nerves. Constitutional symptoms are absent, and the course is more

indolent than that of PAN. The erythrocyte sedimentation rate may be elevated, but other tests for systemic disease are negative. Nevertheless, clinically silent involvement of other organs is likely, and vasculitis is frequently found in muscle biopsied at the same time as nerve.

Vasculitic neuropathy may also be seen as part of the vasculitis syndrome occurring in the course of other connective tissue disorders. The most frequent is rheumatoid arthritis, but ischemic neuropathy due to involvement of vasa nervorum may also occur in mixed cryoglobulinemia, Sjögren's syndrome, Wegener's granulomatosis, hypersensitivity angiitis, and progressive systemic sclerosis. Management of these neuropathies, including the "nonsystemic" vasculitic neuropathy, consists of treatment of the underlying condition as well as the aggressive use of glucocorticoids and other immunosuppressant drugs. One reasonable starting regimen is daily prednisone (initial dose 1 mg/kg per day PO with a gradual taper after 1 month) plus IV pulse (or daily oral) cyclophosphamide for 3–6 months.

ANTI-HU PARANEOPLASTIC NEUROPATHY

This uncommon immune-mediated disorder manifests as a sensory neuronopathy (i.e., selective damage to sensory nerve bodies in dorsal root ganglia). The onset is often asymmetric with dysesthesias and sensory loss in the limbs that soon progress to affect all limbs, the torso, and face. Marked sensory ataxia, pseudoathetosis, and inability to walk, stand, or even sit unsupported are frequent features and are secondary to the extensive deafferentation. Subacute sensory neuronopathy may be idiopathic, but more than half of cases are paraneoplastic, primarily related to lung cancer, and most of those are small cell lung cancer (SCLC). Diagnosis of the underlying SCLC requires awareness of the association, paraneoplastic testing, and often PET scanning for the tumor. The target antigens are a family of RNA binding proteins (HuD, HuC, and Hel-N1) that in normal tissues are only expressed by neurons. The same proteins are usually expressed by SCLC, triggering in some patients an immune response characterized by antibodies and cytotoxic T cells that cross-react with the Hu proteins of the dorsal root ganglion neurons, resulting in immune-mediated neuronal destruction. An encephalomyelitis may accompany the sensory neuronopathy and presumably has the same pathogenesis. Neurologic symptoms usually precede, by ≤6 months, the identification of SCLC. The sensory neuronopathy runs its course in a few weeks or months and stabilizes, leaving the patient disabled. Most cases are unresponsive to treatment with glucocorticoids, IVIg, PE, or immunosuppressant drugs.

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CHAPTER 42

MYASTHENIA GRAVIS AND OTHER DISEASES OF THE NEUROMUSCULAR JUNCTION

Daniel B. Drachman

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Myasthenia gravis (MG) is a neuromuscular disorder characterized by weakness and fatigability of skeletal muscles. The underlying defect is a decrease in the number of available acetylcholine receptors (AChRs) at neuromuscular junctions due to an antibody-mediated autoimmune attack. Treatment now available for MG is highly effective, although a specific cure has remained elusive.

PATHOPHYSIOLOGY

In the neuromuscular junction (**Fig. 42-1**), acetylcholine (ACh) is synthesized in the motor nerve terminal and stored in vesicles (quanta). When an action potential travels down a motor nerve and reaches the nerve terminal, ACh from 150–200 vesicles is released and combines with AChRs that are densely packed at the peaks of postsynaptic folds. The structure of the AChR has been fully elucidated; it consists of five subunits (2α, 1β, 1δ, and 1γ or ε) arranged around a central pore. When ACh combines with the binding sites on the α subunits of the AChR, the channel in the AChR opens, permitting the rapid entry of cations, chiefly sodium, which produces depolarization at the end-plate region of the muscle fiber. If the depolarization is sufficiently large, it initiates an action potential that is propagated along the muscle fiber, triggering muscle contraction. This process is rapidly terminated by hydrolysis of ACh by acetylcholinesterase (AChE), which is present within the synaptic folds, and by diffusion of ACh away from the receptor.

In MG, the fundamental defect is a decrease in the number of available AChRs at the postsynaptic muscle membrane. In addition, the postsynaptic folds are flattened, or "simplified." These changes result in decreased efficiency of neuromuscular transmission. Therefore, although ACh is released normally, it produces small end-plate potentials that may fail to trigger muscle action potentials. Failure of transmission at many neuromuscular junctions results in weakness of muscle contraction.

The amount of ACh released per impulse normally declines on repeated activity (termed *presynaptic rundown*). In the myasthenic patient, the decreased efficiency of neuromuscular transmission combined with the normal rundown results in the activation of fewer and fewer muscle fibers by successive nerve impulses and hence increasing weakness, or *myasthenic fatigue*. This mechanism also accounts for the decremental response to repetitive nerve stimulation seen on electrodiagnostic testing.

The neuromuscular abnormalities in MG are brought about by an autoimmune response mediated by specific anti-AChR antibodies. The anti-AChR antibodies reduce the number of available AChRs at neuromuscular junctions by three distinct mechanisms: (1) accelerated turnover of AChRs by a mechanism involving cross-linking and rapid endocytosis of the receptors; (2) blockade of the active site of the AChR, i.e., the site that

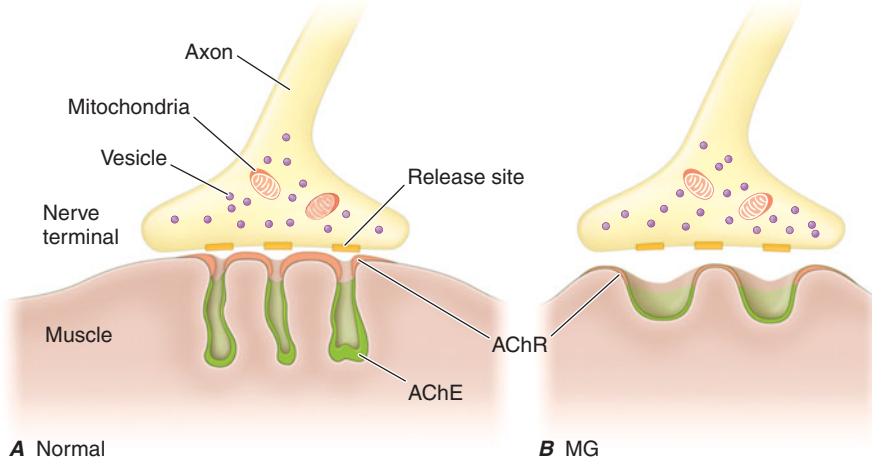

FIGURE 42-1

Diagrams of (*A*) normal and (*B*) myasthenic neuromuscular junctions. AChE, acetylcholinesterase. See text for description of normal neuromuscular transmission. The MG junction demonstrates a normal nerve terminal; a reduced number of AChRs (stippling); flattened, simplified postsynaptic folds; and a widened synaptic space. *(Modified from DB Drachman: N Engl J Med 330:1797, 1994; with permission.)*

normally binds ACh; and (3) damage to the postsynaptic muscle membrane by the antibody in collaboration with complement. An immune response to muscle-specific kinase (MuSK) can also result in myasthenia gravis, possibly by interfering with AChR clustering. The pathogenic antibodies are IgG and are T cell dependent. Thus, immunotherapeutic strategies directed against T cells are effective in this antibody-mediated disease.

How the autoimmune response is initiated and maintained in MG is not completely understood. However, the thymus appears to play a role in this process. The thymus is abnormal in ~75% of patients with MG; in ~65% the thymus is "hyperplastic," with the presence of active germinal centers detected histologically, though the hyperplastic thymus is not necessarily enlarged. An additional 10% of patients have thymic tumors (thymomas). Muscle-like cells within the thymus (myoid cells), which bear AChRs on their surface, may serve as a source of autoantigen and trigger the autoimmune reaction within the thymus gland.

CLINICAL FEATURES

MG is not rare, having a prevalence of 1–7 in 10,000. It affects individuals in all age groups, but peaks of incidence occur in women in their twenties and thirties and in men in their fifties and sixties. Overall, women are affected more frequently than men, in a ratio of ~3:2. The cardinal features are *weakness* and *fatigability* of muscles. The weakness increases during repeated use (fatigue) and may improve following rest or sleep. The course of MG is often variable. Exacerbations and remissions may occur, particularly during the first few years after the onset of the disease. Remissions are rarely complete or permanent. Unrelated infections or systemic disorders often lead to increased myasthenic weakness and may precipitate "crisis" (see later).

The distribution of muscle weakness often has a characteristic pattern. The cranial muscles, particularly the lids and extraocular muscles, are often involved early in the course of MG, and diplopia and ptosis are common initial complaints. Facial weakness produces a "snarling" expression when the patient attempts to smile. Weakness in chewing is most noticeable after prolonged effort, as in chewing meat. Speech may have a nasal timbre caused by weakness of the palate or a dysarthric "mushy" quality due to tongue weakness. Difficulty in swallowing may occur as a result of weakness of the palate, tongue, or pharynx, giving rise to nasal regurgitation or aspiration of liquids or food. Bulbar weakness is especially prominent in MuSK antibody–positive MG. In ~85% of patients, the weakness becomes generalized, affecting the limb muscles as well. If weakness remains restricted to the extraocular muscles for 3 years, it is likely that it will not become generalized, and these patients are said to have *ocular MG*. The limb weakness in MG is often proximal and may be asymmetric. Despite the muscle weakness, deep tendon reflexes are preserved. If weakness of respiration becomes so severe as to require respiratory assistance, the patient is said to be in *crisis*.

DIAGNOSIS AND EVALUATION

(Table 42-1) The diagnosis is suspected on the basis of weakness and fatigability in the typical distribution described above, without loss of reflexes or impairment of sensation or other neurologic function. The suspected diagnosis should always be confirmed definitively before treatment is undertaken; this is essential because (1) other treatable conditions may closely resemble MG,

TABLE 42-1

DIAGNOSIS OF MYASTHENIA GRAVIS (MG)

- History
  - Diplopia, ptosis, weakness
  - Weakness in characteristic distribution
  - Fluctuation and fatigue: worse with repeated activity, improved by rest
  - Effects of previous treatments
- Physical examination
  - Ptosis, diplopia
  - Motor power survey: quantitative testing of muscle strength
  - Forward arm abduction time (5 min)
  - Vital capacity
  - Absence of other neurologic signs
- Laboratory testing
  - Anti-AChR radioimmunoassay: ~85% positive in generalized MG; 50% in ocular MG; definite diagnosis if positive; negative result does not exclude MG. ~40% of AChR antibody-negative patients with generalized MG have anti-MuSK antibodies.
  - Repetitive nerve stimulation; decrement of >15% at 3 Hz: highly probable
  - Single-fiber electromyography: blocking and jitter, with normal fiber density; confirmatory, but not specific
  - Edrophonium chloride (Tensilon) 2 mg + 8 mg IV; highly probable diagnosis if unequivocally positive
  - For ocular or cranial MG: exclude intracranial lesions by CT or MRI

Note: AChR, acetylcholine receptor; MuSK, muscle-specific tyrosine kinase.

Source: From RT Johnson, JW Griffin (eds): *Current Therapy in Neurologic Disease*, 4th ed. St. Louis, Mosby Year Book, 1994; with permission.

and (2) the treatment of MG may involve surgery and the prolonged use of drugs with adverse side effects.

Antibodies to AChR or MuSK

As noted above, anti-AChR antibodies are detectable in the serum of ~85% of all myasthenic patients but in only about 50% of patients with weakness confined to the ocular muscles. The presence of anti-AChR antibodies is virtually diagnostic of MG, but a negative test does not exclude the disease. The measured level of anti-AChR antibody does not correspond well with the severity of MG in different patients. However, in an individual patient, a treatment-induced fall in the antibody level often correlates with clinical improvement. Antibodies to MuSK have been found to be present in ~40% of AChR antibody-negative patients with generalized MG, and their presence is a useful diagnostic test in these patients. MuSK antibodies are rarely present in AChR antibody-positive patients or in patients with MG limited to ocular muscles. These antibodies may interfere with clustering of AChRs at neuromuscular junctions, as MuSK is known to do during early development. There is also evidence that MG patients without demonstrable antibodies to either AChR or MuSK have other—as yet undefined—antibodies that impair neuromuscular transmission.

Electrodiagnostic Testing

Repetitive nerve stimulation often provides helpful diagnostic evidence of MG. Anti-AChE medication is stopped 6–24 h before testing. It is best to test weak muscles or proximal muscle groups. Electric shocks are delivered at a rate of two or three per second to the appropriate nerves, and action potentials are recorded from the muscles. In normal individuals, the amplitude of the evoked muscle action potentials does not change at these rates of stimulation. However, in myasthenic patients there is a rapid reduction of >10–15% in the amplitude of the evoked responses. As a further test, a single dose of edrophonium may be given to prevent or diminish this decremental response.

Anticholinesterase Test

Drugs that inhibit the enzyme AChE allow ACh to interact repeatedly with the limited number of AChRs, producing improvement in the strength of myasthenic muscles. Edrophonium is used most commonly for diagnostic testing because of the rapid onset (30 s) and short duration (~5 min) of its effect. An objective end-point must be selected to evaluate the effect of edrophonium, such as weakness of extraocular muscles, impairment of speech, or the length of time that the patient can maintain the arms in forward abduction. An initial IV dose of 2 mg of edrophonium is given. If definite improvement occurs, the test is considered positive and is terminated. If there is no change, the patient is given an additional 8 mg IV. The dose is administered in two parts because some patients react to edrophonium with side effects such as nausea, diarrhea, salivation, fasciculations, and rarely with severe symptoms of syncope or bradycardia. Atropine (0.6 mg) should be drawn up in a syringe, ready for IV administration if these symptoms become troublesome.

False-positive tests occur in occasional patients with other neurologic disorders, such as amyotrophic lateral sclerosis, and in placebo-reactors. False-negative or equivocal tests may also occur. In some cases it is helpful to use a longer-acting drug such as neostigmine (15 mg PO), since this permits more time for detailed evaluation of strength. The edrophonium test is now reserved for patients with clinical findings that are suggestive of MG but who have negative antibody and electrodiagnostic test results.

Inherited Myasthenic Syndromes

The congenital myasthenic syndromes (CMS) comprise a heterogeneous group of disorders of the neuromuscular junction that are not autoimmune but rather

TABLE 42-2

THE CONGENITAL MYASTHENIC SYNDROMES

TYPE	CLINICAL FEATURES	ELECTROPHYSIOLOGY	GENETICS	END-PLATE EFFECTS	TREATMENT
Slow channel	Most common; weak forearm extensors; onset 2d to 3d decade; variable severity	Repetitive muscle response on nerve stimulation; prolonged channel opening and MEPP duration	Autosomal dominant; α, β, ε AChR mutations	Excitotoxic end-plate myopathy; decreased AChRs; postsynaptic damage	Quinidine: decreases end-plate damage; made worse by anti-AChE
Low-affinity fast channel	Onset early; moderately severe; ptosis, EOM involvement; weakness and fatigue	Brief and infrequent channel openings; opposite of slow channel syndrome	Autosomal recessive; may be heteroallelic	Normal end-plate structure	3,4-DAP; anti-AChE
Severe AChR deficiencies	Early onset; variable severity; fatigue; typical MG features	Decremental response to repetitive nerve stimulation; decreased MEPP amplitudes	Autosomal recessive; ε mutations most common; many different mutations	Increased length of end plates; variable synaptic folds	Anti-AChE; 3,4-DAP
AChE deficiency	Early onset; variable severity; scoliosis; may have normal EOM, absent pupillary responses	Decremental response to repetitive nerve stimulation	Mutant gene for AChE's collagen anchor junctional folds	Small nerve terminals; degenerated	Worse with anti-AChE drugs

Note: AChR, acetylcholine receptor; AChE, acetylcholinesterase; EOM, extraocular muscles; MEPP, miniature end-plate potentials; 3,4-DAP, 3-4-diaminopyridine.

are due to genetic mutations in which virtually any component of the neuromuscular junction may be affected. Alterations in function of the presynaptic nerve terminal or in the various subunits of the AChR or AChE have been identified in the various forms of CMS. These disorders share many of the clinical features of autoimmune MG, including weakness and fatigability of skeletal muscles, in some cases involving extraocular muscles (EOMs), lids, and proximal muscles, similar to the distribution in autoimmune MG. CMS should be suspected when symptoms of myasthenia have begun in infancy or childhood and AChR antibody tests are consistently negative. Features of four of the most common forms of CMS are summarized in Table 42-2. Although clinical features and electrodiagnostic and pharmacologic tests may suggest the correct diagnosis, molecular analysis is required for precise elucidation of the defect; this may lead to helpful treatment as well as genetic counseling. In the forms that involve the AChR, a wide variety of mutations have been identified in each of the subunits, but the ε subunit is affected in ~75% of these cases. In most of the recessively inherited forms of CMS, the mutations are heteroallelic; that is, different mutations affecting each of the two alleles are present.

Differential Diagnosis

Other conditions that cause weakness of the cranial and/or somatic musculature include the nonautoimmune CMS discussed above, drug-induced myasthenia, Lambert-Eaton myasthenic syndrome (LEMS), neurasthenia, hyperthyroidism, botulism, intracranial mass lesions, and progressive external ophthalmoplegia. Treatment with penicillamine (used for scleroderma or rheumatoid arthritis) may result in true autoimmune MG, but the weakness is usually mild, and recovery occurs within weeks or months after discontinuing its use. Aminoglycoside antibiotics or procainamide can cause exacerbation of weakness in myasthenic patients; very large doses can cause neuromuscular weakness in normal individuals.

LEMS is a presynaptic disorder of the neuromuscular junction that can cause weakness similar to that of MG. The proximal muscles of the lower limbs are most commonly affected, but other muscles may be involved as well. Cranial nerve findings, including ptosis of the eyelids and diplopia, occur in up to 70% of patients and resemble features of MG. However, the two conditions are readily distinguished, since patients with LEMS have depressed or absent reflexes, experience autonomic changes such as dry mouth and impotence, and have

incremental rather than decremental responses on repetitive nerve stimulation. LEMS is caused by autoantibodies directed against P/Q type calcium channels at the motor nerve terminals, which can be detected in ~85% of LEMS patients by radioimmunoassay. These autoantibodies result in impaired release of ACh from nerve terminals. Most patients with LEMS have an associated malignancy, most commonly small cell carcinoma of the lung, which may express calcium channels that stimulate the autoimmune response. The diagnosis may signal the presence of a tumor long before it would otherwise be detected, permitting early removal. Treatment of LEMS involves plasmapheresis and immunosuppression, as for MG. 3,4-Diaminopyridine (3,4-DAP) and pyridostigmine may also be symptomatically helpful. 3,4-DAP acts by blocking potassium channels, which results in prolonged depolarization of the motor nerve terminals and thus enhances ACh release. Pyridostigmine prolongs the action of ACh, allowing repeated interactions with AChRs.

Botulism is due to a potent bacterial toxin produced by *Clostridium botulinum*. The toxin interferes with the release of acetylcholine from the presynaptic neuromuscular junction, thereby interfering with neuromuscular transmission. The most common form is food-borne botulism from ingestion of food containing toxin; in wound and intestinal botulism spores germinate and give rise to organisms that produce toxin. Patients present with bulbar weakness (e.g., diplopia, dysarthria, dysphagia), but lack sensory symptoms and signs; deep tendon reflexes are preserved early in the disease course. Weakness generalizes to the limbs and may result in respiratory failure; reflexes may be diminished as the disease progresses. Mentation is normal. Autonomic findings include paralytic ileus, constipation, urinary retention, dilated or poorly reactive pupils, and dry mouth. The demonstration of toxin in serum by bioassay is definitive, but may be negative. Nerve conduction studies reveal findings of presynaptic neuromuscular blockade with reduced compound muscle action potentials (CMAPs) that increase in amplitude following high frequency repetitive stimulation. Treatment may include intubation for airway protection, ventilatory support, or aggressive inpatient supportive care (e.g., nutrition, DVT prophylaxis). Equine antitoxin is given rapidly before the results of laboratory studies are available. The prognosis is better among patients with type B infection who are under the age of 60 years. A vaccine is available for highly exposed individuals.

Neurasthenia is the historic term for a myasthenia-like fatigue syndrome without an organic basis. These patients may present with subjective symptoms of weakness and fatigue, but muscle testing usually reveals the "jerky release" or "give-away weakness" characteristic of nonorganic disorders; the complaint of fatigue in these patients means tiredness or apathy rather than decreasing muscle power on repeated effort. Hyperthyroidism is readily diagnosed or excluded by tests of thyroid function, which should be carried out routinely in patients with suspected MG. Abnormalities of thyroid function (hyper- or hypothyroidism) may increase myasthenic weakness. Botulism can cause myasthenic-like weakness, but the pupils are often dilated, and repetitive nerve stimulation gives an incremental response. Diplopia resembling that in MG may occasionally be due to an intracranial mass lesion that compresses nerves to the EOMs (e.g., sphenoid ridge meningioma), but MRI of the head and orbits usually reveals the lesion.

Progressive external ophthalmoplegia is a rare condition resulting in weakness of the EOMs, which may be accompanied by weakness of the proximal muscles of the limbs and other systemic features. Most patients with this condition have mitochondrial disorders that can be detected on muscle biopsy (Chap. 43).

Search for Associated Conditions

(Table 42-3) Myasthenic patients have an increased incidence of several associated disorders. Thymic abnormalities occur in ~75% of patients, as noted above. Neoplastic change (thymoma) may produce enlargement of the thymus, which is detected by CT or MRI scanning of

TABLE 42-3

DISORDERS ASSOCIATED WITH MYASTHENIA GRAVIS AND RECOMMENDED LABORATORY TESTS

- Associated disorders
  - *Disorders of the thymus:* thymoma, hyperplasia
  - *Other autoimmune disorders:* Hashimoto's thyroiditis, Graves' disease, rheumatoid arthritis, lupus erythematosus, skin disorders, family history of autoimmune disorder
  - *Disorders or circumstances that may exacerbate myasthenia gravis*: hyperthyroidism or hypothyroidism, occult infection, medical treatment for other conditions (see Table 42-4)
  - *Disorders that may interfere with therapy*: tuberculosis, diabetes, peptic ulcer, gastrointestinal bleeding, renal disease, hypertension, asthma, osteoporosis, obesity
- Recommended laboratory tests or procedures
  - CT or MRI of mediastinum
  - Tests for lupus erythematosus, antinuclear antibody, rheumatoid factor, antithyroid antibodies
  - Thyroid-function tests
  - PPD skin test
  - Chest radiography
  - Fasting blood glucose measurement, hemoglobin A1c
  - Pulmonary-function tests
  - Bone densitometry in older patients

Note: PPD, purified protein derivative.

Source: From RT Johnson, JW Griffin (eds): *Current Therapy in Neurologic Disease*, 4th ed. St. Louis, Mosby Year Book, 1993, p 379; with permission.

the anterior mediastinum. A thymic shadow on CT scan may normally be present through young adulthood, but enlargement of the thymus in a patient >40 years old is highly suspicious of thymoma. Hyperthyroidism occurs in 3–8% of patients and may aggravate the myasthenic weakness. Thyroid function tests should be obtained in all patients with suspected MG. Because of the association of MG with other autoimmune disorders, blood tests for rheumatoid factor and antinuclear antibodies should also be carried out. Chronic infection of any kind can exacerbate MG and should be sought carefully. Finally, measurements of ventilatory function are valuable because of the frequency and seriousness of respiratory impairment in myasthenic patients.

Because of the side effects of glucocorticoids and other immunosuppressive agents used in the treatment of MG, a thorough medical investigation should be undertaken, searching specifically for evidence of chronic or latent infection (such as tuberculosis or hepatitis), hypertension, diabetes, renal disease, and glaucoma.

Rx Treatment: MYASTHENIA GRAVIS

The prognosis has improved strikingly as a result of advances in treatment; virtually all myasthenic patients can be returned to full productive lives with proper therapy. The most useful treatments for MG include anticholinesterase medications, immunosuppressive agents, thymectomy, and plasmapheresis or intravenous immunoglobulin (IVIg) (Fig. 42-2).

ANTICHOLINESTERASE MEDICATIONS

Anticholinesterase medication produces at least partial improvement in most myasthenic patients, although improvement is complete in only a few. Pyridostigmine is the most widely used anticholinesterase drug. As a rule, the beneficial action of oral pyridostigmine begins within 15–30 min and lasts for 3–4 h, but individual responses vary. Treatment is begun with a moderate dose, e.g., 30–60 mg 3–4 times daily. The frequency and amount of the dose should be tailored to the patient's individual requirements throughout the day. For example, patients with weakness in chewing and swallowing may benefit by taking the medication before meals so that peak strength coincides with mealtimes. Long-acting pyridostigmine may occasionally be useful to get the patient through the night but should never be used for daytime medication because of variable absorption. The maximum useful dose of pyridostigmine rarely exceeds 120 mg every 3–6 h during daytime. Overdosage with anticholinesterase medication may cause increased weakness and other side effects. In some patients, muscarinic side effects of the anticholinesterase medication (diarrhea, abdominal cramps, salivation, nausea)

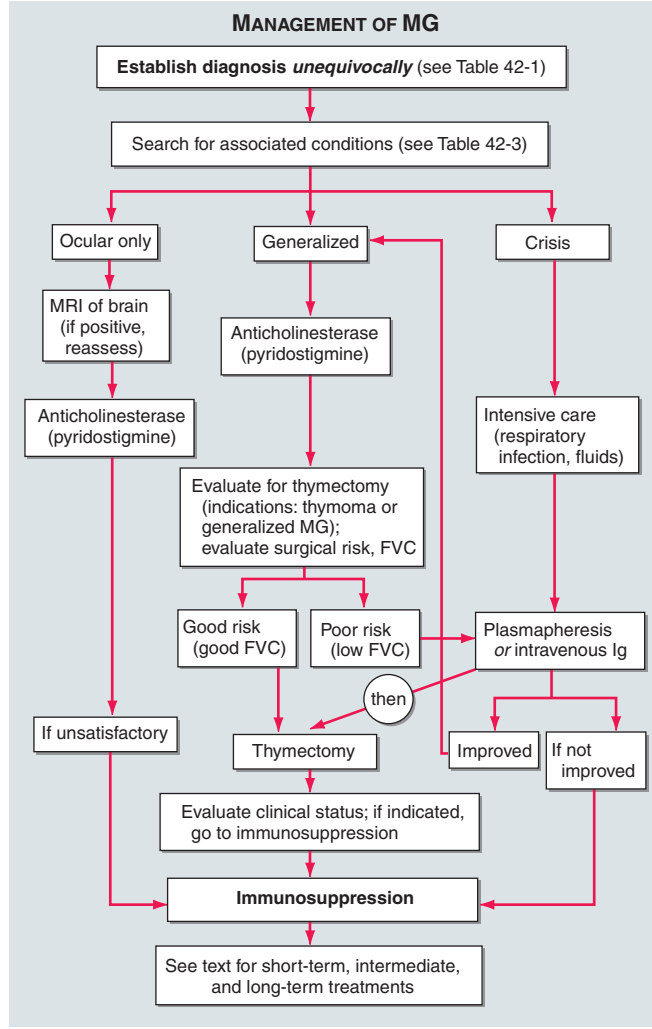

FIGURE 42-2
Algorithm for the management of myasthenia gravis. FVC, forced vital capacity.

may limit the dose tolerated. Atropine/diphenoxylate or loperamide is useful for the treatment of gastrointestinal symptoms.

THYMECTOMY Two separate issues should be distinguished: (1) surgical removal of thymoma, and (2) thymectomy as a treatment for MG. Surgical removal of a thymoma is necessary because of the possibility of local tumor spread, although most thymomas are histologically benign. In the absence of a tumor, the available evidence suggests that up to 85% of patients experience improvement after thymectomy; of these, ~35% achieve drug-free remission. However, the improvement is typically delayed for months to years. The advantage of thymectomy is that it offers the possibility of long-term benefit, in some cases diminishing or eliminating the need for continuing medical treatment. In view of these potential benefits and of the negligible risk in skilled hands, thymectomy has gained widespread

acceptance in the treatment of MG. It is the consensus that thymectomy should be carried out in all patients with generalized MG who are between puberty and at least 55 years of age. Whether thymectomy should be recommended in children, in adults >55 years, and in patients with weakness limited to the ocular muscles is still a matter of debate. There is also evidence that patients with MuSK antibody–positive MG may not respond to thymectomy. Thymectomy must be carried out in a hospital where it is performed regularly and where the staff is experienced in the pre- and postoperative management, anesthesia, and surgical techniques of total thymectomy.

IMMUNOSUPPRESSION Immunosuppression using glucocorticoids, azathioprine, and other drugs is effective in nearly all patients with MG. The choice of drugs or other immunomodulatory treatments should be guided by the relative benefits and risks for the individual patient and the urgency of treatment. It is helpful to develop a treatment plan based on short-term, intermediate-term, and long-term objectives. For example, if immediate improvement is essential either because of the severity of weakness or because of the patient's need to return to activity as soon as possible, IVIg should be administered or plasmapheresis should be undertaken. For the intermediate term, glucocorticoids and cyclosporine or tacrolimus generally produce clinical improvement within a period of 1–3 months. The beneficial effects of azathioprine and mycophenolate mofetil usually begin after many months (up to a year), but these drugs have advantages for the long-term treatment of patients with MG. For the occasional patient with MG that is genuinely refractory to optimal treatment with conventional immunosuppressive agents, a course of high-dose cyclophosphamide may induce long-lasting (possibly permanent) benefit by "rebooting" the immune system. At high doses, cyclophosphamide eliminates mature lymphocytes, but hematopoietic precursors (stem cells) are spared, because they express the enzyme aldehyde dehydrogenase, which hydrolyzes cyclophosphamide. At present, this procedure is reserved for refractory patients and should be administered only in a facility fully familiar with this approach.

Glucocorticoid Therapy Glucocorticoids, when used properly, produce improvement in myasthenic weakness in the great majority of patients. To minimize adverse side effects, prednisone should be given in a single dose rather than in divided doses throughout the day. The initial dose should be relatively low (15–25 mg/d) to avoid the early weakening that occurs in about one-third of patients treated initially with a high-dose regimen. The dose is increased stepwise, as tolerated by the patient (usually by 5 mg/d at 2- to 3-day intervals), until there is marked clinical improvement or a dose of 50–60 mg/d is reached. This dose is maintained for 1–3 months and then is gradually modified to an alternate-day regimen over the course of an additional 1–3 months; the goal is to reduce the dose on the "off day" to zero or to a minimal level. Generally, patients begin to improve within a few weeks after reaching the maximum dose, and improvement continues to progress for months or years. The prednisone dosage may gradually be reduced, but usually months or years may be needed to determine the minimum effective dose, and close monitoring is required. Few patients are able to do without immunosuppressive agents entirely. Patients on long-term glucocorticoid therapy must be followed carefully to prevent or treat adverse side effects. The most common errors in glucocorticoid treatment of myasthenic patients include (1) insufficient persistence—improvement may be delayed and gradual; (2) too early, too rapid, or excessive tapering of dosage; and (3) lack of attention to prevention and treatment of side effects.

Other Immunosuppressive Drugs Mycophenolate mofetil, azathioprine, cyclosporine, tacrolimus, and occasionally cyclophosphamide are effective in many patients, either alone or in various combinations.

Mycophenolate mofetil has become one of the most widely used drugs in the treatment of MG because of its effectiveness and relative lack of side effects. A dose of 1–1.5 g bid is recommended. Its mechanism of action involves inhibition of purine synthesis by the de novo pathway. Since lymphocytes lack the alternative salvage pathway that is present in all other cells, mycophenolate inhibits proliferation of lymphocytes but not proliferation of other cells. It does not kill or eliminate preexisting autoreactive lymphocytes, and therefore clinical improvement may be delayed for many months to a year, until the preexisting autoreactive lymphocytes die spontaneously. The advantage of mycophenolate lies in its relative lack of adverse side effects, with only occasional production of diarrhea and rare development of leukopenia. This drug has become the choice for long-term treatment of myasthenic patients. Unfortunately, the cost of mycophenolate is still very high (~$6400 U.S. annually for 1g bid).

Until recently, azathioprine has been the most widely used of these drugs because of its relative safety in most patients and long track record. Its therapeutic effect may add to that of glucocorticoids and/or allow the glucocorticoid dose to be reduced. However, up to 10% of patients are unable to tolerate azathioprine because of idiosyncratic reactions consisting of flulike symptoms of fever and malaise, bone marrow depression, or abnormalities of liver function. An initial dose of 50 mg/d should be used to test for adverse side effects. If this dose is tolerated, it is increased gradually until the

white blood count falls to ~3000–4000/μL. In patients who are receiving glucocorticoids concurrently, leukocytosis precludes the use of this measure. A reduction of the lymphocyte count to <1000/μL and/or an increase of the mean corpuscular volume of red blood cells may be used as indications of adequacy of azathioprine dosage. The typical dosage range is 2–3 mg/kg total body weight. The beneficial effect of azathioprine takes at least 3–6 months to begin and even longer to peak. In patients taking azathioprine, allopurinol should never be used to treat hyperuricemia, because the two drugs share a common degradation pathway; the result may be severe bone marrow depression due to increased effects of the azathioprine.

The calcineurin inhibitors cyclosporine and tacrolimus (FK506) are approximately as effective as azathioprine and are being used increasingly in the management of MG. Their beneficial effect appears more rapidly than that of azathioprine. Either drug may be used alone, but they are usually used as an adjunct to glucocorticoids to permit reduction of the glucocorticoid dose. The usual dose of cyclosporine is 4–5 mg/kg per day, and the average dose of tacrolimus is 0.1 mg/kg per day, given in two equally divided doses (to minimize side effects). Side effects of these drugs include hypertension and nephrotoxicity, which must be closely monitored. "Trough" blood levels are measured 12 h after the evening dose. The therapeutic range for cyclosporine is 150–200 ng/L, and for tacrolimus it is 5–15 ng/L.

Cyclophosphamide is reserved for occasional patients refractory to the other drugs (see earlier for discussion of high-dose cyclophosphamide treatment).

PLASMAPHERESIS AND INTRAVENOUS IMMUNOGLOBULIN Plasmapheresis has been used therapeutically in MG. Plasma, which contains the pathogenic antibodies, is mechanically separated from the blood cells, which are returned to the patient. A course of five exchanges (3–4 L per exchange) is generally administered over a 10- to 14-day period. Plasmapheresis produces a short-term reduction in anti-AChR antibodies, with clinical improvement in many patients. It is useful as a temporary expedient in seriously affected patients or to improve the patient's condition prior to surgery (e.g., thymectomy).

The indications for the use of IVIg are the same as those for plasma exchange: to produce rapid improvement to help the patient through a difficult period of myasthenic weakness or prior to surgery. This treatment has the advantages of not requiring special equipment or large-bore venous access. The usual dose is 2 g/kg, which is typically administered over 5 days (400 mg/kg per day). If tolerated, the course of IVIg can be shortened to administer the entire dose over a 3-day period. Improvement occurs in ~70% of patients, beginning during treatment, or within a week, and continuing for weeks to months. The mechanism of action of IVIg is not known; the treatment has no consistent effect on the measurable amount of circulating AChR antibody. Adverse reactions are generally not serious but include headache, fluid overload, and rarely aseptic meningitis or renal failure. IVIg should rarely be used as a long-term treatment in place of rationally managed immunosuppressive therapy. Unfortunately, there is a tendency for physicians unfamiliar with immunosuppressive treatments to rely on repeated IVIg infusions, which are inconvenient, usually produce only intermittent benefit, and are costly. The intermediate and long-term treatment of myasthenic patients requires other methods of therapy outlined earlier in this chapter.

MANAGEMENT OF MYASTHENIC CRISIS

Myasthenic crisis is defined as an exacerbation of weakness sufficient to endanger life; it usually consists of respiratory failure caused by diaphragmatic and intercostal muscle weakness. Crisis rarely occurs in properly managed patients. Treatment should be carried out in intensive care units staffed with teams experienced in the management of MG, respiratory insufficiency, infectious disease, and fluid and electrolyte therapy. The possibility that deterioration could be due to excessive anticholinesterase medication ("cholinergic crisis") is best excluded by temporarily stopping anticholinesterase drugs. The most common cause of crisis is intercurrent infection. This should be treated immediately, because the mechanical and immunologic defenses of the patient can be assumed to be compromised. The myasthenic patient with fever and early infection should be treated like other immunocompromised patients. Early and effective antibiotic therapy, respiratory assistance, and pulmonary physiotherapy are essentials of the treatment program. As discussed above, plasmapheresis or IVIg is frequently helpful in hastening recovery.

DRUGS TO AVOID IN MYASTHENIC PATIENTS Many drugs have been reported to have adverse effects in patients with MG (**Table 42-4**). However, not all patients react adversely to all these drugs. Conversely, not all "safe" drugs can be used with impunity in patients with MG. As a rule, the listed drugs should be avoided *whenever possible*, and myasthenic patients should be followed closely when *any new drug* is introduced.

PATIENT ASSESSMENT

In order to evaluate the effectiveness of treatment as well as drug-induced side effects, it is important to assess the patient's clinical status systematically at baseline and

TABLE 42-4

DRUGS WITH INTERACTIONS IN MYASTHENIA GRAVIS (MG)

Drugs that May Exacerbate mg

Antibiotics
- Aminoglycosides: e.g., streptomycin, tobramycin, kanamycin
- Quinolones: e.g., ciprofloxacin, levofloxacin, ofloxacin, gatifloxacin
- Macrolides: e.g., erythromycin, azithromycin, telithromycin

Nondepolarizing muscle relaxants for surgery
- D-Tubocurarine (curare), pancuronium, vecuronium, atracurium

Beta-blocking agents
- Propranalol, atenolol, metoprolol

Local anesthetics and related agents
- Procaine, xylocaine in large amounts
- Procainamide (for arrhythmias)

Botulinum toxin
- Botox exacerbates weakness

Quinine derivatives
- Quinine, quinidine, chloroquine, mefloquine (Lariam)

Magnesium
- Decreases ACh release

Penicillamine
- May cause MG

Drugs with Important Interactions in mg

Cyclosporine
- Broad range of drug interactions, which may raise or lower cyclosporine levels.

Azathioprine
- Avoid allopurinol—combination may result in myelo suppression.

on repeated interval examinations. Because of the variability of symptoms of MG, the interval history and physical findings on examination must be taken into account. The most useful clinical tests include forward arm abduction time (up to a full 5 min), forced vital capacity, range of eye movements, and time to development of ptosis on upward gaze. Manual muscle testing or, preferably, quantitative dynamometry of limb muscles, especially proximal muscles, is also important. An interval form can provide a succinct summary of the patient's status and a guide to treatment results; an abbreviated form is shown in Fig. 42-3. A progressive reduction in the patient's AChR antibody level also provides clinically valuable confirmation of the effectiveness of treatment; conversely, a rise in AChR antibody levels during tapering of immunosuppressive medication may predict clinical exacerbation. For

Myasthenia Gravis Worksheet

History				
General	Normal	Good	Fair	Poor
Diplopia	None	Rare	Occasional	Constant
Ptosis	None	Rare	Occasional	Constant
Arms	Normal	Slightly limited	Some ADL impairment	Definitely limited
Legs	Normal	Walks/runs fatigues	Can walk limited distances	Minimal walking
Speech	Normal	Dysarthric	Severely dysarthric	Unintelligible
Voice	Normal	Fades	Impaired	Severely impaired
Chew	Normal	Fatigue on normal foods	Fatigue on soft foods	Feeding tube
Swallow	Normal	Normal foods	Soft foods only	Feeding tube
Respiration	Normal	Dyspnea on unusual effort	Dyspnea on any effort	Dyspnea at rest

Examination

BP _____ Pulse _____ Wt _____
Edema _____
Vital capacity _____
Cataracts? R _____ L _____
EOMS _____
Ptosis time _____
Face _____

Arm abduction time R_____ L_____
Deltoids R_____ L_____
Biceps R_____ L_____
Triceps R_____ L_____
Grip R_____ L_____
Iliopsoas R_____ L_____
Quadriceps R_____ L_____
Hamstrings R_____ L_____
Other R_____ L_____

FIGURE 42-3
Abbreviated interval assessment form for use in evaluating treatment for myasthenia gravis.

reliable quantitative measurement of AChR antibody levels, it is best to compare antibody levels from prior frozen serum aliquots with current serum samples in simultaneously run assays.

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CHAPTER 43

MUSCULAR DYSTROPHIES AND OTHER MUSCLE DISEASES

Robert H. Brown, Jr. ■ Anthony A. Amato ■ Jerry R. Mendell

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Skeletal muscle diseases, or myopathies, are disorders with structural changes or functional impairment of muscle. These conditions can be differentiated from other diseases of the motor unit (e.g., lower motor neuron or neuromuscular junction pathologies) by characteristic clinical and laboratory findings. Myasthenia gravis and related disorders are discussed in Chap. 42; dermatomyositis, polymyositis, and inclusion body myositis are discussed in Chap. 44.

CLINICAL FEATURES

The most common clinical findings of a myopathy are proximal, symmetric limb weakness (arms or legs) with preserved reflexes and sensation. An associated sensory loss suggests injury to peripheral nerve or the central nervous system (CNS) rather than myopathy. On occasion, disorders affecting the motor nerve cell bodies in the spinal cord (anterior horn cell disease), the neuromuscular junction, or peripheral nerves can mimic findings of myopathy.

Muscle Weakness

Symptoms of muscle weakness can be either intermittent or persistent. Disorders causing *intermittent weakness* (**Fig. 43-1**) include myasthenia gravis, periodic paralyses (hypokalemic, hyperkalemic, and paramyotonia congenita), and metabolic energy deficiencies of glycolysis (especially

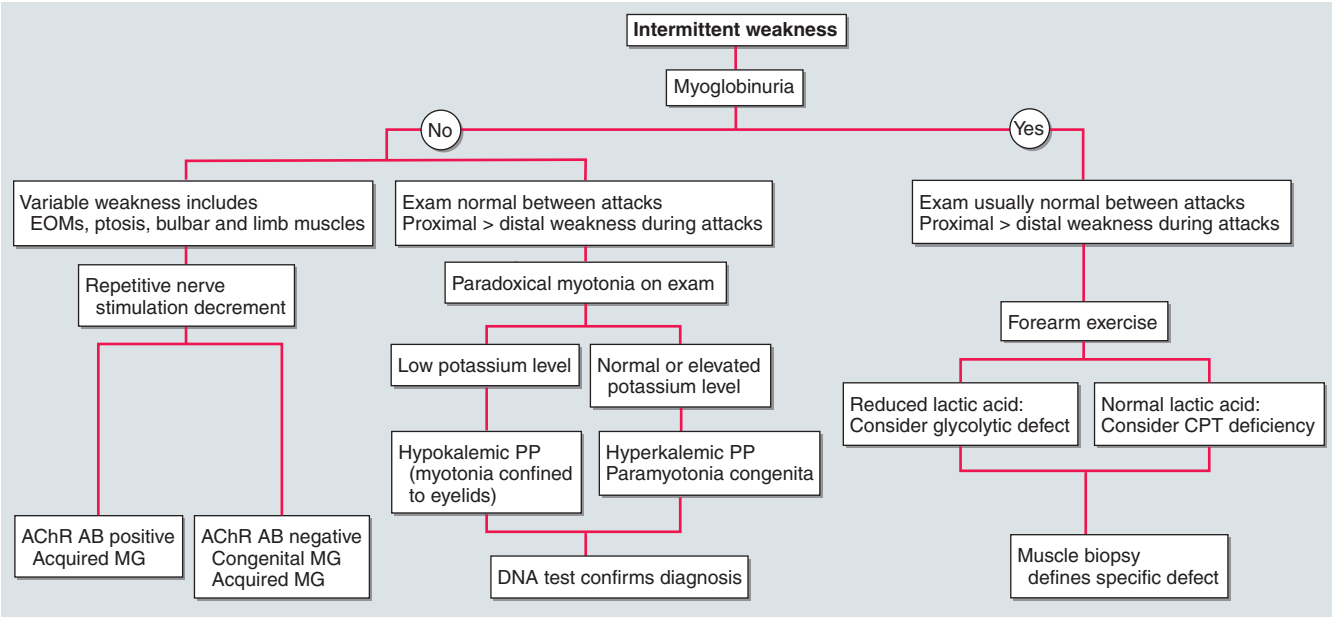

FIGURE 43-1
Diagnostic evaluation of intermittent weakness. EOMs, extraocular muscles; AChR AB, acetylcholine receptor antibody; PP, periodic paralysis; CPT, carnitine palmitoyltransferase; MG, myasthenia gravis.

myophosphorylase deficiency) and fatty acid utilization (carnitine palmitoyltransferase deficiency and some mitochondrial myopathies). The states of energy deficiency cause activity-related muscle breakdown accompanied by myoglobinuria, appearing as light-brown- to dark-brown-colored urine.

Most muscle disorders cause *persistent weakness* (Fig. 43-2). In the majority of these, including most types of muscular dystrophy, polymyositis, and dermatomyositis, the proximal muscles are weaker than the distal and are symmetrically affected, and the facial muscles are spared, a pattern referred to as *limb-girdle*. The differential diagnosis is more restricted for other patterns of weakness. Facial weakness (difficulty with eye closure and impaired smile) and scapular winging (Fig. 43-3) are characteristic of facioscapulohumeral dystrophy. Facial and distal limb weakness associated with hand grip myotonia is virtually diagnostic of myotonic dystrophy. When other cranial nerve muscles are weak, causing ptosis or extraocular muscle weakness, the most important disorders to consider include neuromuscular junction disorders, oculopharyngeal muscular dystrophy, mitochondrial myopathies, or some of the congenital myopathies (Table 43-1). A pathognomonic pattern characteristic of inclusion body myositis is atrophy and weakness of the flexor forearm (e.g., wrist and finger flexors) and quadriceps muscles that is often asymmetric. Less frequently, but important diagnostically, is the presence of a dropped head syndrome indicative of selective neck extensor muscle weakness. The most important neuromuscular diseases associated with this pattern of weakness include myasthenia gravis, amyotrophic lateral sclerosis, late-onset nemaline myopathy, hyperparathyroidism, focal myositis, and some forms of inclusion body myopathy. A final pattern, recognized because of preferential distal extremity weakness, is typical of a unique category of muscular dystrophy, the distal myopathies.

It is important to examine functional capabilities to help disclose certain patterns of weakness (Table 43-2). The Gowers' sign (Fig. 43-4) is particularly useful. Observing the gait of an individual may disclose a lordotic posture caused by combined trunk and hip weakness, frequently exaggerated by toe walking (Fig. 43-5). A waddling gait is caused by the inability of weak hip muscles to prevent hip drop or hip dip. Hyperextension of the knee (genu recurvatum or backkneeing) is characteristic of quadriceps muscle weakness; and a steppage gait, due to footdrop, accompanies distal weakness.

Any disorder causing muscle weakness may be accompanied by *fatigue*, referring to an inability to maintain or sustain a force (pathologic fatigability). This condition must be differentiated from asthenia, a type of fatigue caused by excess tiredness or lack of energy. Associated symptoms may help differentiate asthenia and pathologic fatigability. Asthenia is often accompanied by a tendency to avoid physical activities, complaints of daytime sleepiness, necessity for frequent naps, and difficulty concentrating on activities such as reading. There may be feelings of overwhelming stress and depression. Thus, asthenia is not a myopathy. In contrast, pathologic fatigability occurs in

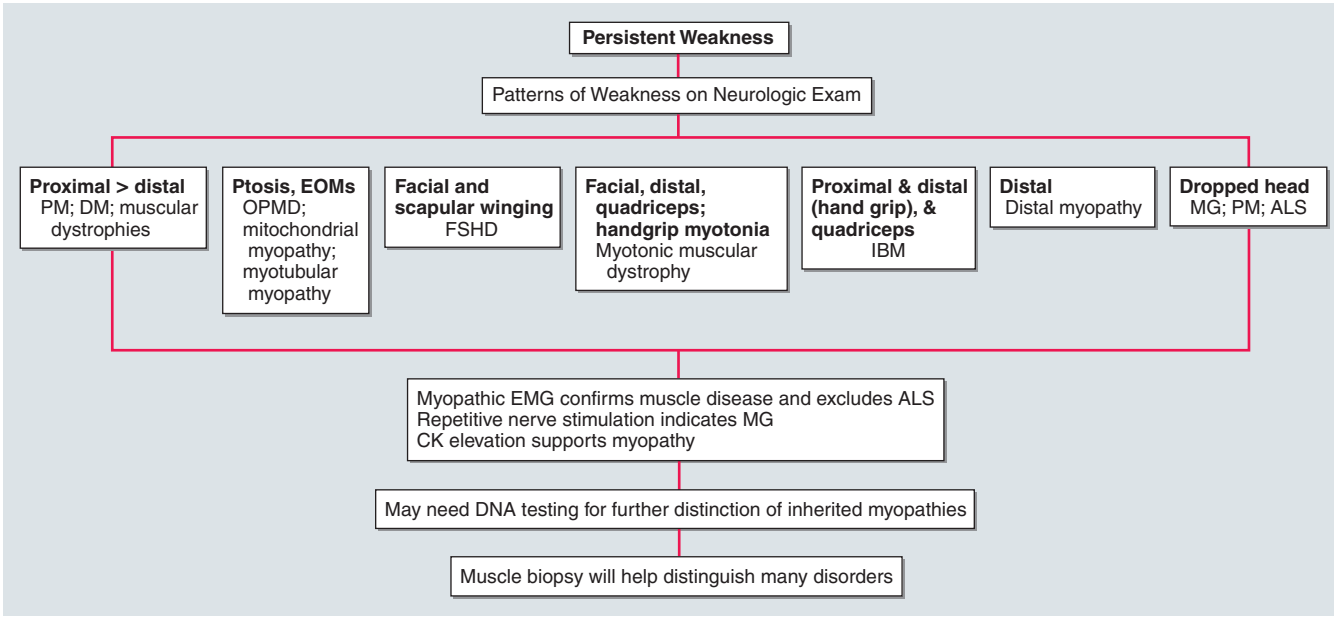

FIGURE 43-2

Diagnostic evaluation of persistent weakness. Examination reveals one of seven patterns of weakness. The pattern of weakness in combination with the laboratory evaluation leads to a diagnosis. EOM, extraocular muscles; OPMD, oculopharyngeal muscular dystrophy; FSHD, facioscapulohumeral dystrophy; IBM, inclusion body myositis; DM, dermatomyositis; PM, polymyositis; MG, myasthenia gravis; ALS, amyotrophic lateral sclerosis; CK, creatine kinase.

disorders of neuromuscular transmission and in disorders altering energy production, including defects in glycolysis, lipid metabolism, or mitochondrial energy production. Pathologic fatigability also occurs in chronic myopathies because of difficulty accomplishing a task with less muscle. Pathologic fatigability is accompanied by abnormal clinical or laboratory findings. Fatigue without those supportive features almost never indicates a primary muscle disease.

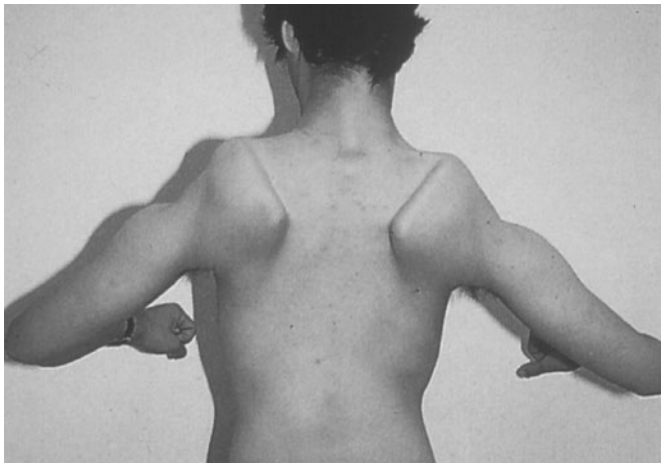

FIGURE 43-3

Facioscapulohumeral dystrophy with prominent scapular winging.

Muscle Pain (Myalgias), Cramps, and Stiffness

Muscle pain can be associated with cramps, spasms, contractures, and stiff or rigid muscles. In distinction, true myalgia (muscle aching), which can be localized or

TABLE 43-1

NEUROMUSCULAR CAUSES OF PTOSIS OR OPHTHALMOPLEGIA

- **Peripheral neuropathy**
  - Guillain-Barré syndrome
  - Miller-Fisher syndrome
- **Neuromuscular junction**
  - Botulism
  - Lambert-Eaton syndrome
  - Myasthenia gravis
  - Congenital myasthenia
- **Myopathy**
  - Mitochondrial myopathies
    - Kearns-Sayre syndrome
    - Progressive external ophthalmoplegia
  - Oculopharyngeal and oculopharyngodistal muscular dystrophy
  - Myotonic dystrophy (ptosis only)
  - Congenital myopathy
    - Myotubular
    - Nemaline (ptosis only)
  - Hyperthyroidism/Graves disease (ophthalmoplegia without ptosis)

TABLE 43-2

OBSERVATIONS ON EXAMINATION THAT DISCLOSE MUSCLE WEAKNESS

FUNCTIONAL IMPAIRMENT	MUSCLE WEAKNESS
Inability to forcibly close eyes	Upper facial muscles
Impaired pucker	Lower facial muscles
Inability to raise head from prone position	Neck extensor muscles
Inability to raise head from supine position	Neck flexor muscles
Inability to raise arms above head	Proximal arm muscles (may be only scapular stabilizing muscles)
Inability to walk without hyperextending knee (backkneeing or genu recurvatum)	Knee extensor muscles
Inability to walk with heels touching the floor (toe walking)	Shortening of the Achilles tendon
Inability to lift foot while walking (steppage gait or footdrop)	Anterior compartment of leg
Inability to walk without a waddling gait	Hip muscles
Inability to get up from the floor without climbing up the extremities (Gowers' sign)	Hip muscles
Inability to get up from a chair without using arms	Hip muscles

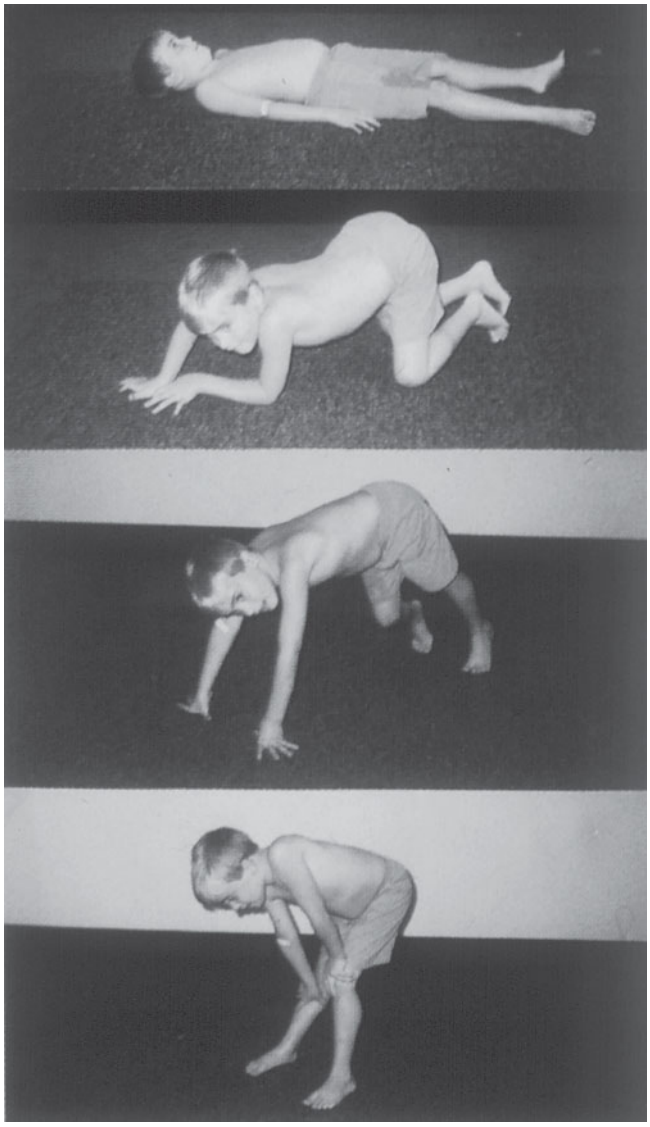

FIGURE 43-4
Gowers' sign showing a patient using arms to climb up the legs in attempting to get up from the floor.

generalized, may be accompanied by weakness, tenderness to palpation, or swelling. Certain drugs cause true myalgia (Table 43-3).

There are two painful muscle conditions of particular importance, neither of which is associated with muscle weakness. *Fibromyalgia* is a common, yet poorly understood type of myofascial pain syndrome. Patients complain of severe muscle pain and tenderness and have specific painful trigger points, sleep disturbances,

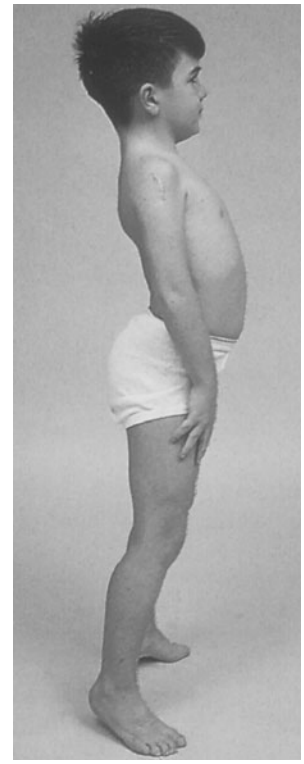

FIGURE 43-5
Lordotic posture, exaggerated by standing on toes, associated with trunk and hip weakness.

TABLE 43-3

DRUGS THAT CAUSE TRUE MYALGIA

Cimetidine
Cocaine
Cyclosporine
Danazol
Emetine
Epsilon aminocaproic acid
Gold
Heroin
Labetalol
Methadone
D-Penicillamine
Statins and other cholesterol-lowering agents
L-Tryptophan
Zidovudine

and easy fatigability. Serum creatine kinase (CK), erythrocyte sedimentation rate (ESR), electromyography (EMG), and muscle biopsy are normal. *Polymyalgia rheumatica* occurs mainly in patients >50 years and is characterized by stiffness and pain in the shoulders, lower back, hips, and thighs. The ESR is elevated, while serum CK, EMG, and muscle biopsy are normal. Temporal arteritis, an inflammatory disorder of medium- and large-sized arteries, usually involving one or more branches of the carotid artery, may accompany polymyalgia rheumatica. Vision is threatened by ischemic optic neuritis. Glucocorticoids can relieve the myalgias and protect against visual loss.

Localized muscle pain is most often traumatic. A common cause of sudden abrupt-onset pain is a ruptured tendon, which leaves the muscle belly appearing rounded and shorter in appearance compared to the normal side. The biceps brachii and Achilles tendons are particularly vulnerable to rupture. Infection or neoplastic infiltration of the muscle is a rare cause of localized muscle pain.

A *muscle cramp* or *spasm* is a painful, involuntary, localized, muscle contraction with a visible or palpable hardening of the muscle. Cramps are abrupt in onset, short in duration, and may cause abnormal posturing of the joint. The EMG shows firing of motor units, reflecting an origin from spontaneous neural discharge. Muscle cramps often occur in neurogenic disorders, especially motor neuron disease (Chap. 27), radiculopathies, and polyneuropathies (Chap. 40), but are not a feature of most primary muscle diseases. Duchenne muscular dystrophy is an exception since calf muscle complaints are a common complaint. Muscle cramps are also common during pregnancy.

A *muscle contracture* is different from a muscle cramp. In both conditions, the muscle becomes hard, but a contracture is associated with energy failure in glycolytic disorders. The muscle is unable to relax after an active muscle contraction. The EMG shows electrical silence. Confusion is created because contracture also refers to a muscle that cannot be passively stretched to its proper length (fixed contracture) because of fibrosis. In some muscle disorders, especially in Emery-Dreifuss muscular dystrophy and Bethlem myopathy, fixed contractures occur early and represent distinctive features of the disease.

Muscle stiffness can refer to different phenomena. Some patients with inflammation of joints and periarticular surfaces feel stiff. This condition is different from the disorders of hyperexcitable motor nerves causing stiff or rigid muscles. In *stiff-person syndrome* spontaneous discharges of the motor neurons of the spinal cord cause involuntary muscle contractions mainly involving the axial (trunk) and proximal lower extremity muscles. The gait becomes stiff and labored, with hyperlordosis of the lumbar spine. Superimposed episodic muscle spasms are precipitated by sudden movements, unexpected noises, and emotional upset. The muscles relax during sleep. Serum antibodies against glutamic acid decarboxylase are present in approximately two-thirds of cases. In *neuromyotonia* (*Isaacs' syndrome*) there is hyperexcitability of the peripheral nerves manifesting as continuous muscle fiber activity. *Myokymia* (groups of fasciculations associated with continuous undulations of muscle) and impaired muscle relaxation are the result. Muscles of the leg are stiff, and the constant contractions of the muscle cause increased sweating of the extremities. This peripheral nerve hyperexcitability is antibody-mediated, targeted against voltage-gated potassium channels. The site of origin of the spontaneous nerve discharges is principally in the distal portion of the motor nerves.

Myotonia is a condition of prolonged muscle contraction followed by slow muscle relaxation. It always follows muscle activation (action myotonia), usually voluntary, but may be elicited by mechanical stimulation (percussion myotonia) of the muscle. Myotonia typically causes difficulty in releasing objects after a firm grasp. In myotonic muscular dystrophy type 1 (DM1), distal weakness usually accompanies myotonia, whereas in DM2 proximal muscles are more affected; thus the related term *proximal myotonic myopathy* (PROMM) is used to describe this condition. Myotonia also occurs with *myotonia congenita* (a chloride channel disorder), but in this condition muscle weakness is not prominent. Myotonia may also be seen in individuals with sodium channel mutations (*hyperkalemic periodic paralysis* or *potassium-sensitive myotonia*). Another sodium channelopathy, *paramyotonia congenita,* also is associated with muscle stiffness. In contrast to other disorders associated with myotonia in which the myotonia is eased by repetitive activity, paramyotonia congenita is named for a paradoxical phenomenon whereby the myotonia worsens with repetitive activity.

Muscle Enlargement and Atrophy

In most myopathies muscle tissue is replaced by fat and connective tissue, but the size of the muscle is usually not affected. However, in many limb-girdle muscular dystrophies (and particularly the dystrophinopathies) enlarged calf muscles are typical. The enlargement represents true muscle hypertrophy, thus the term "pseudohypertrophy" should be avoided when referring to these patients. The calf muscles remain very strong even late in the course of these disorders. Muscle enlargement can also result from infiltration by sarcoid granulomas, amyloid deposits, bacterial and parasitic infections, and focal myositis. In contrast, muscle atrophy is characteristic of other myopathies. In dysferlinopathies (LGMD2B) there is a predilection for early atrophy of the gastrocnemius muscles. Atrophy of the humeral muscles is characteristic of facioscapulohumeral muscular dystrophy.

LABORATORY EVALUATION

A limited battery of tests can be used to evaluate a suspected myopathy. Nearly all patients require serum enzyme level measurements and electrodiagnostic studies as screening tools to differentiate muscle disorders from other motor unit diseases. The other tests described—DNA studies, the forearm exercise test, and muscle biopsy—are used to diagnose specific types of myopathies.

Serum Enzymes

CK is the preferred muscle enzyme to measure in the evaluation of myopathies. Damage to muscle causes the CK to leak from the muscle fiber to the serum. The MM isoenzyme predominates in skeletal muscle, while CK-MB is the marker for cardiac muscle. Serum CK can be elevated in normal individuals without provocation, presumably on a genetic basis or after strenuous activity, minor trauma (including the EMG needle), a prolonged muscle cramp, or a generalized seizure. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), aldolase, and lactic dehydrogenase (LDH) are enzymes sharing an origin in both muscle and liver. Problems arise when the levels of these enzymes are found to be elevated in a routine screening battery, leading to the erroneous assumption that liver disease is present when in fact muscle could be the cause. An elevated γ-glutamyl transferase (GGT) helps to establish a liver origin since this enzyme is not found in muscle.

Electrodiagnostic Studies

EMG, repetitive nerve stimulation, and nerve conduction studies (Chap. 3) are essential methods for evaluation of the patient with suspected muscle disease. In combination they provide the information necessary to differentiate myopathies from neuropathies and neuromuscular junction diseases. Routine nerve conduction studies are typically normal in myopathies but reduced amplitudes of compound muscle action potentials may be seen in atrophied muscles. The needle EMG may reveal irritability on needle placement suggestive of a necrotizing myopathy (inflammatory myopathies, dystrophies, toxic myopathies, myotonic myopathies), whereas a lack of irritability is characteristic of long-standing myopathic disorders (muscular dystrophies, endocrine myopathies, disuse atrophy, and many of the metabolic myopathies). In addition, the EMG may demonstrate myotonic discharges that will narrow the differential diagnosis (Table 43-4). Another important EMG finding is the presence of short-duration, small-amplitude, polyphasic motor unit action potentials (MUAPs). Such MUAPs can be seen in both myopathic and neuropathic disorders; however, the recruitment or firing pattern is different. In myopathies, the MUAPs fire early but at a normal rate to compensate for the loss of individual muscle fibers, whereas in neurogenic disorders the MUAPs fire faster. The EMG is usually normal in steroid or disuse myopathy, both of which are associated with type 2 fiber atrophy; this is because the EMG preferentially assesses the physiologic function of type 1 fibers. The EMG can also be invaluable in helping to choose an appropriately affected muscle to sample for biopsy.

TABLE 43-4

MYOTONIC DISORDERS
Myotonic dystrophy type 1
Myotonic dystrophy type 2/Proximal myotonic myopathy
Myotonia congenita
Paramyotonia congenita
Hyperkalemic periodic paralysis
Chondrodystrophic myotonia (Schwartz-Jampel syndrome)
Centronuclear/myotubular myopathy[a]
Drug-induced
Cholesterol-lowering agents (statin medications, fibrates)
Cyclosporine
Chloroquine
Glycogen storage disorders[a] (Pompe disease, debrancher deficiency, branching enzyme deficiency)
Myofibrillar myopathies[a]

[a]Associated with myotonic discharges on EMG but no clinical myotonia.

DNA Analysis

This now serves as an important tool for the definitive diagnosis of many muscle disorders. Nevertheless, there are a number of limitations in currently available molecular diagnostics. For example, in Duchenne and Becker dystrophies, two-thirds of patients have deletion or duplication mutations that are easy to detect, while the remainder have point mutations that are much more difficult to find.

For patients without identifiable gene defects, the muscle biopsy remains the main diagnostic tool.

Forearm Exercise Test

In myopathies with intermittent symptoms, and especially those associated with myoglobinuria, there may be a defect in glycolysis. Many variations of the forearm exercise test exist. For safety, the test should not be performed under ischemic conditions to avoid an unnecessary insult to the muscle, causing rhabdomyolysis. The test is performed by placing a small indwelling catheter into an antecubital vein. A baseline blood sample is obtained for lactic acid and ammonia. The forearm muscles are exercised by asking the patient to vigorously open and close the hand for 1 min. Blood is then obtained at intervals of 1, 2, 4, 6, and 10 min for comparison with the baseline sample. A three- to fourfold rise of lactic acid is typical. The simultaneous measurement of ammonia serves as a control, since it should also rise with exercise. In patients with myophosphorylase deficiency or other glycolytic defects, the lactic acid rise will be absent or below normal, while the rise in ammonia will reach control values. If there is lack of effort, neither lactic acid nor ammonia will rise. Patients with selective failure to increase ammonia may have myoadenylate deaminase deficiency. This condition has been reported to be a cause of myoglobinuria, but deficiency of this enzyme in asymptomatic individuals makes interpretation controversial.

Muscle Biopsy

Muscle biopsy is an important step in establishing the diagnosis of a suspected myopathy. The biopsy is usually obtained from a quadriceps or biceps brachii muscle, less commonly from a deltoid muscle. Evaluation includes a combination of techniques—light microscopy, histochemistry, immunocytochemistry with a battery of antibodies, and electron microscopy. Not all techniques are needed for every case. A specific diagnosis can be established in many disorders. A combination of stains to identify mononuclear cells (polymyositis), complement (dermatomyositis), and amyloid (inclusion body myositis) helps to distinguish the inflammatory myopathies. In addition, the congenital myopathies have distinctive light and electron microscopy features essential for diagnosis. Mitochondrial and metabolic (e.g., myophosphorylase and acid maltase deficiencies) myopathies also demonstrate distinctive histochemical and electron-microscopic profiles. Biopsied muscle tissue can be sent for metabolic enzyme or mitochondrial DNA analyses. A battery of antibodies is available for the identification of missing components of the dystrophin-glycoprotein complex and related proteins to help diagnose specific types of muscular dystrophies. Western blot analysis on muscle specimens can be performed to determine whether specific muscle proteins are reduced in quantity or are of abnormal size.

HEREDITARY MYOPATHIES

Muscular dystrophy refers to a group of hereditary progressive diseases each with unique phenotypic and genetic features (**Tables 43-5**, **43-6**, and **43-7**).

DUCHENNE MUSCULAR DYSTROPHY

This X-linked recessive disorder, sometimes also called *pseudohypertrophic muscular dystrophy*, has an incidence of ~30 per 100,000 live-born males.

Clinical Features

Duchenne dystrophy is present at birth, but the disorder usually becomes apparent between 3 and 5 years of age. The boys fall frequently and have difficulty keeping up with friends when playing. Running, jumping, and hopping are invariably abnormal. By 5 years, muscle weakness is obvious by muscle testing. On getting up from the floor, the patient uses his hands to climb up himself [Gowers' maneuver (Fig. 43-4)]. Contractures of the heel cords and iliotibial bands become apparent by 6 years, when toe walking is associated with a lordotic posture. Loss of muscle strength is progressive, with predilection for proximal limb muscles and the neck flexors; leg involvement is more severe than arm involvement. Between 8 and 10 years, walking may require the use of braces; joint contractures and limitations of hip flexion, knee, elbow, and wrist extension are made worse by prolonged sitting. By 12 years, most patients are wheelchair dependent. Contractures become fixed, and a progressive scoliosis often develops that may be associated with pain. The chest deformity with scoliosis impairs pulmonary function, which is already diminished by muscle weakness. By 16 to 18 years, patients are predisposed to serious, sometimes fatal pulmonary infections. Other causes of death include aspiration of food and acute gastric dilation.

A cardiac cause of death is uncommon despite the presence of a cardiomyopathy in almost all patients. Congestive heart failure seldom occurs except with severe stress such as pneumonia. Cardiac arrhythmias are rare. The typical electrocardiogram (ECG) shows an increase net RS in lead V_1; deep, narrow Q waves in the precordial leads; and tall right precordial R waves in V_1. Intellectual impairment in Duchenne dystrophy is common; the average intelligence quotient (IQ) is ~1 SD below the mean. Impairment of intellectual function appears to be nonprogressive and affects verbal ability more than performance.

Laboratory Features

Serum CK levels are invariably elevated to between 20 and 100 times normal. The levels are abnormal at birth but decline late in the disease because of inactivity and

TABLE 43-5

PROGRESSIVE MUSCULAR DYSTROPHIES

TYPE	INHERITANCE	DEFECTIVE GENE/PROTEIN	ONSET AGE	CLINICAL FEATURES	OTHER ORGAN SYSTEMS INVOLVED
Duchenne	XR	Dystrophin	<5 years	Progressive weakness of girdle muscles Unable to walk >12 years Progressive kyphoscoliosis Respiratory failure in 2d or 3d decade	Cardiomyopathy Mental impairment
Becker	XR	Dystrophin	Early childhood to adult	Progressive weakness of girdle muscles Able to walk >15 years Respiratory failure may develop by 4th decade	Cardiomyopathy
Limb-girdle	AD/AR	Several (Tables 43-6, 43-7)	Early childhood to early adult	Slow progressive weakness of shoulder and hip girdle muscles	± Cardiomyopathy
Emery-Dreifuss	XR/AD	Emerin/Lamins A/C	Childhood to adult	Elbow contractures, humeral and peroneal weakness	Cardiomyopathy
Congenital	AR	Several	At birth or within first few months	Hypotonia, contractures, delayed milestones Progression to respiratory failure in some; static course in others	CNS abnormalities (hypomyelination, malformation) Eye abnormalities
Myotonic[a] (DM1, DM2)	AD	DM1: Expansion CTG repeat DM2: Expansion CCTG repeat	Usually 2d decade May be infancy if mother affected (DM1 only)	Slowly progressive weakness of face, shoulder girdle, and foot dorsiflexion Preferential proximal weakness in DM2	Cardiac conduction defects Mental impairment Cataracts Frontal baldness Gonadal atrophy
Facioscapulohumeral	AD	Deletion, distal 4q	<20 years	Slowly progressive weakness of face, shoulder girdle, and foot dorsiflexion	Deafness Coats' (eye) disease
Oculopharyngeal	AD	Expansion, poly-A RNA binding protein	5th to 6th decade	Slowly progressive weakness of extraocular, pharyngeal, and limb muscles	—

[a]Two forms of myotonic dystrophy, DM1 and DM2, have been identified. Many features overlap (see text).
Note: XR, X-linked recessive; AD, autosomal dominant; AR, autosomal recessive; CNS, central nervous system.

loss of muscle mass. EMG demonstrates features typical of myopathy. The muscle biopsy shows muscle fibers of varying size as well as small groups of necrotic and regenerating fibers. Connective tissue and fat replace lost muscle fibers. A definitive diagnosis of Duchenne dystrophy can be established on the basis of dystrophin deficiency in a biopsy of muscle tissue or mutation analysis on peripheral blood leukocytes, as discussed below.

Duchenne dystrophy is caused by a mutation of the gene that encodes dystrophin, a 427-kDa protein localized to the inner surface of the sarcolemma of the muscle fiber. The dystrophin gene is >2000 kb in size and thus is one of the largest identified human genes. It is localized to the short arm of the X chromosome at Xp21. The most common gene mutation is a deletion. The size varies but does not correlate with disease severity. Deletions are not uniformly distributed over the gene but rather are most common near the beginning (5′ end) and middle of the gene. Less often, Duchenne dystrophy is caused by a gene duplication or point mutation. Identification of a specific mutation allows for an unequivocal diagnosis, makes possible accurate testing of potential carriers, and is useful for prenatal diagnosis.

A diagnosis of Duchenne dystrophy can also be made by Western blot analysis of muscle biopsy specimens, revealing abnormalities on the quantity and molecular weight of dystrophin protein. In addition, immunocytochemical staining of muscle with dystrophin antibodies can be used to demonstrate absence or deficiency of dystrophin localizing to the sarcolemmal membrane. Carriers of the disease may demonstrate a mosaic pattern, but dystrophin analysis of muscle biopsy specimens for carrier detection is not reliable.

TABLE 43-6

AUTOSOMAL DOMINANT LIMB-GIRDLE MUSCULAR DYSTROPHIES (LGMDS)

DISEASE	CLINICAL FEATURES	LABORATORY FEATURES	LOCUS OR GENE
LGMD1A	Onset 3d to 4th decade Muscle weakness affects distal limb muscles, vocal cords, and pharyngeal muscles	Serum CK 2 × normal EMG mixed myopathy/neuropathy NCS normal	Myotilin
LGMD1B	Onset 1st or 2d decade Proximal lower limb weakness and cardiomyopathy with conduction defects Some cases indistinguishable from Emery-Dreifuss muscular dystrophy with joint contractures	Serum CK 3–5 × normal NCS normal EMG myopathic	Lamin A/C
LGMD1C	Onset in early childhood Proximal weakness Gowers' sign, calf hypertrophy Exercise-related muscle cramps	Serum CK 4–25 × normal NCS normal EMG myopathic	Caveolin-3
LGMD1D	Onset 3d to 5th decade Proximal muscle weakness Cardiomyopathy and arrhythmias	Serum CK 2–4 × normal NCS normal EMG myopathic	Linked to chromosome 7q Gene unidentified
LGMD1E	Childhood onset Proximal muscle weakness	Serum CK usually normal NCS normal EMG myopathic	Linked to chromosome 6q23 Gene unidentified

Note: CK, creatine kinase; NCS, nerve conduction studies; EMG, electromyography.

TABLE 43-7

AUTOSOMAL RECESSIVE LIMB-GIRDLE MUSCULAR DYSTROPHIES (LGMDS)

DISEASE	CLINICAL FEATURES	LABORATORY FEATURES	LOCUS OR GENE
LGMD2A	Onset 1st or 2d decade Tight heel cords Contractures at elbows, wrists, and fingers; rigid spine in some Proximal and distal weakness	Serum CK 3–15 × normal NCS normal EMG myopathic	Calpain-3
LGMD2B	Onset 2d or 3d decade Proximal muscle weakness at onset, later distal (calf) muscles affected Miyoshi myopathy is variant of LGMD2B with calf muscles affected at onset	Serum CK 3–100 × normal NCS normal EMG myopathic Inflammation on muscle biopsy may simulate polymyositis	Dysferlin
LGMD2C–F	Onset in childhood to teenage yrs Clinical condition similar to Duchenne and Becker muscular dystrophies Cardiomyopathy uncommon Cognitive function normal	Serum CK 5–100 × normal NCS normal EMG myopathic	γ, α, β, δ sarcoglycans
LGMD2G	Onset age 10 to 15 Proximal and distal muscle weakness	Serum CK 3–17 × normal NCS normal EMG myopathic	Telethonin
LGMD2H	Onset 1st to 3d decade Proximal muscle weakness	Serum CK 2–25 × normal NCS normal EMG myopathic	TRIM32 gene
LGMD2I	Onset 1st to 3d decade Clinical condition similar to Duchenne or Becker dystrophies Cardiomyopathy (some not all) Cognitive function normal	Serum CK 10–30 × normal NCS normal EMG myopathic	Fukutin-related protein
LGMD2J[a]	Onset 1st to 3d decade Proximal lower limb weakness Mild distal weakness Progressive weakness causes loss of ambulation	Serum CK 1.5–2 × normal NCS normal EMG myopathic	Titin

[a]Tibial muscular dystrophy is a form of titin deficiency with only distal muscle weakness (see Table 43-9).
Note: CK, creatine kinase; NCS, nerve conduction studies; EMG, electromyography.

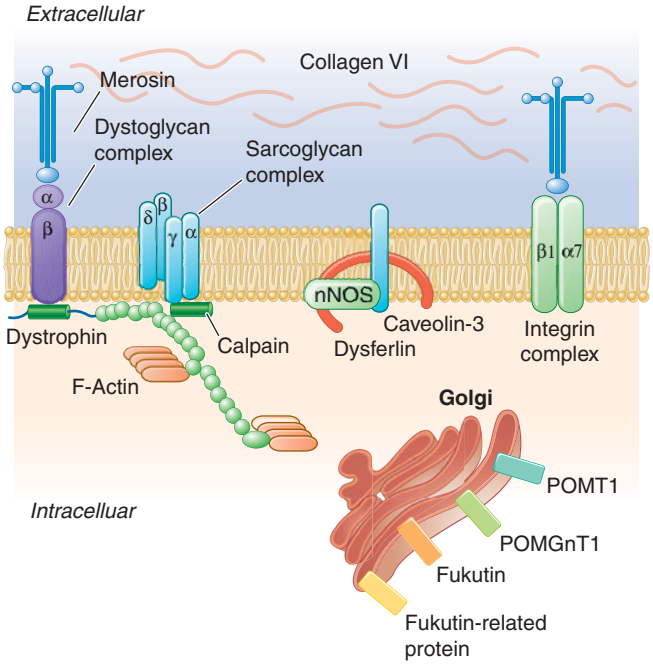

FIGURE 43-6
Selected muscular dystrophy–associated proteins in the cell membrane and Golgi complex.

Pathogenesis

Dystrophin is part of a large complex of sarcolemmal proteins and glycoproteins (Fig. 43-6). Dystrophin binds to F-actin at its amino terminus and to β-dystroglycan at the carboxyl terminus. β-dystroglycan complexes to α-dystroglycan, which binds to laminin in the extracellular matrix (ECM). Laminin has a heterotrimeric molecular structure arranged in the shape of a cross with one heavy chain and two light chains, β1 and γ1. The laminin heavy chain of skeletal muscle is designated laminin α2. Collagen proteins IV and VI are also found in the ECM. Like β-dystroglycan, the transmembrane sarcoglycan proteins also bind to dystrophin; these five proteins (designated α- through ε-sarcoglycan) complex tightly with each other. More recently, other membrane proteins implicated in muscular dystrophy have been found to be loosely affiliated with constituents of the dystrophin complex. These include caveolin-3, α_7 integrin, and collagen VI.

Dystrophin localizes to the cytoplasmic face of the muscle cell membrane. It complexes with two transmembrane protein complexes, the dystroglycans and the sarcoglycans. The dystroglycans bind to the extracellular matrix protein merosin, which is also complexed with β_1 and α_7 integrins (Tables 43-5, 43-6, and 43-7). Dysferlin complexes with caveolin-3 (which binds to neuronal nitric oxide synthase, or nNOS) but not with the dystrophin-associated proteins or the integrins. In each of four congenital dystrophies, there is loss of function of different Golgi-associated proteins: POMT1, POMGnT1, Fukutin, and Fukutin-related protein.

The dystrophin-glycoprotein complex appears to confer stability to the sarcolemma, although the function of each individual component of the complex is incompletely understood. Deficiency of one member of the complex may cause abnormalities in other components. For example, a primary deficiency of dystrophin (Duchenne dystrophy) may lead to secondary loss of the sarcoglycans and dystroglycan. The primary loss of a single sarcoglycan (see Limb-Girdle Muscular Dystrophy, below) results in a secondary loss of other sarcoglycans in the membrane without uniformly affecting dystrophin. In either instance, disruption of the dystrophin-glycoprotein complexes weakens the sarcolemma, causing membrane tears and a cascade of events leading to muscle fiber necrosis. This sequence of events occurs repeatedly during the life of a patient with muscular dystrophy.

℞ Treatment: DUCHENNE MUSCULAR DYSTROPHY

Glucocorticoids, administered as prednisone in a dose of 0.75 mg/kg per day, significantly slow progression of Duchenne dystrophy for up to 3 years. Some patients cannot tolerate glucocorticoid therapy; weight gain and increased risk of fractures in particular represent a significant deterrent for some boys. As in other recessively inherited dystrophies presumed to arise from loss of function of a critical muscle gene, there is optimism that Duchenne disease may benefit from novel therapies that either replace the defective gene or missing protein or implement downstream corrections (e.g., skipping mutated exons or reading through mutations that introduce stop codons).

BECKER MUSCULAR DYSTROPHY

This less severe form of X-linked recessive muscular dystrophy results from allelic defects of the same gene responsible for Duchenne dystrophy. Becker muscular dystrophy is ~10 times less frequent than Duchenne, with an incidence of about 3 per 100,000 live-born males.

Clinical Features

The pattern of muscle wasting in Becker muscular dystrophy closely resembles that seen in Duchenne. Proximal muscles, especially of the lower extremities, are prominently involved. As the disease progresses, weakness becomes more generalized. Significant facial muscle weakness is not a feature. Hypertrophy of muscles, particularly in the calves, is an early and prominent finding.

Most patients with Becker dystrophy first experience difficulties between ages 5 and 15 years, although onset in the third or fourth decade or even later can occur.

By definition, patients with Becker dystrophy walk beyond 15 years of age, whereas patients with Duchenne dystrophy are typically in a wheelchair by 12 years. Patients with Becker dystrophy have a reduced life expectancy, but most survive into the fourth or fifth decade.

Mental retardation may occur in Becker dystrophy, but it is not as common as in Duchenne. Cardiac involvement occurs in Becker dystrophy and may result in heart failure; some patients manifest with only heart failure. Other less common presentations are asymptomatic hyper-CK-emia, myalgias without weakness, and myoglobinuria.

Laboratory Features

Serum CK levels, results of EMG, and muscle biopsy findings closely resemble those in Duchenne dystrophy. The diagnosis of Becker muscular dystrophy requires Western blot analysis of muscle biopsy samples demonstrating a reduced amount or abnormal size of dystrophin or mutation analysis of DNA from peripheral blood leukocytes. Genetic testing reveals deletions or duplications of the dystrophin gene in 65% of patients with Becker dystrophy, approximately the same percentage as in Duchenne dystrophy. In both Becker and Duchenne dystrophies, the size of the DNA deletion does not predict clinical severity; however, in ~95% of patients with Becker dystrophy, the DNA deletion does not alter the translational reading frame of messenger RNA. These "in-frame" mutations allow for production of some dystrophin, which accounts for the presence of altered rather than absent dystrophin on western blot analysis.

℞ Treatment: BECKER MUSCULAR DYSTROPHY

The use of glucocorticoids has not been adequately studied in Becker dystrophy.

LIMB-GIRDLE MUSCULAR DYSTROPHY

The syndrome of limb-girdle muscular dystrophy (LGMD) represents more than one disorder. Both males and females are affected, with onset ranging from late in the first decade to the fourth decade. The LGMDs typically manifest with progressive weakness of pelvic and shoulder girdle musculature. Respiratory insufficiency from weakness of the diaphragm may occur, as may cardiomyopathy.

A systematic classification of LGMD is based on autosomal dominant (LGMD1) and autosomal recessive (LGMD2) inheritance. Superimposed on the backbone of LGMD1 and LGMD2, the classification employs a sequential alphabetical lettering system (LGMD1A, LGMD2A, etc.). Disorders receive letters in the order in which they are found to have chromosomal linkage. This results in an ever-expanding list of conditions. Presently there are 5 autosomal dominant and 10 autosomal recessive disorders, summarized in Tables 43-6 and 43-7. None of the conditions is as common as the dystrophinopathies; however, prevalence data for the LGMDs have not been systematically gathered for any large heterogeneous population. In referral-based clinical populations, Fukutin-related protein (FKRP) deficiency (LGMD2I), calpainopathies (LGMD2A), and to a lesser extent dysferlinopathies (LGMD2B) have emerged as the most common disorders.

EMERY-DREIFUSS MUSCULAR DYSTROPHY

There are two genetically distinct forms of Emery-Dreifuss muscular dystrophy (EDMD). One is inherited as an X-linked disorder, while the other is autosomal dominant. The latter is classified under the rubric of LGMD1B, but clinically the conditions are closely related.

Clinical Features

Prominent contractures can be recognized in early childhood and teenage years, often preceding muscle weakness. The contractures persist throughout the course of the disease and are present at the elbows, ankles, and neck. Muscle weakness affects humeral and peroneal muscles at first and later spreads to a limb-girdle distribution. The cardiomyopathy is potentially life threatening and may result in sudden death. A spectrum of atrial rhythm and conduction defects includes atrial fibrillation and paralysis and atrioventricular heart block. Some patients have a dilated cardiomyopathy. Female carriers of the X-linked variant may have cardiac manifestations that become clinically significant.

Laboratory Features

Serum CK may be elevated two- to tenfold. EMG is myopathic. Muscle biopsy shows nonspecific dystrophic features. Immunohistochemistry reveals absent emerin staining of myonuclei in X-lined EDMD. ECGs demonstrate atrial and atrioventricular rhythm disturbances.

X-linked EDMD arises from defects in the emerin gene encoding a nuclear envelope protein. The autosomal dominant disease is caused by mutations of the *LMNA* gene on chromosome 1q21.2 encoding the lamin proteins A and C. These proteins are alternatively spliced products of the *LMNA* gene that are essential components of the filamentous network underlying the inner nuclear membrane. Loss of structural integrity of the nuclear envelope from defects in emerin or lamin A/C accounts for overlapping phenotypes (**Fig. 43-7**).

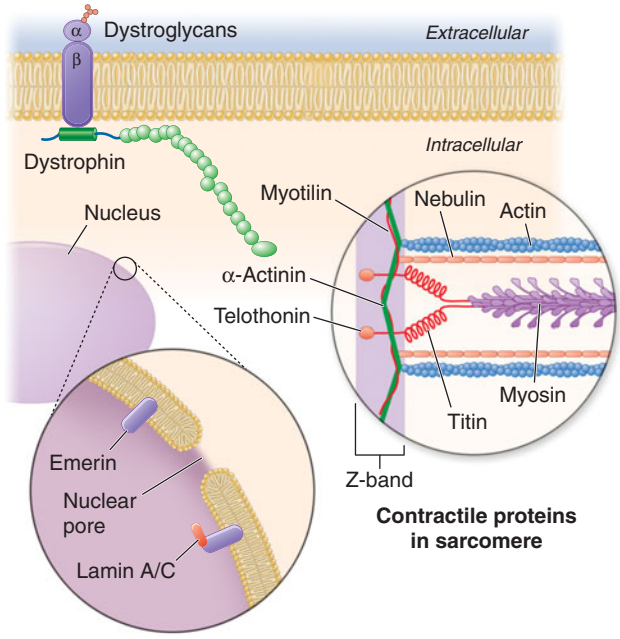

FIGURE 43-7

Selected muscular dystrophy–associated proteins in the nuclear membrane and sarcomere. As shown in the exploded view, emerin and lamin A/C are constituents of the inner nuclear membrane. Several dystrophy-associated proteins are represented in the sarcomere including titin, nebulin, calpain, telethonin, actinin, and myotilin. The position of the dystrophin-dystroglycan complex is also illustrated.

℞ Treatment: EMERY-DREIFUSS MUSCULAR DYSTROPHY

Supportive care should be offered for neuromuscular disability, including ambulatory aids, if necessary. Stretching of contractures is difficult. Management of cardiomyopathy and arrhythmias (e.g., early use of a cardiac pacemaker) may be life saving.

CONGENITAL MUSCULAR DYSTROPHY (CMD)

This is not one entity but rather a group of disorders with varying degrees of muscle weakness, central nervous system impairment, and eye abnormalities (Table 43-8).

Clinical Features

As a group, CMDs present at birth or in the first few months of life with hypotonia and proximal or generalized muscle weakness. Calf muscle hypertrophy is seen in some patients. Facial muscles may be weak, but other cranial nerve–innervated muscles are spared (e.g., extraocular muscles are normal). Most patients have joint contractures of varying degrees at elbows, hips, knees, and ankles. Contractures present at birth are referred to as *arthrogryposis*. Respiratory failure may be seen in some cases.

The CNS is affected in some forms of CMD. In merosin and FKRP deficiency, cerebral hypomyelination may be seen by MRI, though only a small number of patients have mental retardation and seizures. Three forms of congenital muscular dystrophy have severe brain impairment. These include Fukuyama congenital muscular dystrophy (FCMD), muscle-eye-brain (MEB) disease, and Walker-Warburg syndrome (WWS). Patients are severely disabled in all three of these conditions. In MEB disease and WWS, but not in FCMD, ocular abnormalities impair vision. WWS is the most severe congenital muscular dystrophy, causing death by 1 year of age.

Laboratory Features

Serum CK is markedly elevated in all of these conditions. The EMG is myopathic and muscle biopsies show nonspecific dystrophic features. Merosin, or laminin α2 chain (a basal lamina protein), is deficient surrounding muscle fibers in merosin deficiency. Skin biopsies can also demonstrate defects in laminin α2 chain. In the other disorders (FKRP deficiency, FCMD, MEB disease, WWS) there is abnormal alpha-dystroglycan staining in muscle. In merosin deficiency, cerebral hypomyelination is common, and a host of brain malformations are seen in FCMD, MEB disease, and WWS.

All forms of CMD are inherited as autosomal recessive disorders. Chromosomal linkage and specific gene defects are presented in Table 43-8. With the exception of merosin, the other gene defects affect posttranslational glycosylation of alpha-dystroglycan. This abnormality is thought to impair binding with merosin and leads to weakening of the dystrophin-glycoprotein complex, instability of the muscle membrane, and/or abnormalities in muscle contraction. CMDs with brain and eye phenotypes probably involve defective glycosylation of additional proteins, accounting for the more extensive phenotypes.

℞ Treatment: CONGENITAL MUSCULAR DYSTROPHY

There is no specific treatment for CMD. Proper wheelchair seating is important. Management of epilepsy and cardiac manifestations is necessary for some patients.

MYOTONIC DYSTROPHY

Myotonic dystrophy is also known as *dystrophia myotonica* (DM). The condition is composed of at least two clinical disorders with overlapping phenotypes and distinct molecular

TABLE 43-8

CONGENITAL MUSCULAR DYSTROPHIES[a]

DISEASE	CLINICAL FEATURES	LABORATORY FEATURES	LOCUS OR GENE
Merosin deficiency	Onset at birth with hypotonia, joint contractures, delayed milestones, generalized muscle weakness Cerebral hypomyelination, less often cortical dysplasia Normal intelligence usually, some with MR (~6%) and seizures (~8%) Partial deficiency leads to milder phenotype (LGMD picture)	Serum CK 5–35 × normal EMG myopathic NCS abnormal in some cases	Laminin α2 chain
Fukitin-related protein deficiency[b]	Onset at birth or shortly after Hypotonia and feeding problems Weakness of proximal muscles, especially shoulder girdles Hypertrophy of leg muscles Joint contractures Cognition normal	Serum CK 10–50 × normal EMG myopathic NCS normal	Fukutin-related protein
Fukuyama congenital muscular dystrophy[b]	Onset at birth Hypotonia, joint contractures Generalized muscle weakness Hypertrophy of calf muscles Seizures, mental retardation Cardiomyopathy	Serum CK 10–50 × normal EMG myopathic NCS normal MRI shows hydrocephalus and periventricular and frontal hypomyelination	Fukutin
Muscle-eye-brain disease	Onset at birth, hypotonia Eye abnormalities include: progressive myopia, cataracts, and optic nerve, glaucoma, retinal pigmentary changes Progressive muscle weakness Joint contractures Seizures, mental retardation	Serum CK 5–20 × normal MRI shows hydrocephalus, cobblestone lissencephaly, corpus callosum and cerebellar hypoplasia, cerebral hypomyelination	*N*-acetyl-glucosaminyl transferase (POMGnT1)
Walker-Warburg syndrome[b]	Onset at birth, hypotonia Generalized muscle weakness Joint contractures Microphthalmos, retinal dysplasia, buphthalmos, glaucoma, cataracts Seizures, MR	Serum CK 5–20 × normal MRI shows cobblestone lissencephaly, hydrocephalus, encephalocele, absent corpus callosum	*O*-mannoxyl-transferase-1 (POMT1)

[a]All are inherited as recessive traits.
[b]There is phenotypic overlap between disorders related to defective glycosylation. In muscle this is a consequence of altered glycosylation of dystroglycans; in brain/eye, other glycosylated proteins are involved. Clinically, Walker-Warburg syndrome is more severe, with death by 1 year.
Note: CK, creatine kinase; EMG, electromyography; NCS, nerve conduction studies; MR, mental retardation; LGMD, limb-girdle muscular dystrophy.

genetic defects: myotonic dystrophy type 1 (DM1), the classic disease originally described by Steinert, and myotonic dystrophy type 2 (DM2), also called *proximal myotonic myopathy* (PROMM).

Clinical Features

The clinical expression of myotonic dystrophy varies widely and involves many systems other than muscle. Affected patients have a typical "hatchet-faced" appearance due to temporalis, masseter, and facial muscle atrophy and weakness. Frontal baldness is also characteristic of the disease. Neck muscles, including flexors and sternocleidomastoids, and distal limb muscles are involved early. Weakness of wrist extensors, finger extensors, and intrinsic hand muscles impairs function. Ankle dorsiflexor weakness may cause footdrop. Proximal muscles remain stronger throughout the course, although preferential atrophy and weakness of quadriceps muscles occur in many patients. Palatal, pharyngeal, and tongue involvement produce a dysarthric speech, nasal voice, and swallowing problems. Some patients have diaphragm and intercostal muscle weakness, resulting in respiratory insufficiency.

Myotonia, which usually appears by age 5 years, is demonstrable by percussion of the thenar eminence, the tongue, and wrist extensor muscles. Myotonia causes a slow relaxation of hand grip after a forced voluntary closure. Advanced muscle wasting makes myotonia more difficult to detect.

Cardiac disturbances occur commonly in patients with DM1. ECG abnormalities include first-degree heart block and more extensive conduction system involvement. Complete heart block and sudden death can occur; recently, risk factors for sudden death in these patients have been

identified, but whether pacemaker or defibrillator implantation can mitigate this risk remains to be determined. Congestive heart failure occurs infrequently but may result from cor pulmonale secondary to respiratory failure. Mitral valve prolapse also occurs commonly. Other associated features include intellectual impairment, hypersomnia, posterior subcapsular cataracts, gonadal atrophy, insulin resistance, and decreased esophageal and colonic motility.

Congenital myotonic dystrophy is a more severe form of DM1 and occurs in ~25% of infants of affected mothers. It is characterized by severe facial and bulbar weakness, transient neonatal respiratory insufficiency, and mental retardation.

DM2, or PROMM, has a distinct pattern of muscle weakness affecting mainly proximal muscles. Other features of the disease overlap with DM1, including cataracts, testicular atrophy, insulin resistance, constipation, hypersomnia, and cognitive defects. Cardiac conduction defects occur but are less common, and the hatchet face and frontal baldness are less consistent features. A very striking difference is the failure to clearly identify a congenital form of DM2.

Laboratory Features

The diagnosis of myotonic dystrophy can usually be made on the basis of clinical findings. Serum CK levels may be normal or mildly elevated. EMG evidence of myotonia is present in most cases of DM1 but may be more patchy in DM2. Muscle biopsy shows muscle atrophy, which selectively involves type 1 fibers in 50% of cases, and ringed fibers in DM1 but not in DM2. Typically, numerous internalized nuclei can be seen in individual muscle fibers as well as atrophic fibers with pyknotic nuclear clumps in both DM1 and DM2. Necrosis of muscle fibers and increased connective tissue, common in other muscular dystrophies, are less apparent in myotonic dystrophy.

DM1 and DM2 are both autosomal dominant disorders. New mutations do not appear to contribute to the pool of affected individuals. DM1 is transmitted by an intronic mutation consisting of an unstable expansion of a CTG trinucleotide repeat in a serine-threonine protein kinase gene (named *DMPK*) on chromosome 19q13.3. An increase in the severity of the disease phenotype in successive generations (genetic anticipation) is accompanied by an increase in the number of trinucleotide repeats. A similar type of mutation has been identified in fragile X syndrome. The unstable triplet repeat in myotonic dystrophy can be used for prenatal diagnosis. Congenital disease occurs almost exclusively in infants born to affected mothers; it is possible that sperm with greatly expanded triplet repeats do not function well.

DM2 is caused by a DNA expansion mutation consisting of a CCTG repeat in intron 1 of the *ZNF9* gene located at chromosome 3q13.3-q24. The gene is believed to encode an RNA binding protein expressed in many different tissues, including skeletal and cardiac muscle.

The DNA expansions in DM1 and DM2 almost certainly impair muscle function by a toxic gain of function of the mutant mRNA. In both DM1 and DM2, the mutant RNA appears to form intranuclear inclusions composed of aberrant RNA. These RNA inclusions sequester RNA binding proteins essential for proper splicing of a variety of other mRNAs. This leads to abnormal transcription of multiple proteins in a variety of tissues/organ systems, in turn causing the systemic manifestations of DM1 and DM2.

℞ Treatment: MYOTONIC DYSTROPHY

The myotonia in DM1 rarely warrants treatment, though some patients with DM2 are significantly bothered by the discomfort related to the associated muscle stiffness. Phenytoin and mexiletine are the preferred agents for the occasional patient who requires an antimyotonia drug; other agents, particularly quinine and procainamide, may worsen cardiac conduction. A cardiac pacemaker should be considered for patients with unexplained syncope, advanced conduction system abnormalities with evidence of second-degree heart block, or trifascicular conduction disturbances with marked prolongation of the PR interval. Molded ankle-foot orthoses help prevent footdrop in patients with distal lower extremity weakness. Excessive daytime somnolence with or without sleep apnea is not uncommon. Sleep studies, noninvasive respiratory support (BiPAP), and treatment with modafinil may be beneficial.

FACIOSCAPULOHUMERAL (FSH) MUSCULAR DYSTROPHY

This form of muscular dystrophy has a prevalence of ~1 in 20,000. It is distinct from a similar disorder known as scapuloperoneal dystrophy.

Clinical Features

The condition typically has an onset in childhood or young adulthood. In most cases, facial weakness is the initial manifestation, appearing as an inability to smile, whistle, or fully close the eyes. Weakness of the shoulder girdles, rather than the facial muscles, usually brings the patient to medical attention. Loss of scapular stabilizer muscles makes arm elevation difficult. Scapular winging (Fig. 43-3) becomes apparent with attempts at abduction and forward movement of the arms. Biceps and triceps muscles may be severely affected, with relative sparing of the deltoid muscles. Weakness is invariably worse for wrist extension than for wrist flexion, and weakness of the anterior compartment muscles of the legs may lead to footdrop.

In most patients, the weakness remains restricted to facial, upper extremity, and distal lower extremity muscles. In 20% of patients, weakness progresses to involve the pelvic girdle muscles, and severe functional impairment and possible wheelchair dependency result.

Characteristically, patients with FSH dystrophy do not have involvement of other organ systems, although labile hypertension is common, and there is an increased incidence of nerve deafness. *Coats' disease*, a disorder consisting of telangiectasia, exudation, and retinal detachment, also occurs.

Laboratory Features

The serum CK level may be normal or mildly elevated. EMG usually indicates a myopathic pattern. The muscle biopsy shows nonspecific features of a myopathy. A prominent inflammatory infiltrate, which is often multifocal in distribution, is present in some biopsy samples. The cause or significance of this finding is unknown.

An autosomal dominant inheritance pattern with almost complete penetrance has been established, but each family member should be examined for the presence of the disease, since ~30% of those affected are unaware of involvement. FSH dystrophy is caused by deletions of tandem 3.3-kb repeats at 4q35. The deletion reduces the number of repeats to a fragment of <35 kb in most patients. This mutation may result in an overexpression of upstream genes and a loss of DNA binding of a multiprotein complex mediating transcriptional repression of 4q35 genes. The mutation permits carrier detection and prenatal diagnosis. Most sporadic cases represent new mutations.

℞ Treatment: FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

No specific treatment is available; ankle-foot orthoses are helpful for footdrop. Scapular stabilization procedures improve scapular winging but may not improve function.

OCULOPHARYNGEAL DYSTROPHY

This form of muscular dystrophy represents one of several disorders characterized by progressive external ophthalmoplegia, which consists of slowly progressive ptosis and limitation of eye movements with sparing of pupillary reactions for light and accommodation. Patients usually do not complain of diplopia, in contrast to patients having conditions with a more acute onset of ocular muscle weakness (e.g., myasthenia gravis).

Clinical Features

Oculopharyngeal muscular dystrophy has a late onset; it usually presents in the fourth to sixth decade with ptosis and/or dysphagia. The extraocular muscle impairment is less prominent in the early phase but may be severe later. The swallowing problem may become debilitating and result in pooling of secretions and repeated episodes of aspiration. Mild weakness of the neck and extremities also occurs.

Laboratory Features

The serum CK level may be two to three times normal. Myopathic EMG findings are typical. On biopsy, muscle fibers are found to contain rimmed vacuoles, which by electron microscopy are shown to contain membranous whorls, accumulation of glycogen, and other nonspecific debris related to lysosomes. A distinct feature of oculopharyngeal dystrophy is the presence of tubular filaments, 8.5 nm in diameter, in muscle cell nuclei.

Oculopharyngeal dystrophy has an autosomal dominant inheritance pattern with complete penetrance. The incidence is high in French-Canadians and in Spanish-American families of the southwestern United States. Large kindreds of Italian and of eastern European Jewish descent have been reported. The molecular defect in oculopharyngeal muscular dystrophy is a subtle expansion of a modest polyalanine repeat tract in a poly-RNA binding protein (PABP2) in muscle.

℞ Treatment: OCULOPHARYNGEAL DYSTROPHY

Dysphagia can cause inanition, making oculopharyngeal muscular dystrophy a potentially life-threatening disease. Cricopharyngeal myotomy may improve swallowing, although it does not prevent aspiration. Eyelid crutches can improve vision when ptosis obstructs vision; candidates for ptosis surgery must be carefully selected—those with severe facial weakness are not suitable.

DISTAL MYOPATHIES

A group of muscle diseases, the distal myopathies, are notable for their preferential distal distribution of muscle weakness in contrast to most muscle conditions associated with proximal weakness. The major distal myopathies are summarized in **Table 43-9**.

Clinical Features

Welander, Udd, and *Markesbery-Griggs distal myopathies* are all late-onset, dominantly inherited disorders of distal limb

TABLE 43-9

DISTAL MYOPATHIES

DISEASE	CLINICAL FEATURES	LABORATORY FEATURES	INHERITANCE/ LOCUS OR GENE
Welander distal myopathy	Onset in fifth decade Weakness begins in hands Slow progression with spread to distal lower extremities Lifespan normal	Serum CK 2–3 × normal EMG myopathic NCS normal Muscle biopsy shows dystrophic features	AD Chromosome 2p13
Tibial muscular dystrophy (Udd)	Onset 4th to 8th decade Distal lower extremity weakness (tibial distribution) Upper extremities usually normal Lifespan normal	Serum CK 2–4 × normal EMG myopathic NCS normal Muscle biopsy shows dystrophic features Titin absent in M-line of muscle	AD Titin
Markesbery-Griggs distal myopathy	Onset 4th to 8th decade Distal lower extremity weakness (tibial distribution) with progression to distal arms and proximal muscles	Serum CK is usually mildly elevated EMG reveals irritative myopathy Muscle biopsies demonstrate rimmed vacuoles and features of myofibrillar myopathy	AD Z-band alternatively spliced PDX motif-containing protein (ZASP)
Laing distal myopathy	Onset childhood to 3d decade Distal lower extremity weakness (tibial distribution) and neck flexors affected early	Serum CK is normal or slightly elevated Muscle biopsies do not show rimmed vacuoles Large deposits of myosin heavy chain are seen in type 1 muscle fibers	AD Myosin heavy chain 7
Nonaka distal myopathy (autosomal recessive hereditary inclusion body myopathy)	Onset 2d to 3d decade Lower extremity distal weakness Mild distal upper limb weakness may be present early Progression to other muscles sparing quadriceps Ambulation may be lost in 10–15 years	Serum CK 3–10 × normal EMG myopathic NCS normal Dystrophic features on muscle biopsy plus rimmed vacuoles and 15- to 19-nm filaments within vacuoles	AR*GNE* gene: UDP-*N*-acetylglucosamine 2-epimerase/*N*-acetylmannosamine kinase Allelic to hereditary inclusion body myopathy
Miyoshi myopathy	Onset 2d to 3d decade Lower extremity weakness in posterior compartment muscles Progression leads to weakness in other muscle groups Ambulation lost after 10–15 years in about one-third of cases	Serum CK 20–100 × normal EMG myopathic NCS normal Muscle biopsy shows nonspecific dystrophic features often with prominent inflammatory cell infiltration; no rimmed vacuoles	AR Allelic to LGMD2B (see Table 43-7) Dysferlin
Myofibrillar myopathies	Onset from early childhood to late adult life Weakness may be distal, proximal, or generalized Cardiomyopathy and respiratory involvement is not uncommon	Serum CKs can be normal or moderately elevated EMG is myopathic and often associated with myopathic discharges Muscle biopsy demonstrates abnormal accumulation of desmin and other proteins, rimmed vacuoles, and myofibrillar degeneration	Genetically heterogeneous AD: Myotilin (also known as LGMD 1A) ZASP (see Markesbery-Griggs distal myopathy) Filamin-C Desmin Alpha B crystallin AR: Desmin Selenoprotein N1

Note: CK, creatine kinase; AD, autosomal dominant; AR, autosomal recessive; EMG, electromyography; NCS, nerve conduction studies.

muscles, usually beginning after 40 years of age. Welander distal myopathy preferentially involves the wrist and finger extensors, whereas the others are associated with anterior tibial weakness leading to progressive footdrop. *Laing distal myopathy* is also a dominantly inherited disorder heralded by tibial weakness; however, it is distinguished by onset in childhood or early adult life. *Nonaka distal myopathy* and *Miyoshi myopathy* are distinguished by autosomal recessive inheritance and onset in the late teens or twenties. Nonaka myopathy entails anterior tibial weakness, whereas Miyoshi myopathy is unique in that gastrocnemius muscles are preferentially affected at onset. Finally, the *myofibrillar myopathies* (MFM) are a clinically and genetically heterogeneous group of disorders that can be associated with prominent distal weakness; they can be inherited in an autosomal dominant or recessive pattern.

Confounding these clinical features is the observation that proximal muscles can be affected as each of these

disorders progresses (less so for Welander disease than the others). In contrast to many other inherited muscle diseases, the distal myopathies are for the most part limited to skeletal muscle.

Laboratory Features

Serum CK level is particularly helpful in diagnosing Miyoshi myopathy since it is very elevated. In the other conditions serum CK is only slightly increased. EMGs are myopathic. In the myofibrillar myopathies (MFM), myotonic or pseudomyotonic discharges are common. Muscle biopsy shows nonspecific dystrophic features and, with the exception of Laing and Nonaka distal myopathies, often shows rimmed vacuoles. MFM is associated with the accumulation of dense inclusions, as well as amorphous material best seen on Gomori trichrome and myofibrillar disruption on electron microscopy. Immune staining sometimes demonstrates accumulation of desmin and other proteins in MFM, large deposits of myosin heavy chain in the subsarcolemmal region of type 1 muscle fibers in Laing myopathy, and reduced or absent dysferlin in Miyoshi myopathy.

The affected genes and their gene products are listed in Table 43-9. The gene for Welander disease awaits identification.

℞ Treatment: DISTAL MYOPATHIES

Occupational therapy is offered for loss of hand function; ankle-foot orthoses can support distal lower limb muscles. The MFMs can be associated with cardiomyopathy (congestive heart failure or arrhythmias) and respiratory failure that may require medical management.

CONGENITAL MYOPATHIES

These rare disorders are distinguished from muscular dystrophies by the presence of specific histochemical and structural abnormalities in muscle. Although primarily disorders of infancy or childhood, three forms that may present in adulthood are described here: central core disease, nemaline (rod) myopathy, and centronuclear (myotubular) myopathy. Other types, such as minicore myopathy (multi-minicore disease), fingerprint body myopathy, and sarcotubular myopathy, are not discussed.

CENTRAL CORE DISEASE

Patients with central core disease may have decreased fetal movements and breech presentation. Hypotonia and delay in motor milestones, particularly in walking, are common. Later in childhood, patients develop problems with stair climbing, running, and getting up from the floor. On examination, there is mild facial, neck-flexor, and proximal-extremity muscle weakness. Legs are more affected than arms. Skeletal abnormalities include congenital hip dislocation, scoliosis, and pes cavus; clubbed feet also occur. Most cases are nonprogressive, but exceptions are well documented. Susceptibility to malignant hyperthermia must be considered as a potential risk factor for patients with central core disease.

The serum CK level is usually normal. Needle EMG demonstrates a myopathic pattern. Muscle biopsy shows fibers with single or multiple central or eccentric discrete zones (*cores*) devoid of oxidative enzymes. Cores occur preferentially in type 1 fibers and represent poorly aligned sarcomeres associated with Z disk streaming.

Autosomal dominant inheritance is characteristic; sporadic cases also occur. The disease is caused by point mutations of the ryanodine receptor gene on chromosome 19q, encoding the calcium-release channel of the sarcoplasmic reticulum of skeletal muscle; mutations of this gene also account for some cases of inherited malignant hyperthermia. Malignant hyperthermia is an allelic condition; C-terminal mutations of the *RYR1* gene predispose to this complication.

Specific treatment is not required, but establishing a diagnosis of central core disease is extremely important because these patients have a known predisposition to malignant hyperthermia during anesthesia.

NEMALINE MYOPATHY

The term *nemaline* refers to the distinctive presence in muscle fibers of rods or threadlike structures (Greek *nema*, "thread"). Nemaline myopathy is clinically heterogeneous. A severe neonatal form presents with hypotonia and feeding and respiratory difficulties, leading to early death. Nemaline myopathy usually presents in infancy or childhood with delayed motor milestones. The course is nonprogressive or slowly progressive. The physical appearance is striking because of the long, narrow facies, high-arched palate, and open-mouthed appearance due to a prognathous jaw. Other skeletal abnormalities include pectus excavatum, kyphoscoliosis, pes cavus, and clubfoot deformities. Facial and generalized muscle weakness, including respiratory muscle weakness, is common. An adult-onset disorder with progressive proximal weakness may be seen. Myocardial involvement is occasionally present in both the childhood and adult-onset forms. The serum CK level is usually normal or slightly elevated. The EMG demonstrates a myopathic pattern. Muscle biopsy shows clusters of small rods (nemaline bodies), which occur preferentially, but not exclusively, in the sarcoplasm of type 1 muscle fibers. Occasionally, the rods are also apparent in myonuclei. The muscle often shows type 1 muscle fiber predominance. Rods originate from the Z disk material of the muscle fiber.

Five genes have been associated with nemaline myopathy. All code for thin filament–associated proteins, suggesting disturbed assembly or interplay of these structures as a pivotal mechanism. Mutations of the nebulin (*NEB*) gene account for most cases, including both severe neonatal and early childhood forms, inherited as autosomal recessive disorders. Neonatal and childhood cases, inherited as predominantly autosomal dominant disorders, are caused by mutations of the skeletal muscle α-actinin (*ACTA1*) gene. In milder forms of the disease with autosomal dominant inheritance, mutations have been identified in both the slow α-tropomyosin (*TPM3*) and β-tropomyosin (*TPM2*) genes accounting for <3% of cases. Muscle troponin T (*TNNT1*) gene mutations appear to be limited to the Amish population in North America. No specific treatment is available.

CENTRONUCLEAR (MYOTUBULAR) MYOPATHY

Three distinct variants of centronuclear myopathy occur. A neonatal form, also known as *myotubular myopathy*, presents with severe hypotonia and weakness at birth. The late infancy–early childhood form presents with delayed motor milestones. Later, difficulty with running and stair climbing becomes apparent. A marfanoid, slender body habitus, long narrow face, and high-arched palate are typical. Scoliosis and clubbed feet may be present. Most patients exhibit progressive weakness, some requiring wheelchairs. Progressive external ophthalmoplegia with ptosis and varying degrees of extraocular muscle impairment are characteristic of both the neonatal and the late-infantile forms. A third variant, the late childhood–adult form, has an onset in the second or third decade. Patients have full extraocular muscle movements and rarely exhibit ptosis. There is mild, slowly progressive limb weakness that may be distally predominant [some of these patients have been classified as having Charcot-Marie-Tooth disease type 2 (CMT2); Chap. 40].

Normal or slightly elevated CK levels occur in each of the forms. Nerve conduction studies may reveal reduced amplitudes of distal compound muscle action potentials, in particular in adult-onset cases that resemble CMT2. EMG studies often give distinctive results, showing positive sharp waves and fibrillation potentials, complex and repetitive discharges, and rarely myotonic discharges. Muscle biopsy specimens in longitudinal section demonstrate rows of central nuclei, often surrounded by a halo. In transverse sections, central nuclei are found in 25–80% of muscle fibers.

A gene for the neonatal form of centronuclear myopathy has been localized to Xq28; this gene encodes myotubularin, a protein tyrosine phosphatase. Missense, frameshift, and splice-site mutations predict loss of myotubularin function in affected individuals. Carrier identification and prenatal diagnosis are possible. The inheritance pattern for the late infancy–early childhood disorder is probably autosomal recessive, and for the late childhood–adult form is probably autosomal dominant. No specific treatment is available. Some of the autosomal dominant late-onset cases, which are allelic to a form of CMT2, are associated with mutations in the gene that encodes dynamin-2.

DISORDERS OF MUSCLE ENERGY METABOLISM

There are two principal sources of energy for skeletal muscle—fatty acids and glucose. Abnormalities in either glucose or lipid utilization can be associated with distinct clinical presentations that can range from an acute, painful syndrome with rhabdomyolysis and myoglobinuria to a chronic, progressive muscle weakness simulating muscular dystrophy.

GLYCOGEN STORAGE AND GLYCOLYTIC DEFECTS

Disorders of Glycogen Storage Causing Progressive Weakness

α-Glucosidase, or Acid Maltase, Deficiency (Pompe's Disease)

Three clinical forms of α-glucosidase, or acid maltase, deficiency (*type II glycogenosis*) can be distinguished. The infantile form is the most common, with onset of symptoms in the first 3 months of life. Infants develop severe muscle weakness, cardiomegaly, hepatomegaly, and respiratory insufficiency. Glycogen accumulation in motor neurons of the spinal cord and brainstem contributes to muscle weakness. Death usually occurs by 1 year of age. In the childhood form, the picture resembles muscular dystrophy. Delayed motor milestones result from proximal limb muscle weakness and involvement of respiratory muscles. The heart may be involved, but the liver and brain are unaffected. The adult form usually begins in the third or fourth decade but can present as late as the seventh decade. Respiratory failure and diaphragmatic weakness are often initial manifestations, heralding progressive proximal muscle weakness. The heart and liver are not involved.

The serum CK level is 2 to 10 times normal in infantile or childhood-onset Pompe disease but can be normal in adult-onset cases. EMG examination demonstrates a myopathic pattern, but other features are especially distinctive, including myotonic discharges, trains of fibrillation and positive waves, and complex repetitive discharges. EMG discharges are very prominent in the lumbosacral paraspinal muscles. The muscle biopsy in infants typically reveals vacuoles containing glycogen and the lysosomal enzyme acid phosphatase. Electron microscopy reveals membrane-bound and free tissue glycogen. However, muscle biopsies in late-onset Pompe's disease may demonstrate

only nonspecific abnormalities. Enzyme analysis of dried blood spots is a new and sensitive technique to screen for Pompe's disease. A definitive diagnosis is established by enzyme assay in muscle or cultured fibroblasts or by genetic testing.

Acid maltase deficiency is inherited as an autosomal recessive disorder caused by mutations of the α-glucosidase gene. Recently, replacement therapy with IV recombinant human α-glucosidase has been shown to be beneficial in infantile-onset Pompe disease and was approved by the U.S. Food and Drug Administration (FDA). The efficacy in later-onset cases is under study. Clinical benefits in the infantile disease include reduced heart size, improved muscle function, reduced need for ventilatory support, and longer life.

Other Glycogen Storage Diseases with Progressive Weakness

In *debranching enzyme deficiency* (*type III glycogenosis*), a slowly progressive form of muscle weakness can develop after puberty. Rarely, myoglobinuria may be seen. Patients are usually diagnosed in infancy, however, because of hypotonia and delayed motor milestones, hepatomegaly, growth retardation, and hypoglycemia. *Branching enzyme deficiency* (*type IV glycogenosis*) is a rare and fatal glycogen storage disease characterized by failure to thrive and hepatomegaly. Hypotonia and muscle wasting may be present, but the skeletal muscle manifestations are minor compared to liver failure.

Disorders of Glycolysis Causing Exercise Intolerance

Several glycolytic defects are associated with recurrent myoglobinuria: *myophosphorylase deficiency* (*type V glycogenosis*), *phosphofructokinase deficiency* (*type VII glycogenosis*), *phosphoglycerate kinase deficiency* (*type IX glycogenosis*), *phosphoglycerate mutase deficiency* (*type X glycogenosis*), *lactate dehydrogenase deficiency* (*glycogenosis type XI*), and *beta-enolase deficiency*. Myophosphorylase deficiency, also known as *McArdle's disease*, is by far the most common of the glycolytic defects associated with exercise intolerance. These glycolytic defects result in a common failure to support energy production at the initiation of exercise, although the exact site of energy failure remains controversial.

Clinical muscle manifestations in these conditions usually begin in adolescence. Symptoms are precipitated by brief bursts of high-intensity exercise, such as running or lifting heavy objects. A history of myalgia and muscle stiffness usually precedes the intensely painful muscle contractures, which may be followed by myoglobinuria. Acute renal failure accompanies significant pigmenturia.

Certain features help distinguish some enzyme defects. In McArdle's disease exercise tolerance can be enhanced by a slow induction phase (warm-up) or brief periods of rest, allowing for the start of the "second-wind" phenomenon (switching to utilization of fatty acids). Varying degrees of hemolytic anemia accompany deficiencies of both phosphofructokinase (mild) and phosphoglycerate kinase (severe). In phosphoglycerate kinase deficiency, the usual clinical presentation is a seizure disorder associated with mental retardation; exercise intolerance is an infrequent manifestation.

In all of these conditions, the serum CK levels fluctuate widely and may be elevated even during symptom-free periods. CK levels >100 times normal are expected, accompanying myoglobinuria. All patients with suspected glycolytic defects leading to exercise intolerance should undergo a forearm exercise test. An impaired rise in venous lactate is highly indicative of a glycolytic defect. In lactate dehydrogenase deficiency, venous levels of lactate do not increase, but pyruvate rises to normal. A definitive diagnosis of glycolytic disease is made by muscle biopsy and subsequent enzyme analysis or by genetic testing.

Myophosphorylase deficiency, phosphofructokinase deficiency, and phosphoglycerate mutase deficiency are inherited as autosomal recessive disorders. Phosphoglycerate kinase deficiency is X-linked recessive. Mutations can be found in the respective genes encoding the abnormal proteins in each of these disorders.

Training may enhance exercise tolerance, perhaps by increasing perfusion to muscle. Dietary intake of free glucose or fructose prior to activity may improve function but care must be taken to avoid obesity from ingesting too many calories.

LIPID AS AN ENERGY SOURCE AND ASSOCIATED DEFECTS

Lipid is an important muscle energy source during rest and during prolonged, submaximal exercise. Fatty acids are derived from circulating very low density lipoprotein (VLDL) in the blood or from triglycerides stored in muscle fibers. Oxidation of fatty acids occurs in the mitochondria. To enter the mitochondria, a fatty acid must first be converted to an "activated fatty acid," acyl-CoA. The acyl-CoA must be linked with carnitine by the enzyme carnitine palmitoyltransferase (CPT) I for transport into the mitochondria. CPT I is present on the inner side of the outer mitochondrial membrane. Carnitine is removed by CPT II, an enzyme attached to the inside of the inner mitochondrial membrane, allowing transport of acyl-CoA into the mitochondrial matrix for β-oxidation.

Carnitine Palmitoyltransferase Deficiency

CPT II deficiency is the most common recognizable cause of recurrent myoglobinuria, more common than the glycolytic defects. Onset is usually in the teenage years or early twenties. Muscle pain and myoglobinuria typically occur after prolonged exercise but can also be precipitated by fasting or infections; up to 20% of patients do not

exhibit myoglobinuria, however. Strength is normal between attacks. In contrast to disorders caused by defects in glycolysis, in which muscle cramps follow short, intense bursts of exercise, the muscle pain in CPT II deficiency does not occur until the limits of utilization have been exceeded and muscle breakdown has already begun. Episodes of rhabdomyolysis may produce severe weakness. In young children and newborns, CPT II deficiency can present with a very severe clinical picture including hypoketotic hypoglycemia, cardiomyopathy, liver failure, and sudden death.

Serum CK levels and EMG findings are both usually normal between episodes. A normal rise of venous lactate during forearm exercise distinguishes this condition from glycolytic defects, especially myophosphorylase deficiency. Muscle biopsy does not show lipid accumulation and is usually normal between attacks. The diagnosis requires direct measurement of muscle CPT or genetic testing.

CPT II deficiency is much more common in men than women (5:1); nevertheless, all evidence indicates autosomal recessive inheritance. A mutation in the gene for CPT II (chromosome 1p36) causes the disease in some individuals. Attempts to improve exercise tolerance with frequent meals and a low-fat, high-carbohydrate diet, or by substituting medium-chain triglycerides in the diet, have not proven to be beneficial.

Myoadenylate Deaminase Deficiency

The muscle enzyme myoadenylate deaminase converts adenosine 5′-monophosphate (5′-AMP) to inosine monophosphate (IMP) with liberation of ammonia. Myoadenylate deaminase may play a role in regulating adenosine triphosphate (ATP) levels in muscles. Most individuals with myoadenylate deaminase deficiency have no symptoms. There have been a few reports of patients with this disorder who have exercise-exacerbated myalgia and myoglobinuria. Many questions have been raised about the clinical effects of myoadenylate deaminase deficiency, and, specifically, its relationship to exertional myalgia and fatigability, but there is no consensus.

MITOCHONDRIAL MYOPATHIES

In 1972, Olson and colleagues recognized that muscle fibers with significant numbers of abnormal mitochondria could be highlighted with the modified trichrome stain; the term *ragged red fibers* was coined. By electron microscopy, the mitochondria in ragged red fibers are enlarged and often bizarrely shaped and have crystalline inclusions. Since that seminal observation, the understanding of these disorders of muscle and other tissues has expanded.

Mitochondria play a key role in energy production. Oxidation of the major nutrients derived from carbohydrate, fat, and protein leads to the generation of reducing equivalents. The latter are transported through the respiratory chain in the process known as *oxidative phosphorylation*. The energy generated by the oxidation-reduction reactions of the respiratory chain is stored in an electrochemical gradient coupled to ATP synthesis.

A novel feature of mitochondria is their genetic composition. Each mitochondrion possesses a DNA genome that is distinct from that of the nuclear DNA. Human mitochondrial DNA (mtDNA) consists of a double-strand, circular molecule comprising 16,569 base pairs. It codes for 22 transfer RNAs, 2 ribosomal RNAs, and 13 polypeptides of the respiratory chain enzymes. The genetics of mitochondrial diseases differ from the genetics of chromosomal disorders. The DNA of mitochondria is directly inherited from the cytoplasm of the gametes, mainly from the oocyte. The sperm contributes very little of its mitochondria to the offspring at the time of fertilization. Thus, mitochondrial genes are derived almost exclusively from the mother, accounting for maternal inheritance of some mitochondrial disorders.

Patients with mitochondrial disorders have clinical manifestations that fall into three groups: chronic progressive external ophthalmoplegia (CPEO), skeletal muscle–CNS syndromes, and pure myopathy simulating muscular dystrophy or metabolic myopathy.

PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA SYNDROMES WITH RAGGED RED FIBERS

The single most common sign of a mitochondrial myopathy is CPEO, occurring in >50% of all mitochondrial myopathies. Varying degrees of ptosis and weakness of extraocular muscles are seen, usually in the absence of diplopia, a point of distinction from disorders with fluctuating eye weakness (e.g., myasthenia gravis).

KEARNS-SAYRE SYNDROME (KSS)

KSS is a widespread multiorgan system disorder with a defined triad of clinical findings: onset <20 years, CPEO, and pigmentary retinopathy plus one or more of the following features: complete heart block, cerebrospinal fluid (CSF) protein >1.0 g/L (100 mg/dL), or cerebellar ataxia. Some patients with CPEO and ragged red fibers may not fulfill all of the criteria for KSS. The cardiac disease includes syncopal attacks and cardiac arrest related to the abnormalities in the cardiac conduction system: prolonged intraventricular conduction time, bundle branch block, and complete atrioventricular block. Death attributed to heart block occurs in ~20% of the patients. Varying degrees of progressive limb muscle weakness and easy fatigability affect activities of daily living. Endocrine abnormalities are common, including gonadal dysfunction in both sexes with delayed puberty, short stature, and infertility. Diabetes mellitus is a cardinal sign of mitochondrial disorders and

is estimated to occur in 13% of KSS patients. Other less common endocrine disorders include thyroid disease, hyperaldosteronism, Addison's disease, and hypoparathyroidism. Both mental retardation and dementia are common accompaniments to this disorder. Serum CK levels are normal or slightly elevated. Serum lactate and pyruvate levels may be elevated. EMG is myopathic. Nerve conduction studies may be abnormal related to an associated neuropathy. Muscle biopsies reveal ragged red fibers, highlighted in oxidative enzyme stains, many showing defects in cytochrome oxidase. By electron microscopy there are increased numbers of mitochondria that often appear enlarged and contain paracrystalline inclusions.

KSS is a sporadic disorder. The disease is caused by single mtDNA deletions presumed to arise spontaneously in the ovum or zygote. The most common deletion, occurring in about one-third of patients, removes 4977 bp of contiguous mtDNA. Monitoring for cardiac conduction defects is critical. Prophylactic pacemaker implantation is indicated when ECGs demonstrate a bifascicular block. In KSS no benefit has been shown for supplementary therapies, including multivitamins or coenzyme Q10. Of all the proposed options, exercise might be the most applicable but must be approached cautiously because of defects in the cardiac conduction system.

PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA (PEO)

This condition is caused by nuclear DNA mutations affecting mtDNA copy number and integrity and is thus inherited in a Mendelian fashion. Onset is usually after puberty. Fatigue, exercise intolerance, and complaints of muscle weakness are typical. Some patients notice swallowing problems. The neurologic examination confirms the ptosis and ophthalmoplegia, usually asymmetric in distribution. A sensorineural hearing loss may be encountered. Mild facial, neck flexor, and proximal weakness are typical. Rarely, respiratory muscles may be progressively affected and may be the direct cause of death. Serum CK is normal or mildly elevated. The resting lactate level is normal or slightly elevated but may rise excessively after exercise. CSF protein is normal. The EMG is myopathic, and nerve conduction studies are usually normal. Ragged red fibers are prominently displayed in the muscle biopsy. Southern blots of muscle reveal a normal mtDNA band at 16.6 kb and several additional mtDNA deletion bands with genomes varying from 0.5 to 10 kb.

This autosomal dominant form of CPEO has been linked to loci on three chromosomes: 4q35, 10q24, and 15q22-26. In the chromosome 4q–related form of disease, mutations of the gene encoding the heart and skeletal muscle–specific isoform of the adenine nucleotide translocator 1 (*ANT1*) gene are found. This highly abundant mitochondrial protein forms a homodimeric inner mitochondrial channel through which ADP enters and ATP leaves the mitochondrial matrix. In the chromosome 10q–related disorder, mutations of the gene *C10orf2* are found. Its gene product, *twinkle*, co-localizes with the mtDNA and is named for its punctate, starlike staining properties. The function of twinkle is presumed to be critical for lifetime maintenance of mitochondrial integrity. In the cases mapped to chromosome 15q, a mutation affects the gene encoding mtDNA polymerase (*POLG*), an enzyme important in mtDNA replication. Autosomal recessive PEO has also been described with mutations in the *POLG* gene. Point mutations have been identified within various mitochondrial tRNA (Leu, Ile, Asn, Trp) genes in families with maternal inheritance of PEO.

Exercise may improve function but will depend on the patients' ability to participate.

AUTOSOMAL RECESSIVE CARDIOMYOPATHY AND OPHTHALMOPLEGIA (ARCO)

ARCO is a rare mitochondrial disorder clinically important because of an associated life-threatening cardiomyopathy. CPEO is the initial manifestation, occurring between ages 8 and 10. Exercise intolerance and fatigue follow the early symptoms, accompanied by palpitations and chest pain. Examination reveals extraocular muscle weakness, ptosis, facial weakness, reduced muscle bulk, and limb weakness, greater in proximal muscles. A dilated cardiomyopathy is typical, and some patients have conduction system involvement. Death from congestive heart failure occurs as early as 13 years of age. Serum lactate is normal at rest but increases with mild exercise. Serum CK is increased two- to fourfold. EMG is normal or myopathic. Muscle biopsy demonstrates typical ragged red fibers. Multiple mtDNA deletions are seen on Southern blots of muscle. Echocardiograms show reduced ejection fraction. Conduction block is seen on ECGs. The disease is inherited as an autosomal recessive disorder. The gene has not been identified. Heart failure may require orthotopic cardiac transplantation. Cardiac pacemakers are appropriate for patients with heart block.

MTDNA SKELETAL MUSCLE–CENTRAL NERVOUS SYSTEM SYNDROMES

Myoclonic Epilepsy with Ragged Red Fibers (MERRF)

The onset of MERRF is variable, ranging from late childhood to middle adult life. Characteristic features include myoclonic epilepsy, cerebellar ataxia, and progressive muscle weakness. The seizure disorder is an integral part of the disease and may be the initial symptom. Cerebellar ataxia precedes or accompanies epilepsy. It is slowly progressive and generalized. The third major feature of the disease is

muscle weakness in a limb-girdle distribution. Other more variable features include dementia, peripheral neuropathy, optic atrophy, hearing loss, and diabetes mellitus.

Serum CK levels are normal or slightly increased. The serum lactate may be elevated. EMG is myopathic, and in some patients nerve conduction studies show a neuropathy. The electroencephalogram is abnormal, corroborating clinical findings of epilepsy. Typical ragged red fibers are seen on muscle biopsy. MERRF is caused by maternally inherited point mutations of mitochondrial tRNA genes. The most common mutation found in 80% of MERRF patients is an A to G substitution at nucleotide 8344 of tRNA lysine (A8344G $tRNA^{lys}$). Other $tRNA^{lys}$ mutations include base-pair substitutions T8356C and G8363A. Only supportive treatment is possible, with special attention to epilepsy.

Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke-Like Episodes (MELAS)

MELAS is the most common mitochondrial encephalomyopathy. The term *stroke-like* is appropriate because the cerebral lesions do not conform to a strictly vascular distribution. The age of onset in the majority of patients is <20 years. Seizures, usually partial motor or generalized, are common and may represent the first clearly recognizable sign of disease. The cerebral insults that resemble strokes cause hemiparesis, hemianopia, and cortical blindness. A presumptive stroke occurring <40 years should place this mitochondrial encephalomyopathy high in the differential diagnosis. Associated conditions include hearing loss, diabetes mellitus, hypothalamic pituitary dysfunction causing growth hormone deficiency, hypothyroidism, and absence of secondary sexual characteristics. In its full expression MELAS leads to dementia, a bedridden state, and a fatal outcome. Serum lactic acid is typically elevated. The CSF protein is also increased but is usually ≤1.0 g/L (100 mg/dL). Muscle biopsies show ragged red fibers. Neuroimaging demonstrates basal ganglia calcification in a high percentage of cases. Focal lesions that mimic infarction are present predominantly in the occipital and parietal lobes. Strict vascular territories are not respected, and cerebral angiography fails to demonstrate lesions of the major cerebral blood vessels.

MELAS is caused by maternally inherited point mutations of mitochondrial tRNA genes. Most of the tRNA mutations are lethal, accounting for the paucity of multigeneration families with this syndrome. The A3243G point mutation in $tRNA^{Leu(UUR)}$ is the most common, occurring in ~80% of MELAS cases. About 10% of MELAS patients have other mutations of the $tRNA^{Leu(UUR)}$ gene including 3252G, 3256T, 3271C, and 3291C. Other tRNA gene mutations have also been reported in MELAS including G583A $tRNA^{Phe}$, G1642A $tRNA^{Val}$, G4332A $tRNA^{Glu}$, and T8316C $tRNA^{Lys}$. Mutations have also been reported in mtDNA polypeptide-coding genes. Two mutations were found in the ND5 subunit of complex I of the respiratory chain. A missense mutation has been reported at mtDNA position 9957 in the gene for subunit III of cytochrome C oxidase. No specific treatment is available. Supportive treatment is essential for the stroke-like episodes, seizures, and endocrinopathies.

PURE MYOPATHY SYNDROMES

Muscle weakness and fatigue can be the predominant manifestations of mtDNA mutations. When the condition affects exclusively muscle (pure myopathy), the disorder becomes difficult to recognize. Occasionally, mitochondrial myopathies can present with recurrent myoglobinuria without fixed weakness and thus resemble a glycogen storage disorder or CPT deficiency.

Mitochondrial DNA Depletion Myopathy

This disorder, clinically indistinguishable from muscular dystrophy, usually presents in the neonatal period with weakness, hypotonia, and delayed motor milestones. Some cases are rapidly fatal, with death <2 years of age. A milder form affects patients at a slightly later age. These patients have slowly evolving proximal muscle weakness simulating Duchenne muscular dystrophy. In some, seizures and cardiomyopathy may be present. Serum CK can reach levels of 20 to 30 times normal. Resting lactate varies from normal to mildly elevated. The EMG is myopathic, and ragged red fibers are seen on muscle biopsy. The mtDNA depletion syndrome is inherited as an autosomal recessive condition. Mutations have been identified in the *TK2* gene on chromosome 16q22 encoding thymidine kinase-2. The affected gene controls the supply of deoxyribonucleotides used for the synthesis of mtDNA. No specific treatment is available. Supportive care follows the approaches outlined for muscular dystrophy.

DISORDERS OF MUSCLE MEMBRANE EXCITABILITY

Muscle membrane excitability is affected in a group of disorders referred to as *channelopathies*. The heart may also be involved, resulting in life-threatening complications (**Table 43-10**).

CALCIUM CHANNEL DISORDERS OF MUSCLE

Hypokalemic Periodic Paralysis (HypoKPP)

Onset occurs at adolescence. Men are more often affected because of decreased penetrance in women. Episodic weakness with onset >25 years of age is almost never due to periodic paralyses with the exception of thyrotoxic periodic paralysis (see later). Attacks are often provoked

TABLE 43-10

CLINICAL FEATURES OF PERIODIC PARALYSIS AND NONDYSTROPHIC MYOTONIAS

	CALCIUM CHANNEL	SODIUM CHANNEL		POTASSIUM CHANNEL
FEATURE	**HYPOKALEMIC PP**	**HYPERKALEMIC PP**	**PARAMYOTONIA CONGENITA**	**ANDERSON'S SYNDROME[b]**
Mode of inheritance	AD	AD	AD	AD
Age of onset	Adolescence	Early childhood	Early childhood	Early childhood
Myotonia[a]	No	Yes	Yes	No
Episodic weakness	Yes	Yes	Yes	Yes
Frequency of attacks of weakness	Daily to yearly	May be 2–3/d	With cold, usually rare	Daily to yearly
Duration of attacks of weakness	2–12 h	From 1–2 h to >1 d	2–24 h	2–24 h
Serum K^+ level during attacks of weakness	Decreased	Increased or normal	Usually normal	Variable
Effect of K^+ loading	No change	Increased myotonia, then weakness	Increased myotonia	No change
Effect of muscle cooling	No change	Increased myotonia	Increased myotonia, then weakness	No change
Fixed weakness	Yes	Yes	Yes	Yes

[a]May be paradoxical in paramyotonia congenita.
[b]Dysmorphic features and cardiac arrhythmias are distinguishing features (see text).
Note: AD, autosomal dominant; PP, periodic paralysis.

by meals high in carbohydrates or sodium and may accompany rest following prolonged exercise. Weakness usually affects proximal limb muscles more than distal. Ocular and bulbar muscles are less likely to be affected. Respiratory muscles are usually spared but when they are involved, the condition may prove fatal. Weakness may take as long as 24 h to resolve. Life-threatening cardiac arrhythmias related to hypokalemia may occur during attacks. As a late complication, patients commonly develop severe, disabling proximal lower extremity weakness.

Attacks of thyrotoxic periodic paralysis resemble those of primary HypoKPP. Despite a higher incidence of thyrotoxicosis in women, men, particularly those of Asian descent, are more likely to manifest this complication. Attacks abate with treatment of the underlying thyroid condition.

A low serum potassium level during an attack, excluding secondary causes, establishes the diagnosis. Interattack muscle biopsies show the presence of single or multiple centrally placed vacuoles or tubular aggregates. Provocative tests with glucose and insulin to establish a diagnosis are usually not necessary and are potentially hazardous.

In the midst of an attack of weakness, motor conduction studies may demonstrate reduced amplitudes, whereas EMG may show electrical silence in severely weak muscles. In between attacks, the EMG and nerve conduction studies are normal, with the exception that myopathic motor unit action potentials may be seen in patients with fixed weakness.

HypoKPP is caused by mutations in either of two genes. HypoKPP type 1, the most common form, is inherited as an autosomal dominant disorder with incomplete penetrance. These patients have mutations in the voltage-sensitive, skeletal muscle calcium channel gene, *CALCL1A3* (Fig. 43-8). Approximately 10% of cases are HypoKPP type 2, arising from mutations in the voltage-sensitive sodium channel gene (*SCN4A*).

℞ Treatment: HYPOKALEMIC PERIODIC PARALYSIS

The acute paralysis improves after the administration of potassium. Muscle strength and ECG should be monitored. Oral KCl (0.2–0.4 mmol/kg) should be given every 30 min. Only rarely is IV therapy necessary (e.g., when swallowing problems or vomiting is present). Administration of potassium in a glucose solution should be avoided because it may further reduce serum potassium levels. Mannitol is the preferred vehicle for administration of IV potassium. The long-term goal of therapy is to avoid attacks. This may reduce late-onset, fixed weakness. Patients should be made aware of the importance of a low-carbohydrate, low-sodium diet and consequences of intense exercise. Prophylactic administration of acetazolamide (125–1000 mg/d in divided doses) reduces or may abolish attacks in HypoKPP type 1. Paradoxically the potassium is lowered, but this is offset by the beneficial effect of metabolic acidosis. If attacks persist on acetazolamide, oral KCl should be added. Some patients require treatment with triamterine (25–100 mg/d) or spironolactone (25–100 mg/d). However, in patients with HypoKPP type 2, attacks of weakness can be exacerbated with acetazolamide.

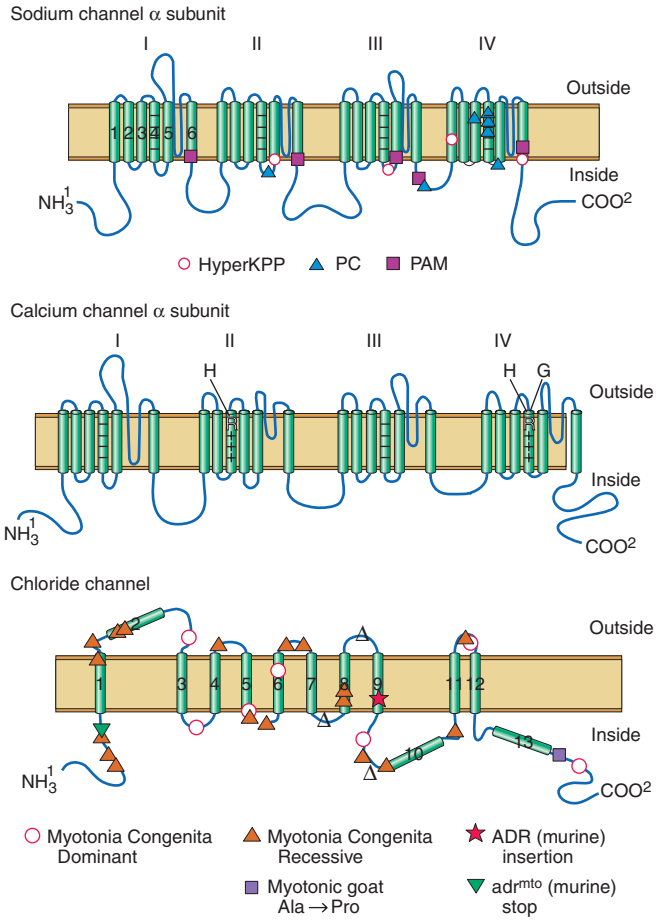

FIGURE 43-8

The sodium and calcium channels are depicted here as containing four homologous domains, each with six membrane-spanning segments. The fourth segment of each domain bears positive charges and acts as the "voltage sensor" for the channel. The association of the four domains is thought to form a pore through which ions pass. Sodium channel mutations are shown along with the phenotype that they confer. HyperKPP, hyperkalemic periodic paralysis; PC, paramyotonia congenita; PAM, potassium-aggravated myotonia. See text for details.

The chloride channel is envisioned to have ten membrane-spanning domains. The positions of mutations causing dominantly and recessively inherited myotonia congenita are indicated, along with mutations that cause this disease in mice and goats.

SODIUM CHANNEL DISORDERS OF MUSCLE

Hyperkalemic Periodic Paralysis (HyperKPP)

The term *hyperkalemic* is misleading since patients are often normokalemic during attacks. The fact that attacks are precipitated by potassium administration best defines the disease. The onset is in the first decade. Attacks are brief and mild, usually lasting 30 min to 4 h. Weakness affects proximal muscles, sparing bulbar muscles. Attacks are precipitated by rest following exercise and fasting. In a variant of this disorder, the predominant symptom is myotonia without weakness (*potassium-aggravated myotonia*). The symptoms are aggravated by cold, and myotonia makes the muscles stiff and painful. This disorder can be confused with paramyotonia congenita, myotonia congenita, and proximal myotonic myopathy (DM2).

Potassium may be slightly elevated but may also be normal during an attack. As in HypoKPP, nerve conduction studies in HyperKPP muscle may demonstrate reduced motor amplitudes and the EMG may be silent in very weak muscles. In between attacks of weakness, the conduction studies are normal. The EMG will often demonstrate myotonic discharges during and between attacks.

The muscle biopsy shows vacuoles that are smaller, less numerous, and more peripheral compared to the hypokalemic form or tubular aggregates. Provocative tests by administration of potassium can induce weakness but are usually not necessary to establish the diagnosis. HyperKPP and potassium-aggravated myotonia are inherited as autosomal dominant disorders. Mutations of the voltage-gated sodium channel *SCN4A* gene (Fig. 43-8) cause these conditions. For patients with frequent attacks, acetazolamide (125–1000 mg/d) is helpful. We have found mexiletine to be helpful in patients with significant myotonia.

Paramyotonia Congenita

In paramyotonia congenita (PC) the attacks of weakness are cold-induced or occur spontaneously and are mild. Myotonia is a prominent feature but worsens with muscle activity (paradoxical myotonia). This is in contrast to classic myotonia in which exercise alleviates the condition. Attacks of weakness are seldom severe enough to require emergency room treatment. Over time patients develop interattack weakness as they do in other forms of periodic paralysis. PC is usually associated with normokalemia or hyperkalemia.

Serum CK is usually mildly elevated. Routine sensory and motor nerve conduction studies are normal. Cooling of the muscle often dramatically reduces the amplitude of the compound muscle action potentials. EMG reveals diffuse myotonic potentials in PC. Upon local cooling of the muscle the myotonic discharges disappear as the patient becomes unable to activate motor unit action potentials.

PC is inherited as an autosomal dominant condition; voltage-gated sodium channel mutations (Fig. 43-8) are responsible and thus this disorder is allelic with HyperKPP and potassium-aggravated myotonia. Patients with PC seldom seek treatment during attacks. Oral administration of glucose or other carbohydrates hastens recovery. Since interattack weakness may develop after repeated episodes, prophylactic treatment is usually indicated. Thiazide diuretics (e.g., chlorothiazide, 250–1000 mg/d) and mexiletine (slowly increase dose from 450 mg/d) are reported to be helpful. Patients should be advised to increase carbohydrates in their diet.

POTASSIUM CHANNEL DISORDERS

Andersen-Tawil Syndrome

This rare disease is characterized by episodic weakness, cardiac arrhythmias, and dysmorphic features (short stature, scoliosis, clinodactyly, hypertelorism, small or prominent low set ears, micrognathia, and broad forehead). The cardiac arrhythmias are potentially serious and life threatening. They include long QT, ventricular ectopy, bidirectional ventricular arrhythmias, and tachycardia. For many years the classification of this disorder was uncertain because episodes of weakness are associated with elevated, normal, or reduced levels of potassium during an attack. In addition, the potassium levels differ among kindreds but are consistent within a family. Inheritance is autosomal dominant, with incomplete penetrance and variable expressivity. The disease is caused by mutations of the inwardly rectifying potassium channel (*Kir 2.1*) gene. The treatment is similar to that for other forms of periodic paralysis and must include cardiac monitoring. The episodes of weakness may differ between patients because of potassium variability. Acetazolamide decreases the attack frequency and severity.

CHLORIDE CHANNEL DISORDERS

Two forms of this disorder, autosomal dominant (*Thomsen's disease*) and autosomal recessive (*Becker's disease*) are related to the same gene abnormality. Symptoms are noted in infancy and early childhood. The severity lessens in the third to fourth decade. Myotonia is worsened by cold and improved by activity. The gait may appear slow and labored at first but improves with walking. In Thomsen's disease muscle strength is normal, but in Becker's, which is usually more severe, there may be muscle weakness. Muscle hypertrophy is usually present. Myotonic discharges are prominently displayed by EMG recordings.

Serum CK is normal or mildly elevated. The muscle biopsy shows hypertrophied fibers. The disease is inherited as dominant or recessive and is caused by mutations of the chloride channel gene (Fig. 43-8). Many patients will not require treatment and learn that the symptoms improve with activity. Medications that can be used to decrease myotonia include quinine, phenytoin, and mexiletine.

ENDOCRINE AND METABOLIC MYOPATHIES

Many endocrine disorders cause weakness. Muscle fatigue is more common than true weakness. The cause of weakness in these disorders is not well defined. It is not even clear that weakness results from disease of muscle as opposed to another part of the motor unit, since the serum CK level is often normal (except in hypothyroidism) and the muscle histology is characterized by atrophy rather than destruction of muscle fibers. Nearly all endocrine myopathies respond to treatment.

THYROID DISORDERS

Abnormalities of thyroid function can cause a wide array of muscle disorders. These conditions relate to the important role of thyroid hormones in regulating the metabolism of carbohydrates and lipids as well as the rate of protein synthesis and enzyme production. Thyroid hormones also stimulate calorigenesis in muscle, increase muscle demand for vitamins, and enhance muscle sensitivity to circulating catecholamines.

Hypothyroidism

Patients with hypothyroidism have frequent muscle complaints, and proximal muscle weakness occurs in about one-third of them. Muscle cramps, pain, and stiffness are common. Some patients have enlarged muscles. Features of slow muscle contraction and relaxation occur in 25% of patients; the relaxation phase of muscle stretch reflexes is characteristically prolonged and best observed at the ankle or biceps brachii reflexes. The serum CK level is often elevated (up to 10 times normal), even when there is minimal clinical evidence of muscle disease. EMG is typically normal. The cause of muscle enlargement has not been determined, and muscle biopsy shows no distinctive morphologic abnormalities.

Hyperthyroidism

Patients who are thyrotoxic commonly have proximal muscle weakness and atrophy on examination, but they rarely complain of myopathic symptoms. Activity of deep tendon reflexes may be enhanced. Bulbar, respiratory, and even esophageal muscles may occasionally be affected, causing dysphagia, dysphonia, and aspiration. When bulbar involvement occurs, it is usually accompanied by chronic proximal limb weakness, but occasionally it presents in the absence of generalized thyrotoxic myopathy. Fasciculations may be apparent and, when coupled with increased muscle stretch reflexes, may lead to an erroneous diagnosis of amyotrophic lateral sclerosis. Other neuromuscular disorders occur in association with hyperthyroidism, including acquired hypokalemic periodic paralysis, myasthenia gravis, and a progressive ocular myopathy associated with proptosis (*Graves' ophthalmopathy*). Serum CK levels are not elevated in thyrotoxic myopathy, the EMG is normal, and muscle histology usually shows only atrophy of muscle fibers.

PARATHYROID DISORDERS

Hyperparathyroidism

Muscle weakness is an integral part of primary and secondary hyperparathyroidism. Proximal muscle weakness, muscle wasting, and brisk muscle stretch reflexes are the

main features of this endocrinopathy. Some patients develop neck extensor weakness (part of the dropped head syndrome). Serum CK levels are usually normal or slightly elevated. Serum parathyroid hormone levels are elevated. Serum calcium and phosphorus levels show no correlation with the clinical neuromuscular manifestations. Muscle biopsies show only varying degrees of atrophy without muscle fiber degeneration.

Hypoparathyroidism

An overt myopathy due to hypocalcemia rarely occurs. Neuromuscular symptoms are usually related to localized or generalized tetany. Serum CK levels may be increased secondary to muscle damage from sustained tetany. Hyporeflexia or areflexia is usually present and contrasts with the hyperreflexia in hyperparathyroidism.

ADRENAL DISORDERS

Conditions associated with glucocorticoid excess cause a myopathy; in fact, steroid myopathy is the most commonly diagnosed endocrine muscle disease. Glucocorticoid excess, either endogenous or exogenous (see Drug-Induced Myopathies, below), produces various degrees of proximal limb weakness. Muscle wasting may be striking. A cushingoid appearance usually accompanies clinical signs of myopathy. Histologic sections demonstrate muscle fiber atrophy, preferentially affecting type 2b fibers, rather than degeneration or necrosis of muscle fibers. Adrenal insufficiency commonly causes muscle fatigue. The degree of weakness may be difficult to assess but is typically mild. In primary hyperaldosteronism (*Conn's syndrome*), neuromuscular complications are due to potassium depletion. The clinical picture is one of persistent muscle weakness. Long-standing hyperaldosteronism may lead to proximal limb weakness and wasting. Serum CK levels may be elevated, and a muscle biopsy may demonstrate degenerating fibers, some with vacuoles. These changes relate to hypokalemia and are not a direct effect of aldosterone on skeletal muscle.

PITUITARY DISORDERS

Patients with acromegaly usually have mild proximal weakness without muscle atrophy. Muscles often appear enlarged but exhibit decreased force generation. The duration of acromegaly, rather than the serum growth hormone levels, correlates with the degree of myopathy.

DIABETES MELLITUS

Neuromuscular complications of diabetes mellitus are most often related to neuropathy, with cranial and peripheral nerve palsies or distal sensorimotor polyneuropathy. *Diabetic amyotrophy* is a clumsy term since the condition represents a neuropathy affecting the proximal major nerve trunks and lumbosacral plexus. More appropriate terms for this disorder include *diabetic proximal neuropathy* and *lumbosacral radiculoplexus neuropathy*.

The only notable myopathy of diabetes mellitus is ischemic infarction of leg muscles, usually involving one of the thigh muscles but on occasion affecting the distal leg. This condition occurs in patients with poorly controlled diabetes and presents with abrupt onset of pain, tenderness, and edema of one thigh. The area of muscle infarction is hard and indurated. The muscles most often affected include the vastus lateralis, thigh adductors, and biceps femoris. CT or MRI can demonstrate focal abnormalities in the affected muscle. Diagnosis by imaging is preferable to muscle biopsy, if possible, as hemorrhage into the biopsy site can occur.

VITAMIN DEFICIENCY

Vitamin D deficiency due to either decreased intake, decreased absorption, or impaired vitamin D metabolism (as occurs in renal disease) may lead to chronic muscle weakness. Pain reflects the underlying bone disease (*osteomalacia*). Vitamin E deficiency may result from malabsorption. Clinical manifestations include ataxic neuropathy due to loss of proprioception and myopathy with proximal weakness. Progressive external ophthalmoplegia is a distinctive finding. It has not been established that deficiency of other vitamins causes a myopathy.

MYOPATHIES OF SYSTEMIC ILLNESS

Systemic illnesses such as chronic respiratory, cardiac, or hepatic failure are frequently associated with severe muscle wasting and complaints of weakness. Fatigue is usually a more significant problem than weakness, which is typically mild.

Myopathy may be a manifestation of chronic renal failure, independent of the better known uremic polyneuropathy. Abnormalities of calcium and phosphorus homeostasis and bone metabolism in chronic renal failure result from a reduction in 1,25-dihydroxyvitamin D, leading to decreased intestinal absorption of calcium. Hypocalcemia, further accentuated by hyperphosphatemia due to decreased renal phosphate clearance, leads to secondary hyperparathyroidism. Renal osteodystrophy results from the compensatory hyperparathyroidism, which leads to osteomalacia from reduced calcium availability and to osteitis fibrosa from the parathyroid hormone excess. The clinical picture of the myopathy of chronic renal failure is identical to that of primary hyperparathyroidism and osteomalacia. There is proximal limb weakness with bone pain.

Gangrenous calcification represents a separate, rare, and sometimes fatal complication of chronic renal failure. In

this condition, widespread arterial calcification occurs and results in ischemia. Extensive skin necrosis may occur, along with painful myopathy and even myoglobinuria.

DRUG-INDUCED MYOPATHIES

Drug-induced myopathies are relatively uncommon in clinical practice with the exception of those caused by the cholesterol-lowering agents and glucocorticoids. Others impact practice to a lesser degree but are important to consider in specific situations. Table 43-11 provides a comprehensive list of drug-induced myopathies with their distinguishing features.

MYOPATHY FROM LIPID-LOWERING AGENTS

All classes of lipid-lowering agents have been implicated in muscle toxicity including fibrates (clofibrate, gemfibrozil), HMG-CoA reductase inhibitors (referred to as *statins*), niacin (nicotinic acid), and ezetimibe. Myalgia, malaise, and muscle tenderness are the most common manifestations. Muscle pain may be related to exercise. Patients may exhibit proximal weakness. Varying degrees of muscle necrosis are seen, and in severe reactions rhabdomyolysis and myoglobinuria occur. Concomitant use of statins with fibrates and cyclosporine is more likely to cause adverse reactions than use of one agent alone. A polymorphism has been identified which increases the risk of statin-induced myopathy. Elevated serum CK is an important indication of toxicity. Muscle weakness is accompanied by a myopathic EMG, and muscle necrosis is observed by muscle biopsy. Severe myalgias, muscle weakness, significant elevations in serum CK (> three times baseline), and myoglobinuria are indications for stopping the drug. Patients usually improve with drug cessation, although this may take several weeks. Rare cases continue to progress after the offending agent is discontinued. It is possible that in such cases the statin may have triggered an immune-mediated necrotizing myopathy, as these individuals may respond to glucocorticoid therapy.

GLUCOCORTICOID-RELATED MYOPATHIES

Glucocorticoid myopathy occurs with chronic treatment or as "acute quadriplegic" myopathy secondary to high-dose, IV glucocorticoids. Chronic administration produces

TABLE 43-11

DRUG-INDUCED MYOPATHIES

DRUGS	MAJOR TOXIC REACTION
Lipid-lowering agents Fibric acid derivatives HMG-CoA reductase inhibitors Niacin (nicotinic acid)	Drugs belonging to all three of the major classes of lipid-lowering agents can produce a spectrum of toxicity: asymptomatic serum creatine kinase elevation, myalgias, exercised-induced pain, rhabdomyolysis, and myoglobinuria.
Glucocorticoids	Acute, high-dose glucocorticoid treatment can cause acute quadriplegic myopathy. These high doses of steroids are often combined with nondepolarizing neuromuscular blocking agents but the weakness can occur without their use. Chronic steroid administration produces predominantly proximal weakness.
Nondepolarizing neuromuscular blocking agents	Acute quadriplegic myopathy can occur with or without concomitant glucocorticoids.
Zidovudine	Mitochondrial myopathy with ragged red fibers.
Drugs of abuse Alcohol Amphetamines Cocaine Heroin Phencyclidine Meperidine	All drugs in this group can lead to widespread muscle breakdown, rhabdomyolysis, and myoglobinuria. Local injections cause muscle necrosis, skin induration, and limb contractures.
Autoimmune toxic myopathy D-Penicillamine	Use of this drug may cause polymyositis and myasthenia gravis.
Amphophilic cationic drugs Amiodarone Chloroquine Hydroxychloroquine	All amphophilic drugs have the potential to produce painless, proximal weakness associated with autophagic vacuoles in the muscle biopsy.
Antimicrotubular drugs Colchicine	This drug produces painless, proximal weakness especially in the setting of renal failure. Muscle biopsy shows autophagic vacuoles.

proximal weakness accompanied by cushingoid manifestations, which can be quite debilitating; the chronic use of prednisone at a daily dose of ≥30 mg/d is most often associated with toxicity. Patients taking fluorinated glucocorticoids (triamcinolone, betamethasone, dexamethasone) appear to be at especially high risk for myopathy. Patients receiving high-dose, IV glucocorticoids for status asthmaticus, chronic obstructive pulmonary disease, or other indications may develop severe generalized weakness. Involvement of the diaphragm and intercostal muscles causes respiratory failure and requires ventilatory support. In this setting, the use of glucocorticoids in combination with nondepolarizing neuromuscular blocking agents to further decrease airway resistance is particularly likely to lead to this complication. In chronic steroid myopathy the serum CK is usually normal. Serum potassium may be low. The muscle biopsy in chronic cases shows preferential type 2 muscle fiber atrophy; this is not reflected in the EMG, which is usually normal. In acute cases with quadriplegic myopathy the muscle biopsy is abnormal, showing a distinctive loss of thick filaments (myosin) by electron microscopy. By light microscopy there is focal loss of ATPase staining in central or paracentral areas of the muscle fiber. Calpain stains show diffusely reactive atrophic fibers. Withdrawal of glucocorticoids will improve the chronic myopathy. In acute quadriplegic myopathy, recovery is slow. Patients require supportive care and rehabilitation.

MYOPATHY OF NONDEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS

Patients may receive nondepolarizing neuromuscular blocking agents because of life-threatening airway resistance. Acute quadriplegic myopathy may result, with or without glucocorticoid use. The clinical features are identical to acute quadriplegic myopathy secondary to glucocorticoids.

DRUG-INDUCED MITOCHONDRIAL MYOPATHY

Zidovudine, used in the treatment of HIV infection, is a thymidine analogue that inhibits viral replication by interrupting reverse transcriptase. Myopathy is a well-established complication of this agent. Patients present with myalgias, muscle weakness, and atrophy affecting the thigh and calf muscles. The complication occurs in about 17% of patients treated with doses of 1200 mg/d for 6 months. The introduction of protease inhibitors for treatment of HIV infection has led to lower doses of zidovudine therapy and a decreased incidence of myopathy. Serum CK is elevated and EMG is myopathic. Muscle biopsy shows ragged red fibers with minimal inflammation; the lack of inflammation serves to distinguish zidovudine toxicity from HIV-related myopathy. If the myopathy is thought to be drug-related, the medication should be stopped or the dosage reduced.

DRUGS OF ABUSE AND RELATED MYOPATHIES

Myotoxicity is a potential consequence of addiction to alcohol and illicit drugs. Ethanol is one of the most commonly abused substances with potential to damage muscle. Other potential toxins include cocaine, heroin, and amphetamines. The most deleterious reactions occur from overdosing leading to coma and seizures, causing rhabdomyolysis, myoglobinuria, and renal failure. Direct toxicity can occur from cocaine, heroin, and amphetamines causing muscle breakdown and varying degrees of weakness. The effects of alcohol are more controversial. Direct muscle damage is less certain, since toxicity usually occurs in the setting of poor nutrition and possible contributing factors such as hypokalemia and hypophosphatemia. Alcoholics are also prone to neuropathy and a variety of CNS disorders (Chap. 50).

Focal myopathies from self-administration of meperidine, heroin, and pentazocine can cause pain, swelling, muscle necrosis, and hemorrhage. The cause is multifactorial; needle trauma, direct toxicity of the drug or vehicle, and infection may all play a role. When severe, there may be overlying skin induration and contractures with replacement of muscle by connective tissue. Elevated serum CK and myopathic EMG are characteristic of these reactions. The muscle biopsy shows widespread or focal areas of necrosis. In conditions leading to rhabdomyolysis, patients need adequate hydration to reduce serum myoglobin and protect renal function. In all of these conditions, counseling is essential to limit drug abuse.

DRUG-INDUCED AUTOIMMUNE MYOPATHIES

The most consistent drug-related inflammatory or antibody-mediated myopathy is caused by D-penicillamine. This drug chelates copper and is used in the treatment of Wilson's disease. It is also used to treat other disorders including scleroderma, rheumatoid arthritis, and primary biliary cirrhosis. Adverse events include drug-induced polymyositis, indistinguishable from the spontaneous disease. The incidence of this inflammatory muscle disease is about 1%. Myasthenia gravis is also induced by d-penicillamine, with a higher incidence estimated at 7%. These disorders resolve with drug withdrawal, although immunosuppressive therapy may be warranted in severe cases.

Scattered reports of other drugs causing an inflammatory myopathy are rare and include a heterogeneous group of agents: cimetidine, phenytoin, procainamide, and propylthiouracil. In most cases, a cause-and-effect relationship is uncertain. A complication of interest was related

to L-tryptophan. In 1989 an epidemic of eosinophilia-myalgia syndrome (EMS) in the United States was caused by a contaminant in the product from one manufacturer. The product was withdrawn, and incidence of EMS diminished abruptly following this action.

OTHER DRUG-INDUCED MYOPATHIES

Certain drugs produce painless, largely proximal, muscle weakness. These drugs include the amphophilic cationic drugs (amiodarone, chloroquine, hydroxychloroquine) and antimicrotubular drugs (colchicine) (Table 43-11). Muscle biopsy can be useful in the identification of toxicity since autophagic vacuoles are prominent pathologic features of these toxins.

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CHAPTER 44

POLYMYOSITIS, DERMATOMYOSITIS, AND INCLUSION BODY MYOSITIS

Marinos C. Dalakas

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The inflammatory myopathies represent the largest group of acquired and potentially treatable causes of skeletal muscle weakness. They are classified into three major groups: polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM).

CLINICAL FEATURES

The prevalence of the inflammatory myopathies is estimated at 1 in 100,000. PM as a stand-alone entity is a rare disease affecting adults. DM affects both children and adults and women more often than men. IBM is three times more frequent in men than in women, more common in whites than blacks, and is most likely to affect persons >50 years of age.

These disorders present as progressive and symmetric muscle weakness except for IBM, which can have an asymmetric pattern. Patients usually report increasing difficulty with everyday tasks requiring the use of proximal muscles, such as getting up from a chair, climbing steps, stepping onto a curb, lifting objects, or combing hair. Fine-motor movements that depend on the strength of distal muscles, such as buttoning a shirt, sewing, knitting, or writing, are affected only late in the course of PM and DM, but fairly early in IBM. Falling is common in IBM because of early involvement of the quadriceps muscle with buckling of the knees. Ocular muscles are spared, even in advanced, untreated cases; if these muscles are affected, the diagnosis of inflammatory myopathy should be questioned. Facial muscles are unaffected in PM and DM, but mild facial muscle weakness is common in patients with IBM. In all forms of inflammatory myopathy, pharyngeal and neck-flexor muscles are often involved, causing dysphagia or difficulty in holding up the head (*head drop*). In advanced and rarely in acute cases, respiratory muscles may also be affected. Severe weakness, if untreated, is almost always associated with muscle wasting. Sensation remains normal. The tendon reflexes are preserved but may be absent in severely weakened or atrophied muscles, especially in IBM where atrophy of the quadriceps and the distal muscles is common. Myalgia and muscle tenderness may occur in a small number of patients, usually early in the disease, and particularly in DM associated with connective tissue disorders. Weakness in PM and DM progresses subacutely over a period of weeks or months and rarely acutely; by contrast, IBM progresses very slowly, over years, simulating a late-life muscular dystrophy (Chap. 43) or slowly progressive motor neuron disorder (Chap. 27).

SPECIFIC FEATURES

(Table 44-1)

TABLE 44-1

FEATURES ASSOCIATED WITH INFLAMMATORY MYOPATHIES

CHARACTERISTIC	POLYMYOSITIS	DERMATOMYOSITIS	INCLUSION BODY MYOSITIS
Age at onset	>18 years	Adulthood and childhood	>50 years
Familial association	No	No	Yes, in some cases
Extramuscular manifestations	Yes	Yes	Yes
Associated conditions			
Connective tissue diseases	Yes[a]	Scleroderma and mixed connective tissue disease (overlap syndromes)	Yes, in up to 20% of cases[a]
Systemic autoimmune diseases[b]	Frequent	Infrequent	Infrequent
Malignancy	No	Yes, in up to 15% of cases	No
Viruses	Yes[c]	Unproven	Yes[c]
Drugs[d]	Yes	Yes, rarely	No
Parasites and bacteria[e]	Yes	No	No

[a]Systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, systemic sclerosis, mixed connective tissue disease.
[b]Crohn's disease, vasculitis, sarcoidosis, primary biliary cirrhosis, adult celiac disease, chronic graft-versus-host disease, discoid lupus, ankylosing spondylitis, Behçet's syndrome, myasthenia gravis, acne fulminans, dermatitis herpetiformis, psoriasis, Hashimoto's disease, granulomatous diseases, agammaglobulinemia, monoclonal gammopathy, hypereosinophilic syndrome, Lyme disease, Kawasaki disease, autoimmune thrombocytopenia, hypergammaglobulinemic purpura, hereditary complement deficiency, IgA deficiency.
[c]HIV (human immunodeficiency virus) and HTLV-I (human T cell lymphotropic virus type I).
[d]Drugs include penicillamine (dermatomyositis and polymyositis), zidovudine (polymyositis), and contaminated tryptophan (dermatomyositis-like illness). Other myotoxic drugs may cause myopathy but not an inflammatory myopathy (see text for details).
[e]Parasites (protozoa, cestodes, nematodes), tropical and bacterial myositis (pyomyositis).

Polymyositis

The actual onset of PM is often not easily determined, and patients typically delay seeking medical advice for several months. This is in contrast to DM, in which the rash facilitates early recognition (see later). PM mimics many other myopathies and is a diagnosis of exclusion. It is a subacute inflammatory myopathy affecting adults, and rarely children, who *do not have* any of the following: rash, involvement of the extraocular and facial muscles, family history of a neuromuscular disease, history of exposure to myotoxic drugs or toxins, endocrinopathy, neurogenic disease, muscular dystrophy, biochemical muscle disorder (deficiency of a muscle enzyme), or IBM as excluded by muscle biopsy analysis (see later). As an isolated entity, PM is a rare (and overdiagnosed) disorder; more commonly, PM occurs in association with a systemic autoimmune or connective tissue disease, or with a known viral or bacterial infection. Drugs, especially d-penicillamine or zidovudine (AZT), may also produce an inflammatory myopathy similar to PM.

Dermatomyositis

DM is a distinctive entity identified by a characteristic rash accompanying, or more often preceding, muscle weakness. The rash may consist of a blue-purple discoloration on the upper eyelids with edema, a flat red rash on the face and upper trunk, and erythema of the knuckles with a raised violaceous scaly eruption (*Gottron's sign*). The erythematous rash can also occur on other body surfaces, including the knees, elbows, malleoli, neck and anterior chest (often in a *V sign*), or back and shoulders (*shawl sign*), and may worsen after sun exposure. In some patients the rash is pruritic, especially on the scalp, chest, and back. Dilated capillary loops at the base of the fingernails are also characteristic. The cuticles may be irregular, thickened, and distorted, and the lateral and palmar areas of the fingers may become rough and cracked, with irregular, "dirty" horizontal lines, resembling *mechanic's hands*. The weakness can be mild, moderate, or severe enough to lead to quadriparesis. At times, the muscle strength appears normal, hence the term *dermatomyositis sine myositis*. When muscle biopsy is performed in such cases, however, significant perivascular and perimysial inflammation is often seen.

DM usually occurs alone but may overlap with scleroderma and mixed connective tissue disease. Fasciitis and thickening of the skin, similar to that seen in chronic cases of DM, have occurred in patients with the *eosinophilia-myalgia syndrome* associated with the ingestion of contaminated l-tryptophan.

Inclusion Body Myositis

In patients ≥50 years, IBM is the most common of the inflammatory myopathies. It is often misdiagnosed as PM and is suspected only later when a patient with presumed PM does not respond to therapy. Weakness and atrophy

of the distal muscles, especially foot extensors and deep finger flexors, occur in almost all cases of IBM and may be a clue to early diagnosis. Some patients present with falls because their knees collapse due to early quadriceps weakness. Others present with weakness in the small muscles of the hands, especially finger flexors, and complain of inability to hold objects such as golf clubs or perform tasks such as turning keys or tying knots. On occasion, the weakness and accompanying atrophy can be asymmetric and selectively involve the quadriceps, iliopsoas, triceps, biceps, and finger flexors, resembling a lower motor neuron disease. Dysphagia is common, occurring in up to 60% of IBM patients, and may lead to episodes of choking. Sensory examination is generally normal; some patients have mildly diminished vibratory sensation at the ankles that presumably is age-related. The pattern of distal weakness, which superficially resembles motor neuron or peripheral nerve disease, results from the myopathic process affecting distal muscles selectively. Disease progression is slow but steady, and most patients require an assistive device such as cane, walker, or wheelchair within several years of onset.

In at least 20% of cases, IBM is associated with systemic autoimmune or connective tissue diseases. Familial aggregation of typical IBM may occur; such cases have been designated as *familial inflammatory IBM*. This disorder is distinct from *hereditary inclusion body myopathy* (h-IBM), which describes a heterogeneous group of recessive, and less frequently dominant, inherited syndromes; the h-IBMs are noninflammatory myopathies. A subset of h-IBM that spares the quadriceps muscles has emerged as a distinct entity. This disorder, originally described in Iranian Jews and now seen in many ethnic groups, is linked to chromosome 9p1 and results from mutations in the UDP-*N*-acetylglucosamine 2-epimerase/*N*-acetylmannosamine kinase (*GNE*) gene.

ASSOCIATED CLINICAL FINDINGS

Extramuscular Manifestations

These may be present to a varying degree in patients with PM or DM, and include:

1. *Systemic symptoms*, such as fever, malaise, weight loss, arthralgia, and Raynaud's phenomenon, especially when inflammatory myopathy is associated with a connective tissue disorder.
2. *Joint contractures,* mostly in DM and especially in children.
3. *Dysphagia and gastrointestinal symptoms,* due to involvement of oropharyngeal striated muscles and upper esophagus, especially in DM and IBM.
4. *Cardiac disturbances,* including atrioventricular conduction defects, tachyarrhythmias, dilated cardiomyopathy, a low ejection fraction, and congestive heart failure, may rarely occur, either from the disease itself or from hypertension associated with long-term use of glucocorticoids.
5. *Pulmonary dysfunction,* due to weakness of the thoracic muscles, interstitial lung disease, or drug-induced pneumonitis (e.g., from methotrexate), which may cause dyspnea, nonproductive cough, and aspiration pneumonia. Interstitial lung disease may precede myopathy or occur early in the disease and develops in up to 10% of patients with PM or DM, most of whom have antibodies to t-RNA synthetases, as described below.
6. *Subcutaneous calcifications,* in DM, sometimes extruding on the skin and causing ulcerations and infections.
7. *Arthralgias,* synovitis, or deforming arthropathy with subluxation in the interphalangeal joints can occur in some patients with DM and PM who have Jo-1 antibodies (see later).

Association with Malignancies

Although all the inflammatory myopathies can have a chance association with malignant lesions, especially in older age groups, the incidence of malignant conditions appears to be specifically increased only in patients with DM and not in those with PM or IBM. The most common tumors associated with DM are ovarian cancer, breast cancer, melanoma, colon cancer, and non-Hodgkin lymphoma. The extent of the search that should be conducted for an occult neoplasm in adults with DM depends on the clinical circumstances. Tumors in these patients are usually uncovered by abnormal findings in the medical history and physical examination and not through an extensive blind search. The weight of evidence argues against performing expensive, invasive, and nondirected tumor searches. A complete annual physical examination with pelvic, breast (mammogram, if indicated), and rectal examinations (with colonoscopy according to age and family history); urinalysis; complete blood count; blood chemistry tests; and a chest film should suffice in most cases. In Asians, nasopharyngeal cancer is common, and a careful examination of ears, nose, and throat is indicated.

Overlap Syndromes

These describe the association of inflammatory myopathies with connective tissue diseases. A well-characterized overlap syndrome occurs in patients with DM who also have manifestations of systemic sclerosis or mixed connective tissue disease, such as sclerotic thickening of the dermis, contractures, esophageal hypomotility, microangiopathy, and calcium deposits (Table 44-1). By contrast, signs of rheumatoid arthritis, systemic lupus erythematosus, or Sjögren's syndrome are very rare in patients with DM. Patients with the overlap syndrome of DM and systemic sclerosis may

have a specific antinuclear antibody, the anti-PM/Scl, directed against a nucleolar-protein complex.

PATHOGENESIS

An autoimmune etiology of the inflammatory myopathies is indirectly supported by an association with other autoimmune or connective tissue diseases; the presence of various autoantibodies; an association with specific major histocompatibility complex (MHC) genes; demonstration of T cell–mediated myocytotoxicity or complement-mediated microangiopathy; and a response to immunotherapy.

Autoantibodies and Immunogenetics

Various autoantibodies against nuclear antigens (antinuclear antibodies) and cytoplasmic antigens are found in up to 20% of patients with inflammatory myopathies. The antibodies to cytoplasmic antigens are directed against ribonucleoproteins involved in protein synthesis (anti-synthetases) or translational transport (anti-signal-recognition particles). The antibody directed against the histidyl-transfer RNA synthetase, called *anti-Jo-1*, accounts for 75% of all the anti-synthetases and is clinically useful because up to 80% of patients with anti-Jo-1 antibodies have interstitial lung disease. Some patients with the anti-Jo-1 antibody also have Raynaud's phenomenon, nonerosive arthritis, and the MHC molecules DR3 and DRw52. DR3 haplotypes (molecular designation DRB1*0301, DQB1*0201) occur in up to 75% of patients with PM and IBM, whereas in juvenile DM there is an increased frequency of DQA1*0501.

Immunopathologic Mechanisms

In DM, humoral immune mechanisms are implicated, resulting in a microangiopathy and muscle ischemia (**Fig. 44-1**). Endomysial inflammatory infiltrates are composed of B cells located in proximity to CD4 T cells, dendritic cells, and macrophages; there is a relative absence of lymphocytic invasion of nonnecrotic muscle fibers. Activation of the complement C5b-9 membranolytic attack complex is thought to be a critical early event that triggers release of proinflammatory cytokines and chemokines, induces expression of vascular cell adhesion molecule (VCAM) 1 and intracellular adhesion molecule (ICAM) 1 on endothelial cells, and facilitates migration of activated lymphoid cells to the perimysial and endomysial spaces. Necrosis of the endothelial cells, reduced numbers of endomysial capillaries, ischemia, and muscle-fiber destruction resembling microinfarcts occur. The remaining capillaries often have dilated lumens in response to the ischemic process. Larger intramuscular blood vessels may also be affected in the same pattern. Residual perifascicular atrophy reflects the endofascicular hypoperfusion that is prominent in the periphery of the muscle fascicles.

By contrast, in PM and IBM a mechanism of T cell–mediated cytotoxicity is likely. CD8 T cells, along with macrophages, initially surround and eventually invade and destroy healthy, nonnecrotic muscle fibers that aberrantly express class I MHC molecules. MHC-I expression, absent from the sarcolemma of normal muscle fibers, is probably induced by cytokines secreted by activated T cells and macrophages. The CD8/MHC-I complex is characteristic of PM and IBM; its detection can aid in confirming the histologic diagnosis of PM, as discussed below. The cytotoxic CD8 T cells contain perforin and granzyme granules directed towards the surface of the muscle fibers and capable of inducing myonecrosis. Analysis of T cell receptor molecules expressed by the infiltrating CD8 cells have revealed clonal expansion and conserved sequences in the antigen-binding region, both suggesting an antigen-driven T cell response. Whether the putative antigens are endogenous (e.g., muscle) or exogenous (e.g., viral) sequences is unknown. Viruses have not been identified within the muscle fibers. Co-stimulatory molecules and their counterreceptors, which are fundamental for T cell activation and antigen recognition, are strongly upregulated in PM and IBM. Key molecules involved in T cell–mediated cytotoxicity are depicted in **Fig. 44-2**.

The Role of Nonimmune Factors in IBM

In IBM, the presence of β-amyloid deposits within vacuolated muscle fibers and abnormal mitochondria with cytochrome oxidase–negative fibers suggest that, in addition to the autoimmune component, there is also a degenerative process. Similar to Alzheimer's disease, the amyloid deposits in IBM are immunoreactive against amyloid precursor protein (APP), chymotrypsin, apolipoprotein E, and phosphorylated tau, but it is unclear whether these deposits are directly pathogenic or represent secondary phenomena. The same is true for the mitochondrial abnormalities, which may also be secondary to the effects of aging or a bystander effect of upregulated cytokines. Expression of cytokines and upregulation of MHC class I by the muscle fibers may cause an endoplasmic reticulum stress response resulting in intracellular accumulation of misfolded glycoproteins and activation of nuclear factor κB (NFκB), leading to further cytokine activation.

Association with Viral Infections and the Role of Retroviruses

Several viruses, including coxsackieviruses, influenza, paramyxoviruses, mumps, cytomegalovirus, and Epstein-Barr virus, have been indirectly associated with myositis.

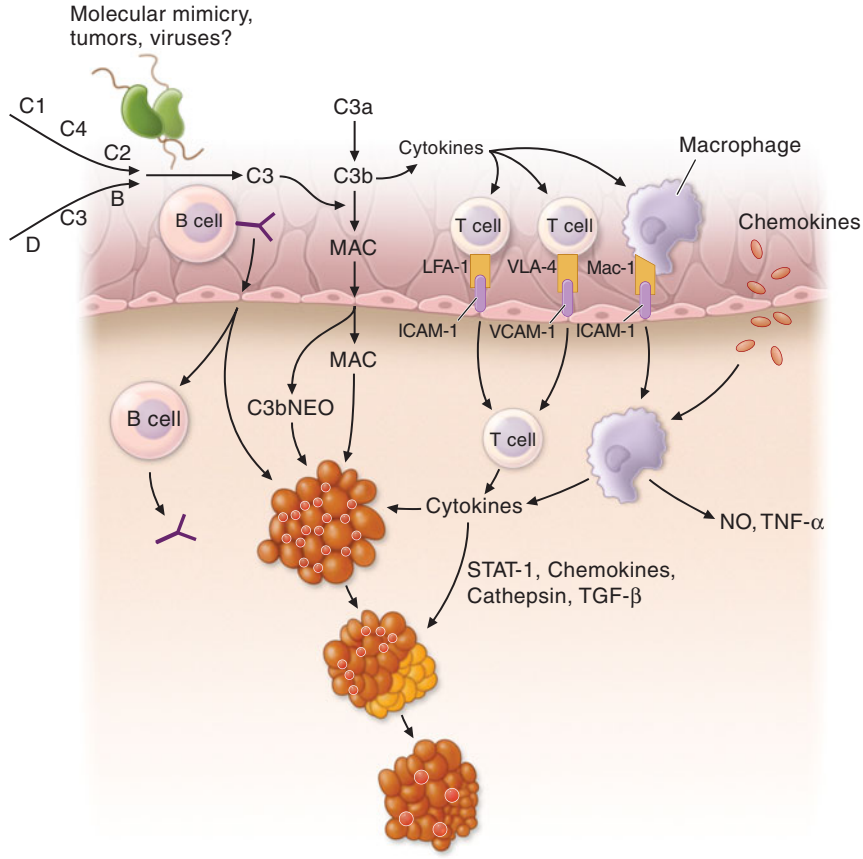

FIGURE 44-1

Immunopathogenesis of dermatomyositis. Activation of complement, possibly by autoantibodies (Y), against endothelial cells and formation of C3 via the classic or alternative pathway. Activated C3 leads to formation of C3b, C3bNEO, and membrane attack complexes (MAC), which are deposited in and around the endothelial cell wall of the endomysial capillaries. Deposition of MAC leads to destruction of capillaries, ischemia, or microinfarcts most prominent in the periphery of the fascicles, and perifascicular atrophy. B cells, CD4 T cells, and macrophages traffic from the circulation to the muscle. Endothelial expression of vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM) is induced by cytokines released by the mononuclear cells. Integrins, specifically very late activation antigen (VLA)-4 and leukocyte function-associated antigen (LFA)-1, bind VCAM and ICAM and promote T cell and macrophage infiltration of muscle through the endothelial cell wall.

For the coxsackieviruses, an autoimmune myositis triggered by molecular mimicry has been proposed because of structural homology between histidyl-transfer RNA synthetase that is the target of the Jo-1 antibody (see earlier) and genomic RNA of an animal picornavirus, the encephalomyocarditis virus. Sensitive polymerase chain reaction (PCR) studies, however, have repeatedly failed to confirm the presence of such viruses in muscle biopsies.

The best evidence of a viral connection in PM and IBM is with the retroviruses. Some individuals infected with HIV or with human T cell lymphotropic virus I (HTLV-I) develop PM or IBM; a similar disorder has been described in nonhuman primates infected with the simian immunodeficiency virus. The inflammatory myopathy may occur as the initial manifestation of a retroviral infection, or myositis may develop later in the disease course. Retroviral antigens have been detected only in occasional endomysial macrophages and not within the muscle fibers themselves, suggesting that persistent infection and viral replication within the muscle does not occur. Histologic findings are identical to retroviral-negative PM or IBM. The infiltrating T cells in the muscle are clonally driven and a number of them are retroviral-specific. This disorder should be distinguished from a toxic myopathy related to long-term therapy with AZT, characterized by fatigue, myalgia, mild muscle weakness, and mild elevation of creatine kinase (CK). AZT-induced myopathy, which generally improves when the drug is discontinued, is a mitochondrial disorder characterized histologically by "ragged-red" fibers. AZT inhibits γ-DNA polymerase, an enzyme found solely in the mitochondrial matrix.

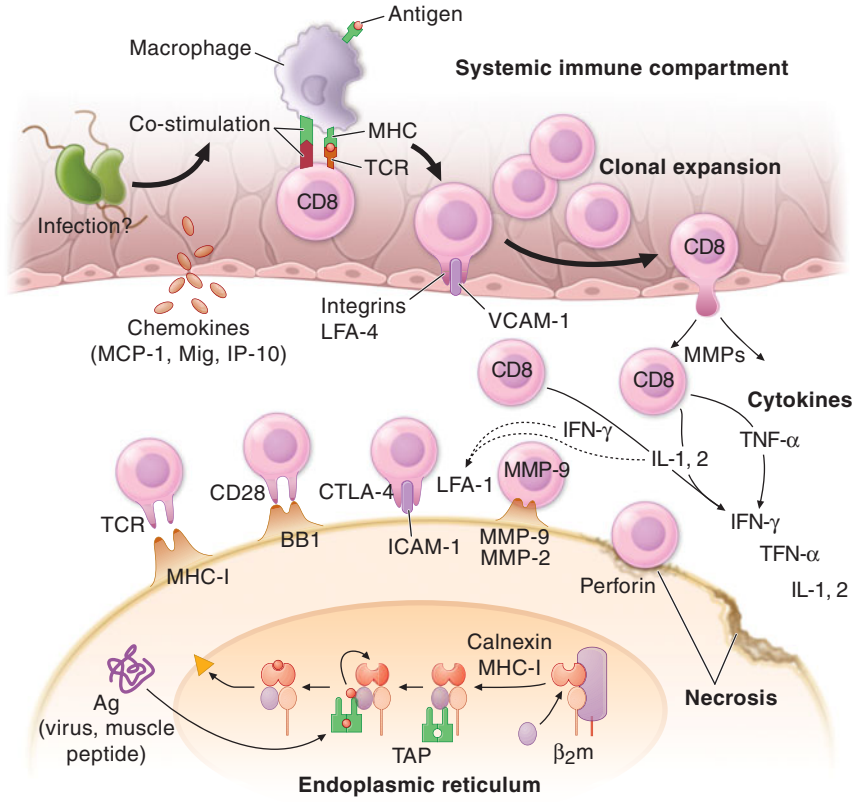

FIGURE 44-2

Cell-mediated mechanisms of muscle damage in polymyositis (PM) and inclusion body myositis (IBM). Antigen-specific CD8 cells are expanded in the periphery, cross the endothelial barrier, and bind directly to muscle fibers via T cell receptor (TCR) molecules that recognize aberrantly expressed MHC-I. Engagement of co-stimulatory molecules (BB1 and ICOSL) with their ligands (CD28, CTLA-4, and ICOS) along with ICAM-1/LFA-1, stabilize the CD8–muscle fiber interaction. Metalloproteinases (MMP) facilitate the migration of T cells and their attachment to the muscle surface. Muscle fiber necrosis occurs via perforin granules released by the autoaggressive T cells. A direct myocytotoxic effect exerted by the cytokines interferon (IFN) γ, interleukin (IL) 1, or tumor necrosis factor (TNF) α may also play a role. Death of the muscle fiber is mediated by necrosis. MHC class I molecules consist of a heavy chain and a light chain [β_2 microglobulin (β_2m)] complexed with an antigenic peptide that is transported into the endoplasmic reticulum by TAP proteins.

DIFFERENTIAL DIAGNOSIS

The clinical picture of the typical skin rash and proximal or diffuse muscle weakness has few causes other than DM. However, proximal muscle weakness without skin involvement can be due to many conditions other than PM or IBM.

Subacute or Chronic Progressive Muscle Weakness

This may be due to denervating conditions such as the spinal muscular atrophies or amyotrophic lateral sclerosis (Chap. 27). In addition to the muscle weakness, upper motor neuron signs in the latter and signs of denervation detected by electromyography (EMG) aid in the diagnosis. The muscular dystrophies (Chap. 43) may be additional considerations; however, these disorders usually develop over years rather than weeks or months and rarely present after the age of 30. It may be difficult, even with a muscle biopsy, to distinguish chronic PM from a rapidly advancing muscular dystrophy. This is particularly true of facioscapulohumeral muscular dystrophy, dysferlin myopathy, and the dystrophinopathies where inflammatory cell infiltration is often found early in the disease. Such doubtful cases should always be given an adequate trial of glucocorticoid therapy and undergo genetic testing to exclude muscular dystrophy. Identification of the MHC/CD8 lesion by muscle biopsy is helpful to identify cases of PM. Some metabolic myopathies, including glycogen storage disease due to myophosphorylase or acid maltase deficiency, lipid storage myopathies due to carnitine deficiency, and mitochondrial diseases produce weakness that is often associated with other characteristic clinical signs; diagnosis rests upon histochemical and biochemical studies of the muscle biopsy. The endocrine myopathies such as

those due to hypercorticosteroidism, hyper- and hypothyroidism, and hyper- and hypoparathyroidism require the appropriate laboratory investigations for diagnosis. Muscle wasting in patients with an underlying neoplasm may be due to disuse, cachexia, or rarely to a paraneoplastic neuromyopathy (Chap. 39).

Diseases of the neuromuscular junction, including myasthenia gravis or the Lambert-Eaton myasthenic syndrome, cause fatiguing weakness that also affects ocular and other cranial muscles (Chap. 42). Repetitive nerve stimulation and single-fiber EMG studies aid in diagnosis.

Acute Muscle Weakness

This may be caused by an acute neuropathy such as Guillain-Barré syndrome (Chap. 41), transverse myelitis (Chap. 30), a neurotoxin, or a neurotropic viral infection such as poliomyelitis or West Nile virus (Chap. 35). When acute weakness is associated with painful muscle cramps, rhabdomyolysis, and myoglobinuria, it may be due to a viral infection or a metabolic disorder such as myophosphorylase deficiency or carnitine palmitoyltransferase deficiency (Chap. 43). Several animal parasites, including protozoa (*toxoplasma*, *trypanosoma*), cestodes (cysticerci), and nematodes (trichinae), may produce a focal or diffuse inflammatory myopathy known as *parasitic polymyositis*. *Staphylococcus aureus*, *Yersinia*, *Streptococcus*, or anaerobic bacteria may produce a suppurative myositis, known as *tropical polymyositis*, or *pyomyositis*. Pyomyositis, previously rare in the west, is now occasionally seen in AIDS patients. Other bacteria, such as *Borrelia burgdorferi* (Lyme disease) and *Legionella pneumophila* (Legionnaire's disease) may infrequently cause myositis.

Patients with periodic paralysis experience recurrent episodes of acute muscle weakness without pain, always beginning in childhood. Chronic alcoholics may develop painful myopathy with myoglobinuria after a bout of heavy drinking. Acute painless muscle weakness with myoglobinuria may occur with prolonged hypokalemia, or hypophosphatemia and hypomagnesemia, usually in chronic alcoholics or in patients on nasogastric suction receiving parenteral hyperalimentation.

Myofasciitis

This distinctive inflammatory disorder affecting muscle and fascia presents as diffuse myalgias, skin induration, fatigue, and mild muscle weakness; mild elevations of serum CK are usually present. The most common form is eosinophilic myofasciitis characterized by peripheral blood eosinophilia and eosinophilic infiltrates in the endomysial tissue. In some patients, the eosinophilic myositis/fasciitis occurs in the context of parasitic infections, vasculitis, mixed connective tissue disease, hypereosinophilic syndrome, or toxic exposures (e.g., toxic oil syndrome, contaminated l-tryptophan) or with mutations in the calpain gene. A distinct subset of myofasciitis is characterized by pronounced infiltration of the connective tissue around the muscle by sheets of periodic acid–Schiff-positive macrophages and occasional CD8 T cells (macrophagic myofasciitis). Such histologic involvement is focal and limited to sites of previous vaccinations, which may have been administered months or years earlier. This disorder, which to date has not been observed outside of France, has been linked to an aluminum-containing substrate in vaccines. Most patients respond to glucocorticoid therapy, and the overall prognosis seems favorable.

Necrotizing Myositis

This is an increasingly recognized entity that has distinct features, even though it is often labeled as PM. It presents often in the fall or winter as an acute or subacute onset of symmetric muscle weakness; CK is typically extremely high. The weakness can be severe. Coexisting interstitial lung disease and cardiomyopathy may be present. The disorder may develop after a viral infection or in association with cancer. Some patients have antibodies against signal recognition particle (SRP). The muscle biopsy demonstrates necrotic fibers infiltrated by macrophages but only rare, if any, T cell infiltrates. Muscle MHC-I expression is only slightly and focally upregulated. The capillaries may be swollen with hyalinization, thickening of the capillary wall, and deposition of complement. Some patients respond to immunotherapy, but others are resistant.

Drug-Induced Myopathies

D-Penicillamine and procainamide may produce a true myositis resembling PM, and a DM-like illness had been associated with the contaminated preparations of l-tryptophan. As noted above, AZT causes a mitochondrial myopathy. Other drugs may elicit a toxic noninflammatory myopathy that is histologically different from DM, PM, or IBM. These include cholesterol-lowering agents such as clofibrate, lovastatin, simvastatin, or pravastatin, especially when combined with cyclosporine or gemfibrozil. Rhabdomyolysis and myoglobinuria have been rarely associated with amphotericin B, ε-aminocaproic acid, fenfluramine, heroin, and phencyclidine. The use of amiodarone, chloroquine, colchicine, carbimazole, emetine, etretinate, ipecac syrup, chronic laxative or licorice use resulting in hypokalemia, and glucocorticoids or growth hormone administration have also been associated with myopathic muscle weakness. Some neuromuscular blocking agents such as pancuronium, in combination with glucocorticoids, may cause an acute critical illness myopathy. A careful drug history is essential for diagnosis of these

drug-induced myopathies, which do not require immunosuppressive therapy.

"Weakness" Due to Muscle Pain and Muscle Tenderness

A number of conditions including *polymyalgia rheumatica* and arthritic disorders of adjacent joints may enter into the differential diagnosis of inflammatory myopathy, even though they do not cause myositis. The muscle biopsy is either normal or discloses type II muscle fiber atrophy. Patients with *fibrositis* and *fibromyalgia* complain of focal or diffuse muscle tenderness, fatigue, and aching, which is sometimes poorly differentiated from joint pain. Some patients, however, have muscle tenderness, painful muscles on movement, and signs suggestive of a collagen vascular disorder, such as an increased erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, or rheumatoid factor, along with modest elevation of the serum CK and aldolase. They demonstrate a "give-way" pattern of weakness with difficulty sustaining effort but not true muscle weakness. The muscle biopsy is usually normal or nonspecific. Many such patients show some response to nonsteroidal anti-inflammatory agents or glucocorticoids, though most continue to have indolent complaints. An indolent fasciitis in the setting of an ill-defined connective tissue disorder may be present, and these patients should not be labeled as having a psychosomatic disorder. *Chronic fatigue syndrome*, which may follow a viral infection, can present with debilitating fatigue, fever, sore throat, painful lymphadenopathy, myalgia, arthralgia, sleep disorder, and headache (Chap. 47). These patients do not have muscle weakness, and the muscle biopsy is normal.

DIAGNOSIS

The clinically suspected diagnosis of PM, DM, or IBM is confirmed by examining the serum muscle enzymes, EMG findings, and muscle biopsy (**Table 44-2**).

The most sensitive enzyme is CK, which in active disease can be elevated as much as 50-fold. Although the CK level usually parallels disease activity, it can be normal in some patients with active IBM or DM, especially

TABLE 44-2

CRITERIA FOR DIAGNOSIS OF INFLAMMATORY MYOPATHIES

	POLYMYOSITIS			
CRITERION	**DEFINITE**	**PROBABLE**	**DERMATOMYOSITIS**	**INCLUSION BODY MYOSITIS**
Myopathic muscle weakness[a]	Yes	Yes	Yes[b]	Yes; slow onset, early involvement of distal muscles, frequent falls
Electromyographic findings	Myopathic	Myopathic	Myopathic	Myopathic with mixed potentials
Muscle enzymes	Elevated (up to 50-fold)	Elevated (up to 50-fold)	Elevated (up to 50-fold) or normal	Elevated (up to 10-fold) or normal
Muscle biopsy findings[c]	"Primary" inflammation with the CD8/MHC-I complex and no vacuoles	Ubiquitous MCH-I expression but minimal inflammation and no vacuoles[d]	Perifascicular, perimysial, or perivascular infiltrates, perifascicular atrophy	Primary inflammation with CD8/MHC-I complex; vacuolated fibers with β-amyloid deposits; cytochrome oxygenase–negative fibers; signs of chronic myopathy[e]
Rash or calcinosis	Absent	Absent	Present[f]	Absent

[a]Myopathic muscle weakness, affecting proximal muscles more than distal ones and sparing eye and facial muscles, is characterized by a subacute onset (weeks to months) and rapid progression in patients who have no family history of neuromuscular disease, no endocrinopathy, no exposure to myotoxic drugs or toxins, and no biochemical muscle disease (excluded on the basis of muscle-biopsy findings).
[b]In some cases with the typical rash, the muscle strength is seemingly normal (dermatomyositis sine myositis); these patients often have new onset of easy fatigue and reduced endurance. Careful muscle testing may reveal mild muscle weakness.
[c]See text for details.
[d]An adequate trial of prednisone or other immunosuppressive drugs is warranted in probable cases. If, in retrospect, the disease is unresponsive to therapy, another muscle biopsy should be considered to exclude other diseases or possible evolution in inclusion body myositis.
[e]If the muscle biopsy does not contain vacuolated fibers but shows chronic myopathy with hypertrophic fibers, primary inflammation with the CD8/MHC-I complex and cytochrome oxygenase–negative fibers, the diagnosis is probable inclusion body myositis.
[f]If rash is absent but muscle biopsy findings are characteristic of dermatomyositis, the diagnosis is probable DM.

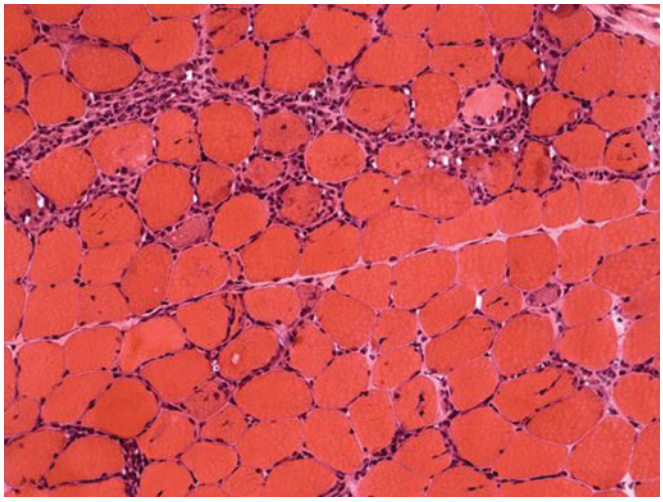

FIGURE 44-3
Cross section of a muscle biopsy from a patient with polymyositis demonstrates scattered inflammatory foci with lymphocytes invading or surrounding muscle fibers. Note lack of chronic myopathic features (increased connective tissue, atrophic or hypertrophic fibers) as seen in inclusion body myositis.

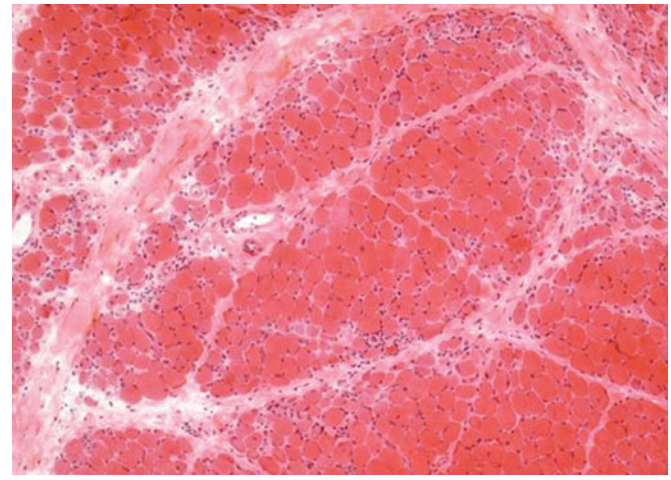

FIGURE 44-4
Cross section of a muscle biopsy from a patient with dermatomyositis demonstrates atrophy of the fibers at the periphery of the fascicle (perifascicular atrophy).

when associated with a connective tissue disease. The CK is always elevated in patients with active PM. Along with the CK, the serum glutamic-oxaloacetic and glutamate pyruvate transaminases, lactate dehydrogenase, and aldolase may be elevated.

Needle EMG shows myopathic potentials characterized by short-duration, low-amplitude polyphasic units on voluntary activation and increased spontaneous activity with fibrillations, complex repetitive discharges, and positive sharp waves. Mixed potentials (polyphasic units of short and long duration) indicating a chronic process and muscle fiber regeneration are often present in IBM. These EMG findings are not diagnostic of an inflammatory myopathy but are useful to identify the presence of active or chronic myopathy and to exclude neurogenic disorders.

MRI is not routinely used for the diagnosis of PM, DM, or IBM. However, it may guide the location of the muscle biopsy in certain clinical settings.

Muscle biopsy is the definitive test for establishing the diagnosis of inflammatory myopathy and for excluding other neuromuscular diseases. Inflammation is the histologic hallmark for these diseases; however, additional features are characteristic of each subtype (**Figs. 44-3, 44-4**, and **44-5**).

In PM the inflammation is *primary*, a term used to indicate that T cell infiltrates, located primarily within the muscle fascicles (endomysially), surround individual, healthy muscle fibers and result in phagocytosis and necrosis (Fig. 44-3). The MHC-I molecule is ubiquitously expressed on the sarcolemma, even in fibers not invaded by CD8+ cells. The CD8/MHC-I lesion is now fundamental for confirming or establishing the diagnosis and to exclude disorders with secondary, nonspecific, inflammation. When the disease is chronic, connective tissue is increased and may react positively with alkaline phosphatase.

In DM the endomysial inflammation is predominantly perivascular or in the interfascicular septae and around, rather than within, the muscle fascicles (Fig. 44-4). The intramuscular blood vessels show endothelial hyperplasia with tubuloreticular profiles, fibrin thrombi, and obliteration of capillaries. The muscle fibers undergo necrosis, degeneration, and phagocytosis, often in groups involving a portion of a muscle fasciculus in a wedge-like shape or at the periphery of the fascicle, due to microinfarcts within the muscle. This results in perifascicular atrophy, characterized by 2–10 layers of atrophic fibers at the periphery of the fascicles. The presence of perifascicular atrophy is diagnostic of DM, *even in the absence of inflammation*.

In IBM (Fig. 44-5), there is endomysial inflammation with T cells invading MHC-I-expressing nonvacuolated muscle fibers; basophilic granular deposits distributed around the edge of slitlike vacuoles (rimmed vacuoles); loss of fibers, replaced by fat and connective tissue, hypertrophic fibers, and angulated or round fibers; eosinophilic cytoplasmic inclusions; abnormal mitochondria characterized by the presence of ragged-red fibers or cytochrome oxidase–negative fibers; amyloid deposits within or next to the vacuoles; and filamentous inclusions seen by electron microscopy in the vicinity of the rimmed vacuoles.

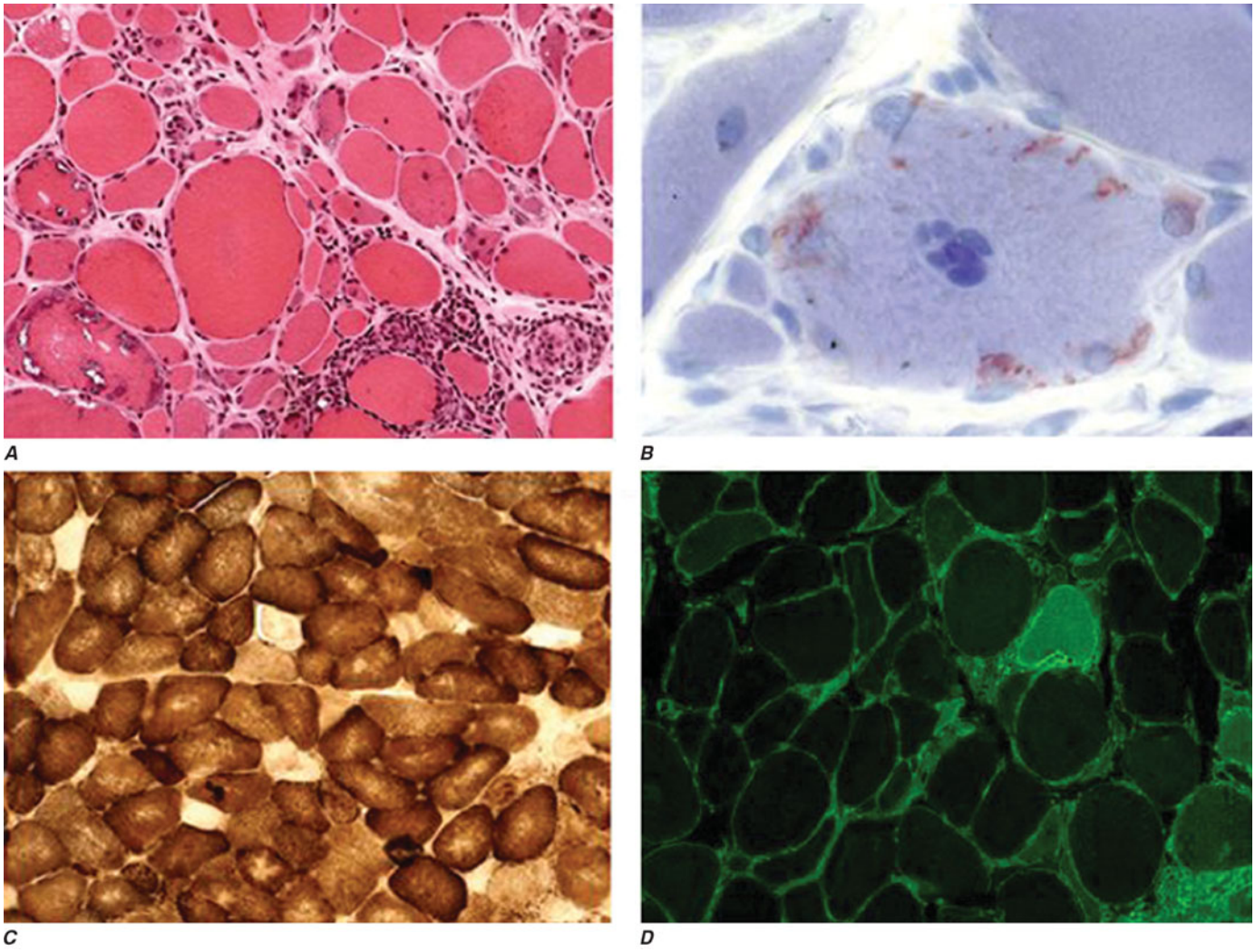

FIGURE 44-5

Cross sections of a muscle biopsy from a patient with inclusion body myositis demonstrate the typical features of vacuoles with lymphocytic infiltrates surrounding nonvacuolated or necrotic fibers (*A*), tiny endomysial deposits of amyloid visualized with crystal violet (*B*), cytochrome oxidase-negative fibers, indicative of mitochondrial dysfunction (*C*), and ubiquitous MHC-I expression at the periphery of all fibers (*D*).

Rx Treatment: INFLAMMATORY MYOPATHIES

The goal of therapy is to improve muscle strength, thereby improving function in activities of daily living, and ameliorate the extramuscular manifestations (rash, dysphagia, dyspnea, fever). When strength improves, the serum CK falls concurrently; however, the reverse is not always true. Unfortunately, there is a common tendency to "chase" or treat the CK level instead of the muscle weakness, a practice that has led to prolonged and unnecessary use of immunosuppressive drugs and erroneous assessment of their efficacy. It is prudent to discontinue these drugs if, after an adequate trial, there is no objective improvement in muscle strength whether or not CK levels are reduced. Agents used in the treatment of PM and DM include:

1. *Glucocorticoids.* Oral prednisone is the initial treatment of choice; the effectiveness and side effects of this therapy determine the future need for stronger immunosuppressive drugs. High-dose prednisone, at least 1 mg/kg per day, is initiated as early in the disease as possible. After 3–4 weeks, prednisone is tapered slowly over a period of 10 weeks to 1 mg/kg every other day. If there is evidence of efficacy and no serious side effects, the dosage is then further reduced by 5 or 10 mg every 3–4 weeks until the lowest possible dose that controls the disease is reached. The efficacy of prednisone is determined by an objective increase in muscle strength and activities of daily living, which almost always occurs by the third month of therapy. A feeling of increased energy or a reduction of the CK level without a concomitant

increase in muscle strength is not a reliable sign of improvement. If prednisone provides no objective benefit after ~3 months of high-dose therapy, the disease is probably unresponsive to the drug and tapering should be accelerated while the next-in-line immunosuppressive drug is started. Although controlled trials have not been performed, almost all patients with true PM or DM respond to glucocorticoids to *some degree and for some period of time*; in general, DM responds better than PM.

The long-term use of prednisone may cause increased weakness associated with a normal or unchanged CK level; this effect is referred to as *steroid myopathy*. In a patient who previously responded to high doses of prednisone, the development of new weakness may be related to steroid myopathy or to disease activity that either will respond to a higher dose of glucocorticoids or has become glucocorticoid-resistant. In uncertain cases, the prednisone dosage can be steadily increased or decreased as desired: the cause of the weakness is usually evident in 2–8 weeks.

2. *Other immunosuppressive* drugs. Approximately 75% of patients ultimately require additional treatment. This occurs when a patient fails to respond adequately to glucocorticoids after a 3-month trial, the patient becomes glucocorticoid-resistant, glucocorticoid-related side effects appear, attempts to lower the prednisone dose repeatedly result in a new relapse, or rapidly progressive disease with evolving severe weakness and respiratory failure develops.

   The following drugs are commonly used but have never been tested in controlled studies: (1) *Azathioprine* is well tolerated, has few side effects, and appears to be as effective for long-term therapy as other drugs. The dose is up to 3 mg/kg daily. (2) *Methotrexate* has a faster onset of action than azathioprine. It is given orally starting at 7.5 mg weekly for the first 3 weeks (2.5 mg every 12 h for 3 doses), with gradual dose escalation by 2.5 mg per week to a total of 25 mg weekly. A rare side effect is methotrexate pneumonitis, which can be difficult to distinguish from the interstitial lung disease of the primary myopathy associated with Jo-1 antibodies (described above). (3) *Mycophenolate mofetil* also has a faster onset of action than azathioprine. At doses up to 2.5 mg/d, it is well tolerated and appears promising for long-term use. (4) Monoclonal anti-CD20 (rituximab) has been shown in a small uncontrolled series to benefit patients with DM. (5) *Cyclosporine* has inconsistent and mild benefit. (6) *Cyclophosphamide* (0.5–1 g IV monthly for 6 months) has limited success and significant toxicity. (7) Tacrolimus (formerly known as FK506) has been effective in some difficult cases of PM.

3. *Immunomodulation*. In a controlled trial of patients with refractory DM, intravenous immunoglobulin (IVIg) improved not only strength and rash but also the underlying immunopathology. The benefit is often short-lived (≤8 weeks); repeated infusions every 6–8 weeks are generally required to maintain improvement. A dose of 2 g/kg divided over 2–5 days per course is recommended. Uncontrolled observations suggest that IVIg may also be beneficial for patients with PM. Neither plasmapheresis nor leukapheresis appears to be effective in PM and DM.

The following sequential empirical approach to the treatment of PM and DM is suggested: *Step 1*: high-dose prednisone; *Step 2*: azathioprine, mycophenolate, or methotrexate for steroid-sparing effect; *Step 3*: IVIg; *Step 4*: a trial, with guarded optimism, of one of the following agents, chosen according to the patient's age, degree of disability, tolerance, experience with the drug, and general health: rituximab, cyclosporine, cyclophosphamide, or tacrolimus. Patients with interstitial lung disease may benefit from aggressive treatment with cyclophosphamide or tacrolimus.

A patient with presumed PM who has not responded to any form of immunotherapy most likely has IBM or another disease, usually a metabolic myopathy, a muscular dystrophy, a drug-induced myopathy, or an endocrinopathy. In these cases, a repeat muscle biopsy and a renewed search for another cause of the myopathy is indicated.

Calcinosis, a manifestation of DM, is difficult to treat; however, new calcium deposits may be prevented if the primary disease responds to the available therapies. Bisphosphonates, aluminum hydroxide, probenecid, colchicine, low doses of warfarin, calcium blockers, and surgical excision have all been tried without success.

IBM is generally resistant to immunosuppressive therapies. Prednisone together with azathioprine or methotrexate is often tried for a few months in newly diagnosed patients, although results are generally disappointing. Because occasional patients may feel subjectively weaker after these drugs are discontinued, some clinicians prefer to maintain some patients on low-dose, every-other-day prednisone or weekly methotrexate in an effort to slow disease progression, even though there is no objective evidence or controlled study to support this practice. In two controlled studies of IVIg in IBM, minimal benefit in up to 30% of patients was found; the strength gains, however, were not of sufficient magnitude to justify its routine use. Another trial of IVIg combined with prednisone was ineffective. Nonetheless, many experts believe that a 2- to 3-month trial with IVIg may be reasonable for selected patients with IBM who experience rapid progression of muscle weakness or choking episodes due to worsening dysphagia.

PROGNOSIS

The 5-year survival rate for treated patients with PM and DM is ~95% and the 10-year survival 84%; death is usually due to pulmonary, cardiac, or other systemic complications. Patients severely affected at presentation or treated after long delays, those with severe dysphagia or respiratory difficulties, older patients, and those with associated cancer have a worse prognosis. DM responds more favorably to therapy than PM and thus has a better prognosis. Most patients improve with therapy, and many make a full functional recovery, which is often sustained with maintenance therapy. Up to 30% may be left with some residual muscle weakness. Relapses may occur at any time.

IBM has the least favorable prognosis of the inflammatory myopathies. Most patients will require the use of an assistive device such as a cane, walker, or wheelchair within 5–10 years of onset. In general, the older the age of onset in IBM, the more rapidly progressive is the course.

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CHAPTER 45
SPECIAL ISSUES IN INPATIENT NEUROLOGIC CONSULTATION

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Inpatient neurologic consultations usually involve questions about specific disease processes or prognostication after various cerebral injuries. Common reasons for neurologic consultation include stroke (Chap. 21), seizures (Chap. 20), altered mental status (Chap. 13), headache (Chap. 6), and management of coma and other critical conditions (Chaps. 14 and 22). This chapter focuses on additional common reasons for consultation that are not addressed elsewhere in the text.

CONSULTATIONS REGARDING CENTRAL NERVOUS SYSTEM DYSFUNCTION

HYPERPERFUSION STATES

A group of neurologic disorders shares the common feature of hyperperfusion playing a key role in pathogenesis. These seemingly diverse syndromes include hypertensive encephalopathy, eclampsia, post-carotid endarterectomy syndrome, and toxicity from calcineurin-inhibitor medications. Modern imaging techniques and experimental models suggest that vasogenic edema is usually the primary process leading to neurologic dysfunction; therefore prompt recognition and management of this condition should allow for clinical recovery if superimposed hemorrhage or infarction has not occurred.

The brain's autoregulatory capability successfully maintains a fairly stable cerebral blood flow in adults despite alterations in systemic mean arterial pressure (MAP) ranging from 50–150 mm Hg. In patients with chronic hypertension, this cerebral autoregulation curve is shifted, resulting in autoregulation working over a much higher range of pressures (e.g., 70–175 mmHg). In these hypertensive patients, cerebral blood flow is kept steady at higher MAP, but a rapid lowering of pressure can more easily lead to ischemia on the lower end of the autoregulatory curve. This autoregulatory phenomenon is achieved through both myogenic and neurogenic influences causing small arterioles to contract and dilate. When the systemic blood pressure exceeds the limits of this mechanism, breakthrough of autoregulation occurs, resulting in hyperperfusion via increased cerebral blood flow, capillary leakage into the interstitium, and resulting edema. The predilection of all of the hyperperfusion disorders to affect the posterior rather than anterior portions of the brain may be due to a lower threshold for autoregulatory breakthrough in the posterior circulation.

TABLE 45-1

SOME COMMON ETIOLOGIES OF HYPERPERFUSION SYNDROME

Disorders in which increased capillary pressure dominates the pathophysiology
Hypertensive encephalopathy, including secondary causes such as renovascular hypertension, pheochromocytoma, cocaine use, etc.
Post-carotid endarterectomy syndrome
Preeclampsia/eclampsia
High-altitude cerebral edema
Disorders in which endothelial dysfunction dominates the pathophysiology
Calcineurin-inhibitor toxicity
Chemotherapeutic agent toxicity (e.g., cytarabine, azathioprine, 5-fluorouracil, cisplatin, methotrexate)
Glucocorticoids
Erythropoietin
HELLP syndrome (*h*emolysis, elevated *l*iver enzyme levels, *l*ow *p*latelet count)
Thrombotic thrombocytopenic purpura (TTP)
Hemolytic uremic syndrome (HUS)
Systemic lupus erythematosus (SLE)
Wegener's granulomatosis

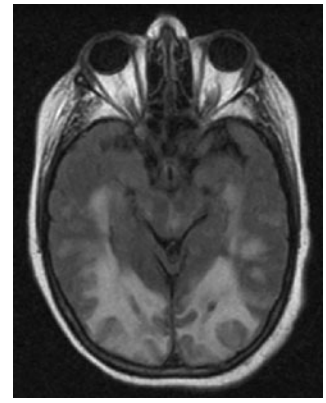

FIGURE 45-1

Axial fluid-attenuated inversion recovery (FLAIR) MRI of the brain in a patient taking cyclosporine after liver transplantation who presented with seizures, headache, and cortical blindness. Increased signal is seen bilaterally in the occipital lobes predominantly involving the white matter, consistent with a hyperperfusion state secondary to calcineurin-inhibitor exposure.

Although elevated or relatively elevated blood pressure is common in many of these disorders, some hyperperfusion states such as calcineurin-inhibitor toxicity occur with no apparent pressure rise. In these cases, vasogenic edema is likely due primarily to dysfunction of the capillary endothelium itself, leading to breakdown of the blood-brain barrier. It is useful to separate disorders of hyperperfusion into those caused primarily by increased pressure and those due mostly to endothelial dysfunction from a toxic or autoimmune etiology (Table 45-1). In reality, both of these pathophysiologic processes are likely playing some role in each of these disorders.

The clinical presentation of the hyperperfusion syndromes is similar, with prominent headaches, seizures, or focal deficits. Headaches have no specific characteristics, range from mild to severe, and may be accompanied by alterations in consciousness ranging from confusion to coma. Seizures may be present, and these can be of multiple types depending on the severity and location of the edema. Nonconvulsive seizures have been described in hyperperfusion states; therefore a low threshold for obtaining an electroencephalogram (EEG) in these patients should be maintained. The typical focal deficit in hyperperfusion states is cortical visual loss, given the tendency of the process to involve the occipital lobes. However, any focal deficit can occur depending on the area affected, as evidenced by patients who, after carotid endarterectomy, exhibit neurologic dysfunction in the ipsilateral newly reperfused hemisphere. In conditions where increased cerebral blood flow plays a role, examination of the inpatient vital signs record will usually reveal a systemic blood pressure that is increased above baseline. It appears as if the rapidity of rise rather than the absolute value of pressure is the most important risk factor.

The diagnosis in all of these conditions is clinical. The symptoms of these disorders are common and nonspecific, so a long differential diagnosis should be entertained, including consideration of other causes of confusion, focal deficits, headache, and seizures. MRI has improved the ability of clinicians to diagnose hyperperfusion syndromes, although cases have been reported with normal imaging. Patients classically exhibit the high T2 signal of edema primarily in the posterior occipital lobes, not respecting any single vascular territory (Fig. 45-1). Diffusion-weighted images are typically normal, emphasizing the vasogenic rather than cytotoxic nature of this edema. Imaging with CT is less sensitive but may show a pattern of patchy hypodensity in the involved territory. Previously this classic radiographic appearance had been termed *reversible posterior leukoencephalopathy* (RPLE). However, this term has fallen out of favor because none of its elements are completely accurate: the radiographic and clinical changes are not always reversible, the territory involved is not uniquely posterior, and gray matter may be affected as well, rather than purely white matter as the word "leukoencephalopathy" intimates. Other ancillary studies such as cerebrospinal fluid (CSF) analysis often yield nonspecific results. It should be noted that many of the substances that have been implicated, such as cyclosporine, can cause this syndrome even at low doses or after years of treatment. Therefore, normal serum levels of these medications do not exclude them as inciting agents.

In cases of hyperperfusion syndromes, treatment should commence urgently once the diagnosis is considered. Hypertension plays a key role commonly, and judicious lowering of the blood pressure with IV agents such as labetolol or nicardipine is advised along with continuous cardiac and blood pressure monitoring, often through an arterial line. It is reasonable to lower mean arterial pressure by ~20% initially, as further lowering of the pressure may cause secondary ischemia as pressure drops below the lower range of the patient's autoregulatory capability. In cases where there is an identified cause of the syndrome, these etiologies should be treated promptly, including discontinuation of offending substances such as calcineurin inhibitors in toxic processes, treatment of immune-mediated disorders such as thrombotic thrombocytopenic purpura (TTP), and prompt delivery of the fetus in eclampsia. Seizures must be identified and controlled, often necessitating continuous EEG monitoring. Anticonvulsants are effective, but in the special case of eclampsia, there is good evidence to support the use of magnesium sulfate for seizure control.

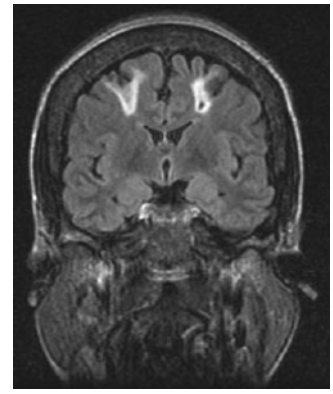

FIGURE 45-2

Coronal fluid-attenuated inversion recovery (FLAIR) MRI of the brain in a patient presenting with altered mental status after an episode of hypotension during coronary artery bypass grafting (CABG). Increased signal is seen in the border zones bilaterally between the middle cerebral artery and anterior cerebral artery territories. Diffusion-weighted MRI sequences demonstrated restricted diffusion in these same locations, suggesting acute infarction.

POST-CARDIAC BYPASS BRAIN INJURY

Central nervous system (CNS) injuries following open heart or coronary artery bypass grafting (CABG) surgery are common and include acute encephalopathy, stroke, and a chronic syndrome of cognitive impairment, which is now increasingly recognized. Hypoperfusion and embolic disease are frequently involved in the pathogenesis of these syndromes, although multiple mechanisms may be involved in these critically ill patients who are at risk for various metabolic and polypharmaceutical complications.

The frequency of hypoxic injury secondary to inadequate blood flow intraoperatively has been markedly decreased by the use of modern surgical and anesthetic techniques. Despite these advances, some patients still experience neurologic complications from cerebral hypoperfusion or may suffer focal ischemia from tight carotid or focal intracranial stenoses in the setting of regional hypoperfusion. Postoperative infarcts in the border zones between vascular territories commonly are blamed on systemic hypotension although some have suggested that these infarcts can also result from embolic disease (**Fig. 45-2**).

Embolic disease is likely the predominant mechanism of cerebral injury during cardiac surgery as evidenced by diffusion-weighted MRI and intraoperative transcranial Doppler studies. It should be noted that some of the emboli that are found histologically in these patients are too small to be detected by standard imaging sequences; therefore, a negative MRI after surgery does not exclude the diagnosis of emboli-related complications. Thrombus in the heart itself as well as atheromas in the aortic arch can become dislodged during cardiac surgeries, releasing a shower of particulate matter into the cerebral circulation. Cross-clamping of the aorta, manipulation of the heart, extracorporeal circulation techniques ("bypass"), arrhythmias such as atrial fibrillation, and introduction of air through suctioning have all been implicated as potential sources of emboli. Histologic studies indicate that literally millions of tiny emboli may be released, even using modern surgical techniques.

This shower of microemboli results in a number of clinical syndromes. Occasionally, a single large embolus leads to an isolated large-vessel stroke that presents with obvious clinical focal deficits. More commonly, the emboli released are multiple and smaller. When there is a high burden of these small emboli, an acute encephalopathy can occur postoperatively, presenting as either a hyperactive or hypoactive confusional state, the latter of which is frequently and incorrectly ascribed to depression. When the burden of microemboli is lower, no acute syndrome is recognized, but the patient may suffer a chronic cognitive deficit. Cardiac surgery can be viewed, like delirium, as a "stress test for the brain." Some patients with a low cerebral reserve due to underlying cerebrovascular disease or an early neurodegenerative process will develop a chronic, cognitive deficit, whereas others with higher reserves may remain asymptomatic despite a similar dose of microemboli. In this manner, cardiac surgery may serve to unmask the early manifestations of disorders such as vascular dementia and Alzheimer's disease.

Since modern techniques have successfully minimized hypoperfusion complications during these surgeries, much attention is now focused on reducing this inevitable shower of microemboli. Off-pump CABG surgeries have the advantages of reducing length of stay and perioperative complications; however, some recent

data suggest that off-pump CABG does not preserve cognitive function compared with on-pump CABG. Filters placed in the aortic arch may have some promise in capturing these emboli, although convincing evidence is currently lacking. Development of successful endovascular operative approaches may provide a reasonable alternative to conventional CABG procedures, especially for patients at high risk of developing cognitive dysfunction after surgery due to advanced age, previous stroke, or severe atheromatous disease of the carotid arteries or aortic arch.

POST-SOLID ORGAN TRANSPLANT BRAIN INJURY

Patients who have undergone solid organ transplantation are at risk for neurologic injury in the postoperative period and for the months to years thereafter. Neurologic consultants should view these patients as a special population at risk for both unique neurologic complications as well as for the usual disorders found in any critically ill inpatient.

Immunosuppressive medications are administered in high doses to patients after solid organ transplant, and many of these compounds have well-described neurologic complications. In patients with headache, seizures, or focal neurologic deficits taking calcineurin inhibitors, the diagnosis of hyperperfusion syndrome should be considered, as discussed above. This neurotoxicity occurs mainly with cyclosporine and tacrolimus and can present even in the setting of normal serum drug levels. Treatment primarily involves lowering the drug dosage or discontinuing the drug. A related newer agent, sirolimus, has very few recorded cases of neurotoxicity and may be a reasonable alternative for some patients. Other examples of immunosuppressive medications and their neurologic complications include OKT3-associated akinetic mutism and the leukoencephalopathy seen with methotrexate, especially when it is administered intrathecally or with concurrent radiotherapy. In any solid organ transplant patient with neurologic complaints, a careful examination of the medication list is required to search for these possible drug effects.

Cerebrovascular complications of solid organ transplant are often first recognized in the immediate postoperative period. Border zone territory infarctions can occur, especially in the setting of systemic hypotension during cardiac transplant surgery. Embolic infarctions classically complicate cardiac transplantation, but all solid organ transplant procedures place patients at risk for systemic emboli. When cerebral embolization accompanies renal or liver transplantation surgery, a careful search for right-to-left shunting should include evaluation of the heart with agitated saline echocardiography, as well as looking for intrapulmonary shunting. Renal and some cardiac transplant patients often have advanced atherosclerosis, providing yet another mechanism for stroke. Imaging with CT or MRI with diffusion is advised when cerebrovascular complications are suspected to confirm the diagnosis and to exclude intracerebral hemorrhage, which most often occurs in the setting of coagulopathy secondary to liver failure or after cardiac bypass procedures.

Because patients with solid organ transplants are chronically immunosuppressed, infections are a common concern. In any transplant patient with new CNS signs or symptoms such as seizure, confusion, or focal deficit, the diagnosis of a nervous system infection should be considered and evaluated through imaging (usually MRI) and possibly lumbar puncture. The most common pathogens responsible for CNS infections in these patients vary based on time since transplant. In the first month posttransplant, common pathogens include the usual bacterial organisms associated with surgical procedures and indwelling catheters. Starting in the second month posttransplant, opportunistic infections of the CNS become more common, including *Nocardia* and *Toxoplasma* species as well as fungal infections such as aspergillosis. Viral infections that can affect the brain of the immunosuppressed patient, such as herpes simplex virus, cytomegalovirus, and varicella, also become more common after the first month posttransplant. After 6 months posttransplant, immunosuppressed patients still remain at risk for these opportunistic bacterial, fungal, and viral infections but can also suffer late CNS infectious complications such as progressive multifocal leukoencephalopathy (PML) associated with JC virus and Epstein-Barr virus–driven clonal expansions of B cells resulting in CNS lymphoma.

COMMON NEUROLOGIC COMPLICATIONS OF ELECTROLYTE DISTURBANCES

A wide variety of neurologic conditions can result from abnormalities in serum electrolytes, and consideration of electrolyte disturbances should be part of any inpatient neurologic consultation.

HYPERNATREMIA AND HYPEROSMOLALITY

The normal range of serum osmolality is around 275–295 mOsm/kg, but neurologic manifestations are usually seen only at levels >325 mOsm/kg. Hyperosmolality is usually due to hypernatremia, hyperglycemia, azotemia, or the addition of extrinsic osmoles such as mannitol, which is commonly used in critically ill neurologic patients. Hyperosmolality itself can lead to a generalized encephalopathy that is nonspecific and without focal findings; however, an underlying lesion such as a mass can become symptomatic under the metabolic stress of a hyperosmolar state, producing focal signs. Some patients with hyperosmolality from severe hyperglycemia

can present, for unclear reasons, with generalized seizures or unilateral movement disorders, which usually respond to lowering of the serum glucose. The treatment of all forms of hyperosmolality involves calculation of apparent water losses and slow replacement so that the serum sodium declines no faster than 2 mmol/L (2 meq/L) per hour.

Hypernatremia leads to the loss of intracellular water, leading to cell shrinkage. In the cells of the brain, solutes such as glutamine and urea are generated under these conditions in order to minimize this shrinkage. Despite this corrective mechanism, when hypernatremia is severe [serum sodium >160 mmol/L (>160 meq/L)] or occurs rapidly, cellular metabolic processes fail and encephalopathy will result. There are many etiologies of hypernatremia including, most commonly, renal and extrarenal losses of water. Causes of neurologic relevance include central diabetes insipidus, where hyperosmolality is accompanied by submaximal urinary concentration due to inadequate release of antidiuretic hormone (ADH) from the posterior pituitary, resulting often from pituitary injury in the setting of surgery, hemorrhage, infiltrative processes, or cerebral herniation.

HYPONATREMIA

Hyponatremia is commonly defined as a serum sodium <135 mmol/L (<135 meq/L). Neurologic symptoms occur at different levels of low sodium, depending not only on the absolute value but also on the rate of fall. In patients with hyponatremia that develops over hours, life-threatening seizures and cerebral edema may occur at values as high as 125 mmol/L. In contrast, some patients with more chronic hyponatremia that has slowly developed over months to years may be asymptomatic even with serum levels <110 mmol/L. Correction of hyponatremia, especially when chronic, must take place slowly in order to avoid additional neurologic complications. Cells in the brain swell in hypotonic hyponatremic states but may compensate over time by excreting solute into the extracellular space, leading to restoration of cell volume when water follows the solute out of the cells. If treatment of hyponatremia results in a rapid rise in serum sodium, cells in the brain may quickly shrink, leading to osmotic demyelination, a process that previously was thought to be limited exclusively to the brainstem (central pontine myelinolysis; see Fig. 22-6), but now has been described elsewhere in the CNS.

Treatment of hyponatremia is dependent on the cause. Hypertonic hyponatremia treatment focuses on the underlying condition, such as hyperglycemia. Isovolemic hyponatremia (syndrome of inappropriate antidiuretic hormone, SIADH) is managed with water restriction or administration of ADH antagonists. The management of choice for patients with hypervolemic hypotonic hyponatremia is free-water restriction and treatment of the underlying edematous disorder, such as nephrotic syndrome or congestive heart failure. Finally, in hypovolemic hypotonic hyponatremia, volume is replaced with isotonic saline while underlying conditions of the kidneys, adrenals, and gastrointestinal tract are addressed.

One neurologic cause of hypovolemic hypotonic hyponatremia is the cerebral salt-wasting syndrome that accompanies subarachnoid hemorrhage and, less commonly, other cerebral processes such as meningitis or stroke. In these cases, the degree of renal sodium excretion can be remarkable, and large amounts of saline, hypertonic saline, or oral sodium may need to be given in a judicious fashion in order to avoid complications from cerebral edema.

HYPOKALEMIA

Hypokalemia, defined as a serum potassium level <3.5 mmol/L (<3.5 meq/L), occurs either because of excessive potassium losses (from the kidneys or gut) or due to an abnormal potassium distribution between the intracellular and extracellular spaces. At very low levels (<1.5 mmol/L), hypokalemia may be life threatening due to the risk of cardiac arrhythmia and may present neurologically with severe muscle weakness and paralysis. Hypokalemic periodic paralysis is a rare disorder caused by excessive intracellular potassium uptake in the setting of a calcium or sodium channel mutation. Treatment of hypokalemia is dependent on the etiology but usually includes replacement of potassium through oral or IV routes as well as correcting the cause of potassium balance problems (e.g., eliminating β_2-adrenergic agonist medications).

HYPERKALEMIA

Hyperkalemia is defined as a serum potassium level >5.5 mmol/L (>5.5 meq/L) and can neurologically present as muscle weakness with or without paresthesias. Hyperkalemia becomes life threatening when it produces electrocardiographic abnormalities such as peaked T waves or a widened QRS complex. In these cases, prompt treatment is essential and consists of strategies that protect the heart against arrhythmias (calcium gluconate administration), promote potassium redistribution into cells (with glucose, insulin, and β_2-agonist medications), and increase potassium removal (through sodium polystyrene sulfonate, loop diuretics, or hemodialysis).

CALCIUM DISTURBANCES

Hypercalcemia usually occurs in the setting of either hyperparathyroidism or systemic malignancy. Neurologic manifestations include encephalopathy as well as muscle weakness due to reduced neuromuscular excitability. Seizures can occur but are more common in states of low calcium.

Hypocalcemia in adults often follows surgical treatment of the thyroid or parathyroid. Seizures and altered mental status dominate the neurologic picture and usually resolve with calcium repletion. Tetany is due to spontaneous, repetitive action potentials in peripheral nerves and remains the classic sign of symptomatic hypocalcemia.

MAGNESIUM DISTURBANCES

Disorders of magnesium are difficult to correlate with serum levels because a very small amount of total-body magnesium is located in the extracellular space. Hypomagnesemia presents neurologically with seizures, tremor, and myoclonus. When intractable seizures occur in the setting of hypomagnesemia, only administration of magnesium will lead to resolution. High levels of magnesium, in contrast, lead to CNS depression. Hypermagnesemia usually occurs only in the setting of renal failure and can lead to confusion and muscular paralysis when severe.

CONSULTATIONS REGARDING PERIPHERAL NERVOUS SYSTEM DYSFUNCTION

ENTRAPMENT NEUROPATHIES

Polyneuropathy is a common cause of outpatient neurologic consultation (Chap. 40). In the inpatient setting, however, mononeuropathies are more frequent, especially the entrapment neuropathies that complicate many surgical procedures and medical conditions. Median neuropathy at the wrist (carpal tunnel syndrome) is the most frequent entrapment neuropathy by far, but it is rarely a cause for inpatient consultation. Mechanisms for perioperative mononeuropathy include traction, compression, and ischemia of the nerve. Imaging with MR neurography may allow these causes to be distinguished definitively. In all cases of mononeuropathy, the diagnosis can be made through the clinical examination and then confirmed with electrodiagnostic studies in the subacute period, if necessary. Treatment consists mainly of avoidance of repetitive trauma but may also include surgical approaches to relieve pressure on the nerve.

RADIAL NEUROPATHY

Radial nerve injury classically presents with weakness of extension of the wrist and fingers ("wrist drop") with or without more proximal weakness of extensor muscles of the upper extremity, depending on the site of injury. Sensory loss is in the distribution of the radial nerve, which includes the dorsum of the hand (**Fig. 45-3*A***). Compression at the level of the axilla, e.g., resulting from use of crutches, includes weakness of the triceps, brachioradialis, and supinator muscles in addition to wrist drop. A more common site of compression occurs in the spiral groove of the upper arm in the setting of a humerus fracture or from sleeping with the arm draped over a bench or chair ("Saturday night palsy"). Sparing of the triceps is the rule when the nerve is injured in this location. Because extensors of the upper extremity are injured preferentially in radial nerve injury, these lesions may be mistaken for the pyramidal distribution of weakness that accompanies upper motor neuron lesions from brain or spinal cord processes.

ULNAR NEUROPATHY

Compression of the ulnar nerve is the second most common entrapment neuropathy after carpal tunnel syndrome. The most frequent site of compression is at the elbow where the nerve passes superficially in the ulnar groove. Symptoms usually begin with tingling in the ulnar distribution, including the fourth and fifth digits of the hand (**Fig. 45-3*B***). Sensory symptoms may be worsened by elbow flexion due to increased pressure on the nerve, hence the tendency of patients to complain of increasing paresthesias at night when the arm is flexed at the elbow during sleep. Motor dysfunction can be disabling and involves most of the intrinsic hand muscles, limiting dexterity and strength of grasp and pinch. Etiologies of ulnar entrapment include trauma to the nerve (hitting the "funny bone"), malpositioning during anesthesia for surgical procedures, and chronic arthritis of the elbow. When a perioperative ulnar nerve injury is considered, stretch injury or trauma to the lower trunk of the brachial plexus should be entertained as well since its symptoms can mimic those of an ulnar neuropathy. If the clinical examination is equivocal, electrodiagnostic studies can definitively distinguish between plexus and ulnar nerve lesions a few weeks after the injury. Conservative methods of treatment are often the first step, but a variety of surgical approaches may be effective, including anterior ulnar nerve transposition and release of the flexor carpi ulnaris aponeurosis.

PERONEAL NEUROPATHY

The peroneal nerve winds around the head of the fibula in the leg below the lateral aspect of the knee, and its superficial location at this site makes it vulnerable to trauma. Patients present with weakness of foot dorsiflexion ("foot drop") as well as with weakness in eversion but not inversion at the ankle. Sparing of inversion, which is a function of muscles innervated by the tibial nerve, helps to distinguish peroneal neuropathies from L5 radiculopathies. Sensory loss involves the lateral aspect of the leg as well as the dorsum of the foot (**Fig. 45-3*C***). Fractures of the fibular head may be responsible for

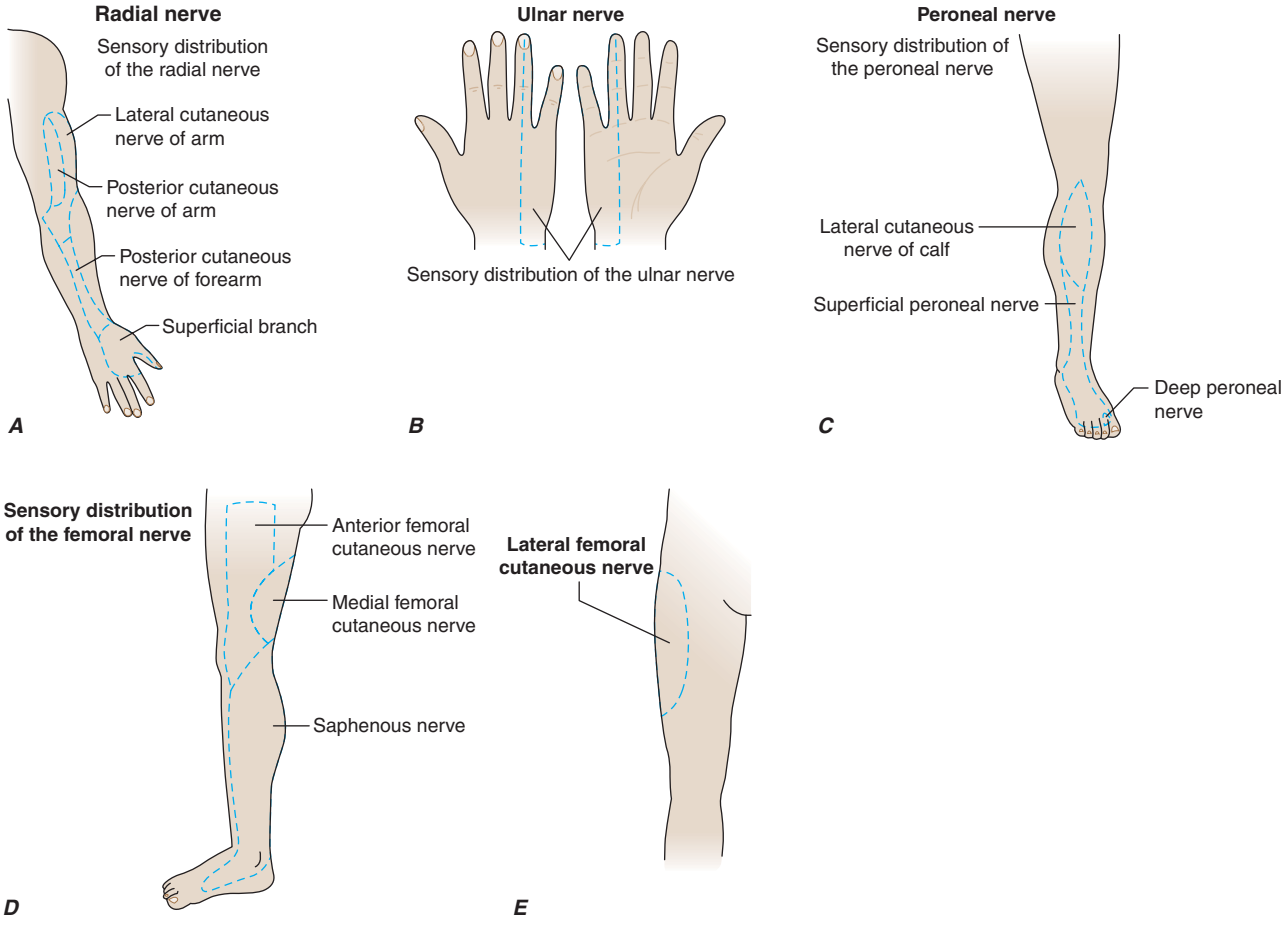

FIGURE 45-3
Sensory distribution of peripheral nerves commonly affected by entrapment neuropathies. ***A***. Radial nerve. ***B***. Ulnar nerve. ***C***. Peroneal nerve. ***D***. Femoral nerve. ***E***. Lateral femoral cutaneous nerve.

peroneal neuropathies, but in the perioperative setting poorly applied braces exerting pressure on the nerve while the patient is unconscious are more often responsible. Tight-fitting stockings or casts of the upper leg can also cause a peroneal neuropathy, and thin individuals and those with recent weight loss are at increased risk.

PROXIMAL FEMORAL NEUROPATHY

Lesions of the proximal femoral nerve are relatively uncommon but may present dramatically with weakness of hip flexion, quadriceps atrophy, weakness of knee extension (often manifesting with leg-buckling falls), and an absent patellar reflex. Adduction of the thigh is spared as these muscles are supplied by the obturator nerve, thereby distinguishing a femoral neuropathy from a more proximal lumbosacral plexus lesion. The sensory loss found is in the distribution of the femoral nerve sensory branches on the anterior part of the thigh (Fig. 45-3*D*). Compressive lesions from retroperitoneal hematomas or masses are common, and a CT of the pelvis should be obtained in all cases of femoral neuropathy to exclude these conditions. Bleeding into the pelvis resulting in hematoma can occur spontaneously, following trauma, or after intrapelvic surgeries such as renal transplantation. In intoxicated or comatose patients, stretch injuries to the femoral nerve are seen following prolonged, extreme hip flexion or extension. Rarely, attempts at femoral vein or arterial puncture can be complicated by injury to this nerve.

LATERAL FEMORAL CUTANEOUS NERVE

The symptoms of lateral femoral cutaneous nerve entrapment, commonly known as "meralgia paresthetica," include sensory loss, pain, and dysesthesia in part of the area supplied by the nerve (Fig. 45-3*E*). There is no motor component to the nerve, and therefore weakness is not a part of this syndrome. Symptoms often are worsened by standing or walking. Compression of the nerve occurs where it enters the leg near the inguinal ligament, usually in the setting of tight-fitting belts,

pants, corsets, or recent weight gain, including that of pregnancy. The differential diagnosis of these symptoms includes hip problems such as trochanteric bursitis.

OBSTETRIC NEUROPATHIES

Pregnancy and delivery place women at special risk for a variety of nerve injuries. Radiculopathy due to a herniated lumbar disc is not common during pregnancy, but compressive injuries of the lumbosacral plexus do occur secondary to either the fetal head passing through the pelvis or the use of forceps during delivery. These plexus injuries are more frequent with cephalopelvic disproportion and often present with a painless unilateral foot drop which must be distinguished from a peroneal neuropathy caused by pressure on the nerve while in lithotomy position during delivery. Other compressive mononeuropathies of pregnancy include meralgia paresthetica, carpal tunnel syndrome, femoral neuropathy when the thigh is abducted severely in an effort to facilitate delivery of the fetal shoulder, and obturator neuropathy during lithotomy positioning. The latter presents with medial thigh pain that may be accompanied by weakness of thigh adduction. There is also a clear association between pregnancy and an increased frequency of idiopathic facial palsy (Bell's palsy).

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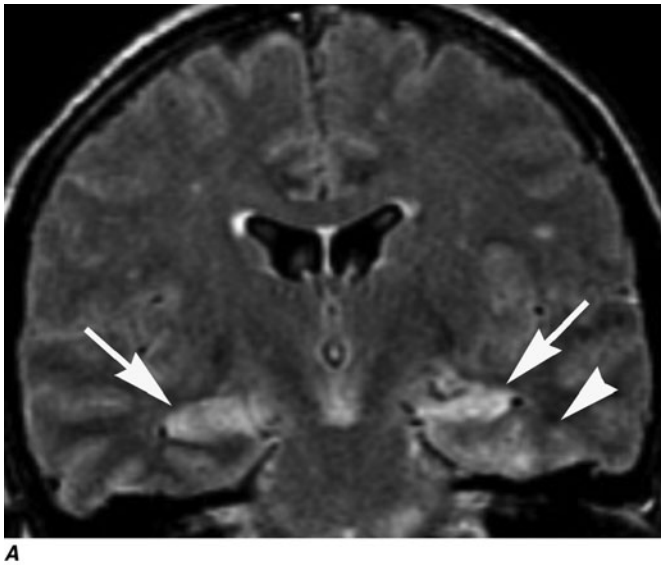
CHAPTER 46

ATLAS OF NEUROIMAGING

Andre Furtado ■ William P. Dillon



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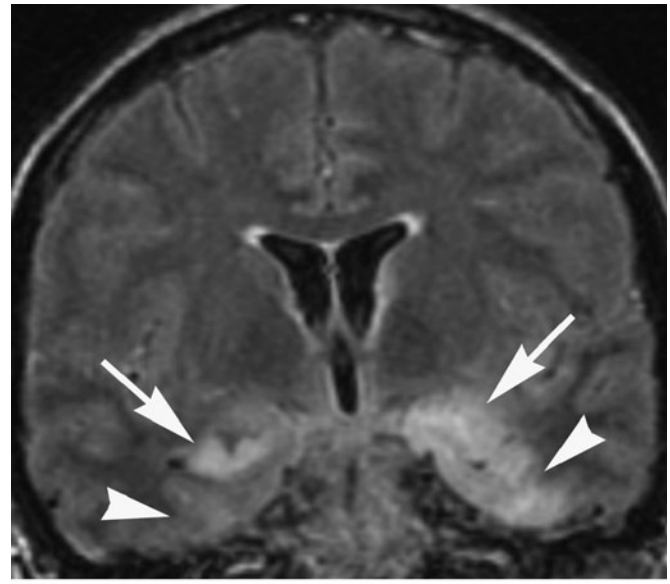

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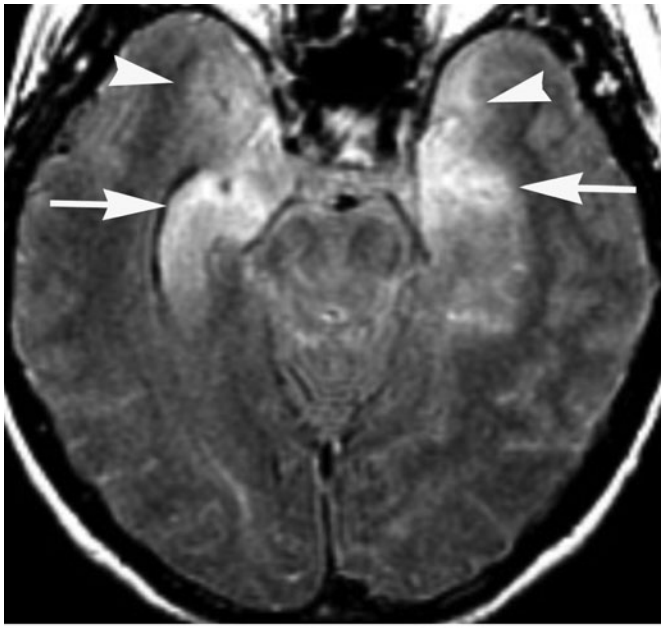
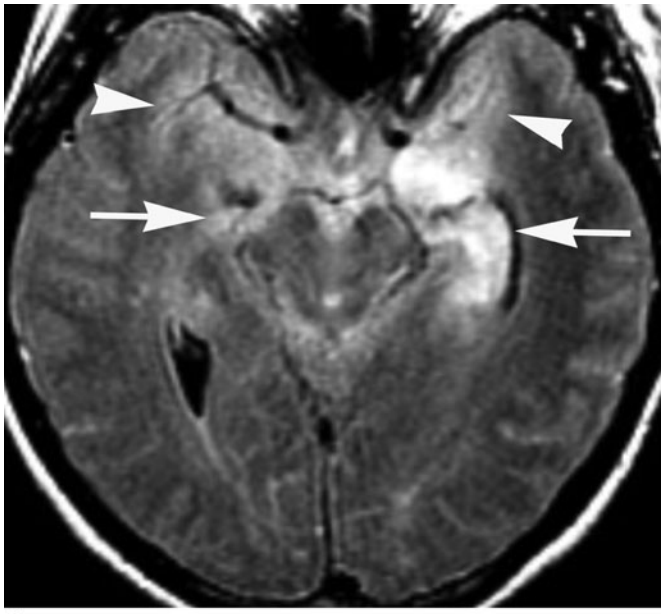


C

FIGURE 46-1

Limbic encephalitis (Chap. 39) Coronal (***A, B***), axial FLAIR (***C, D***), and axial T2-weighted (***E***) MR images demonstrate abnormal high signal involving the bilateral mesial temporal lobes (*arrowheads*) including the hippocampi (left greater than right) without significant mass effect (*arrows*). There was no enhancement on post-gadolinium images (not shown).



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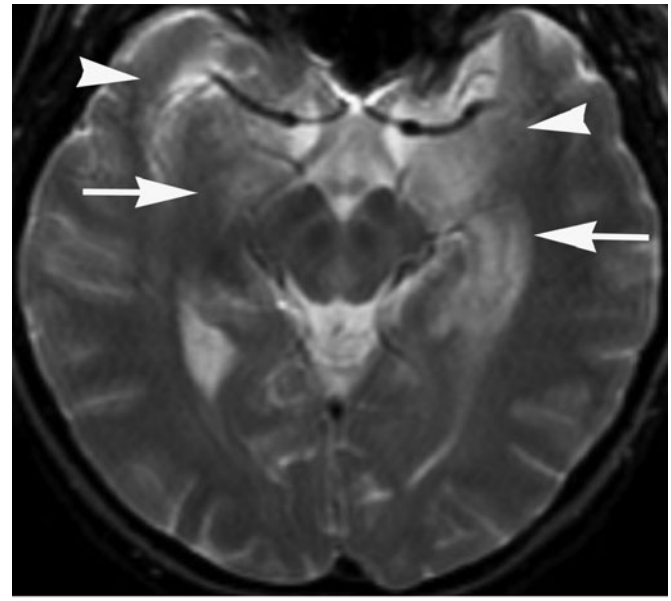
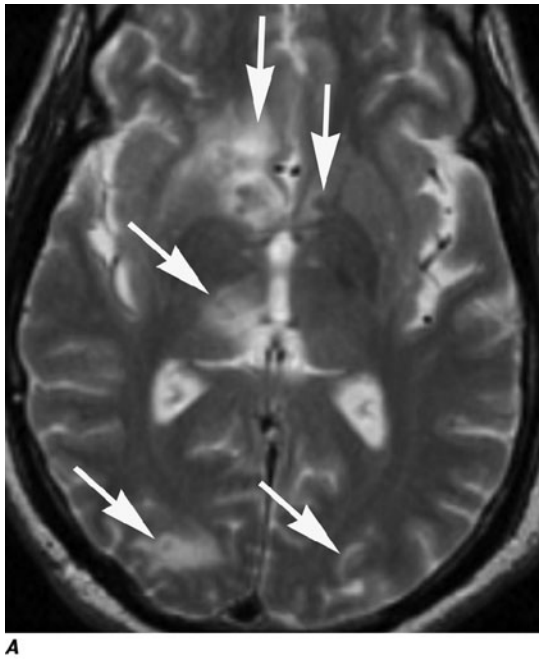
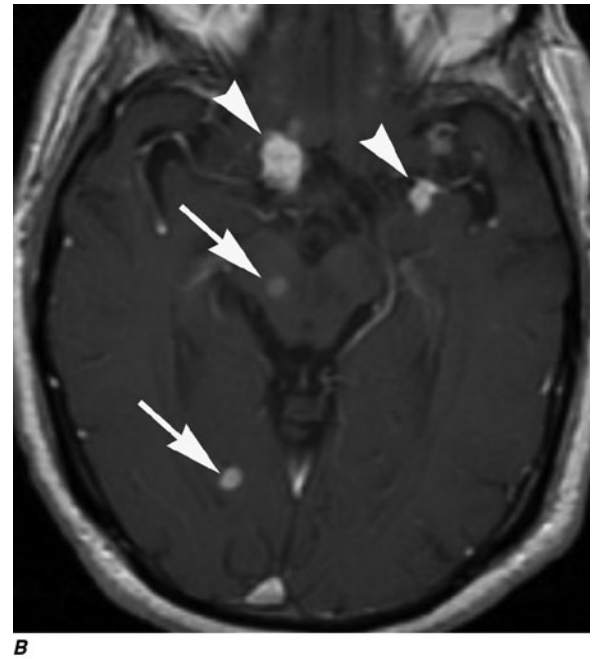


E

FIGURE 46-1 (*Continued*)



A



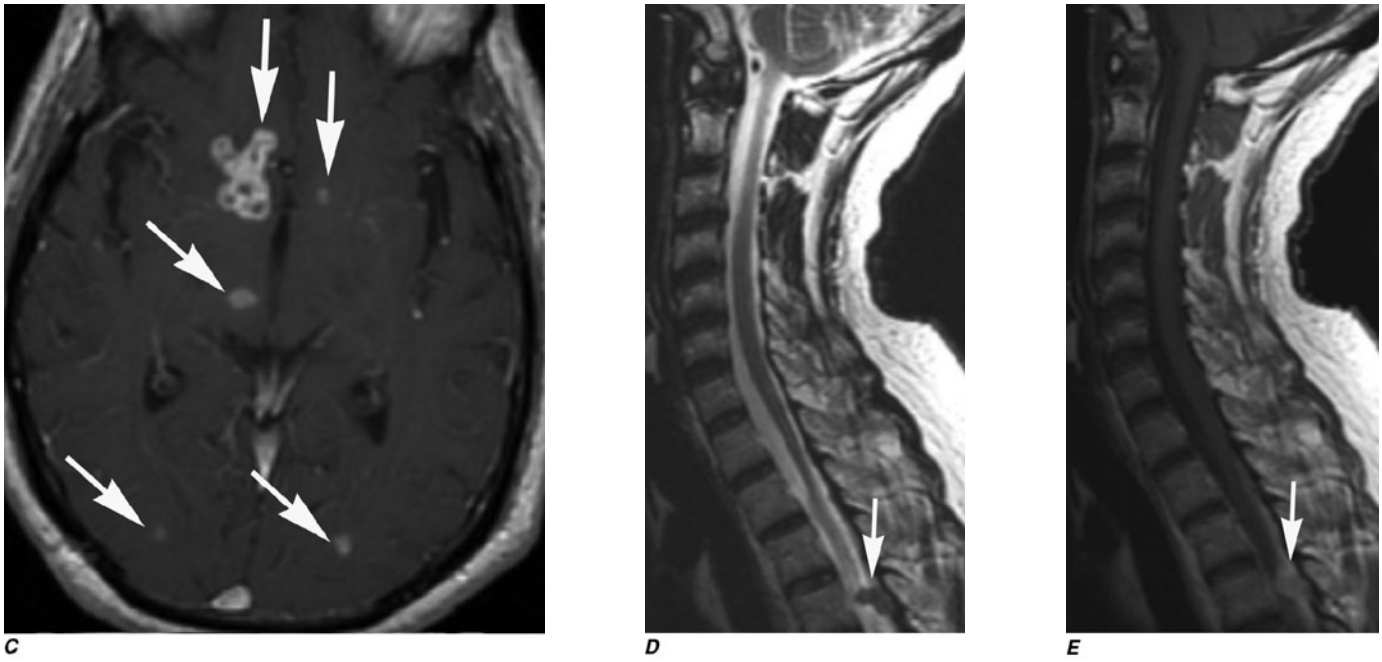
B

FIGURE 46-2

CNS tuberculosis (Chap. 35)

Axial T2-weighted MRI (***A***) demonstrates multiple lesions (*arrows*) with peripheral high signal and central low signal, located predominantly in the cortex and subcortical white matter, as well as in the basal ganglia.

Axial T1-weighted MR images post-gadolinium (***B, C***) demonstrate ring enhancement of the lesions (*arrows*) and additional lesions in the subarachnoid space (*arrowheads*).

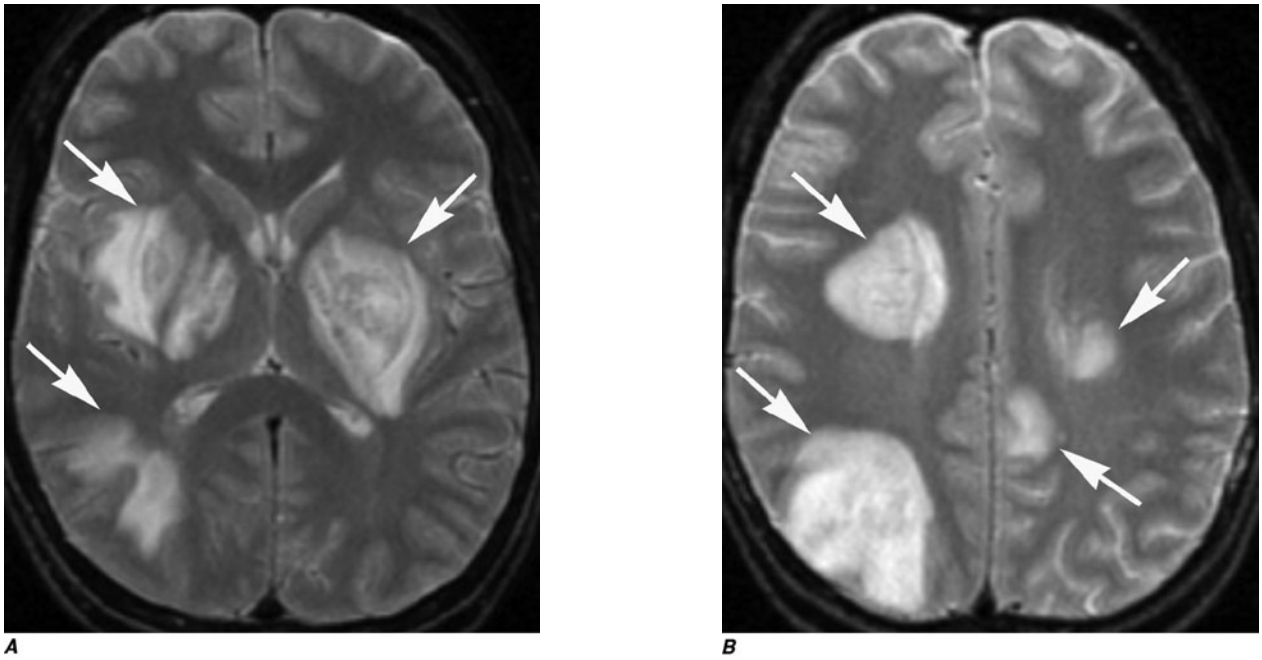


C D E

FIGURE 46-2 (*Continued*)

Sagittal T2-weighted MR image of the cervical spine (***D***) demonstrates a hypointense lesion in the subarachnoid space at the level of T5 (*arrow*).

Sagittal T1-weighted MR image post-gadolinium of the cervical spine (***E***) demonstrates enhancement of the lesion in the subarachnoid space at the level of T5 (*arrow*).



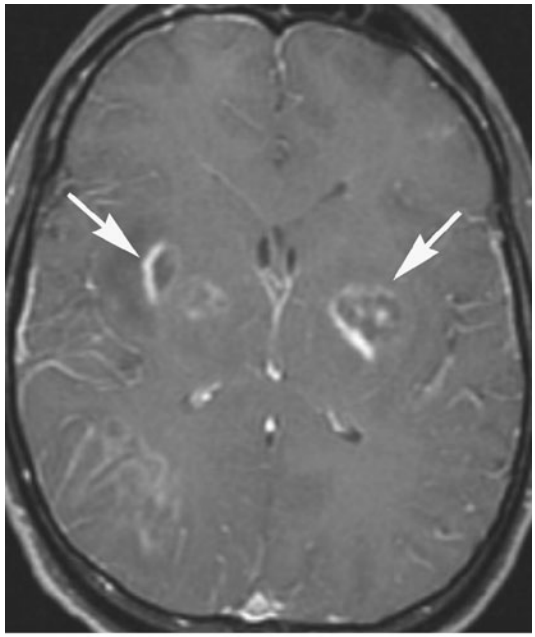
A B

FIGURE 46-3

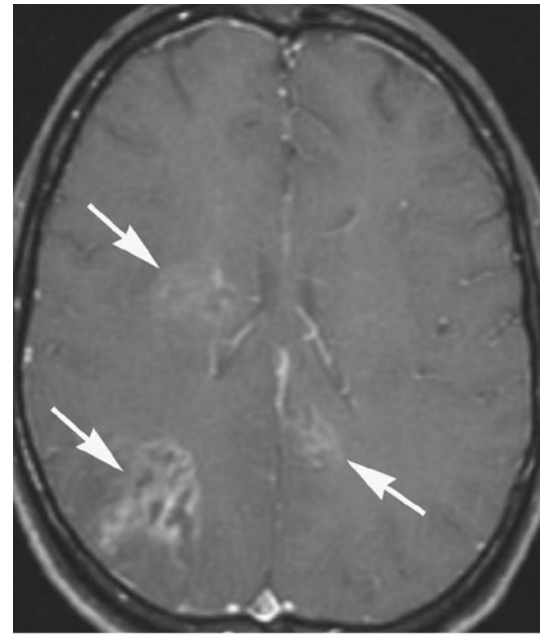
Neurosyphilis (Chap. 35)

Case I

Axial T2-weighted MR images (***A, B***) demonstrate well-defined areas of abnormal high signal in the basal ganglia bilaterally and in a wedge-shaped distribution in the right parietal lobe (*arrows*).



C



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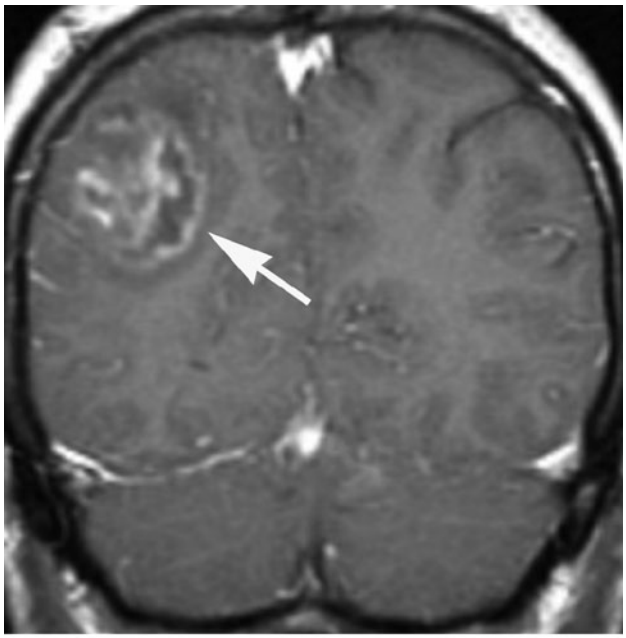
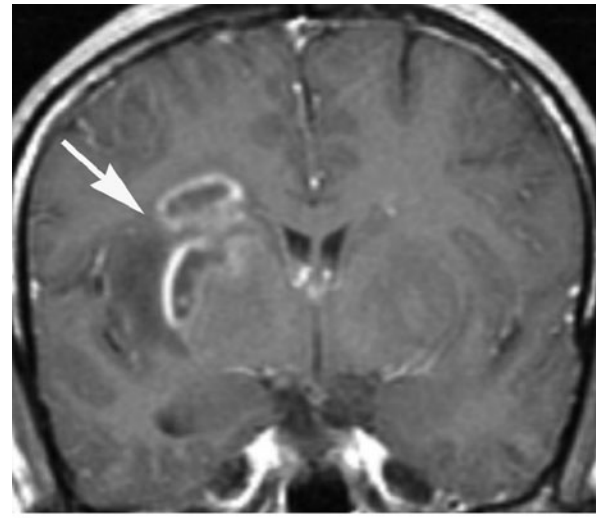
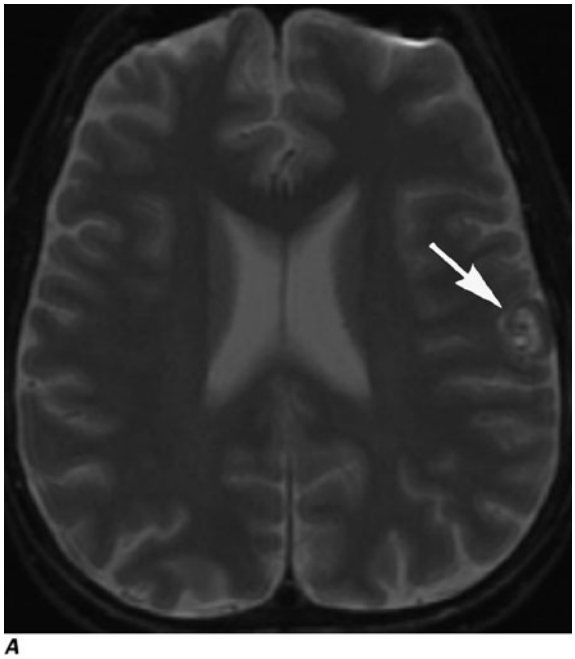


E

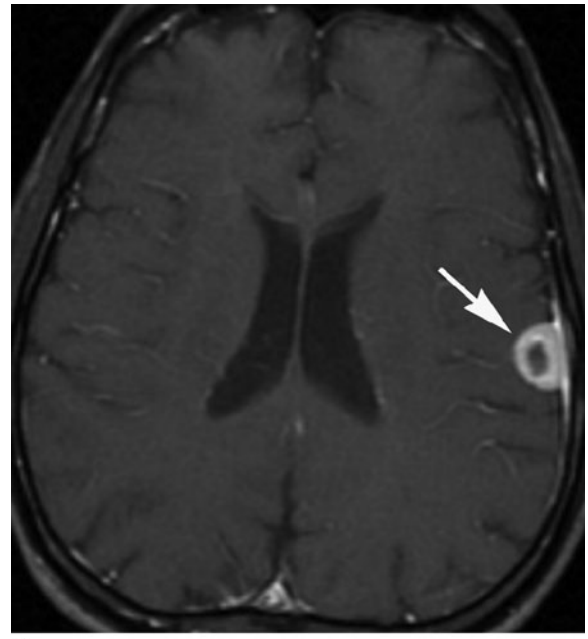


F

FIGURE 46-3 (*Continued*)
Axial (***C, D***) T1-weighted images post-gadiolinium. Coronal (***E, F***) T1-weighted images post-gadolinium demonstrate irregular ring enhancement of the lesions (*arrows*).



A



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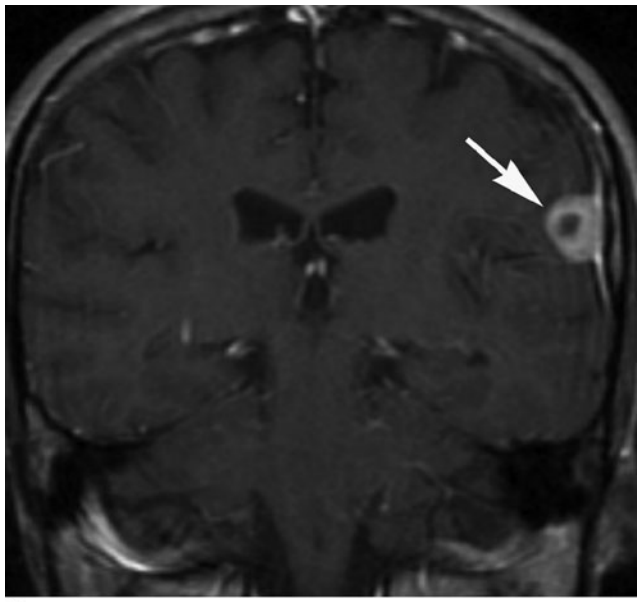


C

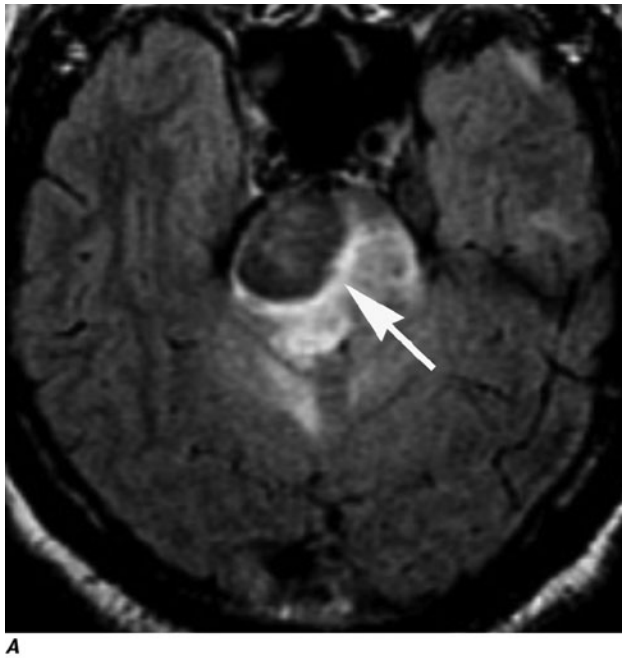
FIGURE 46-4

Neurosyphilis (Chap. 35)

Case II

Axial T2-weighted MRI (***A***) demonstrates a dural-based, peripherally hyperintense and centrally hypointense lesion located lateral to the left frontal lobe (*arrows*).

Axial (***B***) and coronal (***C***) T1-weighted MR images post-gadolinium demonstrate peripheral enhancement of the lesion (*arrows*).



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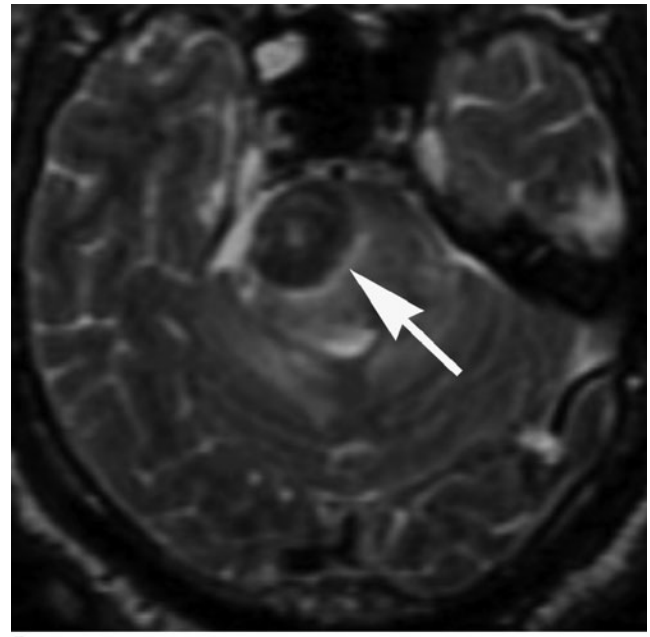

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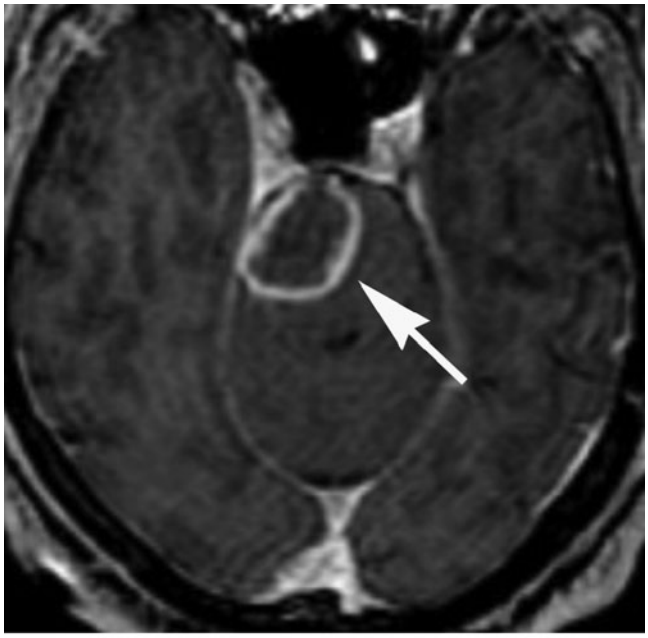
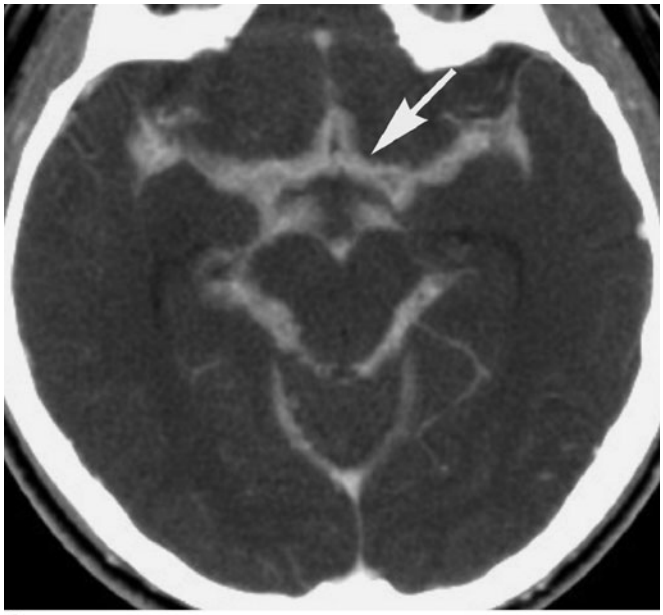


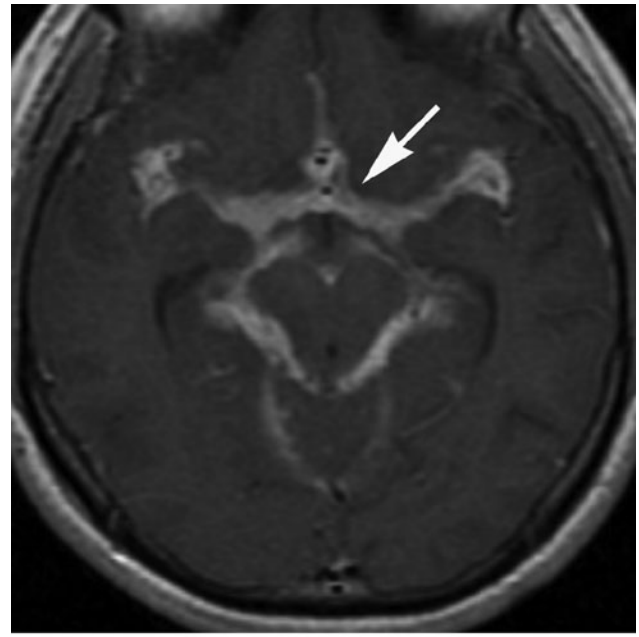
C

FIGURE 46-5

Histoplasmosis of the pons Axial FLAIR (***A***) and T2-weighted (***B***) MR images demonstrate a low signal mass in the right pons (*arrows*) with surrounding vasogenic edema. Axial T1-weighted MR image post-gadolinium (***C***) demonstrates ring enhancement of the lesion in the right pons (*arrows*). Of note, there was no evidence of restricted diffusion (not shown).



A



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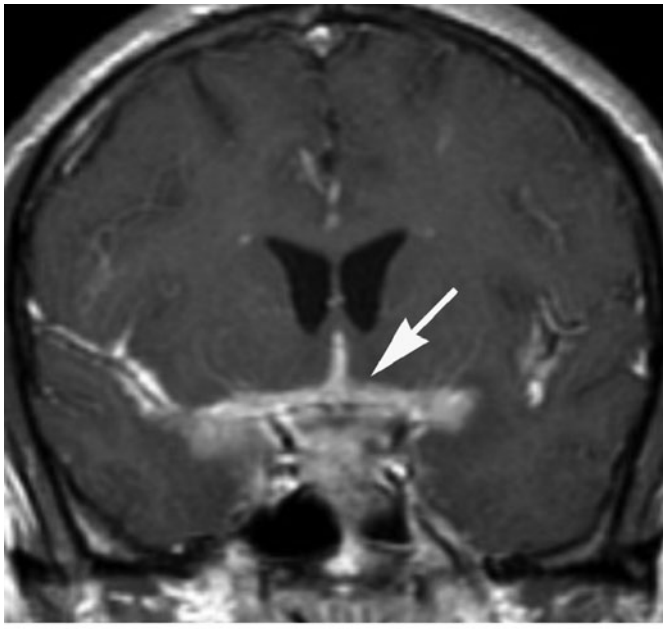


C

FIGURE 46-6

Coccidiomycosis meningitis (Chap. 36)

Axial post-contrast CT (***A***) and axial (***B***) and coronal (***C***) T1-weighted MR images post-gadolinium demonstrate enhancement of the perimesencephalic cisterns (*arrows*), as well as the sylvian and interhemispheric fissures.

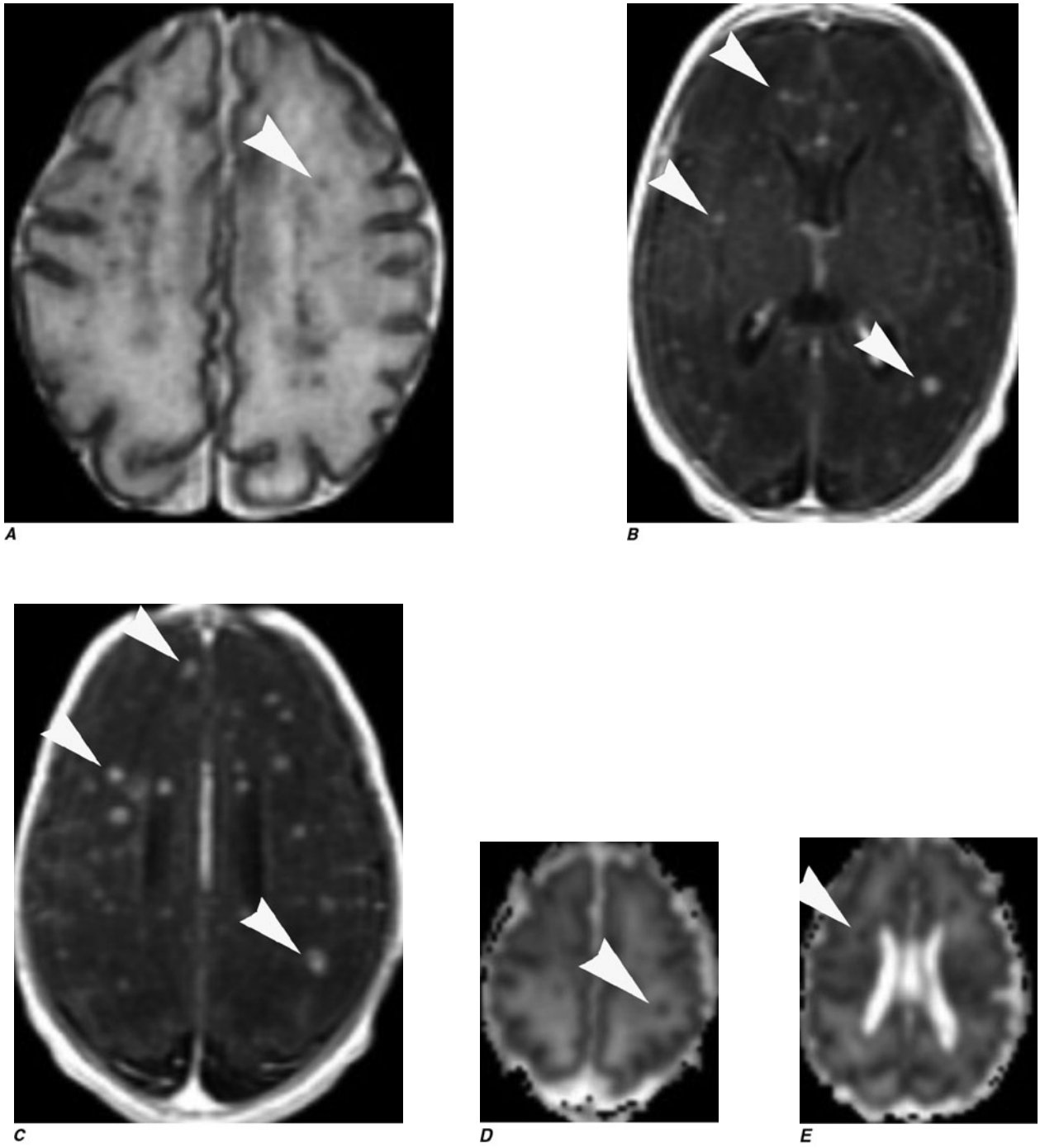


FIGURE 46-7

Candidiasis in a newborn Axial T2-weighted MR image (***A***) demonstrates multiple punctate foci of low signal diffusely distributed in the brain parenchyma (*arrowheads*).
Axial T1-weighted MR images post-gadolinium (***B, C***) demonstrate marked enhancement of the lesions (*arrowheads*).
ADC map (***D, E***) demonstrates restricted diffusion of water molecules in the lesions (*arrowheads*).

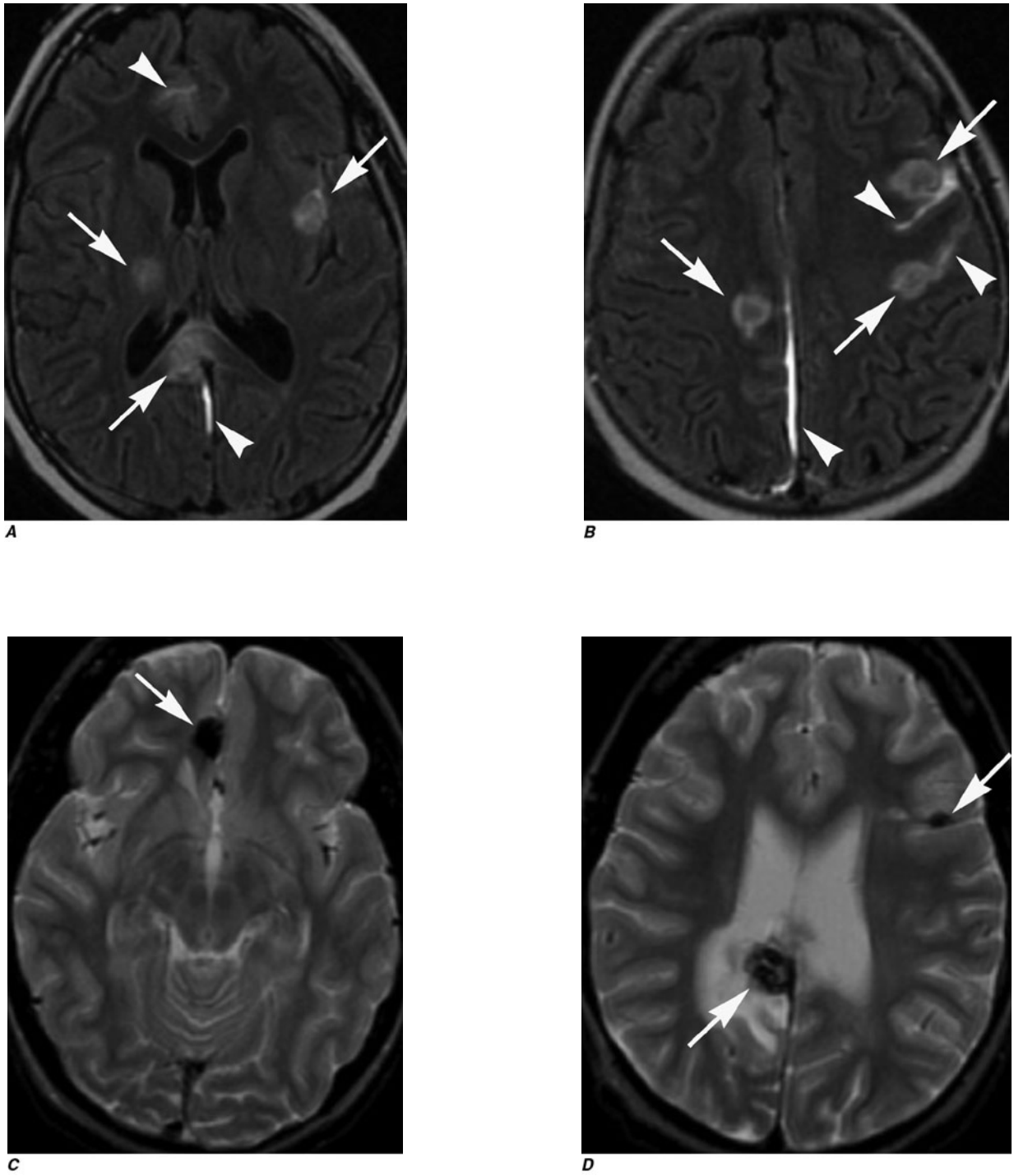
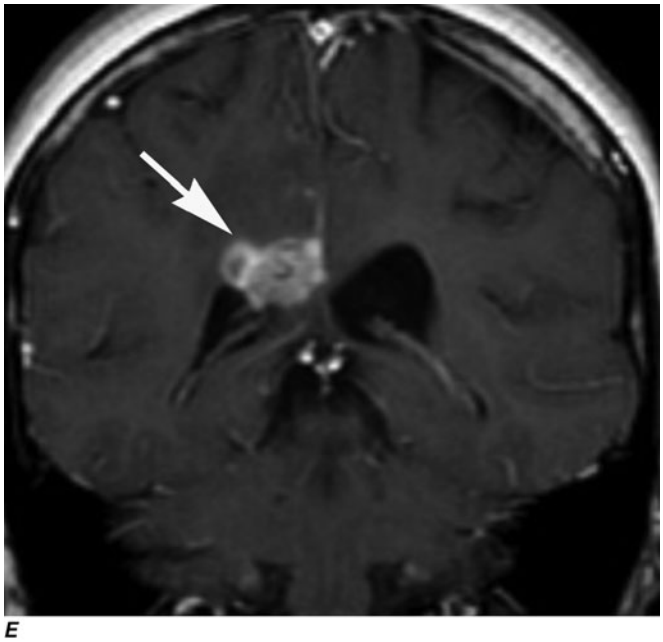


FIGURE 46-8

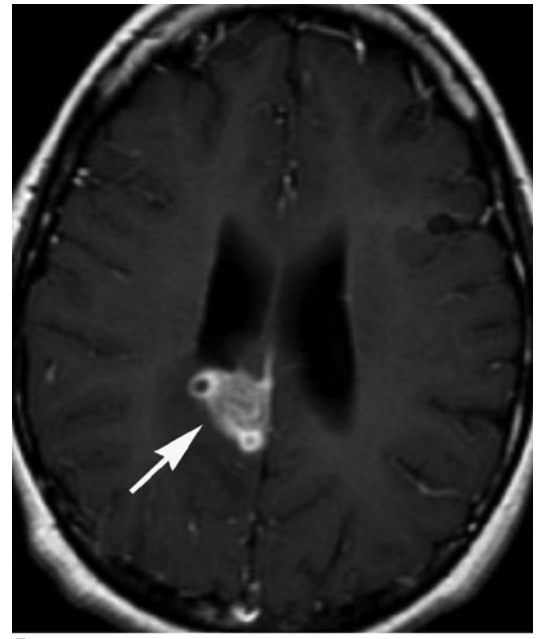
CNS aspergillosis (Chap. 36)

Axial FLAIR MR images (***A, B***) demonstrate multiple areas of abnormal high signal in the basal ganglia as well as cortex and subcortical white matter (*arrows*). There is also abnormal high signal in the subarachnoid space adjacent to the lesions (*arrowhead*) that can correspond to blood or high protein content.

Axial T2-weighted MR images (***C, D***) demonstrate intrinsic low signal in the lesions (*arrows*), suggesting the presence of blood products. Some of the lesions also show vasogenic edema.

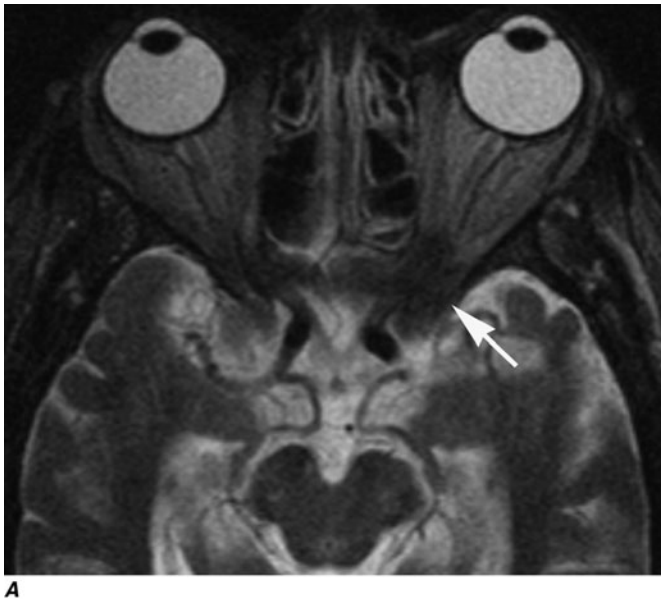


E



F

FIGURE 46-8 (*Continued*)
Coronal (***E***) and axial (***F***) T1-weighted MR images post-gadolinium demonstrate peripheral enhancement of the lesions (*arrows*).



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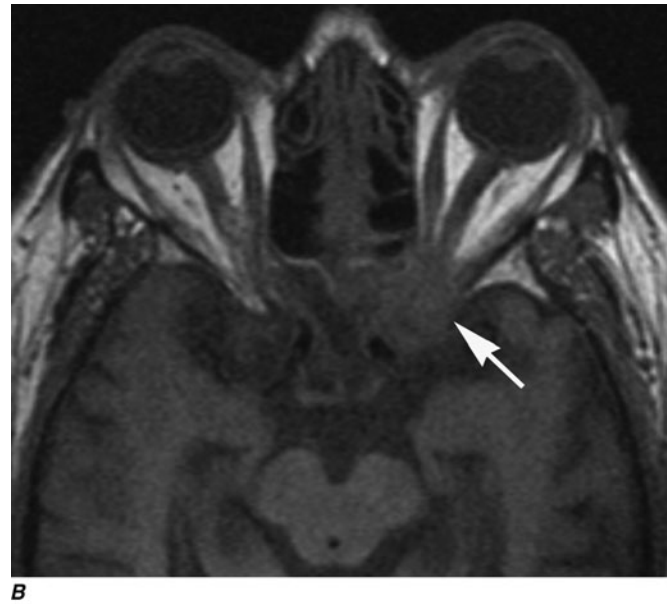
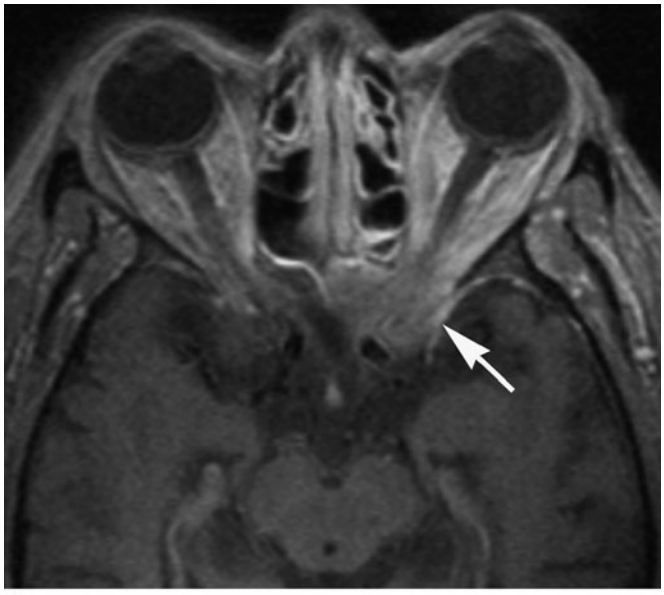


B

FIGURE 46-9
Invasive sinonasal aspergillosis Axial T2-weighted MR image (***A***) demonstrates an irregularly shaped low signal lesion involving the left orbital apex (arrow).

B. T1-weighted image pre-gadolinium demonstrates enhancement of lesion (*arrow*).



C

FIGURE 46-9 (*Continued*)
C. T1-weighted image post-gadolinium demonstrates enhancement of lesion (*arrow*).

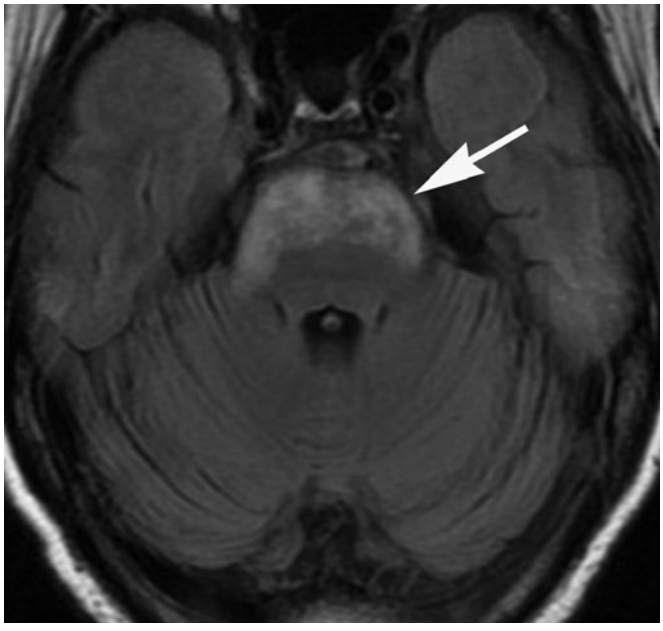
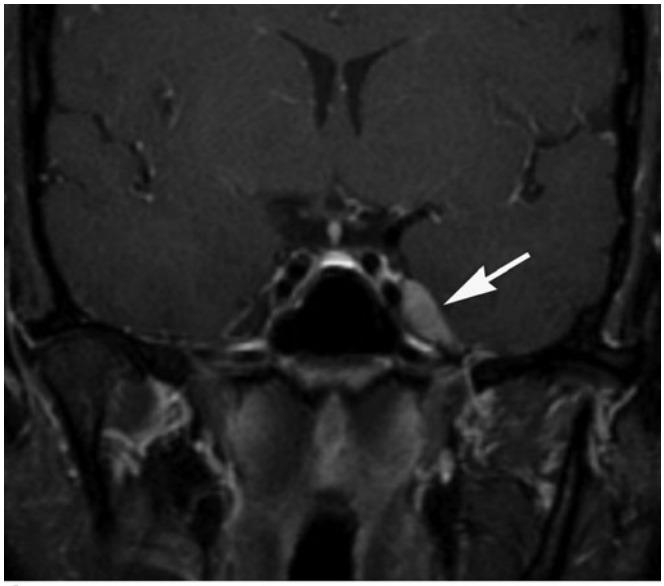


FIGURE 46-10
Behçet's disease Axial FLAIR MRI demonstrates abnormal high signal involving the anterior pons (*arrow*); following gadolinium administration, the lesion was nonenhancing (not shown). Brainstem lesions are typical of Behçet's disease, caused primarily by vasculitis and in some cases demyelinating lesions.



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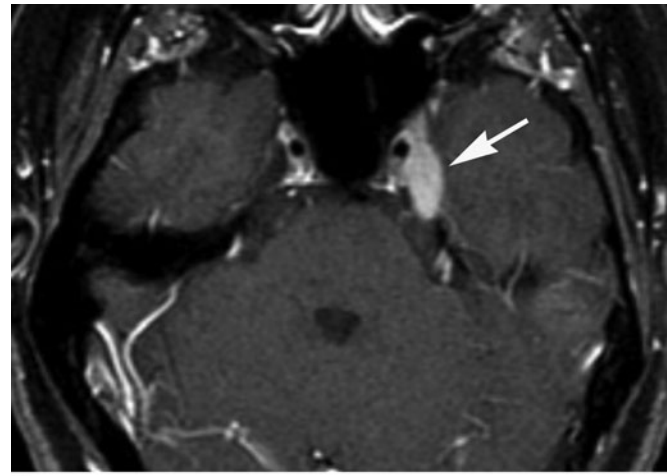


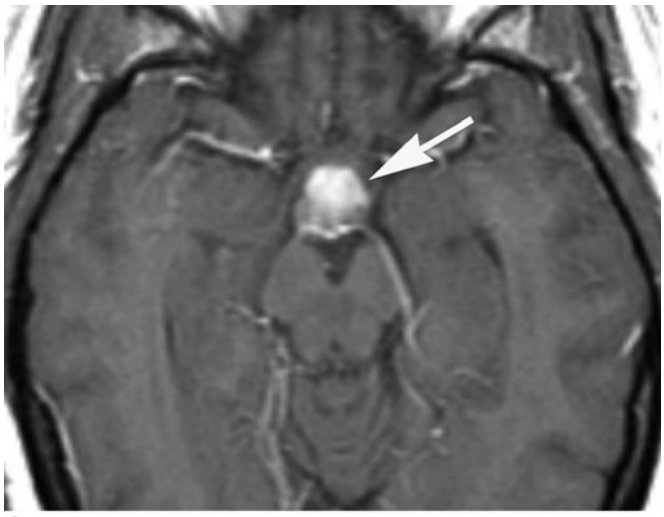
B

FIGURE 46-11

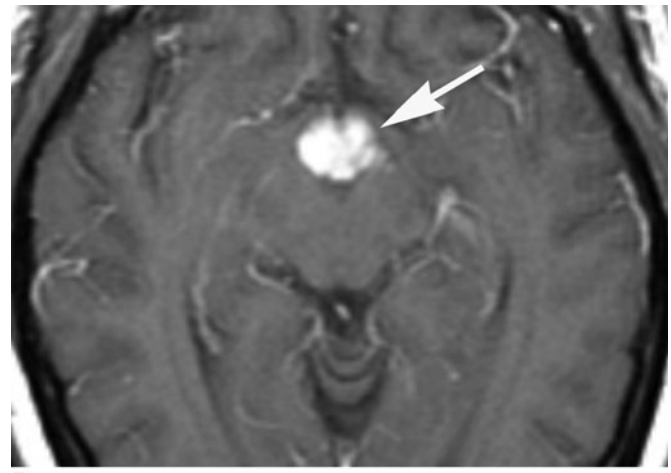
Neurosarcoid

Case I

Axial (***A***) and coronal (***B***) T1-weighted images post-gadolinium with fat suppression demonstrate a homogeneously enhancing well circumscribed mass centered in the left Meckel's cave (*arrows*).



A



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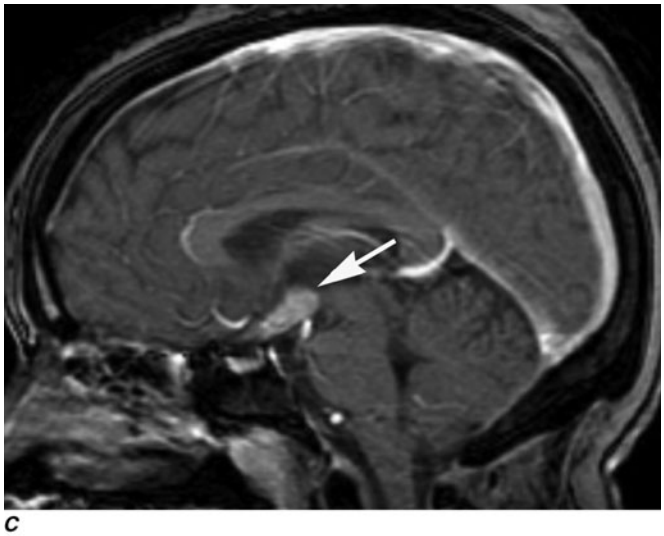


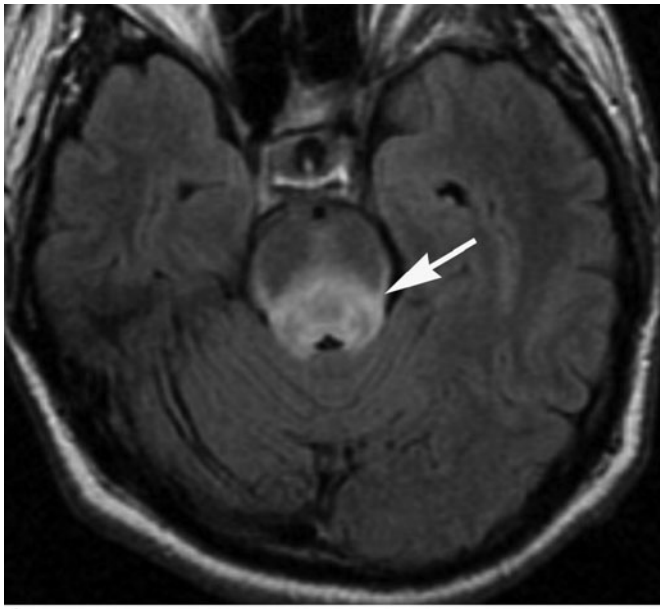
C

FIGURE 46-12

Neurosarcoid

Case II

Axial (***A, B***) and sagittal (***C***) T1-weighted images post-gadolinium with fat suppression demonstrate a homogeneously enhancing mass involving the hypothalamus and the pituitary stalk (*arrows*).



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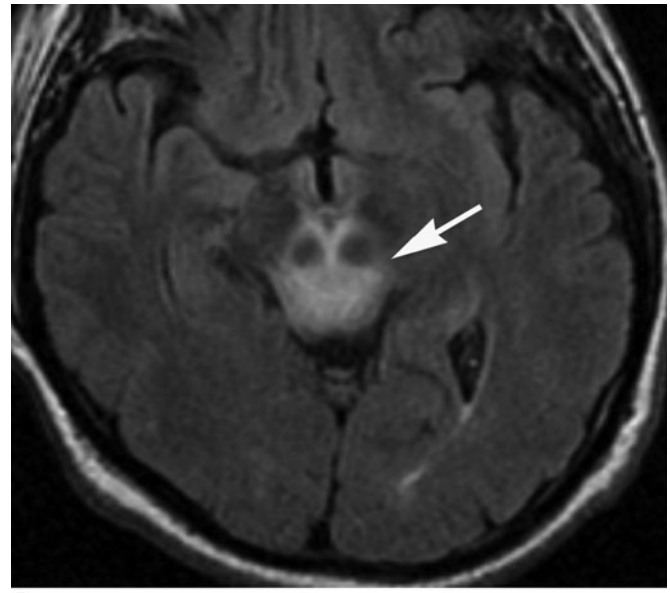
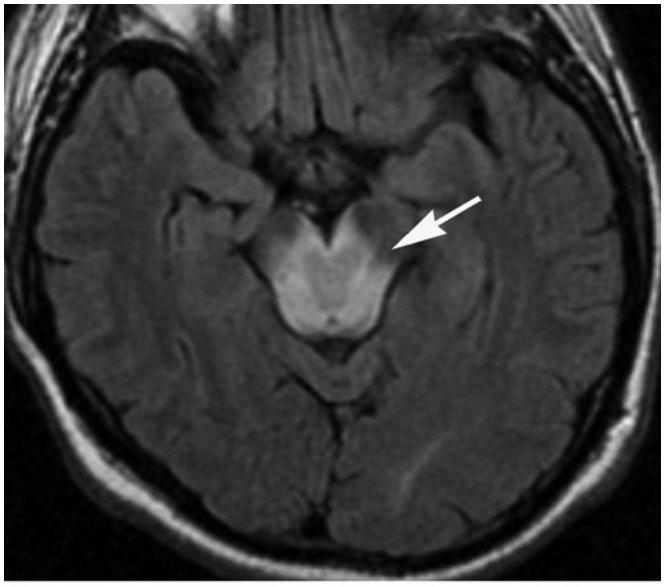
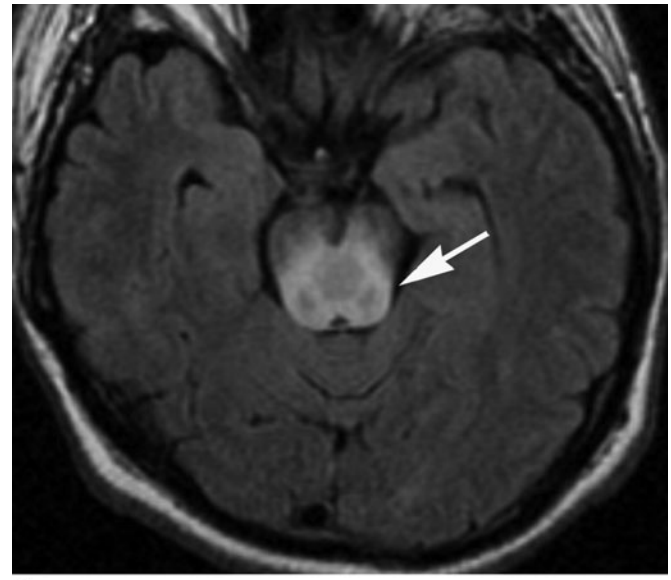


B



C



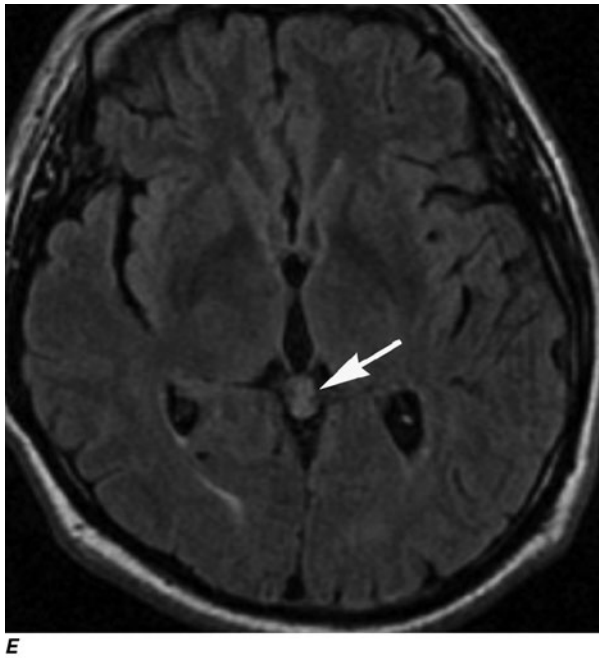
D

FIGURE 46-13

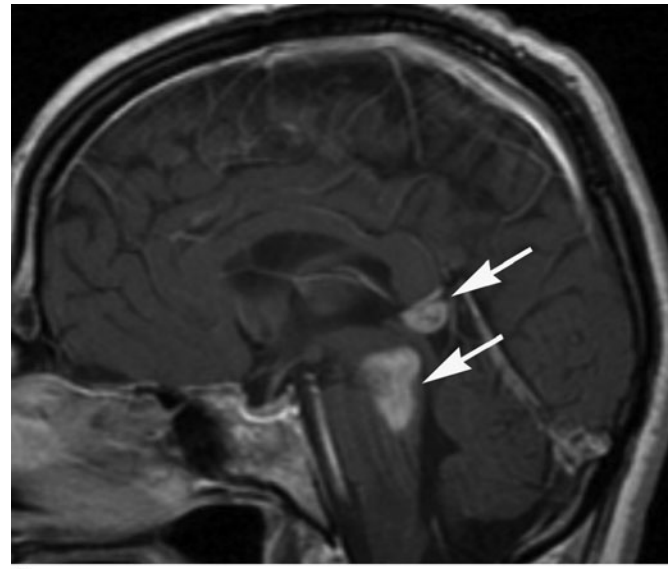
Neurosarcoid

Case III

Axial FLAIR images (***A–E***) demonstrate abnormal high signal and slight expansion in the midbrain, dorsal pons, and pineal region (*arrows*) without significant mass effect.



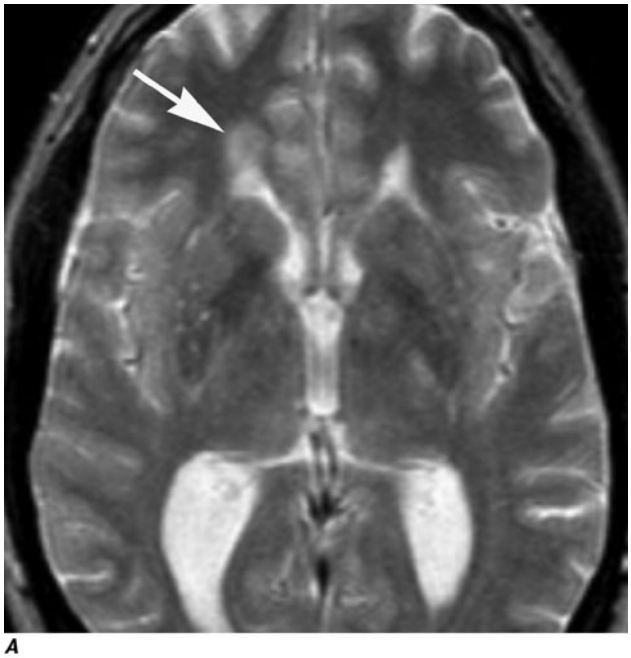
E



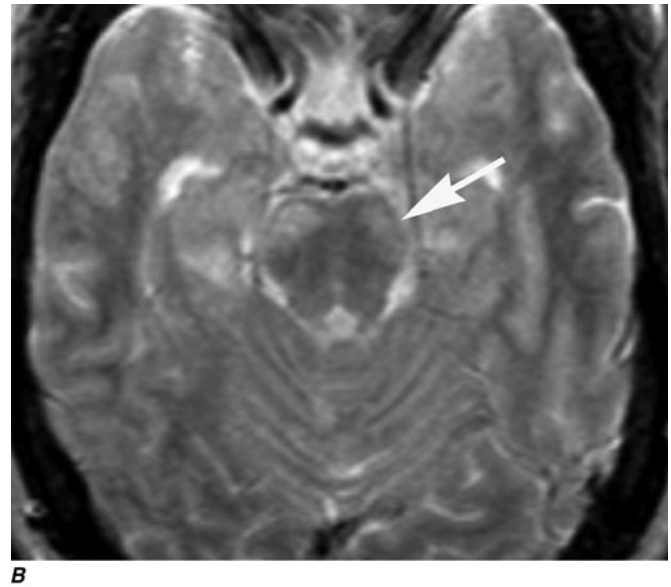
F

FIGURE 46-13 (*Continued*)

Sagittal T1-weighted images post-gadolinium (***F***) with fat suppression demonstrate abnormal enhancement in the midbrain, dorsal pons, and pineal region (*arrows*).



A



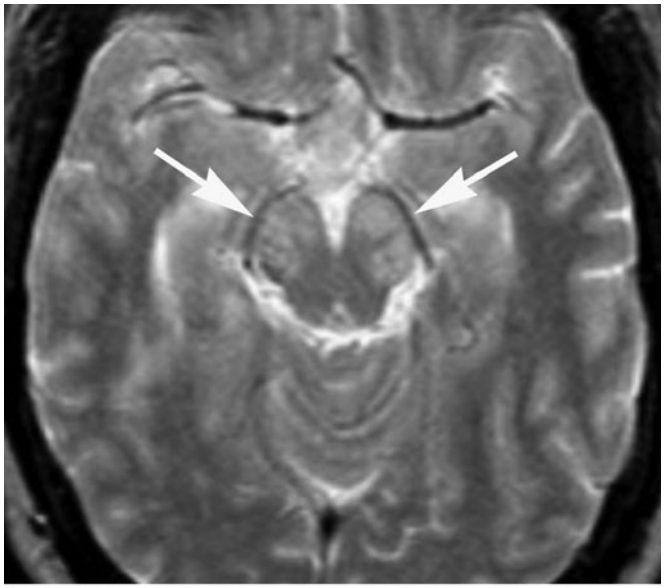
B

FIGURE 46-14

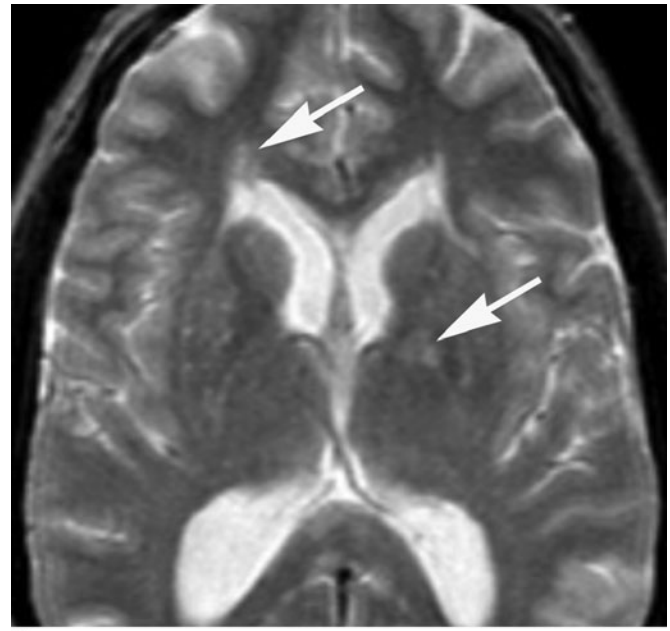
Neurosarcoid

Case IV

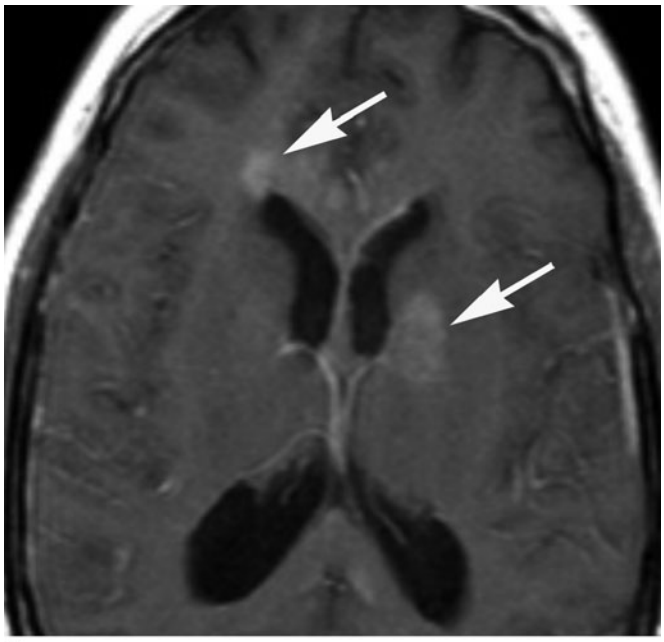
Axial T2-weighted images (***A–D***) demonstrate numerous areas of abnormal hyperintensity involving the corpus callosum, left internal capsule and globus pallidus, bilateral cerebral peduncles, bilateral gyrus rectus, right frontal lobe periventricular white matter, and patchy areas in bilateral temporal lobes.



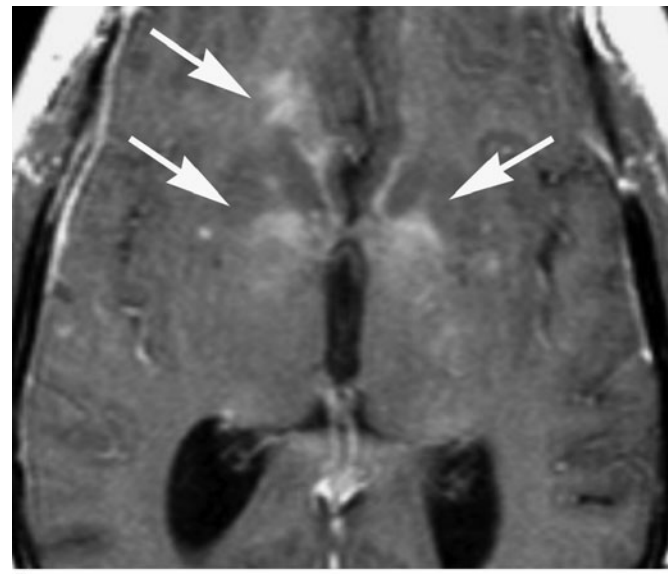
C



D



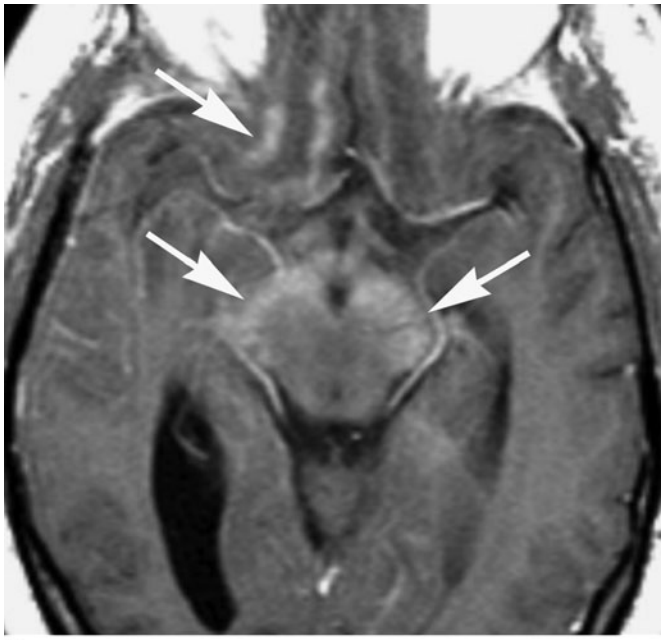
E



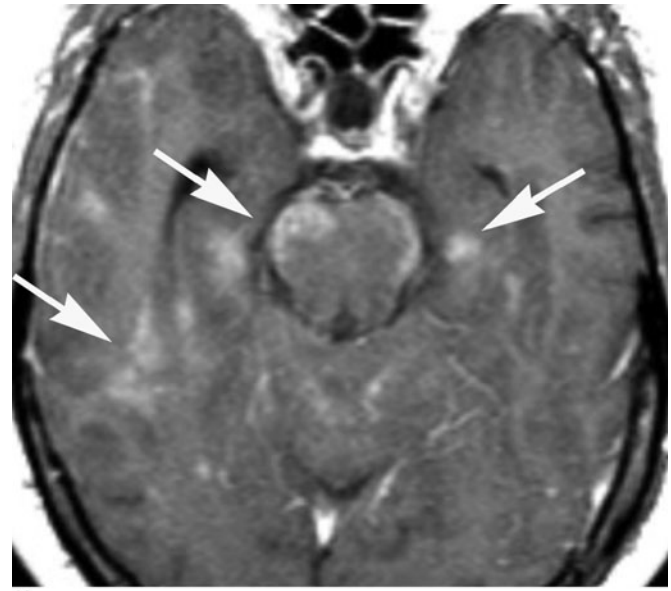
F

FIGURE 46-14 (*Continued*)

T1-weighted images post-gadolinium (***E–H***) demonstrate abnormal enhancement of those areas with high T2 signal. (*Continued*)

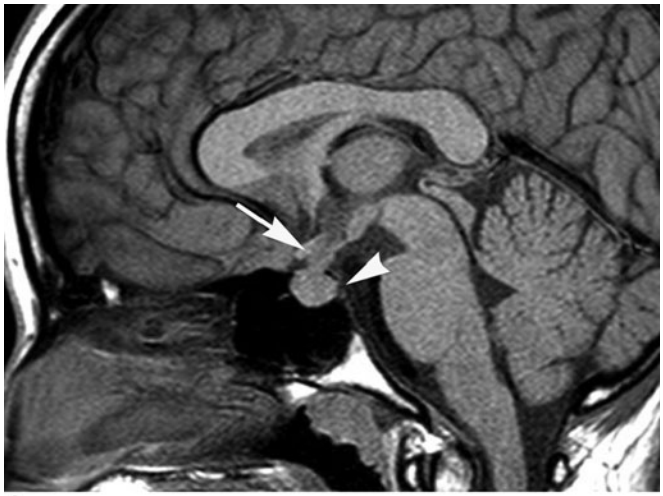


G

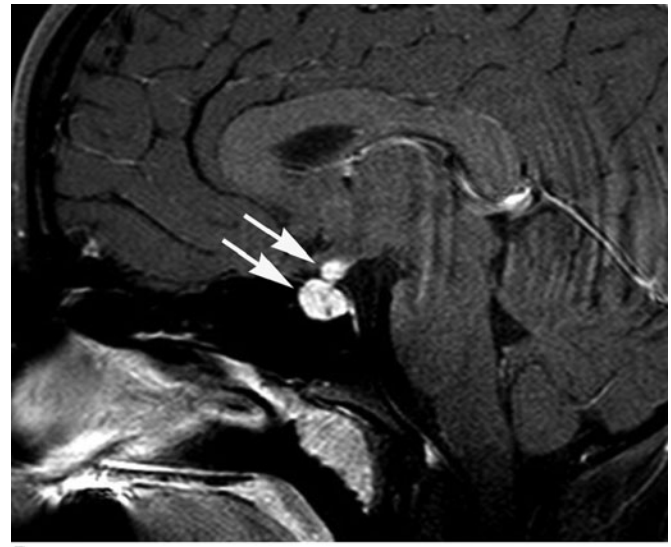


H

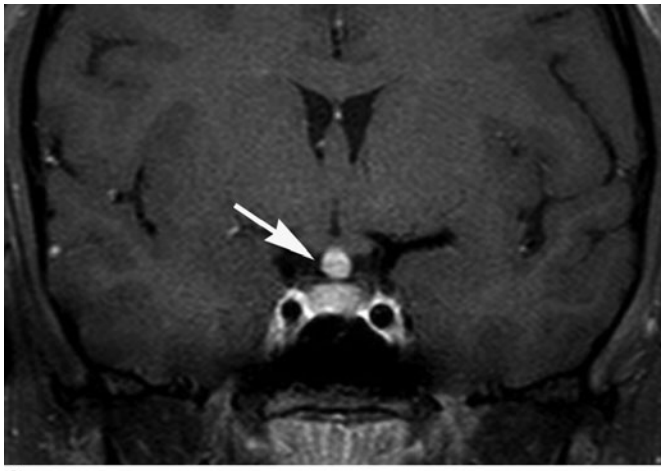
FIGURE 46-14 (*Continued*)



A



B



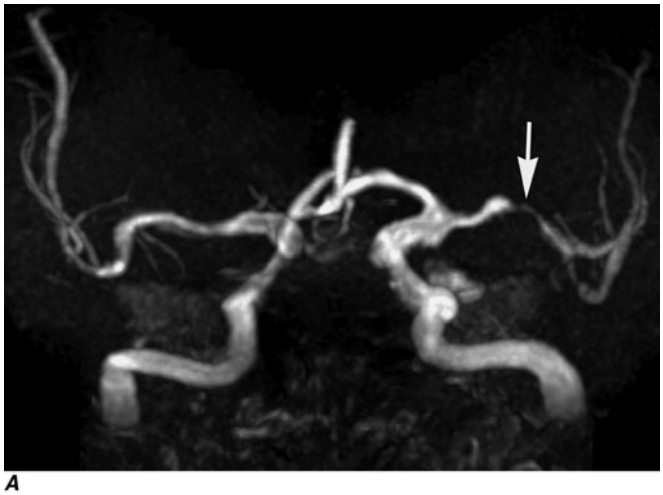
C

FIGURE 46-15

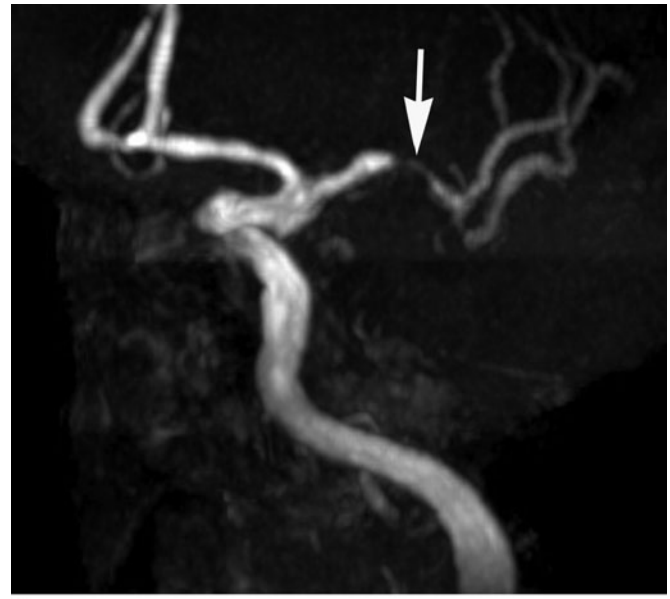
Histiocytosis

Sagittal T1-weighted image (***A***) demonstrates enlargement of the pituitary stalk (*arrow*) and absence of the posterior pituitary intrinsic T1 hyperintensity (*arrowhead*).

Sagittal and coronal T1-weighted images post-gadolinium (***B, C***) demonstrate enhancement of the pituitary stalk and infundibulum (*arrows*).



A

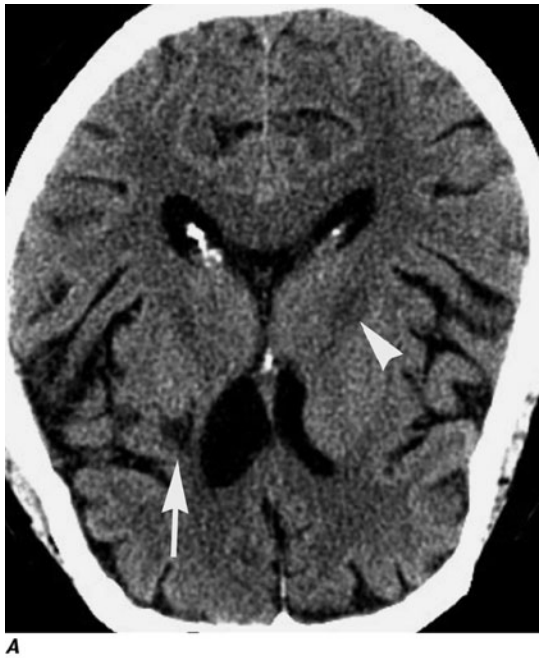


B

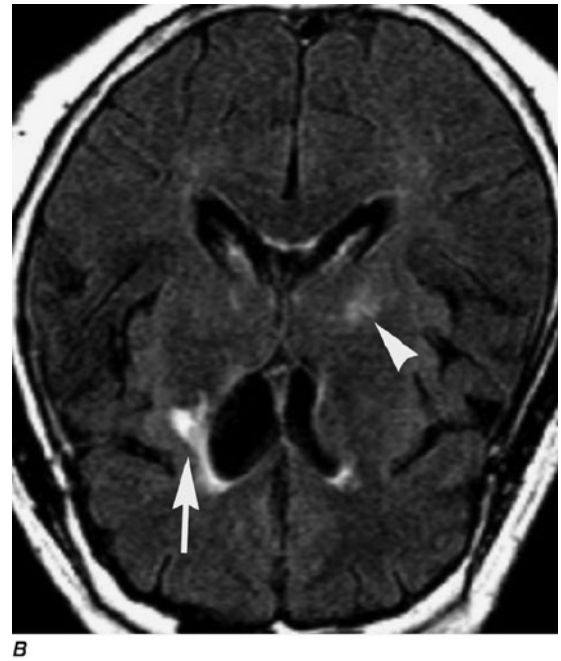
FIGURE 46-16

Middle cerebral artery stenosis (Chap. 21)

Time-of-flight (TOF) MR angiography (MRA) (***A, B***) reveals narrowing within the left M1 segment that is likely secondary to atherosclerosis (*arrows*).



A



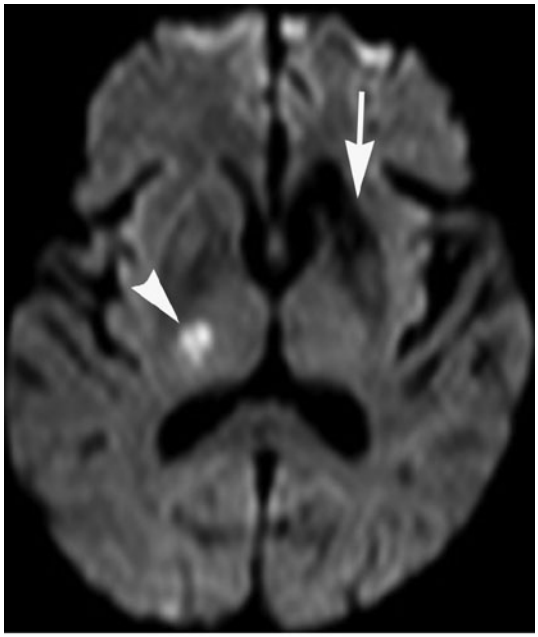
B

FIGURE 46-17

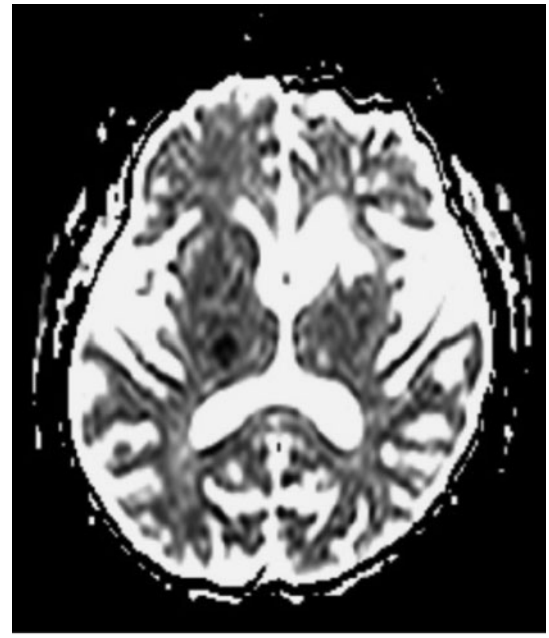
Lacunar infarction (Chap. 21)

Axial noncontrast CT (***A***) demonstrates abnormal hypodensity involving the left anterior putamen and anterior limb of internal capsule with ex-vacuo dilatation of the adjacent frontal horn of the left lateral ventricle, suggestive of an old infarction (*arrow*). A small area of slight hypodensity is also seen in the posterior limb of the right internal capsule that can correspond to an acute infarct (*arrowhead*).

Axial FLAIR MRI (***B***) demonstrates abnormal high signal involving the left anterior putamen and anterior limb of internal capsule with ex-vacuo dilatation of the adjacent frontal horn of the left lateral ventricle, suggestive of an old infarction (*arrow*). A small area of slight hyperintensity is also seen in the posterior limb of the right internal capsule that can correspond to an acute lacunar infarct (*arrowhead*).



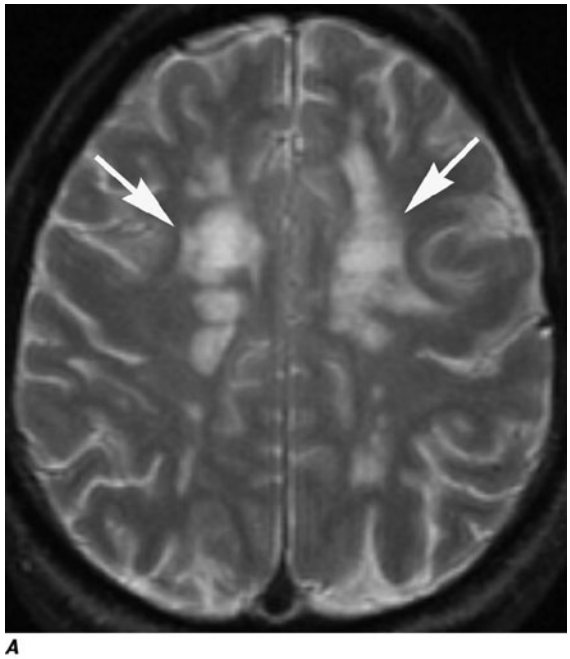
C



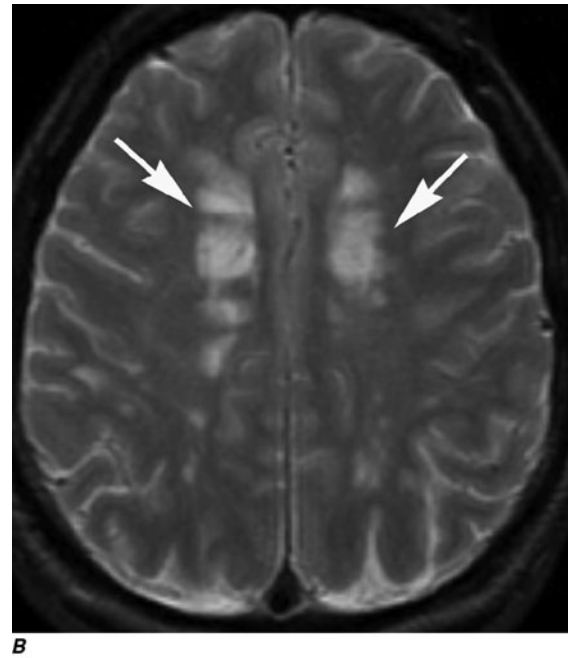
D

FIGURE 46-17 (*Continued*)

Diffusion-weighted image (***C***) and apparent diffusion coefficient (ADC) map (***D***) demonstrate restricted water motion in the lesion of the posterior limb of the right internal capsule, strongly suggestive for an acute lacunar infarct (*arrowhead*). There is no evidence of restricted diffusion in the old infarct (*arrow*).



A

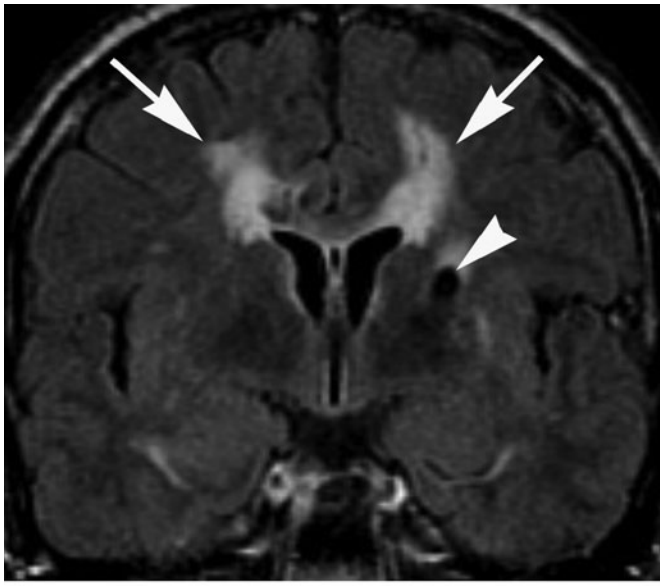


B

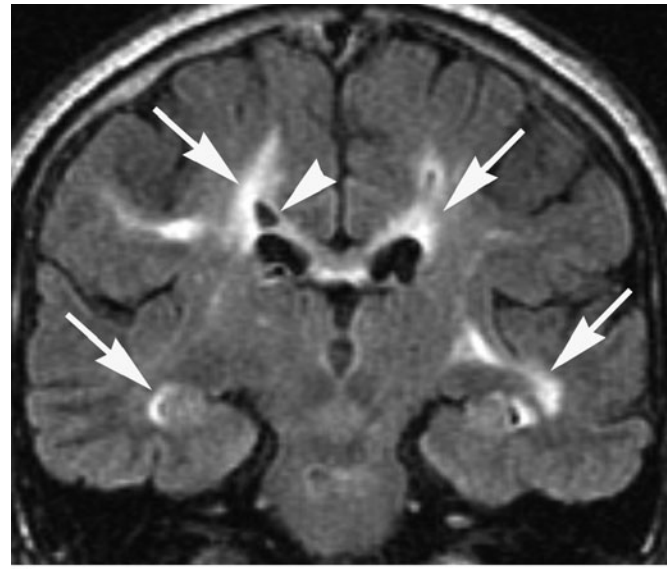
FIGURE 46-18

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (Chap. 21)

Axial T2-weighted MR images (***A, B***) demonstrate multiple patchy areas of abnormal high signal in the periventricular white matter (*arrows*).



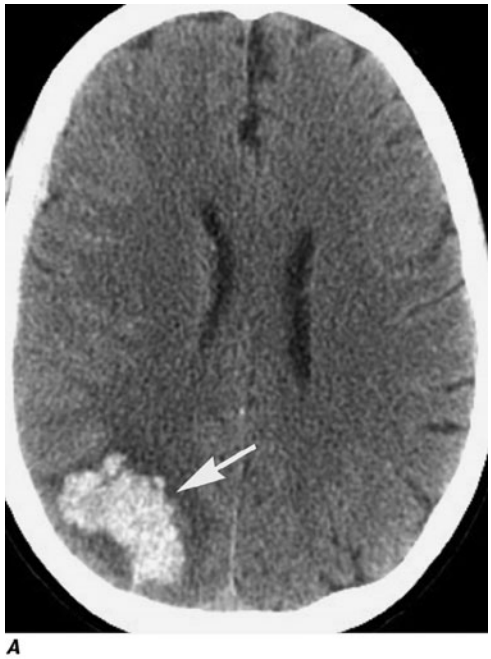
C



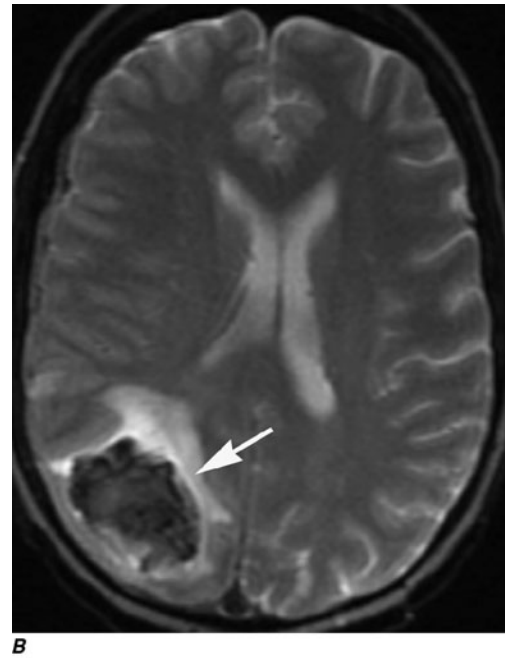
D

FIGURE 46-18 (*Continued*)

Coronal FLAIR MRI (***C, D***) demonstrates multiple patchy areas of abnormal high signal in the periventricular white matter bilaterally, including the temporal lobes (*arrows*). In some of these areas, there are small areas of tissue loss (encephalomalacia) (*arrowheads*).



A



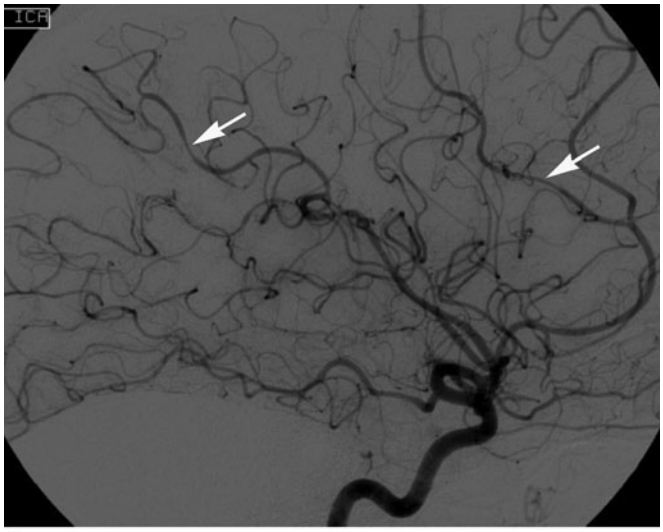
B

FIGURE 46-19

CNS vasculitis

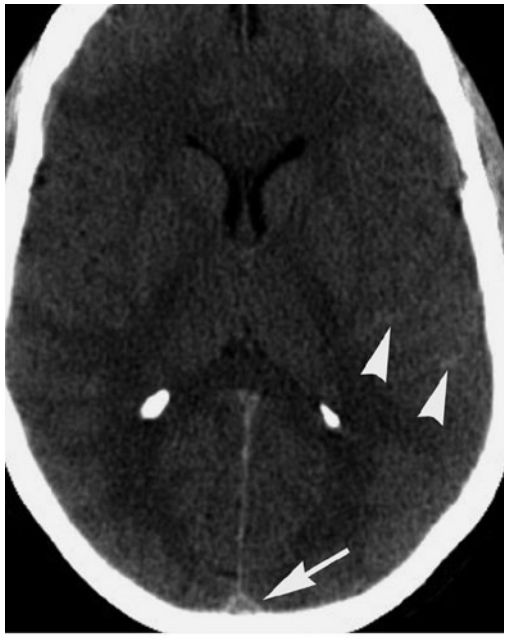
Axial noncontrast CT (***A***) demonstrates a large hyperdense intraparenchymal hematoma surrounded by hypodense vasogenic edema in the right parietal lobe.

Axial T2-weighted MRI (***B***) demonstrates a large hypointense intraparenchymal hematoma surrounded by hyperintense vasogenic edema in the right parietal lobe.

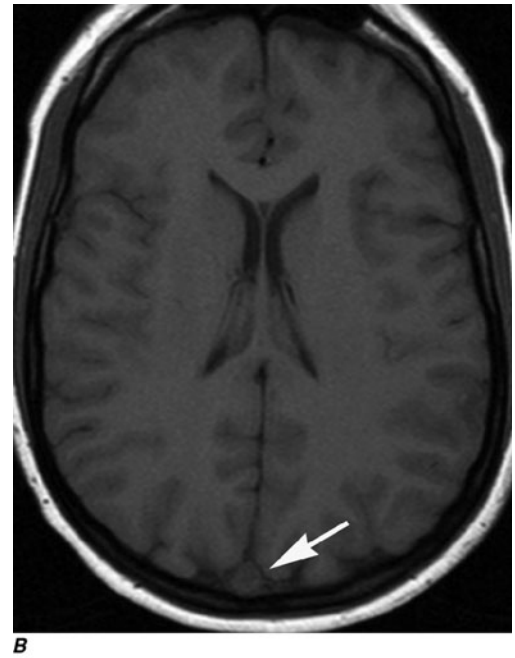


C

FIGURE 46-19 (*Continued*)
Conventional angiography (***C***) demonstrates multiple segments of intracranial arterial narrowing, some of which have associated adjacent areas of focal arterial dilatation. These abnormalities are suggestive of vasculitis.

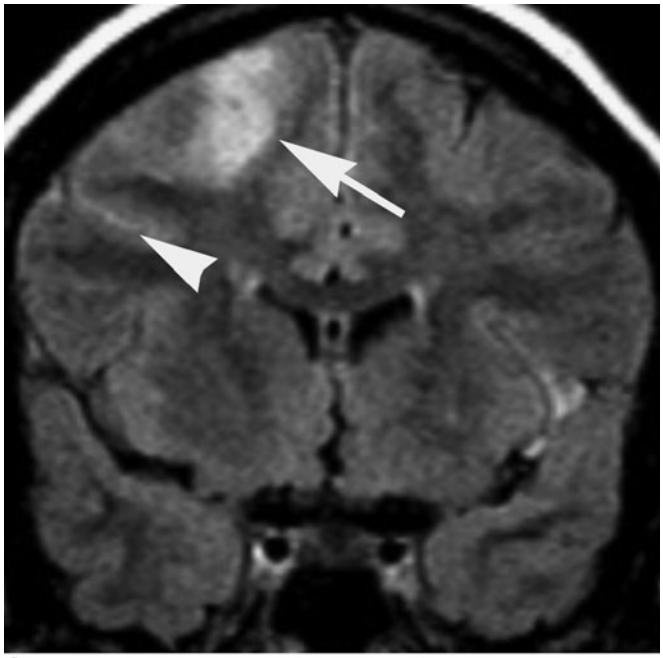


A

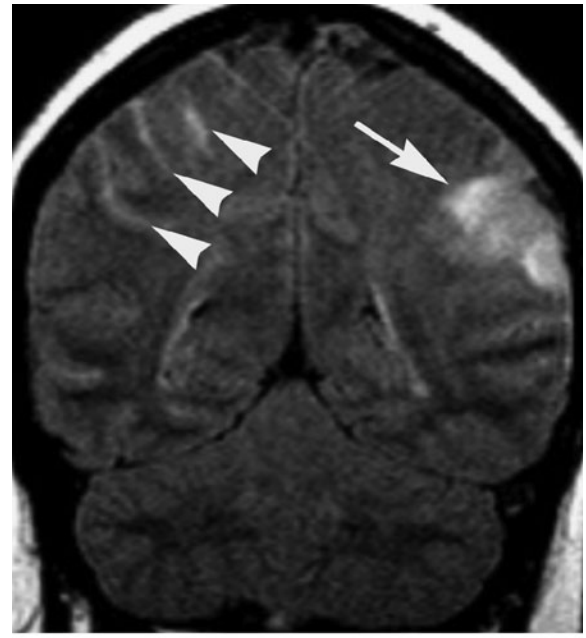


B

FIGURE 46-20
Superior sagittal sinus thrombosis (Chap. 21)
Noncontrast CT of the head (***A***) demonstrates increased density in the superior sagittal sinus, suggestive of thrombosis (*arrow*), and small linear hyperdensities in some temporal lobe sulci, suggestive of subarachnoid hemorrhage (*arrowheads*). Axial T1-weighted MRI (***B***) demonstrates absence of flow void in the superior sagittal sinus, suggestive of thrombosis.

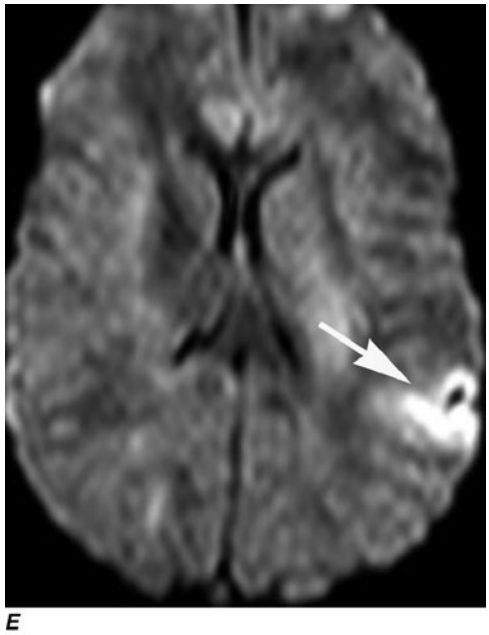


C

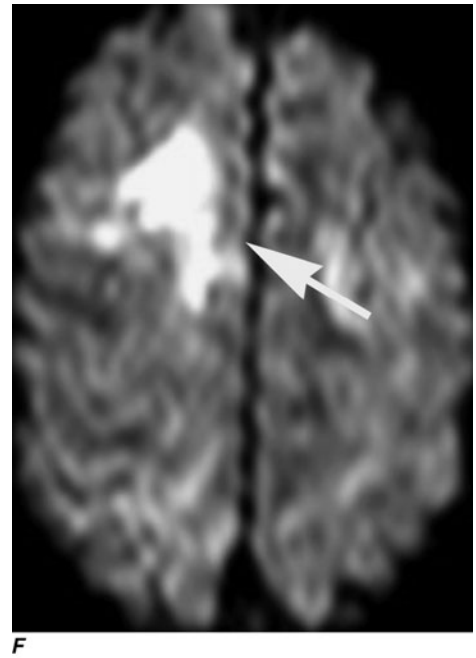


D

FIGURE 46-20 (*Continued*)
Coronal FLAIR images (***C, D***) demonstrate areas of abnormal high signal involving the gray and the subcortical white matter of the right frontal and left parietal lobes, as well as the adjacent sulci. These findings are suggestive of vasogenic edema with subarachnoid hemorrhage (*arrowheads*).

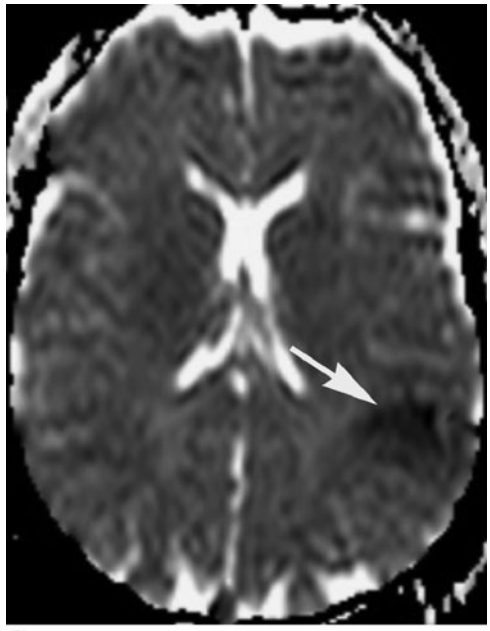


E

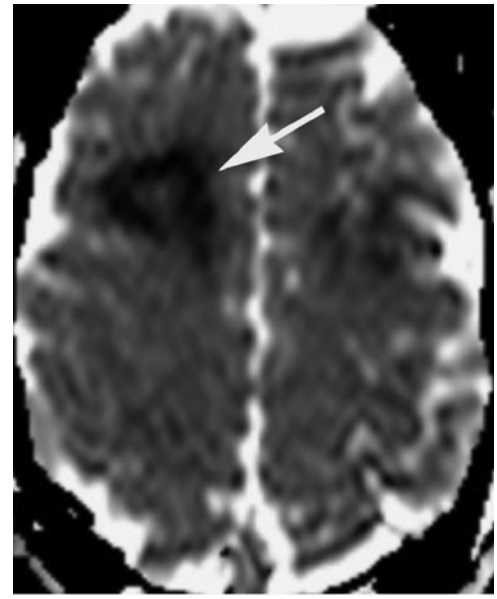


F

FIGURE 46-20 (*Continued*)

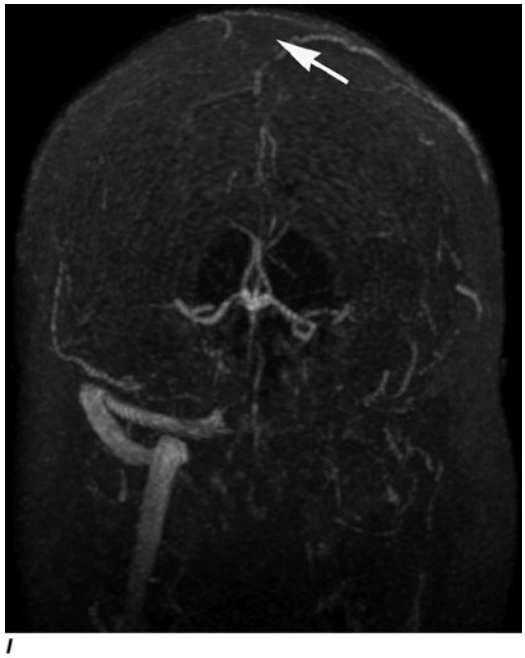


G

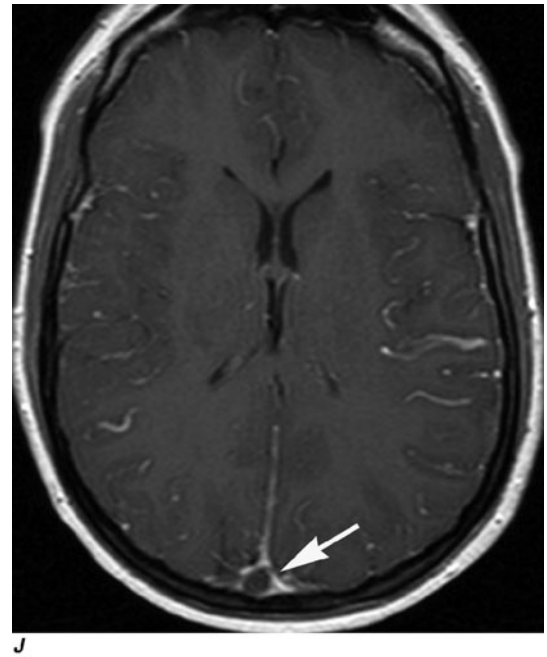


H

FIGURE 46-20 (*Continued*)
Diffusion-weighted images (***E, F***) and ADC maps (***G, H***) demonstrate restricted diffusion of the abnormal areas on FLAIR, suggestive of infarct.

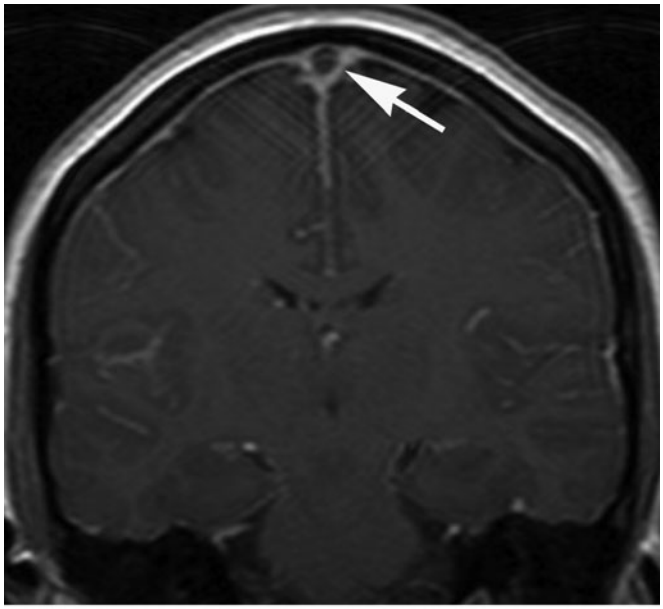


I



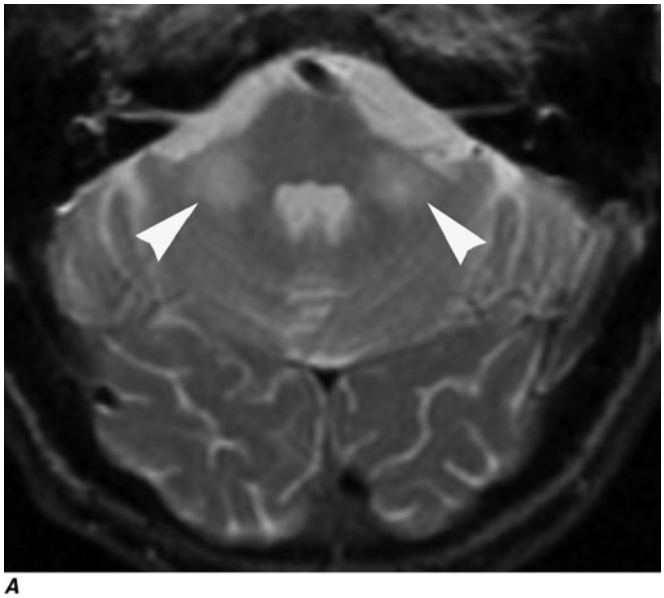
J

FIGURE 46-20 (*Continued*)
Phase-contrast venography of the brain (***I***) demonstrates absence of signal in the superior sagittal sinus down to the torcular herophili, and left transverse sinus and jugular vein.

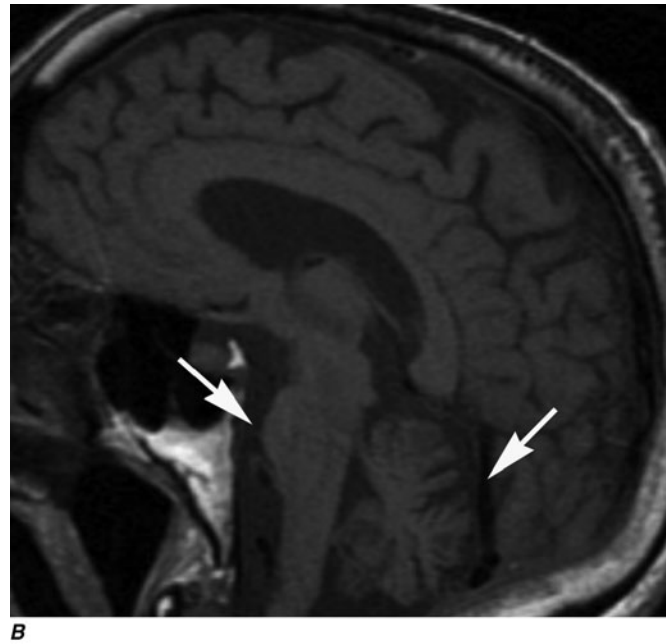


K

FIGURE 46-20 (*Continued*)
Axial (***J***) and coronal (***K***) T1-weighted images post-gadolinium demonstrate a filling defect in the superior sagittal sinus, suggestive of thrombosis.



A



B

FIGURE 46-21
Multiple system atrophy (Chap. 26)
Axial T2-weighted MR image (***A***) reveals symmetric poorly circumscribed abnormal high signal in the middle cerebellar peduncles bilaterally (*arrowheads*).

Sagittal T1-weighted MR image (***B***) demonstrates pontine atrophy and enlarged cerebellar fissures as a result of cerebellar atrophy (*arrows*).

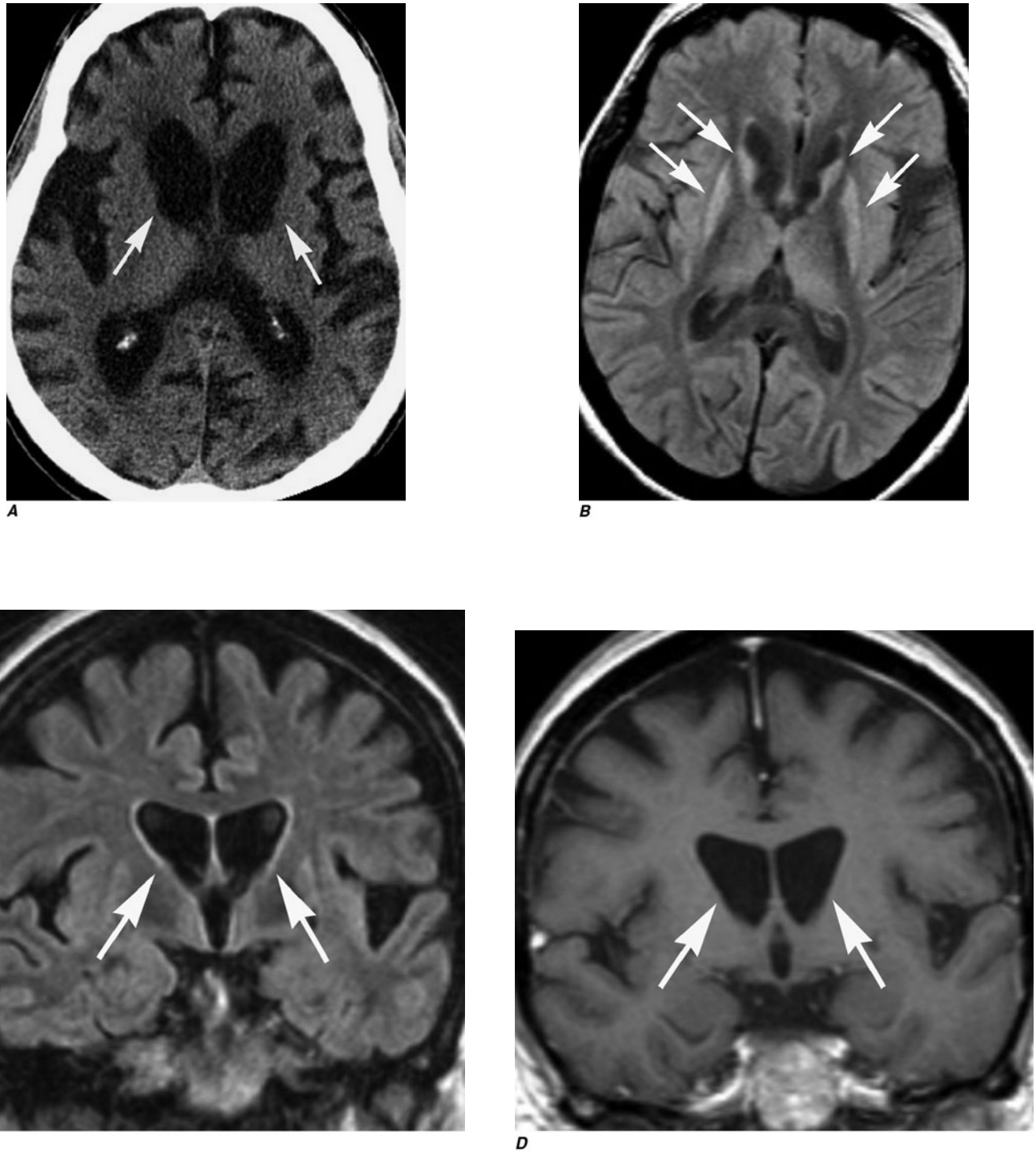
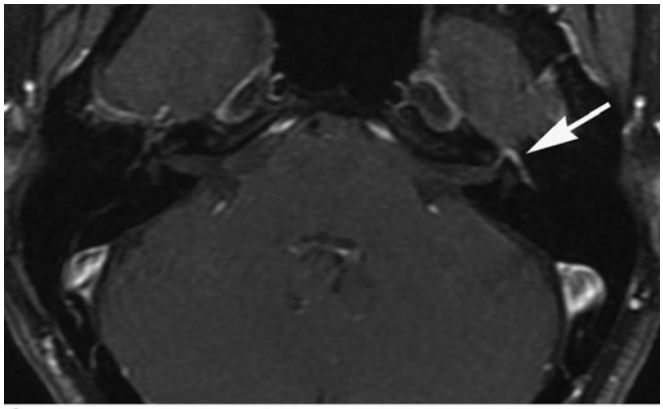


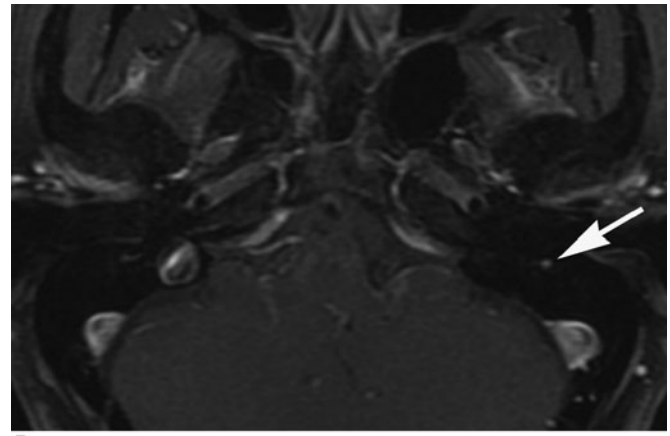
FIGURE 46-22

Huntington's disease (Chap. 25)

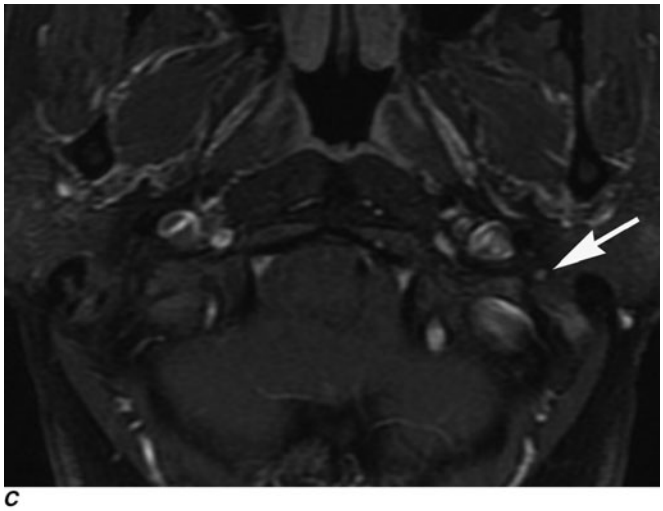
Axial noncontrast CT (***A***) demonstrates symmetric bilateral severe atrophy involving the caudate nuclei, putamen, and globus pallidi bilaterally with consequent enlargement of the frontal horns of the lateral ventricles (*arrows*). There is also diffuse prominence of the sulci indicating generalized cortical atrophy. Axial (***B***) and coronal (***C***) FLAIR images demonstrate bilateral symmetric abnormal high signal in the caudate and putamen. Coronal T1-weighted image (***D***) demonstrates enlarged frontal horns with abnormal configuration. Also note diffusely decreased marrow signal, which could represent anemia or myeloproliferative disease.



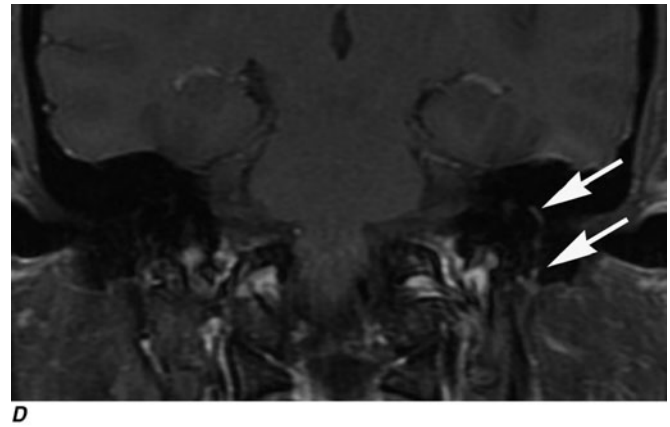
A



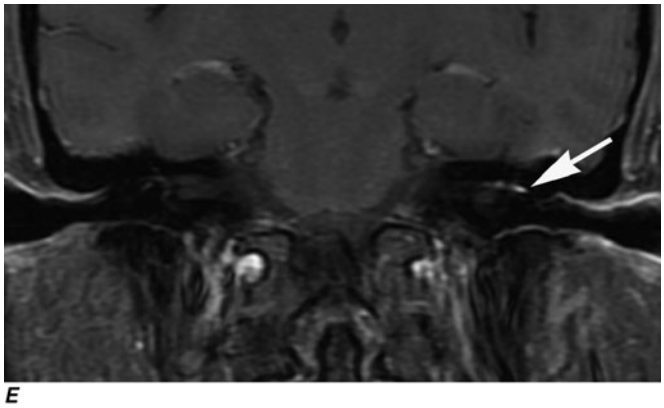
B



C



D



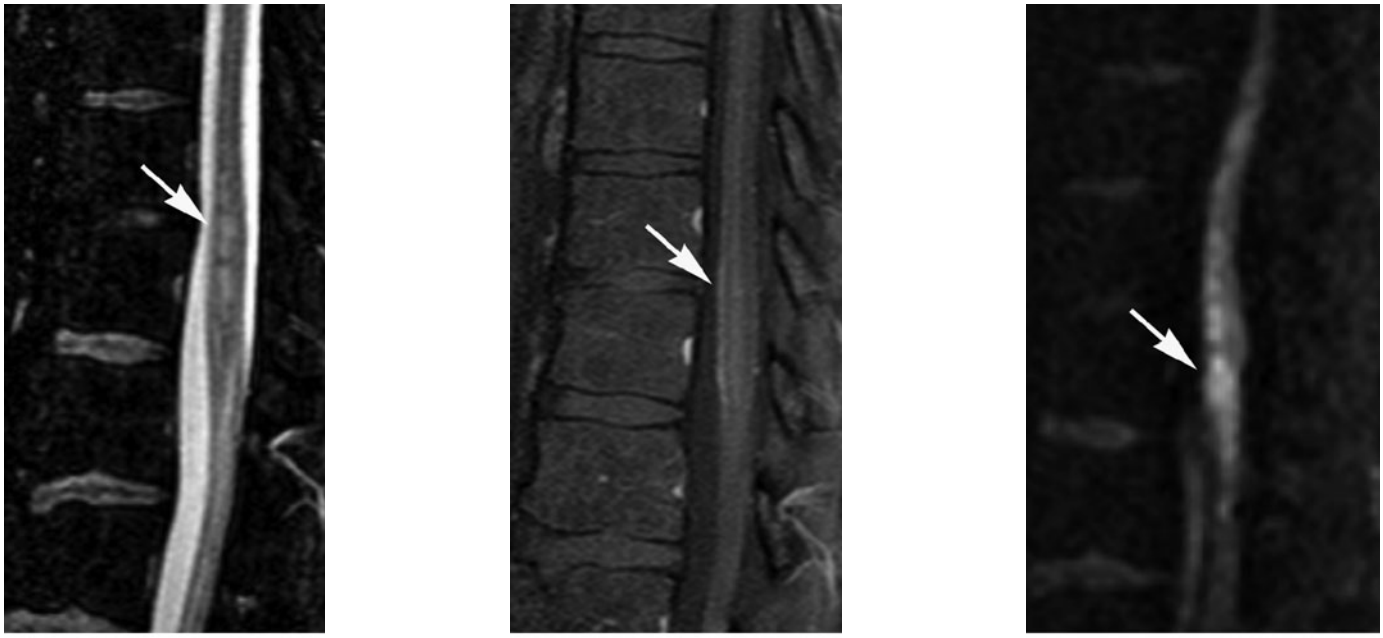
E

FIGURE 46-23

Bell's palsy (Chap. 29)

Axial T1-weighted images post-gadolinium with fat suppression (***A–C***) demonstrate diffuse smooth linear enhancement along the left facial nerve, involving the second and third segments (genus, tympanic, and mastoid) within the temporal bone (*arrows*). Note that there is no evidence of a mass lesion. A potential pitfall for facial nerve enhancement in the stylomastoid foramen is the enhancement of the stylomastoid artery that enters the foramen and supplies the tympanic cavity, the tympanic antrum, mastoid cells, and the semicircular canals.

Coronal T1-weighted images post-gadolinium with fat suppression (***D, E***) demonstrate the course of the enhancing facial nerve (*arrows*). Although these findings are highly suggestive of Bell's palsy, the diagnosis is established on clinical grounds.



A B C

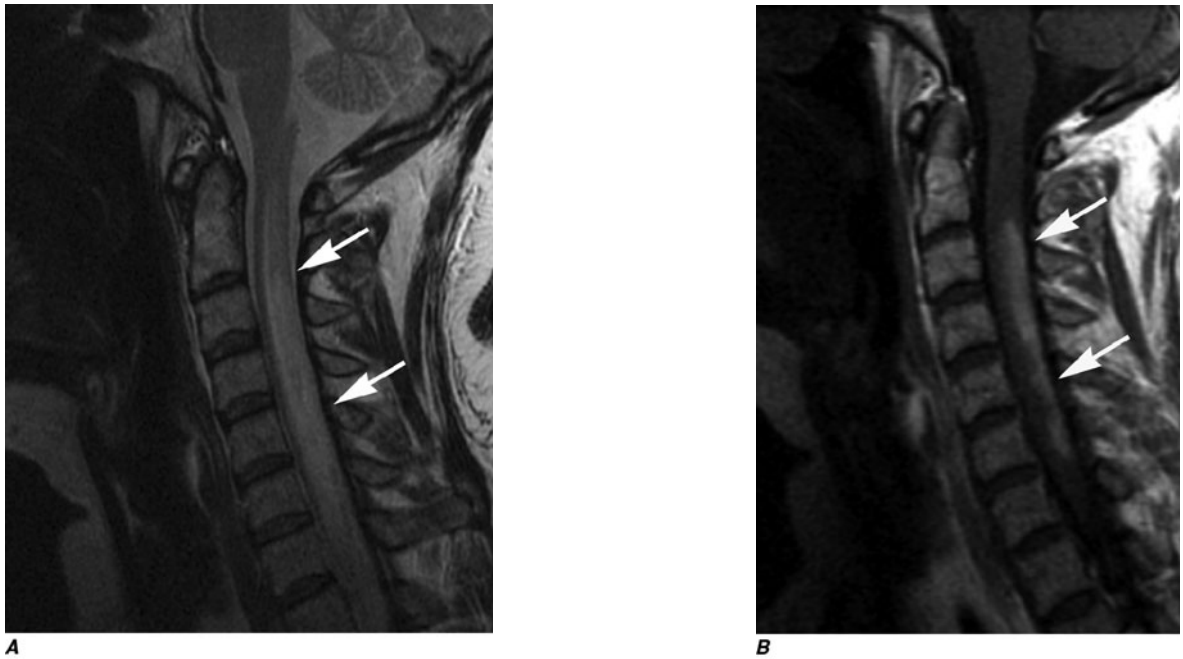
FIGURE 46-24

Spinal cord infarction (Chap. 30)

Sagittal T2-weighted MR image of the lumbar spine (***A***) demonstrates poorly defined areas of abnormal high signal in the conus medullaris and mild cord expansion (*arrow*).

T1-weighted MR image of the lumbar spine post-gadolinium (***B***) demonstrates mild enhancement (*arrow*).

Sagittal diffusion-weighted MR image of the lumbar spine (***C***) demonstrates restricted diffusion (*arrow*) in the areas of abnormal high signal on the T2-weighted image (***A***).



A B

FIGURE 46-25

Acute transverse myelitis (Chap. 30)

Sagittal T2-weighted MR image (***A***) demonstrates abnormal high signal in the cervical cord extending from C1 to T1 with associated cord expansion (*arrows*).

Sagittal T1-weighted MR image post-gadolinium (***B***) demonstrates abnormal enhancement in the posterior half of the cord from C2 to T1 (*arrows*).

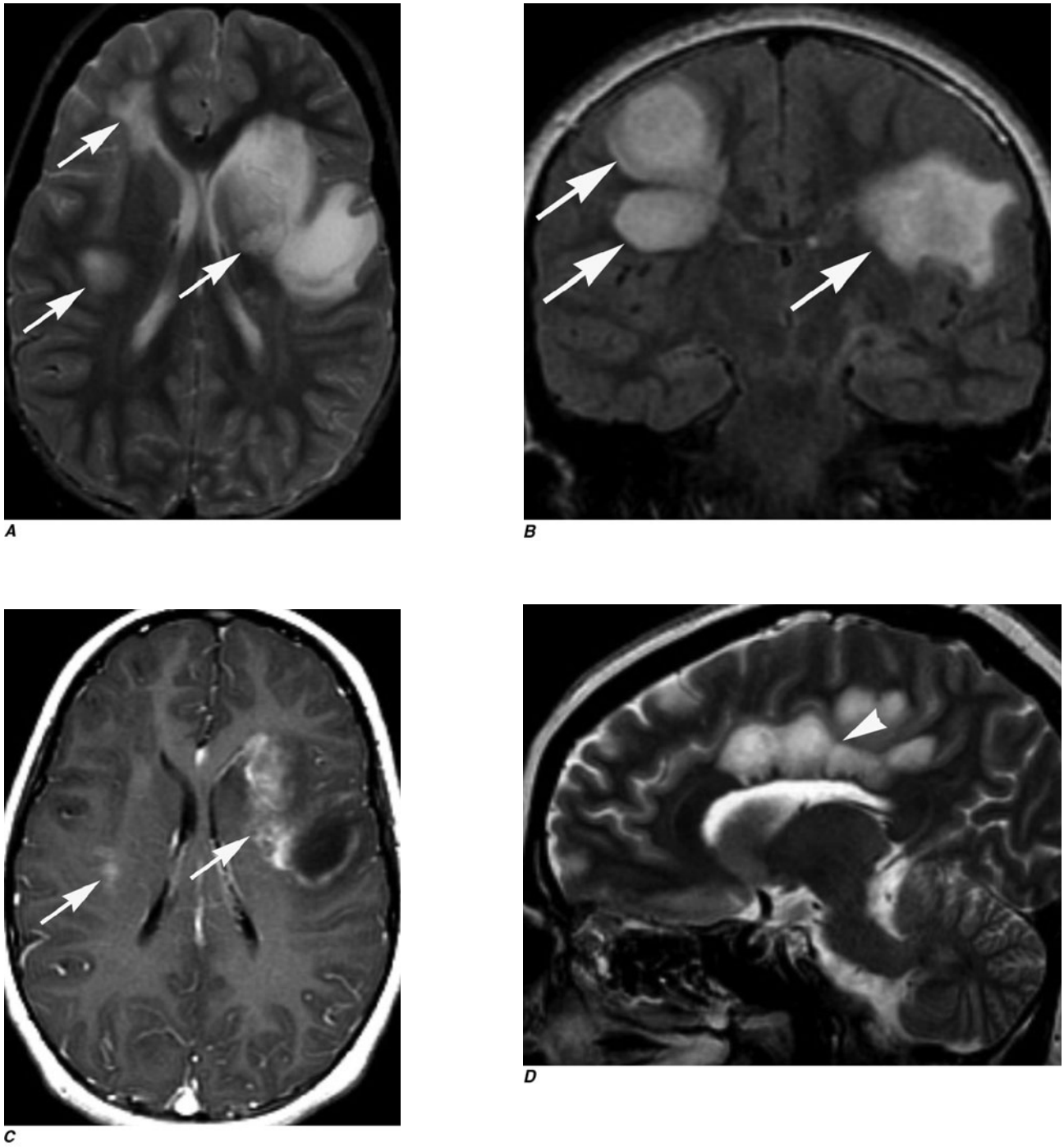
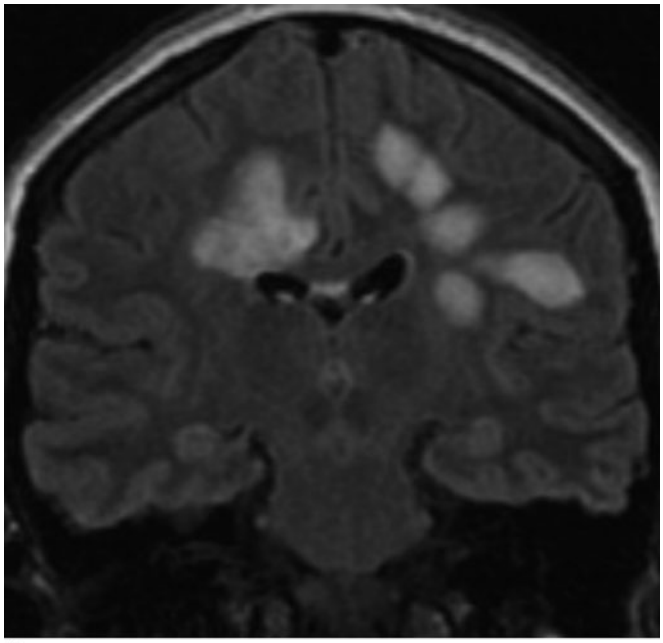
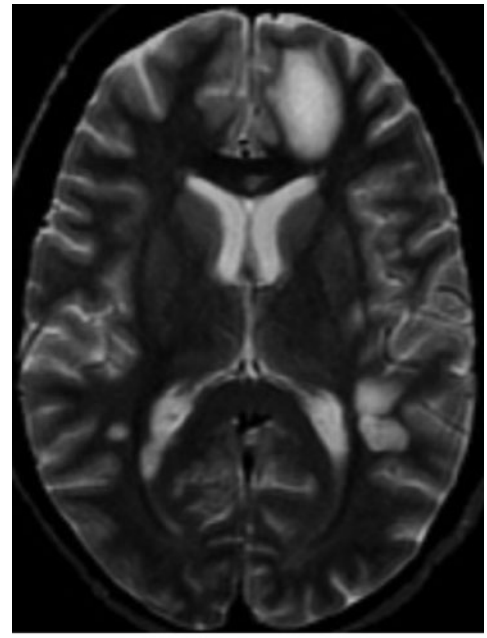


FIGURE 46-26

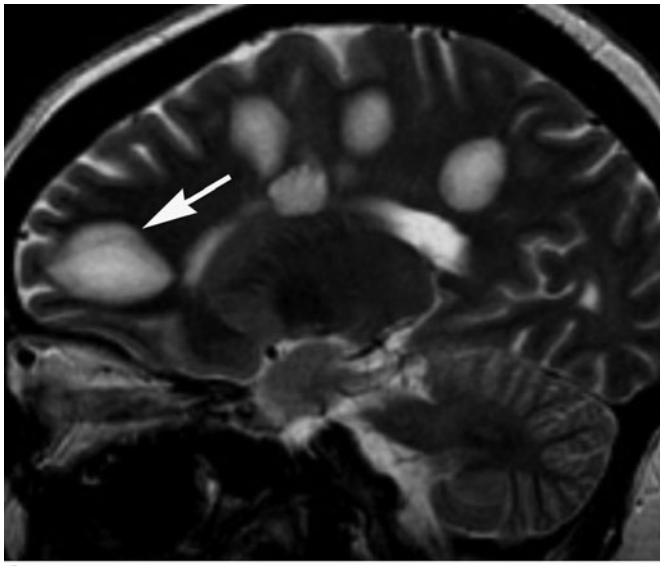
Acute disseminated encephalomyelitis (ADEM) (Chap. 34) Axial T2-weighted (***A***) and coronal FLAIR (***B***) images demonstrate abnormal areas of high signal involving predominantly the subcortical white matter of the frontal lobe bilaterally, and left caudate head. Following administration of gadolinium, corresponding axial (***C***) and coronal (***D***) T1-weighted images demonstrate irregular enhancement consistent with blood-brain barrier breakdown and inflammation; some lesions show incomplete rim enhancement, typical for demyelination.



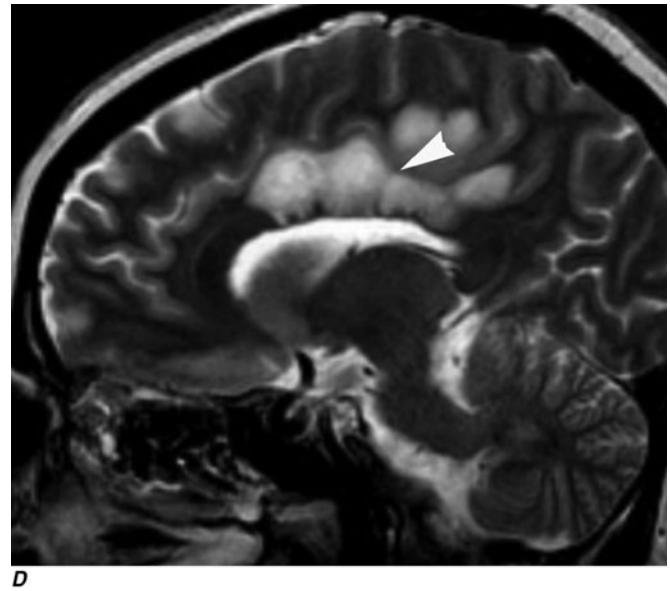
A



B



C

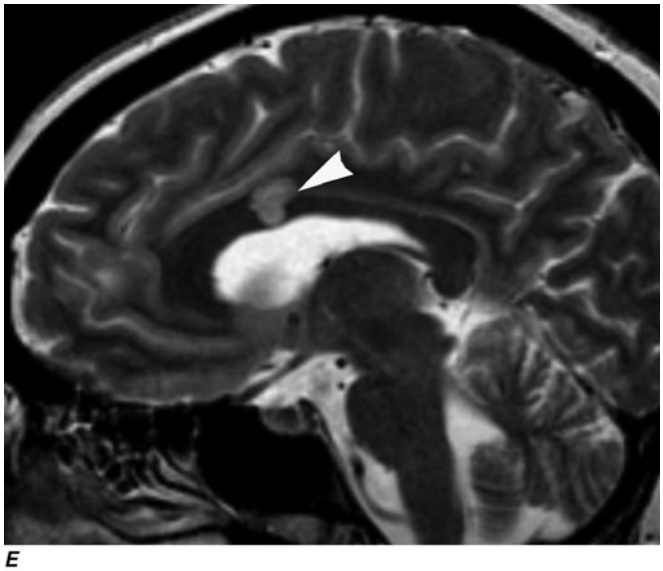


D

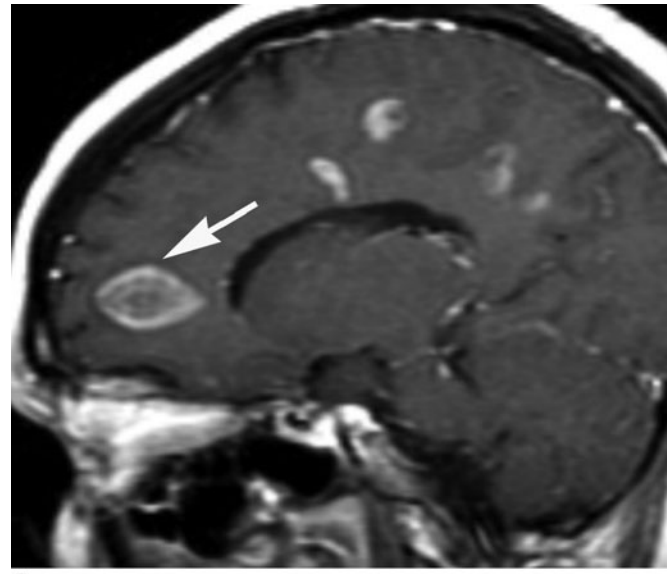
FIGURE 46-27

Balo's concentric sclerosis (a variant of multiple sclerosis) (Chap. 34)

Coronal FLAIR MRI (***A***) demonstrates multiple areas of abnormal high signal in the supratentorial white matter bilaterally. The lesions are ovoid in shape, perpendicular to the orientation of the lateral ventricles, and with little mass effect. Axial (***B***) and sagittal (***C–E***) T2-weighted MR images demonstrate multiple areas of abnormal high signal in the supratentorial white matter bilaterally, as well as the involvement of the body and splenium of the corpus callosum and the callosal-septal interface (*arrowhead*). Some of the lesions reveal concentric layers, typical of Balo's concentric sclerosis (*arrows*).



E



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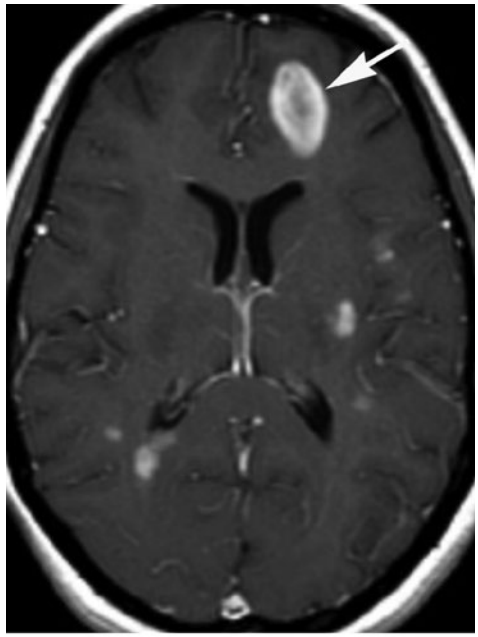
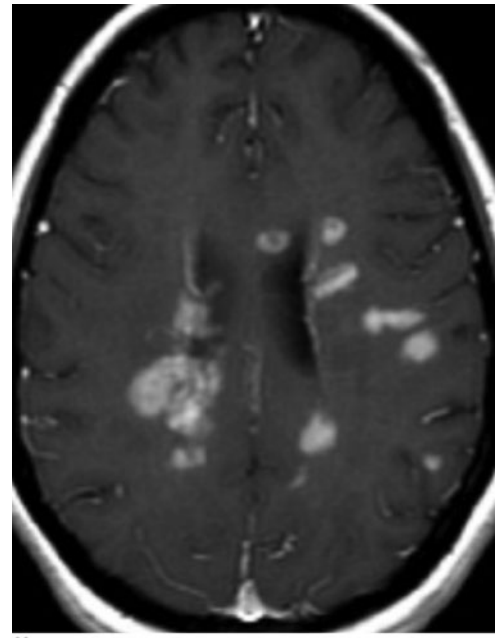
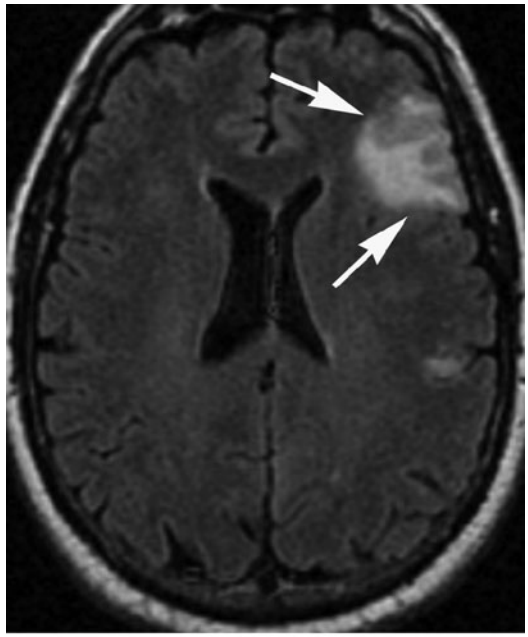


G

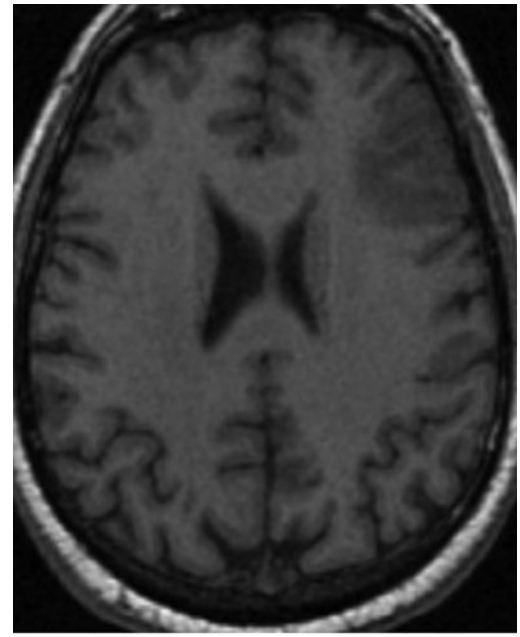


H

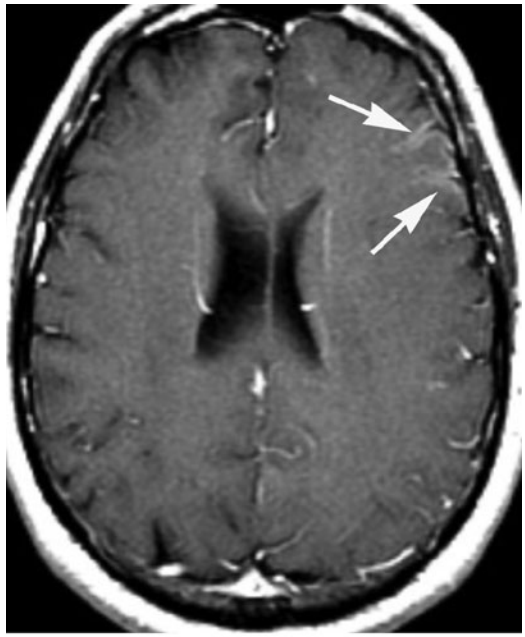
FIGURE 46-27 (*Continued*)
Sagittal (***F***) and axial (***G, H***) T1-weighted MR images post-gadolinium demonstrate abnormal enhancement of all lesions with some of the lesions demonstrating concentric ring enhancement (*arrows*).



A



B



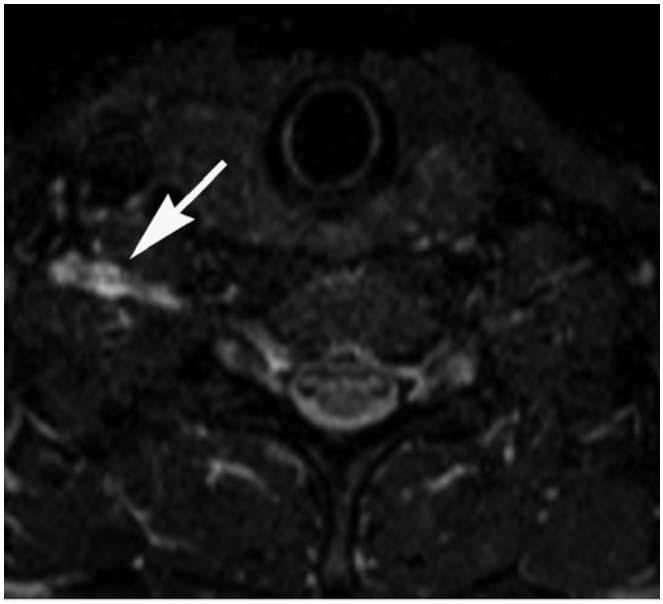
C

FIGURE 46-28

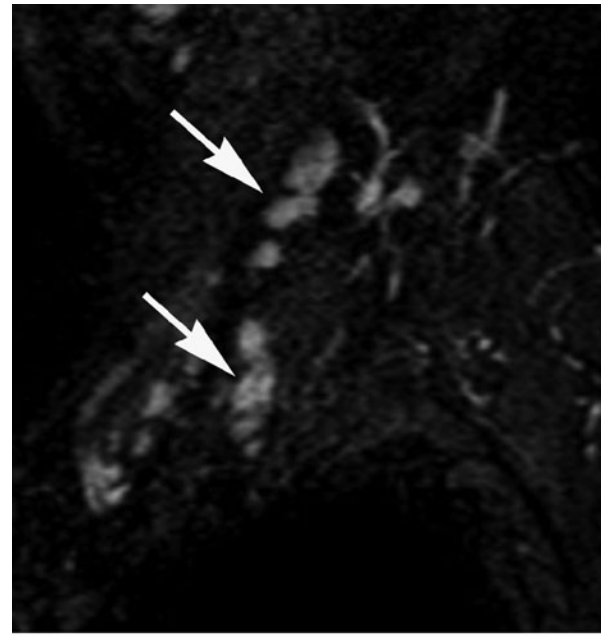
Hashimoto's encephalopathy

Axial FLAIR (***A***) demonstrates focal area of abnormal high signal involving the gray and white matter in the left frontal lobe. There is also a small area of abnormal high signal in the precentral gyrus.

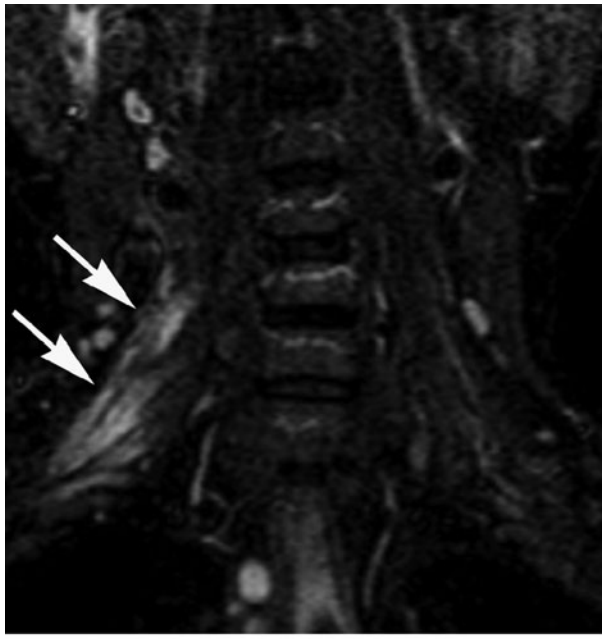
Axial T1-weighted images (***B, C***) pre- and post-gadolinium demonstrate cortical/pial enhancement in the region of high signal on FLAIR.



A



B



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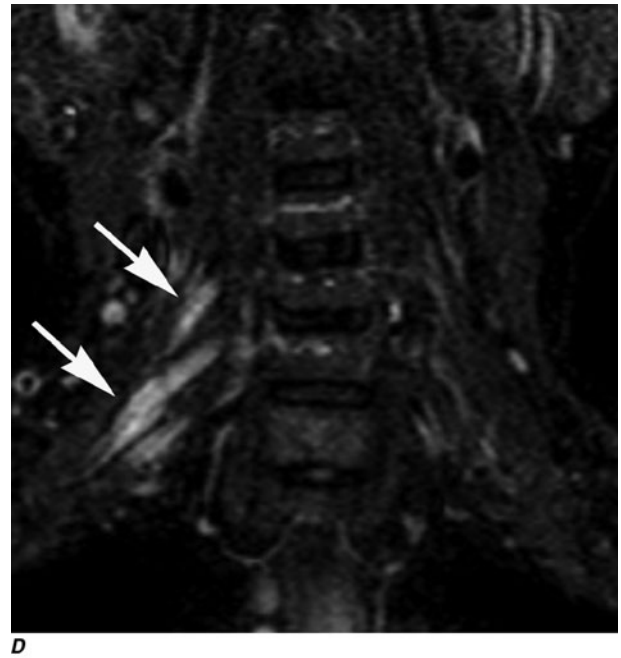
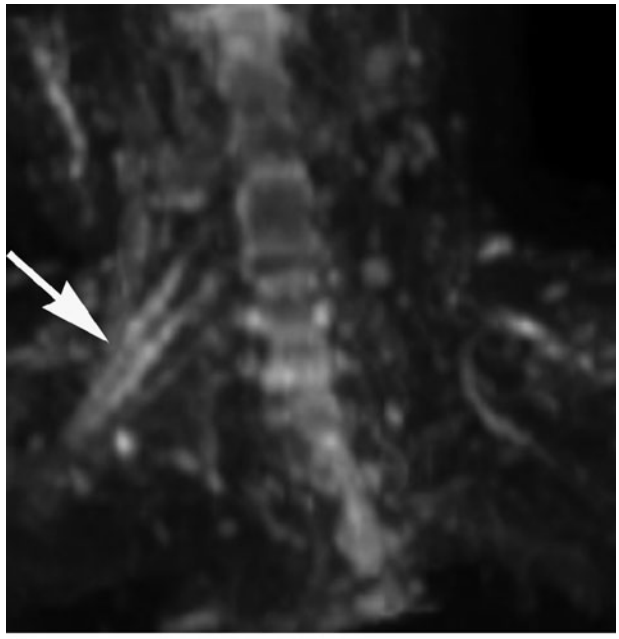


D

FIGURE 46-29

Brachial plexopathy (Chap. 7)

Axial (***A***), sagittal (***B***), and coronal (***C, D***) short tau inversion recovery (STIR) MR images demonstrate abnormal enlargement and abnormal high signal involving the right C6, C7, and C8 nerve roots, and the trunks and divisions that originate from these roots (*arrows*).

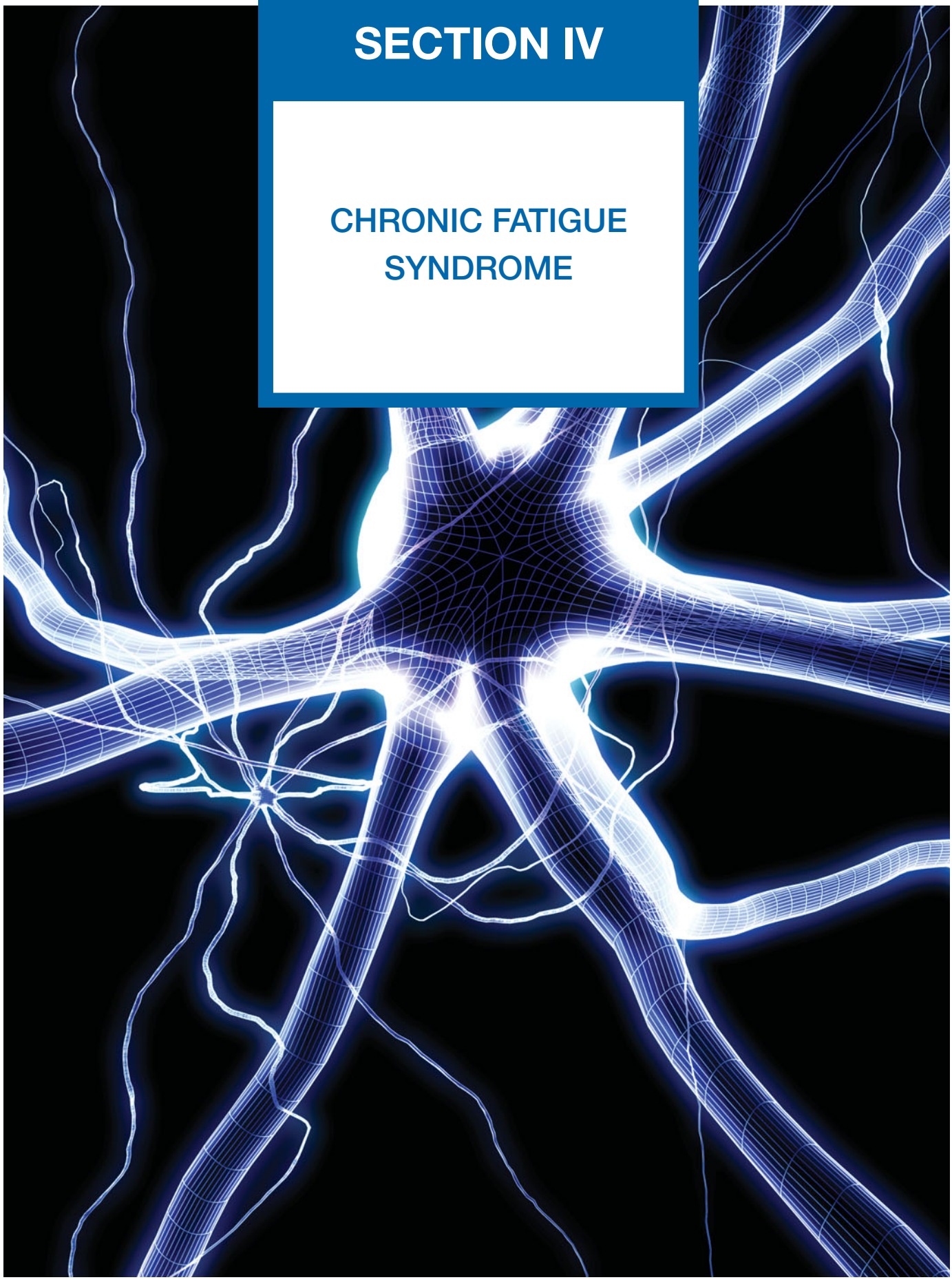


E

FIGURE 46-29 (*Continued*)
Diffusion-weighted MR imaging (***E***) demonstrates abnormal reduced diffusion within the right C6, C7, C8 nerve roots and their corresponding trunks and divisions (*arrow*). These findings are compatible with radiation-induced brachial plexopathy.

SECTION IV

CHRONIC FATIGUE SYNDROME



CHAPTER 47

CHRONIC FATIGUE SYNDROME

Stephen E. Straus†

Epidemiology 650
Pathogenesis 650
Manifestations 651
Diagnosis 652
■ Further Readings 652

Chronic fatigue syndrome (CFS) is the current name for a disorder characterized by debilitating fatigue and several associated physical, constitutional, and neuropsychological complaints (**Table 47-1**). This syndrome is not new; in the past, patients diagnosed with conditions such as the vapors, neurasthenia, effort syndrome, chronic brucellosis, epidemic neuromyasthenia, myalgic encephalomyelitis, hypoglycemia, multiple chemical sensitivity syndrome, chronic candidiasis, chronic mononucleosis, chronic Epstein-Barr virus (EBV) infection, and postviral fatigue syndrome may have had what is now called CFS. A subset of ill veterans of military campaigns suffer from CFS. The U.S. Centers for Disease Control and Prevention (CDC) has developed diagnostic criteria for CFS based upon symptoms and the exclusion of other illnesses (**Table 47-2**).

EPIDEMIOLOGY

Patients with CFS are twice as likely to be women as men and are generally 25–45 years of age, although cases in childhood and in later life have been described.

Cases are recognized in many developed countries. Most arise sporadically, but many clusters have also been reported. Famous outbreaks of CFS occurred in Los Angeles County Hospital in 1934; in Akureyri, Iceland, in 1948; in the Royal Free Hospital, London, in 1955; and in Incline Village, Nevada, in 1985. While these clustered cases suggest a common environmental or infectious cause, none has been identified.

Estimates of the prevalence of CFS have depended on the case definition used and the method of study. Chronic fatigue itself is a common symptom, occurring in as many as 20% of patients attending general medical clinics; CFS is far less common. Community-based studies find that 100–300 individuals per 100,000 population in the United States meet the current CDC case definition.

PATHOGENESIS

The diverse names for the syndrome reflect the many and controversial hypotheses about its etiology. Several common themes underlie attempts to understand the disorder: (1) it is often postinfectious; (2) it is associated with mild immunologic disturbances and sedentary behavior during childhood; and (3) it is commonly accompanied by neuropsychological complaints, somatic preoccupation, and/or depression.

Many studies over the past quarter century sought to link CFS to acute and/or persisting infections with EBV, cytomegalovirus, human herpesvirus type 6, retroviruses, enteroviruses, *Candida albicans*, *Mycoplasma* spp., or *Coxiella burnetii*, among other microbial pathogens. Compared to findings in age-matched control subjects, the titers of antibodies to some microorganisms are elevated in CFS patients. Reports that viral antigens and nucleic acids could be specifically identified in patients with CFS, however, have not been confirmed. One study from the United Kingdom failed to detect any association between acute infections and subsequent prolonged

†Deceased.

TABLE 47-1

SPECIFIC SYMPTOMS REPORTED BY PATIENTS WITH CHRONIC FATIGUE SYNDROME

SYMPTOM	PERCENTAGE
Fatigue	100
Difficulty concentrating	90
Headache	90
Sore throat	85
Tender lymph nodes	80
Muscle aches	80
Joint aches	75
Feverishness	75
Difficulty sleeping	70
Psychiatric problems	65
Allergies	55
Abdominal cramps	40
Weight loss	20
Rash	10
Rapid pulse	10
Weight gain	5
Chest pain	5
Night sweats	5

Source: From SE Straus: J Infect Diseases 157:405, 1988; with permission.

TABLE 47-2

CDC CRITERIA FOR DIAGNOSIS OF CHRONIC FATIGUE SYNDROME

A case of chronic fatigue syndrome is defined by the presence of:

1. Clinically evaluated, unexplained, persistent or relapsing fatigue that is of new or definite onset; is not the result of ongoing exertion; is not alleviated by rest; and results in substantial reduction of previous levels of occupational, educational, social, or personal activities; and
2. Four or more of the following symptoms that persist or recur during six or more consecutive months of illness and that do not predate the fatigue:
   - Self-reported impairment in short-term memory or concentration
   - Sore throat
   - Tender cervical or axillary nodes
   - Muscle pain
   - Multijoint pain without redness or swelling
   - Headaches of a new pattern or severity
   - Unrefreshing sleep
   - Postexertional malaise lasting ≥24 h

Note: CDC, U.S. Centers for Disease Control and Prevention.
Source: Adapted from K Fukuda et al: Ann Intern Med 121:953, 1994; with permission.

fatigue. Another study found that chronic fatigue did not develop after typical upper respiratory infections but did in some individuals after infectious mononucleosis. Thus, while antecedent infections are associated with CFS, a direct microbial causality is unproven and unlikely.

Changes in numerous immune parameters of uncertain functional significance have been reported in CFS. Modest elevations in titers of antinuclear antibodies, reductions in immunoglobulin subclasses, deficiencies in mitogen-driven lymphocyte proliferation, reductions in natural killer cell activity, disturbances in cytokine production, and shifts in lymphocyte subsets have been described. None of these immune findings appears in most patients, nor do any correlate with the severity of CFS. Comparison of monozygotic twin pairs discordant for CFS showed no substantive immunologic differences between affected and unaffected individuals. In theory, symptoms of CFS could result from excessive production of a cytokine, such as interleukin 1, which induces asthenia and other flulike symptoms; however, compelling data in support of this hypothesis are lacking. A recently published population-based study from Wichita, Kansas, reported differences in gene expression patterns and in candidate gene polymorphisms between CFS patients and controls; these results are controversial and await confirmation.

In some but not the more recent studies, patients with CFS commonly manifested sensitivity to sustained upright posture or tilting, resulting in hypotension and syncope, so as to suggest a form of dysautonomia.

Disturbances in hypothalamic-pituitary-adrenal function have been identified in several controlled studies of CFS, with some evidence for normalization in patients whose fatigue abates. These neuroendocrine abnormalities could contribute to the impaired energy and depressed mood of patients.

Mild to moderate depression is present in one-half to two-thirds of patients. Much of this depression may be reactive, but its prevalence exceeds that seen in other chronic medical illnesses. Some propose that CFS is fundamentally a psychiatric disorder and that the various neuroendocrine and immune disturbances arise secondarily.

MANIFESTATIONS

Typically, CFS arises suddenly in a previously active individual. An otherwise unremarkable flulike illness or some other acute stress leaves unbearable exhaustion in its wake. Other symptoms, such as headache, sore throat, tender lymph nodes, muscle and joint aches, and frequent feverishness, lead to the belief that an infection persists, and medical attention is sought. Over weeks to months, despite reassurances that "nothing serious is wrong," the symptoms persist and other features of the syndrome become evident—disturbed sleep, difficulty in concentration, and depression (Table 47-1).

Depending on the dominant symptoms and the beliefs of the patient, additional consultations may be sought from allergists, rheumatologists, infectious disease specialists, psychiatrists, ecologic therapists, homeopaths, or other professionals, frequently with unsatisfactory results. Once the

pattern of illness is established, the symptoms may fluctuate somewhat. Many patients report that CFS symptoms, including cognitive problems, are exacerbated by intensive physical or other stressors, yet recent prospective studies have not confirmed this impression.

Most patients remain capable of meeting family, work, or community obligations despite their symptoms; discretionary activities are abandoned first. Some feel unable to engage in any gainful employment. A minority of individuals requires help with the activities of daily living.

Econometric analyses conducted by the CDC have confirmed that CFS exacts a significant toll on household and workforce productivity.

Ultimately, isolation, frustration, and pathetic resignation can mark the protracted course of illness. Patients may become angry at physicians for failing to acknowledge or resolve their plight. Fortunately, CFS does not appear to progress. On the contrary, many patients experience gradual improvement, and a minority recover fully.

DIAGNOSIS

A thorough history, physical examination, and judicious use of laboratory tests are required to exclude other causes of the patient's symptoms. Prominent abnormalities argue strongly in favor of alternative diagnoses. No laboratory test, however, can diagnose this condition or measure its severity. In most cases, elaborate, expensive workups are not helpful. Early claims that MRI or single photon emission CT can identify abnormalities in the brain of CFS patients have not withstood further study. The dilemma for patient and clinician alike is that CFS has no pathognomonic features and remains a constellation of symptoms and a diagnosis of exclusion. Often the patient presents with features that also meet criteria for other subjective disorders such as fibromyalgia and irritable bowel syndrome. Questions have been raised as to the relative merits of rendering a diagnosis of CFS. Being diagnosed can provide validation of a patient's perceived symptoms but may also perpetuate or exacerbate them. Refusal to label a patient as having CFS, however, can deny the patient the opportunity to undertake treatments that are of proven merit.

Rx Treatment: CHRONIC FATIGUE SYNDROME

After other illnesses have been excluded, there are several points to address in the long-term care of a patient with chronic fatigue.

The patient should be educated about the illness and what is known of its pathogenesis; potential impact on the physical, psychological, and social dimensions of life; and prognosis. Periodic reassessment is appropriate to identify a possible underlying process that is late in declaring itself and to address intercurrent symptoms that should not be simply dismissed as additional subjective complaints.

Many symptoms of CFS respond to treatment. Nonsteroidal anti-inflammatory drugs alleviate headache, diffuse pain, and feverishness. Allergic rhinitis and sinusitis are common; when present, antihistamines or decongestants may be helpful. Although the patient may be averse to psychiatric diagnoses, depression and anxiety are often prominent and should be treated. Expert psychiatric assessment is sometimes advisable. Nonsedating antidepressants improve mood and disordered sleep and may attenuate the fatigue. Even modest improvements in symptoms can make an important difference in the patient's degree of self-sufficiency and ability to appreciate life's pleasures.

Practical advice should be given regarding life-style. Sleep disturbances are common; consumption of heavy meals, alcohol, and caffeine at night can make sleep even more elusive, compounding fatigue. Total rest leads to further deconditioning and the self-image of being an invalid, whereas overexertion may worsen exhaustion and lead to total avoidance of exercise. A carefully graded exercise regimen should be encouraged and has been proven to relieve symptoms and enhance exercise tolerance.

Controlled therapeutic trials have established that acyclovir, fludrocortisone, galantamine, modafinil, and IV immunoglobulin, among other agents, offer no significant benefit in CFS. Low doses of hydrocortisone provide modest benefit but may lead to adrenal suppression. Countless anecdotes circulate regarding other traditional and nontraditional therapies. It is important to guide patients away from those therapeutic modalities that are toxic, expensive, or unreasonable.

The physician should promote the patient's efforts to recover. Several controlled trials conducted in the United Kingdom, in Australia, and in the Netherlands showed cognitive-behavioral therapy to be helpful in adolescents and adults with CFS. This approach aims to dispel misguided beliefs and fears about CFS that can contribute to inactivity and despair. For CFS, as for many other conditions, a comprehensive approach to physical, psychological, and social aspects of well-being is in order.

FURTHER READINGS

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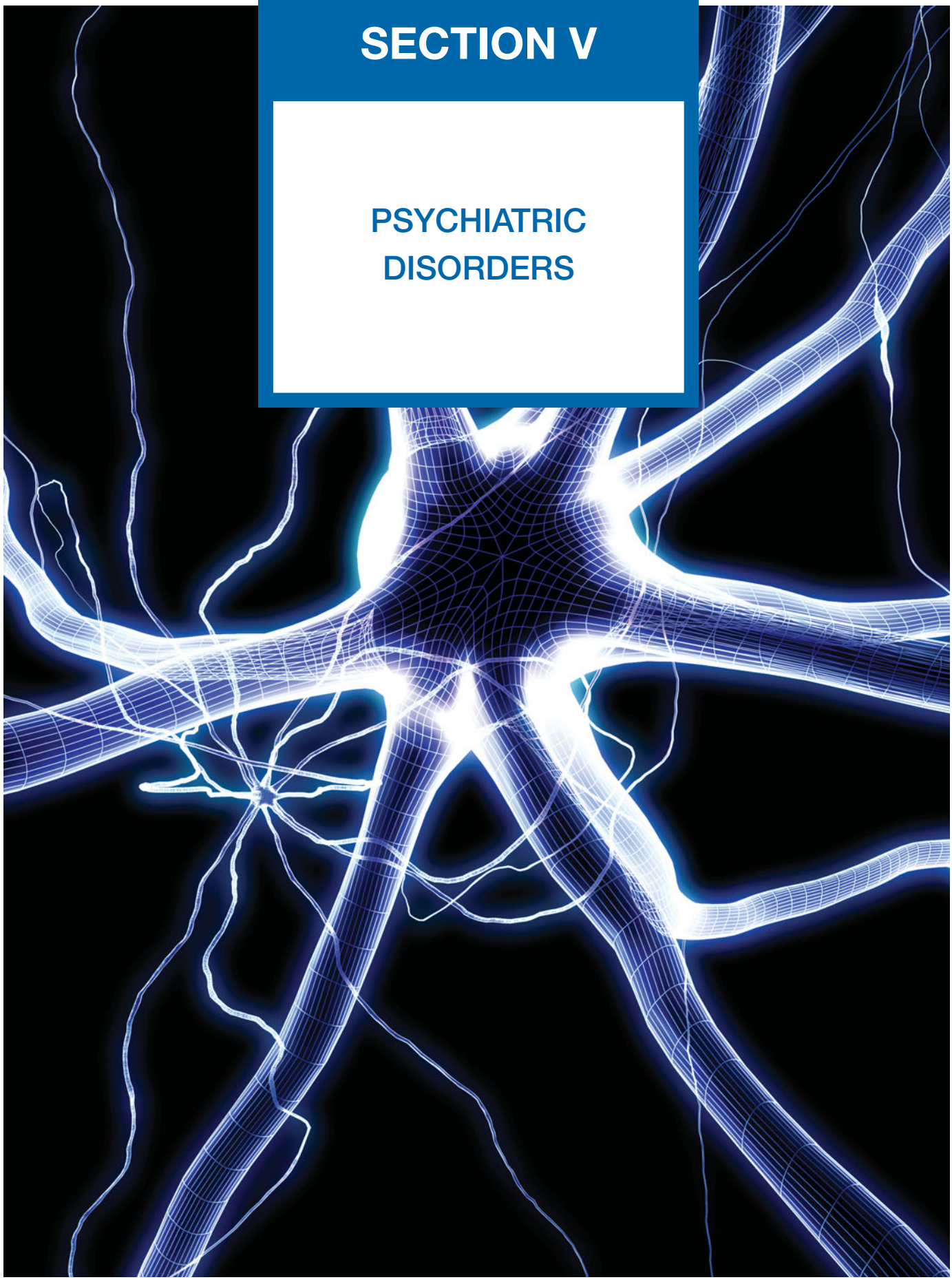
SECTION V

PSYCHIATRIC DISORDERS



CHAPTER 48

BIOLOGY OF PSYCHIATRIC DISORDERS

Steven E. Hyman ■ Eric Kandel

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Psychiatric disorders are a diverse group of brain disorders with symptoms that primarily involve emotion, higher cognitive function, and the ability to control complex behaviors. A compendium of psychiatric disorders can be found in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) of the American Psychiatric Association. This compendium illustrates that the boundary between psychiatric and neurologic disorders, another heterogeneous group of brain disorders, is arbitrary and shifting. In areas of overlap such as autism, Tourette's disorder, and Alzheimer's disease, the disorder is often treated by either a psychiatrist or a neurologist. The term *mental disorders*, while still widely used, fails to acknowledge the neural substrates of these disturbances and their effects on physiology and behavior.

The major psychiatric disorders are common and often run a chronic course. The chronic disorders include anxiety disorders, attention deficit hyperactivity disorder, autism, obsessive-compulsive disorder, and schizophrenia. Other psychiatric disorders such as depressive disorders recur across the life span, but even bipolar disorder, classically characterized as episodic, can run a chronic course.

The symptoms of psychiatric disorders often begin early, impairing the ability of children and adolescents to learn and compromising the functioning of adults at work and in other life roles. As a result of their high prevalence, early onset, and persistence, psychiatric disorders contribute substantially to the burden of illness in all countries in which they have been studied. In the United States they are not only a leading cause of disability but also a significant cause of premature death, because mood disorders, schizophrenia, and to some extent other psychiatric disorders constitute the most potent risk factors for suicide, a leading cause of death worldwide.

ANATOMY

Progress in understanding the pathophysiology of psychiatric disorders has been slow, despite its fundamental importance. Perhaps the most significant challenge is posed by the difficulties inherent in understanding the high-level cognitive and affective functions of the brain that are disrupted in psychiatric disorders. As a result, unlike many neurologic disorders, the common psychiatric disorders appear to involve widely distributed neural networks and lack an obvious, localized neuropathology, which, if present, would help to narrow the hunt for cellular pathology and for underlying biochemical and molecular causes. Thus, the motor disturbances in Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis result from discrete macroscopic lesions in different parts of the motor system. By contrast, in psychiatric disorders, when candidate regions have been identified, as in schizophrenia, depression, and autism, it has proven difficult to differentiate convincingly, these abnormalities from normal variation partly because these target regions form only one component of a disorder involving a much larger neural circuit (Chap. 15).

GENETIC CONSIDERATIONS

Given the challenges of identifying relatively subtle neuropathology, it has long been hoped that the

identification of genetic variants conferring risk for psychiatric disorders would provide effective clues to those underlying neural abnormalities that contribute to the psychiatric disorder in question. This hope is based on the significant body of data derived from family, twin, and adoption studies demonstrating that heredity plays a significant role in the risk of major psychiatric disorders, including schizophrenia, bipolar disorder, depressive disorders, and many others. For example, the rate of schizophrenia in the general population is ~1%. However, when one member of a monozygotic twin pair is diagnosed with schizophrenia, the other twin, who is genetically identical, has nearly a 50% chance of also manifesting the disease. A first-degree relative of an affected proband (who shares on average 50% of DNA sequences) has a 9% risk of schizophrenia. Adoption-at-birth studies provide additional strong support for a genetic contribution to schizophrenia spectrum disorders; in one study from Finland, a schizophrenia-related illness was present in nearly one-quarter of adoptees whose biologic mother carried a similar diagnosis.

While there continue to be promising leads in the search for risk-conferring alleles, research over the past two decades has not succeeded in identifying with certainty risk genes for psychiatric disorders. There have been large efforts using a variety of strategies, including linkage studies and candidate gene studies, in attempts to identify genes responsible for schizophrenia, and more recently several groups have begun to undertake whole-genome association studies. The strongest candidates include: disrupted in schizophrenia (*DISC1*), a gene that was disrupted by a balanced chromosomal translocation in a Scottish family with schizophrenia-like symptoms; dystrobrevin-binding protein 1 (*DTNBP1*); and neuroregulin 1 (*NRG1*), which encodes a protein involved in neuronal migration and in expression of *N*-methyl-D-aspartate (NMDA) glutamate receptors. Other potential candidates include *DAOA*, *RGS4*, and *AKT1*, but the evidence supporting them is weaker (**Table 48-1**).

One problem in identifying risk genes for psychiatric diseases has been the failure to replicate convincingly the discovery of putative risk genes. The failure stems in large part from the complex nature of risk for psychiatric disorders, which appears to involve multiple genes of small effect interacting with nongenetic factors. In addition, there appear to be different risk genes in different population groups, perhaps reflecting new or recent mutations.

It is now relatively straightforward to identify genes that exert large causal effects on disease. Several less common neurologic disorders result from deleterious mutations within single genes. Thus, genes have been identified that contribute to the muscular dystrophies, triplet repeat disorders such as Huntington's disease and fragile X, and Down's syndrome. The discovery of the Huntington gene was followed by the development of powerful tools to investigate the neural basis of the disease by putting the mutated gene into worms, flies, or mice in order to study the mechanisms of pathogenesis. While such tools are only a beginning, and indeed have not yet led to development of therapies, gene identification and the study of its function have already created a strong platform for investigation. It permits, for example, the spatiotemporal characterization in the brain of the expression of disease-related genes, the generation of antibodies against the normal and altered proteins, and the production by genetic engineering of worm, fly, and mouse models that could serve as assays for testing possible therapies. Moreover, the identification of rare, Mendelian forms of Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, and epilepsy has provided significant insights into the more common forms of these disorders. Thus far, however, no Mendelian form of any of the common early-onset psychiatric disorders of the brain has been identified convincingly. A small number of Mendelian disorders have symptoms that overlap with those of common psychiatric disorders. For example, Rett syndrome, which results from mutations in the methyl DNA binding protein MECP2, includes autistic-like symptoms but also many severe symptoms that are not characteristic of autism.

In psychiatric disorders such as schizophrenia, genes are not, by themselves, causative; other factors, a "second hit," must contribute. Unfortunately, these potential environmental factors, the "second hits," have been difficult to identify. One interesting finding, documented in the Netherlands following World War II and in China, is that maternal famine during gestation is correlated with an increased incidence of schizophrenia, perhaps by contributing to de novo germ-line mutations. Other potential risk factors include urban birth, migration, increasing paternal age, and intrauterine exposure to viral infection.

New genetic technologies are now available for the investigation of genetically complex disorders; these include more complete maps of human genetic variability, high-density whole-genome association methods, and efficient high-throughput sequencing technologies using single nucleotide polymorphism (SNP) arrays. The use of these tools has already begun to yield significant results for several common complex disorders, such as inflammatory bowel disease, age-related macular degeneration, and type 2 diabetes mellitus. Psychiatric disorders are well positioned to benefit from these new approaches. In addition, it is expected that additional emerging technologies, including cost-efficient methods for whole-genome sequencing, will soon be available, further increasing the likelihood that risk-conferring alleles for psychiatric disorders will be identified within the next few years. To take full advantage of these new methods, the psychiatric research community will need to collect very large populations for sufficiently powered genetic studies, and identify (by high-resolution imaging, gene

TABLE 48-1

SCHIZOPHRENIA CANDIDATE GENES

PROTEIN	GENE	CH LOCATION	EVIDENCE	FUNCTION
Disrupted in schizophrenia	*DISC1*	1q42	Initially identified through a balanced translocation in a single family with schizophrenia and affective disorder; confirmed by linkage and association in different populations.	Roles in microtubular transport and neuronal migration (via interactions with *Lis1* and *NudEL*); influences postsynaptic responses (interactions with *Citron*); activates phosphodiesterase 4B, increasing cAMP (target of antidepressant rolipram).
Dysbindin (dystrobrevin-binding protein 1)	*DTNBP1*	6p22	Linkage and association; no coding region mutations; no consistent allele or haplotype implicated in different studies; negative symptoms of schizophrenia may associate with a specific haplotype of *DTNBP1*; expression decreased in schizophrenia brain.	Wide distribution in CNS; expression in synaptic terminals of hippocampus; in vitro, reduced levels decrease glutamate in neurons.
Neuregulin 1	*NRG1*	8p12-21	Linkage and association; no coding region mutations; no consistent allele or haplotype implicated in different studies; expression increased in schizophrenia brain.	Suppresses function of NMDA receptors; role in neuronal differentiation and migration.
D-Amino oxidase activator	*DAOA*	13q32-34	Linkage and association; no consistent allele or haplotype implicated in different studies.	Activates D-amino oxidase which oxidies D-serine, an agonist at NMDA receptors; reduced D-serine levels reported in blood and CSF in schizophrenia.
Regulator of G-protein signaling 4	*RGS4*	1q21-22	Linkage and association; susceptibility allele may impair working memory and regionally reduce brain volumes	Modulates postsynaptic signal transduction, including downregulation of 5HT1a (serotonin) receptors.
V-akt murine thymoma viral oncogene homologue 1	*AKT1*	14q22-32	Inconsistent linkage, association, and brain expression studies.	Phosphorylates and inactivates glycogen synthase kinase (GSK) 3 beta.

Note: CH, chromosome; CNS, central nervous system; CSF, cerebrospinal fluid; NMDA, *N*-methyl-D-aspartate.

expression patterns, or other markers) biologically meaningful phenotypes for stratification of the genetic data.

CHALLENGES WITH PHENOTYPING

Psychiatric disorders have an additional obstacle to the identification of risk genes or pathophysiologic processes that cannot be addressed simply by improving genetic technologies. There are at the moment no objective diagnostic measures for any of the common psychiatric disorders. There is not, as yet, a well-defined neuropathology for psychiatric disorders nor are there biologic markers. The diagnostic classification scheme (e.g., DSM-IV) upon which both research and clinical practice rely is derived from expert consensus based on clusters of symptoms and signs and disease course. As a result, failure to delineate well-defined disease entities and to reliably assign individuals, to affected versus nonaffected status have bedeviled psychiatric research.

The lack of objective tests for phenotyping presents enormous difficulties for genetic and other forms of investigation. While type 2 diabetes mellitus and hypertension, for example, are both highly heterogeneous disorders, the measurement of glucose tolerance or of systolic and

diastolic blood pressure creates a strong framework within which subtyping can occur, generally based on additional objective measures. In contrast, it is not at all certain that the boundaries currently drawn around disorders in the DSM-IV lead to an underlying and distinguishable set of neurobiologic factors. For example, there is much debate about the boundaries of schizophrenia. The DSM-IV lists three psychotic disorders as being independent—schizophrenia, schizoaffective disorder, and schizophreniform disorder (American Psychiatric Association, 2000). Yet there is little agreement on whether the latter two are sufficiently homogeneous clinical entities to warrant independent recognition.

Despite the problems with current disease classification in psychiatry, there is agreement on the core symptoms and strong cross-cultural similarity of disease manifestation. In addition, there is a strong familial nature to major psychiatric disorders and also a potent role for heredity, which can be inferred from twin and adoption studies. These findings suggest that the central criteria for diagnosing schizophrenia, bipolar disorder, autism, and other major psychiatric disorders identify, however imperfectly, distinctive, naturally occurring brain diseases.

NEUROIMAGING

In parallel with improved classification and genetic studies, attempts are being made using neuroimaging to define anatomic abnormalities as objective, measurable phenotypes of the disease. For example, new quantitative methods combined with structural MRI have suggested that, in schizophrenia, there may be disease-specific patterns of gray matter loss in frontal and temporal cerebral cortex. Longitudinal studies of individuals with childhood-onset schizophrenia have documented an accelerated loss of gray matter. More recently, attempts have been made to associate specific DISC1 haplotypes with reduced frontal gray matter. While these approaches are in their early stages, the effort to define objective brain-based phenotypes for genetic and clinical studies appears very promising.

Functional imaging of individuals with depression similarly has pinpointed abnormal activity in Brodman area 25, the subgenual prefrontal cortex, a brain region that connects to the amygdala and is thought to play a critical role in the processing of emotion-related information (**Fig. 48-1**). Area 25 exhibits excessive metabolic activity in major depression, which reverses with successful antidepressant treatment. This region is also activated in normal subjects in whom sadness is induced by means of emotion laden stimuli. This information serves as the basis for an experimental approach to severe depression involving the use of deep-brain stimulation of the subgenual prefrontal cortex using implanted electrodes. In an initial series, four of six patients with severe depression unresponsive to all currently proven treatments, including electroconvulsive therapy, had immediate and sustained responses; however, due to the invasiveness, risk, and cost, this approach may not become a widespread treatment. Its significance lies in the putative identification of a circuit involved in mood regulation that can be manipulated to produce therapeutic benefit.

℞ Treatment: PSYCHIATRIC DISORDERS

The high prevalence and serious consequences of psychiatric disorders make the availability of effective treatments a matter of great importance for public health. Since the middle of the twentieth century, several classes of pharmacologic treatments (antipsychotic drugs, antidepressant drugs, lithium, benzodiazepines, and anticonvulsants) and several standardized short-term psychotherapies have been developed and found to be efficacious in clinical trials. The result is an armamentarium of useful treatments for many of the common disorders; however, as is the case for many common, chronic medical disorders, there are no cures for psychiatric disorders. Residual symptoms and recurrences are common, and many pharmacologic treatments have significant side effects.

This state of affairs is typified by schizophrenia, where a large number of drugs have been developed. Initially these drugs were thought to be useful only in the treatment of schizophrenia; however, they are now commonly used to treat any psychosis, irrespective of origin. In schizophrenia, in addition to the psychotic symptoms of hallucinations and delusions, referred to as *positive symptoms*, there are also *negative symptoms* (social withdrawal, impoverished speech, lack of motivation) and *cognitive symptoms* (poor executive function). Both positive and negative symptoms are thought to be related to dopaminergic systems in the brain (**Fig. 48-2**). The primary clinical benefit of antipsychotic drugs is the amelioration of the positive psychotic symptoms. With the exception of clozapine, often described as an atypical antipsychotic drug, which produces improvement in some patients who do not respond to other drugs, all the existing antipsychotic drugs have similar efficacy and differ primarily in their pattern of side effects. Clozapine and some other atypical drugs are thought to exert at least a modest therapeutic effect on the negative symptoms of schizophrenia. None of the drugs, however, is effective against the symptoms that are central to the illness. Furthermore, their residual presence throughout the course of the illness contributes substantially to the persistence of disability over the patient's lifetime. The search for new drugs to treat schizophrenia now focuses extensively on the ability to modify its cognitive symptoms. All antipsychotic drugs

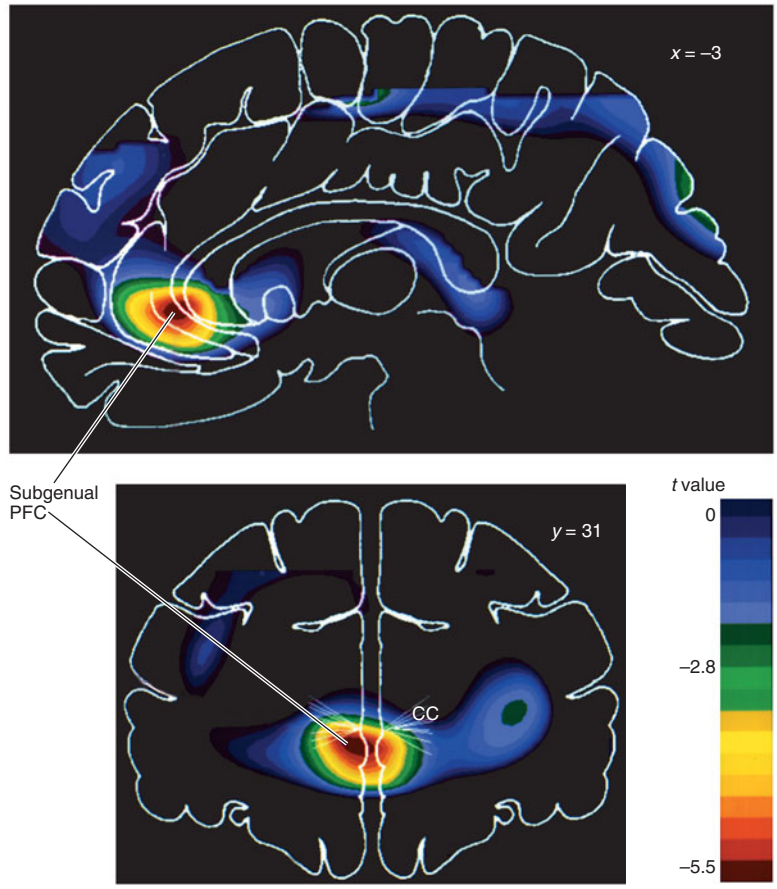

FIGURE 48-1
Some patients with unipolar and bipolar disease show a functional abnormality in the prefrontal cortex ventral to the genu of the corpus callosum. (*From ER Kandel et al: Principles of Neural Science, 4th ed. New York, McGraw-Hill, 2000; with permission.*)

in current use block or diminish the action of dopamine at its D_2 receptors (**Fig. 48-3**); they differ in their relative affinity at D_2 receptors and by their actions at other neurotransmitter receptors. These drugs represent important progress, but safer and more effective treatments are very much needed.

Drugs useful in depression act by increasing synaptic levels of serotonin, norepinephrine, or less commonly dopamine (**Fig. 48-4**). The term *antidepressant* is a misnomer for this diverse class of drugs, however, because their spectrum of action is much broader than depression. These drugs are also effective in treating fear-based anxiety disorders such as panic disorder and generalized anxiety disorder. In high doses, the selective serotonin uptake inhibitors are effective for obsessive-compulsive disorder. The antidepressants are effective in the treatment of depression, but only moderately so. Many patients require sequential trials with a number of different drugs alone or in combination to achieve clinically meaningful benefit, and ~30% of patients derive no benefit at all. When pharmacologic modalities fail in depression, electroconvulsive therapy continues to be an effective treatment option. Lithium and several anticonvulsants dampen mood swings in bipolar disorder and also treat acute manic episodes; however, residual depressive symptoms, recurrences, and significant side effects are the rule. The exact mechanism of action of lithium is not known. At therapeutic levels, lithium interacts with two important signaling pathways: (1) it blocks inositol monophosphatase, thus influencing signaling via inositol phosphates, such as IP_3; and (2) it also blocks glycogen synthase kinase 3 beta (GSK3beta).

Unfortunately, there are currently very few promising drug targets that can be exploited to produce medications with truly novel mechanisms of action. Indeed, all of the major classes of drugs used to treat psychiatric disorders were identified through empirical observations of drug effects in patient populations rather than as a result of understanding pathophysiology. The molecular targets of these drugs were identified by the study

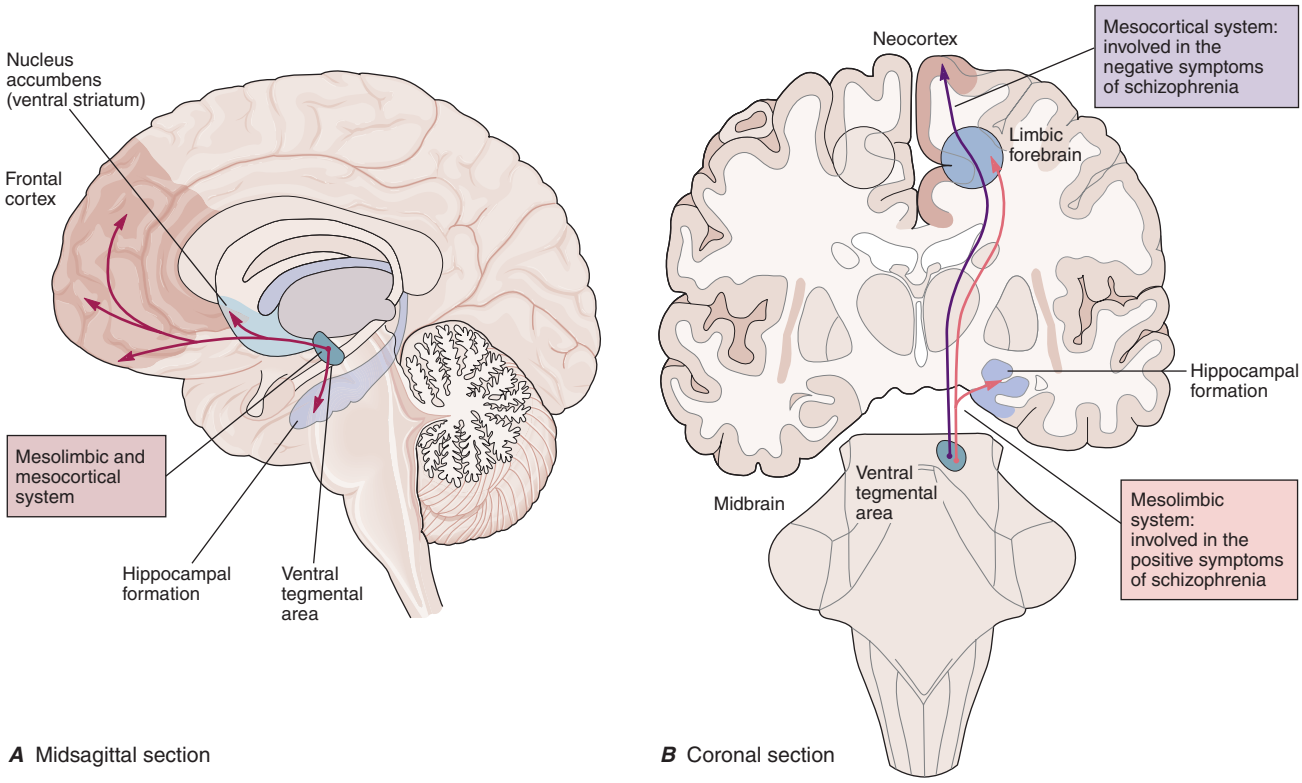

FIGURE 48-2

The major dopaminergic tracts of the brain. (*From ER Kandel et al: Principles of Neural Science, 4th ed. New York, McGraw-Hill, 2000.*)

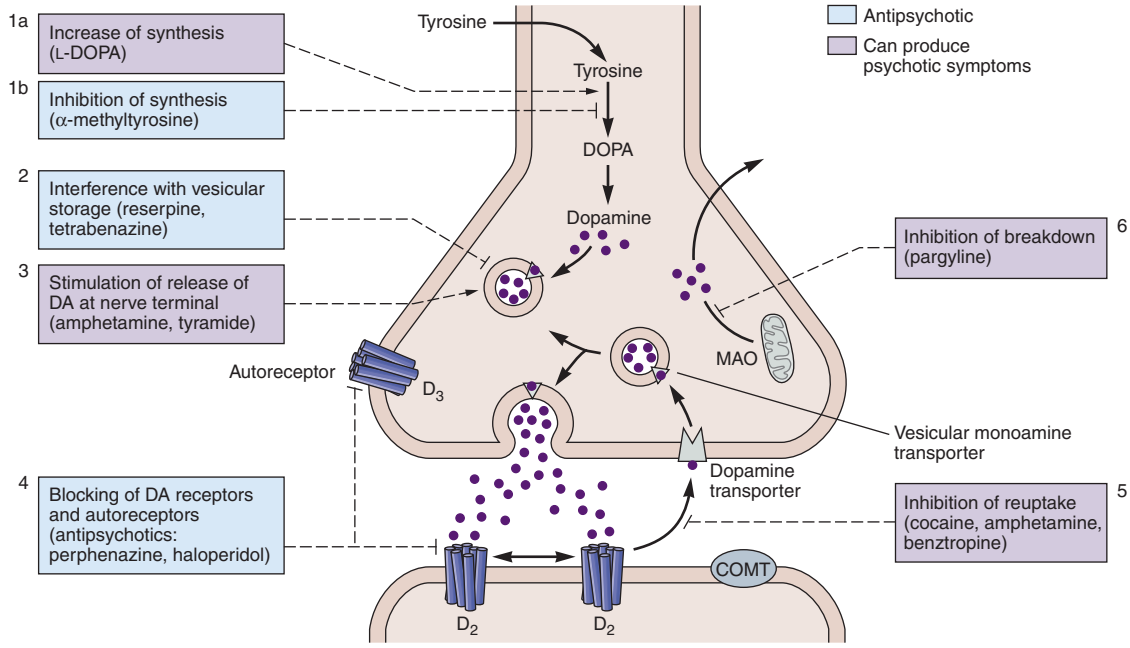

FIGURE 48-3

The key steps in the synthesis and degradation of dopamine and the sites of action of various psychoactive substances at the dopaminergic synapse. (*From ER Kandel et al: Principles of Neural Science, 4th ed. New York, McGraw-Hill, 2000.*)

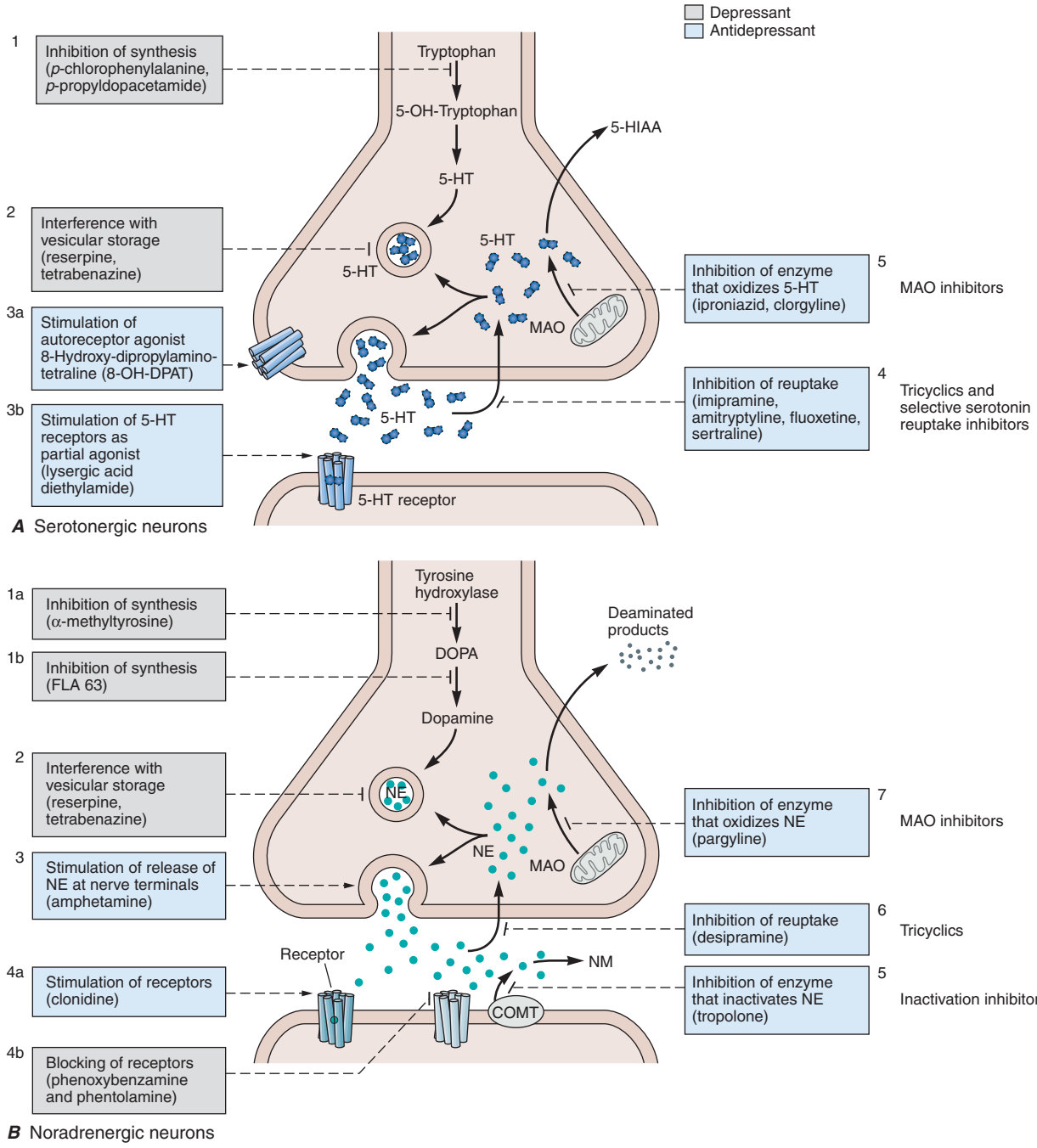

FIGURE 48-4

Actions of antidepressant and other drugs at serotonergic and noradrenergic synapses. (*From ER Kandel et al: Principles of Neural Science, 4th ed. New York, McGraw-Hill, 2000.*)

of efficacious drugs and then exploited to produce improved compounds within the same class.

Cognitive-behavioral psychotherapy designed to focus on the management of specific symptoms has shown benefit in mild to moderately severe depression, fear-based anxiety disorders, and obsessive-compulsive disorder. A significant improvement in the treatment of depression in the past decade has been the standardization of psychotherapy and its evaluation in clinical trials. Instruments such as the Depression Inventory and Suicide Intent Scale are now available for measuring mental illness; these have helped to objectify research in psychopathology.

New insights into the etiology of depression have also helped to guide therapy. Depressed patients have a systematic negative bias in their cognitive styles—in the way they think about themselves and their future. These distorted patterns of thinking reflect not simply

an unconscious conflict within the psyche but a disorder in cognitive style and behavior that is a key etiologic agent in maintaining the disorder.

An approach that focuses on distorted thinking, cognitive therapy has been shown in randomized trials to be an effective psychological treatment for depression. This approach is based on increasing the patients' objectivity regarding their misinterpretations of everyday situations (their cognitive distortions), their misevaluation of their internal processes (body sensations, intrusive thoughts and images), and their negative expectancies. A wide range of professionals can use the methods with highly positive results.

Cognitive therapy has also proved beneficial in individuals at risk for suicide. Validated instruments exist to classify and assess suicidal behaviors, making it possible to identify high-risk individuals prospectively. Of particular importance has been the identification of clinical and psychological variables that predict future suicide. Hopelessness and consequent suicidal ideation, which are better predictors of suicide than clinical depression per se, can be quantified and substantially reduced by cognitive interventions. Several studies with individuals who had recently attempted suicide have demonstrated that a short-term cognitive intervention can significantly reduce subsequent suicide attempts when compared to a control group.

This therapy has been extended to the treatment of other disorders including anxiety states and obsessive-compulsive disorder. With respect to obsessive-compulsive disorders, cognitive therapy has been shown to reverse a metabolic abnormality, identified by neuroimaging, in parallel with the clinical improvement (**Fig. 48-5**).

Cognitive therapy has replaced psychoanalytically based dynamic psychotherapy as the principal psychological treatment provided by specialists in certain countries. Its success has stimulated the development of other forms of short-term psychotherapy, including Interpersonal Psychiatry and Psychoanalytic-Oriented Insight Therapy. These therapies are now also being tested in controlled clinical trials and have been found to be effective in a variety of clinical situations.

Thus, paradoxically, one of the significant advances in the era of the new brain-based biologic psychiatry has been the development of evidence-based psychotherapy, a development based on the evidence that insofar as psychotherapy and other psychiatric treatments work, they do so by altering the functioning and perhaps even the structure of the brain.

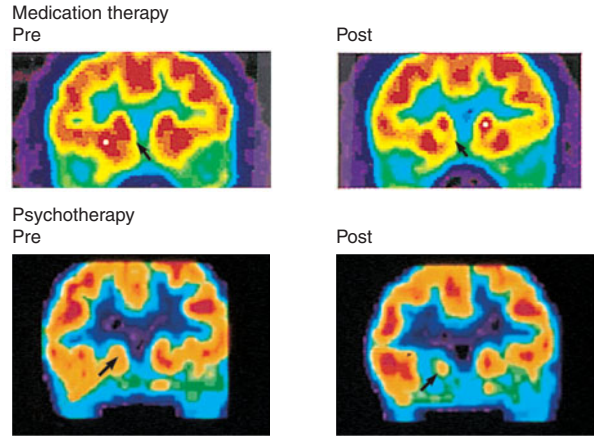

FIGURE 48-5
Patients with obsessive-compulsive disorder tend to show hyperactivity in the head of the caudate. (*From ER Kandel et al: Principles of Neural Science, 4th ed. New York, McGraw-Hill, 2000.*)

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CHAPTER 49

MENTAL DISORDERS

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Mental disorders are common in medical practice and may present either as a primary disorder or as a comorbid condition. The prevalence of mental or substance use disorders in the United States is approximately 30%. Only one-third of these individuals are currently receiving treatment. Global burden of disease statistics indicate that 4 out of the 10 most important causes of disease worldwide are psychiatric in origin.

The revised fourth edition for use by primary care physicians of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-PC) provides a useful synopsis of mental disorders most likely to be seen in primary care practice. The current system of classification is multiaxial and includes the presence or absence of a major mental disorder (axis I), any underlying personality disorder (axis II), general medical condition (axis III), psychosocial and environmental problems (axis IV), and overall rating of general psychosocial functioning (axis V).

Changes in health care delivery underscore the need for primary care physicians to assume responsibility for the initial diagnosis and treatment of the most common mental disorders. Prompt diagnosis is essential to ensure that patients have access to appropriate medical services and to maximize the clinical outcome. Validated patient-based questionnaires have been developed that systematically probe for signs and symptoms associated with the most prevalent psychiatric diagnoses and guide the clinician into targeted assessment. Prime MD (and a self-report form, the PHQ) and the Symptom-Driven Diagnostic System for Primary Care (SDDS-PC) are inventories that require only 10 min to complete and link patient responses to the formal diagnostic criteria of anxiety, mood, somatoform, and eating disorders and to alcohol abuse or dependence.

A physician who refers patients to a psychiatrist should know not only when doing so is appropriate but also how to refer, since societal misconceptions and the stigma of mental illness impede the process. Primary care physicians should base referrals to a psychiatrist on the presence of signs and symptoms of a mental disorder and not simply on the absence of a physical explanation for a patient's complaint. The physician should discuss with the patient the reasons for requesting the referral or consultation and provide reassurance that he or she will continue to provide medical care and work collaboratively with the mental health professional. Consultation with a psychiatrist or transfer of care is appropriate when physicians encounter evidence of psychotic symptoms, mania, severe depression, or anxiety; symptoms of posttraumatic stress disorder (PTSD); suicidal or homicidal preoccupation; or a failure to respond to first-order treatment. The pathogenesis of psychiatric and addictive disorders are discussed in Chap. 48.

ANXIETY DISORDERS

Anxiety disorders, the most prevalent psychiatric illnesses in the general community, are present in 15–20% of medical clinic patients. Anxiety, defined as a subjective sense of unease, dread, or foreboding, can indicate a primary psychiatric condition or can be a component of, or reaction to, a primary medical disease. The primary anxiety disorders are classified according to their duration and course and the existence and nature of precipitants.

When evaluating the anxious patient, the clinician must first determine whether the anxiety antedates or postdates a medical illness or is due to a medication side effect. Approximately one-third of patients presenting with anxiety have a medical etiology for their psychiatric symptoms, but an anxiety disorder can also present with somatic symptoms in the absence of a diagnosable medical condition.

PANIC DISORDER

Clinical Manifestations

Panic disorder is defined by the presence of recurrent and unpredictable panic attacks, which are distinct episodes of intense fear and discomfort associated with a variety of physical symptoms, including palpitations, sweating, trembling, shortness of breath, chest pain, dizziness, and a fear of impending doom or death (Table 49-1). Paresthesias, gastrointestinal distress, and feelings of unreality are also common. Diagnostic criteria require at least 1 month of concern or worry about the attacks or a change in behavior related to them. The lifetime prevalence of panic disorder is 1–3%. Panic attacks have a sudden onset, developing within 10 min and usually resolving over the course of an hour, and they occur in an unexpected fashion. The frequency and severity of panic attacks vary, ranging from once a week to clusters of attacks separated by months of well-being. The first attack is usually outside the home, and onset is typically in late adolescence to early adulthood. In some individuals, anticipatory anxiety develops over time and results in a generalized fear and a progressive avoidance of places or situations in which a panic attack might recur. *Agoraphobia*, which occurs commonly in patients with panic disorder, is an acquired irrational fear of being in places where one might feel trapped or unable to escape (Table 49-2). Typically, it leads the patient into a progressive restriction in lifestyle and, in a literal sense, in geography. Frequently, patients are embarrassed that they are housebound and dependent on the company of others to go out into the world and do not volunteer this information; thus physicians will fail to recognize the syndrome if direct questioning is not pursued.

TABLE 49-1

DIAGNOSTIC CRITERIA FOR PANIC ATTACK

A discrete period of intense fear or discomfort, in which four or more of the following symptoms developed abruptly and reached a peak within 10 min:

1. Palpitations, pounding heart, or accelerated heart rate
2. Sweating
3. Trembling or shaking
4. Sensations of shortness of breath or smothering
5. Feeling of choking
6. Chest pain or discomfort
7. Nausea or abdominal distress
8. Feeling dizzy, unsteady, lightheaded, or faint
9. Derealization (feelings of unreality) or depersonalization (being detached from oneself)
10. Fear of losing control or going crazy
11. Fear of dying
12. Paresthesias (numbness or tingling sensations)
13. Chills or hot flushes

Source: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC, American Psychiatric Association, 2000.

TABLE 49-2

DIAGNOSTIC CRITERIA FOR AGORAPHOBIA

1. Anxiety about being in places or situations from which escape might be difficult (or embarrassing) or in which help may not be available in the event of having an unexpected or situationally predisposed panic attack or panic-like symptoms. Agoraphobic fears typically involve characteristic clusters of situations that include being outside the home alone; being in a crowd or standing in a line; being on a bridge; and traveling in a bus, train, or automobile.
2. The situations are avoided (e.g., travel is restricted) or else are endured with marked distress or with anxiety about having a panic attack or panic-like symptoms, or require the presence of a companion.
3. The anxiety or phobic avoidance is not better accounted for by another mental disorder, such as social phobia (e.g., avoidance limited to social situations because of fear of embarrassment), specific phobia (e.g., avoidance limited to a single situation like elevators), obsessive-compulsive disorder (e.g., avoidance of dirt in someone with an obsession about contamination), posttraumatic stress disorder (e.g., avoidance of stimuli associated with a severe stressor), or separation anxiety disorder (e.g., avoidance of leaving home or relatives).

Source: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC, American Psychiatric Association, 2000.

Differential Diagnosis

A diagnosis of panic disorder is made after a medical etiology for the panic attacks has been ruled out. A variety of cardiovascular, respiratory, endocrine, and neurologic conditions can present with anxiety as the chief complaint. Patients with true panic disorder will often focus on one specific feature to the exclusion of others. For example, 20% of patients who present with syncope as a primary medical complaint have a primary diagnosis of a mood, anxiety, or substance-abuse disorder, the most common being panic disorder. The differential diagnosis of panic disorder is complicated by a high rate of comorbidity with other psychiatric conditions, especially alcohol and benzodiazepine abuse, which patients initially use in an attempt at self-medication. Some 75% of panic disorder patients will also satisfy criteria for major depression at some point in their illness.

When the history is nonspecific, physical examination and focused laboratory testing must be used to rule out anxiety states resulting from medical disorders such as pheochromocytoma, thyrotoxicosis, or hypoglycemia. Electrocardiogram (ECG) and echocardiogram may detect some cardiovascular conditions associated with panic, such as paroxysmal atrial tachycardia and mitral valve prolapse. In two studies, panic disorder was the primary diagnosis in 43% of patients with chest pain who had normal coronary angiograms and was present in 9% of all outpatients referred for cardiac evaluation. Panic disorder has also been diagnosed in many patients referred for pulmonary function testing or with symptoms of irritable bowel syndrome.

Etiology and Pathophysiology

The etiology of panic disorder is unknown but appears to involve a genetic predisposition, altered autonomic responsivity, and social learning. Panic disorder shows familial aggregation; the disorder is concordant in 30–45% of monozygotic twins, and genome-wide screens have identified suggestive risk loci. Acute panic attacks appear to be associated with increased noradrenergic discharges in the locus coeruleus. Intravenous infusion of sodium lactate evokes an attack in two-thirds of panic disorder patients, as do the α_2-adrenergic antagonist yohimbine, cholecystokinin tetrapeptide (CCK-4), and carbon dioxide inhalation. It is hypothesized that each of these stimuli activates a pathway involving noradrenergic neurons in the locus coeruleus and serotonergic neurons in the dorsal raphe. Agents that block serotonin reuptake can prevent attacks. Panic-disorder patients have a heightened sensitivity to somatic symptoms, which triggers increasing arousal, setting off the panic attack; accordingly, therapeutic intervention involves altering the patient's cognitive interpretation of anxiety-producing experiences as well as preventing the attack itself.

℞ Treatment: PANIC DISORDER

Achievable goals of treatment are to decrease the frequency of panic attacks and to reduce their intensity. The cornerstone of drug therapy is antidepressant medication (Tables 49-3, 49-4, and 49-5). Selective serotonin reuptake inhibitors (SSRIs) benefit the majority of panic disorder patients and do not have the adverse effects of tricyclic antidepressants (TCAs). Fluoxetine, paroxetine, and sertraline have received approval from the U.S. Food and Drug Administration (FDA) for this indication. SSRIs should be started at one-third to one-half of their usual antidepressant dose (e.g., 5–10 mg fluoxetine, 25–50 mg sertraline, 10 mg paroxetine). Monoamine oxidase inhibitors (MAOIs) are also effective and may specifically benefit patients who have comorbid features of atypical depression (i.e., hypersomnia and weight gain). Insomnia, orthostatic hypotension, and the need to maintain a low-tyramine diet (avoidance of cheese and wine) have limited their use, however. Antidepressants typically take 2–6 weeks to become effective, and doses may need to be adjusted based upon the clinical response.

Because of anticipatory anxiety and the need for immediate relief of panic symptoms, benzodiazepines are useful early in the course of treatment and sporadically thereafter (Table 49-6). For example, alprazolam, starting at 0.5 mg qid and increasing to 4 mg/d in divided doses, is effective, but patients must be monitored closely, as some develop dependence and begin to escalate the dose of this medication. Clonazepam, at a final maintenance dose of 2–4 mg/d, is also helpful; its longer half-life permits twice-daily dosing, and patients appear less likely to develop dependence on this agent.

Early psychotherapeutic intervention and education aimed at symptom control enhances the effectiveness of drug treatment. Patients can be taught breathing techniques, educated about physiologic changes that occur with panic, and learn to expose themselves voluntarily to precipitating events in a treatment program spanning 12–15 sessions. Homework assignments and monitored compliance are important components of successful treatment. Once patients have achieved a satisfactory response, drug treatment should be maintained for 1–2 years to prevent relapse. Controlled trials indicate a success rate of 75–85%, although the likelihood of complete remission is somewhat lower.

GENERALIZED ANXIETY DISORDER

Clinical Manifestations

Patients with generalized anxiety disorder (GAD) have persistent, excessive, and/or unrealistic worry associated with muscle tension, impaired concentration, autonomic

TABLE 49-3

ANTIDEPRESSANTS

NAME	USUAL DAILY DOSE, mg	SIDE EFFECTS	COMMENTS
SSRIs			
Fluoxetine (Prozac)	10–80	Headache; nausea and other GI effects; jitteriness; insomnia; sexual dysfunction; can affect plasma levels of other meds (except sertraline); akathisia rare	Once daily dosing, usually in A.M.; fluoxetine has very long half-life; must not be combined with MAOIs
Sertraline (Zoloft)	50–200		
Paroxetine (Paxil)	20–60		
Fluvoxamine (Luvox)	100–300		
Citalopram (Celexa)	20–60		
Escitalopram (Lexapro)	10–30		
TCAs			
Amitriptyline (Elavil)	150–300	Anticholinergic (dry mouth, tachycardia, constipation, urinary retention, blurred vision); sweating; tremor; postural hypotension; cardiac conduction delay; sedation; weight gain	Once daily dosing, usually qhs; blood levels of most TCAs available; can be lethal in O.D. (lethal dose = 2 g); nortriptyline best tolerated, especially by elderly
Nortriptyline (Pamelor)	50–200		
Imipramine (Tofranil)	150–300		
Desipramine (Norpramin)	150–300		
Doxepin (Sinequan)	150–300		
Clomipramine (Anafranil)	150–300		
Mixed norepinephrine/ serotonin reuptake inhibitors			
Venlafaxine (Effexor)	75–375	Nausea; dizziness; dry mouth; headaches; increased blood pressure; anxiety and insomnia	Bid-tid dosing (extended release available); lower potential for drug interactions than SSRIs; contraindicated with MAOI
Duloxetine (Cymbalta)	40–60	Nausea, dizziness, headache, insomnia, constipation	May have utility in treatment of neuropathic pain and stress incontinence
Mirtazapine (Remeron)	15–45	Somnolence; weight gain; neutropenia rare	Once daily dosing
Mixed-action drugs			
Bupropion (Wellbutrin)	250–450	Jitteriness; flushing; seizures in at-risk patients; anorexia; tachycardia; psychosis	Tid dosing, but sustained release also available; fewer sexual side effects than SSRIs or TCAs; may be useful for adult ADD
Trazodone (Desyrel)	200–600	Sedation; dry mouth; ventricular irritability; postural hypotension; priapism rare	Useful in low doses for sleep because of sedating effects with no anticholinergic side effects
Nefazodone (Serzone)	300–600	Sedation; headache; dry mouth; nausea; constipation	Discontinued sale in United States and several other countries due to risk of liver failure
Amoxapine (Asendin)	200–600	Sexual dysfunction	Lethality in overdose; EPS possible
MAOIs			
Phenelzine (Nardil)	45–90	Insomnia; hypotension; anorgasmia; weight gain; hypertensive crisis; toxic reactions with SSRIs	May be more effective in patients with atypical features or treatment-refractory depression
Tranylcypromine (Parnate)	20–50		
Isocarboxazid (Marplan)	20–60		
Transdermal selegiline (Emsam)	6–12	Local skin reaction; hypertension	No dietary restrictions with 6-mg dose

Note: ADD, attention deficit disorder; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; EPS, extrapyramidal symptoms.

arousal, feeling "on edge" or restless, and insomnia (**Table 49-7**). Onset is usually <20 years, and a history of childhood fears and social inhibition may be present. The lifetime prevalence of GAD is 5–6%; the risk is higher in first-degree relatives of patients with the diagnosis. Interestingly, family studies indicate that GAD and panic disorder segregate independently. Over 80% of patients with GAD also suffer from major depression, dysthymia, or social phobia. Comorbid substance abuse is common in these patients, particularly alcohol and/or

TABLE 49-4

MANAGEMENT OF ANTIDEPRESSANT SIDE EFFECTS

SYMPTOMS	COMMENTS AND MANAGEMENT STRATEGIES
Gastrointestinal	
Nausea, loss of appetite	Usually short-lived and dose-related; consider temporary dose reduction or administration with food and antacids
Diarrhea	Famotidine, 20–40 mg/d
Constipation	Wait for tolerance; try diet change, stool softener, exercise; avoid laxatives
Sexual dysfunction	Consider dose reduction; drug holiday
Anorgasmia/impotence; impaired ejaculation	Bethanechol, 10–20 mg, 2 h before activity, or cyproheptadine, 4–8 mg 2 h before activity, or bupropion, 100 mg bid or amantadine, 100 mg bid/tid
Orthostasis	Tolerance unlikely; increase fluid intake, use calf exercises/support hose; fludrocortisone, 0.025 mg/d
Anticholinergic	Wait for tolerance
Dry mouth, eyes	Maintain good oral hygiene; use artificial tears, sugar-free gum
Tremor/jitteriness	Antiparkinsonian drugs not effective; use dose reduction/slow increase; lorazepam, 0.5 mg bid, or propranolol, 10–20 mg bid
Insomnia	Schedule all doses for the morning; trazodone, 50–100 mg qhs
Sedation	Caffeine; schedule all dosing for bedtime; bupropion, 75–100 mg in afternoon
Headache	Evaluate diet, stress, other drugs; try dose reduction; amitriptyline, 50 mg/d
Weight gain	Decrease carbohydrates; exercise; consider fluoxetine
Loss of therapeutic benefit over time	Related to tolerance? Increase dose or drug holiday; add amantadine, 100 mg bid, buspirone, 10 mg tid, or pindolol, 2.5 mg bid

TABLE 49-5

POSSIBLE DRUG INTERACTIONS WITH SELECTIVE SEROTONIN REUPTAKE INHIBITORS

AGENT	EFFECT
Monoamine oxidase inhibitors	Serotonin syndrome[a]—absolute contraindication
Serotonergic agonists, e.g., tryptophan, fenfluramine	Potential serotonin syndrome
Drugs that are metabolized by P450 isoenzymes: tricyclics, other SSRIs, antipsychotics, beta blockers, codeine, triazolobenzodiazepines, calcium channel blockers	Delayed metabolism resulting in increased blood levels and potential toxicity—possible fatality secondary to QT prolongation with terfenadine or astemizole
Drugs that are bound tightly to plasma proteins, e.g., warfarin	Increased bleeding secondary to displacement
Drugs that inhibit the metabolism of SSRIs by P450 isoenzymes, e.g., quinidine	Increased SSRI side effects

[a]See Rx Depressive Disorders, later.
Note: SSRI, selective serotonin reuptake inhibitor.

sedative/hypnotic abuse. Patients with GAD worry excessively over minor matters, with life-disrupting effects; unlike in panic disorder, complaints of shortness of breath, palpitations, and tachycardia are relatively rare.

Etiology and Pathophysiology

Anxiogenic agents share in common the property of altering the binding of benzodiazepines to the γ-aminobutyric acid $(GABA)_A$ receptor/chloride ion channel complex, implicating this neurotransmitter system in the pathogenesis of anxiety and panic attacks. Benzodiazepines are thought to bind two separate $GABA_A$ receptor sites: type I, which has a broad neuroanatomic distribution, and type II, which is concentrated in the hippocampus, striatum, and neocortex. The antianxiety effects of the various benzodiazepines and side effects such as sedation and memory impairment are influenced by their relative binding to type I and type II receptor sites. Serotonin [5-hydroxytryptamine (5HT)] and 3α-reduced neuractive steroids (allosteric modulators of $GABA_A$) also appear to have a role in anxiety, and buspirone, a partial $5HT_{1A}$ receptor agonist, and certain $5HT_{2A}$ and $5HT_{2C}$ receptor antagonists (e.g., nefazodone) may have beneficial effects.

℞ Treatment: GENERALIZED ANXIETY DISORDER

A combination of pharmacologic and psychotherapeutic interventions is most effective in GAD, but complete symptomatic relief is rare. A short course of a benzodiazepine is usually indicated, preferably lorazepam, oxazepam, or temazepam. (The first two of these agents

TABLE 49-6

ANXIOLYTICS

NAME	EQUIVALENT PO DOSE, mg	ONSET OF ACTION	HALF-LIFE, h	COMMENTS
Benzodiazepines				
Diazepam (Valium)	5	Fast	20–70	Active metabolites; quite sedating
Flurazepam (Dalmane)	15	Fast	30–100	Flurazepam is a pro-drug; metabolites are active; quite sedating
Triazolam (Halcion)	0.25	Intermediate	1.5–5	No active metabolites; can induce confusion and delirium, especially in elderly
Lorazepam (Ativan)	1	Intermediate	10–20	No active metabolites; direct hepatic glucuronide conjugation; quite sedating
Alprazolam (Xanax)	0.5	Intermediate	12–15	Active metabolites; not too sedating; may have specific antidepressant and antipanic activity; tolerance and dependence develop easily
Chlordiazepoxide (Librium)	10	Intermediate	5–30	Active metabolites; moderately sedating
Oxazepam (Serax)	15	Slow	5–15	No active metabolites; direct glucuronide conjugation; not too sedating
Temazepam (Restoril)	15	Slow	9–12	No active metabolites; moderately sedating
Clonazepam (Klonopin)	0.5	Slow	18–50	No active metabolites; moderately sedating
Non-benzodiazepines				
Buspirone (BuSpar)	7.5	2 weeks	2–3	Active metabolites; tid dosing—usual daily dose 10–20 mg tid; nonsedating; no additive effects with alcohol; useful for agitation in demented or brain-injured patients

TABLE 49-7

DIAGNOSTIC CRITERIA FOR GENERALIZED ANXIETY DISORDER

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).
B. The person finds it difficult to control the worry.
C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months):
   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
   6. sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)
D. The focus of the anxiety and worry is not confined to features of an Axis I disorder, e.g., the anxiety or worry is not about having a panic attack (as in panic disorder), being embarrassed in public (as in social phobia), being contaminated (as in obsessive-compulsive disorder), being away from home or close relatives (as in separation anxiety disorder), gaining weight (as in anorexia nervosa), having multiple physical complaints (as in somatization disorder), or having a serious illness (as in hypochondriasis), and the anxiety and worry do not occur exclusively during posttraumatic stress disorder.
E. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
F. The disturbance is 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 does not occur exclusively during a mood disorder, a psychotic disorder, or a pervasive developmental disorder.

Source: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC, American Psychiatric Association, 2000.

are metabolized via conjugation rather than oxidation and thus do not accumulate if hepatic function is altered.) Administration should be initiated at the lowest dose possible and prescribed on an as-needed basis as symptoms warrant. Benzodiazepines differ in their milligram per kilogram potency, half-life, lipid solubility, metabolic pathways, and presence of active metabolites. Agents that are absorbed rapidly and are lipid soluble, such as diazepam, have a rapid onset of action and a higher abuse potential. Benzodiazepines should generally not be prescribed for >4–6 weeks because of the development of tolerance and the risk of abuse and dependence. Withdrawal must be closely monitored as relapses can occur. It is important to warn patients that concomitant use of alcohol or other sedating drugs may be neurotoxic and impair their ability to function. An optimistic approach that encourages the patient to clarify environmental precipitants, anticipate his or her reactions, and plan effective response strategies is an essential element of therapy.

Adverse effects of benzodiazepines generally parallel their relative half-lives. Longer-acting agents, such as diazepam, chlordiazepoxide, flurazepam, and clonazepam, tend to accumulate active metabolites, with resultant sedation, impairment of cognition, and poor psychomotor performance. Shorter-acting compounds, such as alprazolam and oxazepam, can produce daytime anxiety, early morning insomnia, and, with discontinuation, rebound anxiety and insomnia. Although patients develop tolerance to the sedative effects of benzodiazepines, they are less likely to habituate to the adverse psychomotor effects. Withdrawal from the longer half-life benzodiazepines can be accomplished through gradual, stepwise dose reduction (by 10% every 1–2 weeks) over 6–12 weeks. It is usually more difficult to taper patients off shorter-acting benzodiazepines. Physicians may need to switch the patient to a benzodiazepine with a longer half-life or use an adjunctive medication, such as a beta blocker or carbamazepine, before attempting to discontinue the benzodiazepine. Withdrawal reactions vary in severity and duration; they can include depression, anxiety, lethargy, diaphoresis, autonomic arousal, and, rarely, seizures.

Buspirone is a nonbenzodiazepine anxiolytic agent. It is nonsedating, does not produce tolerance or dependence, does not interact with benzodiazepine receptors or alcohol, and has no abuse or disinhibition potential. However, it requires several weeks to take effect and requires thrice-daily dosing. Patients who were previously responsive to a benzodiazepine are unlikely to rate buspirone as equally effective, but patients with head injury or dementia who have symptoms of anxiety and/or agitation may do well with this agent. Escitalopram, paroxetine, and venlafaxine are FDA approved for the treatment of GAD, usually at doses that are comparable to their efficacy in major depression. Benzodiazepines are contraindicated during pregnancy and breast-feeding.

Anticonvulsants with GABAergic properties may also be effective against anxiety. Gabapentin, oxcarbazepine, tiagabine, pregabalin, and divalproex have all shown some degree of benefit in a variety of anxiety-related syndromes. Agents that selectively target $GABA_A$ receptor subtypes are currently under development, and it is hoped that these will lack the sedating, memory-impairing, and addicting properties of benzodiazepines.

PHOBIC DISORDERS

Clinical Manifestations

The cardinal feature of phobic disorders is a marked and persistent fear of objects or situations, exposure to which results in an immediate anxiety reaction. The patient avoids the phobic stimulus, and this avoidance usually impairs occupational or social functioning. Panic attacks may be triggered by the phobic stimulus or may occur spontaneously. Unlike patients with other anxiety disorders, individuals with phobias usually experience anxiety only in specific situations. Common phobias include fear of closed spaces (claustrophobia), fear of blood, and fear of flying. Social phobia is distinguished by a specific fear of social or performance situations in which the individual is exposed to unfamiliar individuals or to possible examination and evaluation by others. Examples include having to converse at a party, use public restrooms, and meet strangers. In each case, the affected individual is aware that the experienced fear is excessive and unreasonable given the circumstance. The specific content of a phobia may vary across gender, ethnic, and cultural boundaries.

Phobic disorders are common, affecting ~10% of the population. Full criteria for diagnosis are usually satisfied first in early adulthood, but behavioral avoidance of unfamiliar people, situations, or objects dating from early childhood is common.

In one study of female twins, concordance rates for agoraphobia, social phobia, and animal phobia were found to be 23% for monozygotic twins and 15% for dizygotic twins. A twin study of fear conditioning, a model for the acquisition of phobias, demonstrated a heritability of 35–45%, and a genome-wide linkage scan identified a risk locus on chromosome 14 in a region previously implicated in a mouse model of fear. Animal studies of fear conditioning have indicated that processing of the fear stimulus occurs through the lateral nucleus of the amygdala, extending through the central nucleus and projecting to the periaqueductal gray region, lateral hypothalamus, and paraventricular hypothalamus.

Rx Treatment: PHOBIC DISORDERS

Beta blockers (e.g., propranolol, 20–40 mg orally 2 h before the event) are particularly effective in the treatment of "performance anxiety" (but not general social phobia) and appear to work by blocking the peripheral manifestations of anxiety, such as perspiration, tachycardia, palpitations, and tremor. MAOIs alleviate social phobia independently of their antidepressant activity, and paroxetine, sertraline, and venlafaxine have received FDA approval for treatment of social anxiety. Benzodiazepines can be helpful in reducing fearful avoidance, but the chronic nature of phobic disorders limits their usefulness.

Behaviorally focused psychotherapy is an important component of treatment, as relapse rates are high when medication is used as the sole treatment. Cognitive-behavioral strategies are based upon the finding that distorted perceptions and interpretations of fear-producing stimuli play a major role in perpetuation of phobias. Individual and group therapy sessions teach the patient to identify specific negative thoughts associated with the anxiety-producing situation and help to reduce the patient's fear of loss of control. In desensitization therapy, hierarchies of feared situations are constructed and the patient is encouraged to pursue and master gradual exposure to the anxiety-producing stimuli.

Patients with social phobia, in particular, have a high rate of comorbid alcohol abuse, as well as of other psychiatric conditions (e.g., eating disorders), necessitating the need for parallel management of each disorder if anxiety reduction is to be achieved.

STRESS DISORDERS

Clinical Manifestations

Patients may develop anxiety after exposure to extreme traumatic events such as the threat of personal death or injury or the death of a loved one. The reaction may occur shortly after the trauma (*acute stress disorder*) or be delayed and subject to recurrence (PTSD) (**Table 49-8**). In both syndromes, individuals experience associated symptoms of detachment and loss of emotional responsivity. The patient may feel depersonalized and unable to recall specific aspects of the trauma, though typically it is reexperienced through intrusions in thought, dreams, or flashbacks, particularly when cues of the original event are present. Patients often actively avoid stimuli that precipitate recollections of the trauma and demonstrate a resulting increase in vigilance, arousal, and startle response. Patients with stress disorders are at risk for the development of other disorders related to anxiety, mood, and substance abuse (especially alcohol). Between 5 and

TABLE 49-8

DIAGNOSTIC CRITERIA FOR POSTTRAUMATIC STRESS DISORDER

A. The person has been exposed to a traumatic event in which both of the following were present:
   1. The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others
   2. The person's response involved intense fear, helplessness, or horror
B. The traumatic event is persistently reexperienced in one (or more) of the following ways:
   1. Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions
   2. Recurrent distressing dreams of the event
   3. Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated)
   3. Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event
   4. Physiologic reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event
C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three or more of the following:
   1. Efforts to avoid thoughts, feelings, or conversations associated with the trauma
   2. Efforts to avoid activities, places, or people that arouse recollections of the trauma
   3. Inability to recall an important aspect of the trauma
   4. Markedly diminished interest or participation in significant activities
   5. Feeling of detachment or estrangement from others
   6. Restricted range of affect (e.g., unable to have loving feelings)
   7. Sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span)
D. Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:
   1. Difficulty falling or staying asleep
   2. Irritability or outbursts of anger
   3. Difficulty concentrating
   4. Hypervigilance
   5. Exaggerated startle response
E. Duration of the disturbance (symptoms in criteria B, C, and D) is >1 month.
F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

Source: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC, American Psychiatric Association, 2000.

10% of Americans will at some time in their life satisfy criteria for PTSD, with women more likely to be affected than men.

Risk factors for the development of PTSD include a past psychiatric history and personality characteristics of high neuroticism and extroversion. Twin studies show a substantial genetic influence on all symptoms associated with PTSD, with less evidence for an environmental effect.

Etiology and Pathophysiology

It is hypothesized that in PTSD there is excessive release of norepinephrine from the locus coeruleus in response to stress and increased noradrenergic activity at projection sites in the hippocampus and amygdala. These changes theoretically facilitate the encoding of fear-based memories. Greater sympathetic responses to cues associated with the traumatic event occur in PTSD, although pituitary adrenal responses are blunted.

℞ Treatment: STRESS DISORDERS

Acute stress reactions are usually self-limited, and treatment typically involves the short-term use of benzodiazepines and supportive/expressive psychotherapy. The chronic and recurrent nature of PTSD, however, requires a more complex approach employing drug and behavioral treatments. PTSD is highly correlated with peritraumatic dissociative symptoms and the development of an acute stress disorder at the time of the trauma. TCAs such as imipramine and amitriptyline, the MAOI phenelzine, and the SSRIs can all reduce anxiety, symptoms of intrusion, and avoidance behaviors, as can prazosin, an α_1 antagonist. Propranolol given during the acute stress period may have beneficial effects in preventing the development of PTSD. Trazodone, a sedating antidepressant, is frequently used at night to help with insomnia (50–150 mg qhs). Carbamazepine, valproic acid, or alprazolam have also independently produced improvement in uncontrolled trials. Psychotherapeutic strategies for PTSD help the patient overcome avoidance behaviors and demoralization and master fear of recurrence of the trauma; therapies that encourage the patient to dismantle avoidance behaviors through stepwise focusing on the experience of the traumatic event are the most effective.

OBSESSIVE-COMPULSIVE DISORDER

Clinical Manifestations

Obsessive-compulsive disorder (OCD) is characterized by obsessive thoughts and compulsive behaviors that impair everyday functioning. Fears of contamination and germs are common, as are handwashing, counting behaviors, and having to check and recheck such actions as whether a door is locked. The degree to which the disorder is disruptive for the individual varies, but in all cases obsessive-compulsive activities take up >1 h/d and are undertaken to relieve the anxiety triggered by the core fear. Patients often conceal their symptoms, usually because they are embarrassed by the content of their thoughts or the nature of their actions. Physicians must ask specific questions regarding recurrent thoughts and behaviors, particularly if physical clues such as chafed and reddened hands or patchy hair loss (from repetitive hair pulling, or trichotillomania) are present. Comorbid conditions are common, the most frequent being depression, other anxiety disorders, eating disorders, and tics. OCD has a lifetime prevalence of 2–3% worldwide. Onset is usually gradual, beginning in early adulthood, but childhood onset is not rare. The disorder usually has a waxing and waning course, but some cases may show a steady deterioration in psychosocial functioning.

Etiology and Pathophysiology

A genetic contribution to OCD is suggested by twin studies. Family studies show an aggregation with Tourette's disorder. OCD is also more common in males and in first-born children.

The anatomy of obsessive-compulsive behavior is thought to include the orbital frontal cortex, caudate nucleus, and globus pallidus. The caudate nucleus appears to be involved in the acquisition and maintenance of habit and skill learning, and interventions that are successful in reducing obsessive-compulsive behaviors also decrease metabolic activity measured in the caudate.

℞ Treatment: OBSESSIVE-COMPULSIVE DISORDER

Clomipramine, fluoxetine, fluvoxamine, and sertraline are approved for the treatment of OCD. Clomipramine is a TCA that is often tolerated poorly owing to anticholinergic and sedative side effects at the doses required to treat the illness (25–250 mg/d). Its efficacy in OCD is unrelated to its antidepressant activity. Fluoxetine (5–60 mg/d), fluvoxamine (25–300 mg/d), and sertraline (50–150 mg/d) are as effective as clomipramine and have a more benign side-effect profile. Only 50–60% of patients with OCD show adequate improvement with pharmacotherapy alone. In treatment-resistant cases, augmentation with other serotonergic agents, such as buspirone, or with a neuroleptic or benzodiazepine may be beneficial. When a therapeutic

response is achieved, long-duration maintenance therapy is usually indicated. Recent studies are beginning to explore the efficacy of deep brain stimulation (DBS) for refractory, severe OCD.

For many individuals, particularly those with time-consuming compulsions, behavior therapy will result in as much improvement as that afforded by medication. Effective techniques include the gradual increase in exposure to stressful situations, maintenance of a diary to clarify stressors, and homework assignments that substitute new activities for compulsive behaviors.

MOOD DISORDERS

Mood disorders are characterized by a disturbance in the regulation of mood, behavior, and affect. Mood disorders are subdivided into (1) depressive disorders, (2) bipolar disorders, and (3) depression in association with medical illness or alcohol and substance abuse (Chaps. 50, 51, and 52). Depressive disorders are differentiated from bipolar disorders by the absence of a manic or hypomanic episode. The relationship between pure depressive syndromes and bipolar disorders is not well understood; depression is more frequent in families of bipolar individuals, but the reverse is not true. In the Global Burden of Disease Study conducted by the World Health Organization, unipolar major depression ranked fourth among all diseases in terms of disability-adjusted life-years and was projected to rank second by the year 2020. In the United States, lost productivity directly related to mood disorders has been estimated at $55.1 billion per year.

DEPRESSION IN ASSOCIATION WITH MEDICAL ILLNESS

Depression occurring in the context of medical illness is difficult to evaluate. Depressive symptomatology may reflect the psychological stress of coping with the disease, may be caused by the disease process itself or by the medications used to treat it, or may simply coexist in time with the medical diagnosis.

Virtually every class of *medication* includes some agent that can induce depression. Antihypertensive drugs, anticholesterolemic agents, and antiarrhythmic agents are common triggers of depressive symptoms. Among the antihypertensive agents, β-adrenergic blockers and, to a lesser extent, calcium channel blockers are the most likely to cause depressed mood. Iatrogenic depression should also be considered in patients receiving glucocorticoids, antimicrobials, systemic analgesics, antiparkinsonian medications, and anticonvulsants. To decide whether a causal relationship exists between pharmacologic therapy and a patient's change in mood, it may sometimes be necessary to undertake an empirical trial of an alternative medication.

Between 20 and 30% of *cardiac* patients manifest a depressive disorder; an even higher percentage experience depressive symptomatology when self-reporting scales are used. Depressive symptoms following unstable angina, myocardial infarction, cardiac bypass surgery, or heart transplant impair rehabilitation and are associated with higher rates of mortality and medical morbidity. Depressed patients often show decreased variability in heart rate (an index of reduced parasympathetic nervous system activity); this has been proposed as one mechanism by which depression may predispose individuals to ventricular arrhythmia and increased morbidity. Depression also appears to increase the risk of developing coronary heart disease; increased serotonin-induced platelet aggregation has been implicated as a possible cause. TCAs are contraindicated in patients with bundle branch block, and TCA-induced tachycardia is an additional concern in patients with congestive heart failure. SSRIs appear not to induce ECG changes or adverse cardiac events and thus are reasonable first-line drugs for patients at risk for TCA-related complications. SSRIs may interfere with hepatic metabolism of anticoagulants, however, causing increased anticoagulation.

In patients with *cancer*, the mean prevalence of depression is 25%, but depression occurs in 40–50% of patients with cancers of the pancreas or oropharynx. This association is not due to the effect of cachexia alone, as the higher prevalence of depression in patients with pancreatic cancer persists when compared to those with advanced gastric cancer. Initiation of antidepressant medication in cancer patients has been shown to improve quality of life as well as mood. Psychotherapeutic approaches, particularly group therapy, may have some effect on short-term depression, anxiety, and pain symptoms.

Depression occurs frequently in patients with *neurologic disorders*, particularly cerebrovascular disorders, Parkinson's disease, dementia, multiple sclerosis, and traumatic brain injury. One in five patients with left-hemisphere stroke involving the dorsolateral frontal cortex experiences major depression. Late-onset depression in otherwise cognitively normal individuals increases the risk of a subsequent diagnosis of Alzheimer's disease. Both TCA and SSRI agents are effective against these depressions, as are stimulant compounds and, in some patients, MAOIs.

The reported prevalence of depression in patients with *diabetes mellitus* varies from 8–27%, with the severity of the mood state correlating with the level of hyperglycemia and the presence of diabetic complications. Treatment of depression may be complicated by effects of antidepressive agents on glycemic control. MAOIs can induce hypoglycemia and weight gain. TCAs can produce hyperglycemia and carbohydrate craving.

SSRIs, like MAOIs, may reduce fasting plasma glucose, but they are easier to use and may also improve dietary and medication compliance.

Hypothyroidism is frequently associated with features of depression, most commonly depressed mood and memory impairment. Hyperthyroid states may also present in a similar fashion, usually in geriatric populations. Improvement in mood usually follows normalization of thyroid function, but adjunctive antidepressant medication is sometimes required. Patients with subclinical hypothyroidism can also experience symptoms of depression and cognitive difficulty that respond to thyroid replacement.

The lifetime prevalence of depression in *HIV-positive* individuals has been estimated at 22–45%. The relationship between depression and disease progression is multifactorial and likely to involve psychological and social factors, alterations in immune function, and central nervous system disease. Chronic hepatitis C infection is also associated with depression, which may worsen with interferon-α treatment.

Some chronic disorders of uncertain etiology, such as chronic fatigue syndrome (Chap. 47) and fibromyalgia, are strongly associated with depression and anxiety; patients may benefit from antidepressant treatment, usually at lower than normal dosing.

DEPRESSIVE DISORDERS

Clinical Manifestations

Major depression is defined as depressed mood on a daily basis for a minimum duration of 2 weeks (**Table 49-9**). An episode may be characterized by sadness, indifference, apathy, or irritability and is usually associated with: changes in sleep patterns, appetite, and weight; motor agitation or retardation; fatigue; impaired concentration and decision-making; feelings of shame or guilt; and thoughts of death or dying. Patients with depression have a profound loss of pleasure in all enjoyable activities, exhibit early morning awakening, feel that the dysphoric mood state is qualitatively different from sadness, and often notice a diurnal variation in mood (worse in morning hours).

Approximately 15% of the population experiences a major depressive episode at some point in life, and 6–8% of all outpatients in primary care settings satisfy diagnostic criteria for the disorder. Depression is often undiagnosed, and, even more frequently, it is treated inadequately. If a physician suspects the presence of a major depressive episode, the initial task is to determine whether it represents unipolar or bipolar depression or is one of the 10–15% of cases that are secondary to general medical illness or substance abuse. Physicians should also assess the risk of suicide by direct questioning, as patients are often reluctant to verbalize such thoughts without prompting. If specific plans are uncovered or if significant risk factors exist (e.g., a past history of suicide attempts, profound hopelessness, concurrent medical illness, substance abuse, or social isolation), the patient must be referred to a mental health specialist for immediate care. The physician should specifically probe each of these areas in an empathic and hopeful manner, being

TABLE 49-9

CRITERIA FOR MAJOR DEPRESSIVE EPISODE

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. **Note:** Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.
   1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)
   2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
   3. Significant weight loss when not dieting or weight gain (e.g., a change of >5% of body weight in a month), or decrease or increase in appetite nearly every day
   4. Insomnia or hypersomnia nearly every day
   5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
   6. Fatigue or loss of energy nearly every day
   7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
   8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
   9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a mixed episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

D. The symptoms 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., hypothyroidism)

E. The symptoms are not better accounted for by bereavement; i.e., after the loss of a loved one, the symptoms persist for >2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation

Source: *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. Washington, DC, American Psychiatric Association, 2000.

sensitive to denial and possible minimization of distress. The presence of anxiety, panic, or agitation significantly increases near-term suicidal risk. Approximately 4–5% of all depressed patients will commit suicide; most will have sought help from a physician within 1 month of their death.

In some depressed patients, the mood disorder does not appear to be episodic and is not clearly associated with either psychosocial dysfunction or change from the individual's usual experience in life. *Dysthymic disorder* consists of a pattern of chronic (at least 2 years), ongoing, mild depressive symptoms that are less severe and less disabling than those found in major depression; the two conditions are sometimes difficult to separate, however, and can occur together ("double depression"). Many patients who exhibit a profile of pessimism, disinterest, and low self-esteem respond to antidepressant treatment. Dysthymic disorder exists in ~5% of primary care patients. The term *minor depression* is used for individuals who experience at least two depressive symptoms for 2 weeks but who do not meet the full criteria for major depression. Despite its name, minor depression is associated with significant morbidity and disability and also responds to pharmacologic treatment.

Depression is approximately twice as common in women as in men, and the incidence increases with age in both sexes. Twin studies indicate that the liability to major depression in adult women is largely genetic in origin. Negative life events can precipitate and contribute to depression, but genetic factors influence the sensitivity of individuals to these stressful events. In most cases, both biologic and psychosocial factors are involved in the precipitation and unfolding of depressive episodes. The most potent stressors appear to involve death of a relative, assault, or severe marital or relationship problems.

Unipolar depressive disorders usually begin in early adulthood and recur episodically over the course of a lifetime. The best predictor of future risk is the number of past episodes; 50–60% of patients who have a first episode have at least one or two recurrences. Some patients experience multiple episodes that become more severe and frequent over time. The duration of an untreated episode varies greatly, ranging from a few months to ≥1 year. The pattern of recurrence and clinical progression in a developing episode are also variable. Within an individual, the nature of episodes (e.g., specific presenting symptoms, frequency and duration) may be similar over time. In a minority of patients, a severe depressive episode may progress to a psychotic state; in elderly patients, depressive symptoms may be associated with cognitive deficits mimicking dementia ("pseudodementia"). A seasonal pattern of depression, called *seasonal affective disorder*, may manifest with onset and remission of episodes at predictable times of the year. This disorder is more common in women, whose symptoms are anergy, fatigue, weight gain, hypersomnia, and episodic carbohydrate craving. The prevalence increases with distance from the equator, and improvement may occur by altering light exposure.

Etiology and Pathophysiology

Although evidence for genetic transmission of unipolar depression is not as strong as in bipolar disorder, monozygotic twins have a higher concordance rate (46%) than dizygotic siblings (20%), with little support for any effect of a shared family environment. There is some evidence that a functional polymorphism in the serotonin transporter (*5-HTT*) gene may interact with stressful life events to markedly increase risk of depression and suicide. Positron emission tomography (PET) studies show decreased metabolic activity in the caudate nuclei and frontal lobes in depressed patients that returns to normal with recovery. Single-photon emission computed tomography (SPECT) studies show comparable changes in blood flow.

Postmortem examination of brains of suicide victims indicate altered noradrenergic activity, including increased binding to α_1-, α_2-, and β-adrenergic receptors in the cerebral cortex and decreased numbers of noradrenergic neurons in the locus coeruleus. Involvement of the serotonin system is suggested by findings of reduced plasma tryptophan levels, a decreased cerebrospinal fluid level of 5-hydroxyindolacetic acid (the principal metabolite of serotonin in brain), and decreased platelet serotonergic transporter binding. An increase in brain serotonin receptors in suicide victims and decreased expression of the cyclic AMP response element-binding (CREB) protein are also reported. Depletion of blood tryptophan, the amino acid precursor of serotonin, rapidly reverses the antidepressant benefit in depressed patients who have been successfully treated. However, a decrement in mood after tryptophan reduction is considerably less robust in untreated patients, indicating that, if presynaptic serotonergic dysfunction occurs in depression, it likely plays a contributing rather than a causal role.

Neuroendocrine abnormalities that reflect the neurovegetative signs and symptoms of depression include (1) increased cortisol and corticotropin-releasing hormone (CRH) secretion, (2) an increase in adrenal size, (3) a decreased inhibitory response of glucocorticoids to dexamethasone, and (4) a blunted response of thyroid-stimulating hormone (TSH) level to infusion of thyroid-releasing hormone (TRH). Antidepressant treatment leads to normalization of these pituitary-adrenal abnormalities. Major depression is also associated with an upregulation of proinflammatory cytokines, which normalizes with antidepressant treatment.

Diurnal variations in symptom severity and alterations in circadian rhythmicity of a number of neurochemical and neurohumoral factors suggest that biologic

differences may be secondary to a primary defect in regulation of biologic rhythms. Patients with major depression show consistent findings of a decrease in rapid eye movement (REM) sleep onset (REM latency), an increase in REM density, and, in some subjects, a decrease in stage IV delta slow-wave sleep.

Although antidepressant drugs inhibit neurotransmitter uptake within hours, their therapeutic effects typically emerge over several weeks, implicating adaptive changes in second messenger systems and transcription factors as possible mechanisms of action. Antidepressant drugs have been shown to regulate neural plasticity and cell survival by increasing the expression of brain-derived neurotrophic factor (BDNF) through upregulation of the CREB protein and to alter stress responsivity through an increase in glucocorticoid receptor transcription. Secondary effects on activation of the mitogen-activated protein (MAP) kinase and phosphoinositol-3 kinase/AKT pathways and increased expression of the antiapoptotic protein, Bcl-2, are also thought to be critical to antidepressant actions.

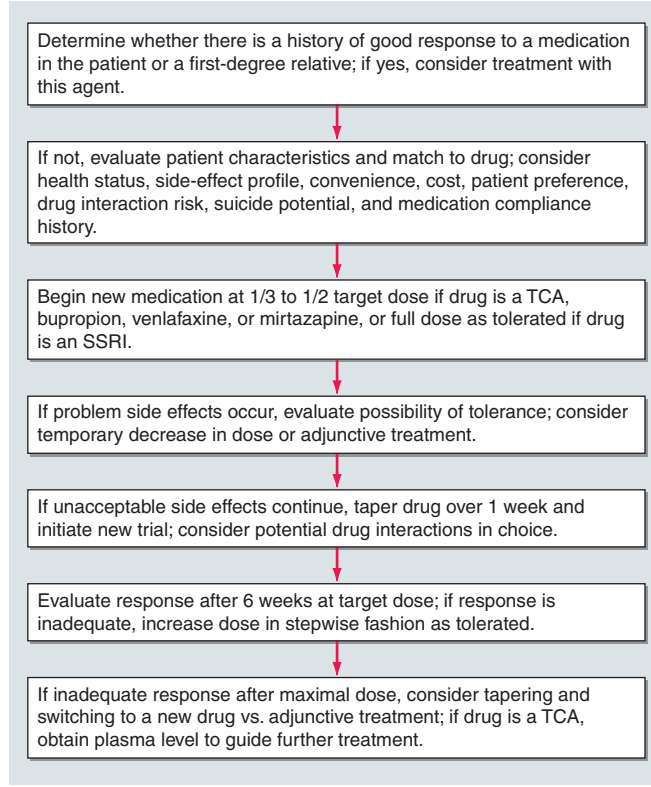

FIGURE 49-1
A guideline for the medical management of major depressive disorder. SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Rx Treatment: DEPRESSIVE DISORDERS

Treatment planning requires coordination of short-term strategies to induce remission combined with longer term maintenance designed to prevent recurrence. The most effective intervention for achieving remission and preventing relapse is medication, but combined treatment, incorporating psychotherapy to help the patient cope with decreased self-esteem and demoralization, improves outcome (Fig. 49-1). Approximately 40% of primary care patients with depression drop out of treatment and discontinue medication if symptomatic improvement is not noted within a month, unless additional support is provided. Outcome improves with (1) increased intensity and frequency of visits during the first 4–6 weeks of treatment, (2) supplemental educational materials, and (3) psychiatric consultation as indicated. Despite the widespread use of SSRIs and other second-generation antidepressant drugs, there is no convincing evidence that this class of antidepressant is more efficacious than TCAs. Between 60 and 70% of all depressed patients respond to any drug chosen, if it is given in a sufficient dose for 6–8 weeks. There is no ideal antidepressant; no current compound combines rapid onset of action, moderate half-life, a meaningful relationship between dose and blood level, a low side-effect profile, minimal interaction with other drugs, and safety in overdose.

A rational approach to selecting which antidepressant to use involves matching the patient's preference and medical history with the metabolic and side effect profile of the drug (Tables 49-4 and 49-5). A previous response, or a family history of a positive response, to a specific antidepressant often suggests that that drug be tried first. Before initiating antidepressant therapy, the physician should evaluate the possible contribution of comorbid illnesses and consider their specific treatment. In individuals with suicidal ideation, particular attention should be paid to choosing a drug with low toxicity if taken in overdose. The SSRIs and other newer antidepressant drugs are distinctly safer in this regard; nevertheless, the advantages of TCAs have not been completely superseded. The existence of generic equivalents make TCAs relatively cheap, and for several tricyclics, particularly nortriptyline, imipramine, and desipramine, well-defined relationships among dose, plasma level, and therapeutic response exist. The steady-state plasma level achieved for a given drug dose can vary more than tenfold between individuals. Plasma levels may help in interpreting apparent resistance to treatment and/or unexpected drug toxicity. The principal side effects of TCAs are antihistamine (sedation) and anticholinergic (constipation, dry mouth, urinary hesitancy, blurred vision). Cardiac toxicity due to conduction block or arrhythmias can also occur but is uncommon at therapeutic levels. TCAs are

contraindicated in patients with serious cardiovascular risk factors. Overdoses of tricyclic agents can be lethal, with desipramine carrying the greatest risk. It is judicious to prescribe only a 10-day supply when suicide is a risk. Most patients require a daily dose of 150–200 mg of imipramine or amitriptyline or its equivalent to achieve a therapeutic blood level of 150–300 ng/mL and a satisfactory remission; some patients show a partial effect at lower doses. Geriatric patients may require a low starting dose and slow escalation. Ethnic differences in drug metabolism are significant; Hispanic, Asian, and African-American patients generally require lower doses than whites to achieve a comparable blood level. P450 profiling using genetic chip technology may be clinically useful in predicting individual sensitivity.

Second-generation antidepressants include amoxapine, maprotiline, trazodone, and bupropion. Amoxapine is a dibenzoxazepine derivative that blocks norepinephrine and serotonin reuptake and has a metabolite that shows a degree of dopamine blockade. Long-term use of this drug carries a risk of tardive dyskinesia. Maprotiline is a potent noradrenergic reuptake blocker that has little anticholinergic effect but may produce seizures. Bupropion is a novel antidepressant whose mechanism of action is thought to involve enhancement of noradrenergic function. It has no anticholinergic, sedating, or orthostatic side effects and has a low incidence of sexual side effects. It may, however, be associated with stimulant-like side effects, may lower seizure threshold, and has an exceptionally short half-life, requiring frequent dosing. An extended-release preparation is available.

SSRIs such as fluoxetine, sertraline, paroxetine, citalopram, and escitalopram cause a lower frequency of anticholinergic, sedating, and cardiovascular side effects but a possibly greater incidence of gastrointestinal complaints, sleep impairment, and sexual dysfunction than do TCAs. Akathisia, involving an inner sense of restlessness and anxiety in addition to increased motor activity, may also be more common, particularly during the first week of treatment. One concern is the risk of "serotonin syndrome," thought to result from hyperstimulation of brainstem $5HT_{1A}$ receptors and characterized by myoclonus, agitation, abdominal cramping, hyperpyrexia, hypertension, and potentially death. Serotonergic agonists taken in combination should be monitored closely for this reason. Considerations such as half-life, compliance, toxicity, and drug-drug interactions may guide the choice of a particular SSRI. Fluoxetine and its principal active metabolite, norfluoxetine, for example, have a combined half-life of almost 7 days, resulting in a delay of 5 weeks before steady-state levels are achieved and a similar delay for complete drug excretion once its use is discontinued. All the SSRIs may impair sexual function, resulting in diminished libido, impotence, or difficulty in achieving orgasm. Sexual dysfunction frequently results in noncompliance and should be asked about specifically. Sexual dysfunction can sometimes be ameliorated by lowering the dose, by instituting weekend drug holidays (two or three times a month), or by treatment with amantadine (100 mg tid), bethanechol (25 mg tid), buspirone (10 mg tid), or bupropion (100–150 mg/d). Paroxetine appears to be more anticholinergic than either fluoxetine or sertraline, and sertraline carries a lower risk of producing an adverse drug interaction than the other two. Rare side effects of SSRIs include angina due to vasospasm and prolongation of the prothrombin time. Escitalopram is the most specific of currently available SSRIs and appears to have no specific inhibitory effects on the P450 system.

Venlafaxine and duloxetine block the reuptake of both norepinephrine and serotonin but produce relatively little in the way of traditional tricyclic side effects. Unlike the SSRIs, venlafaxine has a relatively linear dose-response curve. Patients should be monitored for a possible increase in diastolic blood pressure, and multiple daily dosing is required because of the drug's short half-life. An extended-release form is available and has a somewhat lower incidence of gastrointestinal side effects. Mirtazapine is a tetracyclic antidepressant that has a unique spectrum of activity. It increases noradrenergic and serotonergic neurotransmission through a blockade of central α_2-adrenergic receptors and postsynaptic $5HT_2$ and $5HT_3$ receptors. It is also strongly antihistaminic and, as such, may produce sedation.

With the exception of citalopram and escitalopram, each of the SSRIs may inhibit one or more cytochrome P450 enzymes. Depending on the specific isoenzyme involved, the metabolism of a number of concomitantly administered medications can be dramatically affected. Fluoxetine and paroxetine, for example, by inhibiting 2D6, can cause dramatic increases in the blood level of type 1C antiarrhythmics, while sertraline, by acting on 3A4, may alter blood levels of carbamazepine, or digoxin.

The MAOIs are highly effective, particularly in atypical depression, but the risk of hypertensive crisis following intake of tyramine-containing food or sympathomimetic drugs makes them inappropriate as first-line agents. Transdermal selegiline may avert this risk at low dose. Common side effects include orthostatic hypotension, weight gain, insomnia, and sexual dysfunction. MAOIs should not be used concomitantly with SSRIs, because of the risk of serotonin syndrome, or with TCAs, because of possible hyperadrenergic effects.

Electroconvulsive therapy is at least as effective as medication, but its use is reserved for treatment-resistant cases and delusional depressions. Transcranial magnetic stimulation (TMS) is an investigational treatment of depression that has been shown to have efficacy in

several controlled trials; it is uncertain whether the observed benefits were clinically meaningful, however. Vagus nerve stimulation (VNS) has recently been approved for treatment-resistant depression, but its degree of efficacy is controversial.

Regardless of the treatment undertaken, the response should be evaluated after ~2 months. Three-quarters of patients show improvement by this time, but if remission is inadequate the patient should be questioned about compliance and an increase in medication dose should be considered if side effects are not troublesome. If this approach is unsuccessful, referral to a mental health specialist is advised. Strategies for treatment then include selection of an alternative drug, combinations of antidepressants, and/or adjunctive treatment with other classes of drugs, including lithium, thyroid hormone, and dopamine agonists. A large randomized trial (STAR-D) was unable to show preferential efficacy. Patients whose response to an SSRI wanes over time may benefit from the addition of buspirone (10 mg tid) or pindolol (2–5 mg tid) or small amounts of a TCA such as desipramine (25 mg bid or tid). Most patients will show some degree of response but aggressive treatment should be pursued until remission is achieved, and drug treatment should be continued for at least 6–9 more months to prevent relapse. In patients who have had two or more episodes of depression, indefinite maintenance treatment should be considered.

It is essential to educate patients both about depression and the benefits and side effects of medications they are receiving. Advice about stress reduction and cautions that alcohol may exacerbate depressive symptoms and impair drug response are helpful. Patients should be given time to describe their experience, their outlook, and the impact of the depression on them and their families. Occasional empathic silence may be as helpful for the treatment alliance as verbal reassurance. Controlled trials have shown that cognitive-behavioral and interpersonal therapies are effective in improving psychological and social adjustment and that a combined treatment approach is more successful than medication alone for many patients.

TABLE 49-10

CRITERIA FOR A MANIC EPISODE

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary)
B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:
   1. Inflated self-esteem or grandiosity
   2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
   3. More talkative than usual or pressure to keep talking
   4. Flight of ideas or subjective experience that thoughts are racing
   5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
   6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
   7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
C. The symptoms do not meet criteria for a mixed episode.
D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
E. The symptoms are not due to the direct physiologic effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Note: Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of bipolar I disorder.
Source: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC, American Psychiatric Association, 2000.

BIPOLAR DISORDER

Clinical Manifestations

Bipolar disorder is characterized by unpredictable swings in mood from mania (or hypomania) to depression. Some patients suffer only from recurrent attacks of *mania*, which in its pure form is associated with increased psychomotor activity; excessive social extroversion; decreased need for sleep; impulsivity and impairment in judgment; and expansive, grandiose, and sometimes irritable mood (Table 49-10). In severe mania, patients may experience delusions and paranoid thinking indistinguishable from schizophrenia. Half of patients with bipolar disorder present with a mixture of psychomotor agitation and activation with dysphoria, anxiety, and irritability. It may be difficult to distinguish *mixed mania* from *agitated depression*. In some bipolar patients (*bipolar II disorder*), the full criteria for mania are lacking, and the requisite recurrent depressions are separated by periods of mild activation and increased energy (hypomania). In *cyclothymic disorder*, there are numerous hypomanic periods, usually of relatively short duration, alternating with clusters of depressive symptoms that fail, either in severity or duration, to meet the criteria of major depression. The mood fluctuations are chronic and should be present for at least 2 years before the diagnosis is made.

Manic episodes typically emerge over a period of days to weeks, but onset within hours is possible, usually in the early morning hours. An untreated episode of either depression or mania can be as short as several weeks or

last as long as 8–12 months, and rare patients have an unremitting chronic course. The term *rapid cycling* is used for patients who have four or more episodes of either depression or mania in a given year. This pattern occurs in 15% of all patients, almost all of whom are women. In some cases, rapid cycling is linked to an underlying thyroid dysfunction and, in others, it is iatrogenically triggered by prolonged antidepressant treatment. Approximately half of patients have sustained difficulties in work performance and psychosocial functioning.

Bipolar disorder is common, affecting ~1.5% of the population in the United States. Onset is typically between 20 and 30 years of age, but many individuals report premorbid symptoms in late childhood or early adolescence. The prevalence is similar for men and women; women are likely to have more depressive and men more manic episodes over a lifetime.

Differential Diagnosis

The differential diagnosis of mania includes toxic effects of stimulant or sympathomimetic drugs as well as secondary mania induced by hyperthyroidism, AIDS, or neurologic disorders, such as Huntington's or Wilson's disease, or cerebrovascular accidents. Comorbidity with alcohol and substance abuse is common, either because of poor judgment and increased impulsivity or because of an attempt to self-treat the underlying mood symptoms and sleep disturbances.

Etiology and Pathophysiology

Genetic predisposition to bipolar disorder is evident from family studies; the concordance rate for monozygotic twins approaches 80%. Multiple genes are likely to be involved.

The pathophysiologic mechanisms underlying the profound and recurrent mood swings of bipolar disorder remain unknown. Neuroimaging studies have reported anatomic changes in amygdala volume as well as increases in white matter hyperintensities. Molecular studies have implicated changes in membrane Na^+- and K^+-activated ATPase and disordered signal transduction involving the phosphoinositol system and GTP-binding proteins as possible contributing mechanisms. Patients with bipolar disorder also appear to have altered circadian rhythmicity, and lithium may exert its therapeutic benefit through a resynchronization of intrinsic rhythms keyed to the light/dark cycle.

TABLE 49-11
CLINICAL PHARMACOLOGY OF MOOD STABILIZERS

AGENT AND DOSING	SIDE EFFECTS AND OTHER EFFECTS
Lithium Starting dose: 300 mg bid or tid Therapeutic blood level: 0.8–1.2 meq/L	*Common side effects:* Nausea/anorexia/diarrhea, fine tremor, thirst, polyuria, fatigue, weight gain, acne, folliculitis, neutrophilia, hypothyroidism Blood level is increased by thiazides, tetracyclines, and NSAIDs Blood level is decreased by bronchodilators, verapamil, and carbonic anhydrase inhibitors *Rare side effects:* Neurotoxicity, renal toxicity, hypercalcemia, ECG changes
Valproic acid Starting dose: 250 mg tid Therapeutic blood level: 50–125 μg/mL	*Common side effects:* Nausea/anorexia, weight gain, sedation, tremor, rash, alopecia Inhibits hepatic metabolism of other medications *Rare side effects:* Pancreatitis, hepatotoxicity, Stevens-Johnson syndrome
Carbamazepine/oxcarbazepine Starting dose: 200 mg bid for carbamazepine, 150 bid for oxcarbazepine Therapeutic blood level: 4–12 μg/mL for carbamazepine	*Common side effects:* Nausea/anorexia, sedation, rash, dizziness/ataxia Carbamazepine, but not oxcarbazepine, induces hepatic metabolism of other medications *Rare side effects:* Hyponatremia, agranulocytosis, Stevens-Johnson syndrome
Lamotrigine Starting dose: 25 mg/d	*Common side effects:* Rash, dizziness, headache, tremor, sedation, nausea *Rare side effect:* Stevens-Johnson syndrome

Note: NSAID, nonsteroidal anti-inflammatory drug; ECG, electrocardiogram.

Rx Treatment: BIPOLAR DISORDER

(Table 49-11) Lithium carbonate is the mainstay of treatment in bipolar disorder, although sodium valproate and olanzapine are equally effective in acute mania, as is lamotrigine in the depressed phase. The response rate to lithium carbonate is 70–80% in acute mania, with beneficial effects appearing in 1–2 weeks. Lithium also has a prophylactic effect in prevention of recurrent mania and, to a lesser extent, in the prevention of recurrent depression. A simple cation, lithium is rapidly absorbed from the gastrointestinal tract and remains unbound to plasma or tissue proteins. Some 95% of a given dose is excreted unchanged through the kidneys within 24 h.

Serious side effects from lithium are rare, but minor complaints such as gastrointestinal discomfort, nausea,

diarrhea, polyuria, weight gain, skin eruptions, alopecia, and edema are common. Over time, urine-concentrating ability may be decreased, but significant nephrotoxicity does not usually occur. Lithium exerts an antithyroid effect by interfering with the synthesis and release of thyroid hormones. More serious side effects include tremor, poor concentration and memory, ataxia, dysarthria, and incoordination. There is suggestive, but not conclusive, evidence that lithium is teratogenic, inducing cardiac malformations in the first trimester.

In the treatment of acute mania, lithium is initiated at 300 mg bid or tid, and the dose is then increased by 300 mg every 2–3 days to achieve blood levels of 0.8–1.2 meq/L. Because the therapeutic effect of lithium may not appear until after 7–10 days of treatment, adjunctive usage of lorazepam (1–2 mg every 4 h) or clonazepam (0.5–1 mg every 4 h) may be beneficial to control agitation. Antipsychotics are indicated in patients with severe agitation who respond only partially to benzodiazepines. Patients using lithium should be monitored closely, since the blood levels required to achieve a therapeutic benefit are close to those associated with toxicity.

Valproic acid may be better than lithium for patients who experience rapid cycling (i.e., more than four episodes a year) or who present with a mixed or dysphoric mania. Tremor and weight gain are the most common side effects; hepatotoxicity and pancreatitis are rare toxicities.

Carbamazepine and oxcarbazepine, although not formally approved by the FDA for bipolar disorder, have clinical efficacy in the treatment of acute mania. Second-generation antipsychotic drugs (olanzapine, quetiapine, risperidone, ziprasidone, and aripiprazole) have also been shown to be effective, either alone or in combination with a mood stabilizer. An increased risk of weight gain and other metabolic abnormalities is a concern with these agents.

The recurrent nature of bipolar mood disorder necessitates maintenance treatment. A sustained blood lithium level of at least 0.8 meq/L is important for optimal prophylaxis and has been shown to reduce risk of suicide, a finding not yet apparent for other mood stabilizers. Compliance is frequently an issue and often requires enlistment and education of concerned family members. Efforts to identify and modify psychosocial factors that may trigger episodes are important, as is an emphasis on lifestyle regularity. Antidepressant medications are sometimes required for the treatment of severe breakthrough depressions, but their use should generally be avoided during maintenance treatment because of the risk of precipitating mania or accelerating the cycle frequency. Loss of efficacy over time may be observed with any of the mood-stabilizing agents. In such situations, an alternative agent or combination therapy is usually helpful.

Consensus guidelines for the treatment of acute mania and bipolar depression are described in Table 49-12.

TABLE 49-12

CONSENSUS GUIDELINES FOR DRUG TREATMENT OF ACUTE MANIA AND BIPOLAR DEPRESSION

CONDITION	PREFERRED AGENTS
Euphoric mania	Lithium
Mixed/dysphoric mania	Valproic acid
Mania with psychosis	Valproic acid with olanzapine, conventional antipsychotic, or risperidone
Hypomania	Lithium, lamotrigine, or valproic acid alone
Severe depression with psychosis	Venlafaxine, bupropion, or paroxetine *plus* lithium *plus* olanzapine, *or* risperidone; consider ECT
Severe depression without psychosis	Bupropion, paroxetine, sertraline, venlafaxine, *or* citalopram *plus* lithium
Mild to moderate depression	Lithium *or* lamotrigine alone; add bupropion if needed

Note: ECT, electroconvulsive therapy.
Source: From GS Sachs et al: Postgrad Med, April, 2000.

SOMATOFORM DISORDERS

Clinical Manifestations

Patients with multiple somatic complaints that cannot be explained by a known medical condition or by the effects of alcohol or of recreational or prescription drugs are commonly seen in primary care practice; one survey indicated a prevalence of such complaints of 5%. In *somatization disorder*, the patient presents with multiple physical complaints referable to different organ systems (Table 49-13). Onset is usually <30 years, and the disorder is persistent. Formal diagnostic criteria require the recording of at least four pain, two gastrointestinal, one sexual, and one pseudoneurologic symptom. Patients with somatization disorder often present with dramatic complaints, but the complaints are inconsistent. Symptoms of comorbid anxiety and mood disorder are common and may be the result of drug interactions due to regimens initiated independently by different physicians. Patients with somatization disorder may be impulsive and demanding and frequently qualify for a formal comorbid psychiatric diagnosis. In *conversion disorder*, the symptoms focus on deficits that involve motor or sensory function and on psychological factors that initiate

TABLE 49-13

DIAGNOSTIC CRITERIA FOR SOMATIZATION DISORDER

A. A history of many physical complaints beginning <30 years that occur over a period of several years and result in treatment being sought or significant impairment in social, occupational, or other important areas of functioning.

B. Each of the following criteria must have been met, with individual symptoms occurring at any time during the course of the disturbance:
   1. *Four pain symptoms:* a history of pain related to at least four different sites or functions (e.g., head, abdomen, back, joints, extremities, chest, rectum, during menstruation, during sexual intercourse, or during urination)
   2. *Two gastrointestinal symptoms:* a history of at least two gastrointestinal symptoms other than pain (e.g., nausea, bloating, vomiting other than during pregnancy, diarrhea, or intolerance of several different foods)
   3. *One sexual symptom:* a history of at least one sexual or reproductive symptom other than pain (e.g., sexual indifference, erectile or ejaculatory dysfunction, irregular menses, excessive menstrual bleeding, vomiting throughout pregnancy)
   4. *One pseudoneurologic symptom:* a history of at least one symptom or deficit suggesting a neurologic condition not limited to pain (conversion symptoms such as impaired coordination or balance, paralysis or localized weakness, difficulty swallowing or lump in throat, aphonia, urinary retention, hallucinations, loss of touch or pain sensation, double vision, blindness, deafness, seizures; dissociative symptoms such as amnesia; or loss of consciousness other than fainting)

C. Either of the following:
   1. After appropriate investigation, each of the symptoms in criterion B cannot be fully explained by a known general medical condition or the direct effects of a substance (e.g., a drug of abuse, a medication)
   2. When there is a related general medical condition, the physical complaints or resulting social or occupational impairment are in excess of what would be expected from the history, physical examination, or laboratory findings

D. The symptoms are not intentionally produced or feigned (as in factitious disorder or malingering).

Source: *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. Washington, DC, American Psychiatric Association, 2000.

or exacerbate the medical presentation. Like somatization disorder, the deficit is not intentionally produced or simulated, as is the case in factitious disorder (malingering). In *hypochondriasis*, the essential feature is a belief of serious medical illness that persists despite reassurance and appropriate medical evaluation. As with somatization disorder, patients with hypochondriasis have a history of poor relationships with physicians stemming from their sense that they have been evaluated and treated inappropriately or inadequately. Hypochondriasis can be disabling in intensity and is persistent, with waxing and waning symptomatology.

In *factitious illnesses*, the patient consciously and voluntarily produces physical symptoms of illness. The term *Munchausen's syndrome* is reserved for individuals with particularly dramatic, chronic, or severe factitious illness. In true factitious illness, the sick role itself is gratifying. A variety of signs, symptoms, and diseases have been either simulated or caused by factitious behavior, the most common including chronic diarrhea, fever of unknown origin, intestinal bleeding or hematuria, seizures, and hypoglycemia. Factitious disorder is usually not diagnosed until 5–10 years after its onset, and it can produce significant social and medical costs. In *malingering*, the fabrication derives from a desire for some external reward, such as a narcotic medication or disability reimbursement.

℞ Treatment: SOMATOFORM DISORDERS

Patients with somatization disorders are frequently subjected to many diagnostic tests and exploratory surgeries in an attempt to find their "real" illness. Such an approach is doomed to failure and does not address the core issue. Successful treatment is best achieved through behavior modification, in which access to the physician is tightly regulated and adjusted to provide a sustained and predictable level of support that is less clearly contingent on the patient's level of presenting distress. Visits can be brief and should not be associated with a need for a diagnostic or treatment action. Although the literature is limited, some patients with somatization disorder may benefit from antidepressant treatment.

Any attempt to confront the patient usually creates a sense of humiliation and causes the patient to abandon treatment from that caregiver. A better strategy is to introduce psychological causation as one of a number of possible explanations and to include factitious illness as an option in the differential diagnoses that are discussed. Without directly linking psychotherapeutic intervention to the diagnosis, the patient can be offered a face-saving means by which the pathologic relationship with the health care system can be examined and alternative approaches to life stressors developed.

PERSONALITY DISORDERS

Clinical Manifestations

Personality disorders are characteristic patterns of thinking, feeling, and interpersonal behavior that are relatively inflexible and cause significant functional impairment or

subjective distress for the individual. The observed behaviors are not secondary to another mental disorder, nor are they precipitated by substance abuse or a general medical condition. This distinction is often difficult to make in clinical practice, as personality change may be the first sign of serious neurologic, endocrine, or other medical illness. Patients with frontal lobe tumors, for example, can present with changes in motivation and personality while the results of the neurologic examination remain within normal limits. Individuals with personality disorders are often regarded as "difficult patients" in clinical medical practice because they are seen as excessively demanding and/or unwilling to follow recommended treatment plans. Although DSM-IV portrays personality disorders as qualitatively distinct categories, there is an alternative perspective that personality characteristics vary as a continuum between normal functioning and formal mental disorder.

Personality disorders have been grouped into three overlapping clusters. *Cluster A* includes paranoid, schizoid, and schizotypal personality disorders. It includes individuals who are odd and eccentric and who maintain an emotional distance from others. Individuals have a restricted emotional range and remain socially isolated. Patients with schizotypal personality disorder frequently have unusual perceptual experiences and express magical beliefs about the external world. The essential feature of paranoid personality disorder is a pervasive mistrust and suspiciousness of others to an extent that is unjustified by available evidence. *Cluster B* disorders include antisocial, borderline, histrionic, and narcissistic types and describe individuals whose behavior is impulsive, excessively emotional, and erratic. *Cluster C* incorporates avoidant, dependent, and obsessive-compulsive personality types; enduring traits are anxiety and fear. The boundaries between cluster types are to some extent artificial, and many patients who meet criteria for one personality disorder also meet criteria for aspects of another. The risk of a comorbid major mental disorder is increased in patients who qualify for a diagnosis of personality disorder.

Rx Treatment: PERSONALITY DISORDERS

Dialectical behavior therapy (DBT) is a cognitive-behavioral approach that focuses on behavioral change while providing acceptance, compassion, and validation of the patient. Several randomized trials have demonstrated the efficacy of DBT in the treatment of personality disorders. Antidepressant medications and low-dose antipsychotic drugs have some efficacy in cluster A personality disorders, while anticonvulsant mood-stabilizing agents and MAOIs may be considered for patients with cluster B diagnoses who show marked mood reactivity, behavioral dyscontrol, and/or rejection hypersensitivity. Anxious or fearful cluster C patients often respond to medications used for axis I anxiety disorders (see earlier). It is important that the physician and the patient have reasonable expectations vis-à-vis the possible benefit of any medication used and its side effects. Improvement may be subtle and observable only over time.

SCHIZOPHRENIA

Clinical Manifestations

Schizophrenia is a heterogeneous syndrome characterized by perturbations of language, perception, thinking, social activity, affect, and volition. There are no pathognomonic features. The syndrome commonly begins in late adolescence, has an insidious (and less commonly acute) onset, and, often, a poor outcome, progressing from social withdrawal and perceptual distortions to recurrent delusions and hallucinations. Patients may present with positive symptoms (such as conceptual disorganization, delusions, or hallucinations) or negative symptoms (loss of function, anhedonia, decreased emotional expression, impaired concentration, and diminished social engagement) and must have at least two of these for a 1-month period and continuous signs for at least 6 months to meet formal diagnostic criteria. As individuals age, positive psychotic symptoms tend to attenuate and some measure of social and occupational function may be regained. "Negative" symptoms predominate in one-third of the schizophrenic population and are associated with a poor long-term outcome and a poor response to drug treatment. However, marked variability in the course and individual character of symptoms is typical.

The four main subtypes of schizophrenia are catatonic, paranoid, disorganized, and residual. Many individuals have symptoms of more than one type. *Catatonic-type* describes patients whose clinical presentation is dominated by profound changes in motor activity, negativism, and echolalia or echopraxia. *Paranoid-type* describes patients who have a prominent preoccupation with a specific delusional system and who otherwise do not qualify as having *disorganized-type* disease, in which disorganized speech and behavior are accompanied by a superficial or silly affect. In *residual-type* disease, negative symptomatology exists in the absence of delusions, hallucinations, or motor disturbance. The term *schizophreniform disorder* describes patients who meet the symptom requirements but not the duration requirements for schizophrenia, and *schizoaffective disorder* is used for those who manifest symptoms of schizophrenia and independent periods of mood disturbance. Prognosis depends not on symptom severity but on the response to antipsychotic medication.

A permanent remission without recurrence does occasionally occur. About 10% of schizophrenic patients commit suicide.

Schizophrenia is present in 0.85% of individuals worldwide, with a lifetime prevalence of ~1–1.5%. An estimated 300,000 episodes of acute schizophrenia occur annually in the United States, resulting in direct and indirect costs of $62.7 billion.

Differential Diagnosis

The diagnosis is principally one of exclusion, requiring the absence of significant associated mood symptoms, any relevant medical condition, and substance abuse. Drug reactions that cause hallucinations, paranoia, confusion, or bizarre behavior may be dose-related or idiosyncratic; parkinsonian medications, clonidine, quinacrine, and procaine derivatives are the most common prescription medications associated with these symptoms. Drug causes should be ruled out in any case of newly emergent psychosis. The general neurologic examination in patients with schizophrenia is usually normal, but motor rigidity, tremor, and dyskinesias are noted in one-quarter of untreated patients.

Epidemiology and Pathophysiology

Epidemiologic surveys identify several risk factors for schizophrenia including genetic susceptibility, early developmental insults, winter birth, and increasing parental age. Genetic factors are involved in at least a subset of individuals who develop schizophrenia. Schizophrenia is observed in ~6.6% of all first-degree relatives of an affected proband. If both parents are affected, the risk for offspring is 40%. The concordance rate for monozygotic twins is 50%, compared to 10% for dizygotic twins. Schizophrenia-prone families are also at risk for other psychiatric disorders, including schizoaffective disorder and *schizotypal* and *schizoid personality disorders*, the latter terms designating individuals who show a lifetime pattern of social and interpersonal deficits characterized by an inability to form close interpersonal relationships, eccentric behavior, and mild perceptual distortions.

Despite evidence for a genetic causation, the results of molecular genetic linkage studies in schizophrenia are inconclusive. Major gene effects appear unlikely. Possible susceptibility genes include: neuregulin-1 (chromosome 8p21); dysbindin (6p22.3); proline dehydrogenase (22q11); D-amino-acid oxidase activator (13q34); disrupted in schizophrenia 1, (DISC1), (1q42); and catechol-*O*-methyl transferase (COMT). Neuregulin-1, dysbindin, and D-amino-acid oxidase activator appear to be involved in glutamatergic function, increasing interest in *N*-methyl-D-aspartate (NMDA)–mediated glutamate signaling as a possible therapeutic target for treatment. COMT is involved in the removal of dopamine from synapses, and DISC1 is a scaffolding protein that participates in a variety of protein-protein interactions important in neuronal development. One group has reported risk variants in the $\alpha 7$ nicotinic acetylcholine receptor subunit gene and linked it to a specific auditory processing deficit.

Schizophrenia is also associated with gestational and perinatal complications, including Rh factor incompatibility, fetal hypoxia, prenatal exposure to influenza during the second trimester, and prenatal nutritional deficiency. Studies of monozygotic twins discordant for schizophrenia have reported neuroanatomic differences between affected and unaffected siblings, supporting a "two-strike" etiology involving both genetic susceptibility and an environmental insult. The latter might involve localized hypoxia during critical stages of brain development.

A number of structural and functional abnormalities have been identified in schizophrenia, including (1) cortical atrophy and ventricular enlargement; (2) specific volume losses in the amygdala, hippocampus, right prefrontal cortex, fusiform gyrus, and thalamus; (3) progressive reduction in cortical volume over time; (4) reduced metabolism in the thalamus and prefrontal cortex; (5) abnormalities of the planum temporale; and (6) changes in the size, orientation, and density of cells in the hippocampus and prefrontal cortex, and decreased numbers of cortical interneurons. These observations have suggested that schizophrenia may result from a disturbance in a cortical striatal–thalamic circuit resulting in abnormalities in sensory filtering and attention.

Schizophrenic individuals are highly distractible and demonstrate deficits in perceptual-motor speed, ability to shift attention, and filtering out of background stimuli. Event-related evoked potential studies of schizophrenia have defined a reduction in P300 amplitude to a novel stimulus, which implicates an impairment in cognitive processing. Impaired information processing is also found in unaffected family members.

The *dopamine hypothesis* of schizophrenia is based on the discovery that agents that diminish dopaminergic activity also reduce the acute symptoms and signs of psychosis, specifically agitation, anxiety, and hallucinations. Amelioration of delusions and social withdrawal is less dramatic. Thus far, however, evidence for increased dopaminergic activity in schizophrenia is indirect, although decreased D_2 receptor occupancy by dopamine has been shown in drug-naïve patients. An increase in the activity of nigrostriatal and mesolimbic systems and a decrease in mesocortical tracts innervating the prefrontal cortex is hypothesized, although it is likely that other neurotransmitters, including serotonin, acetylcholine, glutamate, and GABA, also contribute to the pathophysiology of the illness. Possible involvement of excitatory amino acids is supported by the genetic data cited above and findings that NMDA receptor antagonists and channel blockers, such as phencyclidine (PCP) and ketamine,

produce characteristic signs of schizophrenia in normal individuals; cycloserine, an NMDA receptor agonist, can decrease the negative symptoms of psychosis.

Rx Treatment: SCHIZOPHRENIA

Antipsychotic agents (**Table 49-14**) are the cornerstone of acute and maintenance treatment of schizophrenia and are effective in the treatment of hallucinations, delusions and thought disorders, regardless of etiology. The mechanism of action involves, at least in part, binding to dopamine D_2/D_3 receptors in the ventral striatum; the clinical potencies of traditional antipsychotic drugs parallel their affinities for the D_2 receptor, and even the newer "atypical" agents exert some degree of D_2 receptor blockade. All neuroleptics induce expression of the immediate-early gene c-*fos* in the nucleus accumbens, a dopaminergic site connecting prefrontal and limbic cortices. The clinical efficacy of newer atypical neuroleptics, however, may involve NMDA receptor blockade, α_1- and α_2-noradrenergic activity, altering the relationship between $5HT_2$ and D_2 receptor activity, as well as faster dissociation of D_2 binding and effects on neuroplasticity.

Conventional neuroleptics differ in their potency and side-effect profile. Older agents, such as chlorpromazine and thioridazine, are more sedating and anticholinergic and more likely to cause orthostatic hypotension, while higher potency antipsychotics, such as haloperidol, perphenazine, and thiothixene, are more likely to induce

TABLE 49-14

ANTIPSYCHOTIC AGENTS

NAME	USUAL PO DAILY DOSE, mg	SIDE EFFECTS	SEDATION	COMMENTS
First-Generation Antipsychotics				
Low-potency				
Chlorpromazine (Thorazine)	100–1000	Anticholinergic effects; orthostasis; photosensitivity; cholestasis; QT prolongation	+++	EPSEs usually not prominent; can cause anticholinergic delirium in elderly patients
Thioridazine (Mellaril)	100–600			
Clozapine (Clozaril)	150–600	Agranulocytosis (1%); weight gain; seizures; drooling; hyperthermia	++	Requires weekly WBC for first 6 months, then biweekly if stable
Mid-potency				
Trifluoperazine (Stelazine)	2–50	Fewer anticholinergic side effects; fewer EPSEs than with higher potency agents.	++	Well tolerated by most patients
Perphenazine (Trilafon)	4–64		++	
Loxapine (Loxitane)	30–100	Frequent EPSEs	++	
Molindone (Moban)	30–100	Frequent EPSEs	0	Little weight gain
High-potency				
Haloperidol (Haldol)	.5–20	No anticholinergic side effects; EPSEs often prominent	0/+	Often prescribed in doses that are too high; long-acting injectable forms of haloperidol and fluphenazine available
Fluphenazine (Prolixin)	1–20	Frequent EPSEs	0/+	
Thiothixene (Navane)	2–50	Frequent EPSEs	0/+	
Second-Generation Antipsychotics				
Risperidone (Risperdal)	2–8	Orthostasis	+	Requires slow titration; EPSEs observed with doses >6 mg qd
Olanzapine (Zyprexa)	10–30	Weight gain	++	Mild prolactin elevation
Quetiapine (Seroquel)	350–800	Sedation; weight gain; anxiety	+++	Bid dosing
Ziprasidone (Geodon)	120–200	Orthostatic hypotension	+/++	Minimal weight gain; increases QT interval
Aripiprazole (Abilify)	10–30	Nausea, anxiety, insomnia	0/+	Mixed agonist/antagonist

Note: EPSEs, extrapyramidal side effects; WBC, white blood count.

extrapyramidal side effects. The model first-generation antipsychotic agent is *clozapine*, a dibenzodiazepine that has a greater potency in blocking the $5HT_2$ than the D_2 receptor and a much higher affinity for the D_4 than the D_2 receptor. Its principal disadvantage is a risk of blood dyscrasias. Unlike other antipsychotics, clozapine does not cause a rise in prolactin level. Approximately 30% of patients who do not benefit from conventional antipsychotic agents will have a better response to this drug, which also has a demonstrated superiority to other antipsychotic agents in preventing suicide; however, its side-effect profile makes it most appropriate for treatment-resistant cases. *Risperidone*, a benzisoxazole derivative, is more potent at $5HT_2$ than D_2 receptor sites, like clozapine, but it also exerts significant α_2 antagonism, a property that may contribute to its perceived ability to improve mood and increase motor activity. Risperidone is not as effective as clozapine in treatment-resistant cases but does not carry a risk of blood dyscrasias. *Olanzapine* is similar neurochemically to clozapine but has a significant risk of inducing weight gain. *Quetiapine* is distinct in having a weak D_2 effect but potent α_1 and histamine blockade. *Ziprasidone* causes minimal weight gain and is unlikely to increase prolactin but may increase QT prolongation. *Aripiprazole* also has little risk of weight gain or prolactin increase but may increase anxiety, nausea, and insomnia as a result of its partial agonist properties.

Antipsychotic agents are effective in 70% of patients presenting with a first episode. Improvement may be observed within hours or days, but full remission usually requires 6–8 weeks. The choice of agent depends principally on the side-effect profile and cost of treatment or on a past personal or family history of a favorable response to the drug in question. Atypical agents appear to be more effective in treating negative symptoms and improving cognitive function. An equivalent treatment response can usually be achieved with relatively low doses of any drug selected, i.e., 4–6 mg/d of haloperidol, 10–15 mg of olanzapine, or 4–6 mg/d of risperidone. Doses in this range result in >80% D_2 receptor blockade, and there is little evidence that higher doses increase either the rapidity or degree of response. Maintenance treatment requires careful attention to the possibility of relapse and monitoring for the development of a movement disorder. Intermittent drug treatment is less effective than regular dosing, but gradual dose reduction is likely to improve social functioning in many schizophrenic patients who have been maintained at high doses. If medications are completely discontinued, however, the relapse rate is 60% within 6 months. Long-acting injectable preparations (risperidone) are considered when noncompliance with oral therapy leads to relapses. In treatment-resistant patients, a transition to clozapine usually results in rapid improvement, but a prolonged delay in response in some cases necessitates a 6- to 9-month trial for maximal benefit to occur.

Antipsychotic medications can cause a broad range of side effects, including lethargy, weight gain, postural hypotension, constipation, and dry mouth. Extrapyramidal symptoms such as dystonia, akathisia, and akinesia are also frequent with first-generation agents and may contribute to poor adherence if not specifically addressed. Anticholinergic and parkinsonian symptoms respond well to trihexyphenidyl, 2 mg bid, or benztropine mesylate, 1–2 mg bid. Akathisia may respond to beta blockers. In rare cases, more serious and occasionally life-threatening side effects may emerge, including ventricular arrhythmias, gastrointestinal obstruction, retinal pigmentation, obstructive jaundice, and neuroleptic malignant syndrome (characterized by hyperthermia, autonomic dysfunction, muscular rigidity, and elevated creatine phosphokinase levels). The most serious adverse effects of clozapine are agranulocytosis, which has an incidence of 1%, and induction of seizures, which has an incidence of 10%. Weekly white blood cell counts are required, particularly during the first 3 months of treatment.

The risk of type 2 diabetes mellitus appears to be increased in schizophrenia, and second-generation agents as a group produce greater adverse effects on glucose regulation, independent of effects on obesity, than traditional agents. Clozapine, olanzapine, and quetiapine seem more likely to cause hyperglycemia, weight gain, and hypertriglyceridemia than other atypical antipsychotic drugs. Close monitoring of plasma glucose and lipid levels are indicated with the use of these agents.

A serious side effect of long-term use of first generation antipsychotic agents is *tardive dyskinesia*, characterized by repetitive, involuntary, and potentially irreversible movements of the tongue and lips (bucco-linguo-masticatory triad), and, in approximately one-half of cases, choreoathetosis. Tardive dyskinesia has an incidence of 2–4% per year of exposure, and a prevalence of 20% in chronically treated patients. The prevalence increases with age, total dose, and duration of drug administration. The risk associated with second-generation agents appears to be much lower. The cause may involve formation of free radicals and perhaps mitochondrial energy failure. Vitamin E may reduce abnormal involuntary movements if given early in the syndrome.

The CATIE study, a large scale investigation of the effectiveness of antipsychotic agents in "real world" patients, revealed a high rate of discontinuation of treatment over 18 months. Olanzapine showed greater effectiveness than quetiapine, risperidone, perphenazine, or ziprasidone but also a higher discontinuation rate due to weight gain and metabolic effects. Surprisingly, perphenazine, a first-generation agent, showed little evidence of inferiority to newer drugs. A recent long-term

study of schizophrenic patients transitioning from older to newer-generation antipsychotics did not demonstrate any effect on mortality.

Drug treatment of schizophrenia is by itself insufficient. Educational efforts directed toward families and relevant community resources have proved to be necessary to maintain stability and optimize outcome. A treatment model involving a multidisciplinary case-management team that seeks out and closely follows the patient in the community has proved particularly effective.

ASSESSMENT AND EVALUATION OF VIOLENCE

Primary care physicians may encounter situations in which family, domestic, or societal violence is discovered or suspected. Such an awareness can carry legal and moral obligations; many state laws mandate reporting of child, spousal, and elder abuse. Physicians are frequently the first point of contact for both victim and abuser. Approximately 2 million older Americans and 1.5 million U.S. children are thought to experience some form of physical maltreatment each year. Spousal abuse is thought to be even more prevalent. An interview study of 24,000 women in 10 countries found a lifetime prevalence of physical or sexual violence that ranged from 15–71%; these individuals are more likely to suffer from depression, anxiety, somatization disorder, and substance abuse and to have attempted suicide. In addition, abused individuals frequently express low self-esteem, vague somatic symptomatology, social isolation, and a passive feeling of loss of control. Although it is essential to treat these elements in the victim, the first obligation is to ensure that the perpetrator has taken responsibility for preventing any further violence. Substance abuse and/or dependence and serious mental illness in the abuser may contribute to the risk of harm and require direct intervention. Depending on the situation, law enforcement agencies, community resources such as support groups and shelters, and individual and family counseling can be appropriate components of a treatment plan. A safety plan should be formulated with the victim, in addition to providing information about abuse, its likelihood of recurrence, and its tendency to increase in severity and frequency. Antianxiety and antidepressant medications may sometimes be useful in treating the acute symptoms, but only if independent evidence for an appropriate psychiatric diagnosis exists.

MENTAL HEALTH PROBLEMS IN THE HOMELESS

There is a high prevalence of mental disorders and substance abuse among homeless and impoverished individuals. Depending on the definition used, estimates of the total number of homeless individuals in the United States range from 800,000–2 million, one-third of whom qualify as having a serious mental disorder. Poor hygiene and nutrition, substance abuse, psychiatric illness, physical trauma, and exposure to the elements combine to make the provision of medical care challenging. Only a minority of these individuals receive formal mental health care; the main points of contact are outpatient medical clinics and emergency departments. Primary care settings represent a critical site in which housing needs, treatment of substance dependence, and evaluation and treatment of psychiatric illness can most efficiently take place. Successful intervention is dependent on breaking down traditional administrative barriers to health care and recognizing the physical constraints and emotional costs imposed by homelessness. Simplifying health care instructions and follow-up, allowing frequent visits, and dispensing medications in limited amounts that require ongoing contact are possible techniques for establishing a successful therapeutic relationship.

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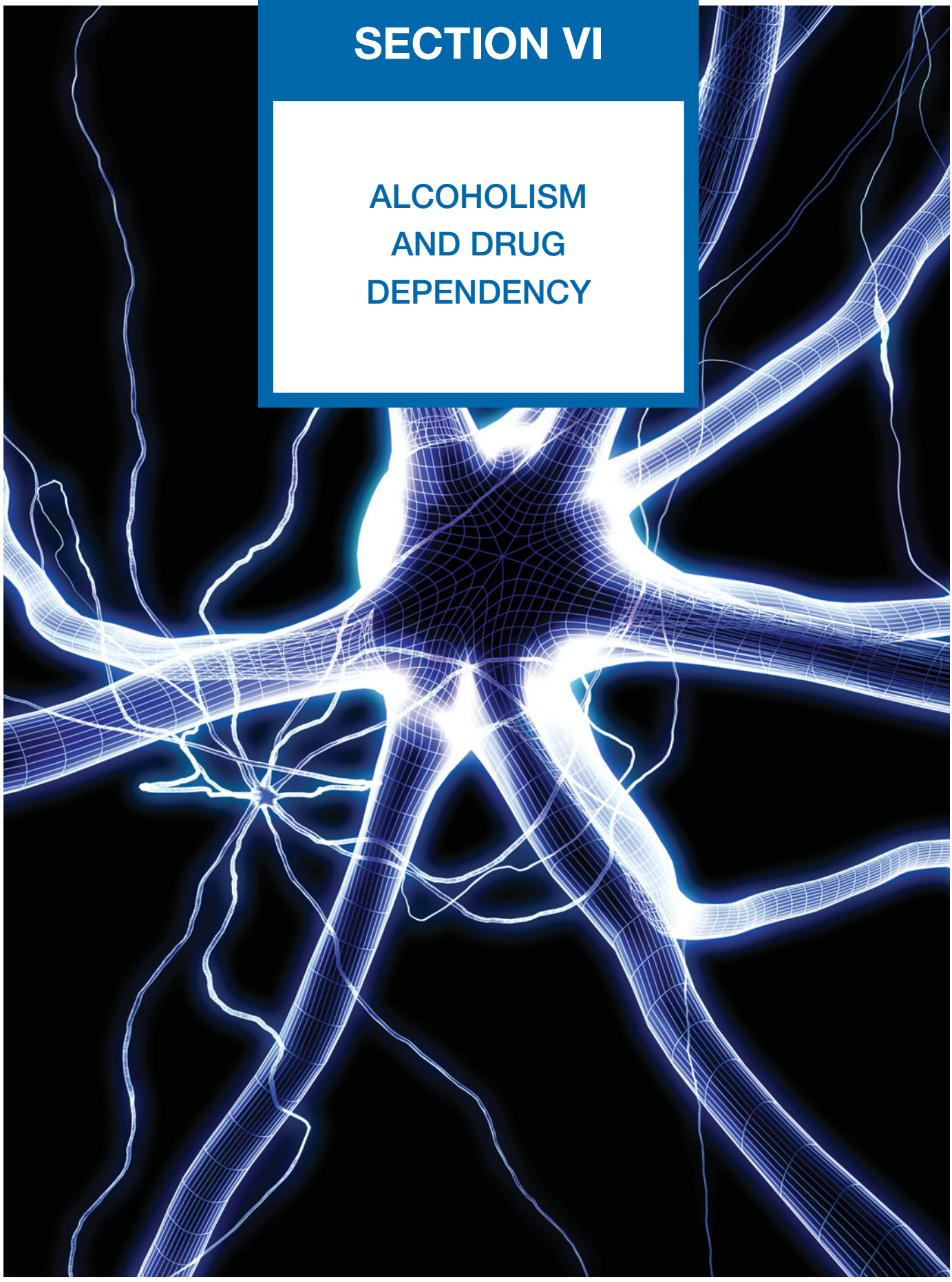
SECTION VI

ALCOHOLISM AND DRUG DEPENDENCY



CHAPTER 50

ALCOHOL AND ALCOHOLISM

Marc A. Schuckit

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Alcohol, a drug, is consumed at some time by up to 80% of the population. At low doses alcohol can have some beneficial effects such as decreased rates of myocardial infarction, stroke, gallstones, and possibly vascular and Alzheimer's dementias. However, the consumption of more than two standard drinks per day increases the risk for health problems in many organ systems. Heavy repetitive drinking, as is seen in alcohol abuse and dependence, cuts short the life span by an estimated decade in both genders, all cultural groups, and all socioeconomic strata. Unless an individual stops drinking, a diagnosis of alcohol dependence carries a ≥80% risk for continued severe problems over the next 5 years. In addition, even relatively low doses of alcohol can adversely affect many preexisting disease states and alter the effectiveness or blood levels of most over-the-counter and prescribed medications.

PHARMACOLOGY AND NUTRITIONAL IMPACT OF ETHANOL

Ethanol is a weakly charged molecule that moves easily through cell membranes, rapidly equilibrating between blood and tissues. The level of alcohol in the blood is expressed as milligrams or grams of ethanol per deciliter (e.g., 100 mg/dL or 0.10 g/dL), with blood values of about 0.02 g/dL resulting from the ingestion of one typical drink. In round figures, 340 mL (12 oz) of beer, 115 mL (4 oz) of nonfortified wine, and 43 mL (1.5 oz) (a shot) of 80-proof beverage such as whisky, gin, or vodka each contain ~10–15 g of ethanol; 0.5 L (1 pint) of 80-proof beverage contains ~160 g (about 16 standard drinks), and 1 L of wine contains ~80 g of ethanol. These beverages also have additional components, called *congeners*, that affect the taste and effects; congeners include low-molecular-weight alcohols (e.g., methanol and butanol), aldehydes, esters, histamine, phenols, tannins, iron, lead, and cobalt. Such congeners might also contribute to the adverse health consequences associated with heavy drinking.

Ethanol is a central nervous system (CNS) depressant that decreases neuronal activity, although some behavioral stimulation is observed at low blood levels. This drug has cross-tolerance with other depressants, including benzodiazepines and barbiturates, and all produce similar behavioral alterations. Alcohol is absorbed from mucous membranes of the mouth and esophagus (in small amounts), from the stomach and large bowel (in modest amounts), and from the proximal portion of the small intestine (the major site).

The rate of absorption is increased by rapid gastric emptying (as can be induced by carbonated beverages);

by the absence of proteins, fats, or carbohydrates (which interfere with absorption); by the absence of congeners; and by dilution to a modest percentage of ethanol (maximum at ~20% by volume).

Between 2% (at low blood alcohol concentrations) and 10% (at high blood alcohol concentrations) of ethanol is excreted directly through the lungs, urine, or sweat, but the greater part is metabolized to acetaldehyde, primarily in the liver. The most important pathway occurs in the cell cytosol where alcohol dehydrogenase (ADH) produces acetaldehyde, which is then rapidly destroyed by aldehyde dehydrogenase (ALDH) in the cytosol and mitochondria (**Fig. 50-1**). A second pathway in the microsomes of the smooth endoplasmic reticulum (the microsomal ethanol-oxidizing system, or MEOS), is responsible for ≥10% of ethanol oxidation at high blood alcohol concentrations.

While alcohol supplies calories (a drink contains ~300 kJ, or 70–100 kcal), these are devoid of nutrients such as minerals, proteins, and vitamins. Alcohol can also interfere with absorption of vitamins in the small intestine and decreases their storage in the liver with modest effects on folate (folacin or folic acid), pyridoxine (B_6), thiamine (B_1), nicotinic acid (niacin, B_3), and vitamin A.

An ethanol load in a fasting, healthy individual is likely to produce transient hypoglycemia within 6–36 h, secondary to the acute actions of ethanol on gluconeogenesis. This can temporarily result in abnormal glucose tolerance tests (with a resulting erroneous diagnosis of diabetes mellitus) until the alcoholic has abstained for 2–4 weeks. Alcohol ketoacidosis, probably reflecting a decrease in fatty acid oxidation coupled with poor diet or recurrent vomiting, can be misdiagnosed as diabetic ketosis. With the former, patients show an increase in serum ketones along with a mild increase in glucose but a large anion gap, a mild to moderate increase in serum lactate, and a β-hydroxybutyrate/lactate ratio of between 2:1 and 9:1 (with normal being 1:1).

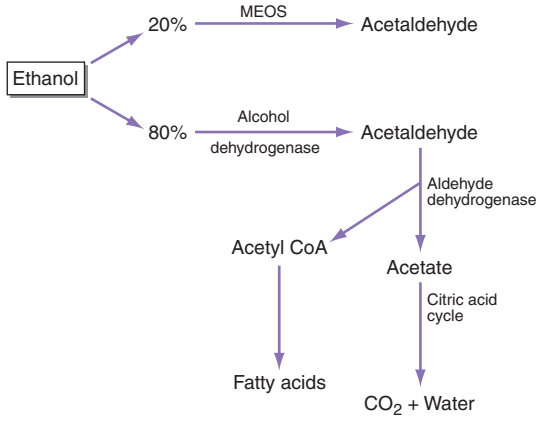

FIGURE 50-1
The metabolism of alcohol. MEOS, microsomal ethanol-oxidizing system.

BEHAVIORAL EFFECTS, TOLERANCE, AND DEPENDENCE

The acute effects of a drug depend on many factors. These include the dose, the rate of increase in plasma, the concomitant presence of other drugs, and the past experience with the agent. With alcohol, an additional factor is whether blood alcohol levels are rising or falling; the effects are more intense during the former period.

"Legal intoxication" in the United States requires a blood alcohol concentration of at least 0.08–0.10 g/dL, while levels of 0.04 or even lower are cited in some other countries. However, behavioral, psychomotor, and cognitive changes are seen at levels as low as 0.02–0.03 g/dL (i.e., after one to two drinks) (**Table 50-1**). Deep but disturbed sleep can be seen at twice the legal intoxication level, and death can occur with levels between 0.30 and 0.40 g/dL. Beverage alcohol is probably responsible for more overdose deaths than any other drug.

The intoxicating effects of alcohol reflect the actions of this drug on a wide range of neurotransmitters, receptors, and transporters. Most prominently, alcohol acutely enhances actions at γ-aminobutyric acid A ($GABA_A$) receptors and inhibits *N*-methyl-D-aspartate (NMDA) receptors. There are also effects on adenosine, with an inhibition of uptake of this transmitter, and a translocation of the cyclic AMP–dependent protein kinase catalytic subunit from the cytoplasm to the nucleus. Alcohol also affects opioid systems and cannabinol receptors, enhances activity of the dopamine-rich reward system, increases serotonin actions, and directly or indirectly affects most other neurochemical systems. As with most depressants, neurons adapt quickly to these actions, and tolerance to many effects develops; after repeated exposure, abrupt decreases in blood alcohol levels are likely to produce physiologic changes that are opposite to the

TABLE 50-1
EFFECTS OF BLOOD ALCOHOL LEVELS IN THE ABSENCE OF TOLERANCE

BLOOD LEVEL, g/dL	USUAL EFFECT
0.02	Decreased inhibitions, a slight feeling of intoxication
0.08	Decrease in complex cognitive functions and motor performance
0.20	Obvious slurred speech, motor incoordination, irritability, and poor judgment
0.30	Light coma and depressed vital signs
0.40	Death

acute effects of this drug (i.e., withdrawal). The presence of tolerance and/or withdrawal characterizes physical dependence.

Tolerance is a complex phenomenon involving at least three types of compensatory mechanisms. (1) After 1–2 weeks of daily drinking, *metabolic or pharmacokinetic tolerance* can be seen, with up to a 30% increase in the rate of hepatic ethanol metabolism. This alteration disappears almost as rapidly as it develops. (2) *Cellular or pharmacodynamic tolerance* develops through neurochemical changes that maintain relatively normal physiologic functioning despite the presence of alcohol. Subsequent decreases in blood levels contribute to symptoms of withdrawal. (3) Individuals learn to adapt their behavior so that they can function better than expected under influence of the drug (*behavioral tolerance*).

The cellular changes caused by chronic ethanol exposure may not resolve for several weeks or longer following cessation of drinking. The resulting withdrawal syndrome is most intense during the first 5 days, but some symptoms (e.g., disturbed sleep and anxiety) can take up to 4–6 months to resolve.

THE EFFECTS OF ETHANOL ON ORGAN SYSTEMS

Although one to two drinks per day in an otherwise healthy and nonpregnant individual can have some beneficial cardiovascular effects, at higher doses alcohol is toxic to most organ systems. Knowledge about the deleterious effects of alcohol helps the physician to identify alcoholic patients and provides information that can be used to help motivate patients to abstain. The information offered here generally applies to all, regardless of age or gender, although some differences apply. It is important to remember that the typical white- or blue-collar alcoholic often functions at a fairly high level for years, holding a job and maintaining ties with friends and relatives who may be unaware of the severity of the drinking problem. Not everyone develops each of the problems described below.

NERVOUS SYSTEM

Approximately 35% of drinkers (and a much higher percentage of alcoholics) experience a *blackout*, an episode of temporary anterograde amnesia, in which the person forgets all or part of what occurred during a drinking evening. Another common problem, one seen after as few as several drinks, is disturbed sleep. Although alcohol might initially help a person to fall asleep, it disrupts sleep throughout the rest of the night. The stages of sleep are also altered, and time spent in rapid eye movement (REM) and deep sleep is reduced. Patients may experience prominent and sometimes disturbing dreams. Alcohol relaxes muscles in the pharynx, which can cause snoring and exacerbate sleep apnea; symptoms of the latter occur in 75% of alcoholic men >60 years. Another common consequence of alcohol use is impaired judgment and coordination, increasing the risk of accidents and injury; 40% of drinkers in the United States have at some time driven while intoxicated. Heavy drinking can also be associated with headache, thirst, nausea, vomiting, and fatigue the following day, a hangover syndrome that is responsible for significant financial losses in most work environments.

The effect of alcohol on the nervous system is even more pronounced among alcohol-dependent individuals. Chronic high doses cause *peripheral neuropathy* in 5–15% of alcoholics: similar to diabetes, patients experience bilateral limb numbness, tingling, and paresthesias, all of which are more pronounced distally. Approximately 1% of alcoholics develop cerebellar degeneration or atrophy. This is a syndrome of progressive unsteady stance and gait often accompanied by mild nystagmus; neuroimaging studies reveal atrophy of the cerebellar vermis. Fortunately, very few alcoholics (perhaps as few as 1 in 500) develop *Wernicke's* (ophthalmoparesis, ataxia, and encephalopathy) and *Korsakoff's* (retrograde and anterograde amnesia) *syndromes.* These occur as the result of thiamine deficiency, especially in predisposed individuals, e.g., those with transketolase deficiency. Alcoholics can manifest *cognitive problems* lasting for weeks to months after an alcoholic binge. Brain atrophy, evident as ventricular enlargement and widened cortical sulci on MRI and CT scans, occurs in ~50% of chronic alcoholics; these changes are often reversible if abstinence is maintained. There is no single alcoholic dementia syndrome; rather, this label is used to describe patients who have apparently irreversible cognitive changes (possibly from diverse causes) in the context of chronic alcoholism.

As many as two-thirds of alcohol-dependent individuals meet the criteria for a psychiatric syndrome in the *Fourth Diagnostic and Statistical Manual of Mental Disorders,* (DSM-IV) of the American Psychiatric Association (Chap. 49). One-half of these relate to a preexisting antisocial personality manifesting as impulsivity and disinhibition. The lifetime risk is 3% in males, and ≥80% of such individuals demonstrate alcohol and/or drug dependence. Another common comorbidity occurs with dependence on illicit substances. The remaining third of alcoholics with psychiatric syndromes have preexisting conditions such as schizophrenia or manic depressive disease and anxiety disorders such as panic disorder. The reasons for the comorbidities of alcoholism with independent psychiatric disorders are not known, but they might represent an overlap in genetic vulnerabilities, impaired judgment resulting from the independent psychiatric condition, or an attempt to use alcohol to alleviate some of the symptoms of the disorder or side effects of medications.

Many psychiatric syndromes can be seen temporarily during heavy drinking and subsequent withdrawal. These include an intense *sadness* lasting for days to weeks in the midst of heavy drinking seen in 40% of alcoholics (alcohol-induced mood disorder); temporary severe *anxiety* in 10–30% of alcoholics, often beginning during alcohol withdrawal, and which can persist for a month or more after cessation of drinking (alcohol-induced anxiety disorder); and auditory *hallucinations* and/or paranoid delusions in a person who is alert and oriented, seen in 3–5% of alcoholics (*alcohol-induced psychotic disorder*).

Treatment of all forms of alcohol-induced psychopathology includes helping patients achieve abstinence and offering supportive care, as well as reassurance and "talk therapy" such as cognitive-behavioral approaches. However, with the exception of short-term antipsychotics for substance-induced psychosis, substance-induced psychiatric conditions only rarely require medications. Recovery is likely within several days to 4 weeks of abstinence. A history of alcohol intake is an important consideration in any patient with one of these psychiatric symptoms.

The distinction between long-term, independent psychiatric conditions and temporary alcohol-induced syndromes is important because their prognoses and optimal treatments are quite different. Independent syndromes can be recognized because they often began before the alcohol dependence and/or remain after a period of a month or more of abstinence.

THE GASTROINTESTINAL SYSTEM

Esophagus and Stomach

Alcohol intake can result in inflammation of the esophagus and stomach causing epigastric distress and gastrointestinal bleeding. Alcohol is one of the most common causes of hemorrhagic gastritis. Violent vomiting can produce severe bleeding through a Mallory-Weiss lesion, a longitudinal tear in the mucosa at the gastroesophageal junction.

Pancreas and Liver

The incidence of acute pancreatitis (~25 per 1000 per year) is almost threefold higher in alcoholics than in the general population, accounting for an estimated 10% or more of the total cases. Alcohol impairs gluconeogenesis in the liver, resulting in a fall in the amount of glucose produced from glycogen, increased lactate production, and decreased oxidation of fatty acids. This contributes to an increase in fat accumulation in liver cells. In healthy individuals these changes are reversible, but with repeated exposure to ethanol, more severe changes in the liver occur, including alcohol-induced hepatitis, perivenular sclerosis, and cirrhosis, with the latter observed in an estimated 15% of alcoholics.

CANCER

Drinking as few as 1.5 drinks per day increases a woman's risk of breast cancer 1.4-fold. For both genders, four drinks per day increases the risk for oral and esophageal cancers approximately threefold and rectal cancers by a factor of 1.5; seven to eight or more drinks per day enhances approximately fivefold the risks for many cancers.

HEMATOPOIETIC SYSTEM

Ethanol causes an increase in red blood cell size [mean corpuscular volume, (MCV)], which reflects its effects on stem cells. If heavy drinking is accompanied by folic acid deficiency, there can also be hypersegmented neutrophils, reticulocytopenia, and a hyperplastic bone marrow; if malnutrition is present, sideroblastic changes can be observed. Chronic heavy drinking can decrease production of white blood cells, decrease granulocyte mobility and adherence, and impair delayed-hypersensitivity responses to novel antigens (with a possible false-negative tuberculin skin test). Finally, many alcoholics have mild thrombocytopenia, which usually resolves within a week of abstinence unless there is hepatic cirrhosis or congestive splenomegaly.

CARDIOVASCULAR SYSTEM

Acutely, ethanol decreases myocardial contractility and causes peripheral vasodilation, with a resulting mild decrease in blood pressure and a compensatory increase in cardiac output. Exercise-induced increases in cardiac oxygen consumption are higher after alcohol intake. These acute effects have little clinical significance for the average healthy drinker but can be problematic in men and women with persisting cardiac disease.

The consumption of three or more drinks per day results in a dose-dependent increase in blood pressure, which returns to normal within weeks of abstinence. Thus, heavy drinking is an important factor in mild to moderate hypertension. Chronic heavy drinkers have a sixfold increased risk for coronary artery disease as well as an increased risk for cardiomyopathy. Symptoms range from unexplained arrhythmias in the presence of left ventricular impairment to heart failure with dilation of all four heart chambers and hypocontractility of heart muscle. Perhaps one-third of cases of cardiomyopathy are alcohol-induced. Mural thrombi can form in the left atrium or ventricle, while heart enlargement >25% can cause mitral regurgitation. Atrial or ventricular arrhythmias, especially paroxysmal tachycardia, can also occur after a drinking binge in individuals showing no other evidence of heart disease—a syndrome known as the "holiday heart." This condition is observed transiently in the majority of alcoholics entering treatment.

Chronic intake of modest doses of alcohol can have some beneficial effects. A maximum of one to two drinks per day may decrease the risk for cardiovascular death, perhaps through an increase in high-density lipoprotein (HDL) cholesterol or changes in clotting mechanisms. In one large national study, cardiovascular mortality was reduced by 30–40% among individuals reporting one or more drinks daily compared to nondrinkers, with overall mortality lowest among those consuming approximately one drink per day. Recent data have also corroborated that regular light drinking decreases the risk for ischemic, but not hemorrhagic, stroke.

GENITOURINARY SYSTEM CHANGES, SEXUAL FUNCTIONING, AND FETAL DEVELOPMENT

Acutely, modest ethanol doses (e.g., blood alcohol concentrations of 0.06 gm/dL) can increase sexual drive but also decrease erectile capacity in men. Even in the absence of liver impairment, a significant minority of chronic alcoholic men show irreversible testicular atrophy with shrinkage of the seminiferous tubules, decreases in ejaculate volume, and a lower sperm count.

The repeated ingestion of high doses of ethanol by women can result in amenorrhea, a decrease in ovarian size, absence of corpora lutea with associated infertility, and an increased risk of spontaneous abortion. Heavy drinking during pregnancy results in the rapid placental transfer of both ethanol and acetaldehyde, which may have serious consequences for fetal development. The *fetal alcohol syndrome* can include any of the following: facial changes with epicanthal eye folds; poorly formed ear concha; small teeth with faulty enamel; cardiac atrial or ventricular septal defects; an aberrant palmar crease and limitation in joint movement; and microcephaly with mental retardation. The amount of ethanol required and the time of vulnerability during pregnancy have not been defined, making it advisable for pregnant women to abstain completely.

OTHER EFFECTS OF ETHANOL

Between one-half and two-thirds of alcoholics have skeletal muscle weakness caused by acute *alcoholic myopathy*, a condition that improves but which might not fully remit with abstinence. Effects of repeated heavy drinking on the *skeletal system* include changes in calcium metabolism, lower bone density, and decreased growth in the epiphyses, leading to an increased risk for fractures and osteonecrosis of the femoral head. *Hormonal changes* include an increase in cortisol levels, which can remain elevated during heavy drinking; inhibition of vasopressin secretion at rising blood alcohol concentrations and enhanced secretion at falling blood alcohol concentrations (with the final result that most alcoholics are likely to be slightly overhydrated); a modest and reversible decrease in serum thyroxine (T_4); and a more marked decrease in serum triiodothyronine (T_3). Hormone irregularities should be reevaluated after a month of abstinence.

ALCOHOLISM (ALCOHOL ABUSE OR DEPENDENCE)

Because many drinkers occasionally imbibe to excess, temporary alcohol-related pathology is common in nonalcoholics, especially those in the late teens to the late twenties. When repeated problems in multiple life areas develop, the individual is likely to meet criteria for alcohol abuse or dependence.

DEFINITIONS AND EPIDEMIOLOGY

Alcohol dependence is defined in DSM-IV as repeated alcohol-related difficulties in at least three of seven areas of functioning that cluster together over a 12-month period. Two of these seven items, tolerance and withdrawal, may have special importance as they are associated with a more severe clinical course. Alcohol dependence is seen in all countries where alcohol is available and occurs in men and women from all socioeconomic strata and all racial backgrounds. The diagnosis of alcohol dependence predicts a course of recurrent problems with the use of alcohol and the consequent shortening of the life span by a decade on average.

Alcohol abuse is defined as repetitive problems with alcohol in any one of four life areas—social, interpersonal, legal, and occupational—or repeated use in hazardous situations such as driving while intoxicated. If an individual is not alcohol dependent, he or she still may be given a diagnosis of alcohol abuse.

The lifetime risk for alcohol dependence in most western countries is about 10–15% for men and 5–8% for women. Rates are generally similar in the United States, Canada, Germany, Australia, and England; rates tend to be lower in most Mediterranean countries, such as Italy, Greece, and Israel, and may be higher in Ireland, France, and Scandinavia. Even higher rates have been reported for several native cultures including Native Americans, Eskimos, Maori groups, and aboriginal tribes of Australia. These differences reflect both cultural and genetic influences, as described later in the chapter. When alcohol abuse is also considered, the rates of alcohol use disorders increase. In western countries, the typical alcoholic does not fulfill the common stereotype of a "skid-row" denizen but is more often a blue- or white-collar worker or homemaker. The lifetime

risk for alcoholism among physicians is similar to that of the general population.

GENETICS OF ALCOHOLISM

Several separate and distinct characteristics appear to contribute to the risk. For example, some families carry a risk for both alcoholism and drug dependence associated with the characteristic of high levels of impulsivity, as can be seen in the antisocial personality disorder. In other families, the risk for both alcohol and drug dependence may relate to a genetic vulnerability to schizophrenia, panic disorder, or manic depressive disease. A third and different mechanism increases only the alcoholism risk (e.g., in some offspring of alcoholics and Native Americans) through a low response to alcohol and subsequent drinking higher doses to achieve the desired effects. The relatively low response to alcohol contributes to attitudes and drinking patterns that increase the risk for alcohol-related problems and alcoholism. By contrast, a decreased risk for heavy drinking can result from a more intense response to alcohol, as seen in approximately one-half of Asian men and women. This is due primarily to a mutation that causes the production of an inactive form of the enzyme ALDH, which results in higher levels of acetaldehyde following alcohol ingestion.

NATURAL HISTORY

Although the age of the first drink is similar in alcoholics and nonalcoholics, earlier onset of regular drinking and drunkenness is associated with a higher risk for later problems. By the early to mid-twenties, most nonalcoholic men and women moderate their drinking (perhaps learning from minor problems), whereas alcoholics are likely to escalate their patterns of drinking despite difficulties. The first major life problem from alcohol often appears in the early to mid-twenties. Once established, the course of alcoholism is likely to be one of exacerbations and remissions. As a rule, there is little difficulty in stopping alcohol use when problems develop, and this step is often followed by days to months of abstinence and then a period of carefully controlled drinking. Unless abstinence is maintained, however, these phases almost inevitably give way to escalations in alcohol intake and subsequent problems. The course is not hopeless; following treatment, between one-half and two-thirds of alcoholics maintain abstinence for years, and often permanently. Even without formal treatment or self-help groups there is at least a 20% chance of spontaneous remission with long-term abstinence. However, should the alcoholic continue to drink, the life span is shortened by 10–15 years on average, with the leading causes of death, in decreasing order, the result of heart disease, cancer, accidents, and suicide.

IDENTIFICATION OF THE ALCOHOLIC AND INTERVENTION

Even in affluent areas ~20% of patients have an alcohol use disorder. It is important to pay attention to the alcohol-related symptoms and signs as well as laboratory tests that are likely to be abnormal in the context of regular consumption of six to eight or more drinks per day. The two blood tests with ≥70% sensitivity and specificity for heavy alcohol consumption are γ-glutamyl transferase (GGT) (>35 units) and carbohydrate-deficient transferrin (CDT) (>20 units/L); the combination of the two is likely to be more accurate than either alone. Physicians should consider using these tests to screen all patients as indicators of possible alcoholism. These serologic markers of heavy drinking can also be useful in monitoring abstinence, as they are likely to return toward normal within several weeks of the cessation of drinking; thus, increases in values of as little as 10% are likely to indicate a resumption of heavy alcohol intake. Other blood tests that can be useful in identifying individuals consuming six or more standard drinks per day include high-normal MCVs (≥91 μm^3) and serum uric acid (>416 mol/L, or 7 mg/dL). Physical signs and symptoms that can be useful in identifying alcoholism include mild and fluctuating hypertension, repeated infections such as pneumonia, and otherwise unexplained cardiac arrhythmias. Other disorders suggestive of dependence include cancer of the head and neck, esophagus, or stomach as well as cirrhosis, unexplained hepatitis, pancreatitis, bilateral parotid gland swelling, and peripheral neuropathy.

The clinical diagnosis of alcohol abuse or dependence ultimately rests on the documentation of a pattern of repeated difficulties associated with alcohol use; the definition is not based on the quantity and frequency of alcohol consumption. Thus, in screening it is important to probe for life problems and then attempt to tie in use of alcohol or another substance. Information regarding marital or job problems, legal difficulties, histories of accidents, medical problems, evidence of tolerance, etc., are important. While all physicians should be able to take the time needed to gather such information, some standardized questionnaires can be helpful, including the 10-item Alcohol Use Disorder Screening Test (AUDIT) (**Table 50-2**). However, these are only screening tools, and a careful face-to-face interview is still required for a meaningful diagnosis.

After alcoholism is identified, the diagnosis must be shared with the patient as part of an intervention. The presenting complaint can be used as an entrée to the alcohol problem. For instance, the patient with insomnia

TABLE 50-2

THE ALCOHOL USE DISORDERS IDENTIFICATION TEST (AUDIT)[a]

ITEM	5-POINT SCALE (LEAST TO MOST)
1. How often do you have a drink containing alcohol?	Never (0) to 4+ per week (4)
2. How many drinks containing alcohol do you have on a typical day?	1 or 2 (0) to 10+ (4)
3. How often do you have six or more drinks on one occasion?	Never (0) to daily or almost daily (4)
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never (0) to daily or almost daily (4)
5. How often during the last year have you failed to do what was normally expected from you because of drinking?	Never (0) to daily or almost daily (4)
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never (0) to daily or almost daily (4)
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never (0) to daily or almost daily (4)
8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never (0) to daily or almost daily (4)
9. Have you or someone else been injured as a result of your drinking?	No (0) to yes, during the last year (4)
10. Has a relative, friend, doctor or other health worker been concerned about your drinking or suggested that you should cut down?	No (0) to yes, during the last year (4)

Note: [a]The AUDIT is scored by simply summing the values associated with the endorsed response.

Source: Adapted from DF Reinert, GP Allen: *Alcoholism: Clinical & Experimental Research* 26:272, 2002, and from MA Schuckit, 2006.

or hypertension can be told that these are clinically important problems which, in conjunction with other physical findings and laboratory tests, indicate that alcohol is increasing the risk for further medical and psychological problems. The physician should share information about the course of alcoholism and explore possible avenues of addressing the problem. This process can be carried out by any physician or other health care provider. Several protocols, categorized as *brief interventions* and *motivational interviewing,* are available for health care workers to follow. The technique of brief interventions has been shown to be effective in decreasing alcohol use and problems when instituted as two 15-min sessions 1 month apart, along with a telephone follow-up reminder. Motivational interviewing uses the clinician's level of concern and understanding of the need for patients to progress through their own stages of enhanced understanding of their problems to optimize their ability to alter their drinking behaviors.

The process of intervention is rarely accomplished in one session. Multiple sessions to explain the problem, the optimal treatments, and the benefits of making certain lifestyle changes are often required. For the person who refuses to stop drinking at the first intervention, a logical step is to "keep the door open," establishing future meetings so that help is available as problems escalate. In the meantime the family may benefit from counseling or referral to self-help groups such as Al-Anon (the Alcoholics Anonymous group for family members) and Alateen (for teenage children of alcoholics).

THE ALCOHOL WITHDRAWAL SYNDROME

Once the brain has been repeatedly exposed to high doses of alcohol, any sudden decrease in intake can produce withdrawal symptoms, many of which are the opposite of those produced by intoxication. Features include tremor of the hands (shakes or jitters); agitation and anxiety; autonomic nervous system overactivity including an increase in pulse, respiratory rate, and body temperature; and insomnia, sometimes accompanied by frightening dreams. Because alcohol has a short half-life, these withdrawal symptoms generally begin within 5–10 h of decreasing ethanol intake, peak in intensity on day 2 or 3, and improve by day 4 or 5. Anxiety, insomnia, and mild levels of autonomic dysfunction may persist to some degree for 4–6 months as a protracted abstinence syndrome, which may contribute to the tendency to return to drinking.

At some point in their lives, between 2 and 5% of alcoholics experience withdrawal seizures, often within 48 h of stopping drinking. These rare events usually involve a single generalized seizure, and electroencephalographic abnormalities generally return to normal within several days.

The term *delirium tremens* (DTs) refers to an uncommon state of intense acute withdrawal that includes delirium (mental confusion, agitation, and fluctuating levels of consciousness) associated with a tremor and autonomic overactivity (e.g., marked increases in pulse, blood pressure, and respirations). Fortunately, this serious and potentially life-threatening complication of alcohol withdrawal is seen in <5% of alcohol-dependent individuals; the chance of DTs during any single withdrawal is <1%. DTs are most likely to develop in patients with concomitant severe medical disorders and can usually be avoided by identifying and treating the underlying medical conditions.

Rx Treatment: ALCOHOL-RELATED CONDITIONS

ACUTE INTOXICATION The first priority is to assess vital signs and manage respiratory depression, cardiac arrhythmia, or blood pressure instability, if present. The possibility of intoxication with other drugs should be considered, and blood and urine samples are obtained to screen for opioids or other CNS depressants such as benzodiazepines or barbiturates. Other medical conditions that must be considered include hypoglycemia, hepatic failure, or diabetic ketoacidosis.

Patients who are medically stable should be placed in a quiet environment. If recumbent, patients should lie on their side to minimize the risk of aspiration. When the intoxicated person is aggressive or violent, hospital procedures should be followed, including planning for the possibility of a show of force with an intervention team. In the context of aggressiveness, patients should be reminded in a clear and nonthreatening way that the staff wants to help them to feel better and to avoid problems. If the aggressive behavior continues, relatively low doses of a short-acting benzodiazepine such as lorazepam (e.g., 1–2 mg PO or IV) may be used and can be repeated as needed, but care must be taken so that the addition of this second CNS depressant does not destabilize vital signs or worsen confusion. An alternative approach is to use an antipsychotic medication (e.g., 0.5–5 mg of haloperidol PO or IM every 4-8 h if needed), but this has the potential danger of lowering the seizure threshold. Two other medications useful for agitation are ziprasidone (10 mg IM every 2 h as needed, up to 40 mg) and olanzapine (2.5–10 mg IM repeated at 2 h and 6 h, if needed). If aggression escalates, the patient might require a short-term admission to a locked ward, where medications can be used more safely and vital signs more closely monitored.

WITHDRAWAL The first step is to perform a thorough physical examination in all alcoholics who are considering stopping drinking, including a search for evidence of liver failure, gastrointestinal bleeding, cardiac arrhythmia, infection, and glucose or electrolyte imbalance.

The second step is to offer reassurance that the acute withdrawal is short lived and to offer adequate nutrition and rest. All patients should be given oral multiple B vitamins, including 50–100 mg of thiamine daily for a week or more. Because most alcoholics who enter withdrawal are either normally hydrated or mildly overhydrated, IV fluids should be avoided unless there is evidence of significant recent bleeding, vomiting, or diarrhea. Medications can usually be administered orally.

The third step in treatment is to recognize that most withdrawal symptoms are caused by the rapid removal of a CNS depressant, in this case, alcohol. The symptoms can be controlled by administering any drug of this class in doses that decrease the agitation, and gradually taper the dose over 3–5 days. While most CNS depressants are effective, benzodiazepines (Chap. 49) have the highest margin of safety and lowest cost and are, therefore, the preferred class of drugs. Benzodiazepines with short half-lives are especially useful for patients with serious liver impairment or evidence of preexisting encephalopathy or brain damage. However, short-acting benzodiazepines such as lorazepam can produce rapidly changing drug blood levels and must be given every 4 h to avoid abrupt fluctuations that may increase the risk for seizures. Therefore, most clinicians use drugs with longer half-lives, such as diazepam or chlordiazepoxide, administering enough drug on day 1 to alleviate most of the symptoms of withdrawal (e.g., the tremor and elevated pulse) and then gradually decreasing the dose over a period of 3–5 days. The approach is flexible; the dose is increased if signs of withdrawal escalate, and the medication is withheld if the patient is sleeping or shows signs of increasing orthostatic hypotension. The average patient requires 25–50 mg of chlordiazepoxide or 10 mg of diazepam given PO every 4–6 h on the first day.

Treatment of the patient with DTs can be challenging, and the condition is likely to run a course of 3–5 days regardless of the therapy employed. The focus of care is to identify and correct medical problems and to control behavior and prevent injuries. Many clinicians recommend the use of high doses of a benzodiazepine (as much as 800 mg/d of chlordiazepoxide has been reported), a treatment that will decrease agitation and raise the seizure threshold but probably does little to improve the confusion. Other clinicians recommend the use of antipsychotic medications, such as haloperidol, ziprasidone, or olanzapine as discussed above, although these drugs have not been directly evaluated for DTs. Antipsychotics are less likely to exacerbate confusion but may increase the risk of seizures; they have no place in the treatment of mild withdrawal symptoms.

Generalized withdrawal seizures rarely require aggressive pharmacologic intervention beyond that given to the usual patient undergoing withdrawal, i.e., adequate doses of benzodiazepines. There is little evidence that anticonvulsants such as phenytoin or gabapentin are effective in drug-withdrawal seizures, and the risk of seizures has usually passed by the time effective drug levels are reached. The rare patient with status epilepticus must be treated aggressively (Chap. 20).

While alcohol withdrawal is often treated in a hospital, efforts at reducing costs have resulted in the development of outpatient detoxification for relatively mild abstinence syndromes. This is appropriate for patients in

good physical condition who demonstrate mild signs of withdrawal despite low blood alcohol concentrations and for those without prior history of DTs or withdrawal seizures. Such individuals still require a careful physical examination, appropriate blood tests, and vitamin supplementation. Benzodiazepines can be given in a 1- to 2-day supply to be administered to the patient by a spouse or other family member four times a day. Patients are asked to return daily for evaluation of vital signs and to come to the emergency room if signs and symptoms of withdrawal escalate.

REHABILITATION OF ALCOHOLICS After completing alcoholic rehabilitation, ≥60% of alcoholics, especially middle class patients, maintain abstinence for at least a year, and many achieve lifetime sobriety.

The core of treatment begins with helping patients recognize the need to change, while working with them to alter their behaviors to enhance compliance. Therapeutic maneuvers fall into several general categories, which are applied to all patients regardless of age or ethnic group. The manner in which the treatments are used should be sensitive to the practices and needs of specific populations. The first step is to help the alcoholic achieve and maintain a high level of motivation toward abstinence. This includes education about alcoholism and instructions to family and/or friends to stop protecting the patient from problems caused by alcohol. The second step is to help the patient readjust to life without alcohol and to reestablish a functional lifestyle through counseling, vocational rehabilitation, and self-help groups such as Alcoholics Anonymous (AA). The third component, called *relapse prevention*, helps the patient to identify situations in which a return to drinking is likely, formulate ways of managing these risks, and develop coping strategies that increase the chances of a return to abstinence if a slip occurs.

For many patients, especially those who are highly motivated and have supportive social systems, treatment can be on an outpatient basis. However, more intense interventions work better than less intensive measures, and some alcoholics do not respond to outpatient approaches. The decision to hospitalize or utilize residential care can be made if (1) the patient has medical problems that are difficult to treat outside a hospital; (2) depression, confusion, or psychosis interferes with outpatient care; (3) there is a severe life crisis that makes it difficult to work in an outpatient setting; (4) outpatient treatment has failed; or (5) the patient lives too far from the treatment center to participate in an outpatient program. The best predictors of continued abstinence include evidence of higher levels of life stability (e.g., supportive family and friends) and higher levels of functioning (e.g., job skills, higher levels of education, and absence of crimes unrelated to alcohol).

Whether the treatment begins in an inpatient or an outpatient setting, subsequent outpatient contact should be maintained for a minimum of 6 months and preferably a full year after abstinence is achieved. Counseling with an individual physician or through groups focuses on day-to-day living, emphasizing areas of improved functioning in the absence of alcohol (i.e., why it is a good idea to continue to abstain) and helping the patient to manage free time without alcohol, develop a nondrinking peer group, and handle stresses on the job.

The physician serves an important role in identifying the alcoholic, diagnosing and treating associated medical or psychiatric syndromes, overseeing detoxification, referring the patient to rehabilitation programs, and providing counseling. Physicians are also responsible for selecting which (if any) medication might be appropriate during alcoholism rehabilitation. Patients often complain of continuing sleep problems or anxiety when acute withdrawal treatment is over, problems that may be a component of protracted withdrawal. In general, hypnotics or antianxiety drugs should be avoided in this situation. Patients should be reassured that the trouble sleeping is normal after alcohol withdrawal and will improve over the subsequent weeks and months. Patients should follow a rigid bedtime and awakening schedule and avoid naps or the use of caffeine in the evenings. The sleep pattern will improve with time, and the patient can avoid the rebound insomnia associated with most hypnotics and the risk for developing dependence on another depressant. Anxiety can be addressed by helping the person to gain insight into the temporary nature of the symptoms and to develop strategies to achieve relaxation as well as by using forms of cognitive therapy.

While the mainstay of alcoholic rehabilitation involves counseling, education, and cognitive approaches, several medications might be useful. The optimal length of time to continue these drugs in the context of a positive response is unclear, but most clinicians would recommend 6–12 months. The first is the opioid-antagonist drug naltrexone, 50–150 mg/d, which has been reported to decrease the probability of a return to drinking and to shorten periods of relapse. Recently a once-per-month injection of this drug (380 mg) has been developed to help improve compliance. By blocking opioid receptors, naltrexone may decrease activity in the dopamine-rich ventral tegmental reward system, or decrease the feeling of pleasure or reward if alcohol is imbibed. The improved rate of functioning and abstinence with this drug is modest. The side effects are relatively few at the recommended doses and include gastrointestinal distress. A second medication, acamprosate (Campral), 2 g/d, has been widely tested in patients in the United States and Europe; results are generally similar to those

reported for naltrexone. This drug inhibits the actions of NMDA receptors and has been hypothesized to act by decreasing mild symptoms of protracted withdrawal. There are few side effects, aside from mild gastrointestinal distress. Several long-term trials of combined naltrexone and acamprosate using doses similar to those noted above have reported that the combination may be superior to either drug alone, although not all studies agree.

Disulfiram, an ALDH inhibitor, has been used extensively in the past for treatment of alcoholism. In doses of 250 mg/d this drug produces an unpleasant (and potentially dangerous) reaction in the presence of alcohol, a phenomenon related to rapidly rising blood levels of the first metabolite of alcohol, acetaldehyde. Few adequate controlled trials have demonstrated a clear superiority of disulfiram over placebo. Drinking alcohol while taking disulfiram produces a reaction involving an increased pulse, changes in blood pressure, and vomiting and diarrhea. This can be dangerous, especially for patients with heart disease, stroke, diabetes mellitus, or hypertension. The drug itself has also been reported to carry potential risks of depression, psychotic symptoms, peripheral neuropathy, and liver damage. Thus, most clinicians reserve this medication for patients who have a clear history of longer-term abstinence associated with prior use of disulfiram, and for those who might take the drug under the supervision of another individual (such as a spouse), especially during discrete periods identified as representing high-risk drinking situations for them (such as the Christmas holiday). Other drugs under investigation for possible use in alcoholism rehabilitation include the serotonin antagonist ondansetron; topiramate, an anticonvulsant with possible effects on dopamine; and the cannabinol receptor antagonist ramonibant; at present, there are insufficient data to support their use in clinical settings.

Additional support for alcoholics and their relatives and friends is available through self-help programs such as AA. These groups, which typically consist of recovering alcoholics, offer an effective model of abstinence, provide a sober peer group, and make crisis intervention freely available when the urge to drink escalates. This can help patients optimize their chances for recovery, especially when incorporated into a more structured treatment milieu.

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CHAPTER 51

OPIOID DRUG ABUSE AND DEPENDENCE

Marc A. Schuckit

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It is difficult to imagine modern medical practice without the use of opioid analgesics. These drugs have been part of health care since 300 B.C. Opium and codeine were isolated in the early nineteenth century, opioid-like substances produced by the body were recognized in the 1970s, and the first endogenous opioid was isolated in 1995. As important as these substances are to modern medicine, opioid drugs have many disadvantages, including overdosage and dependency; close to 1 million individuals in the United States are opioid-dependent. All opioid drugs are capable of producing a heroin-like intoxication, as well as tolerance and withdrawal.

PHARMACOLOGY

The prototypic opiates, morphine and codeine (3-methoxymorphine), are derived from the juice of the poppy *Papaver somniferum*. The semisynthetic drugs produced from morphine or thebane molecules include hydromorphone, diacetylmorphine (heroin), and oxycodone. The purely synthetic opioids and their cousins include meperidine, propoxyphene, diphenoxylate, fentanyl, buprenorphine, tramadol, methadone, and pentazocine.

The body's own endogenous opioid peptides (e.g., enkephalins, endorphins, dynorphins, and others) have distinct distributions in the central nervous system (CNS) and appear to be natural ligands for opioid receptors. As summarized in **Table 51-1**, the receptors with which opioid peptides interact differentially produce analgesia, respiratory depression, constipation, euphoria, and other actions. Substances capable of antagonizing one or more of these actions include nalorphine, levallorphan, cyclazocine, butorphanol, buprenorphine, and pentazocine, each of which has mixed agonist and antagonist properties, as well as naloxone, nalmefene, and naltrexone, which are pure opiate antagonists.

The availability of relatively specific antagonists has helped identify at least three receptor subtypes. These include μ receptors, which influence some of the more classic opioid actions such as pain control, reinforcement, constipation, hormone levels, and respiration; κ receptors, with possible similar functions along with sedation and effects on hormones; and δ receptors, thought to relate mostly to analgesia, mood, reinforcement, and breathing. A fourth possible receptor subtype, sensitive to another endogenous peptide, is sometimes called *nociceptin* or *orphanin* and may influence pain. The major features of tolerance, dependence, and withdrawal are thought to be mediated primarily by μ receptors, and these are affected by all prescription opioids.

The most rapid and pronounced effects of opioids occur through IV administration, with only slightly less efficient absorption after smoking or inhaling the vapor ("chasing the dragon"). The slowest onset and least intense effects occur after oral consumption. Most of the metabolism of opioids occurs in the liver, primarily through conjugation with glucuronic acid, and only small amounts are excreted directly in the urine or feces. The plasma half-lives of these drugs range from 2.5–3 h for morphine to >22 h for methadone.

Street heroin is typically only 5–10% pure and is usually mixed with sugars, quinine, powdered milk, phenacetin,

TABLE 51-1

ACTIONS OF OPIOID RECEPTORS

RECEPTOR TYPE	ACTIONS
Mu (μ) (e.g., morphine)	Analgesia, reinforcement euphoria, cough and appetite suppression, decreased respirations, decreased GI motility, sedation, hormone changes, dopamine and acetylcholine release
Kappa (κ) (e.g., butorphanol)	Decreased dysphoria, decreased GI motility, decreased appetite, decreased respiration, psychotic symptoms, sedation, diuresis, analgesia
Delta (δ) (e.g., etorphine)	Hormone changes, appetite suppression, dopamine release

Note: GI, gastrointestinal.

caffeine, antipyrine, and strychnine. Unexpected increases in the purity of street drugs can cause unintentional lethal overdoses.

ACUTE AND CHRONIC EFFECTS OF OPIOIDS

With the exception of overdose and physical dependence, most opioid effects are rapidly reversible. A major danger, however, comes through the use of contaminated needles by IV users, which increases the risk of hepatitis B and C, bacterial endocarditis, and infection with HIV (Chap. 37).

Effects on Organ Systems

Euphoria and rewarding effects of opioids are due, at least in part, to stimulation of dopaminergic pathways originating in the midbrain and terminating in the nucleus accumbens. Effects on other neurotransmitter systems also occur. CNS effects of opioid drugs include nausea and vomiting (medulla), decreased pain perception (spinal cord, thalamus, and periaqueductal gray region), and sedation (reticular activating system). The adulterants added to street drugs may contribute to nervous system damage, including peripheral neuropathy, amblyopia, myelopathy, and leukoencephalopathy. Acute opioid administration inhibits release of some hormones from the hypothalamus, including corticotropin-releasing factor (CRF) and luteinizing hormone, with a subsequent reduction in some sex hormones, actions that might contribute to a decreased sex drive and problems in handling stress. Other hormonal changes include a decrease in the release of thyrotropin and increases in prolactin and possibly growth hormone.

Acute changes in the respiratory system include a CNS-mediated decrease in the cough reflex (which can be useful as an antitussive) and respiratory depression, which result from a decreased response of the brainstem to carbon dioxide tension, a component of the drug overdose syndrome described below. At even low drug doses, this effect can be clinically significant for individuals with pulmonary disease. Aspiration pneumonia is an additional risk. The gastrointestinal effects of opioids can include decreased gut motility (useful in treating diarrhea), nausea, constipation, and anorexia with weight loss. Cardiovascular changes following modest doses tend to be relatively mild, with no direct opioid effect on heart rhythm or myocardial contractility, but orthostatic hypotension can occur, probably secondary to histamine release and dilation of peripheral vessels. Bacterial endocarditis with septic emboli and stroke can occur from contaminated needles.

Opioid Toxicity and Overdosage

High doses of opioids can result in a potentially lethal overdose. This occurs at some point in over half of opioid-dependent persons, especially with the more potent drugs such as fentanyl (80–100 times more powerful than morphine). The typical syndrome, which occurs immediately with IV overdose, includes shallow and slow respirations, pupillary miosis (with mydriasis once brain anoxia develops), bradycardia, hypothermia, and stupor or coma (Chap. 14). If not treated rapidly, respiratory depression, cardiorespiratory arrest, and death can ensue. Postmortem examination reveals few specific changes except for diffuse cerebral edema. An "allergic-like" reaction to IV heroin, perhaps in part related to adulterants, can also occur and is characterized by decreased alertness, frothy pulmonary edema, and an elevation in the blood eosinophil count.

℞ Treatment: OPIOID OVERDOSE

The first step in managing overdose is to support vital signs, using intubation if needed. Definitive treatment is the administration of a narcotic antagonist such as naloxone, 0.4–2 mg IV or IM. A response should occur in 1–2 min, but if needed, the dose can be repeated every 2–3 min up to 10 mg. With the exception of buprenorphene overdoses, a lack of response after 10 mg makes a toxic reaction due solely to opioids unlikely. It is important to titrate the dose relative to the patient's symptoms to ameliorate the respiratory depression but not provoke a severe withdrawal state; the latter cannot be aggressively treated until overdose-related vital signs are relatively stable. Because the effects of naloxone diminish within several hours, the individual must be monitored for at least 24 h after a heroin overdose and 72 h after an overdose of a longer-acting drug such as methadone. If there is little response to an opioid antagonist, the possibility of a

concomitant overdose with a benzodiazepine should be considered and a challenge with IV flumazenil, 0.2 mg/min up to a maximum of 3 mg in an hour, might be used. This drug should be administered with caution as it can precipitate seizures and increase intracranial pressure.

Treatment of either the typical or the "allergic" type of opioid toxic reaction requires continued respiratory support (often with oxygen supplementation and positive-pressure breathing for the "allergic" type of overdose), IV fluids, and pressor agents when needed to support blood pressure. Activated charcoal (e.g., 1 g/kg suspended in water) should be considered if ingestion of large doses of oral opioids is suspected; alternatively, gastric lavage can be used to remove any remaining drug. Intubation is often required to prevent aspiration in the stuporous or comatose patient. Cardiac arrhythmias and/or seizures may also be part of the opioid toxic reaction, especially with codeine, propoxyphene, or meperidine.

OPIOID ABUSE AND DEPENDENCE

Definition and Epidemiology

The *Fourth Diagnostic and Statistical Manual* of Mental Disorders, (DSM-IV) of the American Psychiatric Association defines dependence as repeated use of a drug to the point of causing repetitive problems in multiple life areas. The definition requires evidence of three or more such problems clustered together within the same 12-month period of time, including tolerance, withdrawal, use of greater amounts of opiates than intended, and use despite consequences. Patients who do not have dependence but demonstrate repeated opioid-related difficulties with the law, impaired ability to meet obligations, use in hazardous situations, or continued use despite problems can be labeled as having abuse.

The use of opioids for intoxication is less prevalent than the use of alcohol, marijuana, and stimulants such as cocaine or amphetamines. A national survey of adolescents and young adults published in 2005 reported that 13.5% of 12th graders (high school seniors) had tried an opioid outside of a doctor's prescription, including 1.5% who had used heroin. Figures for young adults and college students were almost 17.6% and 1.9%, respectively. In all studies, prevalence rates were only slightly higher in males than females. The prevalence of opioid dependence is estimated as a lifetime risk of about 1%.

Genetics

Genetic factors appear to influence an individual's specific risk for opioid dependence as well as a more general vulnerability toward substance-related problems. The proportion of the total risk explained by genes is estimated at ~50%. Specific genes potentially include variations in the α_2 subunit of the γ-aminobutyric acid (GABA)-A receptor; this might affect the risk of abuse or dependence on a wide range of substances through effects on impulsivity and sensation-seeking. All genetic influences operate in the context of environmental factors as well.

Natural History

While an opioid use disorder can develop in anyone, at least three groups are at increased risk for dependence or misuse. First, a minority of persons with chronic pain syndromes (e.g., back, joint, and muscle disorders) misuse their prescribed drugs. If physical dependence is established, any drop in opioid blood levels can intensify the pain and promote continued drug intake. Physicians can avoid contributing to physical dependence by helping the patient to accept the goal of moderation rather than disappearance of the pain, and to recognize that discomfort may not be completely eliminated. Analgesic medication should be only one component of treatment and should be limited to the oral administration of the least potent analgesic that is able to "take the edge off" the pain (e.g., naproxen or ibuprofen). Behavior-modification techniques, such as muscle relaxation and meditation, and carefully selected exercises should be used as appropriate to help increase function and decrease pain. Finally, nonmedicinal approaches, including electrical transcutaneous neurostimulation for muscle and joint disease, may be useful.

The second group at high risk consists of physicians, nurses, and pharmacists, primarily because of easy access to opioids. Physicians may begin use to help with sleep or to reduce stress or physical aches and pains, and then escalate doses as tolerance develops. Because of the growing awareness of these problems, programs have been developed to identify and aid substance-impaired physicians, providing peer support and education before problems escalate to the point of licensure revocation. All physicians are advised never to prescribe opioids for themselves or family members

The third group is those who buy illicit drugs to get high. While some of these individuals have severe antisocial problems, many had a relatively high level of premorbid functioning. The typical person begins using opioids occasionally, often after experimenting with tobacco, then alcohol, then marijuana, and then brain depressants or stimulants. Occasional opioid use, or "chipping," might continue for some time, and some individuals never escalate their intake to the point of developing dependence. For others, the frequency of use and quantity needed increase, tolerance develops, excuses are made for associated problems, and a full dependence syndrome appears.

Opioid-dependent individuals are not likely to give up their intake of other drugs. Alcohol may be used to moderate withdrawal problems, to enhance the opioid high, and to serve as a substitute when the opioid is not available,

including during methadone or other maintenance or antagonist treatments. Problematic drinking, including alcohol dependence, is seen in about half of opioid-dependent persons. Cocaine appears to be taken for many of the same reasons, and is often administered IV with the opioid in a mixture known as a "speedball." Another relevant class of drugs is the benzodiazepines, taken for a high or alleviation of withdrawal symptoms, especially among people in methadone maintenance.

Once persistent opioid use is established, severe problems are likely to develop. At least 25% of opioid-dependent individuals die within 10–20 years (a mortality rate 15-fold higher than the general population) from suicide, homicide, accidents, or infectious diseases such as tuberculosis, hepatitis, or AIDS. The latter has become an epidemic among injection drug users, with as many as 60% of these men and women in some locales carrying the HIV virus (Chap. 37). Although the majority of opioid-dependent persons experience frequent exacerbations and remissions, it is important to remember that even without treatment ~35% achieve long-term, often permanent, abstinence, especially after 40 years of age. As is true with most drugs of abuse, a favorable prognosis is associated with a prior history of marital and employment stability and fewer prior criminal activities unrelated to drugs.

℞ Treatment: OPIOID ABUSE AND DEPENDENCE

The first step in treatment is to identify the problem. It is important to discard the erroneous stereotype that opioid-dependent individuals are unemployed and homeless. Abuse or dependence is possible in any patient who demonstrates symptoms of what might be opioid withdrawal; anyone who has a chronic pain syndrome; physicians, nurses, and pharmacists or others with easy access to opioids; and patients who repeatedly seek out prescription analgesics. Before prescribing an opioid analgesic, it is important to gather a complete history that elucidates patterns of life problems and any history of opioid use. If a problem with opioids is suspected, gathering further data from a relative or close friend can be helpful. Additionally, clinicians should search for physical stigmata of misuse (e.g., needle marks) and, when appropriate, screen blood or urine for opioids.

After identifying opioid dependence, the next step is intervention as described for alcoholism in Chap. 50. Motivational interviewing techniques of empathy, careful listening, presenting options, and gauging the patient's motivational readiness to change are important, as are efforts to enlist the help of relatives and friends. Ongoing treatment even after the patient achieves abstinence is important; this includes offering help in establishing a drug-free lifestyle.

SYMPTOMS OF WITHDRAWAL Withdrawal symptoms (which are generally the opposite of the acute effects of the drug) include nausea, diarrhea, coughing, lacrimation, mydriasis, rhinorrhea, profuse sweating, twitching of muscles, and piloerection (or "goose bumps") as well as mild elevations in body temperature, respiratory rate, and blood pressure. In addition, diffuse body pain, insomnia, and yawning occur, along with intense drug craving. Withdrawal from opioids with shorter half-lives, such as morphine or heroin, usually causes symptoms within 8–16 h of the last dose; intensity peaks within 36–72 h after discontinuation of the drug; and the acute syndrome disappears within 5–8 days. A protracted abstinence phase of mild moodiness, autonomic dysfunction, and changes in pain threshold and sleep patterns may persist for ≥6 months and probably contributes to relapse. For longer-acting opioids such as methadone or continuous-release morphine, symptoms may not appear for several days, and may not peak until 7–10 days later.

TREATMENT OF THE WITHDRAWAL SYNDROME A thorough physical examination, including an assessment of neurologic function and a search for focal and systemic infections, especially abscesses, is essential. Laboratory testing includes assessment of liver function and, in IV users, HIV and hepatitis B and C status.

One treatment approach to withdrawal is to administer an opioid (e.g., 10–25 mg of methadone bid) on day 1 to decrease symptoms. After several days of a stabilized drug dose, the opioid is then decreased by 10–20% of the original day's dose each day. However, the use of opioids for detoxification is proscribed or limited in most states. Thus, pharmacologic treatments often center on relief of symptoms of diarrhea with loperamide, of "sniffles" with decongestants, and pain with nonopioid analgesics (e.g., ibuprofen). Comfort can be enhanced with administration of the α_2-adrenergic agonist clonidine in doses up to 0.3 mg given two to four times a day to decrease sympathetic nervous system overactivity. Blood pressure must be closely monitored. Some clinicians augment this regimen with low to moderate doses of benzodiazepines for 2–5 days to decrease agitation and promote sleep. An ultra-rapid detoxification procedure using deep sedation and withdrawal precipitated by naltrexone has been proposed but has many inherent dangers and few, if any, advantages.

REHABILITATION The basic strategy, similar to that for alcoholics, includes detoxification and the establishment of realistic goals for abstinence and improvement of life functioning, along with counseling and education to increase motivation toward abstinence. A long-term commitment by the patient to maintain a lifestyle without illicit substances is essential for preventing relapse.

In most programs, patients are educated about their responsibility for improving their lives, and motivation

for abstinence is increased by providing information about the medical and psychological problems that can be expected if dependence continues. Patients and families are encouraged to establish an opioid-free lifestyle by learning to cope with chronic pain and develop realistic vocational planning. The dependent person is also advised to establish a drug-free peer group and to participate in self-help groups such as Narcotics Anonymous or Alcoholics Anonymous; the latter is appropriate for substance-dependent persons regardless of their usual drug of abuse. Another important treatment component is relapse prevention aimed at identifying triggers for a return to drugs and developing appropriate coping strategies.

Much of this advice and counseling can be given by the physician or by referring patients to formal drug programs, including methadone maintenance clinics, programs using narcotic antagonists, and therapeutic communities. Long-term follow-up of treated patients indicates that approximately one-third are completely drug free, and 60% no longer use opioids.

Opioid Maintenance Maintenance programs with methadone or buprenorphene should be used only in combination with education and counseling. The goal is to provide a substitute drug that is legally accessible, safer, can be taken orally, and has a relatively long half-life so that it can be taken once a day. This can help persons who have repeatedly failed in drug-free programs to improve functioning within the family and job, to decrease legal problems, and to improve health. Individuals who stay in methadone maintenance are likely to show less antisocial behavior and improvement in employment status.

Methadone is a long-acting opioid optimally dosed at 80–120 mg/d (a goal met through slow, careful increases over time). This dose is effective in blocking heroin-induced euphoria while decreasing craving, thereby helping patients to maintain abstinence from illegal opioids. Over three-quarters of patients in well-supervised methadone clinics are likely to remain heroin-free for ≥6 months. Methadone is usually administered as an oral liquid given once a day at the program, with weekend doses taken at home. After a period of maintenance (usually 6 months to ≥1 year), the clinician can work to slowly decrease the dose by ~5% per week. Some individuals, however, are unable to taper off the drug and require long-term maintenance.

An alternative medication that has been used for maintenance treatment is buprenorphine, a μ opioid agonist and antagonist. A dose of 6–12 mg buprenorphine is roughly equivalent to 35–60 mg of methadone. Administered either as a sublingual liquid or tablet, doses can be gradually increased to 8–16 mg/d over the first 2 months. Doses of 16–32 mg per treatment day may be needed if the drug is given three times per week. Buprenorphine is available as monotherapy or in combination with the antagonist naltrexone (2–8 mg buprenorphine with 0.5–2 mg naltrexone), which precipitates withdrawal if the patient dissolves the pills and injects them IV. Buprenorphine has several advantages including low overdose danger, potentially easier detoxification than is seen with methadone, and a probable ceiling effect in which higher doses do not increase euphoria. It can also be given in the doctor's office by physicians who have completed a required training program. While some studies report equal effectiveness of buprenorphine and methadone, others suggest higher dropout rates or more concomitant illicit drug use with buprenorphine compared to methadone. As with all opioids, there is a danger of misuse of this drug.

In the past, the British have used heroin maintenance with goals and guidelines similar to those of current methadone programs. There is no evidence that heroin maintenance has any advantages over methadone maintenance, but the heroin approach increases the risk that the drug will be sold on the streets.

Opioid Antagonists The opioid antagonists (e.g., naltrexone) compete with heroin and other opioids at receptors, reducing the effects of the opioid agonists. Administered over long periods with the intention of blocking the opioid "high," these drugs can be useful as part of an overall treatment approach that includes counseling and support. Naltrexone doses of 50 mg/d antagonize 15 mg of heroin for 24 h, and the possibly more effective higher doses (125–150 mg) block the effects of 25 mg of IV heroin for up to 3 days. To avoid precipitating a withdrawal syndrome, patients must be free of opioids for a minimum of 5 days before beginning treatment with naltrexone and should first be challenged with 0.4 or 0.8 mg of the shorter-acting agent naloxone to be certain they can tolerate the long-acting antagonist. A test dose of 10 mg of naltrexone is then given, which can produce withdrawal symptoms in 0.5–2 h. If none appear, the patient can begin with the usual dose of 40–150 mg three times per week.

Drug-Free Programs Most opioid-dependent individuals enter treatment programs that are based primarily on the cognitive behavioral approaches of enhancing commitment to abstinence, helping individuals to rebuild their lives without substances, and preventing relapse. Whether carried out in inpatient, residential, or outpatient settings, patients usually do not receive maintenance medications.

A variation of this approach can be used for persons who are having problems maintaining a drug-free state. Here, the basic elements of treatment are incorporated into long-term (often a year or more) residence in a therapeutic community. The person begins with almost full immersion in the environment in which other individuals at various

stages of recovery become the primary support group, offering advice and a drug-free atmosphere in which the opioid-dependent person progresses through ever-increasing levels of independence, including assuming a job outside the therapeutic atmosphere.

As is true for treatments of all substance-use disorders, it is likely that counseling, behavioral treatments, and relatively simple approaches to psychotherapy add significantly to a positive outcome. Most programs focus on teaching participants to cope with stress, enhancing their understanding of personality attributes, teaching better cognitive styles, and, through the process of relapse prevention, addressing issues that might contribute to increased craving, easy access to drugs, or periods of decreased motivation. A combination of these therapies with the approaches described above appears to give the best results.

Finally, it is important to discuss prevention. Except for the terminally ill, physicians should carefully monitor opioid drug use in their patients, keeping doses as low as is practical while still controlling pain, and administering opioids over as short a period as the level of pain would warrant in the average person. Physicians must be vigilant regarding their own risk for opioid abuse and dependence, never prescribing these drugs for themselves. For the nonmedical IV drug–dependent person, all possible efforts must be made to prevent AIDS, hepatitis, bacterial endocarditis, and other consequences of contaminated needles both through methadone maintenance and by considering needle-exchange programs.

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CHAPTER 52

COCAINE AND OTHER COMMONLY ABUSED DRUGS

Jack H. Mendelson† ■ Nancy K. Mello

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Initiation and perpetuation of the abuse of cocaine and other psychostimulants are determined by a complex interaction between the pharmacologic properties and relative availability of each drug, the personality and expectations of the user, and the environmental context in which the drug is used. Polydrug abuse, the concurrent use of several drugs with different pharmacologic effects, is increasingly common. Some forms of polydrug abuse, such as the combined use of heroin and cocaine intravenously, are especially dangerous and remain a major problem in hospital emergency departments. Sometimes one drug is used to enhance the effects of another, as with the combined use of benzodiazepines and methadone, or cocaine and heroin in methadone-maintained patients.

Chronic cocaine and psychostimulant abuse may cause a number of adverse health consequences, ranging from pulmonary disease to reproductive dysfunction. Preexisting disorders such as hypertension and cardiac disease may be exacerbated by drug abuse, and the combined use of two or more drugs may accentuate medical complications associated with abuse of one of them. The adverse health consequences of drug abuse are further complicated by increased vulnerability to infections.

Drug abuse increases the risk of exposure to HIV. Cocaine and psychostimulant abuse contribute to the risk for HIV infection in part by suppression of immune function. In addition, concurrent use of cocaine and opiates (the "speedball") is frequently associated with needle-sharing by IV drug users. Intravenous drug abusers continue to represent the largest single group of persons with HIV infection in several major metropolitan areas in the United States as well as in urban areas in Scotland, Italy, Spain, Thailand, and China.

COCAINE

Cocaine is a stimulant and local anesthetic with potent vasoconstrictor properties. The leaves of the *coca* plant (*Erythroxylon coca*) contain ~0.5–1% cocaine. The drug produces physiologic and behavioral effects when administered PO, intranasally, IV, or via inhalation following pyrolysis (smoking). The reinforcing effects of cocaine appear to be related to activation of dopaminergic neurons in the mesolimbic system. Cocaine increases synaptic concentrations of the monamine neurotransmitters dopamine, norepinephrine, and serotonin by binding to transporter proteins in presynaptic neurons and blocking reuptake.

Prevalence of Cocaine Use

Cocaine is widely available throughout the United States, and cocaine abuse occurs in virtually all social and economic strata of society. The prevalence of cocaine abuse in the general population has been accompanied by an increase in cocaine abuse by heroin-dependent persons,

†Deceased.

including those in methadone maintenance programs. Intravenous cocaine is often used concurrently with IV heroin. This combination purportedly attenuates the postcocaine "crash" and substitutes a cocaine "high" for the heroin "high" blocked by methadone.

Acute and Chronic Intoxication

There has been an increase in both IV administration and inhalation of pyrolyzed cocaine via smoking. Following intranasal administration, changes in mood and sensation are perceived within 3–5 min, and peak effects occur at 10–20 min. The effects rarely last more than 1 h. Inhalation of pyrolyzed materials includes inhaling crack/cocaine or smoking coca paste, a product made by extracting cocaine preparations with flammable solvents, and cocaine free-base smoking. Free-base cocaine, including the free base prepared with sodium bicarbonate (crack), has become increasingly popular because of the relative high potency of the compound and its rapid onset of action (8–10 s following smoking).

Cocaine produces a brief, dose-related stimulation and enhancement of mood and an increase in cardiac rate and blood pressure. Body temperature usually increases following cocaine administration, and high doses of cocaine may induce lethal pyrexia or hypertension. Because cocaine inhibits reuptake of catecholamines at adrenergic nerve endings, the drug potentiates sympathetic nervous system activity. Cocaine has a short plasma half-life of approximately 45–60 min. Cocaine is metabolized by plasma esterases, and cocaine metabolites are excreted in urine. The very short duration of the euphorigenic effects of cocaine observed in chronic abusers is probably due to both acute and chronic tolerance. Frequent self-administration of the drug (two to three times per hour) is often reported by chronic cocaine abusers. Alcohol is used to modulate both the cocaine high and the dysphoria associated with the abrupt disappearance of cocaine's effects. A metabolite of cocaine, cocaethylene, has been detected in blood and urine of persons who concurrently abuse alcohol and cocaine. Cocaethylene induces changes in cardiovascular function similar to those of cocaine alone, and the pathophysiologic consequences of alcohol abuse plus cocaine abuse may be additive when both are used together.

The prevalent assumption that cocaine inhalation or IV administration is relatively safe is contradicted by reports of death from respiratory depression, cardiac arrhythmias, and convulsions associated with cocaine use. In addition to generalized seizures, neurologic complications may include headache, ischemic or hemorrhagic stroke, or subarachnoid hemorrhage. Disorders of cerebral blood flow and perfusion in cocaine-dependent persons have been detected with magnetic resonance spectroscopy (MRS) studies. Severe pulmonary disease may develop in individuals who inhale crack cocaine; this effect is attributed both to the direct effects of cocaine and to residual contaminants in the smoked material. Hepatic necrosis has been reported to occur following crack/cocaine use.

Although men and women who abuse cocaine may report that the drug enhances libidinal drive, chronic cocaine use causes significant loss of libido and adversely affects reproductive function. Impotence and gynecomastia have been observed in male cocaine abusers, and these abnormalities often persist for long periods following cessation of drug use. Women who abuse cocaine may experience major derangements in menstrual cycle function including galactorrhea, amenorrhea, and infertility. Chronic cocaine abuse may cause persistent hyperprolactinemia as a consequence of disordered dopaminergic inhibition of prolactin secretion by the anterior pituitary. Cocaine abuse by pregnant women, particularly the smoking of crack, has been associated with both an increased risk of congenital malformations in the fetus and perinatal cardiovascular and cerebrovascular disease in the mother. However, cocaine abuse per se is probably not the sole cause of these perinatal disorders, since many problems associated with maternal cocaine abuse, including poor nutrition and health care status as well as polydrug abuse, also contribute to the risk for perinatal disease.

Protracted cocaine abuse may cause paranoid ideation and visual and auditory hallucinations, a state that resembles alcoholic hallucinosis. Psychological dependence on cocaine, indicated by inability to abstain from frequent compulsive use, has also been reported. Although the occurrence of withdrawal syndromes involving psychomotor agitation and autonomic hyperactivity remains controversial, severe depression ("crashing") following cocaine intoxication may accompany drug withdrawal.

℞ Treatment: COCAINE OVERDOSE AND CHRONIC ABUSE

Treatment of cocaine overdose is a medical emergency that is usually best managed in an intensive care unit. Cocaine toxicity produces a hyperadrenergic state characterized by hypertension, tachycardia, tonic-clonic seizures, dyspnea, and ventricular arrhythmias. Intravenous diazepam in doses up to 0.5 mg/kg administered over an 8-h period has been shown to be effective for control of seizures. Ventricular arrhythmias have been managed successfully by administration of 0.5–1.0 mg of propranolol IV. Because many instances of cocaine-related mortality have been associated with concurrent use of other illicit drugs (particularly heroin), the physician must be prepared to institute effective emergency treatment for multiple drug toxicities.

Treatment of chronic cocaine abuse requires the combined efforts of primary care physicians, psychiatrists,

and psychosocial care providers. Early abstinence from cocaine use is often complicated by symptoms of depression and guilt, insomnia, and anorexia, which may be as severe as those observed in major affective disorders. Individual and group psychotherapy, family therapy, and peer group assistance programs are often useful for inducing prolonged remission from drug use. A number of medications used for the treatment of various medical and psychiatric disorders have been administered to reduce the duration and severity of cocaine abuse and dependence. However, no available medication is both safe and highly effective for either cocaine detoxification or maintenance of abstinence. Some psychotherapeutic interventions may be effective; however, no specific form of psychotherapy or behavioral modification is uniquely beneficial.

MARIJUANA AND CANNABIS COMPOUNDS

Cannabis sativa contains >400 compounds in addition to the psychoactive substance, delta-9-tetrahydrocannabinol (THC). Marijuana cigarettes are prepared from the leaves and flowering tops of the plant, and a typical marijuana cigarette contains 0.5–1 g of plant material. Although the usual THC concentration varies between 10 and 40 mg, concentrations >100 mg per cigarette have been detected. Hashish is prepared from concentrated resin of *C. sativa* and contains a THC concentration of between 8 and 12% percent by weight. "Hash oil," a lipid-soluble plant extract, may contain a THC concentration of 25–60% and may be added to marijuana or hashish to enhance its THC concentration. Smoking is the most common mode of marijuana or hashish use. During pyrolysis, >150 compounds in addition to THC are released in the smoke. Although most of these compounds do not have psychoactive properties, they do have potential physiologic effects.

THC is quickly absorbed from the lungs into blood and is then rapidly sequestered in tissues. It is metabolized primarily in the liver, where it is converted to 11-hydroxy-THC, a psychoactive compound, and >20 other metabolites. Many THC metabolites are excreted through the feces at a rate of clearance that is relatively slow in comparison to that of most other psychoactive drugs.

Specific cannabinoid receptors (CB_1 and CB_2) have been identified in the central nervous system, including the spinal cord, and in the peripheral nervous system. High densities of these receptors have been found in the cerebral cortex, basal ganglia, and hippocampus. T and B lymphocytes also have cannabinoid receptors, and these appear to mediate anti-inflammatory and immunoregulatory properties of cannabinoids. A naturally occurring THC-like ligand has been identified in the nervous system, where it is widely distributed.

Prevalence of Use

Marijuana is the most commonly used illegal drug in the United States. Use is particularly prevalent among adolescents; studies suggest that ~37% of high school students in the United States have used marijuana. Marijuana is relatively inexpensive and is often considered to be less hazardous than other controlled drugs and substances. Very potent forms of marijuana (sinsemilla) are now available in many communities, and concurrent use of marijuana with crack/cocaine and phencyclidine is increasing.

Acute and Chronic Intoxication

Acute intoxication from marijuana and cannabis compounds is related to both the dose of THC and the route of administration. THC is absorbed more rapidly from marijuana smoking than from orally ingested cannabis compounds. Acute marijuana intoxication usually consists of a subjective perception of relaxation and mild euphoria resembling mild to moderate alcohol intoxication. This condition is usually accompanied by some impairment in thinking, concentration, and perceptual and psychomotor function. Higher doses of cannabis may produce behavioral effects analogous to severe alcohol intoxication. Although the effects of acute marijuana intoxication are relatively benign in normal users, the drug can precipitate severe emotional disorders in individuals who have antecedent psychotic or neurotic problems. As with other psychoactive compounds, both set (user's expectations) and setting (environmental context) are important determinants of the type and severity of behavioral intoxication.

As with abuse of cocaine, opioids, and alcohol, chronic marijuana abusers may lose interest in common socially desirable goals and steadily devote more time to drug acquisition and use. However, THC does not cause a specific and unique "amotivational syndrome." The range of symptoms sometimes attributed to marijuana use is difficult to distinguish from mild to moderate depression and the maturational dysfunctions often associated with protracted adolescence. Chronic marijuana use has also been reported to increase the risk of psychotic symptoms in individuals with a past history of schizophrenia. Persons who initiate marijuana smoking before the age of 17 may subsequently develop severe cognitive and neuropsychological disorders, and they may also be at higher risk for polydrug and alcohol abuse problems in later life.

Physical Effects

Conjunctival injection and tachycardia are the most frequent immediate physical concomitants of smoking marijuana. Tolerance for marijuana-induced tachycardia develops rapidly among regular users. However, marijuana smoking may precipitate angina in persons with a history of coronary insufficiency. Exercise-induced angina may be increased after marijuana use to a greater extent than

after tobacco cigarette smoking. Patients with cardiac disease should be strongly advised not to smoke marijuana or use cannabis compounds.

Significant decrements in pulmonary vital capacity have been found in regular daily marijuana smokers. Because marijuana smoking typically involves deep inhalation and prolonged retention of marijuana smoke, marijuana smokers may develop chronic bronchial irritation. Impairment of single-breath carbon monoxide diffusion capacity (DL_{CO}) is greater in persons who smoke both marijuana and tobacco than in tobacco smokers.

Although marijuana has also been associated with a number of other adverse effects, many of these studies await replication and confirmation. A reported correlation between chronic marijuana use and decreased testosterone levels in males has not been confirmed. Decreased sperm count and sperm motility and morphologic abnormalities of spermatozoa following marijuana use have been reported. Prospective studies demonstrated a correlation between impaired fetal growth and development and heavy marijuana use during pregnancy. Marijuana has also been implicated in derangements of the immune system; in chromosomal abnormalities; and in inhibition of DNA, RNA, and protein synthesis; however, these findings have not been confirmed or related to any specific physiologic effect in humans.

Tolerance and Physical Dependence

Habitual marijuana users rapidly develop tolerance to the psychoactive effects of marijuana and often smoke more frequently and try to secure more potent cannabis compounds. Tolerance for the physiologic effects of marijuana develops at different rates; e.g., tolerance develops rapidly for marijuana-induced tachycardia but more slowly for marijuana-induced conjunctival injection. Tolerance for both behavioral and physiologic effects of marijuana decreases rapidly upon cessation of marijuana use.

Withdrawal signs and symptoms have been reported in chronic cannabis users, with the severity of symptoms related to dosage and duration of use. These include tremor, nystagmus, sweating, nausea, vomiting, diarrhea, irritability, anorexia, and sleep disturbances. Withdrawal signs and symptoms observed in chronic marijuana users are usually relatively mild in comparison to those observed in heavy opiate or alcohol users and rarely require medical or pharmacologic intervention. More severe and protracted abstinence syndromes may occur after sustained use of high-potency cannabis compounds.

Therapeutic Use of Marijuana

Marijuana, administered as cigarettes or as a synthetic oral cannabinoid (dronabinol), has been proposed to have a number of medicinal properties that may be clinically useful in some situations. These include antiemetic effects in chemotherapy recipients, appetite-promoting effects in AIDS patients, reduction of intraocular pressure in glaucoma, and reduction of spasticity in multiple sclerosis and other neurologic disorders. With the possible exception of AIDS-related cachexia, none of these attributes of marijuana compounds is clearly superior to other readily available therapies.

METHAMPHETAMINE

Methamphetamine is also referred to as "meth," "speed," "crank," "chalk," "ice," "glass," or "crystal." In the United States, hospital admissions for treatment of methamphetamine abuse increased substantially (from 3–8%) between 1994 and 2004. This increase occurred despite drug seizures, closures of clandestine laboratories that produce methamphetamine illegally, and an increase in methamphetamine abuse prevention programs.

Methamphetamine can be self-administered PO or by smoking, snorting, and IV injection. Individuals who abuse or become dependent upon methamphetamine report that use of this drug induces feelings of euphoria and decreases fatigue associated with difficult life situations. Adverse consequences of methamphetamine abuse include headache, difficulty concentrating, diminished appetite, abdominal pain, vomiting or diarrhea, disordered sleep, paranoid or aggressive behavior, and psychosis. Chronic methamphetamine abuse can result in severe dental caries, described as blackened, rotting, crumbling teeth. Severe, life-threatening methamphetamine toxicity may present as hypertension, cardiac arrhythmia or failure, subarachnoid hemorrhage, ischemic stroke, intracerebral hemorrhage, convulsions, or coma. Methamphetamines increase the release of monoamine neurotransmitters (dopamine, norepinephrine, and serotonin) from presynaptic neurons. It is thought that the euphoric and reinforcing effects of this class of drugs are mediated through dopamine and the mesolimbic system, whereas the cardiovascular effects are related to norepinephrine. MRS studies of the brain suggest that chronic abusers have neuronal damage in the frontal areas and basal ganglia.

Therapy of acute methamphetamine overdose is largely symptomatic. Ammonium chloride may be useful to acidify the urine and enhance clearance of the drug. Hypertension may respond to sodium nitroprusside or α-adrenergic antagonists. Sedatives may reduce agitation and other signs of central nervous system hyperactivity. Treatment of chronic methamphetamine dependence may be accomplished in either an inpatient or outpatient setting using strategies similar to those described earlier for cocaine abuse.

MDMA (3,4-methylenedioxymethamphetamine), or *Ecstasy*, is a derivative of methamphetamine. Ecstasy is usually taken PO but may be injected or inhaled; its effects last for 3–6 h. In addition to amphetamine-like effects,

MDMA can induce hyperthermia and vivid hallucinations and other perceptual distortions.

During the past decade, an eighteenfold increase in MDMA-related emergency department incidents has been reported in the United States. Recent studies have revealed that MDMA use is associated with cognitive and memory impairment and a mild withdrawal syndrome after cessation of use. The long-term consequences of recreational use of MDMA by young persons are poorly understood.

LYSERGIC ACID DIETHYLAMIDE (LSD)

The discovery of the psychedelic effects of LSD in 1947 led to an epidemic of LSD abuse during the 1960s. Imposition of stringent constraints on the manufacture and distribution of LSD (classified as a Schedule I substance by the U.S. Food and Drug Administration), as well as public recognition that psychedelic experiences induced by LSD were a health hazard, have resulted in a reduction in LSD abuse. LSD still remains popular among adolescents and young adults, and there are indications that LSD use among young persons has been increasing in some communities in the United States.

LSD is a very potent drug; oral doses as low as 20 μg may induce profound psychological and physiologic effects. Tachycardia, hypertension, pupillary dilation, tremor, and hyperpyrexia occur within minutes following oral administration of 0.5–2 μg/kg. A variety of bizarre and often conflicting perceptual and mood changes, including visual illusions, synesthesias, and extreme lability of mood, usually occur within 30 min after LSD intake. These effects of LSD may persist for 12–18 h, even though the half-life of the drug is only 3 h.

Tolerance develops rapidly for LSD-induced changes in psychological function when the drug is used one or more times per day for >4 days. Abrupt abstinence following continued use does not produce withdrawal signs or symptoms. There have been no clinical reports of death caused by the direct effects of LSD.

The most frequent acute medical emergency associated with LSD use is a panic episode (the "bad trip"), which may persist up to 24 h. Management of this problem is best accomplished by supportive reassurance ("talking down") and, if necessary, administration of small doses of anxiolytic drugs. Adverse consequences of chronic LSD use include enhanced risk for schizophreniform psychosis and derangements in memory function, problem solving, and abstract thinking. Treatment of these disorders is best carried out in specialized psychiatric facilities.

PHENCYCLIDINE

Phencyclidine (PCP), a cyclohexylamine derivative, is widely used in veterinary medicine to briefly immobilize large animals and is sometimes described as a dissociative anesthetic. PCP binds to ionotropic *N*-methyl-*D*-aspartate (NMDA) receptors in the nervous system, blocking ion current through these channels. PCP is easily synthesized; its abusers are primarily young people and polydrug users. It is used PO, by smoking, or by IV injection. It is also used as an adulterant in THC, LSD, amphetamine, or cocaine. The most common street preparation, *angel dust*, is a white granular powder that contains 50–100% of the drug. Low doses (5 mg) produce agitation, excitement, impaired motor coordination, dysarthria, and analgesia. Users may have horizontal or vertical nystagmus, flushing, diaphoresis, and hyperacusis. Behavioral changes include distortions of body image, disorganization of thinking, and feelings of estrangement. Higher doses of PCP (5–10 mg) may produce profuse salivation, vomiting, myoclonus, fever, stupor, or coma. PCP doses of ≥10 mg cause convulsions, opisthotonus, and decerebrate posturing, which may be followed by prolonged coma.

The diagnosis of PCP overdose is difficult because the patient's initial symptoms may suggest an acute schizophrenic reaction. Confirmation of PCP use is possible by determination of PCP levels in serum or urine. PCP assays are available at most toxicologic centers. PCP remains in urine for 1–5 days following high-dose intake.

PCP overdose requires life-support measures, including treatment of coma, convulsions, and respiratory depression in an intensive care unit. There is no specific antidote or antagonist for PCP. PCP excretion from the body can be enhanced by gastric lavage and acidification of urine. Death from PCP overdose may occur as a consequence of some combination of pharyngeal hypersecretion, hyperthermia, respiratory depression, severe hypertension, seizures, hypertensive encephalopathy, and intracerebral hemorrhage.

Acute psychosis associated with PCP use should be considered a psychiatric emergency since patients may be at high risk for suicide or extreme violence toward others. Phenothiazines should not be used for treatment because these drugs potentiate PCP's anticholinergic effects. Haloperidol (5 mg IM) has been administered on an hourly basis to induce suppression of psychotic behavior. PCP, like LSD and mescaline, produces vasospasm of cerebral arteries at relatively low doses. Chronic PCP use has been shown to induce insomnia, anorexia, severe social and behavioral changes, and, in some cases, chronic schizophrenia.

POLYDRUG ABUSE

Although drug abusers often report a preference for a particular drug, such as alcohol or opiates, the concurrent use of other drugs is common. Polydrug abuse often involves substances that may have different pharmacologic effects from the preferred drug. For example, concurrent use of such dissimilar compounds as stimulants and opiates or stimulants and alcohol is not unusual. The diversity of

reported drug use combinations suggests that achieving some perceptible change in state, rather than any particular direction of change (stimulation or sedation), may be the primary reinforcer in polydrug use and abuse. There is also evidence that intoxication with alcohol or opiates is associated with increased tobacco smoking. There is relatively little systematic information available about multiple drug abuse interactions. However, the combined use of cocaine, heroin, and alcohol increases the risk for toxic effects and adverse medical consequences over risks associated with use of a single drug. One determinant of polydrug use patterns is the relative availability and cost of the drugs. There are many examples of situationally determined drug use patterns. For example, alcohol abuse, with its attendant medical complications, is one of the most serious problems encountered in former heroin addicts participating in methadone maintenance programs.

The physician must recognize that perpetuation of polydrug abuse and drug dependence is not necessarily a symptom of an underlying emotional disorder. Neither alleviation of anxiety nor reduction of depression accounts for initiation and perpetuation of polydrug abuse. Severe depression and anxiety are as frequently the consequences of polydrug abuse as they are the antecedents. There is also evidence that some of the most adverse consequences of drug use may be reinforcing and contribute to the continuation of polydrug abuse.

Rx Treatment: POLYDRUG ABUSE

Adequate treatment of polydrug abuse, as well as other forms of drug abuse, requires innovative programs of intervention. The first step in successful treatment is detoxification, a process that may be difficult because of the abuse of several drugs with different pharmacologic actions (e.g., alcohol, opiates, and cocaine). Because patients may not recall or may deny simultaneous multiple drug use, diagnostic evaluation should always include urinalysis for qualitative detection of psychoactive substances and their metabolites. Treatment of polydrug abuse often requires hospitalization or inpatient residential care during detoxification and the initial phase of drug abstinence. When possible, specialized facilities for the care and treatment of chemically dependent persons should be used. Outpatient detoxification of polydrug abuse patients is likely to be ineffective and may be dangerous.

Drug abuse disorders often respond to effective treatment, but episodes of relapse may occur unpredictably. The physician should continue to assist patients during relapse and recognize that occasional recurrent drug use is not unusual in this complex behavioral disorder.

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REVIEW AND SELF-ASSESSMENT*

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QUESTIONS

DIRECTIONS: Choose the ***one best*** response for each question.

1. Delirium, an acute confusional state, is a common disorder that remains a major cause of morbidity and mortality in the United States. Which patient is at the highest risk for developing delirium?

   A. A 36-year-old man admitted to the medical ward with a deep venous thrombosis
   B. A 55-year-old man postoperative day 2 from a total colectomy
   C. A 68-year-old woman admitted to the intensive care unit (ICU) with esophageal rupture
   D. A 74-year-old woman in the preoperative clinic before hip surgery
   E. An 84-year-old man living in an assisted living facility

2. A 46-year-old man presents for evaluation of severe unilateral headache. He states that he has had episodes of intermittent headache for the past 3 years. He describes the headaches as a stabbing pain located near his right temple. They occur abruptly and last up to 3 h at a time, during which he feels incapacitated, rating the pain as a 10 out of 10. Most of the time, the headaches begin in the early morning hours. When they occur, he finds it impossible to sleep. He feels that rubbing his head improves the pain but has noticed no other factors that relieve the pain. Specifically, he has had no improvement with acetaminophen, naprosyn, or oxycodone. When the headaches occur, he develops nasal congestion and tearing on the side of the pain. He believes the headaches occur in cycles. He will have the headaches almost daily for up to 2 weeks at a time, but then have no headaches at all for as long as 3 months. He has decided to seek medical advice because he is worried about the possibility of a brain tumor because of the severity of the headaches. He takes no medicines regularly. His vital signs and physical examination are normal. What is the best approach to treatment of these headaches?

   A. Fluticasone nasal spray and loratadine, 10 mg orally
   B. Indomethacin, 25 mg three times daily
   C. Oxygen at 10–12 L/min by nasal cannula at the onset of an attack

2. (*Continued*)

   D. Sumatriptan, 50 mg orally, at the onset of an attack
   E. Surgical consultation for microvascular decompression of the trigeminal nerve

3. You are seeing your patient with polymyositis in follow-up. He has been taking prednisone at high doses for 2 months, and you initiated mycophenolate mofetil at the last clinic visit for a steroid-sparing effect. He began a steroid taper 2 weeks ago. His symptoms were predominantly in the lower extremities and face, and he has improved considerably. He no longer needs a cane and his voice has returned to normal. Laboratory data show a creatine kinase (CK) of 1300 U/L, which is unchanged from 2 months ago. What is the most appropriate next step in this patient's management?

   A. Continue current management
   B. Continue high-dose steroids with no taper
   C. Switch mycophenolate to methotrexate
   D. Repeat muscle biopsy

4. A patient complains of numbness in his neck. Over months, the numbness has become more pronounced and involves a dense area bilaterally from the sternal notch to the area behind the ear. On examination, scalp sensation, cranial nerve function, and upper extremity motor examination are normal. The patient has decreased pain and temperature sensation in the distribution of C4. Vibration sense is normal. Cranial and caudal to the affected area, sensation is intact. Bladder and anal sphincter function are also normal. What is the most likely cause of this patient's neurologic disorder?

   A. Amyotrophic lateral sclerosis
   B. Disc herniation
   C. Intramedullary tumor
   D. Knife or bullet injury
   E. Neurosyphilis

5. A 56-year-old man is admitted to the intensive care unit with a hypertensive crisis after cocaine use. Initial blood pressure is 245/132. On physical examination the patient is unresponsive except to painful stimuli. He has been intubated for airway protection

*Questions and answers were taken from Wiener C, et al (eds). *Harrison's Principles of Internal Medicine Self-Assessment and Board Review, 17th ed.* New York: McGraw-Hill, 2008.

5. (*Continued*)
and is being mechanically ventilated, with a respiratory rate of 14. His pupils are reactive to light, and there are normal corneal, cough, and gag reflexes. The patient has a dense left hemiparesis. When presented with painful stimuli, the patient responds with flexure posturing on the right side. Computed tomography (CT) reveals a large area of intracranial bleeding in the right frontoparietal area. Over the next several hours the patient deteriorates. The most recent examination reveals a blood pressure of 189/100. The patient now has a dilated pupil on the right side. The patient continues to have corneal reflexes. You suspect rising intracranial pressure related to the intracranial bleed. All but which of the following can be done to decrease the patient's intracranial pressure?

A. Administer intravenous mannitol at a dose of 1 g/kg body weight
B. Administer hypertonic fluids to achieve a goal sodium level of 155 to 160 meq/L
C. Consult neurosurgery for an urgent ventriculostomy.
D. Initiate intravenous nitroprusside to decrease the mean arterial pressure to a goal of 100 mmHg
E. Increase the respiratory rate to 30

6. For the last 5 weeks a 35-year-old woman has had episodes of intense vertigo that last several hours. Each episode is associated with tinnitus and a sense of fullness in the right ear; during the attacks she prefers to lie on the left side. Examination during an attack shows that she has fine rotary nystagmus that is maximal on gaze to the left. There are no ocular palsies, cranial nerve signs, or long-tract signs. An audiogram shows high-tone hearing loss in the right ear, with recruitment but no tone decay. The most likely diagnosis in this patient is

A. labyrinthitis
B. Ménière's disease
C. vertebral-basilar insufficiency
D. acoustic neuroma
E. multiple sclerosis

7. Lumbar puncture should be preceded by CT or MRI in all of the following subsets of patients suspected of having meningitis *except* those with:

A. depressed consciousness
B. focal neurologic abnormality
C. known central nervous system (CNS) mass lesion
D. positive Kernig's sign
E. recent head trauma

8. You are a physician practicing in a small community in the Rocky Mountains near Aspen, Colorado.

8. (*Continued*)
A 33-year-old woman comes to your office for evaluation of a bilateral tingling sensation in the fingertips. She describes the sensation as affecting all the fingers on both hands. She has no medical problems and takes no medications. She is a vegetarian and is visiting the area from San Diego, California. She denies any other symptoms, including headache, nausea, vomiting, shortness of breath, and urinary frequency. On physical examination the patient has a normal sensory examination, including reaction to light touch and pinprick and vibratory sensation. She is able to stand normally with the arms extended and the eyes closed. A cerebellar examination reveals normal finger-to-nose testing and no dysdiadochokinesis. Her gait is normal, including tandem gait, toe walking, and heel walking. What would you recommend as the next step?

A. Blood tests for serum vitamin B_{12}
B. Fasting blood glucose level
C. Reassurance
D. Serologic testing for syphilis
E. Treatment with acetazolamide for altitude sickness

9. You are doing rounds and see a patient admitted with weakness. He is a 46-year-old man who noticed the gradual onset of facial weakness and slurred speech 1 day prior to presentation. At the onset of his symptoms, he also complained of right arm weakness and double vision. He went to bed and woke up the next morning without any residual neurologic deficits. He came to the emergency department for evaluation. On examination of the patient on evening rounds, you note 3/5 weakness in the upper and lower extremities, with increasing weakness with exertion. He has intact phonation and mental status, but you also note a disconjugate gaze. He denies any pain. Sensation is intact. What is the most likely location of his neurologic disease?

A. Brainstem
B. Muscle
C. Neuromuscular junction
D. Peripheral nerve
E. Spinal root

10. A 34-year-old woman complains of lower extremity weakness for the last 3 days. She has noted progressive weakness in the lower extremities with loss of sensation "below the belly button" and incontinence. She had had some low-grade fevers for the last week. She denies recent travel. Past medical history is unremarkable. Physical examination is notable for a sensory level at the level of the umbilicus.

10. (*Continued*)
The lower extremities show +3/5 strength bilaterally, proximally, and distally. Reflexes, cerebellar examination, and mental status are normal. All the following are appropriate steps in evaluating this patient *except*

A. antinuclear antibodies
B. electromyography
C. lumbar puncture
D. MRI of the spine
E. viral serologies

11. Which clinical signs would you expect in a 53-year-old man with gait ataxia and these MRI findings (see **Fig. 11**)?

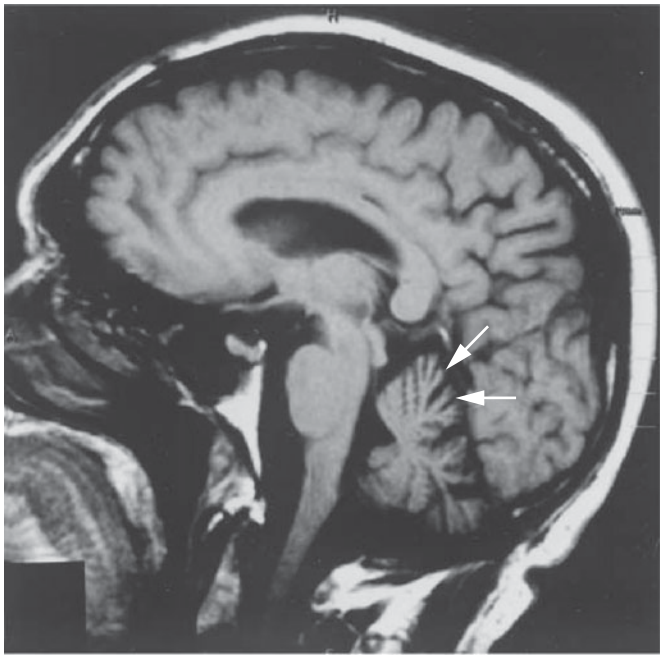

FIGURE 11

A. Gait instability, urinary incontinence, dementia
B. Hypertension, tachycardia, diaphoresis
C. Migraine headache, limb weakness, breathing difficulties
D. Scanning speech, oscillatory tremor of the head, nystagmus

12. A 17-year-old adolescent is seen in clinic several weeks after he suffered a concussion during a high-school football game. At the time of the event, paramedics reported that he experienced no loss of consciousness but was confused for a period of about 10 min. Head imaging was normal. He describes a generalized headache that is present all the time since his trauma, and he occasionally feels dizzy. His mother is concerned that he is having a hard time concentrating in school and seems depressed to her

12. (*Continued*)
lately; she describes him as very energetic prior to his concussion. The patient's physical examination is entirely normal except for a somewhat flattened affect. Which of the following statements regarding his condition is true?

A. He has an excellent prognosis.
B. He meets criteria for postconcussive syndrome and should improve over 1–2 months.
C. He should avoid contact sports for the next month.
D. He is most likely malingering.
E. Low-dose narcotics should be started for headache.

13. Variant Creutzfeldt-Jakob disease (vCJD) has been diagnosed in which of the following populations?

A. Family members with well-defined germ-line mutations leading to autosomal dominant inheritance of a fatal neurodegenerative disease
B. New Guinea natives practicing cannibalism
C. Patients accidentally inoculated with infected material during surgical procedures
D. Worldwide, in sporadic cases mostly during the fifth and sixth decades of life
E. Young adults in Europe thought to have been exposed to tainted beef products

14. A 44-year-old man with a history of hypertension and Paget's disease has had lower back pain for the past 3 months. The pain is worse with standing and improves with sitting. Walking does not necessarily exacerbate his symptoms. He has no leg or buttock pain. On examination, he has mild weakness on the right at the hip flexors, knee extenders, and knee flexors and more distally to the same degree. Reflexes are diminished in the right lower extremity. He has no sensory findings in the lower extremities or in the perineum. What is the most likely diagnosis?

A. Intervertebral disk herniation
B. Lumbar spinal stenosis
C. Metastatic malignancy
D. Occlusive aortoiliac atherosclerosis
E. Tethered cord syndrome

15. On the neurologic consultation service, you are asked to evaluate a patient with mesial temporal lobe epilepsy syndrome. The patient has a history of intractable complex partial seizures that rarely generalize. Her seizures often begin with an aura and commonly manifest as behavioral arrests, complex automatisms, and unilateral posturing. MRI findings include small temporal lobes and a small hippocampus with increased signal on T2-weighted sequences.

15. (*Continued*)
Which of these additional historic factors are also likely to be present in this patient?

A. History of febrile seizures
B. Hypothyroidism
C. Neurofibromas
D. Recurring genital ulcers
E. Type 2 diabetes mellitus

16. The patient in the preceding scenario was admitted with refractory seizures. You are asked to see the patient and offer treatment options. What treatment option will be the most efficacious in a patient with mesial temporal lobe epilepsy (MTLE) syndrome?

A. Acyclovir
B. Amygdalohippocampectomy
C. Levetiracetam
D. Primidone
E. Vagus nerve stimulation

17. The deep tendon reflex requires all of the following structures to be functional *except*

A. a motor neurons
B. γ motor neurons
C. pyramidal neurons
D. spindle afferent neurons

18. The most common presenting finding or symptom of multiple sclerosis is

A. internuclear ophthalmoplegia
B. transverse myelitis
C. cerebellar ataxia
D. optic neuritis
E. urinary retention

19. You are evaluating a patient with neck pain and you suspect cervical degenerative disk disease based on the history. Based on the most common findings with cervical disk disease, which finding do you expect when you examine this patient?

A. Biceps weakness
B. Decreased light touch sensation in the axilla and medial arm
C. Decreased pin-prick sensation over the lateral deltoid
D. Weak finger flexors

20. A 64-year-old woman is brought to the emergency department by her family with complaint of weakness. The patient reports difficulty walking and frequent falls. She also has blurry vision bilaterally. She denies light headedness or vertigo. These symptoms have been present for at least the past 9 months and

20. (*Continued*)
are getting progressively worse. She has great difficulty walking from the waiting room to the examination room but is not dizzy while doing so. On further questioning she denies numbness or tingling. On physical examination, her cranial nerves are intact, and strength examination shows 5 out of 5 strength in both upper and lower extremities. Reflexes are normal throughout. Light touch sensation is normal, and she is not orthostatic. You order a noncontrast head CT and it is read as normal. Which test is most likely to reveal the correct diagnosis?

A. Cerebrospinal fluid viral polymerase chain reaction
B. Lithium level
C. Rapid plasma reagent (RPR)
D. Serum alcohol level
E. Vitamin B_{12} deficiency

21. A 78-year-old woman with a long history of vascular disease presents after an embolic cerebrovascular accident (CVA) with severe and unrelenting pain on the right side. She describes the pain as burning as if she had been bathed in acid. Where is the most likely site of the recent embolic CVA?

A. Frontal lobe
B. Hypothalamus
C. Pons
D. Temporal lobe
E. Thalamus

22. A 34-year-old man presents with complaints of 1 week of dizziness, vertigo, tinnitus, and right-sided gait ataxia. Electronystagmography (calorics) with sequential administration of warm and cold water into the ear canal is performed. On the left, cold water causes right-beating nystagmus and warm water causes left-beating nystagmus. On the right ear, there is no response to the cold caloric. What is the cause of this patient's dizziness and vertigo?

A. Acoustic neuroma
B. Aminoglycoside antibiotics
C. Cerebellar ischemia
D. Otoconia (ear otoliths)

23. A 49-year-old man is admitted to the hospital with a seizure. He does not have a history of seizures and he currently takes no medications. He has AIDS and is not under any care at this time. His physical examination is most notable for small, shoddy lymphadenopathy in the cervical region. A head CT shows a ring-enhancing lesion in the right temporal lobe, with edema but no mass effect. A lumbar puncture

23. (*Continued*)
shows no white or red blood cells, and the Gram stain is negative. His serum *Toxoplasma* IgG is positive. Which of the following is the best course of action for this patient at this time?

A. Biopsy of the central nervous system (CNS) lesion
B. Dexamethasone
C. Search for systemic malignancy
D. Treatment for CNS toxoplasmosis
E. Whole-brain radiation therapy

24. The patient in the preceding scenario returns for reevaluation after 2 weeks of appropriate therapy. The CNS lesion has not changed in size, and he has not had any more seizures. All microbiologic cultures and viral studies, including Epstein-Barr virus DNA from the cerebrospinal fluid are negative. What is the best course of action for this patient at this time?

A. Continue treatment for CNS toxoplasmosis
B. Dexamethasone
C. Intravenous acyclovir
D. Stereotactic brain biopsy
E. Whole-brain radiation therapy

25. Which of the following statements about syringomyelia is true?

A. More than half the cases are associated with Chiari malformations.
B. Symptoms typically begin in middle age.
C. Vibration and position sensation are usually diminished.
D. Syrinx cavities are always congenital.
E. Neurosurgical decompression is usually effective in relieving the symptoms.

26. A 34-year-old woman presents with complaints of weakness and double vision for the last 3 weeks. She has also noted a change in her speech, and her friends tell her that she is "more nasal." She has noticed decreased exercise tolerance and difficulty lifting objects and getting out of a chair. The patient denies pain. The symptoms are worse at the end of the day and with repeated muscle use. You suspect myasthenia gravis. All the following are useful in the diagnosis of myasthenia gravis *except*

A. acetylcholine receptor (AChR) antibodies
B. edrophonium
C. electrodiagnostic testing
D. muscle-specific kinase (MuSK) antibodies
E. voltage-gated calcium channel antibodies

27. A 49-year-old woman presents for a second opinion regarding symptoms of tremors, difficulty with ambulation, and periodic flushing. Her symptoms originally began ~3 years ago. At that time, she was hospitalized for a syncopal episode, after which she was told to increase her salt intake. Since then, she has had progressive motor difficulties including bilateral tremors and a stiff slow gait. She also has had several more episodes of syncope. She states that she knows when these syncopal events will occur because she feels faint and weak. She has never had an injury from syncope. A final recent symptom has been periodic flushing and sweating. A neurologist previously diagnosed her with Parkinson's disease and prescribed therapy with ropinirole. Despite increasing doses, she does not feel improved, but rather has recently noticed uncontrollable movements that she describes at tics of her face. Her only other medical history is recent recurrent urinary tract infections. Her medications are ropinirole, 24 mg daily, and nitrofurantoin, 100 mg daily. She reports no history of drug use. On physical examination, her blood pressure is 130/70 mmHg with a heart rate of 78 beats/min while sitting. Upon standing, her blood pressure drops to 90/50 mmHg with a heart rate of 110 beats/min. Her ocular movements are full and intact. She has recurrent motor movements of the right side of her face. Her neurologic examination shows increased muscle tone in the lower extremities with bilateral 4-Hz tremor. Deep tendon reflexes are brisk and 3+ in upper and lower extremities. Three beats of myoclonus is present at the ankles bilaterally. She walks with a spastic gait. Strength is normal. What is the most likely diagnosis?

A. Corticobasal degeneration
B. Diffuse Lewy body dementia
C. Drug-induced Parkinson's disease
D. Multiple systems atrophy with parkinsonian features (Shy-Drager syndrome)
E. Parkinson's disease with inadequate treatment

28. A 68-year-old man is brought to clinic for evaluation by his wife. She has noticed that over past 2–3 months he has had increasingly slowed thinking and a change in his personality in that he has become very withdrawn. His only complaint is a mild, but persistent, diffuse headache. There is no history of head trauma, prior neurologic or psychiatric disease, or family history of dementia. Physical examination is only notable for a moderate cognitive deficit with a mini-mental examination of 19/30. His head

28. (*Continued*)
CT is shown in **Fig. 28**. What is the most likely diagnosis?

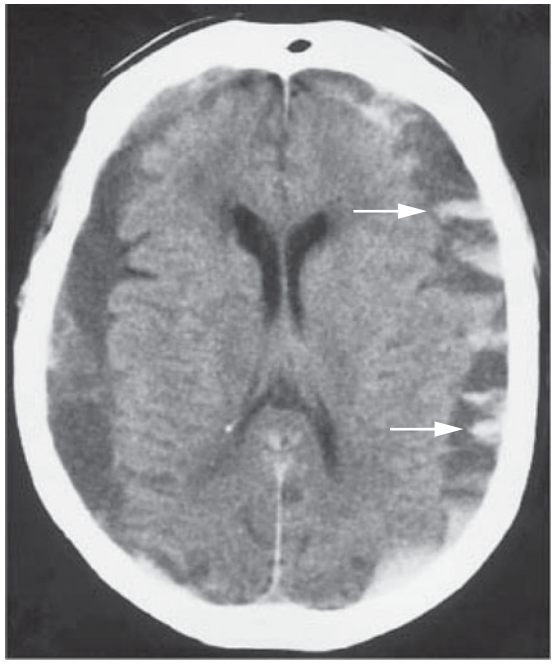

FIGURE 28

A. Acute epidural hematoma
B. Acute subarachnoid hemorrhage
C. Alzheimer's disease
D. Chronic subdural hematoma
E. Normal-pressure hydrocephalus

29. You are evaluating a patient who has complaint of vertigo. The patient complains of seeing the room spin and feeling faint with certain head movements to the left. In your office, you perform provocative maneuvers to differentiate the cause of this patient's vertigo. He has been diagnosed with benign paroxysmal positional vertigo (BPPV), but symptoms have remained for many months. Which of the following findings would be suggestive of a central positional vertigo?

A. Disappearance of the symptoms with maintenance of the offending position
B. Immediate vertigo and nystagmus with head turning to the affected side
C. Lessening of symptoms with repeated trials
D. Increased severity of symptoms with provocative testing

30. A 65-year-old man presents to your office with complaints of a tremor and progressive gait abnormalities. He states that he first noticed a slowing of his gait ~6 months ago. He has difficulty rising to a standing position and states that he shuffles when he walks. In addition, he states that his right hand shakes more so than his left, and he is right-handed. He believes it to be worse when not moving but states there are times when he spills his morning coffee because of the tremors. He has retired but states he is not able to play tennis and golf any longer because of his motor symptoms. He denies syncope or presyncope, difficulty swallowing, changes to his voice, or memory difficulties. His past medical history is significant for hypertension and hypercholesterolemia. His medications are hydrochlorothiazide, 25 mg daily, ezetimibe, 10 mg daily, and lovastatin, 40 mg daily. He drinks a glass of wine with dinner daily and is a lifelong nonsmoker. On physical examination, he has masked facies. His gait shows decreased arm swing with slow shuffling steps. He turns en bloc. A pill-rolling tremor is present on the right side. There is cogwheel rigidity bilaterally. Eye movements are full and intact. There is no orthostatic hypotension. A brain MRI with gadolinium shows no evidence of mass lesions, hydrocephalus, or vascular disease. You diagnose the patient with Parkinson's disease. The patient asks about his prognosis and likelihood of disability. Which of the following is correct about the clinical course and treatment of Parkinson's disease?

A. Early initiation of therapy with levodopa will not affect the risk of a higher likelihood of dyskinesias early in the disease.
B. Early therapy with bilateral deep-brain stimulation of the subthalamic nuclei slows progression of Parkinson's disease.
C. Initial treatment with a dopamine agonist such as pramipexole is likely to be effective in controlling his motor symptoms for 1–3 years before the addition of levodopa or another agent is necessary.
D. Levodopa should be started immediately to prevent development of disabling rigidity.
E. Monotherapy with selegiline, a monoamine oxydase (MAO) inhibitor, causes a marked improvement in tremors in most individuals with Parkinson's disease.

31. A 74-year-old woman comes to clinic with a complaint of muscle weakness. She has bilateral deltoid weakness, which has been present for 4 months. She has myalgias as well throughout the day. Her symptoms are exacerbated by activity and when she initially lays down to sleep. Neurologic examination shows intact cranial nerves II through XII, except for poor vision due to cataracts. She has hyperesthesia in her arms in the area of her deltoids, but otherwise sensation is normal. Deep tendon reflexes are normal. Strength examination shows weakness initially, but it improves with encouragement. Creatine

31. (*Continued*)
kinase, erythrocyte sedimentation rate, and C-reactive protein are within normal limits. An MRI of the deltoid muscles shows joint degeneration and a partial rotator cuff tear on the left. You are considering a muscle biopsy. What is the biopsy most likely to show?

A. Endomysial deposits of amyloid
B. Necrotic muscle
C. Normal muscle
D. Scattered inflammatory foci surrounding muscle fibers

32. Which of the following criteria suggests the diagnosis of trigeminal neuralgia?

A. Deep-seated steady facial pain
B. Elevated erythrocyte sedimentation rate (ESR)
C. Known metastatic brain tumor
D. Objective signs of sensory loss on physical examination
E. None of the above

33. CT scanning is superior to MRI of the back in which setting?

A. Delineation of the extent of a syrinx
B. Evaluation of old lumbar-spine fracture
C. Evaluation of paraspinal mass
D. Imaging of the lateral recesses of the spinal canal

34. All the following cause primarily a sensory neuropathy *except*

A. acromegaly
B. critical illness
C. HIV infection
D. hypothyroidism
E. vitamin B_{12} deficiency

35. A 45-year-old woman presents for evaluation of a tingling sensation in her feet that has become more apparent over the past 5 months. She states that it currently is causing a painful sensation and is interfering with her sleep at night. On physical examination, you identify decreased sensation to pinprick and light touch in her feet extending to her mid-calf area. All of the following laboratory tests may be useful in determining the cause of her peripheral neuropathy *except*

A. blood lead level
B. fasting blood glucose
C. hemoglobin A1C
D. rapid plasma reagin for syphilis
E. red blood cell folate levels

36. A young man with a history of a low-grade astrocytoma comes into your office with complaints of weight gain and low energy. He is status post resection of his low-grade astrocytoma and had a course of whole-brain radiation therapy (WBRT) 1 year ago. A laboratory workup reveals a decreased morning cortisol level of 1.9 μg/dL. In addition to depressed adrenocorticotropic hormone (ACTH) function, which of the following hormones is most sensitive to damage from whole-brain radiation therapy?

A. Growth hormone
B. Follicle stimulating hormone
C. Prolactin
D. Thyroid stimulating hormone

37. A 29-year-old man being treated for lung cancer comes into your office for an acute visit. He has had backache for a few weeks that has improved with ibuprofen but has developed right lower abdominal pain and inguinal pain. On physical examination, he has tenderness over the lower thoracic spinous processes and hyperesthesia in the T11 distribution on the right. Strength is normal in the upper extremities, but he has symmetric weakness in the lower extremities with hyperreflexia. He also has decreased sensation below the T11 distribution symmetrically. What is the next step in the management of this patient?

A. Add gabapentin to his pain regimen
B. Order a paraneoplastic antibody panel
C. Start treatment with glucocorticoids
D. Order thoracic and lumbar radiographs

38. A 50-year-old man presents with complaint of weakness. His symptoms began as difficulty with buttoning his shirt and using keys to open doors about 2 years ago. He was treated empirically with nonsteroidal anti-inflammatory medications for arthritis, but responded only minimally. His symptoms have slowly progressed to the point where he has weakness in both hands and feet. He avoids going outside because of frequent falls. On examination, he has weakness and atrophy of the foot extensor and finger flexors. Proximal muscle strength is normal. Reflexes are normal, and sensation is intact. He is able to rise out of a chair, but the Romberg test is not able to be performed due to weakness once standing. Cranial nerves are intact. Serum creatine kinase is 600 units/L. Complete blood count, differential, electrolytes, and thyroid-stimulating hormone (TSH) are normal. Based on the clinical presentation, what is the most likely diagnosis?

A. Dermatomyositis
B. Eosinophilic myofasciitis

38. (*Continued*)

C. Inclusion body myositis
D. Polymyositis
E. Hyperthyroidism

39. You are conducting research on a cellular model of myasthenia gravis in which you measure features of the acetylcholine (ACh) neuromuscular junction and its microenvironment. In a patient with untreated myasthenia gravis, which of the following do you expect to find at the neuromuscular junction after release of ACh from the presynaptic neuron?

A. Decreased levels of ACh-esterase
B. Decreased numbers of available ACh receptors
C. Decreased release of ACh from the presynaptic neuron
D. High numbers of mitochondria in the postsynaptic neuron

40. You have just admitted a young man with a prior history of seizure disorder who was witnessed to have a seizure. His family's description suggests a simple partial seizure involving the left hand that spread to involve the entire arm. He did not lose consciousness. He was brought in 2 h after symptom onset and is currently awake, alert, and oriented. He has not had any further seizures but has been unable to move his left hand since his seizure. His electrolytes and complete blood count are within normal limits. A noncontrast CT scan of his head is unremarkable. On examination, sensation is intact in the affected limb but his strength is 0 out of 5 in the musculature of the left hand. What is the best course of action at this time?

A. Cerebral angiogram
B. Lumbar puncture
C. Magnetic resonance angiogram
D. Psychiatric evaluation
E. Reassess in a few hours

41. A 78-year-old man with diabetes mellitus presents with fever, headache and altered sensorium. On physical exam his temperature is 40.2°C, heart rate is 103 beats/min, blood pressure is 84/52 mmHg. His neck is stiff and he has photophobia. His cerebrospinal fluid (CSF) examination shows 2100 cells/μL, with 100% neutrophils, glucose 10 mg/dL, and protein 78 mg/dL. CSF gram stain is negative. Empirical therapy should include which of the following?

A. Amphotericin
B. Dexamethasone after antibiotics
C. Dexamethasone prior to antibiotics
D. Doxycycline
E. Piperacillin/tazobactam

42. A 24-year-old woman seeks evaluation for headaches. She first began having recurrent headaches her senior year of high school. The headaches increased in frequency during college, and she has always attributed her headaches to tension. The headaches would be more prominent during times of sleep loss, stress, and in the perimenstrual period. She states that she expected her headaches to improve now that she has finished college and has a more regular schedule. She works as a financial counselor for a university in the human resources department and denies a large degree of stress in her job. She has had this job for 2 years, but the headaches continue to disrupt her life. She states the headaches occur about seven times monthly. She estimates that the headaches occur >90% of the time on the right side and have a throbbing nature. She has no aura before the onset of a headache but describes occasional visual disturbance and photophobia during the headache. She also states that she frequently develops sensitivity of her scalp on the side of the headache with associated paresthesias. She rates the pain as about 7 to 8 out of 10 for a usual headache. On two occasions over the past 6 months, she has developed severe vertigo that resolved over the course of several hours in association with a mild headache. She has never had to miss work because of headache, but feels like her productivity is limited when she feels unwell. Other triggers for her headaches include red wine and aged cheese, which she has restricted from her diet for this reason. Ibuprofen, acetaminophen, and naprosyn sodium have no effect on the duration of her headaches. She is otherwise healthy and denies associated rhinorrhea or lacrimation. Her only medication is oral contraceptive pills. Her family history is significant for a maternal aunt with classic migraine headaches with aura. The physical examination is normal without any evidence of neurologic deficits and normal blood pressure. What is the most appropriate next step in evaluation and management of this patient?

A. Ask the subject to keep a headache diary for the next 2 months to assess the frequency and severity of headaches and assess for specific triggers.
B. Encourage the patient to keep a regular routine including consistent sleep-wake cycle and regular exercise such as yoga.
C. Initiate therapy with rizatriptan, 10 mg orally, at onset of attacks.
D. Perform an MRI of the brain.
E. A, B, and C
F. All of the above

43. Which of the following cranial nerve physical examination techniques represents the correct approach to the patient with suspected neurologic disease?

43. (*Continued*)
    A. Olfactory nerve: With eyes closed, ask the patient to sniff a pungent stimulus such as ammonia or alcohol.
    B. Optic nerve: Check visual acuity in both eyes using a Snellen chart without having the patient use their corrective lenses.
    C. Trigeminal nerve: Examine the motor territories on each side of the face by testing jaw clench, eyebrow elevation and forehead wrinkling.
    D. Accessory nerve: Check shoulder shrug and head rotation on each side against resistance.

44. You are going on morning rounds to see a 38-year-old woman who presented the prior day with weakness and double vision. It is reported that on examination at that time she had pronounced weakness in cranial nerves VII and XII. She also had weakness in the extraocular muscles, which is described to you as "googly eyes" with repeat examinations. The patient reports that she has profound double vision almost exclusively when she watches television in the evening. On your examination, you find no neurologic abnormalities. A head CT is unremarkable. The patient denies any other past medical history and has a mini-mental status examination score of 30/30. What is the next appropriate step in the management of this patient?

    A. Formal psychiatric evaluation
    B. MRI of the brain
    C. Serum anti-acetylcholine receptor antibodies
    D. Serum lead level
    E. Slit-lamp examination

45. A 37-year-old man is witnessed by his family to have a generalized tonic-clonic seizure at a party. He does not have a known seizure disorder. There is no history of head trauma, stroke, or tumor. The patient is unemployed, married, and takes no medication. Physical examination shows no skin abnormalities and no stigmata of chronic liver or renal disease. The patient is postictal. His neck is difficult to maneuver due to stiffness. His white blood cell count is 19,000/μL, hematocrit 36%, and platelets 200,000/μL. Glucose is 102 mg/dL, sodium 136 meq/ dL, calcium 9.5 mg/dL, magnesium 2.2 mg/dL, SGOT 18 U/L, blood-urea nitrogen 7 mg/dL, and creatinine 0.8 mg/dL. Urine toxicology screen is positive for cocaine metabolites. A head CT was negative. Which next step is most appropriate in this patient's management?

    A. Electroencephalogram (EEG)
    B. Intravenous loading with antiepileptic medication
    C. Lumbar puncture
    D. Magnetic resonance imaging
    E. Substance abuse counseling

46. All of the following myopathies would be inherited from the female parent *except*

    A. Becker muscular dystrophy
    B. Duchenne muscular dystrophy
    C. Kearns-Sayre syndrome
    D. limb-girdle muscular dystrophy
    E. myoclonic epilepsy with ragged red fibers (MERFF)

47. A patient is brought to the emergency room after a head-on motor vehicle collision. The patient is unresponsive even to painful stimuli and is apneic; however, he does have a pulse. Which of the following clinical findings would exclude a diagnosis of brain death?

    A. Bilateral positive Babinski signs
    B. Constricted pupils
    C. Invariant pulse rate
    D. Positive deep tendon reflexes
    E. Presence of diabetes insipidus

48. A 45-year-old man presents with a daily headache. He describes two attacks per day over the last 3 weeks. Each attack lasts about 1 h and awakens the patient from sleep. The patient has noted associated tearing and reddening of the right eye as well as nasal stuffiness. The pain is deep, excruciating, and limited to the right side of the head. The neurologic examination is nonfocal. The most likely diagnosis of this patient's headache is

    A. migraine headache
    B. cluster headache
    C. tension headache
    D. brain tumor
    E. giant cell arteritis

49. A 72-year-old woman presents with recurrent episodes of incapacitating facial pain lasting from second to minutes and then dissipating. The episodes occur usually twice per day, usually without warning, but are also occasionally provoked by brushing of her teeth. On physical examination, she appears well with normal vital signs. Detailed cranial nerve examination reveals no sensory or motor abnormalities. The remainder of her neurologic examination is normal. What is the next step in her management?

    A. Brain MRI
    B. Brain MRI plus carbamazepine therapy
    C. Carbamazepine therapy
    D. Glucocorticoid therapy
    E. Referral to Otolaryngology for surgical cure

50. A 26-year-old man presents to the emergency room with complaints of weakness and difficulty breathing.

50. (*Continued*)
He first noticed a feeling of weakness in his legs with difficulty climbing the stairs to his third-floor apartment 5 days ago. Over the ensuing days, his weakness has progressed such that he feels like he is tripping when he walks on flat surfaces and was unable to climb to his apartment yesterday. In addition, he now states that he is having difficulty lifting his arms above his head to comb his hair and twice dropped a bottle of soda on the floor due to a feeling of weakness in his arms. He also states that he feels short of breath, especially if lying flat. He complains of a tingling in his hands and feet. His past medical history is notable for sickle cell trait. Three weeks ago, he was treated for dehydration in the emergency department for food poisoning with diarrhea, abdominal pain, and low-grade fevers. This resolved within 2 days, and he had been feeling in his usual state of health prior to the onset of the current symptoms. He is on no medication and has no history of illicit drug use. He has no recent travel and has not eaten shellfish, honey, or home-canned foods. On physical examination, he appears breathless, has difficulty completing sentences, and is using accessory muscles of respiration. His vital signs show a respiratory rate of 32 breaths/min, a heart rate of 95 beats/min, a blood pressure of 112/76 mmHg, and a temperature of 37.6°C. His weight is 80 kg. His ocular movements are full. There is no papillary dilatation. On pulmonary examination, his breath sounds are clear. There is paradoxical motion of the abdomen with inspiration. Neurologic examination shows 3/5 strength symmetrically in the upper and lower extremities with absent deep tendon reflexes. Cardiovascular, gastrointestinal, and skin examinations are normal. Arterial blood gases show a pH of 7.55, a Pa_{CO_2} of 28 mmHg, and a Pa_{O_2} of 84 mmHg while breathing room air. His vital capacity is 800 mL. What is the most appropriate treatment for this individual?

A. Botulinum antitoxin
B. Intravenous immunoglobulin (IVIg)
C. IVIg and mechanical ventilation
D. IVIg, mechanical ventilation, and ciprofloxacin
E. Plasmapheresis and glucocorticoids

51. The most common cause of a cerebral embolism is

A. cardiac prosthetic valves
B. rheumatic heart disease
C. dilated cardiomyopathy
D. endocarditis
E. atrial fibrillation

52. When evaluating a patient for low back pain, which statement is true regarding the utility of the straight leg raise test?

52. (*Continued*)
A. Passive dorsiflexion of the foot during the maneuver will elicit pain from the contralateral nerve root.
B. The crossed straight leg raise is more specific for disk herniation than the straight leg raise.
C. The reverse straight leg raise is indicative of back pain referred from visceral organs.
D. The straight leg raise test is positive if there is restricted range of motion of the affected limb.

53. A 37-year-old woman presents with complaints of headache and blurry vision that have been present for a year and are slowly getting worse. As part of her evaluation an MRI is obtained and shown in **Fig. 53** below:

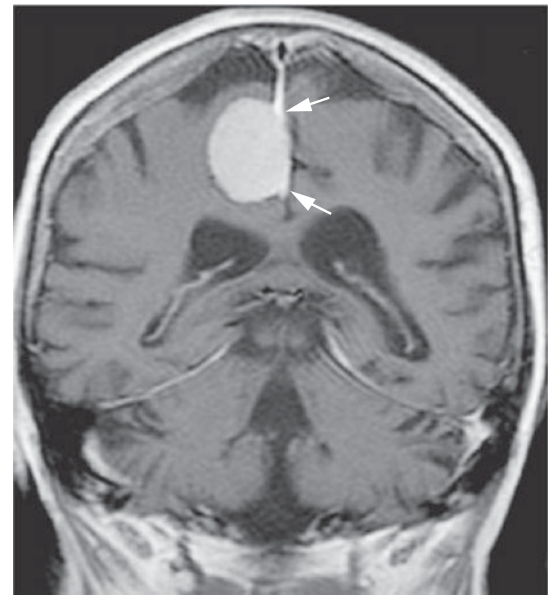

FIGURE 53

What is the most likely diagnosis in this patient?

A. Brain abscess
B. Glioblastoma
C. Low-grade astrocytoma
D. Meningioma
E. Oligodendroglioma

54. All but which of the following statements regarding epilepsy are true?

A. The incidence of suicide is higher in epileptic patients than it is in the general population.
B. Mortality is no different in patients with epilepsy than it is in age-matched controls.
C. A majority of patients with epilepsy that is completely controlled with medication eventually will be able to discontinue therapy and remain seizure free.
D. Surgery for mesial temporal lobe epilepsy (MTLE) decreases the number of seizures in over 70% of patients.
E. Tricyclic antidepressants lower the seizure threshold and may precipitate seizures.

55. A 54-year-old man is referred to your clinic for evaluation of atrial fibrillation. He first noted the irregular heartbeat 2 weeks ago and presented to his primary care physician. He denies chest pain, shortness of breath, nausea, or gastrointestinal symptoms. Past medical history is unremarkable. There is no history of hypertension, diabetes, or tobacco use. His medications include metoprolol. The examination is notable for a blood pressure of 126/74 mmHg and a pulse of 64 beats/min. The jugular venous pressure is not elevated. His heart is irregularly irregular, with normal S_1 and S_2. The lungs are clear, and there is no peripheral edema. An echocardiogram shows a left atrial size of 3.6 cm. Left ventricular ejection fraction is 60%. There are no valvular or structural abnormalities. Which of the following statements regarding his atrial fibrillation and stroke risk is true?

A. He requires no antiplatelet therapy or anticoagulation because the risk of embolism is low.
B. Lifetime warfarin therapy is indicated for atrial fibrillation in this situation to reduce the risk of stroke.
C. He should be admitted to the hospital for intravenous heparin and undergo electrical cardioversion; afterward there is no need for anticoagulation.
D. His risk of an embolic stroke is less than 1%, and he should take a daily aspirin.
E. He should be started on subcutaneous low-molecular-weight heparin and transitioned to warfarin.

56. A 34-year-old woman seeks evaluation for weakness. She has noted tripping when walking, particularly in her left foot, for the past 2 years. She recently also began to drop things, once allowing a full cup of coffee to spill onto her legs. In this setting, she also feels as if the appearance of her face has changed over the course of many years, stating that she feels as if her face is becoming more hollow and elongated although she hasn't lost any weight recently. She has not seen a physician in many years and has no past medical history. Her only medications are a multivitamin and calcium with vitamin D. Her family history is significant for similar symptoms of weakness in her brother who is 2 years older. Her mother, who is 58 years old, was diagnosed with mild weakness after her brother was evaluated, but is not symptomatic. On physical examination, the patient's face appears long and narrow with wasting of the temporalis and masseter muscles. Her speech is mildly dysarthric, and the palate is high and arched. Strength is 4/5 in the intrinsic muscles of the hand, wrist extensors, and ankle dorsiflexors. After testing handgrip strength, you notice that there is a delayed relaxation of the muscles of the hand. What is the most likely diagnosis?

56. (*Continued*)
A. Acid maltase deficiency (Pompe's disease)
B. Becker muscular dystrophy
C. Duchenne muscular dystrophy
D. Myotonic dystrophy
E. Nemaline myopathy

57. A 20-year-old woman is brought to the emergency department after a witnessed generalized tonic-clonic seizure. She has no identifying information, and her past medical history is unknown. What is the most likely cause of her seizure?

A. Amyloid angiopathy
B. Fever
C. Genetic disorder
D. Illicit drug use
E. Uremia

58. The presence of startle myoclonus in a 60-year-old man with rapidly progressive deficits in cortical dysfunction is which one of the following?

A. Neither sensitive nor specific for Creutzfeldt-Jacob disease (CJD) but does represent grounds to explore further for this condition with an electroencephalogram (EEG)
B. Neither sensitive nor specific for CJD but does represent grounds to explore further for this condition with an EEG and brain MRI
C. Sensitive but not specific for CJD and is not enough to prompt a further workup for this condition unless other clinical criteria are met
D. Specific but not sensitive for CJD and should therefore prompt immediate referral for brain biopsy to confirm the diagnosis
E. Virtually diagnostic for CJD, and further workup including EEG, brain MRI, and perhaps brain biopsy serves only a prognostic purpose

59. Which nerve functions are spared in a patient with ventral cord syndrome due to an anterior spinal cord infarct?

A. Bladder sphincter control
B. Motor strength
C. Pain sensation
D. Proprioception
E. Tendon reflexes

60. A 33-year-old woman presents with complaint of a rash on her chest. She has had a nonpruritic red rash on the upper chest for 4 weeks associated with a raised erythematous rash on her hands. She does not wear V-neck shirts, but the chest rash is in a V-neck distribution. Her hands have a scaly reddish-purple eruption, and her finger pads have become thicker

60. (*Continued*)
and rougher (see **Fig. 60**). She also has a slight red hue on the upper eyelids.

What other findings are likely to be present in this patient?

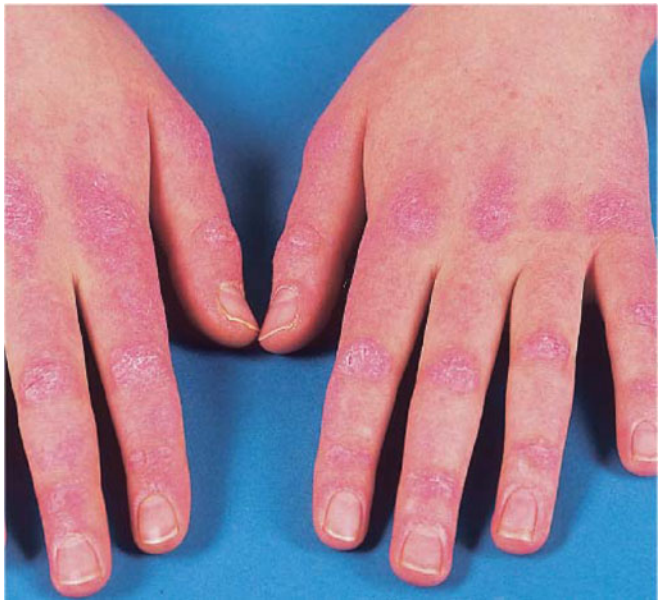

FIGURE 60

A. Delayed relaxation phase of deep tendon reflexes
B. Hepatosplenomegaly
C. Muscle weakness
D. Situs inversus
E. Subcutaneous nodules on the back of the forearm

61. A 65-year-old man presents with severe right-sided eye and facial pain, nausea, vomiting, colored halos around lights, and loss of visual acuity. His right eye is quite red, and that pupil is dilated and fixed. Which of the following diagnostic tests would confirm the diagnosis?

A. CT of the head
B. MRI of the head
C. Cerebral angiography
D. Tonometry
E. Slit-lamp examination

62. A 21-year-old man presents to your clinic with complaint of progressive weakness in the feet for the last 2 years. He describes slowly progressive difficulty in lifting his feet off the ground when walking. The legs have "gotten smaller" in bulk. Past medical history is unremarkable. The family history is significant for his father, brother, and paternal grandmother all having similar "weaknesses." The examination is

62. (*Continued*)
notable for distal atrophy below the midcalves and for prominent high arches. There is obvious footdrop, and dorsiflexion of the foot is severely diminished bilaterally. You suspect a form of Charcot-Marie-Tooth disease and order nerve conduction studies. Which of the following statements about CMT disease is true?

A. CMT disease is usually a motor neuropathy; sensory features are rare and should prompt an alternative diagnosis.
B. Immunotherapy with intravenous immune globulin and/or plasmapheresis may slow the progression of CMT disease.
C. CMT disease affects approximately 1 in 100,000 individuals.
D. Transmission is most commonly autosomal dominant but may be autosomal recessive or X-linked.
E. The age of this patient at presentation is atypical; patients usually present in the fourth and fifth decades of life.

63. Which of the following groups of patients should receive empirical antibiotic therapy that includes coverage of *Listeria monocytogenes* in cases of presumed meningitis?

A. Immunocompromised patients
B. Elderly patients
C. Infants
D. All of the above

64. Which of the following neurologic phenomena is classically associated with herniation of the brain through the foramen magnum?

A. Third-nerve compression and ipsilateral papillary dilation
B. Catatonia
C. "Locked-in" state
D. Miotic pupils
E. Respiratory arrest

65. A 72-year-old woman presents with brief, intermittent excruciating episodes of lancinating pain in the lips, gums, and cheek. These intense spasms of pain may be initiated by touching the lips or moving the tongue. The results of a physical examination are normal. MRI of the head is also normal. The most likely cause of this patient's pain is

A. acoustic neuroma
B. meningioma
C. temporal lobe epilepsy
D. trigeminal neuralgia
E. facial nerve palsy

66. A 38-year-old woman patient with facial and ocular weakness has just been diagnosed with myasthenia gravis. You intend to initiate therapy with anticholinesterase medications and glucocorticoids. All of the following tests are necessary before instituting this therapy *except*

A. CT or MRI of the chest
B. purified protein derivative skin test
C. lumbar puncture
D. pulmonary function tests
E. thyroid-stimulating hormone

67. A 76-year-old nursing home resident is brought to the local emergency department after falling out of bed. The fall was not witnessed; however, she was suspected to have hit her head. She is not responsive to verbal or light tactile stimuli. At baseline she is able to converse but is frequently disoriented to place and time. She has a medical history that includes stable coronary disease, mild emphysema, and multi-infarct dementia. Immediately after triage she is taken for a CT scan of the head. Which of the following is true regarding head injury and hematomas?

A. More than 80% of patients with subdural hematomas will experience a lucid interval prior to loss of consciousness.
B. Epidural hematomas generally arise from venous sources.
C. Epidural hematomas are common among the elderly with minor head trauma.
D. Most patients presenting with epidural hematomas are unconscious.
E. Subdural hematomas lead to rapid increases in intracranial pressure and can require arterial ligation.

68. A 45-year-old man presents with complaint of severe right arm pain. He gives a history of having slipped on the ice and severely contusing his right shoulder approximately 1 month ago. At this time he has sharp knifelike pain in the right arm and forearm. Physical examination reveals a right arm that is more moist and hairy than the left arm. There is no specific weakness or sensory change. However, the right arm is clearly more edematous than the left, and the skin appears somewhat atrophic in the affected limb. The patient's pain most likely is due to

A. subclavian vein thrombosis
B. brachial plexus injury
C. reflex sympathetic dystrophy
D. acromioclavicular separation
E. cervical radiculopathy

69. Which of the following statements regarding the long-term outcomes in individuals with severe migraines is true?

69. (*Continued*)

A. Factors such as cigarette smoking and hypertension have no modifying risk on the development of ischemic stroke in individuals who have migraine with aura.
B. In both women and men, migraine with aura is associated with an increased risk of ischemic stroke.
C. Migraines generally persist unchanged in severity throughout life.
D. Migraine with or without aura is associated with an increased risk of subclinical posterior circulation infarction on MRI.
E. Women on oral contraceptives who have migraines without aura should discontinue these medications because of a marked increased risk of ischemic stroke.

70. A 40-year-old man has recurrent bouts of tinnitus. Except for a fairly severe upper respiratory tract infection 1 year ago, he has been healthy for all of his life. In the last year he has had two self-limited episodes of tinnitus associated with dizziness and a decrement in his hearing. His symptoms are always unilateral on the same side and have required him to take off from work for a few days each time. He comes into your office at the outset of his third bout of tinnitus. He has taken meclizine at home with no relief. In your office, he has tinnitus and vertigo while seated, which is exacerbated with ambulation. His symptoms of dizziness are not reproduced with Dix-Hallpike maneuvers. Which is the best long-term treatment option for the patient at this time?

A. Diuretic
B. Glucocorticoid
C. Epley procedure
D. Metoclopramide
E. Scopolamine transdermal

71. While you are working in the urgent care center, a babysitter brings in a 7-year-old boy who complains of visual changes. He complains of difficulty with blue-yellow color discrimination. He has no other past medical history. On examination, visual acuity in the right eye is 20/60 and in the left eye 20/80. He has blue-yellow color blindness. He has cerebellar ataxia on neurologic examination as well as ophthalmoparesis. His strength is 5 out of 5 in all major muscle groups, and all reflexes are normal except for extensor plantar responses. When the mother arrives, you find out that many relatives on the father's side of the family, including the father, have been diagnosed with cerebellar ataxia but she does not know more than that. You decide to perform a funduscopic examination. What do you expect to find on examination of this patient's fundi?

A. Lipemia retinalis
B. Normal examination

71. (*Continued*)
C. Papilledema
D. Proliferative retinopathy
E. Retinal pigmentary degeneration

72. All the following have been shown to reduce the risk of atherothrombotic stroke in primary or secondary prevention *except*

A. aspirin
B. blood pressure control
C. clopidogrel
D. statin therapy
E. warfarin

73. All the following are associated with a decreased sense of smell *except*

A. head trauma
B. HIV infection
C. influenza B infection
D. Kallmann syndrome
E. parainfluenza virus type 3 infection

74. All the following are side effects of phenytoin *except*

A. ataxia
B. gum hyperplasia
C. hirsutism
D. leukopenia
E. lymphadenopathy

75. All but which of the following statements about Becker's muscular dystrophy are true?

A. The inheritance is X-linked.
B. Serum creatinine kinase levels are elevated.
C. The underlying genetic defect is in the myosin gene.
D. Survival is better than it is in patients with Duchenne's muscular dystrophy (DMD).
E. Cardiomyopathy may occur, resulting in heart failure.

76. You are following a patient who has a ruptured L4-L5 intervertebral disk with herniation. He has had left lower extremity weakness that has been constant for 6 months. He is still able to perform his daily activities. His pain is intermittent and he uses chronic narcotics on an as-needed basis. What findings would prompt you to refer this patient for surgery?

A. Absent deep tendon reflexes on the right
B. MRI shows L3-L4 herniation as well
C. Nighttime symptoms
D. Physical examination demonstrates progressive weakness

77. All of the following conditions may cause episodic generalized paresis *except*

77. (*Continued*)
A. carotid artery stenosis
B. hypokalemia
D. multiple sclerosis
E. myasthenia gravis
F. transient ischemic attack

78. You are examining a 78-year-old patient in your clinic who is referred to you for difficulty in walking. During your motor examination with the patient lying supine, you place your hands behind one knee and rapidly raise the knee off the bed. During the maneuver, the ankle (of the same leg) is also lifted off the examining table. On repeat examination of the same leg, you find varying levels of resistance, and the ankle drags for varying distances before being lifted off the bed. The finding is not seen in the other leg nor in the upper extremities when examining the elbow/wrist. What is the significance of this finding?

A. The patient has decreased motor tone, which may be indicative of a motor neuron disease.
B. The patient has decreased motor tone related to musculoskeletal injury.
C. The patient's paratonia may be a normal reaction.
D. The patient's rigidity is a manifestation of parkinsonism.

79. Which of the following medicines has been most commonly implicated in the development of noninfectious chronic meningitis?

A. Acetaminophen
B. Acyclovir
C. β-lactam antibiotics
D. Ibuprofen
E. Phenobarbital

80. A 72-year-old right-handed man with a history of atrial fibrillation and chronic alcoholism is evaluated for dementia. His son gives a history of a stepwise decline in the patient's function over the last 5 years with the accumulation of mild focal neurologic deficits. On examination he is found to have a pseudobulbar affect, mildly increased muscle tone, and brisk deep tendon reflexes in the right upper extremity and an extensor plantar response on the left. The history and examination are most consistent with which of the following?

A. Binswanger's disease
B. Alzheimer's disease
C. Creutzfeldt-Jakob disease
D. Vitamin B_{12} deficiency
E. Multi-infarct dementia

81. A 50-year-old man presents with complaints of weakness and numbness in the hands for the last month. He describes paresthesias in the thumb and the index and middle fingers. The symptoms are worse at night. He also describes decreased grip strength bilaterally. He works as a mechanical engineer. The patient denies fevers, chills, or weight loss. The examination is notable for atrophy of the thenar eminences bilaterally and decreased sensation in a median nerve distribution. All the following are causes of carpal tunnel syndrome *except*

A. amyloidosis
B. chronic lymphocytic leukemia
C. diabetes mellitus
D. hypothyroidism
E. rheumatoid arthritis

ANSWERS

1. The answer is C.
(Chap. 13) Confusion is defined as a mental and behavioral state of reduced comprehension, coherence, and capacity to reason. Delirium is used to describe an acute confusional state. Delirium often goes unrecognized despite clear evidence that it is often a cognitive manifestation of many medical and neurologic illnesses. Delirium is a clinical diagnosis that may be hyperactive (e.g., alcohol withdrawal) or hypoactive (e.g., opiate intoxication). There is often dramatic fluctuation between states. Delirium is associated with a substantial mortality with in-hospital mortality estimates ranging from 25–33%. Overall estimates of delirium in hospitalized patients range from 15–55% with higher rates in the elderly. Patients in the ICU have especially high rates of delirium, ranging from 70–87%. The clinic setting would represent the lowest risk. Postoperative patients, especially status post hip surgery, have an incidence of delirium that is somewhat higher than patients admitted to the medical wards.

2. The answer is C.
(Chap. 6) This patient is presenting with typical cluster headaches, one of the three recognized trigeminal autonomic cephalgias (TACs). TACs are characterized by intense episodes of head pain associated with cranial autonomic symptoms such as tearing, rhinorrhea, and conjunctival injection. Because of these associated symptoms, patients may be misdiagnosed as having sinus headache due to allergic rhinitis and treated inappropriately with antihistamine and nasal steroids. A typical presentation of cluster headaches is one of episodic severe headaches that occur at least once daily at about the same time for a period of 8–10 weeks. An attack usually lasts from 15–180 minutes, and 50% of headaches will have nocturnal onset. Between episodes of headache, the patient is generally well. The period between headache cycles typically lasts about 1 year. Men are affected three times more commonly with cluster headaches than women, and alcohol ingestion may trigger cluster headaches. A distinguishing feature between cluster headaches and migraine headaches is that individuals with cluster headaches tend to move about during attacks and frequently rub their head for relief, whereas those with migraines tend to remain motionless during attacks. Interestingly, unilateral phonophobia and photophobia can occur with cluster headaches but do not with migraines. Treatment of acute attacks of cluster headaches requires a treatment with a fast onset as the headaches reach peak intensity very quickly but are of relatively short duration. High-flow oxygen (10–12 L/min for 15–20 min) has been very effective in relieving the headaches. Alternatively, subcutaneous or intranasal delivery of sumatriptan will also halt an attack. The oral-route triptan medications are less effective because of the time to onset of effect is too great. Preventive treatment may be considered in individuals with prolonged bouts of cluster headaches or chronic cluster headaches that occur without a pain-free interval.

The other TAC syndromes are paroxysmal hemicrania and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (commonly known as SUNCT). Paroxysmal hemicrania is characterized by unilateral severe headaches lasting only 2–45 min but occurring up to five times daily. There is marked autonomic symptoms, and paroxysms of headaches last <3 days. Indomethacin is very effective at preventing this syndrome. SUNCT is a rare syndrome in which the headaches last <4 min at a time. Diagnosis requires at least 20 attacks. There is no acute treatment of SUNCT because of their short duration, but preventative therapy with lamotrigine, topiramate, gabapentin, or carbamazepine may be effective.

3. The answer is A.
(Chap. 44) A common mistake in the management of patients with inflammatory myopathy is to "chase the CK" instead of adjusting therapy based on the clinical response. The goal of therapy is to improve strength. If that goal is being achieved, no augmentation of therapy is necessary. In this case, the plan to switch to long-term maintenance with steroid-sparing immunosuppressants should still be pursued. There have been no controlled studies comparing mycophenolate to methotrexate for the long-term use in polymyositis, and in the absence of an adverse reaction to mycophenolate, therapy should not be

changed. Despite an elevated CK, patients with polymyositis who are responding to therapy do not need a repeat muscle biopsy.

4. The answer is C.
(Chap. 10) The central cord syndrome manifests clinically as a sensory disorder as the spinothalamic fibers in the ventral commissure of the spinal cord are disrupted. Dermatomes above and below the level of the destruction are usually spared, creating a "suspended sensory level" on physical examination. As the lesion grows, corticospinal tract or anterior horn involvement can produce weakness in the affected myotome. Common causes include syringomyelia, intramedullary tumor, and hyperextension in a patient with cervical spondylosis. Tabes dorsalis impairs proprioception and sensation and causes weakness. Disc herniation most commonly affects posterior cord function and nerve roots. A lateral hemisection syndrome (the Brown-Séquard syndrome) is classically due to penetrating trauma from a knife or bullet injury and produces ipsilateral weakness and contralateral loss of pain and temperature sensation. Amyotrophic lateral sclerosis presents with combined upper and lower motor neuron findings; sensory deficits are uncommon.

5. The answer is D.
(Chap. 22) This patient has evidence of increased intracranial pressure and needs to be managed urgently. A variety of maneuvers may decrease intracranial pressure acutely. Hyperventilation causes vasoconstriction, reducing cerebral blood volume and decreasing intracranial pressure. However, this can be used only for a short period as the decrease in cerebral blood flow is of limited duration. Mannitol, an osmotic diuretic, is recommended in cases of increased intracranial pressure resulting from cytotoxic edema. Hypotonic fluids should be avoided. Instead, hypertonic saline is given to elevate sodium levels and prevent worsening of edema. A more definitive treatment to decrease intracranial pressure is to have a ventriculostomy placed by which excessive pressure can be relieved by draining cerebrospinal fluid (CSF). Further decreases in mean arterial pressure may worsen the patient's clinical status. The patient already has had more than a 20% reduction in mean arterial pressure, which is the recommended reduction in cases of hypertensive emergency. In addition, the patient is exhibiting signs of increased intracranial pressure, which indicates that cerebral perfusion pressure [mean arterial pressure (MAP)–intracranial pressure (ICP)] has been lowered. Paradoxically, the patient may need a vasopressor agent to increase MAP and thus improve cerebral perfusion. Finally, in cases of increased intracranial pressure, nitroprusside is not a recommended intravenous antihypertensive agent because it causes arterial vasodilation and may decrease cerebral perfusion pressure and worsen neurologic function.

6. The answer is B.
(Chap. 9) The symptoms and signs described in this question are most consistent with Ménière's disease. In this disorder paroxysmal vertigo resulting from labyrinthine lesions is associated with nausea, vomiting, rotary nystagmus, tinnitus, high-tone hearing loss with recruitment, and, most characteristically, fullness in the ear. Labyrinthitis would be an unlikely diagnosis in this case because of the hearing loss and multiple episodes. Vertebral-basilar insufficiency and multiple sclerosis typically are associated with brainstem signs. Acoustic neuroma only rarely causes vertigo as the initial symptom, and the vertigo it does cause is mild and intermittent.

7. The answer is D.
(Chap. 35) In a patient with suspected bacterial meningitis empirical therapy should be administered promptly to reduce mortality and morbidity. The decision to obtain an imaging study prior to lumbar puncture is based on the concern of precipitating herniation in a patient with elevated intracranial pressure or focal CNS lesions. Therefore, patients with the presence of papilledema on physical examination, history of recent head trauma, known or suspected intracranial lesions (immunosuppressed, known malignancy), focal neurologic findings, or depressed level of consciousness should have a head CT or MRI prior to lumbar puncture. Kernig's sign is elicited in a supine patient by flexing the thigh and knee. A positive sign occurs when the patient has head/neck pain when passively straightening the knee. The sensitivity and specificity of this sign (also Brudzinski's) for bacterial meningitis are unknown, but they imply meningeal irritation, not an intracranial lesion or elevated intracranial pressure. While cerebrospinal fluid cultures may be impacted by administration of antibiotics prior to lumbar puncture, stains, antigen tests, and polymerase chain reaction tests will not be affected.

8. The answer is C.
(Chap. 12) The patient's nonspecific dysesthesia is related to hyperventilation in response to the patient's change in altitude from sea level to a mountainous area. The normal respiratory response to decreased atmospheric oxygen tension is to increase the respiratory rate. This hyperventilation causes a mild respiratory alkalosis and is experienced as acral and periorbital dysesthesias. Acetazolamide is often given to patients who have a past history of altitude sickness manifested as headache, nausea with vomiting, and in severe cases pulmonary edema. This patient is experiencing none of those symptoms, and in fact, dysesthesias are a common side effect related to treatment with acetazolamide. No further blood testing is necessary as the symptoms are not associated with any neurologic abnormalities. Diabetes mellitus, vitamin B_{12} deficiency, and tertiary syphilis are all associated with a sensory neuropathy, which this patient does not demonstrate.

9. The answer is C.
(Chap. 1) This patient demonstrates increasing weakness with repeated exertion, which is characteristic of neuromuscular junction diseases such as myasthenia gravis. The course can fluctuate over the course of a day, which may explain why his symptoms appear worse at the end of the day. The absence of any sensory deficit is also characteristic of a neuromuscular junction disorder. Diseases of the muscle usually do not exhibit such a marked difference on the examination over the course of hours. Spinal root disorders are symptomatic in a nerve root distribution, and limb pain is usually a prominent component. Clues to a brainstem disease are isolated cranial nerve palsies and "crossed" weakness and sensory abnormalities of the head and limbs.

10. The answer is B.
(Chap. 30) This patient has a history and examination consistent with a myelopathy. The rapidity of onset and the lack of other antecedent symptoms (e.g., pain) make a noncompressive etiology most likely. An MRI is the initial test of choice and will easily identify a structural lesion such as a neoplasm or subluxation. Non-compressive myelopathies result from five basic causes: spinal cord infarction; systemic disorders such as vasculitis, systemic lupus erythematosus (SLE), and sarcoidosis; infections (particularly viral); demyelinating disease such as multiple sclerosis; and idiopathic. Therefore, serologies for antinuclear antibodies, viral serologies such as HIV and HTLVI, and lumbar puncture are all indicated. Because the clinical scenario is consistent with a myelopathy, an electromyogram is not indicated.

11. The answer is D.
(Chap. 26) This MRI shows cerebellar atrophy consistent with the diagnosis of spinocerebellar ataxia (SCA). The SCAs are a group of autosomal dominant diseases. SCA1, previously known as olivopontocerebellar atrophy, is a disease of early or middle adult life. Patients develop cerebellar ataxia of the trunk and limbs with impairment of equilibrium and gait, scanning speech, nystagmus, and oscillatory tremor of the head and trunk. There may also be mild dementia. Cerebellar and brainstem atrophy are evident on MRI. Migraine headache, limb weakness, and breathing difficulties are nonspecific but may be seen in serotonin syndrome or alcohol withdrawal. Gait instability, urinary incontinence, and dementia constitute the clinical triad for normal-pressure hydrocephalus, which does not have cerebellar atrophy on MRI. Hypertension, tachycardia, and diaphoresis may be seen in a patient with an Arnold-Chiari malformation. MRI will often show abnormalities in the base of the skull.

12. The answer is A.
(Chap. 31) Concussions result from blunt head trauma that causes anterior-posterior movement of the brain within the skull. Transient loss of consciousness is common, as are confusion and amnesia. Head imaging is typically normal. Postconcussive syndrome is a constellation of symptoms including fatigue, headache, dizziness, and difficulty concentrating that follows a concussion. The patient described above fits this diagnosis; strict diagnostic criteria do not exist. Typically patients will improve over a 6- to 12-month period. Patients who were energetic and highly functioning prior to their trauma have an excellent prognosis. Treatment is aimed at reassurance and relieving prominent symptoms. Dizziness can be treated with phenergan, which acts as a vestibular suppressant. He should avoid contact sports at least until his symptoms resolve.

13. The answer is E.
(Chap. 38) Prions are infectious particles that cause central nervous system degeneration. The human prion diseases described to date include Creutzfeldt-Jacob disease, kuru, Gerstmann-Straüssler-Scheinker disease, and fatal insomnia. The most common prion disease is sporadic CJD (sCJD) which occurs in a seemingly random pattern in adults in their fifth and sixth decades of life. sCJD accounts for about 85% of cases of CJD and occurs in ~1 per 1 million population. Variant CJD (vCJD) results from infection from bovine exposure to tainted beef from cattle with bovine spongiform encephalopathy (BSE). Infectious CJD (iCJD) has resulted from injection of tainted human growth hormone, as well as transplant of infected dura mater grafts into humans. Familial CJD (fCJD) is due to germ-line mutations that follow an autosomal dominant inheritance. Kuru is due to infection through ritualistic cannibalism. Gerstmann-StraüsslerScheinker disease and familial fatal insomnia (FFI) occur as dominantly inherited prion diseases. Sporadic cases of fatal insomnia (sFI) have been described.

14. The answer is B.
(Chap. 7) Neurogenic claudication (back or leg pain induced by walking or standing and relieved by sitting) is the most common symptom of lumbar spinal stenosis. Unlike vascular claudication, symptoms are provoked by standing without walking. Symptoms are often not present, and severe findings such as paralysis and urinary incontinence are rare. Lumbar spinal stenosis can be congenital or acquired. Acquired factors that contribute to spinal stenosis include trauma, osteoporosis, hypoparathyroidism, renal osteodystrophy, and Paget's disease. Tethered cord syndrome usually presents as a cauda equina disorder (urinary incontinence, perineal anesthesia) in a young adult. Pain associated with disk herniation is differentiated from spinal stenosis when the pain is made worse with sitting. Vertebral metastases are a common cause of back pain in patients at risk of common malignancies. The pain tends to be constant, dull, unrelieved by rest, and worst at night.

15. The answer is A.
(Chap. 20) Complex partial seizures are characterized by focal seizure activity plus impairment of the patient's ability to maintain contact with the environment. Mesial temporal lobe epilepsy is the most common syndrome associated with complex partial seizures. Patients are unable to respond to verbal or visual commands during the seizure and they often manifest complex automatisms or complex posturing. An aura is common before the seizures. There is postictal memory loss or disorientation. Patients often have a history of febrile seizures or a family history of seizures. MRI will show hippocampal sclerosis, a small temporal lobe, or enlarged temporal horn. Hypothyroidism, herpes virus infection, diabetes, and tuberous sclerosis are not associated with mesial temporal lobe epilepsy.

16. The answer is B.
(Chap. 20) MTLE is important to recognize because it tends to be refractory to treatment with anticonvulsants but responds extremely well to surgical intervention. Primidone is an alternative for treatment of partial and generalized tonic-clonic seizures. Levetiracetam is an alternative for simple partial, complex partial, and secondarily generalized seizures. Vagus nerve stimulation is an option for patients refractory to antiepileptic medication with seizures arising from more than one site. Herpes virus infection is not a cause of MTLE.

17. The answer is C.
(Chap. 10) A deep tendon reflex is elicited when a tap on a tendon stretches muscle spindles which are chronically activated by γ motor neurons. Spindle afferent neurons directly stimulate a motor neurons in the spinal cord, causing a muscle contraction. The reflex arc operates independent of upper motor neurons (pyramidal neurons); however, loss of the inhibitory input from upper motor neurons produces an exaggerated deep tendon reflex.

18. The answer is D.
(Chap. 34) Optic neuritis is the initial symptom in approximately 40% of persons who are eventually diagnosed with multiple sclerosis. This rapidly developing ophthalmologic disorder is associated with partial or total loss of vision, pain on motion of the involved eye, scotoma affecting macular vision, and a variety of other visual field defects. Ophthalmoscopically visible optic papillitis occurs in about half these patients.

19. The answer is A.
(Chap. 7) The most commonly affected nerve roots in cervical disk disease are C7 and C6. As such, common motor findings include biceps and triceps weakness. Common sensory findings include abnormal sensation in the thumb and fingers (except the little finger), radial hand, and dorsal forearm. Decreased pin-prick sensation over the lateral deltoid would be mediated by injury to the C5 nerve root. Finger flexors and sensation to the axilla and medial arm are mediated by C8 and T1. (See Table 7-4)

20. The answer is C.
(Chap. 26) The patient describes cerebellar ataxia, which is differentiated from ataxia associated with vestibular or labyrinthine disease by the absence of vertiginous complaints. True cerebellar ataxia is devoid of vertiginous symptoms and is clearly an unsteady gait due to imbalance. CT scanning can miss pathology in the cerebellum due to the surrounding bony structures. Alcohol intoxication, lithium toxicity, and viral cerebritis usually cause acute or subacute (days to weeks) cerebellar ataxia. Tertiary syphilis is a common cause of chronic cerebellar ataxia (months to years).

21. The answer is E.
(Chap. 12) Thalamic pain syndrome may follow an embolic or lacunar thalamic infarct if it affects the ventral posterolateral (VPL) nucleus or the adjacent white matter. The pain is persistent and severe, affecting only the contralateral side of the body. Other symptoms that may be associated with thalamic infarcts include hemianesthesia, hemiataxia, choreoathetoid movements, and athetoid posture. The eponym applied to this syndrome is Déjerine-Roussy syndrome.

22. The answer is A.
(Chap. 9) In the acute evaluation of vertigo, vestibular function tests can help to establish the side of the abnormality and differentiate between central and peripheral etiologies. When performing electronystagmography using cold and warm water sequentially, the velocity of the slow-phase of nystagmus is compared from side to side. When warm water at 44°C is infused into an ear, the normal response is nystagmus with the fast component toward the infused ear. The opposite response occurs when cold water at 30°C is infused; the normal response is nystagmus with the fast component away from the cold water–infused ear. The volume of water can be increased if no response occurs with the initial attempt. Velocity of the slow phase should be similar in patients without vestibular nerve abnormalities. An absence of response to the cold caloric indicates a labyrinth system that is "dead" and nonfunctional, such as in complete destruction of the neural input with acoustic neuroma. Otoconia are not a result of and do not cause peripheral nerve dysfunction. The caloric testing is normal in patients with otoconia. The peripheral nerve dysfunction seen with aminoglycoside antibiotics is usually bilateral. Unilateral symptoms should raise the suspicion for an anatomic as opposed to a systemic cause of the vertigo. Labyrinthine ischemia will also manifest as a "dead" labyrinth; however, the patient's age makes ischemic brainstem lesions less likely than a schwannoma.

23. The answer is D.

(Chap. 32) This scenario represents a common dilemma in the care of patients with HIV infection. The differential diagnosis usually falls between CNS toxoplasmosis or CNS lymphoma. The standard approach in a neurologically stable patient is to treat the patient for toxoplasmosis for 2–3 weeks then repeat neuroimaging. If the imaging shows clear improvement, continue antibiotics. If not, then a stereotactic brain biopsy is indicated. Whole-brain radiation therapy is part of the treatment for CNS lymphoma, which is not yet diagnosed in this patient, and should not be instituted empirically. In the absence of neurologic collapse, it is reasonable to treat empirically for toxoplasmosis in such a patient. The leptomeninges are a common site for metastases for patients with systemic lymphoma and those patients usually have a B cell lymphoma or leukemia. Dexamethasone is indicated for focal CNS lesions with evidence of mass effect or extensive surrounding edema.

24. The answer is D.

(Chap. 32) In this immunocompromised patient who has not responded to treatment for CNS toxoplasmosis, a positive CNS EBV DNA would be diagnostic of CNS lymphoma. However, in the absence of a definitive diagnosis, a biopsy should be pursued for a definitive diagnosis. If there is no response to therapy after 2 weeks, therapy does not need to be continued. Treatments directed at viral infections of the CNS or CNS lymphomas are not indicated at this time since a diagnosis is still yet to be made. In the absence of a change in neurologic status or evidence of mass effect on CT, there is no indication for dexamethasone.

25. The answer is A.

(Chap. 30) Syringomyelia is a developmental, slowly enlarging cavitary expansion of the cervical cord that produces a progressive myelopathy. Symptoms typically begin in adolescence or early adulthood. They may undergo spontaneous arrest after several years. More than half are associated with Chiari malformations. Acquired cavitations of the spinal cord are referred to as syrinx cavities. They may result from trauma, myelitis, infection, or tumor. The classic presentation is that of a central cord syndrome with sensory loss of pain and temperature sensation and weakness of the upper extremities. Vibration and position sensation are typically preserved. Muscle wasting in the lower neck, shoulders, arms, and hands with asymmetric or absent reflexes reflects extension of the cavity to the anterior horns. With progression, spasticity and weakness of the lower extremities and bladder and bowel dysfunction may occur. MRI scans are the diagnostic modality of choice. Surgical therapy is generally unsatisfactory. Syringomyelia associated with Chiari malformations may require extensive decompressions of the posterior fossa. Direct decompression of the cavity is of debatable benefit. Syringomyelia secondary to trauma or infection is treated with decompression and a drainage procedure, with a shunt often inserted that drains into the subarachnoid space. Although relief may occur, recurrence is common.

26. The answer is E.

(Chap. 42) Myasthenia gravis (MG) is a neuromuscular disorder characterized by weakness and fatigability of skeletal muscles. The primary defect is a decrease in the number of acetylcholine receptors at the neuromuscular junction secondary to autoimmune antibodies. MG is not rare, affecting at least 1 in 7500 individuals. Women are affected more frequently than are men. Women present typically in the second and third decades of life, and men present in the fifth and sixth decades. The key features of MG are weakness and fatigability. Clinical features include weakness of the cranial muscles, particularly the lids and extraocular muscles. Diplopia and ptosis are common initial complaints. Weakness in chewing is noticeable after prolonged effort. Speech may be affected secondary to weakness of the palate or tongue weakness. Swallowing may result from weakness of the palate, tongue, or pharynx. In the majority of patients the weakness becomes generalized. The diagnosis is suspected after the appearance of the characteristic symptoms and signs. Edrophonium is an acetylcholinesterase inhibitor that allows ACh to interact repeatedly with the limited number of AChRs, producing improvement in the strength of myasthenic muscles. False-positive tests may occur in patients with other neurologic diseases. Electrodiagnostic testing may show evidence of reduction in the amplitude of the evoked muscle action potentials with repeated stimulation. Testing for the specific antibodies to AChR are diagnostic. In addition to anti-AChR antibodies, antibodies to MuSK have been found in some patients with clinical MG. Antibodies to voltage-gated calcium channels are found in patients with the Lambert-Eaton syndrome.

27. The answer is D.

(Chap. 24) The differential diagnosis of Parkinson's disease is broad, and the disease can be difficult to diagnose, with an estimated misdiagnosis of 10–25% even by experienced physicians. This patient exhibits several atypical features that should alert the physician to search for alternative diagnoses. These include early age of onset, prominent orthostasis, autonomic symptoms of flushing and diaphoresis, and failure to respond to dopaminergic agents. In addition, recurrent urinary tract infections should prompt an evaluation for urinary retention due to autonomic dysfunction in this patient. These symptoms are most consistent with multiple systems atrophy with parkinsonian features (MSA-p). The average age of onset is 50 years, and these individuals more frequently present with bilateral, symmetric tremor and more prominent spasticity than those with Parkinson's disease. Orthostasis and autonomic symptoms are typically prominent. On

MRI, one would expect to find volume loss and T2-hyperintensity in the area of the putamen, globus pallidus, and white matter. On pathologic examination, a-synuclein-positive inclusions would be seen in the affected areas. Median survival after diagnosis is 6–9 years. Dopaminergic agents are not helpful in treatment of this disorder and are usually associated with drug-induced dyskinesias of the face and neck, rather than the limbs and trunk. Corticobasal degeneration is a sporadic tauopathy that presents in the sixth to seventh decades. In contrast to Parkinson's disease, this disorder is frequently associated with myoclonic jerks and involuntary purposeful movements of a limb. Its progressive nature leads to spastic paraplegia. Diffuse Lewy body disease has prominent dementia with parkinsonian features. Neuropsychiatric complaints including paranoia, delusions, and personality changes are more common than in Parkinson's disease. Drug-induced Parkinson's disease is not seen with nitrofurantoin, and the patient has no history of illicit drugs such as MTPT, which could cause Parkinson's disease. Finally, this is unlikely to be inadequately treated Parkinson's disease because one would expect at least an initial improvement on dopaminergic agents.

28. The answer is D.
(Chap. 31) The head CT shows bilateral hypodense fluid collections in the subdural space. Acute hematomas (which would be as bright as the resolving blood shown in arrows) become hypodense in comparison with adjacent brain after ~2 months. During the isodense phase (2–6 weeks after injury), they may be difficult to discern. Chronic subdural hematoma may present without a history of trauma or injury in 20–30% of patients. Headache is common. Other symptoms may be vague as in this patient, or there may be focal signs including hemiparesis mimicking stroke. Underlying cortical damage may serve as a seizure focus. In relatively asymptomatic patients with small hematomas, observation and serial imaging may be reasonable; however, surgical evacuation is often necessary for large or symptomatic chronic hematomas.

29. The answer is B.
(Chap 9) Positional vertigo is precipitated by a recumbent head position, either to the right or the left. The benign form that affects the posterior semicircular canal is the most common and is due to the accumulation of otoconia. Central positional vertigo (CPV) is due to lesions of the fourth ventricle and is much less common than BPPV. BPPV can be diagnosed and potentially treated with characteristic maneuvers (i.e., Dix-Hallpike position). With the head supine, the head is turned to the affected side (left ear down, in this case). Torsional nystagmus and vertigo will result with characteristic eye movements. In BPPV, the time from assuming head position and onset of symptoms is 3–40 s, whereas in CPV, the onset is immediate. With BPPV, symptoms will abate while the head position is maintained, and repeat trials lessen the symptoms each time and may extinguish them completely. With central causes of vertigo, symptoms are often less severe than with peripheral vertigo. Isolated horizontal nystagmus without a torsional component is also more suggestive of a central cause of vertigo.

30. The answer is C.
(Chap. 24) Therapy for Parkinson's disease should be initiated when symptoms interfere with the patient's quality of life. Choice of initial drug therapy is usually with dopamine agonists, levodopa, or MAO inhibitors. The initial choice in most individuals is a dopamine agonist (pramipexole, ropinirole), and monotherapy with dopamine agonists usually controls motor symptoms for several years before levodopa therapy becomes necessary. Over this period, escalating doses are frequently required, and side effects may be limiting. It is thought that dopamine agonists delay the onset of dyskinesias and on-off motor symptoms, such as freezing. By 5 years, over one-half of individuals will require levodopa to control motor symptoms. Levodopa remains the most effective therapy for the motor symptoms of Parkinson's disease, but once levodopa is started, dyskinesias and on-off motor fluctuations become more common. MAO inhibitors work by decreasing postsynaptic breakdown of dopamine. As monotherapy, these agents have only small effects and are most often used as adjuncts to levodopa. Surgical procedures such as pallidotomy and deep-brain stimulation are reserved for advanced Parkinson's disease with intractable tremor or drug-induced motor fluctuations or dyskinesias. In this setting, deep-brain stimulation can alleviate disabling symptoms.

31. The answer is C.
(Chap. 44) This patient does not have signs of an inflammatory myositis. In particular, the "give-away" weakness and improvement with encouragement suggests that this patient's "weakness" may actually be due to muscular pain. Fibrositis, polymyalgia rheumatica or fibromyalgia may present this way, although the normal erythrocyte sedimentation rate makes polymyalgia rheumatica less likely. Necrotic muscle can be seen in any of the inflammatory myopathies or necrotizing myositis. Endomysial deposits of amyloid can be seen in inclusion body myositis. Scattered inflammatory foci are seen in polymyositis.

32. The answer is E.
(Chap. 29) Trigeminal neuralgia is a clinical diagnosis based entirely on patient history. The disorder is characterized by *paroxysms* of excruciating pain in the lips, gums, cheeks, and chin that resolves over seconds to minutes. It is caused by ectopic action potentials in afferent pain fibers of the fifth cranial nerve, due either to nerve compression or other cause of demyelination. Symptoms are often, but not always, elicited by tactile stimuli on the face, tongue or

lips. An elevated ESR is not part of the clinical syndrome. Elevated ESR is associated with temporal arteritis, a vasculitis associated with jaw claudication, unilateral vision loss, and symptoms of polymyalgia rheumatica. Trigeminal neuralgia is specifically notable for a lack of sensory findings on examination, unless the diagnosis comes in conjunction with another disorder such as midbrain mass lesion or aneurysm. First-line therapy is with carbamazepine followed by phenytoin, rather than gabapentin. Deep-seated facial and head pain is more a feature of migraine headache, dental pathology, or sinus disease.

33. The answer is B.
(Chap. 7) MRI is the radiologic test of choice for evaluation of most serious processes involving the spine. However, CT scanning is the preferred test when imaging of the bony structures is most important. In acute processes such as fracture or dislocation, MRI may reveal the edema associated with the acute inflammation, but for more chronic bony conditions, CT scanning is the test of choice. MRI is better than CT scanning for imaging the soft tissues surrounding the spine. Imaging the spinal cord itself, in the case of syringomyelia, is also better accomplished with MRI. Similarly, MRI is better than CT scanning for imaging the lateral recesses of the spinal cord; however, CTmyelography is preferred over MRI for that indication.

34. The answer is B.
(Chap. 40) Peripheral neuropathy is a general term indicating peripheral nerve disorders of any cause. The causes are legion, but peripheral neuropathy can be classified by a number of means: axonal versus demyelinating, mononeuropathy versus polyneuropathy versus mononeuritis multiplex, sensory versus motor, and the tempo of the onset of symptoms. Mononeuropathy typically results from local compression, trauma, or entrapment of a nerve. Polyneuropathy often results from a more systemic process. The distinction between axonal and demyelinating can often be made only with nerve conduction studies. HIV infection causes a common, distal, symmetric, mainly sensory polyneuropathy. Vitamin B_{12} deficiency typically causes a sensory neuropathy that predominantly involves the dorsal columns. Hypothyroidism and acromegaly may both cause compression and swelling of nerve fibers, resulting first in sensory symptoms and later in disease with motor symptoms. Critical illness polyneuropathy is predominantly motor in presentation. These patients may recover over the course of weeks to months. The etiology is unknown, but an association may exist with neuromuscular blockade and corticosteroids.

35. The answer is E.
(Chap. 40) Peripheral neuropathy is a common disorder affecting 2–8% of the adult population and increasing with age. The causes of peripheral neuropathy are myriad and can be classified by location, fiber type, histopathology, and time course. Specific features of the history and physical examination should lead the clinician toward a possible diagnosis. For example, lead toxicity is frequently associated with motor abnormalities in addition to sensory neuropathy. Laboratory examination with specific testing may be useful in assessing for a variety of etiologies of peripheral neuropathy, including diabetes mellitus, heavy metal toxicity, metabolic abnormalities, vasculitis, and infections (syphilis, Lyme disease, HIV). Of the choices listed in the question, folate deficiency is not associated with peripheral neuropathy.

36. The answer is A.
(Chap. 32) Endocrine dysfunction resulting in hypopituitarism frequently follows exposure of the hypothalamus or pituitary gland to therapeutic radiation. Growth hormone is the most sensitive to the damaging effects of WBRT, and thyroid-stimulating hormone is the least sensitive. ACTH, prolactin, and gonadotropins have an intermediate sensitivity. Other complications of radiation therapy to the brain include acute radiation injury manifest by headache, sleepiness, and worsening of preexisting neurologic defects. Early delayed radiation injury occurs within the first 4 months after therapy. It is associated with increased white matter signal on MRI and is steroid-responsive. Late delayed radiation injury occurs >4 months after therapy, typically 8–24 months. There may be dementia, gait apraxia, focal necrosis (after focal irradiation), or development of secondary malignancies.

37. The answer is C.
(Chap. 32) Spinal cord compression from solid tumor metastases usually results from growth of a bony vertebral metastasis into the epidural space. The most common primary tumors that metastasize to the bone include lung, breast, and prostate. The thoracic cord is most often involved. Back pain is a prominent symptom in 90% of patients with vertebral metastases and spinal cord compression. Concerning features of this patient's presentation include the symptoms of radicular injury as well as the signs of radicular and spinal cord impingement on physical examination. Once signs of spinal cord compression develop, they usually progress rapidly and warrant rapid therapy. Appropriate therapy includes emergent scanning with an MRI as well as immediate glucocorticoids if there are signs of spinal cord impingement. Subsequent management will depend on the extent of involvement and the primary tumor. Conservative pain management measures are not appropriate in this patient since he has very concerning neurologic findings for spinal cord compression and delay will increase the likelihood of irreversible defects. Antibody-mediated paraneoplastic neurologic syndromes are unlikely to cause focal findings such as in this patient. Radiographs may show bony metastases but will not show spinal cord damage.

38. The answer is C.

(Chap. 44) The inflammatory myopathies (polymyositis, dermatomyositis, and inclusion body myositis) are associated with unique clinical features. Inclusion body myositis is usually seen in patients ≥50 years and initially involves the distal muscles, especially the foot extensors and finger flexors. Atrophy is seen along with weakness as this inflammatory myopathy runs a slowly progressive course, compared to polymyositis or dermatomyositis. Polymyositis is a rare disorder that usually involves the proximal not distal muscles. It is a diagnosis of exclusion after a thorough medical examination and muscle biopsy. Dermatomyositis is distinguished by the classic heliotrope rash and associated skin findings, which may precede the development of clinical muscular weakness. Eosinophilic myofasciitis is associated with myalgias, skin induration, fatigue, and eosinophilia in the peripheral blood as well as in endomysial tissue. Hyperthyroidism would cause a reduced TSH. It may cause weakness, but is generally associated with other findings such as tremor, skin changes, and irritability.

39. The answer is B.

(Chap. 42) In myasthenia gravis, the primary defect is decreased number of available ACh receptors in the postsynaptic neuron at the neuromuscular junction (NMJ). This occurs as a result of antibody-mediated cross-linking of the ACh receptor, which causes increased turnover of ACh receptors, blockage of the active site, and damage to the postsynaptic muscle. The defect is not due to a defect in the release of ACh. Low levels of ACh-esterase would cause increased activation at the NMJ. Finally, the defect in myasthenia gravis occurs at the NMJ, not at nerve synapses.

40. The answer is E.

(Chap. 20) Simple partial seizures cause motor, sensory, autonomic, or psychic symptoms without an obvious alteration in consciousness. The phenomenon of abnormal motor movements beginning in a restricted area then progressing to involve a larger area is termed *Jacksonian march*. The patient is describing Todd's paralysis, which may take minutes to many hours to return to normal. Although meningitis is a common cause of seizure in young patients, it is unlikely to be the cause in someone who has a known seizure disorder. If his symptoms were to persist beyond many hours, it would be reasonable to investigate a different etiology of his hand weakness with imaging studies. Overt deficits in strength are not compatible with a primary psychiatric disorder. Magnetic resonance angiogram and cerebral angiogram are useful to evaluate for cerebrovascular disorders, but there is no evidence of subarachnoid bleeding or vasculitis.

41. The answer is C.

(Chap. 35) The release of bacterial cell wall components after killing by antibiotics may evoke a marked inflammatory cytokine response in the subarachnoid space. This inflammation may lead to increased damage of the blood brain barrier and central nervous system damage. Glucocorticoids can blunt this response by inhibiting tumor necrosis factor and interleukin-1. They work best if administered before antibiotics. Clinical trials have demonstrated that dexamethasone, 10 mg IV administered 20 min before antibiotics, reduced unfavorable outcomes, including death. The dexamethasone was continued for 4 days. The benefits were most striking in pneumococcal meningitis. Because this is the most common cause of meningitis in the elderly, empirical coverage should include this intervention as well. Empirical antibiotics in this case should include a third-generation cephalosporin, vancomycin, and ampicillin. However, dexamethasone may decrease vancomycin penetration into the CSF, so its use should be considered carefully in cases where the most likely organism requires vancomycin coverage.

42. The answer is E.

(Chap. 6) This patient has typical symptoms of migraine headaches without concerning features for an underlying disorder. Specifically, there is no report of worsening severity of headaches, fever, intractable vomiting, or abnormal neurologic examination that would be worrisome for an intracranial process. Vertigo is not an indication of a more serious intracranial process, as an estimated 33% of individuals with migraine experience vertigo both with and without accompanying headache. Therefore, imaging of the brain is unnecessary in this clinical situation. Migraine headaches are the second most common headache syndromes after tension headaches and affect 15% of women and 6% of men. The onset of headaches is usually in late adolescence, with peak prevalence of migraine occurring in the mid-thirties. Migraine headaches are typically classified as occurring with aura (previously called *classic migraine*) or without an aura. A more simplified diagnostic criterion for migraine has been adopted by the International Headache Society. Migraine is defined as repeated attacks of headache lasting 4–72 h in individuals with a normal physical examination. To be classified as a migraine, the headaches must fulfill at least two of the following symptoms: unilateral pain, throbbing quality, aggravation by movement, and moderate to severe intensity. At least one additional accompanying feature should be present, including either nausea/vomiting, phonophobia, or photophobia. Patient education and trigger avoidance are important in the management of migraine headaches. Migraines can frequently be controlled, but not eliminated, by lifestyle modifications, and it is important to understand an individual's triggers for migraine. A headache diary will help identify patterns of headaches as well as triggers. It will also provide an estimate of headache frequency and severity to aid in determining whether prophylactic medication would be required. Other nonpharmacologic treatment of

migraines includes regular exercise, maintain a regular sleep-wake cycle, and stressor avoidance. Yoga, biofeedback, hypnosis, and meditation are interventions that may help alleviate stress and may have benefit in migraine treatment. Once an acute migraine is experienced, timely treatment is warranted to decrease the duration of the attack and minimize loss of productivity. If attacks are mild, analgesics such as nonsteroidal anti-inflammatory drugs or acetaminophen may be useful. However, the most effective drugs for the treatment of moderate to severe migraines are the 5-hydroxytriptamine agonists—ergotamines and the triptan drugs. Rizatriptan and almotriptan are the most efficacious of the triptan drugs. If migraine attacks occur more than five times monthly or are poorly responsive to abortive treatment, additional drug therapy for prevention is indicated.

43. The answer is D.
(Chap. 1) Cranial nerve XI (accessory nerve) is correctly paired with the proper examination technique. Testing cranial nerve I (olfactory nerve) should be performed with a mild stimulus (e.g., coffee or toothpaste) to eliminate any potential stimulation of pain fibers in the nasopharynx (trigeminal nerve) by noxious stimuli such as ammonia or alcohol. When testing visual acuity (cranial nerve II), corrective lenses should be worn by the patient, if necessary. This allows for testing of the neuronal aspects of vision without confounding by problems within the lens. It is also important to test each eye individually. The trigeminal (cranial nerve V) is predominantly a sensory nerve and has three sensory branches. The motor component of the trigeminal nerve predominantly innervates the masseter muscles used for chewing. Eyebrow elevation and forehead wrinkling are functions of cranial nerve VII.

44. The answer is C.
(Chap. 42) This patient's presentation with facial and ocular weakness in a nocturnal pattern is consistent with a typical presentation of myasthenia gravis. It is not uncommon for symptoms to be mostly nocturnal and be relatively asymptomatic in the early morning hours. Examining these patients in the evening or doing repetitive strength testing may bring out more subtle findings and requires a heightened index of suspicion. Lead poisoning would be uncommon in a woman of this age, and the findings would not be restricted to the cranial region. Psychiatric diagnoses do not correlate with myasthenia gravis, and repeat examination to corroborate the reported physical examination should be performed first. MRI of the brain is not indicated at this time as the physical examination findings point towards a serologic diagnosis. Slit-lamp examination is useful for finding abnormalities in the anterior portion of the eye, such as the iris, lens, and cornea.

45. The answer is C.
(Chap. 20) Nuchal rigidity and an elevated white blood cell count is very concerning for meningitis as the etiology for this patient, and lumbar puncture must be performed to rule this out. In addition, acute cocaine intoxication is a plausible reason for this new-onset seizure. Figure 20-2 illustrates the evaluation of the adult patient with a seizure. MRI would be indicated if the patient had a negative metabolic and toxicologic screening. Substance abuse counseling, while indicated, is not indicated at this point in his workup since he is postictal. The patient is not having seizures, does not have a known seizure disorder, and has not been treated for the underlying metabolic abnormality, making intravenous loading with an antiepileptic medication premature at this time.

46. The answer is D.
(Chap. 43) Becker and Duchenne muscular dystrophy are both X-linked recessive disorders associated with different mutations of the dystrophin gene located on the short arm of the X chromosome. This 2000-kb gene is among the largest identified human genes. In both Becker and Duchenne muscular dystrophy, the most common mutation is a deletion. However, deletions in Becker muscular dystrophy do not result in frame-shift mutations, yielding a delayed presentation and milder presentation of disease. Limb-girdle muscular dystrophy designates a clinical syndrome that presents as progressive weakness of pelvic and shoulder girdle muscles. There are 12 recognized limb-girdle muscular dystrophies with unique mutations. This disorder can be inherited in both an autosomal dominant or recessive fashion, depending on the mutation present. Kearns-Sayre syndrome and myoclonic epilepsy with ragged red fibers (MERFF) are mitochondrial myopathies. Each mitochondrion possesses a DNA genome unique from the nuclear genome and is inherited primarily from the oocytes, accounting for the maternal inheritance of mitochondrial disorders. Kearns-Sayre syndrome is a multisystem disorder with chronic progressive external ophthalmoplegia (CPEO). Varying degrees of proximal muscle weakness are present. MERFF presents in late childhood to adulthood with clinical features of myoclonic epilepsy, progressive weakness, and cerebellar ataxia.

47. The answer is B.
(Chap. 14) Brain death is defined by the cessation of cerebral function while somatic function is maintained by artificial means and the heart continues to pump. It is the only type of brain damage that is considered equivalent to death. The diagnosis of brain death should be confirmed with the following clinical findings: unresponsiveness to any stimuli, indicating widespread cortical destruction; brainstem damage, as evidenced by enlarged or mid-sized pupils without light reaction; absent corneal and oculovestibular reflexes; and apnea, indicating medullary destruction. The heart rate should be invariant. Because the spinal cord is intact, spinal reflexes may be present. The presence or absence of the Babinski sign does not contribute to the diagnosis of brain death. Central diabetes

insipidus occurs with dysfunction of the hypothalamus or posterior pituitary. It has been described in patients with brain death but is not a component of the diagnosis.

48. The answer is B.

(Chap. 6) Cluster headaches, which can cause excruciating hemicranial pain, are notable for their occurrence during characteristic episodes. Usually attacks occur during a 4- to 8-week period in which the patient experiences one to three severe brief headaches daily. There may then be a prolonged pain-free interval before the next episode. Men between 20 and 50 years are most commonly affected. The unilateral pain is usually associated with lacrimation, eye reddening, nasal stuffiness, ptosis, and nausea. During episodes alcohol may provoke the attacks. Even though the pain caused by brain tumors may awaken a patient from sleep, the typical history and normal neurologic examination do not mandate evaluation for a neoplasm of the central nervous system. Acute therapy for a cluster headache attack consists of oxygen inhalation, although intranasal lidocaine and subcutaneous sumatriptan may also be effective. Prophylactic therapy with prednisone, lithium, methysergide, ergotamine, or verapamil can be administered during an episode to prevent further cluster headache attacks.

49. The answer is C.

(Chap. 29) Trigeminal neuralgia is a clinical diagnosis based entirely on patient history, and as such should be treated once a patient comes with the virtually pathognomonic complaints of paroxysms of excruciating pain in the lips, gums, cheeks, and chin that resolve over seconds to minutes. Carbamazepine is first-line therapy, followed by phenytoin for the ~30–50% of patients who do not respond adequately to therapy. Surgical approaches, such as radiofrequency thermal rhizotomy, gamma-knife radiosurgery, and microvascular decompression, should be considered only when medical options fail. Steroids have no therapeutic role, as trigeminal neuralgia is not an inflammatory condition. Neuroimaging is not indicated, unless other clinical features or a focal neurologic deficit elicited on history or physical examination suggest another possible diagnosis such as intracranial mass or multiple sclerosis.

50. The answer is C.

(Chap. 41) The patient fulfills the diagnostic criteria for GuillainBarré syndrome (GBS) with progressive weakness of two or more limbs, areflexia, disease course <4 weeks, and no other identifiable cause. Other characteristic features include lack of a fever, symmetric weakness, and minimal sensory symptoms. The diagnosis is further suggested by an antecedent gastrointestinal illness. In the United States, 20–30% of all cases of GBS are associated with a preceding infection with *Campylobacter jejuni*. This patient also has evidence of impending respiratory failure from neuromuscular weakness manifested by tachypnea, accessory muscle use, and paradoxical respiration. His arterial blood gas shows a respiratory alkalosis with an increase in the A–a gradient to 33 mmHg. His vital capacity is 12.5 mL/kg body weight. Laboratory findings would include normal serum chemistries with an increased cerebrospinal fluid protein without pleocytosis. Electromyography would show evidence of demyelination. Treatment for this individual should include endotracheal intubation with mechanical ventilation in addition to IVIg or plasmapheresis. IVIg is administered as five daily infusions of 2 g/kg body weight. Plasmapheresis is equally effective in treating GBS and is performed four times over the first week. Mechanical ventilation is indicated in GBS when the vital capacity <20 mL/kg (*ND Lawn et al: Arch Neurol 58(6):893, 2001*). There is no role for glucocorticoids in the treatment of GBS. Ciprofloxacin is an effective treatment to decrease symptom duration in *C. jejuni* infection if given early in the course of the illness, but has no effect in treatment of GBS following *C. jejuni* infection. Botulism also presents as an ascending symmetric paralysis. Cranial nerves are more frequently involved than in GBS. In this patient, there is no associated risk factor for botulism such as home-canned foods or injection wounds from drug use.

51. The answer is E.

(Chap. 21) Cardioembolism accounts for up to 20% of all ischemic strokes. Stroke caused by heart disease is due to thrombotic material forming on the atrial or ventricular wall or the left heart valves. If the thrombus lyses quickly, only a transient ischemic attack may develop. If the arterial occlusion lasts longer, brain tissue may die and a stroke will occur. Emboli from the heart most often lodge in the middle cerebral artery (MCA), the posterior cerebral artery (PCA), or one of their branches. Atrial fibrillation is the most common cause of cerebral embolism overall. Other significant causes of cardioembolic stroke include myocardial infarction, prosthetic valves, rheumatic heart disease, and dilated cardiomyopathy. Furthermore, paradoxical embolization may occur when an atrial septal defect or a patent foramen ovale exists. This may be detected by bubble-contrast echocardiography. Bacterial endocarditis may cause septic emboli if the vegetation is on the left side of the heart or if there is a paradoxical source.

52. The answer is B.

(Chap. 7) The crossed straight leg raise is positive when flexion of one leg reproduces the pain in the opposite leg or buttocks. This sign is more specific for disk herniation than the straight leg raise. The nerve or nerve root lesion is always on the side of the pain. The straight leg raise test is positive if passive flexion of the leg reproduces the patient's usual back pain. The reverse straight leg raise is performed by standing the patient next to the examination table and passively extending the leg with the knee flexed. This maneuver stretches the L2-L4 nerve roots. Back pain referred from visceral organs may be palpated

on abdominal examination but should not be reproduced by straight leg raise. Passive dorsiflexion of the foot during the straight leg raise will add to the stretch but does not add any more diagnostic information.

53. The answer is D.
(Chap. 32) This figure illustrates a mass attached to the meninges with a dural tail. Other dural tumors may appear this way, but of the options listed, the meningioma is by far the most likely to appear this way. Meningiomas derive from the cells that give rise to the arachnoid granulations. They are usually benign and attached to the dura. They rarely invade the brain. They are more frequent in women than men and have a peak incidence in middle age. Total surgical resection of a meningioma is curative. Low-grade astrocytoma and high-grade astrocytoma (glioblastoma) often infiltrate into adjacent brain and rarely have the clear margins seen in this figure. Oligodendroma comprise ~15% of all gliomas and show calcification in roughly 30% of cases. They have a more benign course and are more responsive than other gliomas to cytotoxic therapy. For low-grade oligodendromas, the median survival is 7–8 years. Brain abscess will have distinctive ring-enhancing features with a capsule, often have mass effect, and will have evidence of inflammation on MRI scanning.

54. The answer is B.
(Chap. 20) Optimal medical therapy for epilepsy depends on the underlying cause, type of seizure, and patient factors. The goal is to prevent seizures and minimize the side effects of therapy. The minimal effective dose is determined by trial and error. In choosing medical therapies, drug interactions are a key consideration. Certain medications, such as tricyclic antidepressants, may lower the seizure threshold and should be avoided. Patients who respond well to medical therapy and have completely controlled seizures are good candidates for the discontinuation of therapy, with about 70% of children and 60% of adults being able to discontinue therapy eventually. Patient factors that aid in this include complete medical control of seizures for 1 to 5 years, a normal neurologic examination, a normal EEG, and single seizure type. On the other end of the spectrum, about 20% of these patients are completely refractory to medical therapy and should be considered for surgical therapy. In the best examples, such as mesial temporal sclerosis, resection of the temporal lobe may result in about 70% of these patients becoming seizure free and an additional 15–25% having a significant reduction in the incidence of seizures. In patients with epilepsy other considerations are critical. Psychosocial sequelae such as depression, anxiety, and behavior problems may occur. Approximately 20% of epileptic patients have depression, with their suicide rate being higher than that of age-matched controls. There is an impact on the ability to drive, perform certain jobs, and function in social situations. Furthermore, there is a twofold to threefold increase in mortality for patients with epilepsy compared with age-matched controls. Although most of the increased mortality results from the underlying etiology of epilepsy, a significant number of these patients die from accidents, status epilepticus, and a syndrome known as sudden unexpected death in epileptic patients (SUDEP). The cause is unknown, but research has centered on brainstem-mediated effects of seizures on cardiopulmonary function.

55. The answer is D.
(Chap. 21) Nonrheumatic atrial fibrillation is the most common cause of cerebral embolism overall. The presumed stroke mechanism is thrombus formation in the fibrillating atrium or atrial appendage. The average annual risk of stroke is around 5%. However, the risk varies with certain factors: age, hypertension, left ventricular function, prior embolism, diabetes, and thyroid function. Patients younger than 60 years of age without structural heart disease or without one of these risk factors have a very low annual risk of cardioembolism: <0.5%. Therefore, it is recommended that these patients only take aspirin daily for stroke prevention. Older patients with numerous risk factors may have annual stroke risks of 10–15% and must take warfarin indefinitely. Cardioversion is indicated for symptomatic patients who want an initial opportunity to remain in sinus rhythm. However, studies have shown that there is an increased stroke risk for weeks to months after a successful cardioversion, and these patients must remain on anticoagulation for a long period. Similarly, recent studies have shown that patients who do not respond to cardioversion and do not want catheter ablation have mortality and morbidity with rate control and anticoagulation similar to those of patients who opt for cardioversion. Low-molecular-weight heparin may be used as a bridge to warfarin therapy and may facilitate outpatient anticoagulation in selected patients.

56. The answer is D.
(Chap. 43) There are two recognized clinical forms of myotonic dystrophy, both of which are characterized by autosomal dominant inheritance. Myotonic dystrophy 1 (DM1) is the most common form and the most likely disorder in this patient. Characteristic clinical features of this disorder include a "hatchet-faced" appearance, due to wasting of the facial muscles, and weakness of the neck muscles. In contrast to the muscular dystrophies (Becker and Duchenne), distal limb muscle weakness is more common in DM1. Palatal, pharyngeal, and tongue involvement are also common and produce the dysarthric voice that is frequently heard. The failure of relaxation after a forced hand grip is characteristic of myotonia. Myotonia can also be elicited by percussion of the thenar eminence. In most individuals, myotonia is present by age 5, but clinical symptoms of weakness that lead to diagnosis may not be present until adulthood. Cardiac conduction abnormalities and heart failure are also common in

myotonic dystrophy. Diagnosis can often be made by clinical features alone in an individual with classic symptoms and a positive family history. An electromyogram would confirm myotonia. Genetic testing for DM1 would show a characteristic trinucleotide repeat on chromosome 19. Genetic anticipation occurs with an increasing number of repeats and worsening clinical disease over successive generations. Myotonic dystrophy 2 (DM2) causes proximal muscle weakness primarily and is also known by the name proximal myotonic myopathy (PROMM). Other features of the disease overlap with DM1. Acid maltase deficiency (glucosidase deficiency, or Pompe's disease) has three recognized forms, only one of which has onset in adulthood. In the adult-onset form, respiratory muscle weakness is prominent and often is the presenting symptoms. As stated previously, Becker and Duchenne muscular dystrophies present with primarily proximal muscle weakness and are X-linked recessive disorders. Becker muscular dystrophy presents at a later age than Duchenne muscular dystrophy and has a more prolonged course. Otherwise, features are similar to one another. Nemaline myopathy is a heterogeneous disorder marked by the threadlike appearance of muscle fibers on biopsy. Nemaline myopathy usually presents in childhood and has a striking facial appearance similar to myotonic dystrophy with a long, narrow face. This disease is inherited in an autosomal dominant fashion.

57. The answer is D.
(Chap. 20) Adolescence and early adulthood mark the period where idiopathic or genetic epilepsy syndromes become less common and seizures due to acquired CNS lesions become more common. The most common causes of seizures in the young adults are head trauma, central nervous system (CNS) infections, brain tumors, congenital CNS lesions, illicit drug use, or alcohol withdrawal. Fever rarely causes seizure in patients >12 years. Amyloid angiopathy and uremia are more common in older adults.

58. The answer is B.
(Chap. 38) Startle myoclonus is a worrisome sign but is not specific for CJD, though it is more so if it occurs during sleep. Lewy body dementia, Alzheimer's disease, central nervous system infections, and myoclonic epilepsy can all cause myoclonus. EEG and MRI can both help differentiate CJD from these disorders. The MRI finding of cortical ribboning and intensity in the basal ganglia on fluid-attenuated inversion recovery sequences are characteristic of CJD. EEG is useful if stereotypical periodic bursts every 1–2 s are present, but this is seen in only 60% of cases, and other findings may be less specific. Demonstration of specific immunoassays for proteolytic products of disease-causing prion proteins (PrP^{Sc}) at brain biopsy may be necessary to confirm diagnosis in some cases. However, these proteins are not uniformly distributed throughout the brain and false-negative biopsies occur. Both surgeons and pathologists must be warned to use standard precautions under these circumstances. These proteins cannot be measured from cerebrospinal fluid (CSF). CSF in CJD is usually normal except for a minimally elevated protein. Many patients with CJD have elevated CSF stress protein 14-3-3. This test alone is neither sensitive nor specific, as patients with herpes simplex virus encephalitis, multi-infarct dementia, and stroke may have similar elevations.

59. The answer is D.
(Chap. 10) The ventral spinal cord includes the corticospinal tracts, spinothalamic tracts, and descending autonomic tracts. Disruption of these tracts causes weakness/areflexia, loss of pain/temperature sensation, and bladder sphincter dysfunction, respectively. The dorsal columns include vibratory sense and proprioception, which are spared in the ventral cord syndrome. Other causes of the syndrome include disc herniation, radiation myelitis, and human T-lymphocyte virus 1 infection.

60. The answer is C.
(Chap. 44) This patient's skin findings are an example of Gottron's sign of the hands and the heliotrope facial rash of dermatomyositis. Usually the rash precedes the muscular weakness. In addition to the V-sign, as described in the scenario, one can also see the shawl sign, in which the erythematous rash is found around the shoulders and posterior neck region. In addition to the skin manifestations, skeletal muscle weakness, particularly the proximal muscles, is part of the presentation of dermatomyositis. Extra-muscular manifestations include constitutional symptoms, joint contractures, dysphagia, cardiac disturbances, pulmonary dysfunction, and arthralgias. Hepatosplenomegaly is not an associated clinical finding. Situs inversus is not associated with dermatomyositis. Hypothyroidism is associated with delayed deep tendon relaxation. In hypothyroidism the skin appears swollen, dry, and coarse with a cool waxy appearance. Subcutaneous nodules on the elbows, back of the forearms, and metacarpophalangeal joints of the hands are characteristic of rheumatoid arthritis, particularly in the active phase.

61. The answer is D.
(Chap. 17) This patient has acute angle-closure glaucoma resulting from obstruction of the outflow of aqueous humor at the iris. The buildup of intraocular pressure can be confirmed by measurement and requires urgent treatment with hyperosmotic agents. Permanent treatment requires laser or surgical iridotomy. Angle-closure glaucoma is less common than is primary open-angle glaucoma, which is asymptomatic and is usually detectable only through measurements of intraocular pressure at a routine eye examination.

62. The answer is D.
(Chap. 40) CMT disease is a heterogeneous group of inherited peripheral neuropathies. Transmission is usually

autosomal dominant but may be recessive or X-linked. Numerous genetic defects are associated with CMT disease. It is very common, affecting up to 1 in 2500 persons. Clinically, patients usually present in the first or second decade of life, but later presentations may occur. The neuropathy affects both motor and sensory nerves. Symptoms may vary, ranging from distal muscle weakness and severe atrophy and disability to only pes cavus and minimal weakness. Although sensory findings and involvement are common, these patients often do not have dominant sensory complaints. However, if patients have no evidence of sensory involvement on detailed neurologic examination or electrodiagnostic studies, an alternative diagnosis should be considered. There is no known effective therapy for CMT disease. Orthotics and physical therapy are mainstays for preserving function.

63. The answer is D.
(Chap. 35) *Listeria* has become an increasingly important cause of bacterial meningitis in neonates (<1 month of age), pregnant women, individuals >60 years, and immunocompromised individuals. Infection is acquired by eating contaminated foods such as unpasteurized dairy products, cole slaw, milk, soft cheeses, delicatessen meats, and uncooked hot dogs. Ampicillin is the agent most often added to the initial empirical regimen to cover *L. monocytogenes*.

64. The answer is E.
(Chap. 14) Foraminal herniation, which forces the cerebellar tonsils into the foramen magnum, leads to compression of the medulla and subsequent respiratory arrest. Central transtentorial herniation occurs when the medial thalamus compresses the midbrain as it moves through the tentorial opening; miotic pupils and drowsiness are the classic clinical signs. A locked-in state is usually caused by infarction or hemorrhage of the ventral pons; other causes include Guillain-Barré syndrome and certain neuromuscular blocking agents. Catatonia is a semi-awake state seen most frequently as a manifestation of psychotic disorders such as schizophrenia. Third-nerve palsies arise from an uncal transtentorial herniation where the anterior medial temporal gyrus herniates into the anterior portion of the tentorial opening anterior to the adjacent midbrain. Coma may occur due to compression of the midbrain.

65. The answer is D.
(Chap. 29) Brief paroxysms of severe, sharp pains in the face without demonstrable lesions in the jaw, teeth, or sinuses are called tic douloureux, or trigeminal neuralgia. The pain may be brought on by stimuli applied to the face, lips, or tongue or by certain movements of those structures. Aneurysms, neurofibromas, and meningiomas impinging on the fifth cranial nerve at any point during its course typically present with trigeminal neuropathy, which will cause sensory loss on the face, weakness of the jaw muscles, or both; neither symptom is demonstrable in this patient. The treatment for this idiopathic condition is carbamazepine or phenytoin if carbamazepine is not tolerated. When drug treatment is not successful, surgical therapy, including the commonly applied percutaneous retrogasserian rhizotomy, may be effective. A possible complication of this procedure is partial facial numbness with a risk of corneal anesthesia, which increases the potential for ulceration.

66. The answer is C.
(Chap. 42) Except for lumbar puncture, all of the options listed are indicated at this time. Thymic abnormalities are present in 75% of patients with myasthenia gravis. A CT or MRI of the mediastinum may show enlargement or neoplastic changes in the thymus and is recommended upon diagnosis. Hyperthyroidism occurs in 3–8% of patients with myasthenia gravis and may aggravate weakness. Testing for rheumatoid factor and antinuclear antibodies should also be obtained because of the association of myasthenia gravis to other autoimmune diseases. Due to side effects of immunosuppressive therapy, a thorough evaluation should be undertaken to rule out latent or chronic infections such as tuberculosis. Measurements of ventilatory function are valuable as a baseline because of the frequency and seriousness of respiratory impairment in myasthenic patients, and they can be used as an objective measure of response to therapy.

67. The answer is D.
(Chap. 31) Hemorrhages beneath the dural layer (subdural) or between the skull and the dura (epidural) are common sequelae of head trauma. They can be life-threatening, and prompt evaluation and management are imperative. Several clinical features allow these conditions to be distinguished from one another. Acute subdural hematomas typically arise from venous sources, often the bridging veins located immediately under the dura mater. As the brain volume decreases with age, traction on these venous structures increases and even minor head trauma in the elderly can lead to a subdural hematoma. Approximately 33% of patients with an acute subdural bleed will experience a lucid interval after the event, which is followed by obtundation. Subdural bleeding is typically slower than epidural bleeding due to their different sources. Small subdural bleeds are asymptomatic and often do not require evacuation. Epidural hematomas, on the other hand, can arise quickly and typically represent arterial bleeding. They are often caused by a lacerated middle meningeal artery from an overlying skull fracture. Rapid increase in intracranial pressure from these bleeds can necessitate arterial ligation or emergent craniotomy. Most patients with epidural bleeding are unconscious when first evaluated; a "lucid interval" can occasionally be seen.

68. The answer is C.
(Chap. 29) Pain, loss of function (without clear-cut sensory or motor deficits), and a localized autonomic impairment are called reflex sympathetic dystrophy (also known as

shoulder-hand syndrome or causalgia). Precipitating events in this unusual syndrome include myocardial infarction, shoulder trauma, and limb paralysis. In addition to the neuropathic-type pain, autonomic dysfunction, possibly resulting from neuroadrenergic and cholinergic hypersensitivity, produces localized sweating, changes in blood flow, and abnormal hair and nail growth as well as edema or atrophy of the affected limb. Treatment is difficult; however, anticonvulsants such as phenytoin and carbamazepine may be effective, as they are in other conditions in which neuropathic pain is a major problem.

69. The answer is B.
(Chap. 6) The peak prevalence of migraine headaches occurs in the fourth to fifth decades of life. Many women experience decreased severity and frequency of headaches after menopause, and some individuals cease to have migraines as they age. Migraine has been demonstrated to be a risk factor for ischemic stroke in both men and women. In addition, women who have migraine with aura appear to be at greater risk of ischemic stroke if they are concurrently taking oral contraceptives. The American College of Gynecology has recommended that women who are >35 years or have focal neurologic symptoms with their migraine attacks should not take oral contraceptives, but low-dose contraceptive can otherwise be taken safely in women with migraine headaches. Any risk factors that are known to increase stroke risk such as hypertension or cigarette smoking also contribute to stroke in individuals with migraine. Interestingly, asymptomatic women with migraines have been shown to have a greater likelihood of white matter changes on MRI, and those with aura had a significant increased risk of subclinical posterior circulation infarcts.

70. The answer is A.
(Chap. 9) This patient has classic symptoms and history consistent with Ménière's disease. Patients have recurrent unilateral labyrinthine dysfunction marked by hearing loss and tinnitus. The symptoms are very debilitating, and patients may be incapacitated by the tinnitus and vertigo. The severity and recurrent nature suggest Ménière's disease and argue against a central process. Ménière's disease responds to diuretic therapy and/or a low-salt diet. In addition, patients should attempt to ambulate in an attempt to induce central compensatory mechanisms. Scopolamine transdermal patches and anticholinergic medications are useful only for motion sickness. The Epley procedure attempts to reposition particulate debris within the semicircular canals such as in benign paroxysmal positional vertigo. Glucocorticoids are useful for the acute treatment of vertigo but are used only in the acute setting and have no role in the long-term treatment of Ménière's disease. Metoclopramide may be used to treat nausea but has no role in the tinnitus and vertigo of Ménière's disease.

71. The answer is E.
(Chap. 26) Cerebellar ataxia with a strong family history suggests one of the autosomal spinocerebellar ataxias (SCA). SCA7 is distinguished from all of the other SCAs by the presence of retinal pigmentary degeneration. The visual abnormalities first appear as blue-yellow color blindness and proceed to frank visual loss with macular degeneration. Proliferative retinopathy would be expected in someone who has poorly controlled diabetes. Lipemia retinalis is often seen in patients with hypertriglyceridemia. Papilledema is seen in increased intracranial pressure, which is not present in SCA.

72. The answer is E.
(Chap. 21) Numerous studies have identified key risk factors for ischemic stroke. Old age, family history, diabetes, hypertension, tobacco smoking, and cholesterol are all risk factors for atherosclerosis and therefore stroke. Hypertension is the most significant among these risk factors. All cases of hypertension must be controlled in the setting of stroke prevention. Antiplatelet therapy has been shown to reduce the risk of vascular atherothrombotic events. The overall relative risk reduction of nonfatal stroke is about 25–30% across most large clinical trials. The "true" absolute benefit is dependent on the individual patient's risk; therefore, patients with a low risk for stroke (e.g., younger, with minimal cardiovascular risk factors) may have a relative risk reduction with antiplatelet therapy but a meaningless "benefit." Numerous studies have shown the benefit of statin therapy in the reduction of stroke risk even in the absence of hypercholesterolemia. Although anticoagulation is the treatment of choice for atrial fibrillation and cardioembolic causes of stroke, there is no proven benefit in regard to the prevention of atherothrombotic stroke; therefore, warfarin cannot be recommended.

73. The answer is C.
(Chap. 18) Head trauma is the most common etiology of a decreased sense of smell in young adults and children. In most cases this is permanent, with only 10% of these patients experiencing recovery. In older adults viral infections predominate. Parainfluenza virus type 3 is the most common associated virus. Patients with HIV also frequently have a distorted sense of smell, and this is associated with HIV wasting syndrome. Although rare, genetic defects such as Kallmann syndrome and albinism are also causes of anosmia. Influenza virus is not a cause of anosmia.

74. The answer is D.
(Chap. 20) Phenytoin is a commonly used anticonvulsant. Its principal use is in patients with tonic-clonic seizures. It may be given either orally or intravenously. Typical dosing is about 300 to 400 mg/d in adults. The therapeutic range is between 10 and 20 μg/mL. Neurologic side effects include dizziness, ataxia, diplopia, and confusion. Systemic

side effects include gum hyperplasia, hirsutism, facial coarsening, and osteomalacia. These patients may develop lymphadenopathy and Stevens-Johnson syndrome. Toxicity may be enhanced by liver disease and competition with other medications. Phenytoin alters folate metabolism and is teratogenic. Leukopenia is not a typical side effect and is seen more often with carbamazepine.

75. The answer is C.
(Chap. 43) The muscular dystrophies are hereditary progressive diseases. Becker's muscular dystrophy is a less severe form of X-linked recessive muscular dystrophy than Duchenne's muscular dystrophy. It occurs 10 times less frequently than DMD. The underlying defect is in the same protein, dystrophin, which is part of a large complex of sarcolemmal proteins and glycoproteins. Clinically, Becker's muscular dystrophy (BMD) shows a similar pattern of proximal muscle weakness. Weakness becomes generalized with progression of the disease. Hypertrophy of muscles, particularly the calves, is an early feature. Most patients experience the initial symptoms in the first and second decades of life, but a later onset may occur. These patients have reduced life expectancy but are significantly more functional than are patients with DMD. Mental retardation may also occur in patients with BMD, and cardiac involvement may result in congestive heart failure. Serum creatinine kinase (CK) levels are elevated, and electrodi-agnostic findings are similar to those seen in DMD. The diagnosis is made by demonstrating a reduced amount of dystrophin on Western blot analysis.

76. The answer is D.
(Chap. 7) There are four indications for surgical repair of an intervertebral disk herniation: objective progressive motor weakness, signs of spinal cord compression (e.g., bowel or bladder incontinence), incapacitating nerve root pain despite conservative treatment, and recurrent incapacitating nerve root pain. Absent deep tendon reflexes, nighttime symptoms, and more than one level of disk herniation are not uncommon findings in patients with a disk herniation and do not mandate surgery.

77. The answer is A.
(Chap. 10) Episodic generalized weakness is caused by disorders of the central nervous system (CNS) or the motor unit. Weakness from CNS disorders is usually associated with altered consciousness or cognition, increased muscle tone and reflexes, and changes in sensation. Motor unit disorders include a variety of electrolyte disturbances (hypokalemia, hyperkalemia, hypercalcemia, hypernatremia, hyponatremia, hypophosphatemia, hypermagnesemia), inborn errors of metabolism (carbohydrate or fatty acid metabolism, mitochondrial function), toxins (botulism, curare), neuromuscular junction disorders (myasthenia gravis, Lambert-Eaton syndrome), and channelopathies (periodic paralysis). Transient ischemic attacks of the brainstem, but not in any other part of the brain, may also cause episodic generalized weakness. Multiple sclerosis may cause episodic generalized weakness. Atherosclerotic occlusive carotid disease may cause focal but not generalized weakness.

78. The answer is C.
(Chap. 1) The patient in this scenario is demonstrating *paratonia* (fluctuating changes in resistance during testing of motor tone). Paratonia may be seen in patients who have difficulty relaxing during the examination or may be evidence of aberrant frontal lobe pathways, as in some forms of dementia. The patient has increased tone, making muscle injury less likely. Dystonia, as seen in parkinsonism, manifests as cogwheel rigidity and jerky interruptions of resistance without the focality that is seen in this scenario. Motor neuron diseases, such as amyotrophic lateral sclerosis, may present with either flaccidity or spasticity. Usually patients with motor neuron disease have abnormalities that can be elicited in more than one muscle group (although asymmetry is common).

79. The answer is D.
(Chap. 36) Ibuprofen, isoniazid, ciprofloxacin, tolmetin, sulfa-containing medicines, and phenazopyridine have been implicated in drug hypersensitivity leading to meningitis. The cerebrospinal fluid (CSF) will typically show neutrophils, but mononuclear cells or eosinophils are occasionally present. Most causes of chronic (not recurrent) meningitis cause a predominance of mononuclear cells. The differential for chronic meningitis is broad and a diagnosis is often difficult to make. The treating physician needs to consider a diverse array of viral, fungal, bacterial, mycobacterial, helminthic, and protozoal pathogens, both common and exotic, and therefore should obtain a detailed social history and consult an expert in the field. Recurrent meningitis is often due to herpes simplex virus type 2 infection and this should be ruled out, particularly if active genital ulcers develop concurrently. Malignancy, sarcoidosis, and vasculitis are all potential causes, and history, physical examination, and appropriate further testing should dictate the degree to which these possibilities are explored. Medications are often overlooked as a cause of chronic meningitis and should always be carefully considered. When CSF neutrophils predominate after 3 weeks of illness, nocardia, actinomyces, brucella, tuberculosis (<10% of cases), fungal, and noninfectious causes of chronic meningitis should be considered.

80. The answer is E.
(Chaps. 15 and 23) All the choices given in the question are causes of or may be associated with dementia. Binswanger's disease, the cause of which is unknown, often occurs in patients with long-standing hypertension and/or atherosclerosis; it is associated with diffuse subcortical white matter damage and has a subacute insidious course.

Alzheimer's disease, the most common cause of dementia, is also slowly progressive and can be confirmed at autopsy by the presence of amyloid plaques and neurofibrillary tangles. Creutzfeldt-Jakob disease, a prion disease, is associated with a rapidly progressive dementia, myoclonus, rigidity, a characteristic EEG pattern, and death within 1–2 years of onset. Vitamin B_{12} deficiency, which often is seen in the setting of chronic alcoholism, most commonly produces a myelopathy that results in loss of vibration and joint position sense and brisk deep tendon reflexes (dorsal column and lateral corticospinal tract dysfunction). This combination of pathologic abnormalities in the setting of vitamin B_{12} deficiency is also called subacute combined degeneration. Vitamin B_{12} deficiency may also lead to a subcortical type of dementia. Multi-infarct dementia, as in this case, presents with a history of sudden stepwise declines in function associated with the accumulation of bilateral focal neurologic deficits. Brain imaging demonstrates multiple areas of stroke.

81. The answer is B.

(Chap. 40) Carpal tunnel syndrome is caused by entrapment of the median nerve at the wrist. Symptoms begin with paresthesias in the median nerve distribution. With worsening, atrophy and weakness may develop. This condition is most commonly caused by excessive use of the wrist. Rarely, systemic disease may result in carpal tunnel syndrome. This may be suspected when bilateral disease is apparent. Tenosynovitis with arthritis as in the case of rheumatoid arthritis and thickening of the connective tissue as in the case of amyloid or acromegaly are also causes. Other systemic diseases, such as hypothyroidism and diabetes mellitus, are also possible etiologies. Leukemia is not typically associated with carpal tunnel syndrome.

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